TB challenges in hard-to-reach populations and children

Addressing TB control in Europe & imaging paediatric TB in Africa

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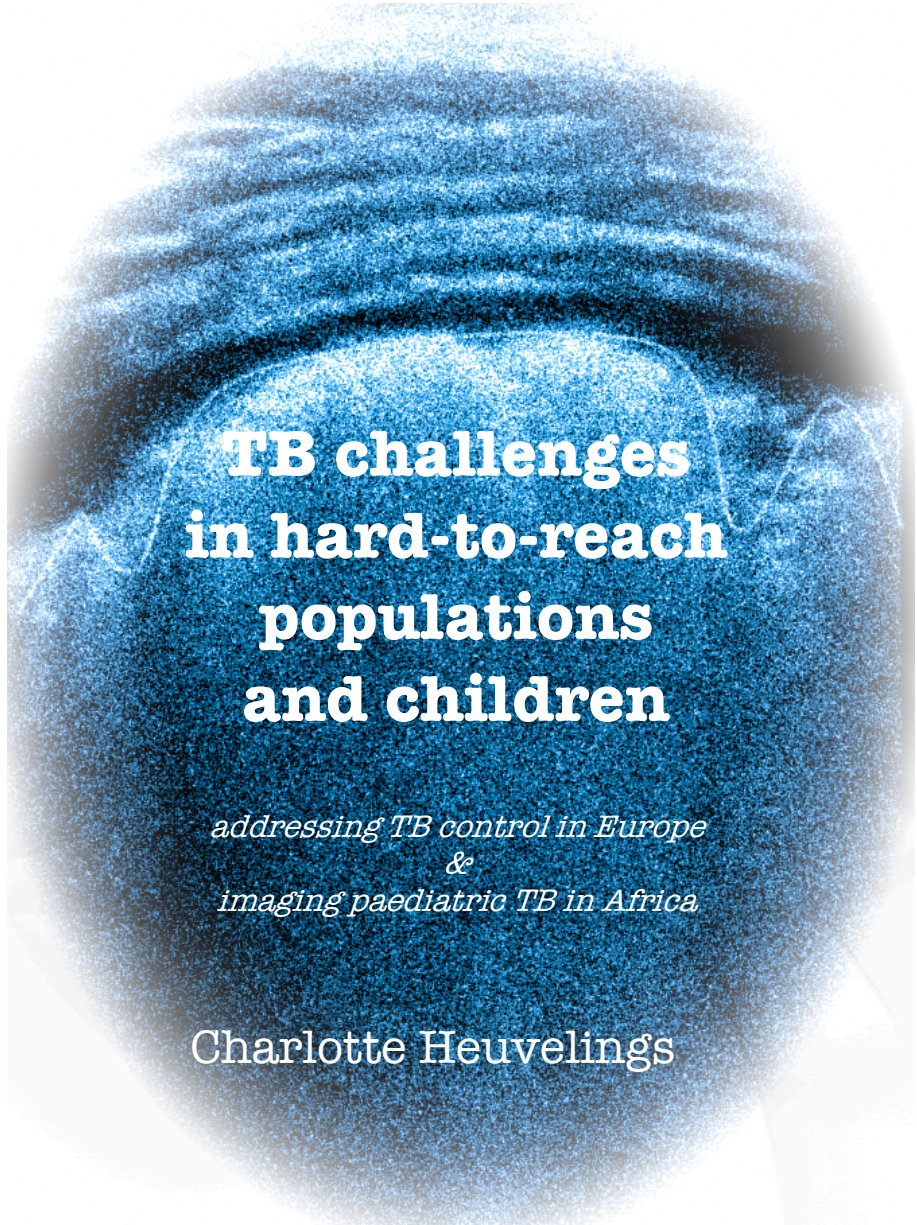

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ten overstaan van een door het College voor Promoties ingestelde commissie,
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‘It always seems impossible until it is done’
Nelson Mandela 2001

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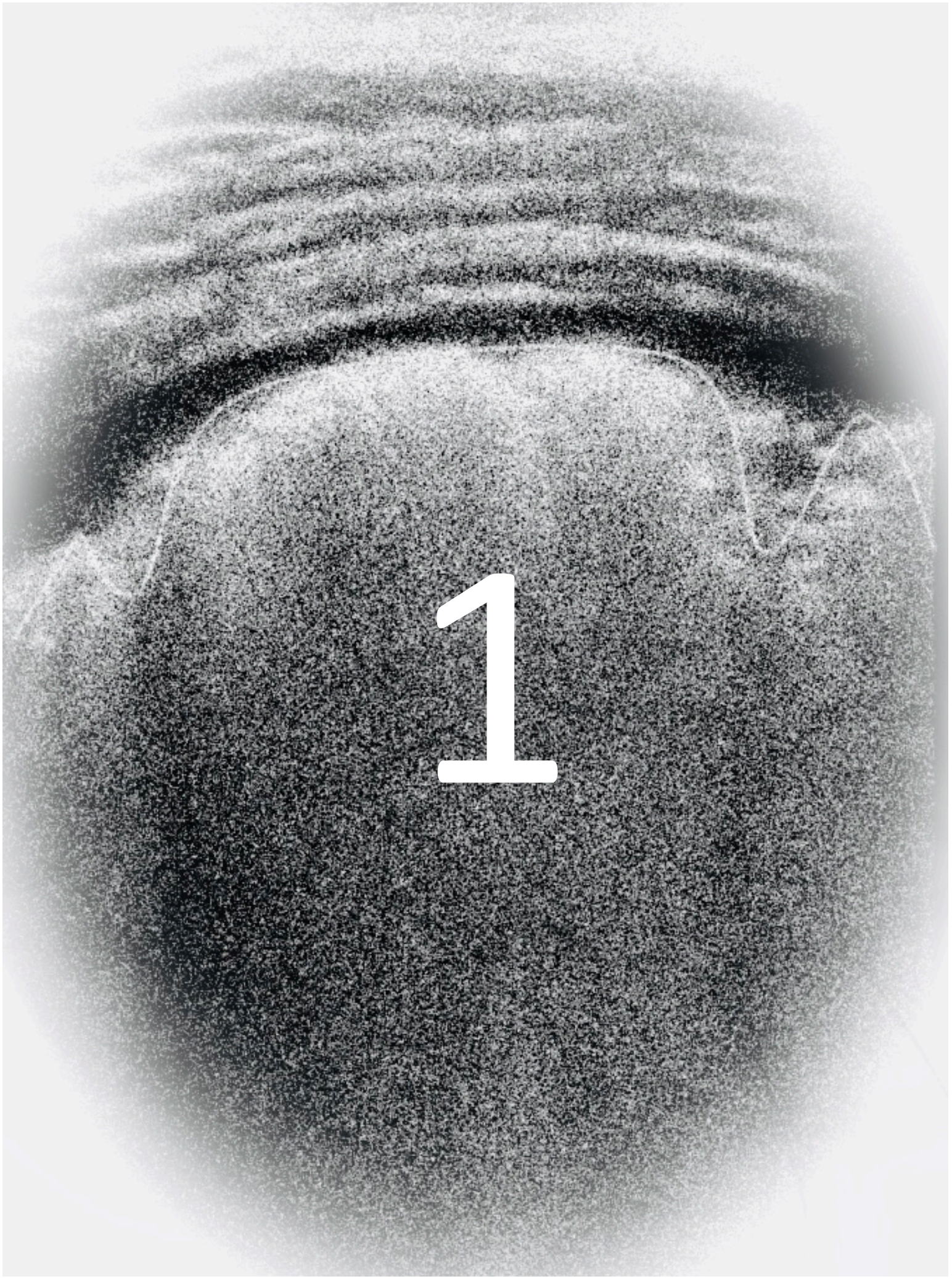
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chapter 1

GENERAL INTRODUCTION

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Historical background

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). *M. tuberculosis* has been around for about 3 million years.[1] The earliest TB infection identified in humans was around 9,000 years ago. Archaeologists found *M. tuberculosis* in the bones of a mother and her child buried in the same tomb in a city off the coast of Israel.[2] It was not until 1882 that Robert Koch discovered that TB is caused by a bacterium, *M. tuberculosis*.[3] TB is an airborne infectious disease that spreads from person to person by droplets released in the air when an infected person coughs or speaks.[4]

In the 1600-1800's, a quarter of all deaths in Europe were caused by TB.[5,6] Due to improved hygiene, living conditions and nutrition, TB prevalence declined across the western world.[7] In the 19th century, the first sanatoria arose in Europe and the United States. The hypothesis was that isolation, clean mountain air and sunshine would decrease TB prevalence even more.[8] In 1943 Selman Waksman discovered that a medicine called streptomycin could cure TB; unfortunately, resistance developed fairly soon.[9] In the 1950's, three-drug therapy (streptomycin, para-aminosalicylate and isonicotinic acid hydrazide, or isoniazid) was found to be effective. It yielded 80-90% cure rates; however, unfortunately, the adverse effects and the duration of treatment (18-24 months) were major drawbacks.[10,11] Over the years, a highly effective quadruple treatment (rifampicin, isoniazid and pyrazinamide plus either ethambutol or streptomycine) was developed, but the length of treatment (6-9 months) still posed a considerable problem for many patients.

Because of effective treatment, TB incidence declined and public awareness faded. Public health departments handed the responsibility of TB control over to the general clinics, TB received less attention than other diseases, and no innovations were made. This and the HIV epidemic led to a resurgence of TB in the late 80's, early 90's. Development of resistance to several TB drugs,[12] also brought TB back on the public health agenda. Three main categories of drug resistance have been described; 1) rifampicin resistant TB (RR-TB); 2) multi-drug resistant TB (MDR-TB), which is resistance to isoniazid (INH) and rifampicin (RIF); and 3) extensively drug resistant TB (XDR-TB), which is MDR-TB plus resistance against at least one fluoroquinolone and one of the second-line injectable drugs (amikacin, capreomycin or kanamycin).[13]

STRATEGIES TO ADDRESS TB

Stop TB strategy

In 1993, the World Health Organization (WHO) declared TB as a global health emergency.[14] Since then several strategies to improve diagnosis, reduce incidence and improve care have been developed. In 2000, the United Nations (UN) established the Millennium Development Goals (MDGs), one of the goals was to 'halt and reverse' TB incidence.[15] A year later, the Stop TB partnership included this goal in their set of targets which aimed to halve the TB prevalence and mortality by 2015.[16] In 2014 the WHO implemented the End TB Strategy aiming to reduce TB deaths with 90% and reducing TB incidence rates with 80% by the year 2030, including a further reduction 5 years later.[17] In 2016, the MDGs were succeeded by the Sustainable Development Goals (SDGs), their goals are 1) to end the TB epidemic by 2030 and 2) that everyone should receive TB prevention, treatment and care.[18]

Strategies to address childhood TB

In 2013, a strategy solely focussing on children was launched, the "Roadmap for Childhood TB: Towards Zero Deaths'.[19] Childhood TB has been neglected for a long time and children struggle with the non-child friendly medication. Diagnosing childhood TB can be difficult due to non-specific signs and symptoms and difficulties in obtaining adequate samples.[20-22] One of the pillars of the roadmap is to address research gaps including the development of new tools, including improved diagnostics. The strategies discussed above contributed to a decline in TB incidence and mortality. The fastest decline of TB incidence (5% annually) and TB mortality (11% annually) was seen in the European region, measured over the 2013-2017 time period. The European region also had the highest TB treatment coverage (>75%) in the world, including >90% treatment coverage for MDR-TB.[23] Because of this success in the European Union (EU)/ European Economic Area (EEA), TB in Europe became a

disease that is mainly concentrated among people with a lower economic status, especially hard-to-reach populations like vulnerable migrants, prisoners, homeless people, drug users and people living with HIV. To reach the SDGs by 2030, TB programs in the EU/EEA should concentrate on those groups.

EPIDEMIOLOGY

Currently an estimated 1.7 billion people are infected with *M. tuberculosis* globally, whilst 5-10% of those will develop TB disease in the course of their lifetime.[23] People with HIV, diabetes mellitus or malnutrition or those who smoke or drink alcohol are at higher risk of developing TB disease. TB disease is almost twice as common in men than in women, and about 90% of the people with TB disease are adults.[23] In 2018, there were around 10 million new TB cases worldwide, two-thirds of those 10 million were seen in the eight high-burden countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Only 2.7% of the cases were reported in the European region. In 2018, an estimated 1.3 million HIV-negative people died of TB, making TB the leading cause of death by a single infectious agent.[23] In that same year (2018), 1.1 million new TB cases were among children, with 205 000 children dying because of TB (including children infected with HIV). Childhood TB is often missed by health care providers and, as said before, it is difficult to diagnose and treat childhood TB, due to atypical signs and symptoms, difficulties in obtaining adequate samples for diagnosis, low bacillary load and non-child friendly medication.[23] As we focus on TB identification and management in hard-to-reach populations in Europe and TB diagnostics in South African children in this thesis, the epidemiology of the disease, with Europe and South Africa as the foci of the work described here, will be discussed below.

Europe

In 2017, the TB notification rate in the EU/EEA was 55 337 (10.7 per 100 000 population). The highest European notification rate (>50 per 100 000 population) was seen in Romania, followed by Bulgaria, Latvia and Lithuania (20-49 per 100 000 population). A third of the cases (18 299 cases) was among people of foreign origin. Adults between 25-44 years had the highest notification rate (13.6 per 100 000 population), children under 15 years accounted for 4.4% of the notified TB cases (2 358 cases, 2.9 per 100 000 child population), males were over-represented in all ages groups. Prisoners have a relative risk of 11.4 to develop TB disease compared to the general population in the EU/EEA. Pulmonary TB presented 77.4% of all the TB cases in the EU/EEA. MDR-TB was diagnosed in 3.7% of all TB cases with available drug-sensitivity testing. The highest percentages of MDR-TB cases were seen in Estonia, Lithuania and Latvia. XDR-TB was seen in 24.3% of all MDR-TB cases. Of all the confirmed TB cases with a known HIV status, 3.9% were HIV positive.[24]

South Africa

In stark contrast, South Africa is still one of the eight high-burden TB countries, but the annual TB incidence in South Africa has been falling at about 7% due to improved TB and HIV prevention and care, including improved anti-retroviral therapy (ART) coverage. In 2018, the TB incidence rate in South Africa was 301 000 (520 per 100 000 population), of which about 7% was in children under the age of 15. Males were over-represented (56% versus 37% in women), 89% of the cases were pulmonary TB. There were 11 000 (19 per 100 000 population) cases of MDR-TB/RR-TB (rifampicin-resistant TB). Of all the TB cases with a known HIV status, 59% were HIV positive (177 000 cases, 306 per 100 000 population). The TB mortality rate in South Africa has fallen as well, particularly the number of TB deaths among HIV positive people. In 2018, 63 000 people died of TB, of which 42 000 were HIV infected.[23] The TB incidence in the Western Cape, the province surrounding Cape Town, has been falling since 2008, except for 2017. In 2017, the TB incidence rose again to 45 000 cases (14.0% of all the TB cases in South Africa), the highest incidence since 2012; with 1 450 (3.2%) MDR-TB cases and 122 (0.3%) XDR-TB cases.[25] Around 13.7% the TB cases were diagnosed in children under the age of 13,[26] what means that there were about 6 000 children with TB in the Western Cape.

DIAGNOSTICS

To diagnose TB, a combination of tests is applied, usually sputum testing and imaging.

Sputum tests

Sputum smear microscopy has been the most commonly used method for a long time. It gives a quick result, it is relatively easy to perform, it is cost-effective and in high prevalent TB settings it has been highly specific.[27] Sputum culture is the gold standard for the diagnosis of TB, with the disadvantage that it can take weeks to obtain a positive result. One of the main objectives of the End TB Strategy is accurate and early diagnostic testing.[22] The cartridge-based test, Xpert MTB/RIF, is a good example of that. It gives a rapid result, in less than 2 hours, and has a better diagnostic accuracy than sputum smear. Xpert MTB/RIF detects the DNA of *M. tuberculosis* and is able to identify genetic mutations associated with rifampicin resistance.[28] Recently Xpert MTB/RIF Ultra (Ultra; Cepheid) has been introduced. In adults, Xpert MTB/RIF Ultra gives a quicker result within 80 minutes, compared to Xpert MTB/RIF. Ultra has a higher sensitivity especially in smear-negative cases, detection of rifampicin resistance was similar, but the specificity was slightly lower.[29] Another objective of the End TB Strategy is universal drug sensitivity testing (DST),[22] with Xpert MTB/RIF covering two of the End TB Strategy objectives. Obtaining an adequate sputum sample can be difficult in children, therefore induced sputum samples or nasopharyngeal aspirates are often used in children. Another challenge in diagnosing childhood TB is that children have a low bacillary load and therefore, sputum smear microscopy is often negative, so sputum smear microscopy has poor sensitivity. A recent study showed that recently introduced Xpert MTB/RIF Ultra had one of the highest yields reported for rapid diagnostic test in children when a single induced sputum sample plus single nasopharyngeal aspirate (80%) were tested and when a single induced sputum sample plus two nasopharyngeal aspirates (87%) were tested.[30]

Imaging

Currently, chest radiography is the imaging tool of choice for the diagnosis and screening of pulmonary TB. The characteristic TB findings are consolidation, effusion, cavitation and lymphadenopathy. Chest radiography is widely available and gives a quick result, but specificity and inter-reader agreement are poor, especially in children.[31-32] Computed tomography (CT) and magnetic resonance imaging (MRI) can also be used for TB diagnosis but those imaging techniques are less widely available. CT comes with a higher radiation exposure than CXR, and children might need to be sedated for CT and MRI scanning. Chest ultrasonography is amongst the most recently emerging ultrasonography applications. For years the prevailing opinion was that ultrasound would be unsuitable for diagnosing lung disease due to air impeding transmission of sound waves. Today, the value of ultrasound in visualizing lung pathologies arising close to the pleura has been clearly documented. Chest ultrasound has been proven to be a sensitive tool for the diagnosis of several pulmonary conditions such as pneumothorax,[33-35] pneumonia[36-38] and pleural effusion.[39] Other advantages are a reduction in time to diagnosis and costs,[11] on top of that there is no exposure to ionising radiation. Recently, several ultrasound studies on TB have been published; 1) focussing on the diagnosis of extra-pulmonary TB[40,41] and the visualisation of mediastinal lymph nodes in children with TB.[42-44] However, there were no ultrasound studies focussing on chest findings in children with pulmonary TB.

Other TB tests are the interferon-gamma-release assay (IGRA) and the tuberculin-skin test (TST), often applied as screening tools; those tests measure the immunologic response to TB antigen. The IGRA and TST tests are, however, not optimally suited to distinguish between infection and active disease. The TST, for example, a positive TST does not necessarily mean TB disease, especially in communities with a high risk of TB infection. Exposure to environmental mycobacteria can give a positive TST as well and immunisation with the BCG vaccine gives a positive TST, however the cut-off of 10 mm normally distinguishes between disease and immunisation; whereas cutaneous anergy in HIV-infected individuals can lead to false-negative results.

TREATMENT

TB is a deadly disease. The case fatality rate for HIV-negative individuals with a positive sputum smear is around 70% if not treated.[45] The duration of the disease (onset to death or cure) is around three years.[45] With the introduction of TB drugs, the case fatality rate was reduced. As discussed above, drug-resistance developed quickly when only one TB drug was given. Nowadays, TB patients with drug-susceptible TB receive a combination of four drugs during the first two months of treatment followed by two drugs for another four months.[46] For TB patients with drug-resistant TB, second- or third-line TB drugs will be used depending on the drug resistance pattern. Those drugs are normally more toxic, with more side effects, are more expensive, might need to be administrated by inject and the treatment duration is normally much longer.[47] As treatment regimens are long, there is an increased risk of non-compliance, therefore the Directly-Observed Therapy, Short course (DOTS) strategy has been adopted worldwide. This means that TB medication will be taken under supervision. Two systematic reviews showed no difference in treatment adherence and treatment outcome between self-administration and DOTS.[48,49] Regardless, DOTS is still widely used to improve TB treatment adherence and reduce the development of TB resistant strains. Currently, major efforts are underway to individualise but simplify and shorten both therapy for drug-sensitive and drug–resistant TB,[50] as reflected in recent WHO TB therapy policy changes.[51-52]

OUTLINE OF THESIS

The quest for improved TB control towards the ultimate elimination and eradication goals requires a multitude of different strategies. To eradicate TB, those strategies should focus on TB control in high incidence settings but TB control in low incidence settings should not be forgotten. This thesis links together TB control in those two different settings to reach these most ambitious goals in the long term. This thesis consists of two parts, in the first part of this thesis, we address TB care in low- and medium-incidence countries and specifically focus on hard-to-reach populations. In the second part we focus on the use of chest ultrasound to diagnose respiratory conditions in a high-incidence, low-to middle-income setting, exemplified by addressing pulmonary TB in South African children.

Part I: TB in hard-to-reach populations

To reach the SDGs and the goals set out in the End TB Strategy, early detection and treatment of people with active TB is an important pillar for preventing transmission of *M. tuberculosis*, severe TB disease and TB mortality.[53] Annually, around 3.6 million active TB cases remain unnotified; as a result of this is a combination of under-reporting and under-diagnosing.[14] In high-income, low TB incidence (<10 per 100 000 population) countries, like many EU/EEA countries, those unnotified (underdiagnosed) TB cases are mainly concentrated around hard-to-reach populations. The challenges in TB control in hard-to-reach populations are that those subgroups of the population are difficult to include in TB screening programmes. In this thesis we define hard-to-reach populations as populations whose socio-economic status make it difficult to recognise TB symptoms, have problems in accessing health care, have difficulty in regularly attending clinic appointments or with self-administration of TB drugs. Illegal migrants may be hard-to-reach as they might be a 'hidden population' and do not want to be found. But legal migrants may also be hard to reach, as they may experience a language barrier or financial impediments to accessing care. Homeless people may not have a registered home address and are therefore possibly hard to contact. People using illegal drugs may be homeless or unable to attend clinic appointments as the may be under influence of drugs at the time of appointment or may forget their appointment. Prisoners who have a higher risk of TB exposure due to overcrowding and clustering of vulnerable people, might not visit clinics regularly, and they might leave prison before the end of their treatment. HIV infected individuals might experience stigma, and might therefore not want to attend TB screening. As well, they are at increased risk of developing TB disease as they might not be immunocompetent.[54] To reduce TB transmission and TB incidence in those low-incidence countries identifying and treating those un-notified cases is essential.[55] This is challenging, as in low-incidence countries health-care workers hardly encounter a patient with TB, and therefore might not recognise the signs and symptoms.[56] Furthermore, some individuals might allocate their symptoms to other causes.[57,58]

Additionally, stigmatisation, fear of death from TB, language barriers and lack of knowledge of TB services are major barriers for seeking help. The lengthy treatment duration and the adverse effects can have a negative impact on TB treatment compliance.[59]

As part of an assignment by the European Centre of Disease Prevention and Control (ECDC) about guidance on tuberculosis control in vulnerable and hard-to-reach populations,[60] three systematic reviews were conducted. The aim of the first review (**Chapter 2**) is to identify the barriers and facilitators for the uptake of TB screening and treatment in hard-to-reach populations in countries with a low or medium TB incidence. In the second review (**Chapter 3**), we discuss the effectiveness of interventions to improve TB screening and TB treatment adherence in hard-to-reach populations in countries with a low or medium TB incidence. In the third review (**Chapter 4**), the effectiveness of service models and organisational structures supporting those interventions to diagnose TB and treat TB in hard-to-reach populations will be discussed.

Part II: Chest ultrasound for the diagnosis of pulmonary TB and other respiratory diseases

TB is often under-diagnosed in children. TB diagnosis in children is challenging as children may present with non-specific signs and symptoms, exhibit a low bacillary load and have difficulties in providing adequate sputum samples, which renders the demonstration of *M. tuberculosis* difficult.[24-26] Because of that, diagnosing pulmonary TB in children normally relies on clinical diagnosis in combination with chest radiography. As said before, chest radiography has its limitations in children, the interreader agreement is poor and the specificity is low,[31-32] additionally the child gets exposed to (low-dose) radiation. Chest ultrasound has increasingly been used for the diagnosis of childhood pneumonia. The advantage of chest ultrasound is that it does not expose the child to ionising radiation; it can be performed by a clinician at the bedside, and it is quick to perform. Several studies showed good diagnostic accuracy of chest ultrasound for the diagnosis of pneumonia in children.[36-38] We performed a systematic review and meta-analysis in **Chapter 5** to assess the diagnostic accuracy of chest ultrasound for the diagnosis of paediatric pulmonary diseases.

Mediastinal ultrasound has been studied for the detection of mediastinal lymphadenopathy in South African children with TB.[42-44] In **Chapter 6,** we describe the technical aspects of mediastinal ultrasound for the use in children and in **Chapters 7** and **8,** we incorporated mediastinal ultrasound in the chest ultrasound protocol.
In **Chapter 7,** we discuss chest ultrasound findings in children with suspected pulmonary TB. In **Chapter 8,** we compare chest ultrasound findings with chest radiography findings.

FASH, the focused sonographic assessment of HIV-associated TB, has recently been applied to diagnose extra-pulmonary TB in adults[40] and in children.[41] Using FASH, the clinician images for signs of extra-pulmonary TB, specifically pericardial fluid, pleural fluid or ascites, enlarged lymph nodes in the abdomen or micro-abscesses in the liver and spleen. Other than pleural fluid, the lungs are not assessed. In our studies (**Chapter 7 and Chapter 8**), describes pulmonary changes on chest ultrasound in children with suspected pulmonary TB. We described normal findings like A-lines (horizontal reverberations of the pleural line), and movement of the pleural line, as well as abnormal findings such as consolidation, pleural effusion or more than three B-lines per intercostal space. A B-line is a vertical laser beam-like line originating from the pleura reaching the bottom of the ultrasound screen and is a sign of interstitial fluid. As mediastinal lymphadenopathy is the diagnostic hallmark of pulmonary TB on chest radiography, we incorporated mediastinal ultrasound in our chest ultrasound protocol to demonstrate mediastinal lymphadenopathy in children with suspected pulmonary TB.

In **Chapter 9,** we present ultrasound findings in five cases of patients infected with HIV, the third case we present was a patient co-infected with HIV and TB. The chest ultrasound findings of this patient are of interest for this thesis.

In the last chapter, **Chapter 10**, we discuss the findings of this thesis and provide future perspectives.

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part I

TUBERCULOSIS IN HARD-TO-REACH POPULATIONS


2

chapter 2

BARRIERS AND FACILITATORS TO THE UPTAKE OF TUBERCULOSIS DIAGNOSTIC AND TREATMENT SERVICES BY HARD-TO-REACH POPULATIONS IN COUNTRIES OF LOW AND MEDIUM TUBERCULOSIS INCIDENCE: A SYSTEMATIC REVIEW OF QUALITATIVE LITERATURE

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ABSTRACT

Tuberculosis disproportionately affects hard-to-reach populations, such as homeless people, migrants, refugees, prisoners, or drug users. These people often face challenges in accessing quality health care. We did a systematic review of the qualitative literature to identify barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by people from hard-to-reach populations in all European Union (EU), European Economic Area, EU candidate, and Organisation for Economic Co-operation and Development countries. The 12 studies included in this review mainly focused on migrants. Views on perceived susceptibility to and severity of tuberculosis varied widely and included many misconceptions. Stigma and challenges regarding access to health care were identified as barriers to tuberculosis diagnosis and treatment uptake, whereas support from nurses, family, and friends was a facilitator for treatment adherence. Further studies are required to identify barriers and facilitators to the improved identification and management of tuberculosis in hard-to-reach populations to inform recommendations for more effective tuberculosis control programmes.

INTRODUCTION

Worldwide, tuberculosis causes the largest loss of disability-adjusted life-years due to an infectious disease, after malaria and HIV.[1] An estimated 9.6 million incident cases of tuberculosis occurred in 2014, of which 5.4 million were in men, 3.2 million were in women, and 1.0 million were in children.[2] In the European Union (EU) and European Economic Area (EEA), a third of 65 000 notified tuberculosis cases were in 18 low-incidence countries (ie, a notification rate of less than ten cases per 100 000 population).[3] In these countries, tuberculosis cases are disproportionately concentrated in big cities, associated with an over-representation of tuberculosis among various hard-to-reach and susceptible populations, such as homeless people, migrants, refugees, prisoners, drug users, sex workers, and people with HIV.[4,5] Although not all people with HIV can be called hard to reach, many hard-to-reach populations are more likely than the general population to acquire or carry HIV.[6–12] Few surveillance and survey data are available for tuberculosis in hard-to-reach populations.[13,14] In the EU and EEA, 28% of new tuberculosis cases occur in individuals of foreign origin, with 13 countries reporting that more than 50% of their tuberculosis cases occur in individuals of foreign origin.3 With the exception of information about tuberculosis in individuals of different origins, ages, and sexes, little information is available about tuberculosis in hard-to-reach groups. Moreover, information about other risk factors or social determinants is not readily available, which hampers policy and guideline development required to optimise tuberculosis control efforts. The global End TB Strategy[15] and Towards Tuberculosis Elimination[16] (a guideline for low-incidence countries) highlighted this scarcity of information and identified the most susceptible and hard-to-reach populations, which are often underserved, as a priority for action.[5]

Hard-to-reach populations often have specific risk factors that render them more exposed and susceptible to infection with Mycobacterium tuberculosis and development of active tuberculosis disease.[17] These risk factors include living in crowded and poorly ventilated areas, comorbidities, substance abuse, HIV infection, and malnutrition. Additionally, hard-to-reach populations face major challenges in accessing health care and adhering to tuberculosis treatment, which include reduced awareness and knowledge of the signs and symptoms of tuberculosis; unstable accommodation; and difficulties in transportation and access to health care, such as the restricted opening hours of testing centres, the cost of testing, and the lengthy duration of treatment.[18–27] The European Centre for Disease Prevention and Control initiated guidance for tuberculosis control in hard-to-reach and susceptible populations.[28] To provide an up-to-date evidence base, we did a systematic review of qualitative literature focusing on the barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services in hard-to-reach populations, covering all EU, EEA, EU candidate, and Organisation for Economic Co-operation and Development (OECD) countries. Information about barriers and facilitators is often best assessed with qualitative research of the perspectives of patients or health-care workers. Additionally, qualitative methods facilitate a more in-depth understanding of barriers and facilitators compared with, and in addition to, quantitative research methods.[29] Synthesised qualitative research findings thus aid the development of new theories, interventions, and policies. The primary question of our systematic review was: What factors help or hinder the uptake of tuberculosis diagnostic and treatment services by people from hard-to-reach populations in EU, EEA, EU candidate, and OECD countries, and how can those barriers be overcome? Secondary review questions were How do views vary between different hard-to-reach populations? and ‘What are the views of service providers? The findings serve as the evidence base for the development of guidance for control of tuberculosis in hard-to-reach and susceptible groups.

METHODS

Selection of studies and data management

In 2010, the National Institute for Health and Care Excellence (NICE) commissioned a systematic review of barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by people from hard-to-reach populations in OECD countries.[30] We updated and extended this review, following standards described by the Cochrane Collaboration[31] and NICE.[32] The results are reported according to the PRISMA guidelines for systematic reviews.[33] We deemed people who were homeless, migrants, travellers (including Roma), refugees, prisoners, drug users, sex workers, and people with HIV as belonging to hard-to-reach populations. Citations identified by

the search were imported into an EndNote database (EndNote X7.1) and duplicate records removed. Three authors (SGdV, CCH, BJV) screened the titles and abstracts of records independently and in parallel using prespecified criteria (panel 1). One author (CCH) screened 100% of the records; the other two authors (SGdV and BJV) screened 50% each. Disagreements were resolved by discussion. We retrieved the full texts of all articles identified in the initial screening, and contacted authors in cases of incomplete data or irretrievable articles. If the article was irretrievable (ie, not accessible from any source or from the authors), the study was excluded. The full text of each selected article was screened by three independent authors (SGdV [100%], CCH [50%], and ALC [50%]) with a full-text assessment inclusion checklist, derived from the previous NICE review.[30] Inter-reviewer agreement and reliability were calculated according to standard methods.[31]

SEARCH STRATEGY AND SELECTION CRITERIA

Using the same search strategies as in O'Mara and colleagues' 2010 National Institute for Health and Care Excellence (NICE) review (which covered Jan 1, 1990, to September, 2010), we searched MEDLINE, MEDLINE In-Process, Embase, PsycINFO, the Centre for Reviews and Dissemination database (for the Database of Abstracts of Reviews of Effects, the National Health Service Economic Evaluation Database, and the Health Technology Assessment database), The Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature. We searched for studies in all European Union (EU), European Economic Area, and EU candidate countries published between January, 1990, and April 10, 2015, and for studies in Organisation for Economic Co-operation and

Development countries published between June 5, 2010, and April 10, 2015. In addition to the hard-to-reach populations covered by the NICE review (migrants, homeless people, people who abuse substances, prisoners, sex workers, and people with HIV), we included children in hard-to-reach populations. Definitions of hard-to-reach groups were those defined by the respective papers. We limited the search to active tuberculosis, excluding latent tuberculosis infection. We included qualitative studies related to either the views of hard-to-reach people regarding perceptions of or attitudes towards tuberculosis services, qualitative descriptions of the variations in views between different hard-to-reach populations, or the views of service providers (appendix). Additionally, we checked all included studies for relevant references; all identified systematic reviews were also checked for relevant references, although they were not included (appendix).

Data extraction, data items, and synthesis

We extracted data by use of the same forms as in the previous NICE review.[30] Two independent authors (SGdV and ALC) extracted data for a random 10% (selected by simple random sampling) of the included studies; for the remaining studies, one author (SGdV) extracted the data, which were checked by a second author (ALC). Any disagreement was resolved by discussion. To structure the data synthesis, we used the Health Belief Model,[34] which explains and predicts health-related behaviours. Two independent reviewers did thematic and content analysis.[35] Data were coded and categorised into potential determinants of health behaviours within five themes of the Health Belief Model framework: (1) perceived susceptibility (risk); (2) perceived severity (consequences, such as mortality and morbidity); (3) perceived facilitators (predisposing factors); (4) perceived barriers (factors that hinder); and (5) cues to action (motivating or precipitating forces, such as contact with someone else who has tuberculosis).

Risk of bias in individual studies and the overall strength of the evidence

Studies were assessed for quality and risk of bias with the modified NICE Quality Assessment Tools for qualitative research.[30] Two authors (SGdV and CCH) assessed 10% of included studies independently; the remaining 90% of studies were assessed by one author (SGdV) and corroborated by a second author (ALC). Disagreements were resolved by discussion. We assigned each study a rating based on the quality assessment: high quality (++), medium quality (+), or low quality (–). We did not investigate publication bias. The evidence was graded and reported, as described previously (panel 2).[30]

PANEL 1: INCLUSION CRITERIA

Studies were included if they:

- had a focus on tuberculosis services of any kind (any study examining tuberculosis or a tuberculosis service delivered to a hard-to-reach population)
- had been done in any of the European Union (EU) or European Economic Area (EEA) countries, EU candidate countries (included Albania, Montenegro, Serbia, Macedonia, and Turkey), or other Organisation for Economic Co-operation and Development (OECD) countries (included Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, South Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the UK, and the USA)
- had been published in 2010, or later for OECD countries
- had been published in 1990, or later for EU, EEA, and EU candidate countries
- presented data on the views of hard-to-reach people regarding perceptions of or attitudes to tuberculosis services
- presented original qualitative data (no systematic reviews)
- did not exclusively focus on latent tuberculosis infection
- included data for any hard-to-reach population, including homeless people, people with alcohol or other drug addictions, sex workers, prisoners or people with a history of imprisonment, susceptible migrant populations (eg, asylum seekers and refugees), but also recent migrants and travelers (including the Roma population), children within susceptible and hard-to-reach populations, and people with HIV infection.

Respondents did not necessarily have to be diagnosed with tuberculosis, studies should not focus exclusively on latent tuberculosis infection, and there were no language restrictions.

PANEL 2: GRADING OF EVIDENCE

No evidence
No evidence or clear conclusions from any studies

Weak evidence
No clear or strong evidence or conclusions from high-quality studies, only tentative evidence or conclusions from moderate-quality studies, or clear evidence or conclusions from low-quality studies

Moderate evidence
Tentative evidence or conclusions from multiple high-quality studies, or clear evidence or conclusions from one high quality study or multiple medium-quality studies, with minimal inconsistencies across all studies

Strong evidence
Clear conclusions from multiple high-quality studies

RESULTS

The figure shows the study selection process. Database searches identified 5915 records. Citation searching of included studies and relevant (but excluded) reviews identified 15 records. Inter-reviewer agreement for the abstract screening was 98.1% before reconciliation; the inter-rater reliability (Cohen's κ) was 0.627. Of the total 5930 abstracts, 1810 duplicate records were removed (figure). In total, 12 studies were included in this review (figure).[19,36–46] The appendix and Table 1 detail the characteristics of included studies.

Of ten studies investigating the views of individuals belonging to hard-to-reach populations on tuberculosis and tuberculosis services, seven were of migrants;[19,37,39,42,43,45,46] one was of a mixed group of homeless people, migrants, and drug users;[36] one was only of people who were homeless;[40] and one was of a Roma population.[44] We identified two studies[38,41] focusing on views of health-care providers on barriers or facilitators to the uptake of tuberculosis services by hard-to-reach populations. Studies were done in the UK,[36,38,39,42] the USA,[13,37,46] Sweden,[41] Norway,[43] Serbia,[44] Canada,[45] and Japan.[40] Table 2 shows the results of the quality assessment. The appendix provides detailed evidence statements for all themes, combined with the findings of the previous NICE review.[30] Here, we present the findings of the update and extension of the NICE review.

Figure: Study selection process

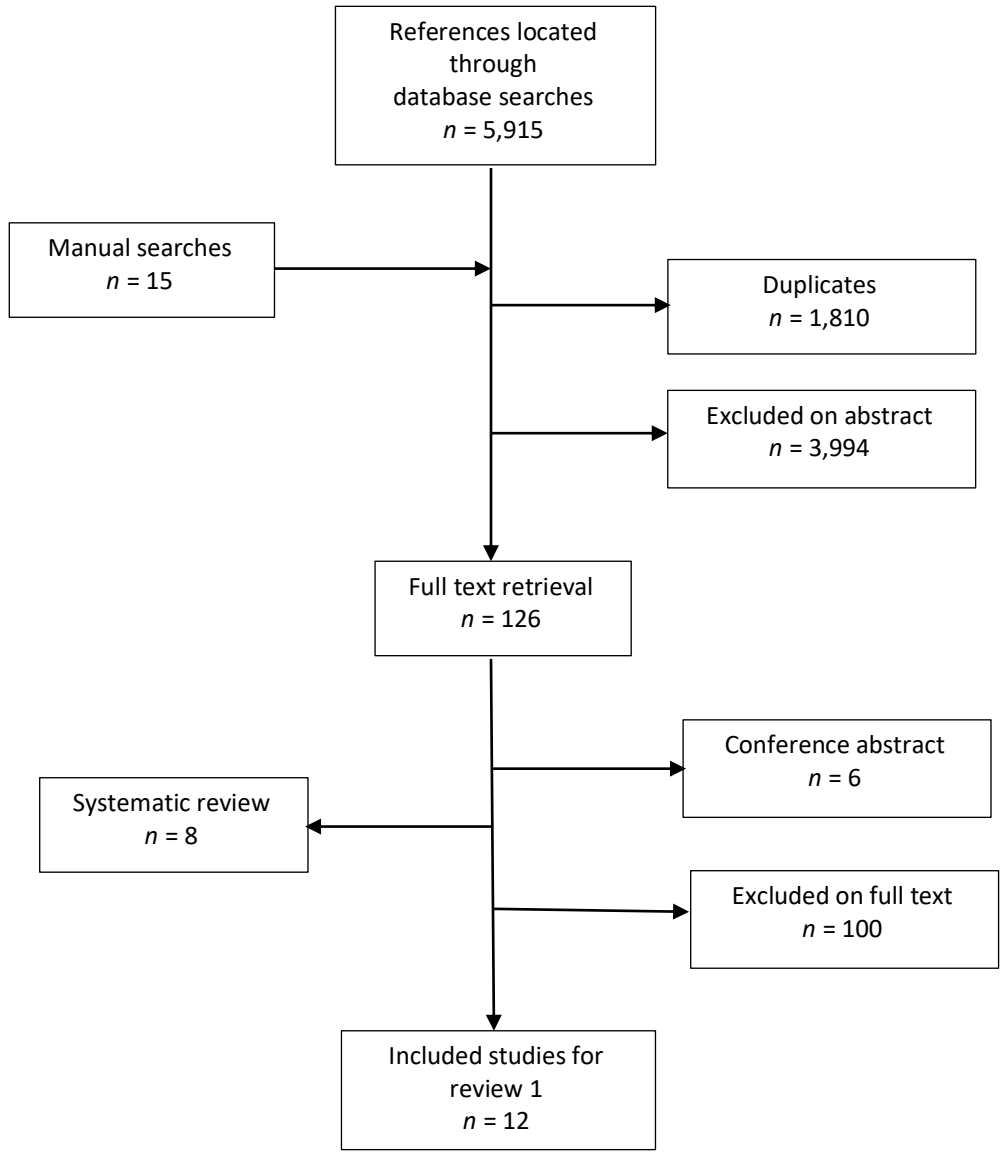

Table 1. Characteristics of included studies

First author (year)	Aims	Method	Number of participants	Location	Study respondents	Quality score
	Additional studies identified in this review					
Bender et al.[45] (2010)	To analyse how the experience of client displacement shapes the relational work of TB nurses.	Observations of the usual contacts between nurses and migrant clients (TB patients currently receiving DOT). Additionally, interviews with nurses and some of the observed clients were held.	33 (nine nurses, 24 tuberculosis patients)	Toronto, Canada	Migrants and service providers	-
Coreil et al.[46] (2010)	To identify the components of stigma perceived as important within non-affected community samples in the two study populations (Haitians in Haiti and Haitian migrants in California); and second, to understand the contextual influences on these stigma components across sites (including affected members as well). For this review, only the views from participants in Florida are considered.	Interviews and observations at clinics with community members of Haitian origin.	128 (community members, health care professionals, and patients, 47in the focus groups and 81 in interviews)	Broward County and in Palm Beach County, California, USA	Migrants and service providers	+
Vukovic and Nagorni-Obradovic[44] (2011)	Exploring the knowledge and beliefs about TB transmission, symptoms and treatment, opinions on appropriate preventive measures, and attitudes towards people with TB among the Roma population.	Focus group discussions with the Roma population in Belgrade, living in selected Roma communities in different conditions (Living in the worst conditions (slums)/ living in conditions similar to the general population in Belgrade / living in conditions between the previous two).	24	Belgrade, Serbia	Migrants	+
Gerrish et al.[42] (2012)	To ascertain the socio-cultural meaning and consequences of TB among people of Somali origin living in the UK.	Interviews with community leaders (CL) from Somali organizations and TB patients (in the Somali community); interviews and focus groups with members of the wider Somali community (CM).	104 (ten community leaders, 80 community members, and 14 patients)	Sheffield, UK	Migrants	++

Table 1. (continued)

Sagbakken et al.[43] (2012)	To explore experiences of being diagnosed with TB among migrants in Norway, with a view to identify factors associated with diagnostic delay.	Interviews with TB patients from Ethiopia and Somalia who had been diagnosed in a hospital and for whom TB treatment had been initiated.	42 (22 patients, and 20 health care professionals)	Oslo, Norway	Migrants and service providers	++
Wieland et al.[19] (2012)	To understand the perceptions and misperceptions about TB among students and staff at an adult education centre. To understand how relationships and social structures influence the perceptions of TB. To understand what the perceived barriers and benefits to health seeking behaviour for TB are.	Separate focus groups at the adult education centre with students (from Somalia, Sudan, Vietnam, Cambodia, Laos, China, Pakistan, Ukraine, Russia, Turkey, Mexico, Colombia and Puerto Rico) and their teachers (from Somalia, Sudan, Asia, US).	83 (54 students, and 29 teachers)	Rochester, USA	Migrants	++
Croft et al.[38] (2013)	To understand the motivation and personal impact of being a peer educator on people with experience of anti-tuberculosis treatment, homelessness and addiction.	Interviews with peer educators who had had treatment for active TB and have experience with homelessness and/or drug/alcohol dependency, and have been a peer educator within the last 3 years of the project (Find & Treat)	6	London, UK	Service care providers - Homeless and drug users	+
Gerrish et al.[39] (2013)	To explore experiences with the diagnosis and management of tuberculosis from the perspective of Somali patients and healthcare professionals involved in their care.	Interviews with Somali TB patients who had received treatment for TB in the UK and with healthcare practitioners with experience in caring for Somali TB patients (GPs, TB specialists, nurses).	32: 14 patients& 18 health care professionals	Sheffield, UK	Migrants and service providers	+
Kawatsu et al.[40] (2013)	To explore the changes experienced by homeless TB patients, and to discuss the possible role of PHC-based DOT treatment in effecting these changes.	Interviews with homeless patients who had received and completed DOT at Shinjuku PHC.	18	Shinjuku, Tokyo, Japan	Homeless	+
Wannheden et al.[41] (2013)	To understand the challenges faced by nurses and physicians in the treatment of patients co-infected with the HIV and TB, with special focus on opportunities for information and communication technology.	Interviews with physicians and nurses of each speciality (HIV & TB), working with HIV/TB co-infected patients.	9 (five nurses, and four physicians)	Stockholm, Sweden	Service providers of HIV and TB co-infected patients, including migrants	+

Table 1. (continued)

Craig et al.[36] (2014)	To analyse patients' knowledge of TB, their experiences of symptoms, and their health care seeking behaviours.	Interviews with TB patients with health and social risk factors likely to complicate adherence to treatment (such as homelessness and drug use) attending a major TB centre.	17	London, UK	Homeless, migrants, drug- and alcohol users, people living with HIV	++
Zuñiga et al.[37] (2014)	Experiences of TB treatment among Mexican Americans living in the Lower Rio Grande Valley.	Interviews with Mexican American adults who were currently receiving DOT treatment.	18	Lower Rio Grande Valley, Texas, USA	Migrants	+
	Studies identified in the previous NICE review[30]					
Curtis et al.[71] (1994)	To examine the responses of injecting drug users (IDUs) to current TB management strategies and to explore the implications of these responses for the implementation of Directly Observed Therapy (DOT).	Ethnographic interviews and observations in locations where drugs were sold and taken. Male and female IDUs were interviewed; Latino, black and white.	68	Brooklyn, New York, USA	Drug users	-
Kitazawa[70] (1995)	To gather the knowledge and views of homeless people living in group shelters concerning tuberculosis, tuberculosis medical care and health education.	Interviews with men and women in homeless shelters who were English and/or Spanish speaking.	20	San Francisco, USA	Homeless	+
Kelly-Rossini et al.[69]	To understand the experiences of respiratory isolation for HIV-infected patients with TB.	Interviews with males and females with a history of HIV infection or HIV risk behaviour, AFB positive sputum smears and confined to respiratory isolation; 30–51 years old.	18	New York, USA	People living with HIV	+
Jackson & Yuan[68] (1997)	To identify the non clinical barriers family physicians may face in managing TB among patients and suggestions for overcoming these barriers.	Focus groups with primary care physicians, infectious disease specialists and respiratory physicians who work with TB patients.	15	Toronto, Canada	Service providers	+

Table 1. (continued)

Ito[66] (1999)	To investigate elements of 'health culture' which affect adherence with preventive treatment for inactive TB among Vietnamese refugees.	Individual interviews and observations with Vietnamese refugees; included individuals who were compliant with treatment and those who were non compliant. Interviews conducted with clinic staff and various community members who were apparently not receiving TB services.	24 (only individual who received treatment); other groups not reported)	California, USA	Migrants	+
Yamada et al.67 (1999)	To understand what Filipino immigrants to the USA know about TB and examine their attitudes and practices concerning TB.	Focus groups with male and female Filipino immigrants in two locations.	36	Hawaii and California, USA	Migrants	++
Fujiwara65 (2000)	To explore the development of culturally appropriate marketing campaigns for TB awareness, testing and treatment for immigrants from China.	To explore the development of culturally appropriate marketing campaigns for TB awareness, testing and treatment for immigrants from China.	47	New York, USA	Chinese migrants	-
Houston et al.64 (2002)	To identify the cultural health beliefs regarding TB and barriers to completion of TB prevention programmes among the Vietnamese population.	Individual interviews and observations with Vietnamese refugees; included individuals who were compliant with treatment and those who were non compliant. Interviews conducted with clinic staff and various community members who were apparently not receiving TB services.	67 (53 in focus groups and 14 individual interviews)	California, USA	Migrants	+
Chemtob et al.[63] (2003)	To identify the barriers to diagnosis, prevention and treatment of TB among immigrants.	Interviews with immigrant Ethiopian families (ranging in size from 2 to 13 members); traditional healers and Israeli health and absorption professionals.	36 (12 families, three traditional healers, 21 health professionals)	Israel	Ethiopian migrants and service providers	-
Joseph et al.[61] (2004)	To identify the factors that influence healthcare workers' adherence to policies for routine tuberculin skin tests and treatment of latent TB infection.	Focus groups with healthcare workers from a range of occupations including clinical, janitorial, administrative, clerical and security staff; US and foreign- born.	106	USA	Service providers	+
Swigart & Kolb[62] (2004)	To examine the factors that homeless people report as influencing their decisions to accept or reject TB screening.	Interviews with homeless men and women who either resided in or were visiting shelters.	55	North-Western USA	Homeless	+

Table 1. (continued)

Gibson et al.[58] (2005)	To examine socio-cultural factors influencing behaviour related to TB prevention and treatment in high-risk cultural populations.	Interviews with immigrants from Hong Kong, China, Philippines, Vietnam, Punjab, Eastern Europe and Aboriginal populations; included those with active TB, those who had taken directly observed treatment (DOT), those who had been offered DOT and refused and those with past history of TB, or a relative with TB.	133	Canada	Migrants	++
Moro et al.[59] (2005)	To explore chest and infectious disease physicians' views of the barriers to effective tuberculosis control.	Focus groups with chest and infectious disease physicians offering TB care.	49 (34 health physician and 15 infectious disease physicians)	Emilia Romagna region, Italy	Service providers	++
Van der Oest et al.[60] (2005)	To explore the opinions of refugee and minority group representatives about the significance of TB for their community and perceptions of TB services.	Community representatives were interviewed from the largest community populations, including Maori and Pacific Island groups, as well as immigrants from China, The Philippines, Somalia, and Kampuchea (Cambodia).	unclear (several groups)	New Zealand	Migrants	-
Brewin et al.[55] (2006)	To understand how acceptable tuberculosis screening is to immigrant populations and to explore immigrants' understandings of TB in relation to screening.	Interviews with adult immigrants from a variety of ethnicities who had been offered TB screening.	53	East London, UK	Migrants	+
Johnson[56] (2006)	To explore how specific cultural health beliefs regarding TB affect the awareness and understanding of the disease among at-risk communities.	Focus groups and interviews with members of the following at-risk populations: Chinese, Nigerian, women refugees, Vietnamese, substance misusers, HIV-positive people, homeless people and prisoners.	67	South East London, UK	Migrants, people living with HIV, drug users, homeless, prisoners	-
Nnoaham et al.[57] (2006)	To describe the perceptions and experiences of African patients with TB, particularly relating to diagnosis, adherence and stigma.	Interviews with patients attending a TB clinic, either for preventive therapy or to receive a diagnosis; African-born; over 18 years.	16	London, UK	Migrants	++

Table 1. (continued)

Brent Refugee Forum[53] (2007)	To examine the level of knowledge, attitudes and perceptions of TB among populations at high risk of social exclusion and deprivation. To identify barriers that different populations face in accessing treatment, and understand how the cultural context of TB affects their lives.	Focus groups with participants from different ethnicities including refugees and asylum seekers, people who are HIV positive, homeless, and prisoners; male and female. Focus groups with healthcare professionals providing TB services to the same communities.	119 (104 migrants and 15 service providers and one patient with tuberculosis)	Brent, UK	Migrants, PLHIV, homeless, prisoners and healthcare professionals	++
Marais[54] (2007)	To identify the structural influences which operate across community and sector levels within the local context which may influence TB risk, healthcare access and outcome in migrant black African communities. To identify the resources to improve TB control which exist or could be strengthened within the sectors and within these migrant black African communities themselves.	Multi-method participatory research using questionnaires, in-depth interviews, community consultations and observations; migrant black Africans over 18 years old who had been in the UK for less than 10 years; key stakeholders including individuals and representatives of populations, organisations or institutions, which could significantly influence public health interventions for TB control.	329 (312 African migrants and 17 stakeholders)	London, UK	Migrants	++
Belling et al.[49] (2008)	To conduct an audit of TB services in relation to the range of services and expertise required to control and treat TB in London.	Interviews with TB service users and TB service lead professionals. Focus groups with TB nurses and external respiratory physicians/epidemiology professionals.	33	London, UK	Service providers	++
Craig et al.[50] (2008)	To explore how a social outreach model of care, including a TB link worker, can be best implemented for marginalised populations with TB.	To explore how a social outreach model of care, including a TB link worker, can be best implemented for marginalised populations with TB.	Tuberculosis link workers of eight tuberculosis care agencies	UK	Service providers	-
West et al.[52] (2008)	To explore the knowledge, attitudes and beliefs about TB among homeless shelter residents and persons attending a drug/alcohol rehabilitation centre.	Focus groups of homeless participants at homeless shelters and people with drug/alcohol abuse problems attending a rehabilitation facility.	11 focus groups with 52 participants	USA	Homeless and alcohol abusers	+
Whoolery[51] (2008)	To explore what it means for homeless people to have TB and how this impacts their opportunities to complete treatment	Semi-structured interviews with homeless persons, some of who were also drug users, commercial sex workers or HIV positive.	16	UK	Homeless	++

Table 1. (continued)

Gerrish et al.47 (2010)	To identify socio-cultural influences on the prevention, diagnosis, and treatment of tuberculosis within the Somali community and to gain insight into healthcare practitioners' perceptions of and experiences with tuberculosis among the Somali community. To identify ways in which culturally appropriate health promotion initiatives regarding tuberculosis can reach the Somali community. To identify ways of supporting healthcare practitioners to provide culturally appropriate care in regard to the screening, diagnosis and management of tuberculosis within the Somali community.	Interviews with Somali community leaders. Interviews and focus groups with members of the Somali community including those with personal experience of tuberculosis. Interviews with healthcare practitioners including GPs, consultants, tuberculosis nurses and Somali nurses with experience of working with the Somali community.	122 (56 in focus groups and 66 from individual interviews)	Sheffield, UK	Somalian Migrants	++
Sagbakken et al.[48] (2010)	To identify the factors associated with diagnostic delay for tuberculosis among immigrants in Norway	Interviews with male and female immigrants from Somalia and Ethiopia who had been diagnosed with tuberculosis.	22	Norway	Migrants	+

- = low quality. + = medium quality. ++ = high quality. DOT =. Directly observed therapy. GP = general practitioner. NICE = National Institute for Health and Care Excellence.

Seven studies analysed whether hard-to-reach groups viewed themselves as susceptible to tuberculosis and were therefore more inclined to undergo testing if they had symptoms of the disease. Five studies focused on migrant populations,[19,37,39,42,46] one on a Roma population,[44] and one on a mixed population of homeless people, drug users, and migrants.[36] Table 3 provides an overview of findings for views on susceptibility through reported concepts of causes and modes of transmission. The appendix provides an overview of illustrative quotations identified for each theme.

A common misconception among migrant students and teachers at a US adult education centre was that tuberculosis was not present in the USA.[19] Mexican- American patients with tuberculosis living on the border between the USA and Mexico discussed being susceptible to tuberculosis because of their proximity to Mexico.[37] In a Somali community in Sheffield, UK, community leaders generally showed accurate knowledge of tuberculosis, but there was great variation among community members. Here, views were relatively accurate, with some people describing tuberculosis as "an airborne disease whereby people became infected by 'breathing in the germ' and once infected, they could pass it on to others".[42] Conversely, in a mixed group of patients with tuberculosis who were homeless, drug users, or migrants in London, UK, knowledge of tuberculosis was generally poor and a wide variety of causes was mentioned.[36]

The way in which communities perceive the severity of tuberculosis, including symptoms, health consequences, and treatability, affects people's health-care-seeking behaviour. Three studies on the views of migrant populations,[19,37,42] one on a Roma population,[44] and one on various hard-to-reach populations in London[36] investigated the perceptions of tuberculosis severity.

Four studies reported on perceived tuberculosis severity in migrants and refugees in the USA,[19] Mexican-American migrants,[37] Somali migrants in the UK,[42] and a Roma population in Belgrade, Serbia.[44] One study exclusively reported on the views of patients with tuberculosis,[37] two reported on the views of patients without tuberculosis,[19,44] and one reported on both populations.[42] Two studies[37,42] reported good knowledge of tuberculosis symptoms, including a persistent (bloody) cough, weight loss, fever, and night sweats. Somali patients with tuberculosis had little knowledge of extrapulmonary tuberculosis, but most were aware of the long duration of treatment with antibiotics and the prospect for good recovery. However, because of the belief that tuberculosis is hereditary, some thought that tuberculosis was incurable. Furthermore, people had various beliefs about the length of time a patient remains infectious.[42]

Similarly, a Roma population in Belgrade, Serbia, had accurate knowledge of symptoms, whereas their views on tuberculosis severity and the effectiveness of treatment varied, ranging from tuberculosis being a very serious and lethal disease to it being a long-lasting, but curable disease.[44]

A mixed group of migrants in the USA reported fear of tuberculosis, which consisted mainly of fear of dying from an incurable disease.[19]

A mixed group of people who were mainly homeless, drug users, people living with HIV, and migrants, with suspected tuberculosis in London, UK, reported on common symptoms for tuberculosis; recognition of symptoms was not always accurate and miscellaneous explanations for common symptoms were reported.[36] Symptoms were often attributed to other undiagnosed illnesses, a poor diet, or drug or alcohol abuse. Eight studies elaborated on the barriers that affect the health-care-seeking behaviour and treatment adherence of patients with tuberculosis, which hinder effective implementation of tuberculosis prevention and control measures; seven studies reported on migrant populations,[19,37,39,42,43,45,46] and one study reported on mixed hard-to-reach groups in London, UK.[36]

Various migrant populations in the USA reported difficulties with transport to the testing centre, the opening hours of testing centres, or the duration and cost of testing as barriers to the testing and treatment of tuberculosis.[19] The challenges of tuberculosis symptoms combined with treatment side-effects were described by Mexican-American[37] and Somalian[19] migrants with tuberculosis in the USA; they had mental and physical conditions, which affected their treatment adherence. Two studies[37,39] commented on stress and depression due to delays in diagnosis and treatment challenges. Somalian patients in the UK[39] reported feeling stressed, anxious, and powerless, especially if the diagnosis took a long time and if they felt they were not being taken seriously. Moreover, these patients thought that the system had let them down and they did not trust their general practitioners (family doctors). Other patients felt relieved after tuberculosis was diagnosed.[39] Depression and

feelings of sadness were described by Mexican-American patients during tuberculosis treatment, often related to (self-chosen) social isolation at home and restricted daily activities to prevent transmission.[37]

Two studies[43,46] identified loss of privacy and breaches in confidentiality as important barriers to treatment adherence. The actions of tuberculosis health-care services and outreach workers were perceived as revealing a patient's tuberculosis status to others; this was mentioned by Haitians in the USA[46] and by Ethiopian and Somalian migrants in Norway.[43] Patients were concerned that health-care workers in directly observed therapy (DOT) aggravated the stigma of tuberculosis and were unaware of the consequences of exposing their tuberculosis status to others. Three studies[37,43,46] described negative attitudes or fear of DOT, which made people reluctant to undergo testing. Haitian Americans associated tuberculosis treatment with incarceration and feared loss of employment.46 Some Somalian and Ethiopian patients in Norway questioned the necessity of DOT, feeling humiliated or discriminated by the frequent home visits; they felt unable to voice criticisms because of their migrant status, a scarcity of alternative tuberculosis services, and the threatening attitudes of nurses in cases of non-cooperation. Some patients did not understand why nurses suspected them of not being compliant with treatment; they argued that DOT should only be used when people needed assistance to be able to manage their treatment.[43] Furthermore, DOT was perceived as imprisoning, forcing the patient into a subservient and confined position, hindering work responsibilities, and, consequently, complicating treatment adherence.[37,43] Somalian and Ethiopian migrants in Norway described the lack of continuity among health personnel as hindering the establishment of a secure and trustful patient–nurse relationship during treatment. Some patients reported that some health-care workers tried to restrict patient contact as much as possible. Patients often did not know which health-care worker was attending and at what time, potentially causing feelings of stress and humiliation.[43]
Economic hardship due to a tuberculosis diagnosis was mentioned by Somalian patients in the UK.[39,42] A Somalian homeless patient described how inadequate accommodation, a lack of social support, and a poor diet complicated management of the disease;[39] Mexican- American migrants reported economic hardship, losing their job, or being unable to work as complicating factors.[37] Mixed migrant populations in the USA reported that knowledge about free tuberculosis medication reduced financial constraints to access of tuberculosis care.[19] Tuberculosis-related stigma was a barrier to seeking treatment and adhering to treatment.[19,37,39,42,43,45,46] We identified five themes: face masks, stigma of association with HIV, self-stigma, consequences of stigma, and stigma due to poor knowledge. Mexican-American patients with tuberculosis associated wearing face masks with physical discomfort and stigma.[37] They were afraid the mask would reveal their tuberculosis status and, therefore, most patients stayed at home or avoided crowded places out of fear of disclosing their status and experiencing discrimination. Similarly, migrants in Canada referred to the mask as an "identifier of tuberculosis" and described the effect of face masks on losing friends, jobs, or being unable to find employment.[45]

One study[46] reported that many Haitian community members in Florida assumed that patients with tuberculosis were HIV positive, thus aggravating stigma. In this study, the tuberculosis and HIV clinics were located together in one building, contributing to this assumption.

Four studies[19,37,39,42] described tuberculosis selfstigmatisation. Mexican patients in the USA felt depressed and guilty about having tuberculosis; they were afraid of being a burden on family or friends. Negative feelings seemed to be intensified by nondisclosure and self-chosen social isolation. Five of 18 participants did not disclose their tuberculosis status because of shame, not wanting to be a burden, protecting family from tuberculosis-related stigma, or protecting themselves from stigmatisation by family, friends, or community members. Some patients only disclosed to their families and hid their tuberculosis status from friends, colleagues, and community members.[37] Some Somalian patients in the UK disclosed their tuberculosis status because they understood the importance of contact tracing, whereas others concealed their tuberculosis diagnosis to avoid distress and discrimination, and maintain isolation.[42] Similarly, mixed migrant populations in the USA[19] mentioned that patients would shy away from family members and other social contacts. Somalian migrants in the UK and Mexican-American migrants perceived selfstigmatisation as a barrier to seeking tuberculosis care and support during treatment.[37,39,42] Four studies (on migrant populations in the USA,[19] Somalian migrants in the UK,[39,42] and Haitians in the USA[46] found that tuberculosis-related stigma was most likely to be caused by poor knowledge of the community.

Table 2. Quality Assessment of the included studies

	Quality score	1. Is a qualitative approach appropriate?	2. Is the study clear in what it seeks to do?	3. How defensible/ rigorous is the research design/ methodology?	4. How well was the data collection carried out?	5. Is the role of the researcher clearly described?	6. Is the context clearly described?	7. Were the methods reliable?	8. Is the data analysis sufficiently rigorous?	9. Is the data 'rich'?	10. Is the analysis reliable?	11. Are the findings convincing?	12. Are the findings relevant to the aims of the study?	13. Conclusions	14. How clear and coherent is the reporting of ethics?
Studies identified in this review															
Bender et al.[45] (2010)	-	Y	Y	Y	NS	NS	N	Y	Y	Y	NS	Y	Y	P	N
Coreil et al.[46] (2010)	+	Y	Y	Y	Y	N	NS	Y	Y	Y	NS	Y	Y	Y	Y
Vukovic and Nagorni-Obradovic[44] (2011)	+	Y	Y	P	P	Y	Y	N	Y	Y	Y	Y	Y	P	Y
Gerrish et al.[42] (2012)	++	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sagbakken et al.[43] (2012)	++	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Wieland et al.[19] (2012)	++	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y
Croft et al.[38] (2013)	+	Y	Y	Y	Y	NS	N	Y	Y	Y	Y	Y	Y	Y	Y
Gerrish et al.[39] (2013)	+	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y
Kawatsu et al.[40] (2013)	+	Y	Y	Y	Y	NS	NS	Y	Y	Y	NS	Y	Y	Y	Y

- = significant risk of bias. + = study may not have addressed all potential sources of bias. ++ = well designed study, minimal risk of bias. N = no, Y = yes, NS = not sure (not reported or inadequately reported), M = mostly relevant. P = partially relevant. NICE = National Institute of Health and Care Excellence.

Table 2. (continued)

Craig et al. [36] (2014)	++	Y	Y	Y	Y	Y	Y	M	Y	Y	Y	Y	Y	Y	Y
Studies identified in NICE review															
Zuninga et al.[37] (2014)	+	Y	Y	Y	Y	N	Y	Y	Y	Y	NS	Y	Y	P	Y
Curtis et al.[71] (1994)	-	Y	M	N	NS	N	NS	Y	N	NS	N	Y	Y	Y	N
Kitazawa[70] (1995)	+	Y	Y	Y	Y	N	Y	NS	N	N	N	Y	Y	Y	Y
Kelly-Rossini et al.[69] (1996)	+	Y	Y	Y	NS	N	NS	Y	Y	Y	Y	Y	Y	Y	Y
Jackson & Yuan[68] (1997)	+	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	M	Y	Y
Ito[66] (1999)	+	Y	Y	Y	Y	NS	Y	NS	NS	Y	NS	Y	Y	Y	NS
Yamada et al.[67] (1999)	++	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	NS
Fujiwara[65] (2000)	-	Y	Y	Y	Y	N	N	N	N	N	N	N	P	N	N
Houston et al.[64] (2002)	+	Y	Y	Y	Y	Y	NS	Y	Y	N	NS	Y	M	Y	NS
Chemtob et al.[63] (2003)	-	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N
Joseph et al.[61] (2004)	+	Y	Y	Y	Y	NS	N	Y	Y	Y	Y	Y	Y	Y	Y
Swigart & Kolb[62] (2004)	+	Y	Y	Y	Y	N	Y	Y	Y	NS	Y	Y	Y	Y	N

Table 2. (continued)

Gibson et al.[58] (2005)	++	Y	Y	Y	Y	Y	Y	Y	Y	NS	Y	Y	Y	Y	Y
Moro et al.[59] (2005)	++	Y	Y	Y	Y	NS	Y	Y	Y	Y	Y	Y	Y	Y	NS
Van der Oest et al.[60] (2005)	-	Y	Y	Y	Y	N	N	NS	N	Y	N	N	Y	Y	N
Brewin et al.[55] (2006)	+	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Johnson[56] (2006)	-	Y	N	N	N	N	Y	Y	N	N	N	N	Y	Y	NS
Nnoaham et al.[57] (2006)	++	Y	Y	Y	Y	NS	NS	NS	Y	Y	NS	Y	Y	Y	Y
Brent Refugee Forum[53] (2007)	++	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Marais[54] (2007)	++	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Belling et al.[49] (2008)	++	Y	Y	Y	Y	NS	Y	Y	NS	M	Y	Y	Y	Y	Y
Craig et al.[50] (2008)	-	Y	Y	N	NS	N	N	Y	N	N	N	N	Y	Y	Y
West et al.[52] (2008)	+	Y	Y	Y	NS	N	Y	Y	Y	N	Y	Y	M	N	N
Whoolery[51] (2008)	++	Y	Y	Y	Y	Y	Y	Y	Y	Y	NS	NS	Y	Y	Y
Gerrish et al.[47] (2010)	++	Y	Y	Y	Y	Y	Y	Y	Y	Y	NS	Y	Y	Y	Y
Sagbakken et al.[48] (2010)	+	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y

Table 3. Factors perceived as affecting tuberculosis susceptibility, causes, and modes of transmission across different hard-to-reach populations

Cause	Total mentions	Mixed populations*	Homeless people	Migrants and travellers			
				Mixed	African (Somalian and Ethiopian)	Asian (Chinese, Vietnamese, and Filipino)	Roma	Mexican and Haitian
Smoking	Ten	One[64]	Two[48,68]	Three[19,58,61]	Two[70,71]	Two[53,62]	-	-
Food related	Nine	One[36]	Two[48,68]	Two[19,61]	Two[62,71]	One[62]	One[44]	-
Heredity	Nine	One[62]	One[62]	Two[58,60]	Four[39,42,63,70]	-	One[44]	-
Other illnesses	Eight	One[36] (HIV)	One[68] (AIDS)	-	Three (influenza and pneumonia,[42] asthma,[70] pneumonia[61])	One[62] (low immunity)	One[44] (influenza, pneumonia)	One[46] (HIV)
Environment (typically 'dirty' or weather)	Eight	One[64]	One[68]	One[58]	Two[62,70]	Three[52,53,62]	-	-
Poverty	Eight	One[36]	One[68]	One[61]	Three[42,70,71]	One[54]	One[44]	-
Lack of self-care, health imbalance	Seven	One[64]	One[68]	Two[58,61]	Two[70,71]	One[52]	-	-
Sharing (eg. cigarettes, cutlery)	Six	One[62]	Two[48,68]	One[61]	Two[42,63]	-	-	-
Sexual contact or saliva	Four	One[62]	-	Two[19,61]	-	-	One[44]	-
Stress	Four	-	-	-	One[42,70]	One[54]	One[44]	-
God	Three	One[36]	-	-	Two[19,42]	-	-	-
Lifestyle factors	Three	One[36]	-	One[19]	One[42]	-	-	-
Blood type	Two	-	-	One[19]	-	-	One[44]	-
Touch	Two	-	-	One[19]	-	-	One[44]	-
Geographical location	Two	-	-	One[19] (not in the USA)	-	-	-	One[37] (proximity to Mexico)

Table 3. continued

Airborne	One	-	-	-	One[42]	-	-
Vectors (rats)	One	-	-	-	-	-	One[44]

* Mixed groups differed by study, but could include any of people who use drugs, migrants, prisoners, people with HIV, and homeless people in the same study. For this updated review and the previous National Institute of Health and Care Excellence review.

Haitians in the USA reported being perceived as a disadvantaged and socially marginalised group that brought tuberculosis and other diseases to the USA.[46] Many Mexican-American patients felt that they were stigmatised by family and friends who stayed away, did not want to share drinks or food, or slept separately. Consequently, most patients felt depressed, but accepted their situation, in the understanding that people wanted to protect themselves from tuberculosis.[37] Consequences of stigma in the Haitian community in Florida, USA, were discrimination, avoidance of tuberculosis patients by others, and negative effects on relationships with family members.[46] Many Somalian patients in Sheffield, UK, were supported by friends and family, but faced sociocultural consequences in their wider social network:[39] in Somalia, tuberculosis is considered shameful for the whole family[42] and, in some cases, the whole family is socially isolated and discriminated against. Some patients said that community members still did not know that tuberculosis is curable. Moreover, the idea that tuberculosis is hereditary implies that the entire family will face stigma, which could affect employment and marriage prospects.[42]

Perceived barriers to testing and treatment of tuberculosis were reported for other hard-to-reach populations. For drug-using patients with tuberculosis in the UK, the fear of opiate withdrawal symptoms resulted in most people seeking health care only when they had reached a crisis point.[36] Fear of hospital admission was also a barrier to seeking health care among drug users in the UK, especially if they were unaware of the availability of methadone to prevent withdrawal symptoms.[36]

Seven studies reported on the facilitators that affect health-care-seeking behaviour and treatment adherence of patients with tuberculosis; five studies reported on migrant populations,[37–39,43,45] one study reported on people who were homeless in Japan,[40] and one study reported on mixed hard-to-reach groups in London.[36] The importance of the nurse's role in tuberculosis treatment was emphasised by mixed migrant and Somalian populations.[39,45] For migrant patients with tuberculosis in Canada, nurses had an important role in supporting treatment adherence.[37,39] Somalian patients with tuberculosis in the UK appreciated support from Somalian health-care workers and tuberculosis specialist nurses.[39] These Somalian patients were mostly supported by their family and friends.[39] Mexican-American patients with tuberculosis who disclosed their diagnosis to their families received support and were accepted; however, those who did not disclose this information were unable to access this support.[37]

A strong relationship of trust between care workers and patients, with care that goes beyond a single focus on drugs, was considered important by homeless patients in Tokyo, Japan. At the end of each successfully completed treatment course, the nurses organised a small ceremony, which was deemed important by patients.[40] These types of support, beyond normal tuberculosis care, generally made the patients feel more cared for and helped them to adhere to treatment.

Two studies[37,43] noted hospital admission as a facilitator for health-care-seeking behaviour or adherence in migrants. Some female Somalian and Ethiopian patients with tuberculosis in Norway described DOT as an expression of genuine care, which reduced their isolation.[43] In one study,[37] most Mexican-American patients with tuberculosis were unable to work and restricted other activities to prevent the transmission of tuberculosis, making the hospital or nursing home visit "the outing for the day". Three studies[36,38,40] noted hospital admission as a facilitator for health-care-seeking behaviour or adherence in other hard-to-reach populations. A patient who was homeless and a drug user in the UK viewed hospital admission as "a welcome break from the street".[36] Some drug users turned to creative and strategic approaches to achieve hospital admission, thus avoiding opiate withdrawal symptoms.[36] Kawatsu and colleagues[40] identified five subcategories of characteristics of patients who were homeless in Tokyo that improved after DOT: mental health, health behaviour, living environment, personal relationships, and attitudes towards society. A peer educator in London with a history of tuberculosis noted the positive effects of DOT on treatment adherence.[38]

Three studies[36,39,44] mentioned cues to action for accessing tuberculosis care. Roma people in Belgrade, Serbia, indicated that Roma people often do not visit a doctor until the symptoms of the disease are so severe that they are unable to work.[44] Conversely, Somalian patients with tuberculosis in the UK were reported to have presented at the general practice shortly after initially feeling unwell.[39] Several participants in a mixed group (including homeless people and migrants) in London, UK, delayed access to medical care because they had been trying to self-manage and had attributed symptoms to other factors, or had sought help only after

reaching a crisis point.[36]

No studies directly compared the views of hard-to-reach populations. Five studies presented the views of tuberculosis health-care or service providers, including those involved in the care of migrants in Canada,[45] Somalian migrants in the UK,[39] Somalian and Ethiopian migrants in Norway,[43] patients with HIV in Sweden,[41] and homeless people and drug users in London, UK.[38]

As barriers to diagnosis and treatment adherence among migrant populations, service providers mentioned fear of stigma,[39,45] use of khat (resulting in the late presentation of Somalian migrants to health-care services
due to its escapist effects),[39] atypical presentation of the disease as a result of different cultural perspectives, language barriers (and the lack of professional translators), a paucity of tuberculosis cases seen each year,[39] the negative psychological effects of wearing masks and experiencing isolation,45 and an aversion to DOT.[43] Norwegian service providers acknowledged the existence of institutional barriers to treatment adherence.[43] Although DOT was generally regarded as effective, most service providers were aware of the implications of DOT on patients' lives, given their vulnerable socioeconomic position in society.[43] Service providers of Somalian patients with tuberculosis in the UK[39] and Norway[43] noted that most patients accepted and complied with treatment; non-adherence was sometimes due to the chaotic situation a patient was in, such as applying for asylum.

In Sweden, physicians and nurses specialised in HIV and tuberculosis were interviewed about the challenges in their work regarding tuberculosis and HIV coinfection,[41] and reported a number of barriers to access to tuberculosis care and treatment adherence. These barriers included reduced continuity among physicians, staff shortages, difficulties in monitoring and managing treatment, insufficient networking between the HIV and tuberculosis specialties, a need for more collaboration, uncertainty about the division of tasks between HIV and tuberculosis clinics, and insufficient communication between team members. Service providers also identified facilitators supporting treatment adherence, including the use of persuasion based on subtle threats,[43] assisting patients with needs beyond the administration of tablets,[43,45] support by tuberculosis specialist nurses and Somalian service providers,[39] acknowledgment of the difficulties of being an immigrant,[45] and support from close family.[39]

Peer educators in London, UK, who had received treatment for active tuberculosis and had been homeless or dependent on drugs or alcohol mentioned that their support could be motivational and have a personal effect on other patients with tuberculosis in similar situations.[38]

DISCUSSION

Our review provides evidence-based qualitative information about several important barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by people from hard-to-reach populations in EU, EEA, EU candidate, and OECD countries of low and medium tuberculosis incidence. We identified 12 studies, in addition to 25 studies[47–71] included in the previous NICE review.[30] In this review,[30] 12 studies reported on migrants,[51–55,58,60,61,63,65,70,71] four on homeless people,[48,57,68,69] two on a mixture of hard-to-reach populations (migrants, homeless people, and prisoners),[62,64] one on drug users,[47] one on people with HIV,[49] and five on the views of health-care professionals.[50,56,59,66,67] Combining the findings of the current review with those of the previous review[30] provides a body of evidence that shows important gaps in the provision of tuberculosis care in countries of low and medium tuberculosis incidence.

Low perceived susceptibility can be a barrier because individuals who do not consider themselves susceptible to tuberculosis might not access health care when they develop symptoms. We found strong evidence that many misconceptions exist regarding susceptibility to tuberculosis among all investigated hard-to-reach populations in our review and the previous review.[19,36,37,39,42,44,46,48,52,53,58,60–64,68,70,71] For tuberculosis severity, migrants, prisoners, drug users, and homeless populations were generally aware of untreated tuberculosis being potentially fatal.[19,62,65,68,70] Previous studies have shown the importance of awareness about the variety of perceptions on illness and health care,[72,73] and many have emphasised the importance of culturally sensitive

programmes.[74,75] Thus, in specific settings, introduction of awareness-raising programmes that acknowledge and appropriately address the variety of local perceptions is relevant, with the aim of enhancing early case-finding and reducing delay in health-care seeking.

We identified numerous barriers to treatment seeking and adherence for migrant populations.[19,37,39,42,46,48,51–53,57,58,60,62–65,70,71] We found strong evidence that tuberculosis-related stigmatisation was perceived as a major barrier in almost all migrant populations and some homeless people.[37,39,43,45,46,52,58,60,63,64,69,70] Stigma can be described as a discrediting attribute negatively affecting social status and position, and often leading to rejection or exclusion.[76] Selfstigmatisation can be defined as "a reduction of an individual's self-esteem or self-worth caused by the individual self-labelling herself or himself as someone who is socially unacceptable",[77] and can lead to denial of diagnosis or hiding of tuberculosis status. Stigma and its social consequences is one of the major factors hindering tuberculosis diagnosis and treatment adherence.[22,78,79] Various interventions exist to prevent stigma and its effects, including family and community sensitisations, treatment-supporter programmes, and counselling. However, stigma is often embedded in a cultural context with deep-seated beliefs,[80] and should, therefore, not be solely ascribed to lack of knowledge because knowledgeable people might also stigmatise. Thus, it is necessary to organise interactive community sensitization programmes that specifically target stigmatising attitudes and actions. Notwithstanding the amount of literature on this topic,[81] tuberculosis-related stigma remains prevalent and, therefore, a focus for international tuberculosis control efforts.[79,82]

Institutional barriers, such as poor health infrastructure, unavailable diagnostic facilities, incorrect diagnosis, minimal training of health-care providers, and poor follow-up routines,[22] were reported to delay tuberculosis diagnosis.[19,36,43,62,63,65,70,71] Additionally, structural barriers were mentioned across studies.[19,37,39,42,43,46,47,49,53,60,65,68,70] Hard-to-reach groups in countries of low and medium tuberculosis incidence often seek care or receive treatment under challenging circumstances, such as an uncertain migrant status, undocumented immigration status, homelessness, addiction to alcohol or drugs, or vulnerable economic and social positions.[78,83] Crucially, countries should reflect on their immigration policies and how they might hamper tuberculosis control.83 Evidence for the effect of incentives is conflicting.[84–86]

We found no strong evidence for perceived facilitators of tuberculosis diagnosis or treatment adherence across hard-to-reach populations.[36,37,40,43,45,46,49,51,63,65,69,70] Possible approaches to improve access to health care in general are support and social networks, multidisciplinary teams, free care and transport, use of outreach services, and trained care providers who are sensitive to gender and culture. A patient-centred approach plays a key role in improving treatment adherence.[78] For many migrants, interpreters or bilingual staff are needed.[87] In drug use and homelessness services, strong collaborations that integrate existing social services with tuberculosis care could be useful.[88] Furthermore, structural barriers should be addressed.

No strong evidence for cues to action that motivate or precipitate health-care seeking was identified. Delay in health-care seeking is often cited as a more complicated obstacle than treatment adherence among hard-to-reach populations, because people who delay seeking care are not yet in the health-care system and, therefore, are difficult to reach. Discontinuity in primary care might also cause diagnostic delays.[71,89–91] Such delays could be reduced by awareness training of health professionals about atypical tuberculosis symptoms, patients' history, and patients' interpretation of tuberculosis symptoms.[71] Moreover, there is a need to improve the accessibility of tuberculosis services to hard-to-reach populations.[91]

The main challenges identified by service providers giving care to migrant patients with tuberculosis were cultural and language barriers,[39,41,43,45,59,65,70] and, with regard to tuberculosis care in general, a scarcity of specialist services and coordination of care,[39,41,43,50,59,66,70] and complex social and clinical interactions.[64,66,67] In settings with a low tuberculosis incidence, poor tuberculosis awareness and expertise among primary care providers is a problem, causing considerable treatment delays and distrust in the health system.[16] Continuous training of health-care providers on tuberculosis and its diagnosis is needed; computer-based decision support has been suggested to improve clinical practice.[41,92] Language and cultural barriers are considerable obstacles;[87,93–98] care providers should have unlimited access to high-quality translation services, which are currently not readily available in many of the studied countries.[87] Cross-cultural training of health-care providers and the availability of bilingual, multidisciplinary teams have been associated with improved health outcomes.[96]

Our systematic review highlights the small number of studies that have been done of hard-to-reach populations in EU candidate, EEA, and OECD countries specifically, and in countries of medium and low tuberculosis incidence in general. A clear knowledge gap exists for drug and alcohol users, homeless people, prisoners, and sex workers regarding the barriers and facilitators to tuberculosis services. Many studies focused on Somalian migrants; as such, most findings are specific to this migrant population and might not be transferable to other hard-to-reach migrant populations. Children are not mentioned in the studies included in both our and the previous systematic review, and yet WHO estimated 10% of the tuberculosis notifications worldwide to be in children.[2] Multidrug resistance and HIV co-infection complicate tuberculosis care; HIV infection exacerbates mortality and facilitates the development of drug resistance.[99] Multidrug-resistant tuberculosis was not cited in any of the identified studies, despite it being a growing problem in Europe.[100,101] The lengthy duration of treatment with toxic drugs with potentially serious side-effects complicates adherence to treatment.[102] Only two studies about tuberculosis and HIV co-infection were identified;[36,41] thus, more qualitative, large-scale, multi-country studies are needed to obtain evidence for operational factors that affect access and delivery of effective tuberculosis services, especially for multidrug-resistant tuberculosis and patients co-infected with tuberculosis and HIV.

Our study had several limitations. One challenge was defining what groups are hard to reach;[103] this definition might vary between settings and, additionally, not every individual within a so-called hard-to-reach group is necessarily equally hard to reach. To be inclusive, we decided to analyse all people with HIV and migrants, because members of those groups are often hard to reach and face higher tuberculosis rates than other groups. Furthermore, we used wide inclusion criteria, which is common practice in qualitative literature synthesis,[104] but can affect reproducibility. Thematic analysis is, in view of its subjective nature, prone to bias; many views expressed in qualitative literature can be interpreted in different ways. We aimed to minimise this bias by following PRISMA guidelines, resulting in a critically appraised and structured analysis of the qualitative literature. The quality of the studies was generally moderate to high (for grading of qualitative research); there were shortcomings in the clarity of the role of the researcher, the description of the context, the reliability of the data collection methods, and the reporting of the method of data analysis. Our evidence is restricted because we identified relatively few studies, especially of non-migrant groups. Additionally, most studies focused on Somalian migrant populations, hindering the formulation of generalized health-care recommendations for other hard-to-reach populations.

Although countries of medium and low tuberculosis incidence might give lower priority to tuberculosis control and research activities than would high-incidence countries, tuberculosis has re-emerged as a significant problem.[16,105] To ensure equitable access to tuberculosis care, increased investments are needed so that an evidence base for tuberculosis knowledge, stigma, DOT, and economic constraints is available to carefully tailor tuberculosis programmes to specific risk groups.[106] Such investment is of particular importance for progress towards tuberculosis elimination globally. The arrival of millions of refugees into Europe from high tuberculosis-endemic regions of Asia, the Middle East, and Africa could increase the numbers of hard-to-reach populations with tuberculosis. The identified gaps in knowledge concerning drug and alcohol abusers, homeless people, prisoners, sex workers, and the new refugees provide an opportunity to do future studies. A focus on patient autonomy, shared decision making, and support systems, particularly for patients from hard-to-reach groups, might improve the uptake of diagnosis and adherence to treatment. The effects of poverty and gender on patients and their treatment adherence require further study.[78] Future research should cover the wide variety of hard-to-reach populations in EU, EEA, and OECD countries to make realistic recommendations to render tuberculosis control programmes maximally effective. Unfortunately, many countries, especially those where tuberculosis is concentrated in hard-to-reach populations, have limited resources at the national level and are not able to follow up such recommendations and take up the coordination.[28,82]

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chapter 3

EFFECTIVENESS OF INTERVENTIONS FOR DIAGNOSIS AND TREATMENT OF TUBERCULOSIS IN HARD-TO-REACH POPULATIONS IN COUNTRIES OF LOW AND MEDIUM TUBERULOSIS INCIDENCE: A SYSTEMATIC REVIEW

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ABSTRACT

Tuberculosis is over-represented in hard-to-reach (underserved) populations in high-income countries of low tuberculosis incidence. The mainstay of tuberculosis care is early detection of active tuberculosis (case finding), contact tracing, and treatment completion. We did a systematic review with a scoping component of relevant studies published between 1990 and 2015 to update and extend previous National Institute for Health and Care Excellence (NICE) reviews on the effectiveness of interventions for identifying and managing tuberculosis in hard-to-reach populations. The analyses showed that tuberculosis screening by (mobile) chest radiography improved screening coverage and tuberculosis identification, reduced diagnostic delay, and was cost-effective among several hard-to-reach populations. Sputum culture for pre-migration screening and active referral to a tuberculosis clinic improved identification. Furthermore, monetary incentives improved tuberculosis identification and management among drug users and homeless people. Enhanced case management, good cooperation between services, and directly observed therapy improved treatment outcome and compliance. Strong conclusions cannot be drawn because of the heterogeneity of evidence with regard to study population, methodology, and quality.

INTRODUCTION

Early detection and diagnosis of tuberculosis, followed by effective treatment, is the cornerstone of global tuberculosis control efforts.[1,2] An estimated 3 million cases of tuberculosis remain undetected each year.[3] Early detection and effective management of tuberculosis can prevent severe disease[4,5] and reduce mortality and transmission.[6–8] Health services rely on people with tuberculosis to recognise their symptoms and seek treatment. To detect cases early, individuals with symptoms need to engage with health care in a timely fashion or need to be actively identified. Furthermore, health-care facilities should be accessible, health-care workers should be able to identify people with signs and symptoms of tuberculosis and request appropriate diagnostic tests, diagnostic tests should be available and done with quality-assured methods, and the results of diagnostic tests should be reported to the health-care worker to be able to start tuberculosis treatment immediately.[9] This sequence of events needs to work optimally to minimise delays between the development of the signs and symptoms of tuberculosis and the start of treatment. Tuberculosis treatment consists of at least a 6-month regimen of anti-tuberculosis drugs.[10] Adherence to this lengthy treatment regimen is challenging for patients with tuberculosis; up to 20% are lost to follow-up.[3,11] In countries of low tuberculosis incidence (fewer than ten tuberculosis cases per 100 000 population),[12] tuberculosis is concentrated in susceptible and hard-to-reach (underserved) populations.[13,14] These hard-to-reach populations, such as people who are migrants, refugees, homeless, prisoners, drug users, or sex workers, and people with HIV, are at increased risk of tuberculosis because of an increased risk of exposure or an impaired host defence.[15] Addressing tuberculosis in these hard-to-reach populations is essential to eliminating the disease.[16] Such a focus poses formidable challenges in regions with a low prevalence of tuberculosis. First, health-care workers practising in these areas rarely encounter patients with tuberculosis and, therefore, might not suspect tuberculosis initially, delaying diagnosis.[17] Second, individuals from hard-to-reach populations commonly attribute symptoms of tuberculosis to other causes.[18,19] Additionally, stigmatisation, fear of death from tuberculosis, language barriers, lack of knowledge of tuberculosis services, the lengthy treatment duration, and side-effects are major barriers to seeking health care and treatment compliance.[20] Consequently, individuals in hard-to-reach populations are often diagnosed late and often do not complete treatment.[21,22] We did a systematic review of interventions with a scoping component to ascertain which interventions are effective and cost-effective for identifying and managing tuberculosis and raising awareness of tuberculosis among hard-to-reach populations, what factors affect the effectiveness of those interventions, how transferable the findings for effectiveness are across hard-to-reach populations or settings, and what adverse or unintended effects exist. The findings of this review served as the evidence base for the development of guidance for controlling tuberculosis in hard-to-reach and susceptible populations by the European Centre for Disease Prevention and Control (ECDC).[23]

METHODS

Selection of studies and data management

In preparation for this systematic review, we identified two reviews[24,25] from the Matrix Knowledge Group, commissioned by the National Institute for Health and Care Excellence (NICE), of interventions for tuberculosis in hard-to-reach populations. We decided to update and extend these NICE reviews by applying the same methodology, but adjusting the focus—ie, excluding latent tuberculosis and expanding geographical coverage. We followed the standards described by the Cochrane Collaboration[26] and NICE.[27] Results are reported according to the PRISMA guidelines.[28] The review protocols are registered in PROSPERO, numbers CRD42015017660 and CRD42015019449.

In addition to the hard-to-reach populations covered by the NICE reviews (migrants, including refugees, asylum seekers, and the Roma population; homeless people, including people who were sleeping rough and using shelters; drug users; prisoners; and sex workers)[24,25] we included people with HIV and children in susceptible and hard-to-reach populations. The previous NICE reviews[24,25] only included studies done in Organisation for Economic Cooperation and Development (OECD) countries (**panel**); we updated this search and expanded the geographical coverage to include all European Union (EU), European Economic Area (EEA), and EU candidate countries.

We included all interventions aiming to improve tuberculosis identification and management in the assessed hard-to-reach populations. Predefined interventions included in the protocol were tuberculosis diagnostics, such as chest radiography; tuberculosis identification tools, such as symptom-based questionnaires and mobile radiography units; incentives and social support; treatment for comorbidities; and directly observed therapy (DOT) to improve tuberculosis management. Use of the tuberculin skin test and interferon-γ release assay (IGRA) were only included if used as an initial step in the diagnostic pathway to identify active tuberculosis cases. Pre-migration and post-migration screening, and sputum smear and culture as part of pre-migration screening, were identified during the review process and were added to the non-exclusive intervention list (**online appendix**).

Search strategy and selection criteria

By use of the same search strategies as in Rizzo and colleagues' 2011 National Institute for Health and Care Excellence (NICE) reviews, we searched MEDLINE, MEDLINE In-Process, and Embase covering the period from Jan 1, 1990, to Sept 30, 2010. Searching over the period of the NICE reviews was not repeated; rather, we updated the search to cover the period from Jan 1, 2010, to April 10, 2015. The search for the expanded geographical scope and hard-to-reach populations (see population section of appendix) covered the period from Jan 1, 1990, to April 10, 2015. We reviewed the reference lists of systematic reviews covering a similar topic for relevant publications. We excluded studies that solely focused on the detection and management of latent tuberculosis infection. No language restrictions were applied.

We included studies if they reported on the effectiveness or cost-effectiveness of interventions in hard-to-reach populations. Effectiveness was defined as an improvement in any measure of screening uptake or treatment outcome, such as an increase in the number (or proportion) of people screened, an increase in the treatment compliance rate, a decrease in tuberculosis-related mortality, or a decrease in tuberculosis incidence. We redefined the comparator during the review process and compared every intervention group with a relevant comparison group, including, for example, no intervention or usual care, another intervention, or a historical comparison. For the cost-effectiveness of interventions, we followed the conclusion of the individual study. We did not exclude studies on the basis of outcomes. Therefore, studies providing a quantitative outcome or a qualitative description of the outcome were included. The **appendix** (online) provides details of the populations, interventions, comparators, outcomes, and designs of the studies and the complete search strategy and results. Information about service models and organizational structures (eg, different types of health-care workers and settings) supporting tuberculosis identification and management was not the focus of this systematic review and is reported in another systematic review (Heuvelings CC, unpublished).

Data extraction, data items, and synthesis

All identified citations were uploaded into an EndNote database and duplicates were removed (EndNote version X7.1). We used the first 25 citations for pilot testing and to refine the inclusion criteria. Three authors (CCH, SGdV, and BJV) screened titles and abstracts independently. One author (CCH) screened 100% of the citations; the other two authors (SGdV and BJV) screened 50% each. Disagreement was resolved by discussion; the full text of articles was assessed in cases of disagreement. The full texts of the included citations were retrieved; irretrievable articles were excluded—ie, those not available online, from the university library, or through contacting authors. Two authors (CCH and SGdV) assessed the full-text records for inclusion using a full-text assessment inclusion checklist. Disagreement was resolved by discussion. We extracted data using the forms used in the previous NICE reviews.[24,25] Information about the characteristics of participants, setting, type of intervention, type of outcome measure, method of analysis, and results was extracted from each included study. Data were extracted independently by two authors (CCH and SGdV) for a random 10% of studies selected by simple random sampling.

Panel: Criteria for study inclusion and exclusion

Studies were included if they:

- discussed an intervention relating to identification and management of tuberculosis cases
- had been done in any European Union (EU), European Economic Area (EEA), EU candidate (included Albania, Montenegro, Serbia, Macedonia, and Turkey), or Organisation for Economic Co-operation and Development (OECD) countries (included Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, South Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the UK, and the USA)
- had been published in 2010 or later for OECD countries
- had been published in 1990 or later for EU, EEA, and EU candidate countries that were not one of the OECD countries
- included data for any hard-to-reach population, including homeless people (including people who were sleeping rough or using shelters), people who misused drugs or alcohol, sex workers, prisoners or people with a history of imprisonment, migrants (including susceptible migrant populations, such as asylum seekers, refugees, and the Roma population), children in susceptible and hard-to-reach populations, and people with HIV
- presented qualitative or quantitative empirical data
- were an effectiveness or a cost-effectiveness study, or any other type of quantitative primary research discussing effectiveness or cost-effectiveness

Studies were excluded if they:

- focused on latent tuberculosis
- solely discussed service models and organisational structures, including different types of health-care workers and settings
- were a systematic review (only used for reference searching)

For the remaining studies, one author (CCH) extracted data, which were checked by a second author (SGdV and PFG checked 50% each). Any disagreement was resolved by discussion. When necessary, authors were contacted by email to verify data or obtain additional data. To maximise the comparability of the results with those of the NICE reviews,[24,25] data synthesis was structured similarly by hard-to-reach population. Data were synthesised with a narrative synthesis approach, and we assessed whether meta-analysis was possible by considering the heterogeneity of the studies (study design, participants, setting, intervention, and outcome).

Risk of bias in individual studies and the overall strength of the evidence

Studies were assessed for quality and risk of bias with the modified NICE Quality Assessment Tool (based on the Graphical Appraisal Tool for Epidemiological studies),[24,25] which assesses selection of the study sample, minimisation of selection bias and contamination, controlling of confounding variables, outcome measurements, analytical methods, and risk of bias. Two authors (CCH and SGdV) independently assessed 10% of the studies. The remaining 90% were assessed by one author (CCH) and checked by a second author (SGdV and PFG checked 50% each). Any disagreement was resolved by discussion. Each study was given a rating based on the quality assessment: high quality (++), medium quality (+), or low quality (–). The strength of conclusions was assessed and reported as described previously (**online appendix**).[24,25]

RESULTS

The figure shows the study selection process. 13 783 unique citations were screened on the basis of title and abstract. Agreement after screening for the title and abstract was 99.5%, with an inter-rater reliability (Cohen's κ) of 0.985. 146 citations were selected for full-text assessment; seven were irretrievable. In total, 16 studies were included in this review, with a further three identified through citation searching (**figure**).[29–47] **Table 1** shows the characteristics of all 19 included studies; the appendix provides evidence tables. 12 studies focused on migrants,[29–36,38,41,43,45] of which one focused on children.[41] Three studies focused on mixed hard-to-reach populations;[39,42,46] two on drug users;[40,44] one on people with HIV,[47] and one on homeless people.[37] None of the included studies focused on sex workers. Eight studies were done in the EU, including two in the UK[39,42] and one each in Estonia,[44] France,[37] Germany,[46] Italy,[47] Norway,[32] and Portugal.[40]

The remaining 11 studies were done outside the EU, including eight in the USA,[29,31,33–36,41,43] two in Israel,[30,38] and one in Switzerland.[45] Interventions to improve identification of tuberculosis included active case finding with (mobile) chest radiography,[30,37–39,42] a symptom-based questionnaire,[45] or the tuberculin skin test or IGRA;[31,36,41] addition of sputum smear[34,39] or culture[29,33,43] to a screening algorithm; and active referral to a tuberculosis clinic.[32,35,40,44] Interventions to manage tuberculosis were enhanced case management (ie, a package of supportive care tailored to patients' needs[40,42,46]) and concomitant tuberculosis and HIV treatment.[47] The appendix shows the results of the quality assessment. Heterogeneity between the included studies in the type of hard-to-reach population, interventions, reported outcomes, and study design made it inappropriate to do a meta-analysis. Table 2 summarises the interventions and outcomes for each hard-to-reach population; the appendix (online) shows detailed evidence statements, combined with the findings of the NICE reviews.[24,25] We divided the 12 studies focusing on tuberculosis identification in migrants into premigration and post-migration screening studies. Mor and colleagues[38] concluded that pre-migration screening by chest radiography of migrants from Ethiopia to Israel was both effective and cost-effective. The sensitivity of chest radiography as a screening tool for the detection of active pulmonary tuberculosis was 80.1% (95% CI 68.1–89.9), and for the detection of sputum-confirmed tuberculosis was 86.1% (72.1–94.7); the specificity was 99.2% (99.1–99.4) and 99.1% (99.0–99.3), respectively. The cost of diagnosis of one patient with pulmonary tuberculosis was US$5820, which the authors deemed cost-effective, because treatment of one migrant with tuberculosis in Israel in 2012 was $7619.38 No further investigations for tuberculosis were done for migrants with negative chest radiography results.[38] Every legal migrant applying for a permanent visa to the USA undergoes pre-entry tuberculosis screening and, in 2007, the Centers for Disease Control and Prevention added sputum culture to the pre-migration screening programme.[74] Three studies[29,33,34] reported that 54.4–80.0% of culture-positive cases were smear-negative; all three studies concluded that these cases would have been missed if sputum culture was not part of the tuberculosis screening algorithm. Two studies[29,43] found that addition of sputum culture to the screening algorithm decreased the number of active tuberculosis cases diagnosed within the first 6–12 months of arrival. The improved tuberculosis screening protocol including sputum culture, combined with DOT, could save the USA $15 million per year.[33] All four studies were retrospective and used two interventions at the same time (sputum culture and DOT). Therefore, the precise contribution of each intervention to the reduction of newly diagnosed cases of active tuberculosis within 1 year of arrival to the USA is unknown.

Mor and colleagues[30] concluded that use of chest radiography for post-migration screening of detained migrants from the Horn of Africa was effective, with a sensitivity of 100%, a specificity of 96.1%, and a positive predictive value of 17.7% for identification of cases with a final diagnosis of tuberculosis (sputum confirmed cases and patients started on tuberculosis treatment without sputum confirmation), since no additional tuberculosis cases were reported during the detention period. To diagnose one migrant with active tuberculosis, 98 people needed to be screened by chest radiography. Sputum testing, done of all migrants with suspected tuberculosis after chest radiography, was done in a tuberculosis clinic; 5.6 people needed to be tested to diagnose one tuberculosis case. The total cost of post-migration screening by chest radiography was $4519 per tuberculosis case diagnosed; this was concluded to be cost-effective because the cost of treatment of one migrant with tuberculosis in Israel in 2015 was $7335.30. Migrants applying for a temporary US visa undergo a tuberculin skin test or an IGRA (QuantiFERON TB Gold [QFT-G] in-Tube assay [Cellestis, Carnegie, VIC, Australia]); if the test is positive, chest radiography is done.[75]

Figure: Study selection process

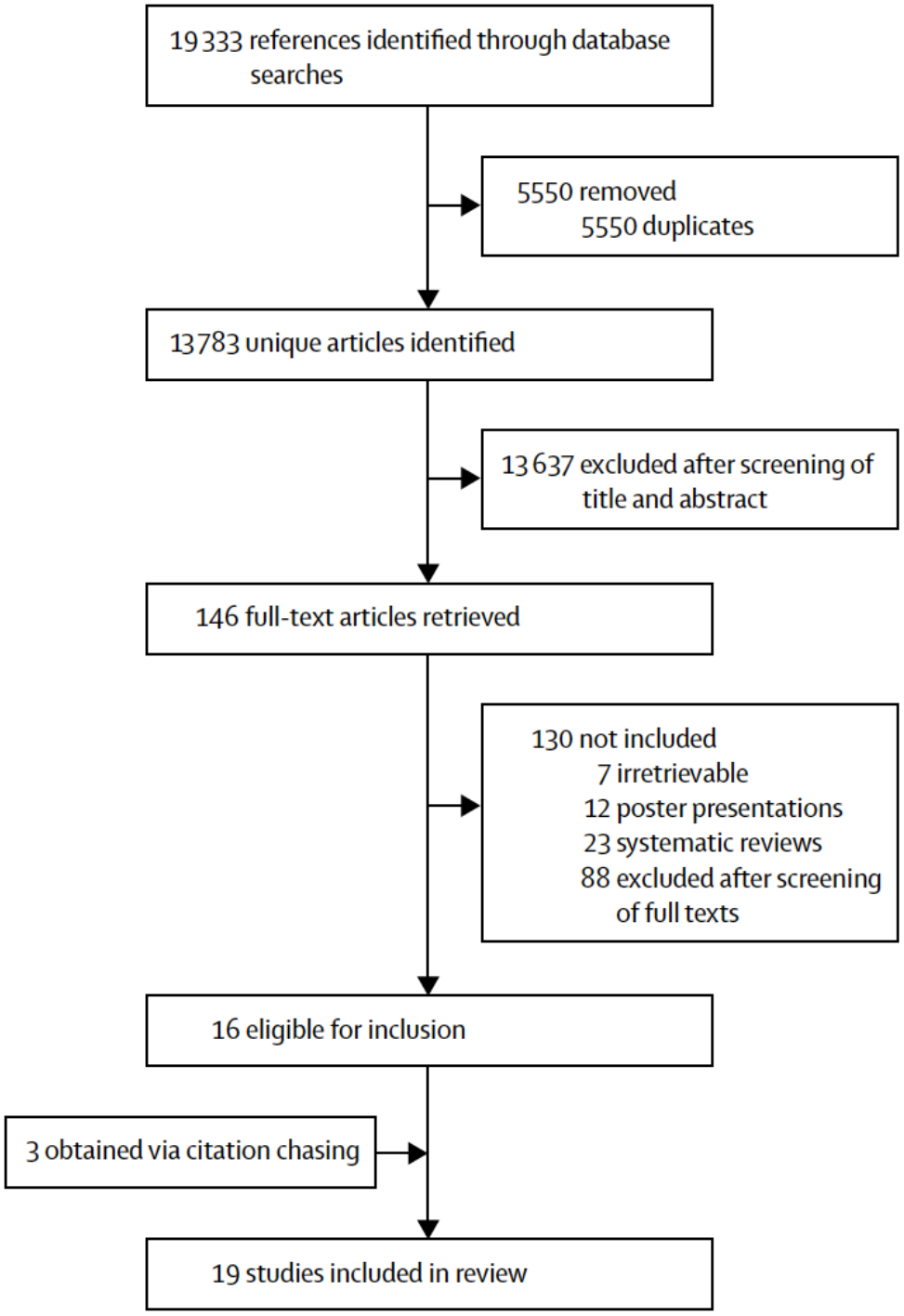

Table 1. Characteristics of studies aiming to improve tuberculosis identification and tuberculosis management

First Author (year)	Hard-to-reach group	Aim	Intervention	Comparator	Study design	Outcome measure	Sample size	Country	Quality score
TB identification (studies identified by this review)									
Schneeberger Geisler et al.[45] (2010)	Migrants	To compare a symptom-based questionnaire (2007-2008) versus chest radiography (2004-2005) to screen for pulmonary tuberculosis	Symptom-based questionnaire	Chest radiography	Retrospective cross-sectional comparison		n = 53,306	Switzerland	+
Duarte et al.[40] (2011)	IVDU	To evaluate the effect of the intervention (key partners promoting health-seeking behaviour, eliminating potential barriers, TB screening at chest clinic and DOT for TB treatment) on diagnosis of TB and treatment compliance.	Active screening / referral	Passive screening / referral	Retrospective review of records; effectiveness comparison	Reported TB cases	n = 590 I: 465 C: 125	Portugal	-
George et al.[41] (2011)	Migrants/ children	To examine the clinical utility of tuberculin skin testing (TST) and subsequent chest radiograph screening for TB disease in recently immigrated, asymptomatic internationally adopted children.	TST	Chest radiography	Prospective cross-sectional	CXR suggestive of TB	n = 566	US	-
Jit et al.[42] (2011)	Homeless, drug users	To assess the cost-effectiveness of the Find and Treat service for diagnosing and managing hard to reach individuals with active tuberculosis in London.	MXU - screening	Self presentation	Observational and cost-effectiveness	Incremental costs from healthcare taxpayer perspective	n = ± 11,000	UK	+

Table 1. (continued)

Lowenthal et al.[43] (2011)	Migrants	To determine whether TB disease importation decreased following the addition of sputum cultures to the pre-migration screening protocol for people with abnormal CXR, symptoms of TB or HIV+ and if the intervention reduced transmission (e.g., smear-positive and culture-positive) of TB.	Expanding screening protocol with sputum culture (and DOTS)	Sputum smear	Retrospective observational effectiveness	Reported TB cases within 6 months of arrival	n = 3,479	US	+
Ruutel et al.[44] (2011)	Drug users	To evaluate case management interventions (active referral to TB centre made by the methadone programme) aimed at increasing tuberculosis screening & treatment entry**.**	Active referral to TB clinic (appointment organised by study)	Passive referral (appointment organised by participant)	Pilot - RCT	TB clinic attendance	n = 189	Estonia	+
Bernard et al.[37] (2012)	Homeless	To measure the impact of an active TB case finding programme on the transmission of TB among the homeless in Paris.	MXU	No MXU	Effectiveness	Screening uptake, active TB cases, related TB cases (same strain)	n = 22,000	France	+
Mor et al.[38] (2012)	Migrants	To determine the validity of pre-migration TB screening by CXR in migrants from Ethiopia wanting to migrate to Israel.	Chest radiography	Sputum smear/culture	Retrospective records review / cost-effectiveness	Accuracy of chest radiography as pre-migration screening tool	n = 13,379	Israel	+

Table 1. (continued)

Story et al.[39] (2012)	Mixed	1. To calculate the sensitivity and specificity of mobile digital CXR for identifying pulmonary TB among high risk groups in an urban setting (London) 2. To determine whether cases of active pulmonary TB identified by MXU were less likely to be sputum smear positive on diagnosis than passively identified cases from the same populations.	1. MXU – screening 2. Sputum smear	1. Sputum culture confirmation 2. Passive presenters	Observational	Sensitivity and specificity of mobile digital chest radiography screening	n = 38,717	UK	+
Assael et al.[34] (2013)	Migrants	To analyse the proportion of positive sputum smears in Mexican migrants with culture confirmed TB.	Sputum smear	Sputum culture	Retrospective effectiveness	Culture confirmed TB cases with a positive sputum smear	n = 122	US	-
Bell et al.[35] (2013)	Migrants	To examine the efficacy of the referral processes at US Port-of-Entry.	Active referral (direct appointment, direct phone number or indirect phone number)	No referral	Effectiveness	TB follow up attendance and time to follow-up visit	n = 1,512	US	+
Painter et al.[36] (2013)	Migrants	To measure the sensitivity of TST and QFT-G in detecting culture-confirmed pulmonary tuberculosis among migrants.	Two-stage screening by TST or QFT-G and CXR	Sputum culture confirmation	Effectiveness	Sensitivity of TST and QFT-G in culture confirmed pulmonary TB cases	n = 20,100	US	+

Table 1. (continued)

Chuke et al.[31] (2014)	Migrants	To evaluate the effectiveness of TST versus QFT-G as part of screening for active TB in US migrants from a country with a high BCG vaccination coverage.	TST and QFT-G	Chest radiography, sputum culture	Effectiveness comparison of different tests	Test agreement QFT-G, TST and chest radiography	n = 1,276	US	-
Harstad et al.[32] (2014)	Migrants	To improve the follow-up of patients with positive TB screening results by increasing the collaboration between healthcare services and new routines for summoning patients.	1. Active referral follow-up (letters, contact by phone) 2. Reduce number of tests	No active referral / follow-up, no adjusted programme	Effectiveness comparison	TB clinic attendance and time from screening to examination	n = 257 I: 123 C: 134	Norway	-
Posey et al.[33] (2014)	Migrants	To report on the implementation of the new pre-migration TB screening programme introduced by the CDC in 2007 (sputum culture and DOT).	Expanding screening protocol with sputum culture	Sputum smear	Report	Smear-ve/ culture+ve TB cases	n = 1,100	US	-
Liu et al.29 (2015)	Migrants	To evaluate the effect of pre-migration screening with a culture-based algorithm on preventing the importation of TB to the United States by migrants and refugees from foreign countries.	Expanding screening protocol with sputum culture (and DOTS)	Sputum smear	Population-based, cross-sectional	Smear-ve/ culture+ve TB cases and annual reported TB cases	n = 3,212,421	US	+
Mor et al.30 (2015)	Migrants	To evaluate the validity of TB screening by CXR and the related costs in detained undocumented migrants from the Horn of Africa (post-migration, during detention in prison).	Chest radiography	Sputum smear/culture	Cross-sectional (cost-) effectiveness	Positive chest radiographs and cost per active TB cases detected	n = 1,087	Israel	-

Table 1. (continued)

Duarte et al.40 (2001)	Drug users	To evaluate the effect of the intervention (key partners promoting health-seeking behaviour, eliminating potential barriers, TB screening at chest clinic and DOT for TB treatment) on diagnosis of TB and treatment compliance.	Period 2003-2005: implemen-tation of DOT, follow-up of non-compliance and providing medical or drug abuse treatment	Period 2001-2003: before the implemen-tation of DOT	Retrospective review of records; effectiveness comparison	Adherence to treatment	I: 465 C: 125	Portugal	-
Jit et al.42 (2011)	Homeless people and drug users	To assess the cost-effectiveness of the "Find and Treat" service for diagnosing and managing hard-to-reach individuals with active tuberculosis in London.	Period 2007-2010: Find and Treat service: Case holding & treatment support by peers	No case holding and peer support	Observational and cost-effectiveness	Incremental costs from healthcare taxpayer perspective	I: 494 C: 315	United Kingdom	+
Girardi et al.47 (2012)	People living with HIV	To estimate the impact of cART on TB outcome.	Concurrent cART and TB treatment	Administration of cART before TB treatment	Multicentre, prospective, observational	Treatment outcome	I: 151 C: 95	Italy	+

Table 1. (continued)

Tuberculosis management (studies identified by the previous NICE review)									
Goetsch et al.46 (2012)	Homeless people and drug users	To establish a sustainable low-threshold CXR screening programme for pulmonary TB among drug users and homeless people and to integrate this into the existing public health programme for active case finding. To estimate the coverage of the programme, assess other risk factors and determine TB rates and treatment outcome in these two groups.	Enhanced case management, hospital admission for initiation of treatment for active TB	Comparing the beginning of the 5 year intervention period with the end	Retrospective effectiveness	Treatment outcome	n = 39	Germany	-
Alwood et al.[67] (1994)	People living with HIV and drug users	To evaluate the effectiveness of supervised therapy for tuberculosis (TB) in patients with HIV infection.	DOT	Partial supervision and self-administration	Retrospective chart review	Adherence to treatment, mortality	n = 78 I: 48 C: 30	US	-
Diez et al.[71] (1996)	Homeless people	To evaluate a social care and health follow-up programme providing directly observed treatment, primary health care and, if necessary, accommodation.	Social care support (DOT, primary health care + accommodation)	Normal care	Retrospective cohort	Annual TB incidence rate	I: 240 C: NR	Spain	-
Oscherwitz et al. [74] (1997)	Drug and alcohol users	To determine which patients TB controllers attempt to detain, how often and where patients are detained, and how many of these patients complete TB treatment.	Legal detention	No legal detention	Retrospective cross-sectional cohort	Adherence to treatment	n = 4,325 I: 67 C; 4,258	US	-

Table 1. (continued)

Bock et al.[68] (2001)	Drug users	To determine whether incentives increase adherence to directly observed therapy (DOT) for tuberculosis (TB) treatment.	DOT plus incentives	DOT only	Historical comparison	Adherence to treatment	n = 112 I: 55 C: 57	US	+
Rodrigo et al.[75] (2002)	Prisoners	To evaluate the TB prevention and control programmes in Barcelona prisons and obtaining conclusions that would allow any necessary modifications to be introduced to improve their effectiveness.	DOT	Treatment as usual (no DOT)	Historical comparison	Adherence to treatment	n = NR	Spain	-
Chemtob et al.[69] (2003)	Migrants	To describe the new programme, using directly observed treatment (DOT), and compare the outcome of treatment prior and after its realisation.	DOT	Treatment as usual (no DOT)	Historical comparison	Adherence to treatment and outcome	n = 877 I: 671 C: 206	Israel	-
MacIntyre et al.[73] (2003)	Migrants	To describe the effectiveness of a family-based programme of directly observed treatment (DOT) for tuberculosis.	DOT delivered by a family member	Self-administration and monthly clinic visits	RCT	Adherence to treatment	n = 173 I: 87 C: 86	Australia	+
Deruaz & Zellweger[70] (2004)	Migrants, alcohol or drug users, homeless people and prisoners	Evaluation of first experience of the directly observed therapy (DOT) programme for tuberculosis introduced in the Canton of Vaud in 1997.	Full DOT DOT delivered at TB clinic	Partial DOT (DOT only first 2 months of treatment) DOT delivered at social outreach site	Historical comparison	Adherence to treatment and outcome	n = 54 I: 36 C: 18	Switzerland	-

Table 1. (continued)

Schwartzman et al.[61] (2005)	Migrants	To model the effectiveness and cost-effectiveness of a pre-migration DOTS programme.	DOTS	No DOTS	Cost-effectiveness model	Cost, TB related morbidity and mortality among Mexican migrants in the US	n = 0	US	++
Juan et al.[72] (2006)	Migrants, homeless people, drug or alcohol users, people living with HIV	To compare directly observed treatment (DOT) of tuberculosis through pharmacy offices with self-administered treatment in patients at risk for non-adherence.	DOT plus incentives	Self-administration	Historical comparison	Adherence to treatment	n = 213 I: 101 C: 112	Spain	+
Ricks[60] (2008)	Drug users	To compare the effectiveness of using peers versus 'standard' public health workers to coordinate TB treatment .	Enhanced case management by peers	Limited case management by heath care professionals	RCT	Adherence to treatment	n = 104 I: 53 C: 49	US	++

Abbreviations

C=Control group; cART= combined Antiretroviral Therapy; CXR = Chest X-ray; CDC = Centers for Disease Control and Prevention; DOT = Direct Observed Treatment; DOTS = Direct Observed Treatment Short-course; HIV = Human Immunodeficiency Virus; HTRG = Hard-To-Reach Group; I= Intervention group; MXU = Mobile X-ray Unit; *n* = number; NICE = National Institute for Health and Clinical Excellence; NR = Not Recorded; POA = Port-Of-Arrival; QFT-G = QuantiFERON-TB Gold Test; RCT = Randomised Controlled Trial; TB = Tuberculosis; T-SPOT = T-SPOT.TB; TST = Tuberculin Skin Test; UK = United Kingdom; US = United States

Results from Chuke and colleagues[31] suggested that neither the QFT-G assay nor the tuberculin skin test were effective tools for identification of migrants from high-incidence countries with high BCG vaccination coverage who had chest radiography results consistent with tuberculosis. Overall test agreement was 50.1% between chest radiography and the tuberculin skin test, and 63.5% between chest radiography and the QFT-G assay. Of all culture confirmed or smear-confirmed tuberculosis cases, 100% had a positive tuberculin skin test and only 43.8% had a positive QFT-G test; the number of sputum-confirmed tuberculosis cases was too low to draw valid conclusions.[31] A 2013 study[36] showed no significant difference between the sensitivities of the QFT-G assay (86.4%, 95% CI 79.3–91.7) and the tuberculin skin test with a cut-off point of 10 mm (81.1%, 73.3–87.5; p=0.12) for identification of culture-confirmed cases when used for tuberculosis screening in migrants from high-incidence countries with high BCG vaccination coverage. However, there was a significant difference between the sensitivities of the QFT-G assay and the tuberculin skin test with a cut-off point of 15 mm (52.3%, 95% CI 43.4–61.0; p<0.001) for this indication. Use of the tuberculin skin test as a screening tool for internationally adopted children was compared with screening by chest radiography in a study with a small sample size.[41] Using a cut-off point of 10 mm induration was suggested to be better than a cut-off point of 5 mm. No participants were identified with active tuberculosis, and not all children had undergone chest radiography. A Swiss study[45] retrospectively evaluated the effectiveness of tuberculosis screening by use of a symptom-based questionnaire. Use of this strategy for screening of asylum seekers had a sensitivity of 55.2% and a specificity of 96.0% compared with the gold standard—ie, microbiologically confirmed tuberculosis for which patients started treatment within 90 days of screening. The same study also compared the symptom-based questionnaire with the previously used screening method, chest radiography, which yielded a sensitivity of 100%.45 The time between screening and the start of treatment was 19 days longer for people screened with the symptom-based questionnaire than for those screened by chest radiography.[45]

Bell and colleagues[35] examined the effect of different support activities for referral to post-arrival follow-up appointments for migrants with suspected non-infectious tuberculosis entering the USA. These migrants were informed to attend a follow-up appointment in the USA within 30 days of arrival. Provision of migrants with any kind of support at the port of entry (scheduled appointment, direct phone number, or indirect phone number) significantly improved follow-up attendance (adjusted hazard ratio [HR] 4.0, 95% CI 3.0–5.2; p<0.0001) and shortened the time between arrival and attendance at the follow-up appointment (16 days vs 69 days) compared with no support. The greatest effect was seen in the group that received a direct telephone number (adjusted HR 7.5, 95% CI 4.8–11.6; p<0.0001); 67% of individuals were seen within 30 days of arrival. Follow-up attendance did not differ significantly between the scheduled appointment and the direct telephone-number groups (adjusted HR 1.1, 95% CI 0.8–1.3; p=0.69).

A comparative study with a small sample size[32] showed that active referral of migrants improved attendance rates at tuberculosis clinics and reduced patient delay in Norway. Patients referred to the tuberculosis clinic were repeatedly contacted through various means, including in person, by telephone, or by letter. Among asylum seekers, attendance at the first clinic appointment increased from 60.9% (95% CI 47–75) before the intervention (no active referral system) to 93.2% (87–100) after the intervention. Among other migrants, the attendance rate increased from 72.4% (95% CI 65–80) to 88.6% (83–94). The median time between screening and tuberculosis clinic attendance decreased for both asylum seekers (15 weeks before the intervention to 8 weeks after; p=0.04) and other migrants (30 weeks before the intervention to 10 weeks after; p<0.001). Three studies[37,39,42] focused on the use of mobile radiography units in tuberculosis screening. Use of this intervention for screening of homeless people at a shelter in Paris, France, increased the number of identified tuberculosis cases over the first 3 years.[37]

Tuberculosis transmission was evaluated by examination of related Mycobacterium tuberculosis strains among newly diagnosed tuberculosis cases. Within 10 years, the number of related cases decreased among shelter users from 14.3 to 2.7 cases per year (p<0.01); a decrease in the proportion of related cases was also found in non-shelter users (from 75% to 25%; p<0.01). The effectiveness of screening by use of mobile radiography units was also evaluated in homeless people, drug users, prisoners, and asylum seekers in London, UK.[39]

Table 2. Main interventions and outcomes aiming to improve TB identification and management

Tuberculosis identification	Outcomes
Migrants	Screening for tuberculosis by chest radiography before and after migration can be effective and cost-effective[30,38]
Tuberculosis screening by chest radiography with or without the TST	Tuberculosis screening by chest radiography has a high diagnostic accuracy for the detection of sputum-confirmed cases (culture or smear; sensitivity was 86.1%-100% and specificity was 96.1%-99.1%)[30,38]
	Active screening by chest radiography or the TST can improve identification of active tuberculosis cases; result in earlier diagnosis, and reduce tuberculosis transmission and importation[56, 58-60]
	Screening migrants by use of chest radiography can be cost-effective, and less costly than screening by the TST[30,38, 53,59]
Sputum culture included in pre-migration screening	Most culture confirmed tuberculosis cases were smear negative (54.4%-80.0%)[29,33,34]
	Including sputum culture as part of screening for tuberculosis in migrants can decrease the number of active tuberculosis cases diagnosed within 6-12 months of arrival in the host country[29,43]
	Inclusion of sputum culture as part of pre-migration screening could save the USA $15 million per year[33]
Active referral	Active referral by letter, scheduled clinic appointment, or provision of a direct phone number for the tuberculosis clinic or an indirect phone number can improve clinic attendance and shorten the time between arrival and clinic attendance. Provision of a direct phone number or a scheduled appointment could have the greatest effect[32,35]
	Not all active tuberculosis cases among new entrants can be detected with active referral[63]
Tuberculosis screening by the interferon gamma release assay or TST	Neither QFT-G nor the TST are effective screening tools for tuberculosis screening in migrants from high-incidence countries with a high BCG vaccination coverage[31]
	The QFT-G and TST with a cut-off point of 10 mm have the same sensitivity for detection of culture-confirmed tuberculosis cases in migrants from high-incidence countries with high BCG vaccination coverage. However, QFT-G has a higher sensitivity than TST with a cut-off point of 15 mm[36]
	In migrant children, the TST with a cut-off point of 10 mm is a better screening tool than is the TST with a cut-off point of 5 mm[41,51]
Tuberculosis screening by symptom-based questionnaire	A Symptom-based questionnaire is not an effective screening tool for tuberculosis in migrants,[30] because of the low sensitivity (55.2%)[45]
Homeless people	
Tuberculosis screening by mobile radiography units	Use of mobile radiography units as a screening tool for homeless people can improve tuberculosis detection and decrease transmission[37]
Incentives	Incentives can increase screening uptake and completion[50,56]

Table 2. (continued)

Drug users	
Active referral	Active referral to the tuberculosis clinic can improve clinic attendance among drug users for minimal extra costs[44]
Incentives	Monetary incentives can improve screening completion[57] and can be cost-effective[58]
Prisoners	
Tuberculosis screening by chest radiography	Tuberculosis screening by chest radiography had a similar diagnostic yield to screening by the TST[59]
	Screening by chest radiography can be more cost-effective than screening by the TST[52]
	All prisoners, not just symptomatic prisoners, should be screened to avoid a substantial number of tuberculosis cases being missed.[66]
Mixed populations	
Tuberculosis screening by mobile radiography units	Mobile radiography units for tuberculosis screening among homeless people, drug users, prisoners and asylum seekers can be sensitive and specific (sensitivity of 81.8% and a specificity of 99.2%). Cases diagnosed with mobile radiography units are less likely to be smear positive; thus reducing tuberculosis transmission.[39]
	Tuberculosis screening of homeless people, drug users and prisoners using mobile radiography units can improve tuberculosis identification, especially among people who are asymptomatic and late presenters[42]
	Tuberculosis screening by mobile radiography units can be cost-effective[42]
TB management	
Migrants	
Directly Observed Treatment	DOT can increase successful treatment outcomes[70]
	DOT administered by a family member does not improve adherence to treatment[71]
	Pre-migration DOT programmes can reduce tuberculosis-related morbidity and mortality in the host country and can be cost-effective[59]
Homeless	
Enhanced case management	Enhanced case management reduced treatment dropout rates[42,46]
	Enhanced case management plus extra health-care services or social support can improve treatment adherence and decrease the annual tuberculosis incidence and tuberculosis-related deaths[46,66]
Incentives	Incentives can improve adherence to treatment[48,49]

Table 2. (continued)

Drug users	
Enhanced case management	Enhanced case management improved treatment compliance and reduced tuberculosis-related mortality46
	Enhanced case management by peers and community health-workers can improve treatment completion rates63
Prisoners	
Directly Observed Treatment	DOT can improve adherence to treatment69
People living with HIV	
Simultaneous tuberculosis and HIV treatment	Simultaneous tuberculosis and HIV treatment can reduce the tuberculosis-related mortality rate47
Directly Observed Treatment	DOT can improve treatment adherence65
Mixed populations	
Case holding and treatment support by peers	Case holding (activities to keep patients in care) and treatment support by peers can improve treatment compliance and reduced lost to follow-up an can be cost-effective42
Directly Observed Treatment	Partial DOT, only given during the first 2 months of treatment, can be as effective as full DOT, given during the whole treatment period[72]
	DOT combined with incentives can improve treatment completion[68,73]
	DOT in the tuberculosis clinic or via social outreach has similar treatment outcomes[70]
Detention for treatment	Legal detention does not improve adherence to treatment[67]

People were referred for further investigations if chest radiography results were suggestive of tuberculosis. Screening results were matched to cases of culture confirmed tuberculosis among hard-to-reach populations in the national tuberculosis register. Mobile radiography units had a sensitivity of 81.8% (95% CI 64.5–93.0) and a specificity of 99.2% (99.1–99.3); cases diagnosed by use of this approach were less likely to be smear-positive than passively identified cases (odds ratio [OR] 0.34, 0.14–0.85; p=0.022). Jit and colleagues[42] examined the effectiveness and cost-effectiveness of the Find and Treat service for homeless people and drug users in London, UK, compared with normal care without this service. The Find and Treat service screened homeless people and drug users by use of mobile radiography units, provided support during treatment, and supported people who had been previously lost to follow-up. The service identified 16 tuberculosis cases per year; 35% of the cases were asymptomatic and 23% were late presenters (with a delay between first symptoms and treatment). The authors concluded that, without the service, these tuberculosis cases were unlikely to have been identified. The Find and Treat service was deemed effective and cost-effective because the incremental cost ratio for the mobile radiography unit was £18 000 per quality-adjusted life year (QALY) gained; the threshold used by NICE is £20 000–30 000 per QALY gained.[76]

A study[44] done in Estonia evaluated the effectiveness of active referral to a tuberculosis clinic organised by the methadone drug treatment programme versus passive referral. When drug users were reminded about their appointment, tuberculosis clinic attendance improved and was more effective than passive referral, whereby drug users made the appointment themselves (OR 3.9, 95% CI 1.4–10.4; p=0.007). The authors calculated that active referral to the tuberculosis clinic would cost €18 per drug user. None of the drug users in this small study were diagnosed with tuberculosis; therefore, the cost made per identified case could not be calculated. Duarte and colleagues[40] evaluated the effectiveness of early identification of active tuberculosis in drug users through improvement of cooperation between key partners (street teams, tuberculosis clinics, drug users support centres, the local public health department, and local hospitals). Key partners were trained to identify people using drugs in their services and settings, increase the tuberculosis screening rate by promoting health-seeking behaviour, hand out notification cards for screening at the tuberculosis clinic, and offer free transport to and free care at the tuberculosis clinic. These strategies were combined with improved screening procedures at the tuberculosis clinic, where a symptom-based questionnaire, tuberculin skin test, and chest radiograph were done. Screening was offered annually for people who had been in contact with someone with tuberculosis or who had tuberculosis symptoms. Uptake of tuberculosis screening improved from screening of 125 drug users before implementation to 465 drug users after implementation. Before implementation, active tuberculosis was identified in 82 drug users, of whom 11 (13%) were identified by screening. Over a similar period following implementation, active tuberculosis was detected in 59 patients, of whom 36 (61%) were identified by screening. Improvements in the cooperation between key partners in the study by Duarte and colleagues[40] led to improved qualitative outcomes for case management (including improved feelings of self-esteem, communication skills, and health-seeking behaviour), extra health-care services, and provision of tuberculosis treatment under supervision for drug users with active tuberculosis. Poor treatment compliance decreased from 48% to 24% (OR 0.34, 95% CI 0.16–0.72), and default rates fell from 35% to 10% (0.21, 0.08–0.54) compared with the time before improved cooperation. Mortality decreased from 18% to 14% (OR 0.7, 95% CI 0.28–1.78). Two studies[42,46] focused on improvements in tuberculosis management in mixed hard-to-reach populations. A small German study[46] showed that community health workers contacting homeless people and drug users to provide tuberculosis education and enhanced case management (community health-worker based) achieved low treatment dropout (11%), whereas routine practice (no community health workers) resulted in 33-50% dropout. Jit and colleagues' study[42] of the Find and Treat service in London, UK, also assessed tuberculosis education, case holding (activities to keep patients in care), and treatment support among drug users and homeless people. Complex cases (in terms of management—ie, those previously lost to follow up or those who have difficulties with treatment adherence) referred to the service were more likely to comply (61% vs 52% after 1 year) and less likely to be lost to follow-up (3% vs 35% after 1 year) compared with patients who presented themselves passively via other services. Furthermore, this part of the service seemed to be cost effective, because the incremental cost ratio for the case management aspect of the service was £4100 per QALY gained. This estimate was based on various assumptions and, in the most unfavourable conditions, would be Åí6800 per QALY gained. Both estimates of the incremental cost-effectiveness ratio are below the threshold used by NICE (£20 000–30 000 per QALY gained).[76] The possible prevention of secondary infections caused by patients with active pulmonary tuberculosis or the prevention of drug-resistant tuberculosis were not considered. We identified one study[47] focusing on tuberculosis management in people with HIV. Simultaneous administration of combination antiretroviral therapy (cART) and tuberculosis treatment significantly reduced the mortality rate compared with tuberculosis treatment without cART in Italy (incidence rate ratio 0.14, 95% CI 0.06–0.30; p<0.001). No studies were identified of the effectiveness or cost-effectiveness of interventions identifying or managing tuberculosis among sex workers. None of the included studies evaluated the effectiveness of improvement of tuberculosis awareness among hard-to-reach populations. Because most of the studies focused on migrants, the transferability of results to other hard-to-reach populations is probably low. None of the studies focused on factors that altered the effectiveness of the interventions. Most of the studies included in this review provided evidence that was of weak to moderate quality. The grading of evidence and a complete overview of the combined evidence of this review and the previous reviews[24,25] is in the evidence statements (appendix).

DISCUSSION

We identified 19 new studies[29–47] published between 2010 and 2015, in addition to the 26 studies,[48–73] published between 1990 and 2010, identified in the NICE reviews.[24,25] Screening of migrants by chest radiography was effective for identification of active tuberculosis cases and lowering of tuberculosis importation; it was also cost-effective and less costly than screening by the tuberculin skin test.[30,38,53,56,58–60] A systematic review and meta-analysis by Paquette and colleagues[77] reported similar findings for the homeless population. In hard-to-reach populations, results should be provided instantly because follow-up attendance might be low. Chest radiography results can be read instantly, which is an advantage over other diagnostic tests, such as the tuberculin skin test, the QFT-G assay, and sputum smears or culture. Use of mobile radiography units makes access to tuberculosis screening easier. Tuberculosis identification was improved for several hard-to-reach populations when mobile radiography units were used; they were also cost effective.[37,39,42,55] One study[64] suggested that all people in the targeted hard-to-reach population should be screened because screening of only symptomatic people would miss a substantial number of tuberculosis cases. A systematic review by Aldridge and colleagues[78] reported high diagnostic yields for pre-migration screening, especially if programmes focused on migrants from high-incidence countries. The addition of sputum culture to the US pre-migration screening programme, initially targeting migrants from high-incidence countries, improved tuberculosis identification in the home country and reduced tuberculosis importation into the host country.[29,33,34,43] For culture results to return from the laboratory takes about 4 weeks, which imposes a small risk of an individual becoming infected while waiting for the results. The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) could be useful as a pre-migration screening tool for migrants from high-incidence countries, because it is more sensitive than sputum smear, provides results within 2 h, and is cheaper than sputum culture in many settings.[79] Studies exploring this intervention are needed. Another effective intervention is active referral to a tuberculosis clinic, either by appointment or by provision of a telephone number. Active referral improved the uptake of tuberculosis screening among migrants[32,35] and drug users[40,44] for little extra costs. The barrier of finding an appropriate tuberculosis clinic and organising an appointment is negated by this intervention. Enhanced case management increased the number of patients completing treatment,[42,46,63] decreased loss to follow-up, reduced tuberculosis-related mortality and tuberculosis incidence,[66] and was cost-effective[42] in homeless people and drug users. Guidance and support to help these populations adhere to long-term treatment increases the number who complete treatment. Although WHO advises integration of HIV and tuberculosis services,[80] we found only one study reporting on simultaneous HIV and tuberculosis treatment,[47] which showed a reduction in tuberculosis-related mortality. A systematic review by Uyie and colleagues[81] found that the WHO recommendation to integrate HIV and tuberculosis services was effective in African countries. Integrated HIV and tuberculosis care in low-incidence countries needs evaluation. The NICE review[25] found that DOT increases successful treatment outcomes[70] and improves treatment adherence among several hard-to-reach populations,[65,69] especially when combined with incentives.[68,73] Partial DOT, given during only the first 2 months of treatment, can be as effective as full DOT.[72] Treatment outcome did not differ significantly according to whether DOT was provided in a tuberculosis clinic or via social outreach.[72] This finding contrasts with other systematic reviews focusing on countries of middle and high tuberculosis incidence, which showed that community DOT was more effective than clinic DOT[82] or self-administration.[83] Treatment compliance did not differ significantly between DOT administered by a family member and receipt of regular treatment consisting of monthly check-ups.[71] A systematic review by Tian and colleagues[84] found that community DOT given by a non-family member was most effective. As with enhanced case management, DOT helps susceptible people in hard-to-reach populations adhere to their lengthy treatment regimen. The NICE reviews[24,25] found that use of incentives improves tuberculosis screening uptake, screening completion, and adherence to treatment among homeless people[48,49] and drug users,[57] and is cost-effective when used to identify tuberculosis cases among drug users.[55] People in those hard-to-reach populations belong to the most disadvantaged groups in society; incentives can help to achieve these individual's daily needs and, therefore, provision of incentives is a valuable intervention. Post-migration screening by use of a symptom-based questionnaire did not seem to be effective,[45] and incarceration reduced the number of patients completing treatment in mixed hard-to-reach populations (80% drug users).[67] No clear conclusions can be drawn about the effectiveness of the QFT-G assay and tuberculin skin test for the identification of active tuberculosis in migrants[31,36] and children adopted from high-incidence areas.[41]

An important strength of this systematic review is that it was done in accordance with the Cochrane Collaboration guidelines for systematic reviews. We followed established screening protocols, including double screening of search results, and the search was highly sensitive. The method closely followed that of the NICE reviews[24,25] to extend the body of evidence. The main limitation is that we were unable to do a meta-analysis in view of substantial heterogeneity across the included studies. The studies focused on different hard-to-reach populations, different interventions, and had different designs and outcomes. Furthermore, the populations defined as hard to reach might be debatable because not every individual in the discussed hard-to-reach populations are hard to reach; the populations could differ by setting and person. To be inclusive, we included migrants and people with HIV because they normally have a higher tuberculosis incidence than do other populations. We used broad and sensitive search terms to include all types of interventions aiming to improve tuberculosis identification and management; this search strategy can affect reproducibility. Most evidence was assessed as being of weak to moderate quality; therefore, few strong conclusions could be drawn. The main areas in which the included studies were lacking were the identification and control of confounding factors and the use of appropriate analytical methods. Most of the studies focused on migrants. No studies focused on sex workers, and few included children in susceptible and hard-to-reach populations, prisoners, homeless people, drug users, and people with HIV. As a result, evidence for these hard-to-reach populations is scarce. Because our review included studies done in EU, EU candidate, EEA, and OECD countries, we did not assess studies of combined HIV and tuberculosis care done in high-incidence countries; therefore, the evidence for people with HIV is restricted. We could not address the secondary research questions because no studies examined factors affecting the effectiveness of the interventions, nor any adverse or unintended effects of the interventions. Only three studies[30,38,42] included in this update of the review, and seven studies[52–55,57,59,61] identified by the NICE reviews,[24,25] focused on economic data. Most of these studies assessed the use of chest radiography in migrants,[30,38,52,53,59] and prisoners,[54] and the use of mobile radiography units in mixed populations.[42,61] In view of the target populations and the setting, completion of clean, unbiased, and unconfounded trials is often challenging. However, efforts should be made to improve the quality of future studies. Future studies could assess use of the Xpert MTB/RIF assay as a pre-migration screening tool for migrants from high-incidence countries. Cases of tuberculosis in migrants can be diagnosed many years after migration and in settings where screening is done.[85] Easy access to health care and tuberculosis awareness are important to identify the disease in this group and other hard-to-reach populations. Future studies should focus on access to health care for hard-to-reach populations and on raising tuberculosis awareness—eg, by evaluating the effects of health education days at shelters, needle exchange programmes, and refugee camps, as well as providing tuberculosis education leaflets on the identification of tuberculosis at pre-migration screening clinics, ports of entry, and HIV clinics. This systematic review developed the evidence base for the ECDC guidance document for control of tuberculosis in hard-to-reach populations in Europe.[23] Our findings can also be used by policy makers to set out guidelines and recommendations to improve identification and management of active tuberculosis among hard-to-reach populations.

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4

chapter 4

EFFECTIVENESS OF SERVICE MODELS AND ORGANISATIONAL STRUCTURES SUPPORTING TUBERCULOSIS IDENTIFICATION AND MANAGEMENT IN HARD-TO-REACH POPULATIONS IN COUNTRIES OF LOW AND MEDIUM TUBERCULOSIS INCIDENCE: A SYSTEMATIC REVIEW

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ABSTRACT

Objective

To determine which service models and organisational structures are effective and cost-effective for delivering tuberculosis services to hard-to-reach populations.

Design

Embase and MEDLINE (1990-2017) were searched in order to update and extend the 2011 systematic review commissioned by NICE, discussing interventions targeting service models and organisational structures for the identification and management of tuberculosis in hard-to-reach populations. The NICE and Cochrane Collaboration standards were followed.

Setting

European Union, European Economic Area, European Union candidate countries and Organisation for Economic Co-operation and Development countries.

Participants

Hard-to-reach populations, including migrants, homeless people, drug users, prisoners, sex workers, people living with HIV and children within vulnerable and hard-to-reach populations.

Primary and secondary outcome measures

Effectiveness and cost-effectiveness of the interventions.

Results

From the 19,720 citations found, five new studies were identified, in addition to the six discussed in the NICE review. Community health workers from the same migrant community, street teams and peers improved tuberculosis screening uptake by providing health education, promoting tuberculosis screening and organising contact tracing. Mobile tuberculosis clinics, specialised tuberculosis clinics and improved cooperation between health care services can be effective at identifying and treating active tuberculosis cases, and are likely to be cost-effective. No difference in treatment outcome was detected when directly observed therapy was delivered at a health clinic or at a convenient location in the community.

Conclusions

Although evidence is limited due to the lack of high quality studies, interventions using peers and community health workers; mobile tuberculosis services, specialised tuberculosis clinics, and improved co-operation between health services can be effective to control tuberculosis in hard-to-reach populations. Future studies should evaluate the (cost-)effectiveness of interventions on TB identification and management in hard-to-reach populations and countries should be urged to publish the outcomes of their TB control systems.

Systematic review registration

PROSPERO *CRD42015017865*.

INTRODUCTION

Prevention and control of tuberculosis (TB) is based on early detection and diagnosis of TB followed by effective treatment. In 2015 there were an estimated 10.4 million incident TB cases worldwide, an estimated 4.3 million cases were either not diagnosed, or diagnosed but not reported to national TB programmes.[1] Trends for TB treatment are encouraging, with most notified TB cases completing their treatment successfully; although treatment success rates in some regions, such as the European region, were considerably below the WHO World Health Assembly target of 85%.[1]

In many countries with a low TB incidence (less than ten TB cases per 100,000 population),[2] TB prevails in the big cities where vulnerable and hard-to-reach (under-served) populations are concentrated.[3] These populations, such as people who are homeless (or have insecure accommodation), misuse drugs or are migrants, are at higher risk of contracting TB and are more likely unable or unwilling to seek medical care and comply with the long term TB treatment. Managing TB in those populations is therefore challenging, due to barriers caused by stigma, cultural barriers, poor access to health care services and low levels of accurate TB knowledge.[4,5-7] This therefore requires special efforts. Health care services need to be organised effectively to identify and diagnose TB cases, and to provide adequate treatment and support. This can be organised in different ways, e.g. mainly as hospital-based[8] or health centre-based;[9] including the public sector, private sector,[10] or civil society and other partners.[11] Sometimes, organisation of the services has proven ineffective in managing TB.[12]

The review question of this systematic review with a scoping component was: 'Which service models and organisational structures, including different types of healthcare workers and settings, are effective and cost-effective for delivering TB services to hard-to-reach populations in low- and medium-incidence countries?'
Findings of this review and the previously published review series [4,13] formed the base for the guidance document by the European Centre for Disease Prevention and Control (ECDC) on controlling TB in hard-to-reach and vulnerable populations.[14]

METHODS

In 2011, the Matrix Knowledge Group published a review, commissioned by the National Institute for Health and Clinical Excellence (NICE), on effectiveness and cost-effectiveness of service models or structures, focussing on the type of health care worker and setting, to identify and manage TB in hard-to-reach populations. We updated and extended the NICE review,[15] using the same methodology but adjusting the focus by excluding latent TB infection and including additional hard-to-reach populations. The review was conducted following standards described by the Cochrane Collaboration[16] and NICE methods guidelines.[17] Results are reported according to PRISMA guidelines.[18] The review protocol was registered in advance in the database of prospectively registered systematic reviews in health and social care, PROSPERO (*CRD42015017865*).

Selection of studies and data management

The same search strategy as for the previous NICE review[15] and the previous published review by Heuvelings et al.[13] was used, searching Embase and MEDLINE through the Ovid platform. The search was expanded by including all European Union (EU)/European Economic Area (EEA) and EU candidate countries to the Organisation for Economic Co-operation and Development (OECD) countries (see Box 1).[15] Two hard-to-reach populations (people living with HIV and children within vulnerable and hard-to-reach populations), were added in addition to the hard-to-reach populations included by the NICE review (migrants including refugees, asylum seekers and the Roma population, homeless people including rough sleepers and shelter users, drug users, prisoners and sex workers).[15] The update of the search conducted for the NICE review[15] covered the period 1 January 2010 (overlapping the end of the search period of the NICE review[15] with a few months) to 24 February 2017. The search for the expanded geographical area and newly included hard-to-reach populations covered a time period from 1 January 1990 (beginning of the search period used in the NICE review[15]) to 24 February 2017. Reference lists of relevant systematic reviews were scanned. No language restrictions were applied.

Studies focussing on the effectiveness and/or cost-effectiveness of interventions for service models and organisational structures supporting TB identification and management of hard-to-reach populations (see Box 1) were included.

Box 1: Inclusion/exclusion criteria for this review

Inclusion criteria:

- Discussing service models and organisational structures, different types of healthcare workers and settings for delivering TB services to hard-to-reach populations;
- Having been conducted in any of the EU/EEA countries (only updated review), the candidate countries* (only updated review) and the other OECD countries**
- Having been published in 2010 or later for the OECD countries**
- Having been published in 1990 or later for the EU/EEA countries and the EU candidate countries* not being one of the OECD countries (only updated review)
- Including data from any hard-to-reach population:
    - homeless people
    - people who abuse drugs or alcohol
    - sex workers
    - prisoners or people with a history of imprisonment
    - migrants, including vulnerable migrant populations such as asylum seekers, refugees and the Roma population
    - children within vulnerable and hard-to-reach populations (only updated review)
    - people living with HIV (only updated review)
- Present quantitative empirical data
- Being a (cost)-effectiveness study, or any other type of quantitative primary research, discussing (cost-) effectiveness

Exclusion criteria:

- Latent TB infection (only updated review)
- Systematic review (only used for reference searching)

EU/EEA = European Union, European Economic Area; OECD = Organisation for Economic Co-operation and Development; TB = Tuberculosis

**EU candidate countries = Albania, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, and Turkey*
*** OECD countries = Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States*

Predefined interventions were using more convenient locations (like specialised TB centres, shelters for homeless people or drug users, needle exchange/methadone programme locations, port of arrival, schools or mobile clinics) and peers or health care workers with the same ethnic or cultural background; however, other interventions could also be included if they supported TB identification or management in hard-to-reach populations. TB identification tools, TB diagnostics, incentives, social support, directly observed therapy and treatment of co-morbidities are discussed in another review.[13] In this review we aim to identify the effectiveness of the type of health worker and setting, to identify and manage TB in hard to reach and vulnerable populations.

The comparator was defined during the review process; interventions were compared to a relevant comparator, for example usual care or no intervention, another intervention, or historical comparison.
Outcomes were defined as any measure of TB identification and management (for example, number of people screened, screening coverage, proportion receiving treatment and treatment completion rate). Effectiveness was

defined as an improvement in any measure of TB identification and/or management. Randomised and non-randomised studies were eligible for inclusion.

See Supplementary Material I for the PROSPERO study protocol, Supplementary Material II for PICOS (Population-Intervention-Comparator-Outcome-Study design) questions and Supplementary Material III for the complete search strategy and search results.

Data extraction, data items, and synthesis

Identified citations were entered into an EndNote database, and duplicates removed (EndNote X7.1, Thomson Reuters 2014). The inclusion criteria were piloted and refined using the first 25 citations. Double screening was conducted by one reviewer screening 100% of the citations (CCH) while another two reviewers screened 50% of the citations each (PFG, SGdV) for inclusion on title and abstract. Disagreement was resolved by discussion. Full text files of included citations were retrieved; irretrievable articles (not available after attempts online, from the university library or through contacting authors) were excluded. Two reviewers assessed full text records for inclusion (CCH, PFG). Disagreement was resolved by discussion. Agreement after screening on title and abstract was 99.6% with an inter-rater reliability (Cohen's kappa) of $\kappa = 0.985$.

Data extraction forms from the NICE review[15] were used to extract information on participant characteristics, settings, types of services/organisational structures, types of healthcare workers delivering the service, outcome measures, methods of analysis and results. For one study data extraction was conducted by two reviewers (CCH, PFG) independently. For the remaining studies, data extraction was conducted by one reviewer (CCH) and checked by a second (PFG); disagreement was resolved by discussion. In one case, the study author was contacted to verify data and obtain additional data.[19]

To facilitate comparability, data synthesis was structured in a similar way to that of the NICE review.[15] Studies were divided into those examining service models and organisational structures for TB identification (screening) and those examining service models and organisational structures for TB management (treatment and support) in hard-to-reach populations. Data were analysed narratively, and appropriateness of meta-analysis considered. Findings were reported as stated by the study authors.

Risk of bias in individual studies and overall strength of evidence

The modified NICE Quality Assessment Tools[17] (based on the Graphical Appraisal Tool for Epidemiological studies) were used to assess quality and risk of bias of included studies. This included an assessment of selection of study sample, minimisation of selection bias and contamination, controlling confounding, outcome measurements, analytical methods and risk of bias. Two reviewers (CCH, PFG) assessed one study independently; the remaining studies were assessed by one reviewer (CCH), and checked by a second reviewer (PFG). Any disagreement was resolved by discussion. Studies were given a quality rating based on the quality assessment: high quality [++], medium quality [+], or low quality [-]. The strength of the evidence was assessed and reported as described in the previous NICE review[15] (Supplementary Material IV).

Patient and public involvement statement

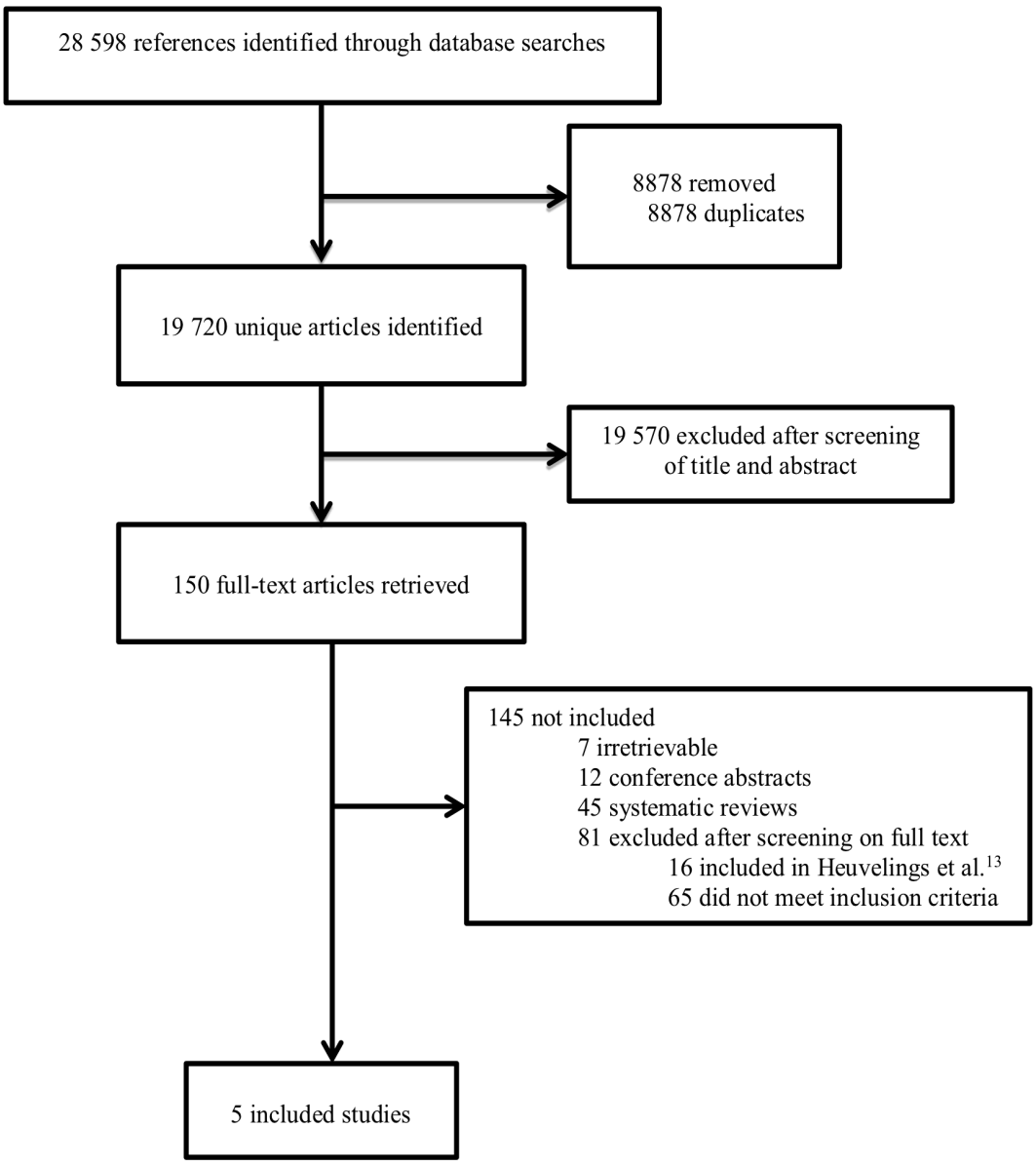
Patient and public were not involved in the design of this systematic review.

RESULTS

Of the 19,720 citations identified by the literature search five studies were included in this review (Figure 1).[11,19-22] These five studies are in addition to the six studies[23-28] included in the NICE review.[15] The results section in this paper focuses on the evidence of the five studies identified in our updated review. The evidence statements (presented in Supplementary Material IV) summarise evidence identified in terms of consistency, quality and applicability, combining evidence from the NICE review[15] and this update.

All five studies were conducted in the EU; two in the United Kingdom (UK),[19,22] one in Germany,[20] one in Portugal[11] and one in Spain.[21] Two studies focussed on homeless people,[19,20] one on homeless people and drug users,[22] one on drug users alone[11] and one on migrants.[21]

Figure 1. Study selection process



For the Organisation for Economic Co-operation and Development (OECD) countries and hard-to-reach populations discussed in the previous NICE review,[13] the study period covers 1 January 2010 to 24 February 2017
For the newly included European Union (EU)/European Economic Area/EU candidate countries, and the newly included hard-to-reach populations (people living with Human Immunodeficiency Virus (HIV) and children within vulnerable and hard-to-reach populations, the study period covers 1 January 1990 to 24 February 2017.

Four studies[5,19-21] addressed the influence of the type of healthcare worker on TB identification and TB management and one study focussed on the influence of different settings on TB identification.[22] A variety of study designs were included; one study was a prospective cluster randomised controlled trial (RCT),[19] one was an economic evaluation using a compartmental model of treated and untreated active TB cases[22], and three studies were retrospective comparison studies.[11,20,21] Study characteristics of included studies are described in Table 1. The data extraction forms by study are presented in Supplementary Material V.

None of the included studies in this review had a low risk of bias, three studies[19,21,22] had a medium risk of bias, the other two studies[5,20] were assessed as having a high risk of bias (Supplementary Material VI).
We did not perform a meta-analysis due to study heterogeneity. Results were synthesised narratively.[29]
Main outcomes for services structures and organisational models for TB identification among hard-to-reach populations, combined with the findings of the NICE review,[15] are summarised in Table 2. For full evidence statements, see Supplementary Material IV.

Three studies[19-21] compared the effect of the type of healthcare worker on TB identification. In the UK, a cluster-randomised trial found that peer educators working together with shelter staff to encourage homeless people to participate in a TB screening programme using mobile X-ray units (MXU), did not improve screening uptake compared to encouragement by shelter staff only (respectively 40%, interquartile range [IQR] 25-61 versus 45%, IQR 33-55; adjusted risk ratio [aRR] 0.98, 95% confidence interval [95% CI] 0.80 to 1.20).[19] Control sites were not 'naïve' for peer intervention which could have caused contamination of the control sites and contributed to the negative finding.

In Germany, introduction of TB education and promotion of voluntary chest X-ray (CXR) screening at least once every two years by community health workers (CHWs) improved screening uptake in homeless people and drug users. Annual screening coverage increased from 10.0% at the beginning of the study period (2002-2004) to 15.0% during the middle part of the study period (2004-2006), the last part of the study period had a 13.4% annual screening coverage (2005-2007). Screening once every two years increased screening coverage from 18.0% (2002-2004) to 26.4% (2004-2006). Coverage was 23.4% at the third and final study period (spanning 2005-2007).[20] The authors did not test for statistical significance, and denominator data (the number of homeless people and drug users in the study area) were estimated.

In Barcelona, Spain, contact tracing organised by CHWs coming from the same migrant community as the person diagnosed with TB, improved contact tracing among migrants to 66.2% (2003-2005) compared to 55.4% (2000-2002) in the period before the implementation of the intervention using CHWs (adjusted odds ratio [aOR] of an index case having their contacts screened before and after the intervention was 1.8, 95% CI 1.3 to 2.5, $p<0.001$).[21] Identification and tracing of at least one contact was taken as appropriate contact tracing, where all contacts at risk should be traced to detect and treat TB transmission early. The population characteristics varied, the age and country of origin was different between both periods. The importance of contact tracing is to identify cases early to reduce transmission, the authors did not report if any of the contacts traced had active TB.

Two studies[11,22] evaluated the effect of the type of healthcare worker and the setting on TB identification and TB management. In Portugal, improved co-operation of 'key partners' (street teams, TB clinics, drug user support centres, local public health department and local hospital) for TB identification and management in drug users was evaluated in a before-and-after study. Representatives of all 'key partners' (authors' term) worked on improving policies, clinic screening procedures and co-operation. Key partners were trained in identifying drug users in their population; and offering health promotion, notification cards, free transport to the TB clinic, free medical and substance abuse care, directly observed therapy (DOT) for active TB cases, identification of non-compliant patients and the cause of non-compliance, and tailor-made strategies to improve compliance. This resulted in an increase of TB screening uptake; from 52 drug users being screened before the intervention (2001-2003 when there was no active screening policy) to 465 drug users screened thereafter (2005-2007). Of all people misusing drugs taking-up screening, the proportion without TB symptoms increased from 41.6% to 93.5% (OR = 21.76; 95% CI 13.03 – 36.33) indicating improved TB awareness and access to screening facilities for drug users.

Table 1. Characteristics of studies applying different service models and organisational structures to improve TB identification and TB management

First Author (year) country	Population	Aims	Intervention	Comparator	Study design	Outcome measure	Quality score
TB identification (studies identified by this review)							
Jit et al. (2011)[22] United Kingdom	Homeless people and drug users	To assess the effectiveness and cost-effectiveness of the Find and Treat service for diagnosing and managing hard-to-reach individuals with active TB in London.	Period 2007-2010: Find and Treat service: - screening by MXU - peers raising awareness - treatment support	Passive case detection and standard treatment at a London TB clinic	Observational and cost-effectiveness study	Identified TB cases, treatment completion, lost to follow-up, incremental costs from healthcare taxpayer perspective	+
Duarte et al. (2011)[11] Portugal	Drug users	To evaluate the effect of an intervention with key partners (TB clinic, drug users support centres, shelters, street teams, public health department and hospital) delivering promotion of health-seeking behaviour, eliminating potential barriers for TB screening at a chest clinic and DOT, on identifying TB cases and treatment compliance.	Improved co-operation of key partners (2005-2007): - health education and screening promotion - improved screening procedures - implementation of DOT - free TB care and transport - providing medical and drug abuse treatment - active follow-up of non-compliant patients, the key partners worked together to reach the patient, identify the	Period before the intervention (2001-2003): - no active screening policy - referral to chest clinic after discharge from hospital - treatment not compulsory - information about disease and treatment given to improve compliance - psychosocial support - free TB treatment, transport and breakfast	Before-after study	Identified TB cases and treatment compliance	-

Table 1. (continued)

			cause and organise suitable treatment strategies				
Goetsch et al. (2012)[20] Germany	Homeless people and drug users	To estimate the coverage of a low-threshold CXR screening programme for pulmonary TB among illicit drug users and homeless persons.	CHWs providing TB education and promoting voluntary CXR screening 1-2x/year	Comparing the beginning of the 5 year intervention period with the end (2002-2007)	Retrospective effectiveness study	Screening coverage	-
Ospina et al. (2012)[21] Spain	Migrants	To evaluate the effectiveness of an intervention with community health workers to improve contact tracing among migrants	CHWs active follow up of cases and contacts, including visits of the cases at home, accompanying at outpatient appointments, providing counselling and information on treatments (2003-2005)	Pre-intervention period (2000-2002)	Before-after study	Number of migrants that were included in contact tracing	+
Aldridge et al. (2015)[19] United Kingdom	Homeless people	To compare TB screening uptake between current practice of encouraging homeless people by shelter staff and encouragement by shelter staff plus volunteer peer educators.	Encouragement of TB screening by peers in addition to shelter staff	Encouragement of TB screening by shelter staff only	Cluster randomised controlled trial	Screening uptake	+

Table 1. (continued)

TB identification (studies identified by the previous NICE review[15])							
El-Hamad et al. (2001)[24] Italy	Migrants	To compare the completion rates of screening procedures for TB infection among undocumented migrants at specialised TB units and non-specialised health clinics	TB screening at specialised TB clinic	TB screening at a general health service for migrants	Prospective cohort	Screening completion	+
Bothamley et al. (2002)[25] United Kingdom	Migrants and homeless people	To compare the yield and costs of TB screening in three settings: a new entrants' clinic within the port of arrival (POA) scheme; a large general practice; and centres for the homeless	TB screening at a general practice (GP)	TB screening at POA and at homeless centres	Cost analysis	Cost per person screened per case of TB prevented	-
Deruaz & Zellweger (2004)[28] Switzerland	Migrants, alcohol or drug users, homeless people and prisoners	Evaluation of first experience of the DOT programme for TB introduced in the Canton of Vaud in 1997	1. Full DOT 2. DOT delivered at TB clinic	1. Partial DOT (DOT only first 2 months of treatment) 2. DOT delivered at social outreach site	Before-after study	Adherence to treatment and outcome	-

Table 1. (continued)

Miller et al. (2006)[26] United States	Homeless people and prisoners	To evaluate and compare the efficiency of a non-state-law-mandated TB screening programme for homeless persons with a state-law-mandated TB screening programme for prisoners	Non-state-law-mandated TB screening programme for homeless persons	State-law-mandated TB screening programme for prisoners	Retrospective comparison of the cost and health impacts	TB cases averted and cost	+
Ricks (2008)[23] United States	Drug users	To compare the effectiveness of using peers versus 'standard' public health workers to coordinate TB treatment	Enhanced case management by peers	Limited case management by heath care professionals	Randomised controlled trial	Adherence to treatment	++
Mor et al. (2008)[27] Israel	Migrants	To examine the effectiveness and cost-effectiveness of pre-migration screening and post-migration screening at POA	Pre-migration screening	Post-migration screening	Retrospective cohort analysis	Active TB cases, time between migration and diagnosis, cost-savings	-

CHW = community health worker; CXR = chest X-ray; C = comparator group; DOT = direct observed treatment; GP = general practice; I = intervention group; IRIS = immune reconstitution inflammatory syndrome; IVDU = intravenous drug users; MXU = mobile X-ray unit; *n* = number of participants; QALYs = quality adjusted life years; POA = port-of-arrival; RCT = randomised controlled trial; TDM = therapeutic drug monitoring; TB = tuberculosis

Study quality: high quality [++], medium quality [+], or low quality [-]

Of all drug users with active TB, the proportion identified by screening increased from 13·4% to 61·0% (OR 10·1; 95% CI: 4.44 – 23.0). Treatment default rates decreased from 35.4% to 10.2% (OR 0·.21, 95% CI 0.08-0.54), compared to the period before the intervention (2001-2003) when TB treatment was not compulsory and compliance was stimulated by TB education and providing information on the importance of treatment completion.[11] Although the absolute number of drug users screened increased, information on the screening coverage was not available as denominator data were not provided. Another limitation is that the results were not adjusted for confounding factors, baseline characteristics might have been different as the two cohorts were recruited over different time periods and participation was voluntary which may have led to selection bias.

In the United Kingdom, the effectiveness and cost-effectiveness of the 'Find and Treat' service (raising awareness of TB screening and providing a mobile TB screening and treatment service) for homeless people and drug users was evaluated and compared to people (with a history of homelessness, imprisonment, drug abuse or mental health problems) self-presenting to a London TB clinic receiving standard TB care at the clinic.[22] The authors estimated that 22.9% of the patients detected by the 'Find and Treat' service with the longest first symptom-to-detection time would not have self-presented plus 35.4% were asymptomatic at time of detection and would not have self-presented, only part of the asymptomatic patients would self-present to a TB clinic at a later stage when symptoms would have developed. The 'Find and Treat' service had a higher treatment completion rate (67.1% versus 56.8%), and a lower lost to follow-up rate (2.1% versus 17.2%) compared to the control group receiving standard TB care at a TB clinic. The authors concluded that the 'Find and Treat' service was cost-effective, when using the threshold used by NICE of £20,000 to £30,000/QALY gained, with an incremental cost ratio of £18,000 per QALY gained for the TB screening service and £4,100 per QALY gained for the TB management service. This study has a few limitations: firstly, it is a non-randomised study, secondly the 'Find and Treat' service identifies extremely hard-to-reach populations of which some would never self-present therefore the findings could be even better in less hard-to-reach populations, and thirdly the economical evaluation is based on a compartmental model that does not take secondary transmission and drug-resistance into account.

DISCUSSION

To tackle TB and disrupt transmission in high-income, low TB incidence settings, improvement of TB care in hard-to-reach populations is of vital importance. In this updated review, five studies,[11,19-22] published between 1 January 2010 and 24 February 2017, evaluating effectiveness of services models and organisational structures supporting TB identification and management of hard-to-reach populations, were identified in addition to the six studies considering active TB[23-28] identified by the NICE review.[15] Only one study[22] evaluated cost-effectiveness. Although the evidence from two reviews is limited, it highlights those interventions that are likely to be effective and those that have no clear evidence of being effective (Table 2). For development of the ECDC guidance document,[14] a scientific panel compiled by ECDC carefully considered these findings. Their main suggestions for action were to involve CHWs or peers to improve TB screening uptake and TB treatment completion among homeless people[20] and drug users;[5,20,23] to use outreach teams to improve TB screening uptake and TB treatment completion among vulnerable populations;[22] and to strengthen relationships and good collaboration between health care workers, peers, communities, and patients to improve treatment outcome among vulnerable populations.[5,20,22,23] The updated systematic review provided evidence for all suggestions except for using peers to improve screening uptake. This is in contrast to an American study[23] included in the original NICE review,[15] which showed that peers improved contact tracing and treatment adherence among drug users.

Table 2. Effectiveness of service models and organisational structures interventions to improve TB identification and TB management

Population	Intervention (I)	Comparator (C)	Studies (first author, year, country)	No. of participants		Comparison	Outcome	Risk of Bias
				I	C			
Homeless people and Drug users	Health/TB education and promotion of screening by street teams, drug users support centres, shelters and CHWs	Beginning of the intervention when CHWs were just introduced	Goetsch et al. 2012 (Germany)[20]	465	125	Retrospective comparison over intervention period	Improved annual TB screening uptake among homeless people and drug users (from 10.0% to 15.0% at the peak).[20] The percentage of all drug users with active TB identified by screening increased from 13.4% to 61.0% (OR 10.1 [95%CI 4·44-23·0]).[11]	High[2]
		No active screening policy	Duarte et al. 2011 (Portugal)[11]			Retrospective before-after comparison		High[3]
Homeless people	TB education and promotion of screening by peers and shelter staff	TB education and promotion of screening by shelter staff only	Aldridge et al. 2015 (United Kingdom)[19]	1150	1192	Comparing randomised intervention cluster with comparator cluster	No difference in screening uptake (I = 40% [IQR 25-61] versus C = 45% [IQR 33-55], aRR= 0.98 [95%CI 0.80-1.20]).	Medium[4]
Migrants	Pre-migration screening	Post-migration screening at POA	Mor et al. 2008, cited in the NICE review (Israel)[27]	162	105	Retrospective Intervention versus comparator comparison	Reduced the risk of developing TB in the new country and was cost-effective (0.28% of the pre-migration versus 0.32% of the post-migration screening migrants developed TB; RR 0.82 p<0.01)). The detection period was shorter as well (193 days versus 487 days between entry and diagnosis; OR=0.72 [95%CI 0.59-0.89] p=0.002).	High[8]

Table 2. (continued)

Prisoners and homeless people	TB screening in a prison	TB screening at a homeless centre	Miller et al. 2006, cited in the NICE review (United States)[26]	22920	822	Retrospective comparison of two cohorts	No difference in screening uptake (94.7% in prison versus 95% in homeless centre p=0.179) but higher proportion of active TB cases were identified at the homeless centre (1.2% versus 0.03% at a prison setting, p<0.001)	Medium[9]
Homeless people and migrants	Active case finding by symptom-based questionnaire at homeless centres	Active case finding by symptom-based questionnaire at POA	Bothamley et al. 2002, cited in the NICE review (United Kingdom)[25]	262	199	Cost analysis	Active case finding at POA was most cost-effective (costs per person screened for every case prevented at POA £10.00, at homeless centre £23.00).	High[10]
Migrants	Active case finding at a specialised TB clinic using 2 visits	Active case finding at a general primary care clinic, with referral for CXR, using 3 visits	El-Hamad et al. 2001, cited in the NICE review (Italy)[24]	749	483	Prospective intervention versus comparator comparison	Improved screening completion among migrants (85.6% in TB clinic versus 71.4% at primary care clinic, p = not reported; OR=2.57 [95%CI 1.92-3.42]).	Medium[5]
Drug users	Contact tracing by peers or CHWs from the same migrant community	Peers versus other health care workers	Ricks 2008, cited in the NICE review (United States)[23]	48	46	RCT	Improved contact tracing among drug users (75% by peers versus 47% by healthcare workers, p = 0.03)[23] and migrants (from 55.4% without CHWs to 66.2% with CHWs; aOR 1.8 [95%CI 1.3-2.5] *p*<0·001).[21]	Low
Migrants		Normal practice before introducing CHWs	Ospina et al. 2012 (Spain)[21]	388	572	Before-after comparison		Medium[1]

Table 2. (continued)

Drug users and homeless people	Mobile TB screening and treatment service at convenient location in the community	Passive case detection and management at a TB clinic	Jit et al. 2011 (United Kingdom)[22]	48	252	Prospective intervention versus comparator comparison plus economic evaluation	Improved TB identification among homeless people and drug users; particularly in asymptomatic patients (35.4% extra identified) and those that delay seeking health care (22.2% extra identified). Higher treatment completion rate (67.1% versus 56.8%) and lower lost to follow-up rate (2.1% versus 17.2%). Both parts of the service are cost-effective (screening = £18,000/QALY gained, treatment is £4,100/QALY gained)	Medium[6]
Drug users	Enhanced case management by peers	Limited case management by regular health care workers	Ricks 2008, cited in the NICE review (United States)[23]	48	46	RCT	Improved treatment completion in drug users (85% by peers versus 61% by health care workers, RR=2.68 [95%CI 1.24-5.82] p=0.01).	Low
Drug users	DOT and active follow-up of non-compliant patients by 'key partners'	Non-compulsory TB treatment and education about TB disease and treatment to improve compliance	Duarte et al. 2011 (Portugal)[11]	465	125	Retrospective before-after comparison	Reduced treatment default rates (from 35.4% to 10.2%; OR 0.21 [95%CI 0.08-0.54]).	High[2]

Table 2. (continued)

Migrants, drug users, homeless people and prisoners	DOT at a convenient location in the community	DOT at a health clinic	Deruaz & Zellweger 2004, cited in the NICE review (Switzerland) [28]	36	18	Retrospective before-after comparison	No significant difference in successful treatment outcome, treatment completion and cure rate (85.2% at convenient location versus 92.6% at health clinic, p=0.67)	High[7]

aOR = adjusted odds ratio, aRR = adjusted risk ratio, C = comparator group, CHWs = community health workers, DOT = directly observed treatment, I = intervention group, IQR = interquartile range, OR = odds ratio, POA = port-of-arrival, RCT = randomised controlled trial, TB = tuberculosis, 95%CI = 95% confidence interval

Footnotes Risk of Bias:

[1] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). Contact tracing of only one contact was enough to be called contact tracing, and the ultimate aim of contact tracing (increase cased detection and reduce transmission) was not analysed in this study.

[2] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). Denominator not given therefore unable to calculate screening coverage.

[3] = Risk of selection bias as participation was voluntary. Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). No statistical test used to show statistical significance of the findings, an estimated number was used for the denominator.

[4] = Most comparator sites were not naïve for peer intervention, no individual information of the participants was collected, the characteristics between the two groups might have been significantly different.

[5] = Not adjusted for difference in baseline characteristics.

[6] = Study was designed to evaluate the cost-effectiveness, no statistical test used to evaluate statistical significant findings. The 'Find and Treat' service identifies extremely hard-to-reach populations that would never self-present, the findings would underestimate the benefit of the service. The economical evaluation is based on a compartmental model that does not take secondary transmission and drug-resistance into account.

[7] = Risk of bias due to difference in collecting treatment adherence outcome at the health clinic a nurse recorded treatment adherence at time of visit, in the social outreach group a health care worker was interviewed up to 6 months after treatment completion and was asked about the treatment adherence, risk of recall bias. Not recorded how many people per setting received 6 months of DOT (full DOT) and how many received 2 months of DOT and 4 months of self-treatment (partial DOT), what was another intervention in this study. Allocation to setting was based on needs of participants what might have caused bias.

[8] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods), pre-migration group had a shorter follow-up period than post-migration group what may have influenced the detection of number of TB cases in the pre-migration group.

[9] = Unclear if the differences in outcome was caused by the setting or by the different methods or to differences in TB prevalence in the different populations.

[10] = TB prevalence might be different in the different populations as the costs are calculated per active case detected this is a major issue, there were only 3 active TB cases detected, all in the POA group. The economic perspective used was not reported and the costs of identification were not discounted.

Strengths and limitations

PRISMA and Cochrane Collaboration reporting guidelines for systematic reviews were followed. Established screening protocols were used, including double screening, and the search was highly sensitive. The methodology from the previous NICE review[15] was followed, in order to connect this update and, so, describe the full body of relevant evidence. High quality evidence is lacking. Only one[23] study from the NICE review[15] was considered to be of high quality, all other studies had some risk of bias (five medium risk[19,21,22,24,26] and five high risk[11,20,25,27,28]). Therefore, only limited conclusions can be drawn. Most studies lacked identification and adjustment for confounding factors and the use of appropriate analytical methods. In addition, many studies were biased, particularly with regard to potential selection bias. A meta-analysis could not be performed, because of heterogeneity across the studies. Gaps in evidence exist; no studies focussing on children within vulnerable and hard-to-reach populations, or on people living with HIV or sex workers were identified. Only three studies provided economic data; one study identified by this review,[22] and two[25,27] by the NICE review.[15]

Our search focussed on publications in databases Embase and MEDLINE. Many European countries have strong organisational structures for TB identification and management, but these countries did not publish their data on these organisational structures in journals, which may have caused a publication bias. Comparing findings of the NICE review[15] with this review comes with some limitations. For the NICE review only 10% of the citations were double screened,[15] compared to 100% for this updated review, therefore studies conducted between 1990-2010 might have been missed. The NICE review focussed their recommendations on the population in the United Kingdom,[15] and this review focussed on populations in high-income, low TB incidence countries. Further methodology was identical.

The evidence identified by this review and the previous NICE review[15] along with evidence presented in a review series covering the barriers and facilitators of seeking TB care,[6] and the effectiveness of interventions for TB identification and management in hard-to-reach populations,[13] was used to develop the ECDC guidance on improving TB identification and management among hard-to-reach and vulnerable populations in Europe.[14] ECDC recommended that implementation of the interventions is context-specific; it depends on the setting, target population, resources available and health-care systems in place. Interventions focussing on one specific hard-to-reach population might not work in another hard-to-reach population, therefore, the interventions have to be adapted and re-assessed per target population.[14] Given the scope of this review, considering settings across Europe, findings presented here are potentially relevant to any low-incidence region, and are relevant to other institutions/governmental organisations seeking to improve service structures for TB identification and management among hard-to-reach populations.

Characteristics of different hard-to-reach populations and their TB epidemiology vary per country and setting. Challenges in identification and management of TB should be identified and targeted, tailored to the specific setting and hard-to-reach population. These TB interventions could be integrated within broader programmes targeting specific populations. A follow-up systematic review should include information from national public health services about their organisational structures for TB identification and management. National public health services are urged to regularly analyse their organisational structures for TB identification and management and publish this data.

Efforts to improve quality of research on service models and organisational structures should be made, even though it is often challenging to perform 'clean', unbiased, and un-confounded trials in hard-to-reach populations, as attrition rates are often high, and confounding factors are plentiful. This includes conducting (cluster) randomised controlled trials and before-and-after studies where appropriate, recruiting an adequate number of participants, using relevant control groups, and minimising selection bias. Standardised case definitions for hard-to-reach populations should be created. Feasibility, effectiveness, cost-effectiveness and impact of interventions should be evaluated. Mathematical economic models can be used to evaluate costs.[14]

CONCLUSIONS

Identification and management of TB in hard-to-reach populations is suboptimal.[2] Therefore, service models and organisational structures to identify and manage TB in hard-to-reach populations should be improved and evaluated regularly.

Our systematic review, in conjunction with the original NICE review[15] provides limited evidence, due to the lack of high quality studies, that interventions such as using peers and CHWs; mobile TB services, specialised TB clinics, screening, or active case finding in non-healthcare settings, as well as improved co-operation between key services can help to improve TB identification and management.

Further research should be undertaken to evaluate other effective and cost-effective ways to identify and manage TB in hard-to-reach populations and countries with good TB control systems are urged to evaluate their system and publish the data.

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part II

CHEST ULTRASOUND FOR PULMONARY TUBERCULOSIS AND OTHER RESPIRATORY DISEASES


5

chapter 5

CHEST ULTRASOUND FOR THE DIAGNOSIS OF PAEDIATRIC PULMONARY DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF DIAGNOSTIC TEST ACCURACY

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ABSTRACT

Background

Chest ultrasound is an emerging imaging modality, for several paediatric pulmonary diseases.

Sources of data

MEDLINE and EMBASE (1946-1947 to 10 March 2017) were searched to collect evidence on the diagnostic accuracy of chest ultrasound, compared to other imaging modalities, for the diagnosis of paediatric pulmonary diseases.

Areas of agreement

Eighteen pneumonia studies, comprising 2,031 children, were included for meta-analysis; the summary estimate sensitivity was 95.0% (95%CI: 90.7%-97.3%) and specificity was 96.1% (95%CI: 89.1%-98.7%).

Areas of controversy

Other pulmonary diseases also yielded high sensitivities and specificities, but a meta-analysis could not be conducted due to a limited number of studies includable, and their heterogeneity.

Growing points

Chest ultrasound should be considered as a first line imaging modality for children with suspected pneumonia.

Areas timely for developing research

Further research should focus on the diagnostic accuracy of chest ultrasound for the diagnosis of paediatric pulmonary diseases, other than pneumonia, comparing against a valid gold standard.

BACKGROUND

Lower respiratory tract infection is a leading infectious cause of morbidity and mortality in the world, particularly in children younger than 5 years (1 billion episodes per year and 703,918 deaths [104.8 deaths per 100,000 children under 5 years]),[1] while other pulmonary diseases are amongst the most common health problems for which acute care is sought for children.[2,3] Accurate diagnosis is important to implement effective treatment. Conventional imaging for the diagnosis of pulmonary disease in children relies largely on chest X-ray (CXR), which exposes children to harmful ionizing radiation.[4] Chest computed tomography (CT) and chest magnetic resonance imaging (MRI) have the potential to delineate more detailed abnormalities, but require radiologic infrastructure and expertise and are therefore more expensive; also CT is associated with higher exposure to ionizing radiation, and MRI requires sedation of young children.

Chest ultrasound is an attractive alternative as it is devoid of ionizing radiation, is quick to perform and easily repeatable, and can be performed and interpreted by non-radiologists. Improved technology has made ultrasound machines smaller and portable, making bedside ultrasound and point-of-care testing feasible. In addition, ultrasound is cheaper and more readily at hand than CT and MRI, especially in resource-limited settings. Chest ultrasound was first used in 1986 to diagnose pneumonia in children, by demonstrating air bronchograms within areas of consolidation.[5] In the past decade there have been increasing numbers of studies of chest ultrasound for the diagnosis of paediatric pulmonary diseases.

Recent systematic reviews found high diagnostic accuracy of chest ultrasound for the diagnosis of pneumonia,[6,7] concluding that it is a useful imaging alternative to CXR for the diagnosis of childhood pneumonia.[7] Could chest ultrasound also be used for other paediatric pulmonary diseases, like pleural effusion, respiratory distress syndrome (RDS), pneumothorax, atelectasis and bronchitis for example? Chest ultrasound is not the standard imaging technique for those diseases. The aim of this systematic review and meta-analysis was to evaluate the diagnostic accuracy of chest ultrasound for the diagnosis of paediatric pulmonary diseases, including pneumonia.

METHODS

This systematic review and meta-analysis was conducted following the PRISMA-DTA guidelines (personal communication M. Leeflang, 10th of October 2017, http://www.prisma-statement.org/Extensions/DTA.aspx). The protocol was registered in the international prospective register for systematic reviews, PROSPERO (*CRD42016033321*).

Eligibility criteria

Studies evaluating the diagnostic accuracy of chest ultrasound for the diagnosis of pulmonary diseases (for example, but not exclusively pneumonia, pleural effusion, pneumothorax, bronchiolitis, or pulmonary tuberculosis) in children up to the age of 18 years were included in this systematic review and meta-analysis. Studies using other imaging modalities like CXR, CT or MRI or clinical diagnosis as a reference standard were included. Studies that used clinical diagnosis as a reference standard had to compare chest ultrasound with another imaging modality to be considered for inclusion. Echocardiography, prenatal ultrasound, intra-operative chest ultrasound and chest ultrasound conducted for underlying diseases other than pulmonary diseases were excluded. Randomized controlled trials, clinical controlled trials, case-control studies and observational cohort studies were included, systematic reviews were used for reference searching, case reports were excluded from this review.

Search strategy and selection criteria

An experienced information specialist (RS) developed and conducted the search strategy with input from the clinical reviewers (CH, SB). We searched MEDLINE (Ovid, 1946 to present) and EMBASE (Ovid, 1947 to present) on March 10th 2017 (see Supplementary Material 1 for details of the sources searched and the search strategies used). We checked reference lists of relevant systematic reviews and included studies for additional relevant citations. No date or language restrictions were applied. In summary, the search terms covered the population (children

under the age of 18 years), the intervention (chest ultrasound) and pulmonary diseases (including pneumonia, bronchitis, pulmonary effusion, pneumothorax, pulmonary tuberculosis). Only studies reporting the sensitivity and specificity as an outcome, or studies providing enough information to calculate the sensitivity and specificity were included. Authors of abstracts which had not been published as full text articles were contacted to verify if the full text will be published and if accepted by a journal we asked for access to their preliminary full text articles to included them in the study.

Study selection and data management

Deduplicated citations were uploaded in a database (Rayyan),[8] two reviewers (CH and SB) screened titles and abstracts to exclude citations beyond the scope of this review. The first 5% of the identified citations were used for pilot-testing and refining of the in- and exclusion criteria. The full text of potentially relevant citations was retrieved to assess eligibility. Double-screening for inclusion was conducted by CH and SB; disagreement was resolved by discussion. Agreement after title and abstract screening was 98.6% with a good inter-rater reliability (Cohen's kappa, $\kappa = 0.93$).

Data collection

Per included citations title, author, journal, year of publication, research question, population size, mean age, gender proportion, study setting, details of index test (chest ultrasound) and reference test (CXR, CT or MRI), sonographer, study methodology, recruitment methods, outcomes, true positives, false positives, true negatives, false negatives, sensitivity, specificity, study conclusion, bias assessment by study authors, bias assessment by review authors, source of funding, and conflict of interest were extracted. For two of the included citations, the data extraction forms were pilot-tested by two reviewers (CH and SB). For the remaining citations, data extraction was conducted by one reviewer (CH) and checked by a second reviewer (SB); disagreement was resolved by discussion. Study authors were contacted by email for any missing or confusing data.[9-15] Complete data extraction forms can be found in Supplementary Material 2.

Quality assessment

The risk of bias and methodological quality was assessed by two reviewers (CH and SB) independently by using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) assessment tool.[16] This tool was pilot-tested on two of the included citations; for the remaining citations, the risk of bias/quality assessments was performed by one reviewer (CH) and checked by a second reviewer (SB). Disagreement was resolved by discussion.

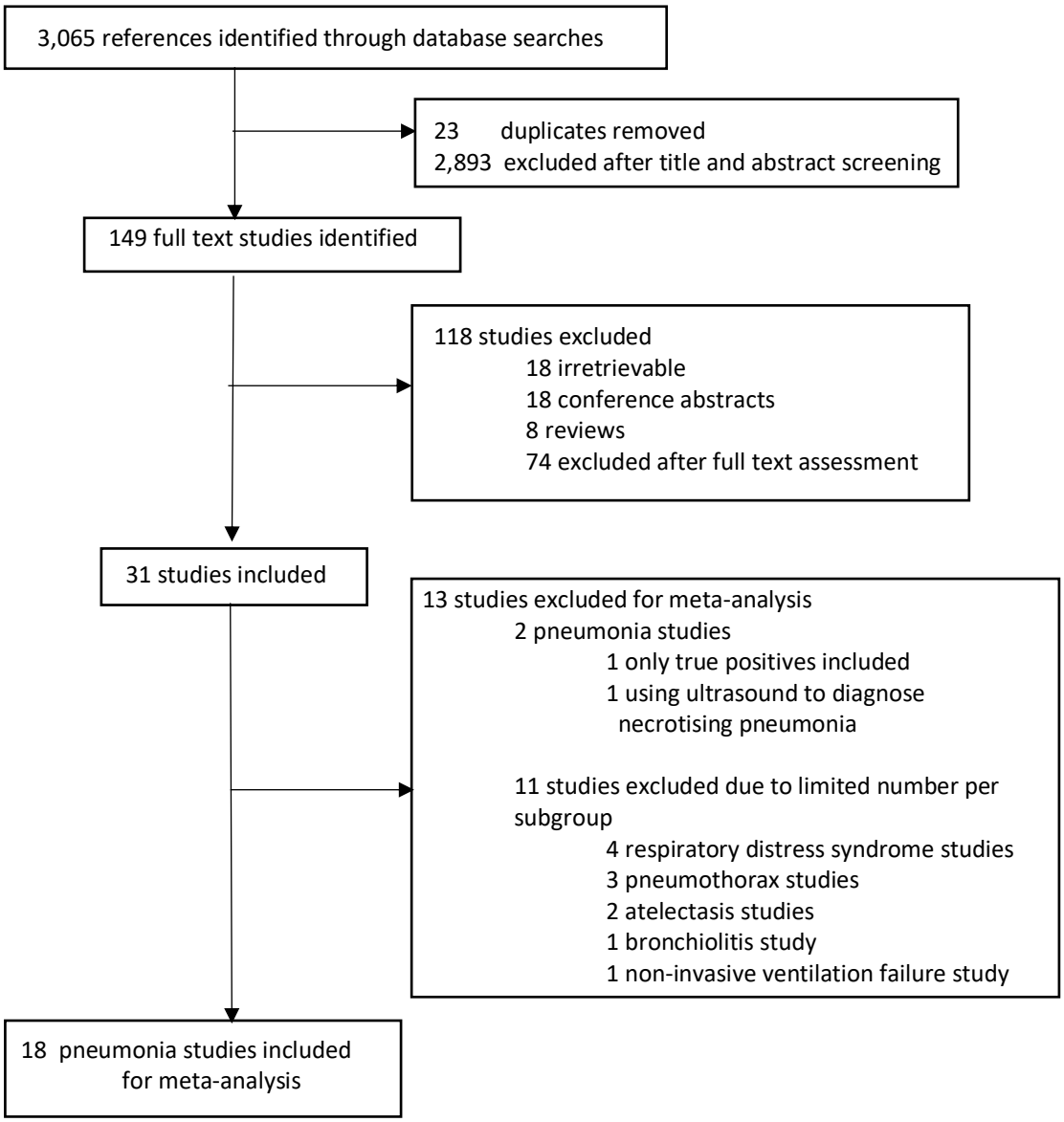
Data analysis

The studies were categorized per diseases, the summary estimate of sensitivity and specificity with corresponding 95% confidence intervals (95%CI) and the positive and negative likelihood ratios (LR) were calculated for every disease. The bivariate model and the hierarchical summary receiver operating characteristic (HSROC) model were used. Forest plots as well as HSROC curves were created. We performed a subgroup analysis to explore the influence of operator experience and age of the children on the accuracy of chest ultrasound. Data analysis was conducted using STATA 14.2 (StataCorp; 2015, TX, US) and R 3.4.1 (the R Foundation for Statistical Computing; 2016, Vienna, Austria).

RESULTS

We screened 3,042 unique citations, of which 2,893 citations were excluded after title and abstract screening, as they did not fulfil the inclusion criteria (see Supplementary Material 3 for protocol including inclusion criteria). Of the remaining 149 citations, 74 citations were excluded after full text assessment as they did not meet the inclusion criteria. Full text was irretrievable for 18 citations, 18 citations were conference abstracts and eight citations were reviews. We included 31 studies[9-15,17-40] in this systematic review (Figure 1).

Figure 1. Flow chart literature search



Of the 31 included studies, 20 reported on pneumonia,[9-12,17-32] four RDS[13,33-35] of which one study also reported on transient tachypnoea of the newborn,[34] three on pneumothorax,[36-38] two on atelectasis,[14,39] one on bronchiolitis,[40] and one on non-invasive ventilation failure.[15] The study characteristics of each study are presented in Table 1. Nine studies were conducted in neonates.[13,15,28,33-37,39] The remaining studies were conducted in the general paediatric population.[9-12,14,17-27,29-32,38,40] Ten studies were conducted in an intensive care unit (ICU),[13,15,25,28,33-37,39] of which nine were in a neonatal ICU (NICU) [13,15,28,33-37,39] and one in a paediatric ICU (PICU),[25] eight studies in a paediatric ward,[11,22-24,26,27,31,40] eight studies in a (paediatric) emergency department[9,10,12,19-21,29,32] and five studies in a radiology department.[14,17,18,30,38] The majority of the studies were conducted in high-income countries (23 studies),[9-12,15,17,20-27,29-32,34,36-38,40] eight studies in middle-income countries,[13,14,18,19,28,33,35,39] none of the included studies were conducted in low-income countries. Across all studies there were 2,796 children included; of which 2,073 were in the pneumonia studies, 369 in the RDS studies, 154 in the pneumothorax studies, 95 in the atelectasis studies, 54 in the non-invasive ventilation failure study and 51 in the bronchiolitis study. The majority of the included children were male (54.5%), with a mean age of 3.0 years (range 0 - 17 years).

A linear probe, varying from 5-12 MHz, was used to perform chest ultrasound in all studies but two,[23,31] which only used a convex probe. Eleven studies used a linear and convex (2-9 MHz) probe to scan their patients.[9-12,17,18,20,25,30,32,33,38] In 11 studies, a radiologist performed the chest ultrasound,[9,10,12-15,17,18,28,33,35] in one study experienced ultrasound technologists scanned the chest,[30] and in 18 studies clinicians performed the chest ultrasound,[11,17,19-27,29,31,34,36,37,39,40] of which five studies reported that the clinician had minimal ultrasound experience (one hour to three days ultrasound training).[20-22,25,29] In all studies, but three,[15,23,30] the same doctor performed and analysed the chest ultrasound. In the study using ultrasound technicians as the sonographer the chest ultrasound was evaluated by a paediatric radiologist or a radiology resident.[30] In one retrospective study it was unclear who analysed the chest ultrasound,[23] and in one study it was unclear who performed the chest ultrasound but the images were analysed by an experienced radiologist.[15]

In the majority of the studies (n=23) patients were scanned in a sitting or supine position, obtaining images of the anterior, posterior, and mid-axillary chest from the apex down to the diaphragm, using an intercostal approach in transverse and longitudinal planes,[9-13,17,19-32,38-40] similar to the method earlier described by Copetti and Cattarossi.[32] Four studies scanned only the anterior and lateral chest, with the patient in a supine or lateral decubitus position.[15,18,34,38] Three studies used the transabdominal approach in addition to the transthoracic approach (Table 2).[15,33,35]

Fourteen studies used CXR as a reference standard,[11-13,15,17,20-22,25,29,31,33,35,37-39] in twelve studies the CXR was interpreted by a radiologist, in two studies the person reviewing the CXR images was not reported.[13,31] In two studies, chest CT was used to confirm the CXR diagnosis in some patients;[38,39] two further studies used chest CT as a reference standard[18,30] and one study used MRI as a reference standard,[14] in all these studies the reference standard was analysed by a radiologist. Eleven studies used the clinical diagnosis as the reference standard, of which seven studies included CXR to arrive at a diagnosis;[9,19,24,26,27,32,34] the four remaining studies compared the accuracy of chest ultrasound with the accuracy of CXR to the clinical diagnosis.[10,23,28,40] The clinical diagnosis was made by a clinician,[19] pediatrician,[9,23,24,26,27,32,40] neonatologist[28,34] or pulmonologist,[26]; one study did not record who made the clinical diagnosis.[10] One study used the detection of a pneumothorax by aspiration as a reference standard.[36]

In all studies but three,[28,35,39] the sonographer was blinded to the findings of the other imaging modality/reference standard (Table 2).

The quality of most of the included studies was high but the risk of bias for patient selection was high in ten studies,[10,13,15,23-25,28,29,31,39] unclear in 11 studies,[18,19,27,30,32-36,38,40] and only ten studies[9,11,12,14,17,20-22,26,37] had a low risk of bias for patient selection (Supplementary Material 4).

The true positive, false positive, false negative, and true negative rate, as well as sensitivity and specificity of each individual study are presented in Table 1.

Two pneumonia studies were excluded for meta-analysis, one study reported on the sensitivity for the detection of necrotizing pneumonia[31] and for one study it was difficult to calculate the diagnostic accuracy as only patients with a positive reference test were included.[30] Eighteen pneumonia studies were included for meta-analysis;[9-12,17-29,32] comprising 2,031 children with a mean age of 4.0 years (range 0-16 years). The summary estimate of sensitivity was 95.0% (95%CI: 90.7%-97.3%), and the summary specificity was 96.1% (95%CI: 89.1%-98.7%) for chest ultrasound. The positive LR was 24.41 (95%CI 8.39-71.02) and the negative LR was 0.05 (95%CI 0.03 – 0.10) (see Figure 2a for a Forest plot of the pneumonia studies and Figure 2b for the HSROC curve).
Due to the limited number of studies for other pulmonary diseases, a meta-analysis was not considered useful for RDS (four studies), pneumothorax (three studies), atelectasis (two studies); and not possible for bronchiolitis (one study) and non-invasive ventilation failure (one study).

Table 1. Characteristics and diagnostic accuracy per included study

Disease	First author (Year)	Country	Study design	Setting	Sample size	%Male	Mean age (years [gestational age])	TP	FP	FN	TN	Sensitivity	Specificity
Pneumonia	Claes (2017)[15]	Belgium	Prospective	Radiology department	143	54	3.4	44	8	1	90	97.8	91.8
	Saraya (2017)[16]	Egypt	Prospective	Radiology department	56	48	2.3	26	1	10	19	72.2	95.0
	Yilmaz (2017)[17]	Turkey	Prospective	Emergency department	160	55	3.3	142	0	7	0	95.3	.
	Boursiani (2016)[7]	Greece	Prospective	Emergency department	69	39	4.5	62	0	4	3	93.9	100
	Guerra (2016)[18]	Italy	Prospective	Emergency department	222	49	4.8	190	17	7	6	96.4	26.1
	Ianniello (2016)[8]	Italy	Retrospective	Emergency department	84	52	6	60	0	1	23	98.4	100
	Samson (2016)[19]	Spain	Prospective	Emergency department	200	58	2.5	74	6	11	109	87.1	94.8
	Zhan (2016)[20]	Denmark	Prospective	Pediatric ward	82	57	1.5	33	7	49	75	40.2	91.5
	Ho (2016)[21]	Taiwan	Retrospective	Pediatric ward	163	56	7.8	159	0	4	0	97.5	.
	Iorio (2015)[22]	Italy	Retrospective	Pediatric ward	52	52	3.5	28	1	1	22	96.5	95.6
	Urbankowska (2015)[9]	Poland	Prospective	Pediatric ward	106	63	4.6	71	0	5	30	93.4	100
	Esposito (2014)[23]	Italy	Prospective	PICU	103	54	5.6	47	3	1	52	97.9	94.5

Table 1. (continued)

Disease	First author (Year)	Country	Study design	Setting	Sample size	%Male	Mean age (years [gestational age])	TP	FP	FN	TN	Sensitivity	Specificity
Pneumonia	Reali (2014)[24]	Italy	Prospective	Pediatric ward	107	56	4	76	1	5	25	93.8	96.2
	Caiulo (2013)[25]	Italy	Prospective	Pediatric ward	102	52	5	88	0	1	13	98.9	100
	Seif El Dien (2013)[26]	Egypt	Prospective	NICU	75	48	0 [37.0]	68	0	5	2	93.2	100
	Shah (2013)[27]	USA	Prospective	Emergency department	200	61	2.9	31	18	5	146	86.1	89.0
	Iuri (2009)[10]	Italy	Prospective	Emergency department	28	61	4.5	22	0	2	8	91.7	100
	Kurian (2009)[28]	USA	Retrospective	Radiology department	19	47	5.4	18	0	0	0	100	.
	Chiu (2008)[29]	Taiwan	Retrospective	Pediatric ward	23	NR	3.5	8	0	15	14	35.0	100
	Copetti (2008)[30]	Italy	Prospective	Emergency department	79	47	5.1	60	0	0	19	100	100
RDS	El-Malah (2015)[31]	Egypt	Prospective	NICU	100	66	0 [37.9]	88	8	2	2	98.0	25.0
	Sawires (2015)[11]	Egypt	Prospective	NICU	90	40	0 [29.9]	90	19	0	21	100	52.5
	Vergine (2015)[32]	Italy	Prospective	NICU	59	61	0 [33.0]	22	2	1	34	95.6	94.4

Table 1. (continued)

Disease	First author (Year)	Country	Study design	Setting	Sample size	%Male	Mean age (years [gestational age])	TP	FP	FN	TN	Sensitivity	Specificity
	Lovrenski (2012)[33]	Serbia	Prospective	NICU	120	NR	0 [31.0]	43	0	2	2	95.6	100
Pneumothorax	Cattarossi (2016)[34]	Italy	Prospective	NICU	49	67	0 [36.0]	23	0	0	26	100	100
	Raimondi (2016)[35]	Italy, Spain, France	Prospective	NICU	42	NR	0 [31.0]	26	0	0	16	100	100
	Kosiak (2016)[36]	Poland	Prospective	Radiology department	63	60	7.8	4	0	0	59	100	100
Atelectasis	Liu (2015)[37]	China	Prospective	NICU and neonatology ward	80	53	0 [NR]	60	0	20	0	75.0	0
	Acosta (2014)[12]	Argentina	Prospective	Radiology department	15	60	4.5	39	15	4	122	90.7	89.1
Bronchiolitis	Caiulo (2011)[38]	Italy	Prospective	Pediatric ward	52	54	0.2	47	0	5	52	90.4	100
NVF	Raimondi (2014)[13]	Italy	Prospective	NICU	54	NR	0 [NR]	18	0	0	36	100	100

Table 2. Chest ultrasound technique, sonographer, reference test, blinding and funding per included study

Disease	First author (Year)	Probe	Technique	Operator experience	Reference test	Reference test reader	Blinding	Funding source
Pneumonia	Claes (2017)[15]	Linear (5-12 MHz) ± convex (4-9 MHz) probe	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in supine and/or prone or sitting position.	3 paediatric radiologists + 1 final year radiology intern	CXR	Pediatric radiologist	Yes	NR
	Saraya (2017)[16]	Linear (6–12 MHz) and convex (2–5 MHz) probe	Anterior and lateral chest was scanned in longitudinal and oblique planes with the patient in supine and lateral decubitus position.	Radiologist	CT chest	Radiologist	Yes	NR
	Yilmaz (2017)[17]	Linear probe (6–13 MHz)	Anterior, lateral and posterior chest was scanned obtaining oblique and parallel views, with the patient in the supine and lateral decubitus position.	Experienced paediatric emergency physician	Clinical diagnosis including CXR	Clinician	Yes	None
	Boursiani (2016)[7]	Linear (5–12 MHz), convex (3-5 MHz) and micro-convex (5–8 MHz) probe	Along the parasternal, mid-clavicular, axillary, paravertebral and axial lines, longitudinal and intercostal scans were obtained with the patient in the sitting and/or supine position.	Experienced paediatric radiologist	Clinical diagnosis including CXR	Paediatrician	Yes	NR

Table 2. (continued)

	Guerra (2016)[18]	Linear (7.5–10-MHz) and convex (3.5–5-MHz) probe	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in supine and/or prone or sitting position. The costophrenic angles and the areas adjacent to lung consolidation were checked for effusion.	3 paediatricians with minimal ultrasound experience	CXR	Radiologist	Yes	None
	Ianniello (2016)[8]	Linear (7.5–10 MHz) and convex (4 MHz) probe	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in supine position.	Radiologist	Clinical diagnosis	NR	Blinded to CXR, aware of clinical data	NR
	Samson (2016)[19]	Linear probe (6–15 MHz)	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in supine and/or sitting position.	7 paediatricians and 5 paediatric residents with varying ultrasound experience	CXR	Radiologist	Yes	NR
	Zhan (2016)[20]	Two linear probes (5-10 MHz and 5-13 MHz)	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in supine and/or sitting position.	A paediatric resident with minimal ultrasound experience	CXR	Pediatric radiologist	Yes	Ultrasound by GE Healthcare
	Ho (2016)[21]	Convex probe (5 MHz)	The anterior, lateral and posterior chest was scanned; oblique and parallel views were obtained with the patient in supine or lateral decubitus position.	Experienced paediatric pulmonologists	Clinical diagnosis	Paediatrician	Unclear	Kaohsiung Medical University Hospital

Table 2. (continued)

Iorio (2015)[22]	Linear probe (5–10 MHz)	Anterior, lateral and posterior chest was scanned with the patient in the supine and sitting position.	A paediatrician with ultrasound experience	Clinical diagnosis including CXR	Paediatrician	Yes	None
Urbankowska (2015)[9]	Linear (5-9 MHz) and convex (3-7 MHz) probe	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in supine position.	Pediatric sonographer	CXR	Radiologist	Blinded to CXR, aware of clinical data	NR
Esposito (2014)[23]	Linear (7.5-12 MHz) and convex (2.5-6.6 MHz) probe	The anterior, lateral and posterior chest was scanned with the patient in a supine or sitting and/or lateral decubitus position.	Pediatric resident with limited ultrasound experience	CXR	Radiologist	Yes	NR
Reali (2014)[24]	Linear probe (7.5–10 MHz)	The chest was scanned down the parasternal, mid-clavicular, anterior, mid-axillary, paravertebral, scapular and posterior-axillary lines, longitudinal and transverses views were obtained with the patient in the supine or sitting position.	Pulmonologist and 2 residents	Clinical diagnosis and CXR	Pulmonologist and paediatrician	Blinded to CXR, aware of clinical data	NR
Caiulo (2013)[25]	Linear probe (6-12 MHz)	The chest was scanned down the parasternal, mid-clavicular, anterior axillary, mid-axillary, paravertebral, scapular and posterior-axillary lines, longitudinal and transverse planes.	A paediatrician with ultrasound experience	Clinical diagnosis including CXR	Paediatrician	Blinded to CXR, aware of clinical data	NR

Table 2. (continued)

	Seif El Dien (2013)[26]	Linear probe (7 MHz)	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in supine and lateral decubitus position.	Radiologist	Clinical diagnosis	Neonatologist	No	NR
	Shah (2013)[27]	Linear probe (7.5-10 MHz)	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in lateral decubitus and sitting position.	15 paediatric emergency physicians with varying ultrasound experience	CXR	Pediatric radiologist	Yes	NR
	Iuri (2009)[10]	Linear (5–12 MHz) and convex (2–5 MHz) probe	The anterior and posterior chest was scanned along the clavicular, parasternal and axillary lines with the patient in sitting position. Longitudinal and axial (intercostal) scans were acquired.	Radiologist	CXR	Radiologist	Yes	NR
	Kurian (2009)[28]	Linear (5–12 MHz), convex (2–5, 4–9, or 5–8 MHz), and vector (5–8 MHz) probe	Anterior, posterior, and mid-axillary chest was scanned in transverse and longitudinal planes with the patient in a supine or decubitus position.	2 experienced ultrasound technologists performed US, radiologist reviewed US	CT chest	Pediatric radiologist	Yes	NR
	Chiu (2008)[29]	Convex probe (5.0 MHz)	Patients were scanned in a supine or sitting position by means of an intercostal approach.	Pulmonologist	CXR	NR	Unclear	NR

Table 2. (continued)

	Copetti (2008)[30]	Linear (7.5–10 MHz) and convex (3.5–5 MHz) probe	Anterior, posterior and lateral chest was scanned in the longitudinal and the transverse plane, with the patient in lateral decubitus and sitting position.	Emergency physician	Clinical findings and CXR, CT, ultrasound	Paediatrician	Yes	NR
RDS	El-Malah (2015)[31]	Linear (7.5 MHz) and convex (5 MHz) probe	The anterior, lateral and posterior chest was scanned with the patient in supine and lateral decubitus position. Longitudinal, transverse and oblique views. The transabdominal approach (transhepatic and transsplenic) in supine position was used to examine the lungbases.	Radiologists	CXR	Radiologist	Yes	NR
	Sawires (2015)[11]	Linear probe (7 MHz)	Anterior, lateral and posterior chest was scanned in longitudinal and transverse sections.	Radiologist	CXR	NR	Yes	NR
	Vergine (2015)[32]	Linear probe (10–12 MHz)	The anterior and lateral chest was scanned between the parasternal and anterior axillary lines and between the anterior and posterior axillary lines, in the longitudinal plane.	Trained neonatologist	Clinical diagnosis including CXR	Neonatologist	Yes	None

Table 2. (continued)

	Lovrenski (2012)[33]	Linear probe (7.5 MHz)	The anterior, lateral and posterior chest was scanned with the patient in supine and lateral decubitus position. Longitudinal, transverse and oblique scans were included. The transabdominal approach (transhepatic and transsplenic) in supine position was used to examine the lung bases.	Experienced paediatric radiologist	CXR	Radiologist	Chest US reported first by same radiologist	NR
Pneumo-thorax	Cattarossi (2016)[34]	A high frequency linear probe (13 MHz)	Not described	5 neonatologists trained in chest ultrasound	Pneumothorax confirmed by aspiration	NA	Blinded to CXR, aware of clinical data	None
	Raimondi (2016)[35]	High-frequency linear probe (10 MHz)	Not described	A neonatologist skilled in chest ultrasound	CXR	Radiologist	Yes	NR
	Kosiak (2016)[36]	Linear (8.0–12.0 MHz) and convex (3.5–5.0 MHz) probes	The anterior and lateral chest was scanned with the patient in the supine position, longitudinal and transverse views were obtained.	Paediatrician with ultrasound experience	CXR or CT	Radiologist	Unclear	None
Atelectasis	Liu (2015)[37]	High-frequency linear (9-12 MHz) probe	The anterior, lateral and posterior chest was scanned with the infants in supine, lateral, or prone position. The probe was positioned perpendicular and parallel to the ribs.	Neonatal expert sonographer	CXR and CT	Radiologist	CXR was performed after chest US if US was positive	None

Table 2. (continued)

	Acosta (2014)[12]	Linear probe (6-12 MHz)	The anterior, lateral, and posterior chest was scanned with the probe perpendicular to the ribs. Intercostal postero-basal (IPB) view for assessment of posterior para-diaphragmatic atelectasis. The probe transvers in intercostal space above hemi-diaphragm and below posterior axillary line.	2 radiologists	MRI	Radiologist	Yes	NR
Bronchiolitis	Caiulo (2011)[38]	High-resolution linear probe (6-12 MHz)	Anterior, lateral and posterior chest was scanned, longitudinal and transverse sections were obtained.	A paediatrician with ultrasound experience	Clinical diagnosis	Paediatrician	Blinded to CXR, aware of clinical data	NR
NVF	Raimondi (2014)[13]	Linear probe (5-12 MHz)	Anterior and lateral chest was scanned with the infant in supine position.	Analysed by experienced paediatric radiologist	CXR	Radiologist	Yes	None

CT: computed tomography, CXR: chest X-ray, MHz: megahertz, MRI: magnetic resonance imaging, NVF: non-invasive ventilation failure, RDS: respiratory distress syndrome, US: ultrasound.

The four prospective RDS studies were conducted on NICU's in Egypte (2x),[13,32] Italy[34] and Serbia.[35] The studies included a total of 369 neonates (sample size range 59 – 120). The sonographer was an experienced radiologist in three studies[13,33,35] and a trained neonatologist in one study.[34] A linear probe (7-12 MHz) was used in all four studies and one study[33] used a convex probe (5 MHz) as well, the anterior and lateral approach was used to scan the chest in all four studies, three studies[13,33,35] scanned used the posterior approach and two studies[33,35] included the transabdominal approach as well. CXR was used the reference standard in three studies[13,33,35] one study[34] used the clinical diagnosis, including CXR, as the reference standard. The sonographer was blinded for the CXR findings in all four studies but in one study[35] the sonographer, a radiologist, reported the CXR after performing the chest ultrasound. The sensitivity ranged from 95.6% to 100% and the specificity from 25.0% to 100% (see table 1, and figure 2c for a forest plot).

The three prospective pneumothorax studies were conducted at the NICU[36,37] and radiology department[38] in Italy,[36,37] Spain,[37] France[37] and Poland.[38] The threes studies combined included 154 children (sample size range: 42 - 63), aged 0 – 17 years. The scans were performed by trained neonatologists[36,37] and a paediatrician with ultrasound experience.[38] A linear probe (8 – 13 MHz) was used in all three studies, one study[38] used a convex probe as well (3.5 – 5 MHz). Only one study[38] described the scanning technique, the anterior and lateral parts of the chest were scanned. The three studies used a different reference standard, confirmation by aspiration,[36] CXR,[37] CXR or CT chest.[38] Two studies[36,37] reported that the sonographer was blinded to CXR readings, one study[38] did not report on blinding. The sensitivity and specificity for chest ultrasound to detect a pneumothorax was 100% in all three studies (see table 1, and figure 2d for a forest plot).

The two prospective studies reporting on atelectasis were conducted on the NICU,[39] neonatology ward[39] and the radiology department[14] in China[39] and Argentina.[14] One study included 80 neonates and one study included 15 children with a mean age of 4.5 years. The Chinese study used an expert neonatal sonographer and the Argentine study used a radiologist to scan the chest. Both studies used a linear probe (6 – 12 MHz) and the anterior, lateral and posterior approach was used. The Chinese study used CXR and CT as a reference standard, but only used it if the chest ultrasound was positive, the Argentine study used MRI. The sensitivity was 75%[39] and 90.7%,[14] only the specificity of the Argentine study could be calculated and was 89.1% (see table 1, and figure 2e for a forest plot).

We included one Italian, prospective, bronchiolitis study,[40] they included 52 children, median age of 2.1 months, from the paediatric ward. A paediatrician with ultrasound experience used a linear probe (6 – 12 MHz) to scan the anterior, lateral and posterior parts of the chest. The reference standard was clinical diagnosis. The sensitivity was 90.4% and the specificity was 100% (table 1).

We included one study that reported on the diagnostic accuracy of chest ultrasound to diagnose non-invasive ventilation failure.[15] This prospective study was conducted in Italy on the NICU, 54 neonates were included. An experience paediatric radiologist used a linear probe (5 – 12 MHz) to scan the anterior and lateral part of the chest. CXR was used the reference standard, the radiologist was blinded to the CXR findings. A sensitivity and specificity of 100% was found (table 1).

Three studies[17,28,29] reported their findings on small consolidations detected on chest ultrasound but not visible on CXR. Claes et al. found that in the eight patients with a consolidation only seen on chest ultrasound, the mean size of the consolidation was significantly smaller (9.4 mm) than in children with a consolidation seen on both imaging modalities (mean size 26 mm).[17] Shah et al. compared chest ultrasound with CXR and found 18 consolidations on chest ultrasound that were not detected on CXR; 13 of these were smaller than one centimeter.[29] Seif El Dien and Abd Ellatif found that chest ultrasound detected a small apical or basal consolidation in 18 patients (39.1%) this was not seen on CXR, in seven patients (15.0%) more extensive consolidations were seen on chest ultrasound than on CXR.[28]

Only three pneumonia studies, with a total of 79 patients, compared chest ultrasound against the gold standard, chest CT.[18,30,32] Kurian et al. showed that chest CT did not provide any additional information to chest ultrasound for the detection of effusion, lung necrosis or abscess as a complication of pneumonia,[30] suggesting that chest ultrasound could replace chest CT to evaluate complications of pneumonia. Saraya et al. found a high specificity (95.0%) for the diagnosis of pneumonia when comparing chest ultrasound with chest CT, and a lower sensitivity (72.2%),[18] but the false negative cases were coded as pneumonitis and bronchiolitis on CT, which are

Figure 2a. Forest plot of sensitivity, specificity, positive likelihood ratio (LR) and negative LR for chest ultrasound in children with pneumonia

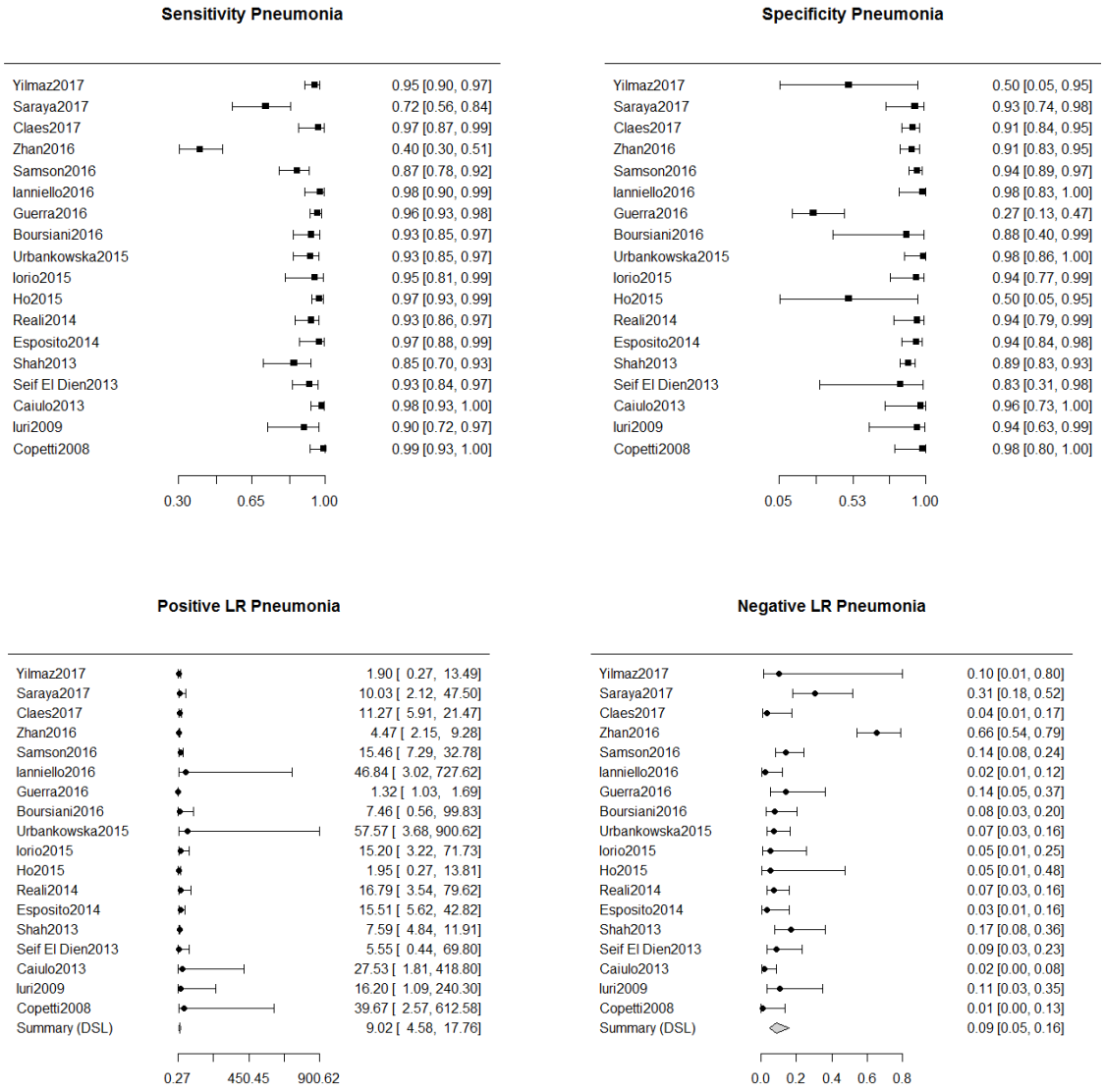


Figure 2b. HSROC curve chest ultrasound for the diagnosis of childhood pneumonia

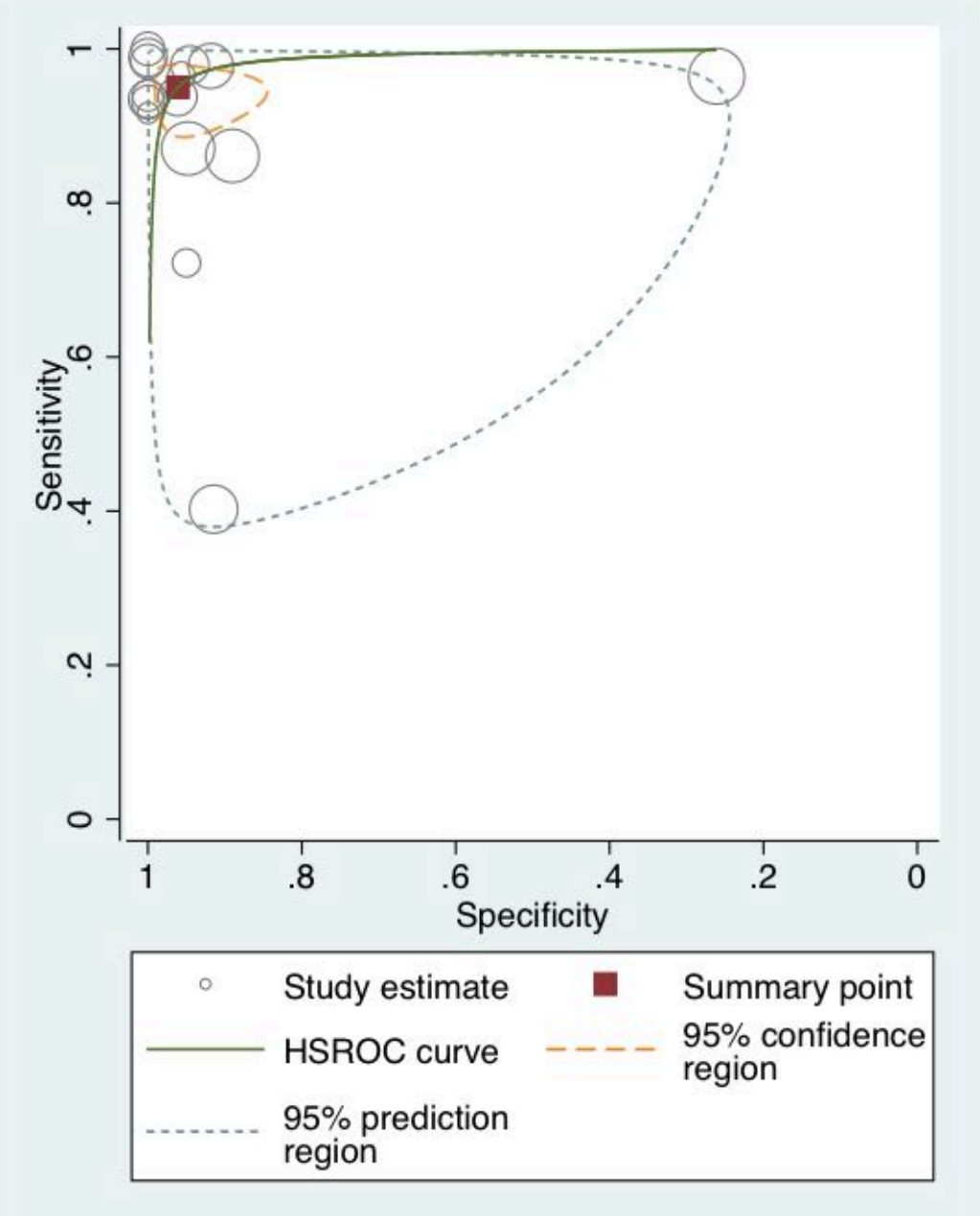


Figure 2c. Forest plot of sensitivity, specificity, positive likelihood ratio (LR) and negative LR for chest ultrasound in children with respiratory distress syndrome (RDS)

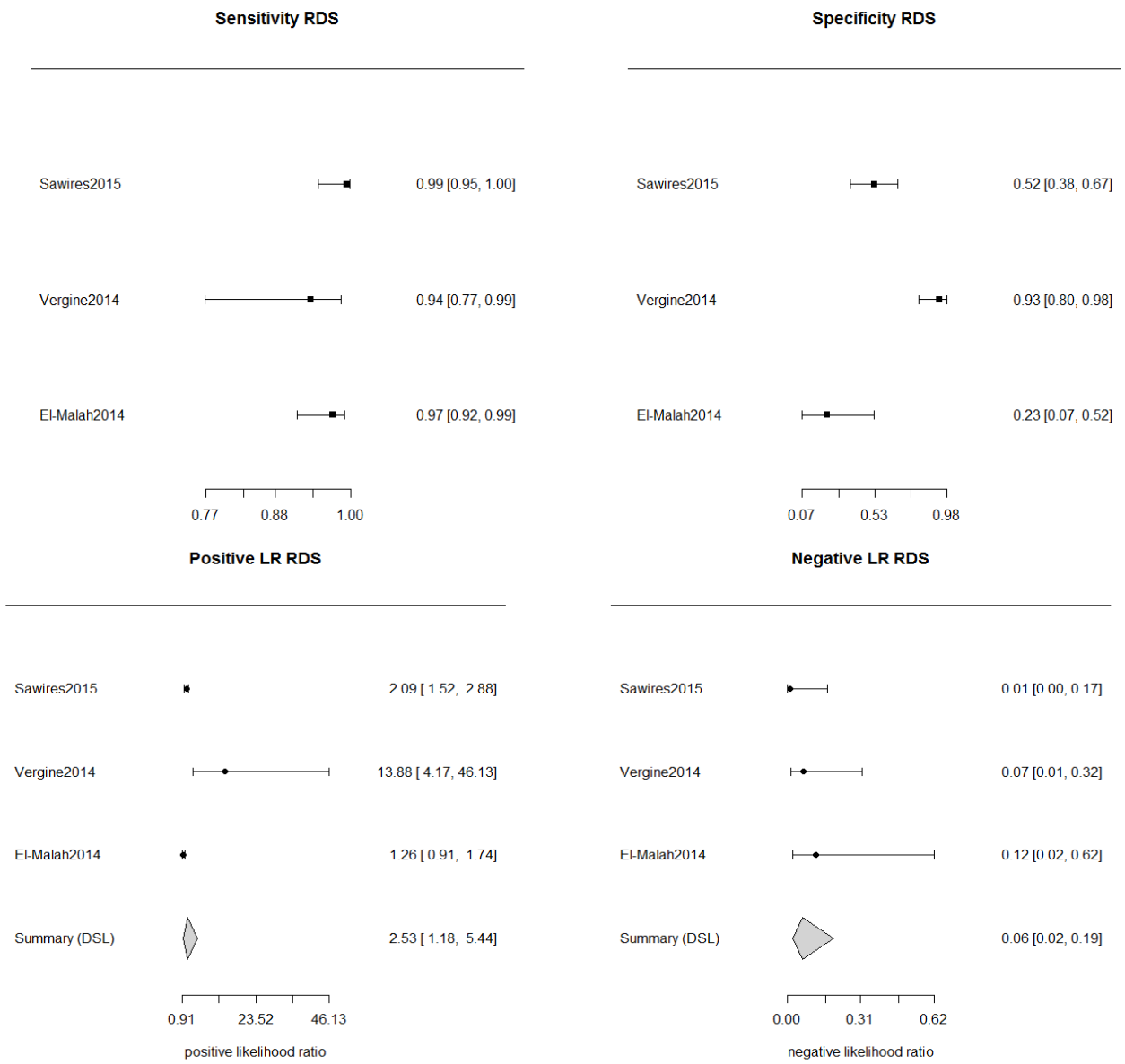


Figure 2d. Forest plot of sensitivity, specificity, positive likelihood ratio (LR) and negative LR for chest ultrasound in children with pneumothorax

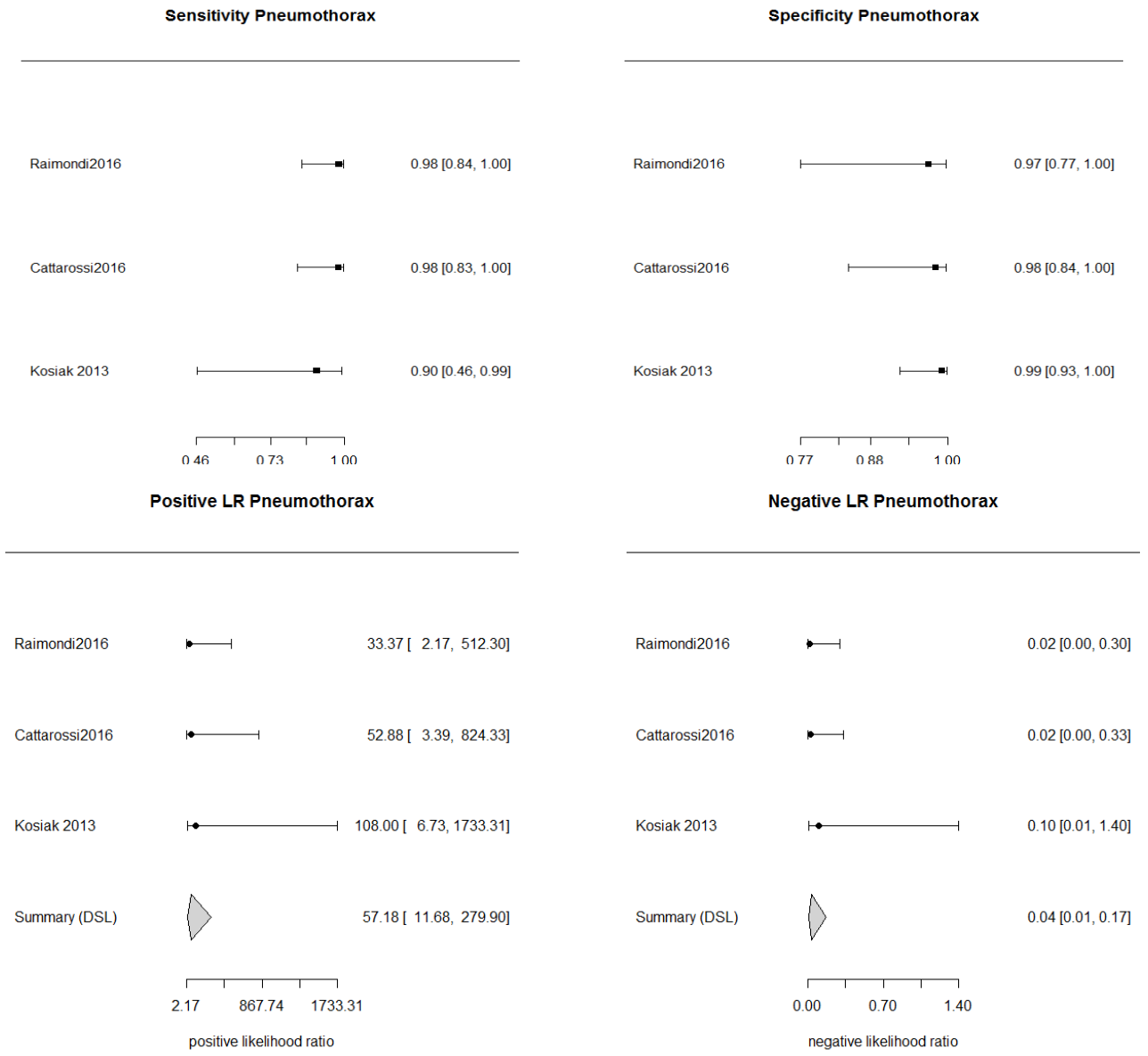
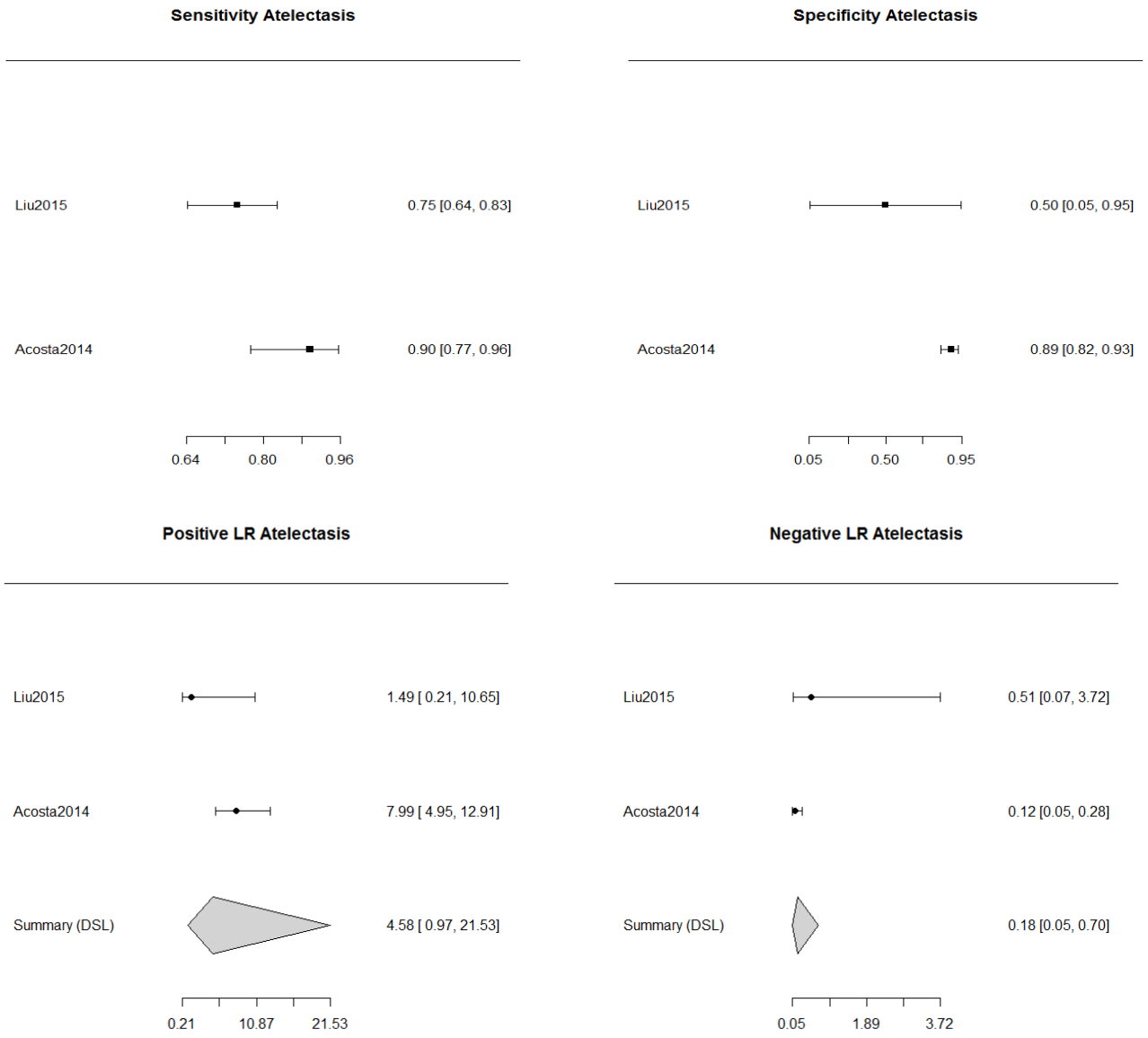


Figure 2e. Forest plot of sensitivity, specificity, positive likelihood ratio (LR) and negative LR for chest ultrasound in children with atelectasis



diseases other than pneumonia, rendering those cases true negatives, so the sensitivity may be higher. Copetti and Cattarossi used chest CT in less than 10% (n=4) of their included patients; they found that chest ultrasound correctly identified a consolidation not diagnosed by CXR in all of the four cases.[32]

Five studies (three pneumonia[10,23,28], one pneumothorax[36] and one bronchiolitis[40] study) did not use an imaging modality as the reference standard but used clinical diagnosis or confirmation by aspiration. In all five studies the sensitivity of chest ultrasound was higher than the sensitivity of CXR (pneumonia chest ultrasound: 93.2%-98.4%, CXR: 78.3%-92.6%; pneumothorax chest ultrasound: 100%, CXR 96.0%; bronchiolitis chest ultrasound: 90.4%, CXR: 73.1%), the specificity was similar for both imaging modalities. Unfortunately, we could not perform a meta-analysis due to limited studies comparing the two imaging modalities.

The diagnostic accuracy of chest ultrasound performed by a radiologist (six studies, 455 children)[9,10,12,17,18,28] or a clinician (12 studies, 1,576 children)[11,19-27,29,32] yielded similar results (sensitivity: radiologist 94.3% [95% CI 88.4%-97.3%], clinician 95.3% [95%CI 88.4%-98.2%]; specificity: radiologist 97.1% [95%CI 82.8%-99.6%], clinician 94.0% [95%CI 81.6%-98.2%]). The diagnostic accuracy was better when the operator was more experienced (13 studies, 1,221 children[9,10,12,17-19,23-28,32] versus five studies, 810 children, on unexperienced operator[11,20-22,29]); sensitivity: experienced operator 96.4% [95%CI 93.4%-98.0%], unexperienced operator 86.7% [95%CI 66.9%-95.4%]; specificity: experienced operator 95.2% [95%CI 89.7%-97.8%], unexperienced operator 89.3% [95%CI 61.8%-97.7%]). The diagnostic accuracy was better in studies with children of a mean age over five years (five studies,[10,23,25,27,32] 531 children, sensitivity 98.0% [95%CI 96.0%- 99.0%], specificity 97.0% [95%CI 82.0%-100%]) than in studies with children with a mean age under five years (13 studies,[9,11,12,17-22,24,26,28,29] 1,500 children, sensitivity 91.0% [95%CI 85.0%-95.0%], specificity 93.0% [95%CI 84.0%-98.0%]).

Nine studies reported the duration of completing chest ultrasound;[9,15,17,22,26,29,33,35,38] the mean time to complete chest ultrasound was 7.4 minutes (range 2-20 minutes). Chest ultrasound was performed quicker in neonates; mean time 3.1 minutes (range 2-4 minutes)[15,33,35] than in non-neonate children; mean time 9.6 minutes (range 2-20 minutes).[9,17,22,26,29,38] Raimondi et al. compared the time between clinical decompensation and completing chest ultrasound versus CXR in neonates with a pneumothorax. Chest ultrasound was completed quicker, mean time 5.3±5.6 minutes, then CXR, mean time 19.0±11.7 minutes ($p<0.001$).[37]

DISCUSSION

This systematic review collates the evidence on the diagnostic accuracy of chest ultrasound for the diagnosis of pulmonary diseases in children; the meta-analysis was only performed for children with pneumonia due to insufficient studies on other pulmonary diseases. We found that chest ultrasound had an overall high sensitivity (95.0%) and specificity (96.1%) for the diagnosis of pneumonia in children, in line with a previous meta-analysis.[41] There is however an issue of expertise in interpreting the chest ultrasound and CXR, the chest ultrasounds are predominantly interpreted by clinicians while the CXRs were predominantly interpreted by radiologists.

Chest ultrasound detected small consolidations not visible on CXR,[17,25,28,29] suggesting that chest ultrasound is better in detecting small consolidations than CXR. However, it remains unclear whether detection of small consolidations changes patient management. Small consolidations may be a correlate of bacterial pneumonia but these findings could also be correlated to other pulmonary diseases, like bronchiolitis or asthma.

Even though the learning curve for chest ultrasound has been reported to be steep,[42] chest ultrasound performed by an experienced operator had a better diagnostic accuracy than chest ultrasound performed by an unexperienced operator. Therefore, chest ultrasound training followed by supervised ultrasound scans should be done to ensure more reliable diagnostic outcomes. Further studies should evaluate the duration and optimal contents of training and the level of nature of ultrasound scanning supervision post-training needed, also exploring the capacity for remote supervision in the context of telemedicine applications.

The few studies[18,30,32] comparing chest ultrasound with chest CT, suggest that chest ultrasound is a valid diagnostic tool for the diagnosis of pneumonia and the complications of pneumonia. However, the number of patients included in studies published to date is low, and CT technology exposes the child to ionizing radiation therefore further studies should carefully consider the need of comparing chest ultrasound with chest CT.

The average time to perform chest ultrasound was 7.4 minutes, allowing for early diagnosis and treatment. Furthermore, chest ultrasound may be cost-effective especially in resource-limited settings but cost-effectiveness studies are lacking. Chest ultrasound could be performed at primary or secondary care facilities, minimizing the need for referral to tertiary care.

A limitation of this review is that the majority of the included studies focused on children with pneumonia. Only a few studies were available on RDS, pneumothorax, atelectasis, bronchiolitis or non-invasive ventilation failure; therefore, a meta-analysis on these subgroups could not be performed. Further research should focus on other pulmonary diseases than pneumonia, to evaluate if chest ultrasound is a good diagnostic tool for other pulmonary diseases in children.

Another limitation is that not all studies used the same reference standard. Most studies compared chest ultrasound directly to CXR, which is not the perfect gold standard for most pulmonary diseases. Using clinical reference as the reference standard increases the risk of bias. As said before, further studies should carefully consider comparing chest ultrasound with chest CT, to evaluate the diagnostic accuracy of chest ultrasound against a valid gold standard and to minimize over-diagnosis and over-treatment with antibiotics as a result of that.

The variability in expertise of the sonographer used in the different studies is another limitation, this could affect the comparability of the studies as well as the wide variability in health care professionals who interpreted the images. To address this issue, we performed a subgroup analysis on operator experience.
One pneumonia study[18] used a different ultrasound scanning protocol, did not scan the posterior chest, the rest of the pneumonia studies used the protocol earlier described by Copetti and Cattarossi.[32] This study[18] showed a lower sensitivity but this could also have been caused by the more sensitive reference test, chest CT.

The risk of bias for patient selection was high in ten studies and unclear in 11 studies, this raises the question about the generalizability of the data. The risk of bias of the index test and reference test was low in most studies.

Most studies were conducted in high-income countries. It is peculiar that chest ultrasound studies for the diagnosis of pulmonary diseases in children in low-income countries are lacking as chest ultrasound is an easy to perform, mobile and a cheap imaging modality.

CONCLUSION

CXR has been the traditional imaging modality for the diagnosis of pulmonary diseases in children for years, but this systematic review shows that chest ultrasound should be considered to replace CXR as the first line imaging modality especially in children with suspected pneumonia. Chest ultrasound has an excellent diagnostic accuracy for the diagnosis of pneumonia; and likely for pneumothorax, RDS, atelectasis, bronchiolitis and non-invasive ventilation failure. The many other advantage of ultrasound over X-ray, like no exposure to ionizing radiation, performed at the bedside by non-radiological trained clinicians, reproducibility and low-costs make chest ultrasound an even more attractive alternative for CXR. However, there is a limited number of studies evaluating chest ultrasound in pulmonary diseases other than pneumonia. Further research should focus on the diagnostic accuracy of chest ultrasound for the diagnosis of pulmonary diseases in children, especially other than pneumonia, comparing against a valid gold standard, like final diagnosis or CT or MRI chest if ethically justified. Furthermore, the optimal training of chest ultrasound, duration and content, should be evaluated, cost-effectiveness studies should be conducted and the usefulness and diagnostic accuracy of chest ultrasound in low-income countries should be evaluated.

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6

chapter 6

TECHNICAL ASPECTS OF MEDIASTINAL ULTRASOUND FOR PEDIATRIC PULMONARY TUBERCULOSIS

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ABSTRACT

Diagnosing childhood pulmonary tuberculosis (TB) may be challenging due to difficulties in obtaining adequate sputum samples, paucibacillary disease and the low sensitivity of diagnostic tests. Chest radiography is an important diagnostic tool for pulmonary TB, but it involves radiation exposure, requires facilities that can house X-ray equipment and has poor inter-reader agreement. The cardinal radiologic finding of mediastinal lymphadenopathy may be detected using mediastinal ultrasound (US). We describe technical aspects of performing mediastinal US, which may assist diagnosis of paediatric pulmonary TB.

INTRODUCTION

In 2015, there were an estimated 1 million new tuberculosis (TB) cases among children; in 70–80% of the cases, TB presented in the lungs.[1] Microbiological diagnosis of TB is challenging in children due to difficulties in obtaining adequate sputum samples and paucibacillary disease.[2] Therefore, diagnosis frequently relies on clinical features together with chest radiographic findings. The most common chest radiographic finding in pediatric pulmonary TB is hilar or mediastinal lymphadenopathy.[3] However, the limitation of diagnosing mediastinal lymphadenopathy on chest radiograph is the poor inter- and intra-reader agreement.[4-6] Standard chest radiography can be limited in visualizing mediastinal adenopathy because the large thymus in children often obscures mediastinal lymphadenopathy.

The use of chest ultrasound (US) to detect mediastinal lymphadenopathy in children with suspected pulmonary TB has been described,[7-9] but no formal protocol or image database exists. Ultrasonography has advantages over conventional radiography: It does not expose children to ionizing radiation, sedation is not needed, it is more cost-effective than other cross-sectional imaging and the recent development of portable, low-cost US machines increases its availability in rural and resource-limited settings.[10,11]

We describe technical aspects of performing mediastinal US to evaluate lymphadenopathy for the diagnosis of pediatric pulmonary TB. We also provide schematic images and sonographic images in healthy children and in children with microbiologically confirmed pulmonary TB as a reference standard.

DESCRIPTION

The technique is designed to detect mediastinal lymphadenopathy. Any grey-scale or colour Doppler US machine with a microconvex (radius of curvature: 5–15mm) or small aperture phased array transducer with a center frequency of approximately 7.5 MHz (range: 5.0 – 8.8 MHz) can be used to access the mediastinum through the window of the suprasternal notch and the intercostal space left of the sternum. Grey-scale US machines without Doppler are cheaper than those with Doppler and can be used in resource-limited settings; however, we suggest using grey-scale US machines with Doppler, which is particularly useful when differentiating vessels from lymphadenopathy.

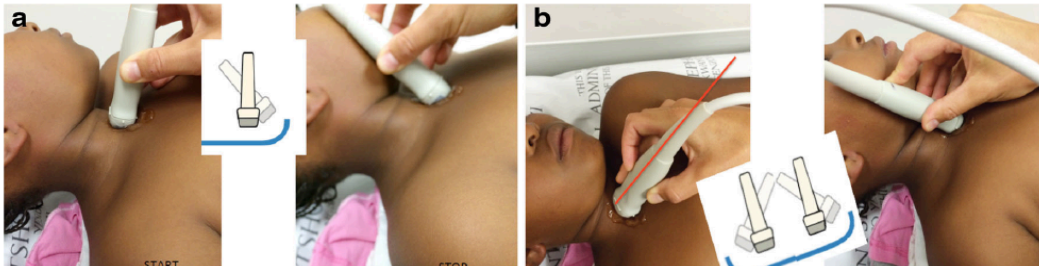
A four-view procedure is described here: two views through the suprasternal notch (the transverse suprasternal view and the oblique suprasternal view), and two views at the left parasternal intercostal space (the transverse left parasternal view and longitudinal left parasternal view). The thymus is used as the acoustic window in all four views. The thymus is overall hyperechoic when compared to the mediastinal vessels and is hypoechoic when compared to the mediastinal fat. The thymus has a distinct appearance by US; it is homogeneous, relatively hypoechoic and contains scattered echogenic foci.

IMAGING THROUGH THE SUPRASTERNAL NOTCH

Sufficient US gel is applied to ensure good contact with the concave depression at the suprasternal notch in children of all sizes. For the first two views, the patient may be supine, but the procedure can be performed with the child sitting or in a caregiver's arms. A supine procedure will be described as the standard. To improve access to the suprasternal notch, the neck can be extended slightly by placing a pillow or a blanket between the scapulae. The child should be encouraged to turn the head to the left to further improve access for a right-handed operator to avoid interference of the chin with the tilt of the probe. In each view described below, a cine clip is taken while changing probe angulation so that later review may be accomplished.

For the transverse suprasternal view, the US probe should be placed transverse in the suprasternal notch, perpendicular to the patient's neck as the starting position, and then the probe should be angled caudally as far as possible into the chest to visualize the mediastinum (Figure 1a). For the oblique suprasternal view, the probe is rotated counter clockwise, the long axis of the US probe is oriented diagonally running from a superior point on the patient's left to an inferior point on the patient's right. The starting point is in the suprasternal notch tilting the probe to point into the thorax in line with the obliquity of the aortic arch (Figure 1b).

Figure 1. Probe position for the transverse suprasternal view (a) and the probe position for the oblique sagittal suprasternal view (b)

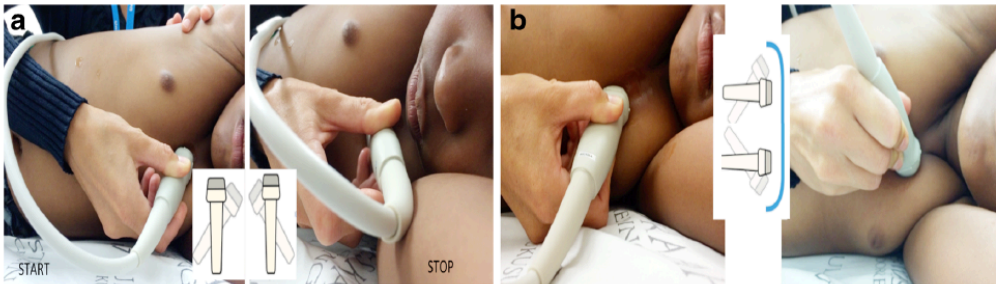


LEFT PARASTERNAL

For these two views, the child may be in a left lateral decubitus position with his/her hands above the head. For the transverse left parasternal view, the probe should be placed at the 2nd-3rd intercostal space that lies approximately two spaces above the nipple line at the left lateral margin of the sternum in the transverse (or axial) position. As a starting position, the probe is slightly tilted medially and cranially and then angled caudally, keeping the probe angled slightly medially in order to capture the left mediastinum (Figure 2a).

For the longitudinal left parasternal view, the probe is placed at the same intercostal space at the left lateral margin of the sternum but in the longitudinal (or sagittal) position. As a starting position, the probe is tilted medially and slightly cranially and then angled laterally to visualize the left mediastinum (Figure 2b).

Figure 2. Probe position for the transverse left parasternal view (a) and the probe position for the longitudinal left parasternal view (b)



ANATOMICAL LANDMARKS

Suprasternal notch

The anatomical landmarks that can be identified in the transverse suprasternal view (Figure 3) are:

- the right and left brachiocephalic veins
- the superior vena cava
- the aorta
- the pulmonary trunk
- and the thymus.

Anatomical landmarks for the oblique suprasternal view (Figure 4) are:

- the left brachiocephalic vein
- the aortic arch giving rise to the brachiocephalic artery, left common carotid artery and left subclavian artery
- and the thymus.

Left parasternal

Anatomical landmarks for the transverse left parasternal view (Figure 5) are:

- the aortic root
- the pulmonary trunk
- and the thymus.

Anatomical landmarks for the longitudinal left parasternal view (Figure 6) are:

- the heart including the left and right atria and left and right ventricles
- and the thymus.

Figure 3. Schematic (a) with corresponding US image (b) of the transverse suprasternal view of the normal mediastinum in a 3-year-old girl. Anatomical landmarks are the confluence of the right and left brachiocephalic veins (Right BCV and Left BCV) to form the superior vena cava (SVC), aorta and pulmonary trunk. Lymphadenopathy may be encountered in the predefined zones A–C interposed between normal structures. Note the homogenous appearance of the thymus occupying zone A when there is no lymphadenopathy

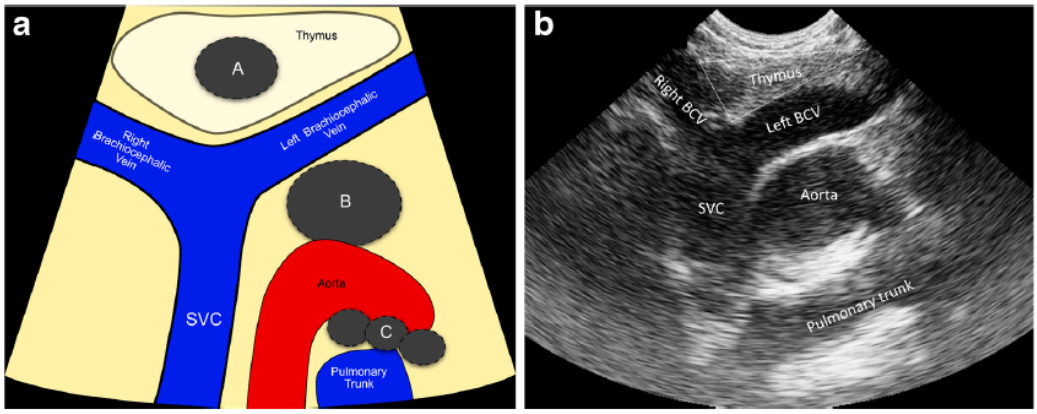


Figure 4. Schematic (a) with corresponding US image (b) of the oblique suprasternal view of the normal mediastinum in a 3-year-old girl. Anatomical landmarks are the left brachiocephalic vein (Lt BCV), the aortic arch and three of its major branches, left common carotid artery (Lt CCA) and left subclavian artery (Lt SCA). Lymphadenopathy may be encountered in the predefined zones D-F or interposed between other normal structures. Note the homogenous triangular appearance of the thymus occupying zone D when there is no lymphadenopathy

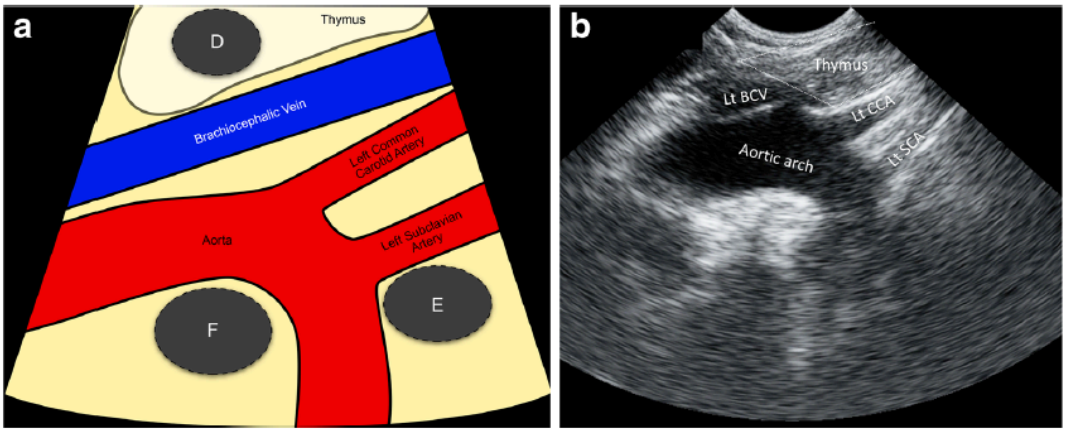


Figure 5. Schematic (a) with corresponding US image (b) of the transverse left parasternal view of the mediastinum in a 7-year-old girl. Anatomical landmarks are the thymus anterior to the pulmonary trunk and the aortic root. Lymphadenopathy may be encountered in the predefined zone G, occupied by the thymus

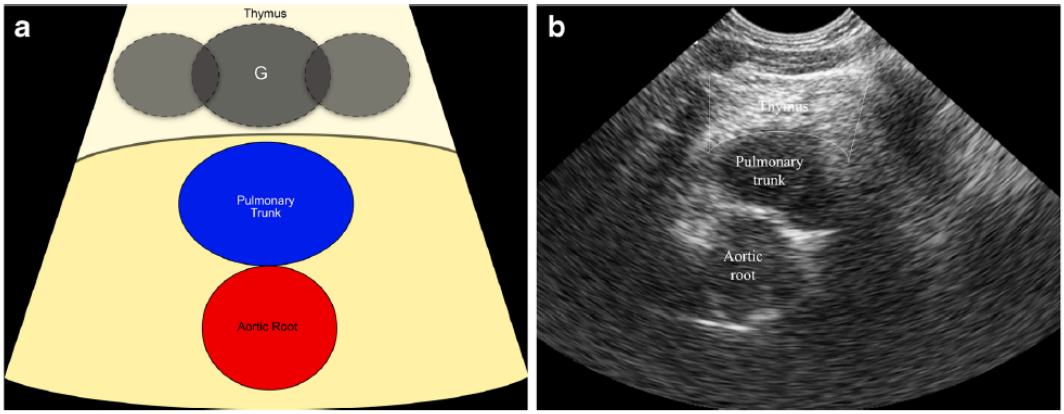
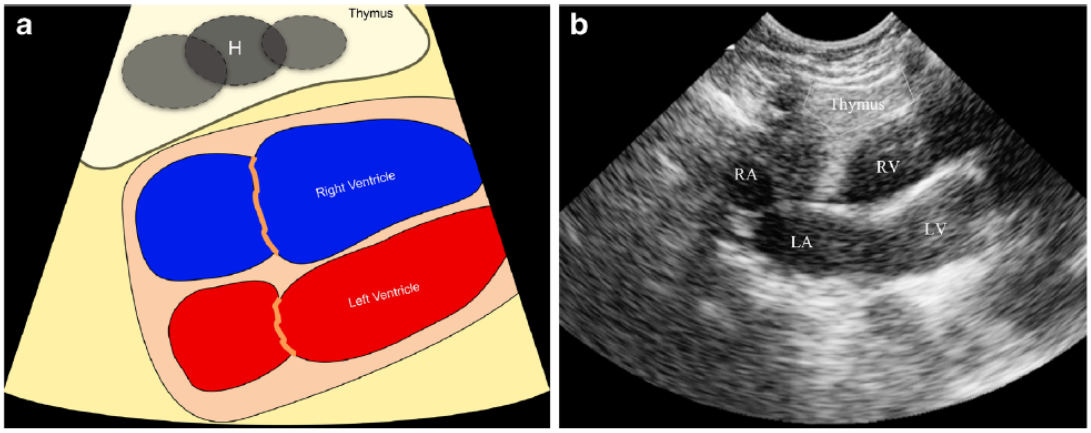


Figure 6. Schematic (a) with corresponding US image (b) of the longitudinal left parasternal view of the mediastinum in a 2-year-old girl. Anatomical landmarks are the thymus anterior to the heart with both the left and right atria (LA and RA) and left and right ventricles (LV and RV) visible. Lymphadenopathy may be encountered in the predefined zone H, occupied by the thymus



LYMPHADENOPATHY

Lymphadenopathy in this paper is defined as oval or round lymph nodes between anatomical landmarks. There is no size criterion defined for lymphadenopathy in children and this is also variable because of the large age range of children scanned with this technique. Any mediastinal lymph nodes detected are considered lymphadenopathy as is customary with other cross-sectional modalities and plain radiographs. These round or oval lymph nodes without fatty hilum are hypoechoic when compared to the thymus or the mediastinal fat and are hyperechoic when compared to blood vessels. These come into view when pointing the US probe toward the mediastinum. Lymphadenopathy can be differentiated from blood vessels, which are anechoic structures that elongate, when rotating the probe to the oblique view and may show branching. Large blood vessels show a hyperechoic rim representing the wall of the blood vessel. Lymphadenopathy greater than 1.0–1.5 cm can cause a mass effect on adjacent structures such as the blood vessels. Tuberculous lymphadenopathy may present as a conglomeration of multiple nodes. Several mediastinal zones were specifically defined for searching and recording of mediastinal lymphadenopathy (Figures 3 and 6) so that communication, data collection and follow-up can be standardized.

The predefined zones in the transverse suprasternal view (Figure 3) are:

- Zone A: anterior to the right and left brachiocephalic vein within the thymic region
- Zone B: between the left brachiocephalic vein and the aorta
- Zone C: between the aorta and the pulmonary trunk.

Predefined zones in the oblique suprasternal view (Figure 4) are:

- Zone D: anterior to the left brachiocephalic vein within the thymic region
- Zone E: lateral to the arch of the aorta and posterior to the left subclavian artery
- Zone F: inferior and posterior to the aortic arch.

The predefined zone in the transverse left parasternal view (Figure 5) is:

- Zone G: anterior and to the left of the pulmonary trunk within the thymic region.

The predefined zone in the longitudinal left parasternal view (Figure 6) is:

- Zone H: anterior and to the left of the right atrium and ventricle within the thymic region.

Figures 7, 8, 9, 10, 11, 12, 13 and 14 demonstrate lymphadenopathy in zones A, B, D, E, F, G and H in children with confirmed TB.

Figure 7. Suprasternal US using the transverse view in an 8-year-old human immunodeficiency virus infected boy with confirmed tuberculosis demonstrates discreet lymphadenopathy (LN) in zone A, size 1.0 cm, in addition to the thymic tissue there.

Left BCV = left brachiocephalic vein, Right BCV = right brachiocephalic vein, SVC = superior vena cava

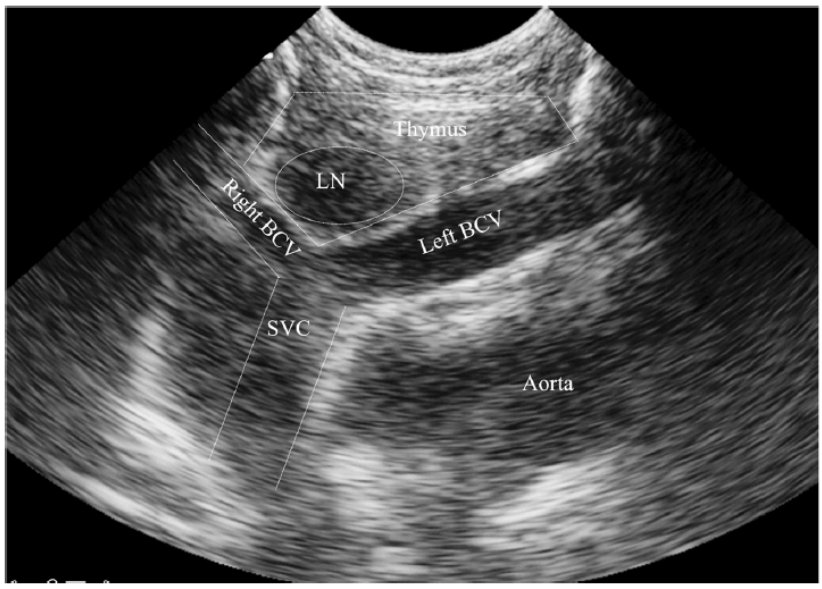


Figure 8. Suprasternal US using the transverse view in an 8-year-old boy without human immunodeficiency virus infection but with confirmed tuberculosis demonstrates a 2.7-cm enlarged lymph node (LN) in zone B causing mass effect on adjacent structures, i.e. compressing the superior vena cava (SVC) and displacing the aorta.

Left BCV = left brachiocephalic vein, Right BCV = right brachiocephalic vein

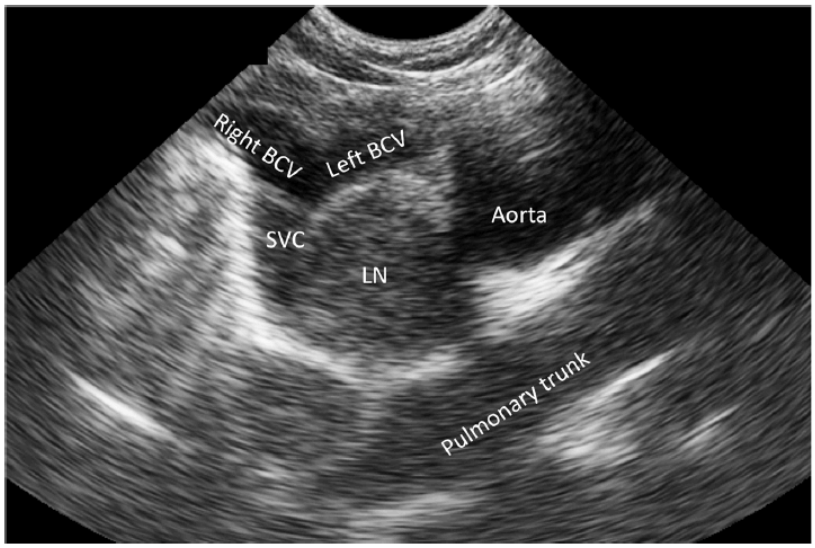


Figure 9. Suprasternal US using the oblique view in a 5-year-old boy without human immunodeficiency virus infection but with confirmed tuberculosis demonstrates a 1.6-cm enlarged lymph node (LN) in zone D in addition to the thymic tissue there. The aortic arch is out of view on this image, which was selected to demonstrate the lymphadenopathy optimally, but its outline (as seen on adjacent image slices not show here) is demonstrated through the use of dashed lines.

Left BCV = left brachiocephalic vein, Left CCA = left common carotid artery

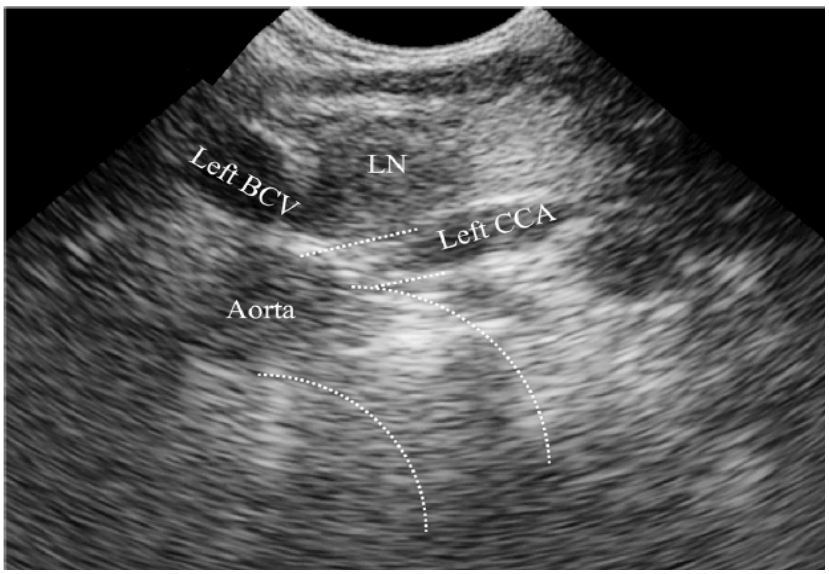


Figure 10. Suprasternal US using the oblique view in a 1-year-old human immunodeficiency virus infected boy with confirmed tuberculosis demonstrates multiple lymph nodes (LN) in zone D. The lymph nodes in zone D in this patient varied from 0.7 to 1.4 cm.

BCA = brachiocephalic artery, Left BCV = left brachiocephalic vein, Left CCA = left common carotid artery, Left SCA = left subclavian artery

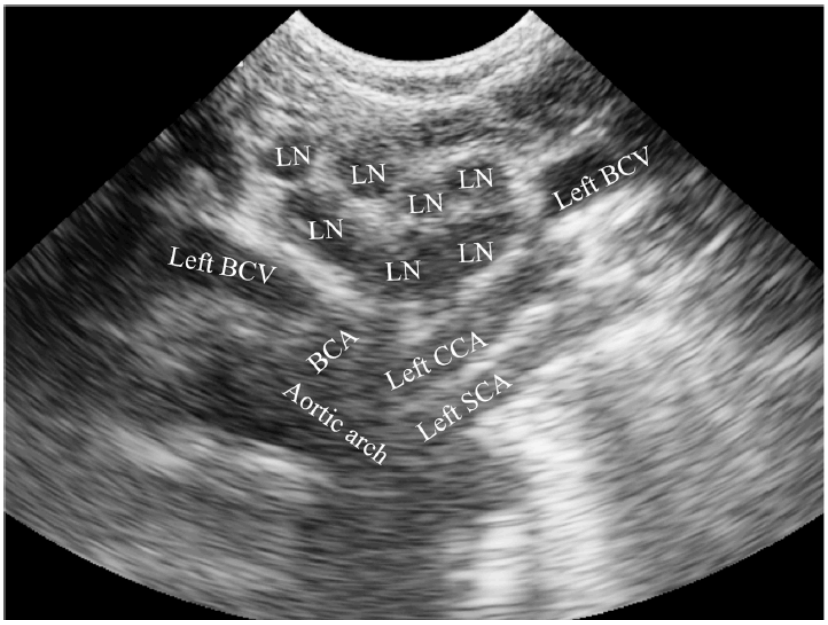


Figure 11. Suprasternal US using the oblique view in a 5-year-old human immunodeficiency virus infected boy with confirmed
tuberculosis demonstrates a 1.5- cm enlarged lymph node (LN) in zone E compressing the left common carotid artery (Left CCA). The aortic arch is out of view on this image, which was selected to demonstrate the lymphadenopathy optimally

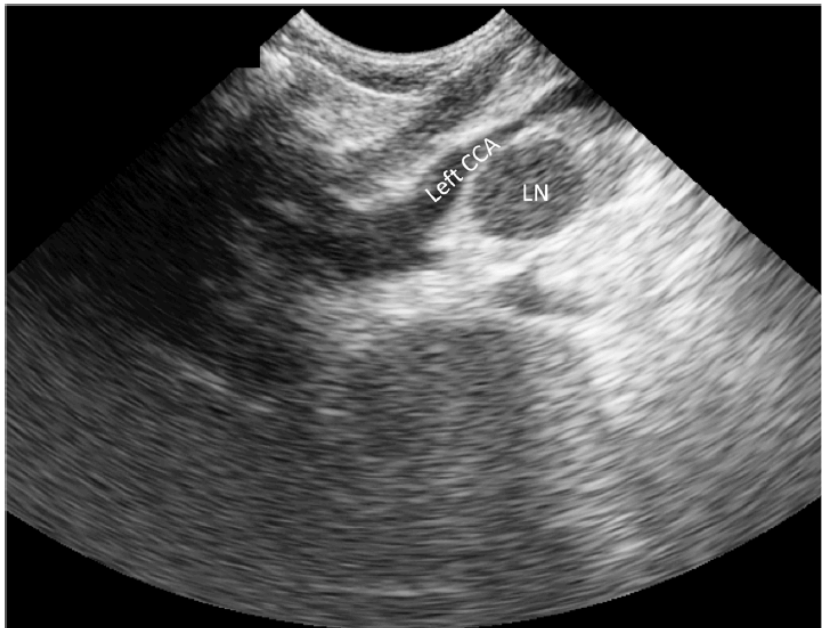


Figure 12. Suprasternal US using the oblique view in an 8-year-old boy without human immunodeficiency virus infection but with confirmed tuberculosis demonstrates a 2.0-cm enlarged lymph node (LN) in zone F – the aortopulmonary window.

Lt CCA = left common carotid artery, Lt SCA = left subclavian artery

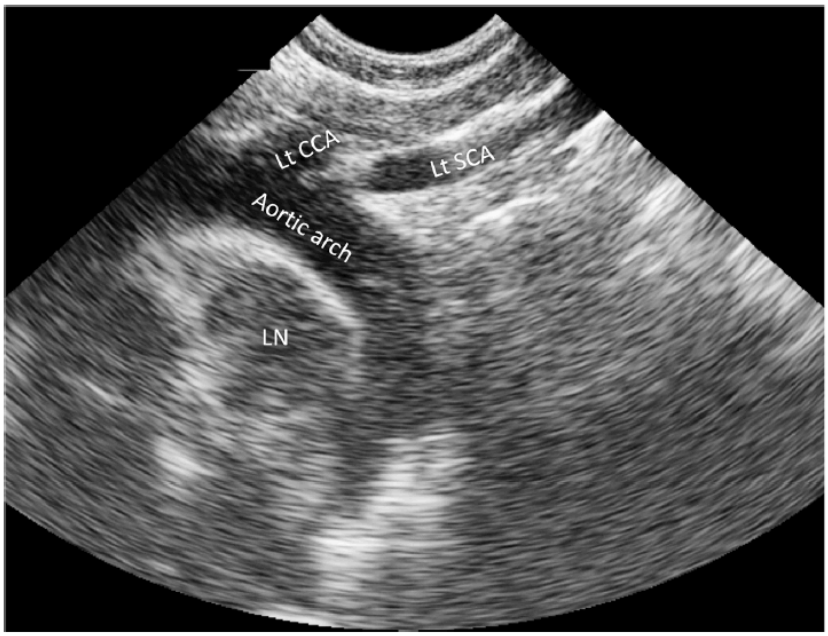


Figure 13. Transverse left parasternal view in a 10-year-old girl without human immunodeficiency virus infection but with confirmed tuberculosis demonstrates lymphadenopathy (LN) in zone G

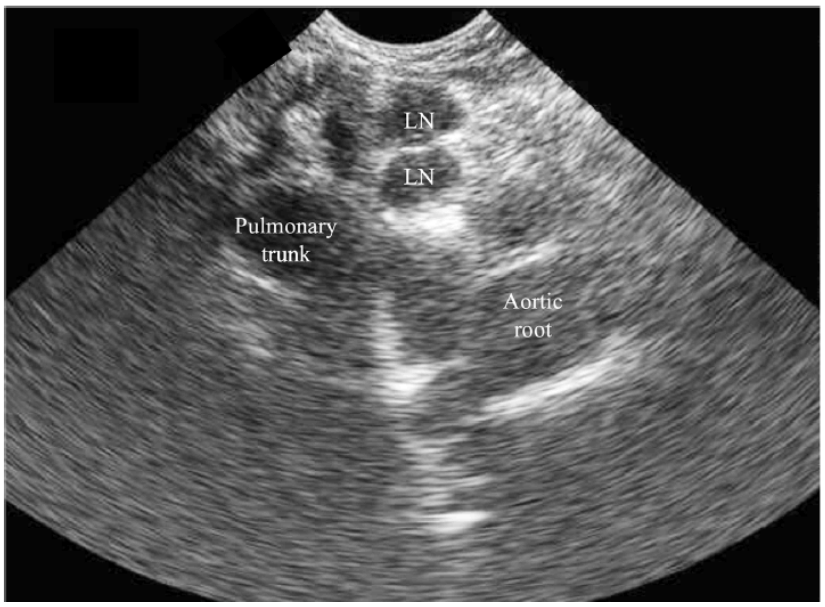
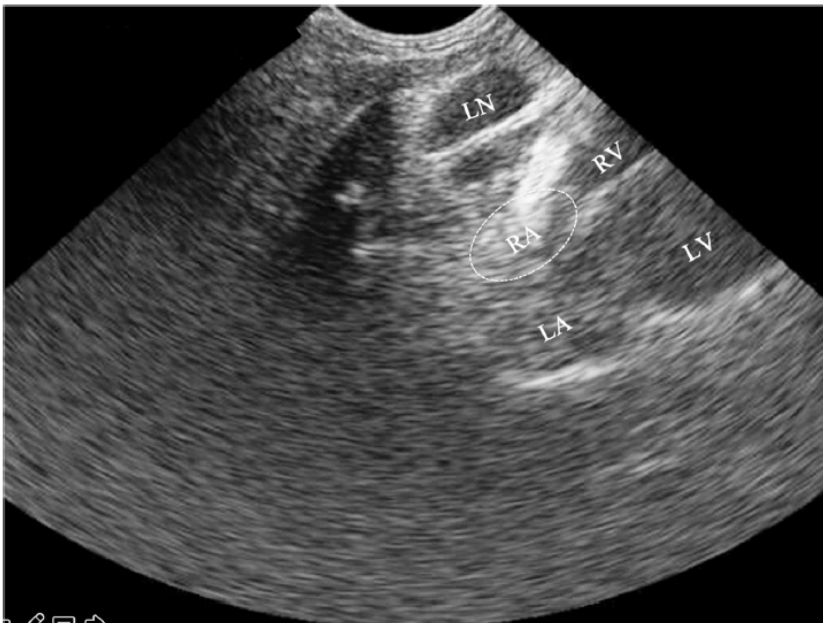


Figure 14. Longitudinal left parasternal view in a 10-year-old girl without human immunodeficiency virus infection but with confirmed tuberculosis demonstrates lymphadenopathy (LN) in zone H. The right atrium (RA) is out of view on this image, which was selected to demonstrate the lymphadenopathy optimally, but its outline (as seen on adjacent image slices not shown here) is demonstrated through the use of dashed lines.

LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle



PITFALLS

Shortcomings to consider are that the quality of the images is operator and patient dependent and that the inferior portion of the left perihilar region is not visible by US due to overlying aerated lung. Younger patients may have a difficult time cooperating during the scan. For the suprasternal views, the thymus can be mistaken for an enlarged lymph node even though the thymus has a distinctly different appearance. The thymus, which is present in young children in zones A and D, is hyperechoic when compared to mediastinal vessels, hypoechoic when compared to mediastinal fat, and does not cause mass effect. It usually appears rhomboid in the transverse view and triangular in the oblique view. With increasing age, the thymus becomes more echogenic. **Figure 7** shows a clear lymph node in zone A, surrounded by thymic tissue.

When there is lymphadenopathy, the normal anatomy might be distorted and it can be difficult to identify the anatomical landmarks. This can give the false impression that the images are of poor quality. The large blood vessels should be identified first and the operator should consider mediastinal lymphadenopathy as the cause of mass effect creating distortion of surrounding landmarks.

As discussed above, blood vessels will elongate in a different view and may demonstrate branching while lymph nodes will remain oval, appear and disappear during the scan arc and have the largest dimensions whilst scanning through their center. Colour Doppler can help differentiate vessels from lymphadenopathy. Lymph nodes may demonstrate tiny perihilar vessels or aberrant vessels on color Doppler imaging. The operator should ensure good contact between the probe and the suprasternal notch to create good quality images.

For the parasternal views, it is important that the probe is placed between the ribs. If the probe is placed on top of a rib, the image quality will be obscured by rib shadowing artifact. In children, the intercostal space is often small, which limits the operator's ability to obtain an adequate window.

The right mediastinum is not seen using this technique. Lymphadenopathy in this region will be missed using this technique.

DISCUSSION

Diagnosing childhood pulmonary TB remains challenging and the search for new diagnostic tools is ongoing. Radiologic confirmation remains a key part of the diagnostic work-up for pulmonary TB, even though the inter-reader agreement of chest radiograph is poor.[3-5] Computed tomography (CT) is considered the gold standard for the detection of mediastinal lymphadenopathy, but it may be inaccessible for children in low resource countries where TB is highly prevalent, may expose children to radiation and may require sedation. The recent introduction of portable, low-cost US machines makes US easy to use at bedside, affordable and cost-effective. In resource-limited settings, US may be the only available imaging modality. Unfortunately, a small convex or phased array transducer is not part of the standard probes provided with most US machines; therefore, the extra cost for the additional probe should be calculated. As an alternative, the C8–5 curved array vaginal transducer can be used to obtain these images. This comes as a standard probe with many US machines, but is more difficult to operate due to the length of the handle.

There are a limited number of pediatric studies that have demonstrated that transcutaneous US successfully detects mediastinal lymphadenopathy in children with suspected pulmonary TB.[6-8]

The quality of the clips and images stored is not only dependent on the sonographer but also on the child being examined. The cooperation of the child is important; infants are less compliant and hence less successfully imaged. In children with a short neck, access to the suprasternal notch is restricted, which may negatively impact image quality. In older children, the mediastinal structures are deeper, meaning that the distance from the suprasternal notch to the aortic arch is greater; the depth setting on the US machine should be adjusted to account for this, but the quality of the picture may be compromised.

Further, mediastinal lymphadenopathy can be caused by several infectious, inflammatory and neoplastic processes and is therefore not specific for pulmonary TB. This is a problem with all imaging used to diagnose pulmonary TB as differentiation of TB lymph nodes from other causes of lymphadenopathy has not been proven despite these having typical appearances with necrotic centers on CT. Detection of lymphadenopathy using US is therefore an adjunct to diagnosis, which must be made in conjunction with the clinical, epidemiological and laboratory data.

To date, no formal protocol for performing mediastinal US has been developed and no image database exists. We have performed 200 mediastinal US examinations in children with suspected pulmonary TB in developing this protocol. However, further evaluation of the accuracy of mediastinal US, and comparison with chest radiograph findings and with CT or MRI findings is needed. Additional studies evaluating training and operational aspects will also be needed to facilitate wider use of this technique.

ACKNOWLEDGMENTS

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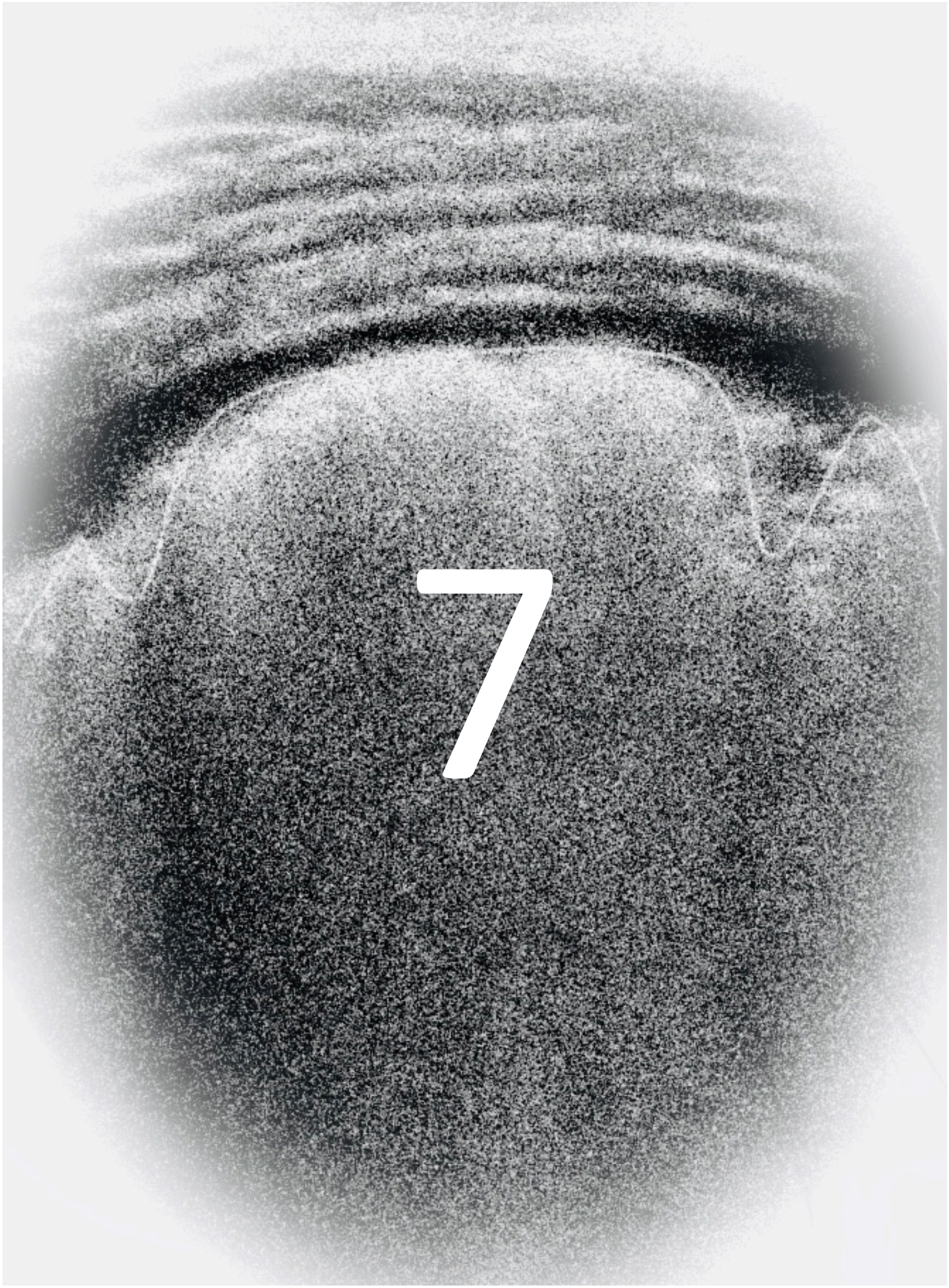
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chapter 7

CHEST ULTRASOUND FINDINGS IN CHILDREN WITH SUSPECTED PULMONARY TUBERCULOSIS

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ABSTRACT

Introduction

Chest ultrasound is increasingly used for the diagnosis of pediatric lung disease but there are limited data for its use in pediatric pulmonary tuberculosis (PTB).

Aim

To describe chest ultrasound findings in children with suspected PTB.

Methods

Consecutive children, presenting with suspected PTB to a tertiary children's hospital in Cape Town between July 2014 and March 2016, were enrolled in this cohort study. Children were categorized into three groups based on microbiological and clinical features; confirmed PTB (microbiologically confirmed), unconfirmed PTB (clinical diagnosis only), and unlikely PTB (respiratory disease not due to PTB). A clinician, blinded to categorization, performed chest and mediastinal ultrasound for consolidation, pleural gaps, pleural effusions, B-lines or enlarged mediastinal lymph nodes at enrolment and one, three and six months thereafter. Two readers interpreted the ultrasounds independently.

Results

170 children (median age 26.6 months) were enrolled; 40 (24%) confirmed PTB, 85 (50%) unconfirmed PTB, and 45 (26%) unlikely PTB. In children with confirmed PTB, pleural effusion was more common (30% versus 9% in unlikely PTB, $p = 0.024$), mediastinal lymph nodes were larger (median size 1.5 cm versus 1.0 cm in unlikely PTB, $p = 0.027$), resolution of consolidation occurred less commonly at one-month follow-up (24% versus 67% unlikely TB, $p = 0.014$) and the proportional size reduction of a consolidation was lower (44% versus 80% in unlikely PTB, $p = 0.009$). Inter-reader agreement was perfect to moderate.

Conclusion

Chest ultrasound identified abnormalities suggestive of PTB with a high inter-reader agreement. Consolidation showed slower resolution in children with confirmed PTB.

INTRODUCTION

Tuberculosis (TB) causes substantial morbidity and mortality in children, with approximately 250,000 child deaths in 2016.[1] Diagnosing pulmonary TB (PTB) in children is challenging, as signs and symptoms are non-specific, and microbiological confirmation can be difficult due to pauci-bacillary disease and limited expertise. Therefore, diagnosis of childhood PTB mainly relies on clinical and radiological findings. Radiological features of PTB in children are hilar or mediastinal lymphadenopathy, miliary pattern, consolidation or unilateral pleural effusion.[2] Older children may exhibit radiological features of adult-type PTB [2]. However, the inter- and intra-reader agreement for the detection of lymphadenopathy on chest X-ray (CXR) is low.[3,4] Radiography also exposes the child to ionizing radiation and in resource-limited settings, may be unavailable.

Chest ultrasound is an emerging imaging modality with good diagnostic accuracy for childhood pneumonia.[5] The advantages of chest ultrasound are non-exposure to ionizing radiation; bedside performance by the treating clinician reducing time to diagnosis; repeatability, thus rendering it a good tool to monitor treatment response; and with the recent development of affordable, portable ultrasound machines this investigation can be cost-effective, especially in resource-limited settings.

A small number of studies have reported on chest ultrasound for diagnosis of PTB in adults. Chest ultrasound of a HIV infected patient with PTB showed a shred sign representing consolidation.[6] Another study, comprising ten adults with miliary PTB, described that TB presents as bilateral B-lines in multiple lung zones plus sub-pleural lesions on chest ultrasound.[7] A cohort study including 60 adults with PTB found hypo-echoic sub-pleural nodules (smaller than 1 cm in diameter) as the commonest ultrasound finding.[8] Three small pediatric studies showed that mediastinal lymphadenopathy can be demonstrated on ultrasound in children with PTB.[9-11] We describe the chest ultrasound findings in children with PTB compared to those with a lower respiratory tract infection caused by other pathogens.

METHODS

Study design

This prospective cohort study was conducted at a tertiary children's hospital in Cape Town, South Africa, between July 2014 and March 2016. Ethical approval was granted by the Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, and written informed consent was provided by the parent or legal guardian.

Inclusion criteria

Children up to the age of 13 years were consecutively enrolled if they presented with a cough plus one of the following symptoms; 1) weight loss or failure to thrive over the past 3 months, 2) a positive tuberculin skin test, 3) CXR suggestive of PTB, and/or 4) close TB contact. Children with extra-pulmonary TB (EPTB) only, or children on TB treatment or TB prophylaxis for more than 72 hours, or unable to provide an adequate sputum sample for microbiological testing were excluded. For microbiological diagnosis, two induced sputum samples were obtained and subjected to liquid mycobacterial culture (BACTEC MGIT; Becton Dickinson, Sparks, MD, USA) and Xpert MTB/RIF (Xpert, Cepheid, Sunnyvale, CA, USA).[12] Drug sensitivity testing was done by using Hain genotype MTBDR test and MGIT culture. Children were categorized as confirmed PTB (*Mycobacterium tuberculosis* detected by either culture or GeneXpert), unconfirmed PTB (clinical diagnosis for PTB but negative microbiological test result) or unlikely PTB (respiratory disease due to other organisms; symptoms improved without TB treatment) according to revised National Institute of Health consensus recommendations.[13] The treating clinician was responsible for commencing TB treatment based on the national TB guidelines.[14] All children underwent chest and mediastinal ultrasound and were followed-up at one and three months after enrolment to repeat chest and mediastinal ultrasound; those with confirmed or unconfirmed PTB were seen six months after enrolment as well. We used a convenience sample of 140 children to longitudinally investigate chest ultrasound changes. We anticipated a 10% lost-to-follow-up and therefore aimed to enroll at least 154 children.

Chest ultrasound

A bedside chest ultrasound was performed at the pediatric ward or the research unit, either by a clinician (CCH) who had attended a 4-day ultrasound training or a trained sonographer (NJL) with 11 years of echocardiography experience. The clinician performed most (85%) of the scans. A portable grey scale ultrasound machine (Mindray DP10, Mindray, Shenzhen, China) with a 5-10 MHz linear probe was used. The scanning protocol described by Copetti and Cattarossi[15] was used to scan the anterior (mid-clavicular line), posterior (mid-scapular line) and lateral (mid-axillar line) chest with the patient in sitting or supine position. The chest was scanned in two planes, longitudinal and transverse (intercostal view) plane, moving the probe from the apex down to the diaphragm. The apices were scanned, placing the probe transversely in the supraclavicular region, tilting the probe caudally.
Additionally, a mediastinal ultrasound scan was done to identify enlarged lymph nodes. The patient was placed in a supine position with the neck slightly extended to improve access to the suprasternal notch. A micro-convex probe (5.0-8.5 MHz) was used. For the transverse view, the probe was positioned transversely at the suprasternal notch, tilting the probe cranially and caudally to obtain a full view. For the oblique view, the probe was positioned diagonally at the suprasternal notch, with the superior tip on the patient's left, pointing the probe towards the aortic arch and tilting from left to right to obtain a full view.[16]

Box 1. Chest ultrasound findings

1. **Lung sliding**: the presence or absence of lung sliding, the movement of the pleural line during inspiration. Absence of lung sliding is a sign of pneumothorax.
2. **A-lines**: a normal finding, these are horizontal reverberation artefacts of the pleural line (E-image 1).
3. **Interruption of the pleural line**: any interruption of the pleural line was recorded and divided into:
    a. Interruption caused by a **consolidation** - presents as a sub-pleural echo-poor area or a tissue-like area > 0.5 cm with or without air-bronchograms interrupting the pleural line (E-image 2).
    b. Interruption caused by a **pleural gap** - a small (< 0.5 cm) sub-pleural nodular consolidations interrupting the pleural line (E-image 3).
    c. Interruption of the pleural line without consolidation that can be caused by **B-lines** which are longitudinal lines, originating from the pleural line to the edge of the ultrasound screen; more than three B-lines per intercostal space in the longitudinal plane in two or more lung regions is a pathological finding for lung interstitial syndrome (E-image 4).
4. **Pleural effusion**: presents as an anechoic collection between the pleural line and the chest wall. Fibrin strands can be visible within the effusion (E-image 5).
5. **Enlarged mediastinal lymph nodes**: lymph nodes are seen as hypoechoic, round or oval structures between the mediastinal blood vessels[16] (E-image 6). We recorded enlarged lymph nodes as lymph nodes ≥ 1 cm in diameter, in the longest dimension.

The clinician (CCH) recorded the findings of all ultrasounds (also the ultrasound scans performed by NJL) on a standardized reporting form, reporting on 14 regions in the chest; namely the left and right, upper and lower, anterior, lateral and posterior chest and left and right apex. Box 1 presents the definitions of the reported chest ultrasound findings.

Both clinicians (CCH and SB) reported the overall quality of the chest ultrasound images as 'good' (pleural line, A-lines and/or findings clearly visible in all views), 'moderate' (pleural line, A-lines and/or findings clearly visible in most views but not all views), or 'poor' (pleural line, A-lines and/or findings not clearly visible in most views). The quality of the mediastinal ultrasound was reported per view as 'good' (all landmarks[16] clearly visible), 'moderate' (most landmarks[16] visible) and 'poor' (landmarks[16] not clearly visible). The sonographer reported on the compliance of the patient as 'good' (patient was cooperative and calm during the examination), 'moderate' (patient cried during the examination but remained calm) or 'poor' (patient was crying and moving during the examination).

A second clinician (SB) with one year of pediatric ultrasound experience also reported on the saved ultrasound clips. The inter-reader agreement for each sonographic finding per patient was compared. In case of discordant readings, the saved clips were re-reviewed and the findings discussed to achieve a concordant final decision.
The sonographer and second clinician reporting on the ultrasounds were blinded to clinical data, PTB category and to each other's findings.

Analysis

STATA 14.2 (StataCorp; 2015, TX, US) was used for analysis. Descriptive statistics were used to describe the study characteristics, mean and standard deviations (SD) for normally distributed continuous data, median and interquartile range (IQR) for non-normally distributed continuous data. Numbers and proportions were used for categorical data. The chi-square test (Fisher's exact test if number <5) was used to evaluate statistical significance of a chest ultrasound finding between two PTB categories, and the Mann-Whitney comparison was used to compare medians. We used the Kappa Cohen coefficient (κ) to evaluate inter-reader agreement.

RESULTS

Characteristics

We included 170 children, median age 26.6 months [IQR 15.2–59.3], 96 (57%) boys. Forty (24%) children were categorized as confirmed PTB, 85 (50%) as unconfirmed PTB and 45 (26%) as unlikely PTB (Figure 1). All children with confirmed PTB had drug sensitive TB. Twenty-three children (14%) were HIV infected. Table 1 describes the baseline characteristics by PTB category.

One-hundred and fifty-four (91%) children (39/40 [98%] confirmed PTB, 73/85 [86%] unconfirmed PTB and 41/45 [91%] unlikely PTB) returned for at least one follow-up chest ultrasound (Figure 1). Of the children that returned for follow-up, 68 (16/39 [41%] confirmed PTB, 52/73 [71%] unconfirmed PTB) received 3-drug TB treatment (rifampicin, isoniazid and pyrazinamide [RHZ]), 44 (23/39 [59%] confirmed PTB and 21/73 [30%] unconfirmed PTB, p = 0.002) received 4-drug TB treatment (RHZ plus ethambutol or ethionamide [RHZE/RHZEto]), and one child in the unlikely PTB category received seven days RHZ. Children with HIV were more likely to receive 4-drug therapy than children without HIV (15/18 [83%] versus 28/94 [30%], p = 0.000). Nine children (2/39 [5%] confirmed PTB and 7/85 [9%] unconfirmed PTB) reported poor adherence to TB treatment, 117 children (29/39 [74%] confirmed PTB, 56/74 [76%] unconfirmed PTB, and 32/41 [78%] unlikely PTB) received antibiotics other than anti-TB medication and 15 children (6/39 [15%] confirmed PTB, 8/74 [11%] unconfirmed PTB and 1/41 [2%] unlikely PTB) received prednisone (Table 2).

Quality chest ultrasound

The quality of the chest ultrasound images was similar in all three categories (E-Table 1), 83% good, 16% moderate and 1% poor quality. Mediastinal ultrasound could only be evaluated in 69% of the children, in 31% mediastinal ultrasound clips were of poor quality or could not be performed at all due to poor compliance. Of the 117 mediastinal ultrasounds that could be evaluated, 62% had a good quality. The image quality of chest and mediastinal ultrasound improved with age.

Chest ultrasound findings at enrolment

The chest ultrasound findings at enrolment are presented in Table 3.
Pleural effusion was seen in 25 (15%) children and was significantly more common in the confirmed PTB category (30%) than in the unlikely PTB category (9%, p = 0.024). In 13/25 (52%) children (8/12 [67%] confirmed PTB, 3/9 [33%] unconfirmed PTB and 2/4 [50%] unlikely PTB) the effusion was seen adjacent to a consolidation. The median age of the children with pleural effusion was 64.6 months [IQR 33.4-104.8] versus 23.9 months [IQR 14.9-48.3] of children without pleural effusion (p = 0.001).

Table 1. Baseline characteristics

	Total n = 170	***Confirmed PTB*[a] n = 40**	***Unconfirmed PTB*[b] n = 85**	***Unlikely PTB*[c] n = 45**
Male, n (%)	96 (57)	26 (65)	50 (59)	20 (44)
Median age in months [IQR]	26.6 [15.2–59.3]	48.5 [18.3-71.0]	23.9 [13.3–43.0]	23.9 [17.3–56.2]
HIV-infected, n (%)	23 (14)	6 (15)	12 (14)	5 (11)
CD4 count $^{n=22}$, median [IQR]	334 [157-626]	310 [206-358]	557 [225-649]	151 [46-157]
CD4% $^{n=19}$, median [IQR]	11.4 [7.5-20.7]	18.6 [14.4-20.7]	10.3 [6.5-18.2]	9.6 [5.1-15.8]
Positive tuberculin skin test $^{n=135}$, n (%)	77 (57)	26 (96)	50 (59)	1 (3)
Clinical signs and symptoms				
Cough, n (%)	143 (84)	32 (80)	70 (82)	41 (91)
Night sweats, n (%)	107 (63)	26 (65)	56 (66)	25 (56)
Weight loss, n (%)	114 (67.1)	27 (68)	53 (62)	34 (76)
Reduced breath sounds, n (%)	9 (5)	3 (8)	3 (4)	3 (7)
Crepitations, n (%)	25 (15)	12 (30)	13 (15)	17 (38)
Wheeze, n (%)	34 (20)	5 (13)	17 (20)	12 (27)

Table 2. Treatment per TB category

TB category	**Returning for at least one follow-up scan, n (%)**	**RHZ n (%)**	**RHZE n (%)**	**Poor adherence n (%)**	**Antibiotics n (%)**	**Prednisone n (%)**
Confirmed PTB	39 (98)	17 (44)	22 (56)	2 (5)	29 (74)	6 (15)
Unconfirmed PTB	74 (87)	49 (66)	25 (34)	7 (9)	56 (76)	8 (11)
Unlikely PTB	41 (91)	1 (3)	0	-	32 (78)	1 (2)

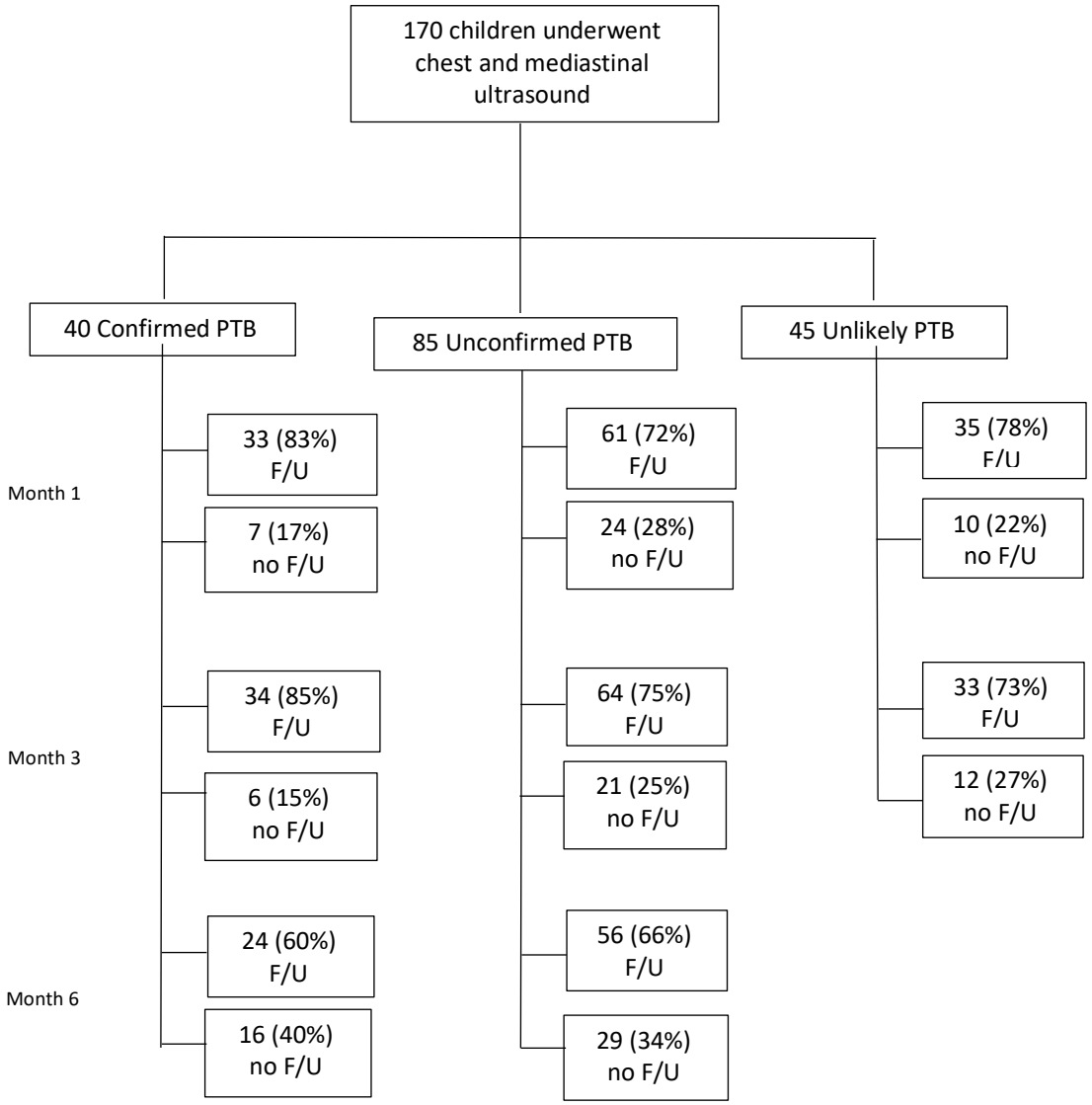
RHZ (Rifampicin, Isoniazid, Pyrazinamide), RHZE (RHZ+Ethambutol or Ethionamide

Enlarged lymph nodes were seen in 27 (22.9%) children; the lymph nodes were significantly larger in the confirmed (median size 1.50 cm [IQR 1.00-1.58 cm]) and unconfirmed PTB category (median size 1.35 cm [IQR 1.30-1.50 cm]) compared to unlikely PTB category (median size 1.00 cm [IQR 1.00-1.01 cm]; p = 0.028 and p = 0.001, respectively). Detection of enlarged lymph nodes was not age-dependent. The youngest child with enlarged lymph nodes was 13 months old, and the oldest child was 8.5 years old.

There was no statistically significant difference between the three PTB categories for the other chest ultrasound findings, i.e. consolidation (>0.5 cm), pleural gaps (consolidations <0.5 cm) or more than three B-lines per intercostal space in more than two lung regions (Table 3).

Two or more and three or more findings were more commonly detected in children with confirmed PTB (58% and 40% respectively) than in children with unlikely PTB (38%, p = 0.107 and 18%, p = 0.070, respectively; E-table 2).

Figure 1. Flow diagram



Chest ultrasound findings at follow-up

Follow-up findings are shown in Table 4.

At one-month follow-up, consolidation resolved in 30/56 (53%) children with consolidation at enrolment. Resolution occurred significantly less commonly in children with confirmed PTB (4/17 [24%]) than in unconfirmed PTB (16/24 [67%]) or unlikely PTB (10/15 [67%], p = 0.014).

In 18 (69%) of the 26 children (8/13 [62%] confirmed PTB, 5/8 [63%] unconfirmed PTB, and 5/5 [100%] unlikely PTB) who still had a consolidation at one-month follow-up, the consolidation had reduced in size. The least proportional size reduction was seen in the confirmed PTB category (44% reduction versus 76% unconfirmed PTB and 80% unlikely PTB, p = 0.009). In five (19%) children (3/13 [23%] confirmed PTB and 2/8 [25%] unconfirmed PTB) the size of the consolidation remained the same, and in three (12%) children (2/13 [15%] confirmed PTB and 1/8 [13%] unconfirmed PTB) the consolidation increased in size.

At three months, consolidation was still more commonly seen in the confirmed PTB category (15/34 [44%]) compared to the unlikely category (5/33 [17%], p = 0.010). In six of the 18 (35%) children (5/8 [63%] confirmed PTB, 1/9 [11%] unconfirmed PTB, 0/1 [0%] unlikely PTB) with pleural effusion at enrolment, the effusion resolved at one-month. One of the 14 children with a pleural effusion at enrolment seen at six-month follow-up,

Table 3. Chest ultrasound findings per TB category

	Confirmed PTB n = 40	**Unconfirmed PTB n = 85**	**Unlikely PTB n = 45**	**p-value confirmed vs unlikely PTB**	**p-value unconfirmed vs unlikely PTB**	**p-value confirmed and unconfirmed vs unlikely PTB**
Interrupted pleural line, n (%)	31 (78)	67 (79)	33 (73)	0.657	0.547	0.488
Consolidation, n (%)	22 (55)	35 (41)	21 (47)	0.443	0.661	0.902
Median size in cm [IQR]	2.78 [1.50 – 4.00]	2.00 [1.08-3.50]	2.74 [1.36-4.20]	0.361	0.286	0.774
Pleural gap, n (%)	17 (43)	49 (58)	19 (42)	0.979	0.136	0.224
>3 B-lines, n (%)	13 (33)	22 (26)	10 (22)	0.287	0.573	0.451
Pleural effusion, n (%)	12 (30)	9 (11)	4 (9)	0.024	1.000	0.230
Enlarged lymph nodes (n=118), n (%)	7/25[a] (28)	9/59 (15)	9/32 (28)	0.992	0.176	0.288
Median size in cm [IQR]	1.50 [1.00-1.58]	1.38 [1.30-1.50]	1.00 [1.00-1.01]	0.028	0.001	0.001
Normal chest ultrasound, n (%)	3 (8)	9 (10)	7 (17)	0.250	0.455	0.277

[a] enumerator = number of children with enlarged lymph nodes on mediastinal ultrasound; denominator = number of children that had a mediastinal ultrasound of sufficient quality to be evaluate

still had a small residual pleural effusion visible at the left lower lobe; at enrolment this child had a very large effusion, with septae, compromising the complete left lung.

In 12/20 (60%) children (2/5 [40%] confirmed PTB, 5/9 [56%] unconfirmed PTB and 5/6 [56%] unlikely PTB) with enlarged mediastinal lymph nodes at enrolment, the lymph nodes were no longer visible at month one. In two children with unconfirmed PTB the size of the lymph nodes reduced, in one child with confirmed PTB the lymph node size remained the same and in five children (2/3 confirmed PTB, 2/4 unconfirmed PTB and 1/1 unlikely PTB) the lymph nodes increased in size.

In another six children, enlarged mediastinal lymph nodes were seen for the first time at month one; of which three children had a poor-quality mediastinal ultrasound scan and one child had lymph nodes smaller than 1 cm on enrolment.

At month three, mediastinal lymphadenopathy was no longer seen in the unlikely PTB category, 8/9 with enlarged lymph nodes at enrolment returned at three-month follow-up.
In 3/8 (38%) children (2/4 [50%] confirmed PTB and 1/4 [25%] unconfirmed PTB) mediastinal lymphadenopathy was still visible at month six, the clinical symptoms in all three children were resolved at month six but in the two confirmed PTB cases ultrasound showed a consolidation as well.

Follow-up findings and treatment

After three months of treatment a pleural effusion was only seen in children treated with RHZ (n=6) and no longer seen in children with RHZE/RHZEto ($p = 0.011$, E-Table 3). Treatment with RHZ or RHZE/RHZEto, adherence to TB treatment, antibiotics other than anti-TB medication, prednisone or HIV infection did not have any influence on the appearance or disappearance of a consolidation or enlarged mediastinal lymph nodes at any time of follow-up (E-Table 3).

Inter-reader agreement

There was a perfect agreement between the sonographer and the second reader for lung sliding and A-lines, and the inter-reader agreement for consolidation and pleural effusion was almost perfect ($\kappa = 0.84$ and $\kappa = 0.89$, respectively). The inter-reader agreement for more than three B-lines per intercostal space in more than two lung areas and for interruption of the pleural line were substantial ($\kappa = 0.73$ and $\kappa = 0.62$ respectively). There was a moderate agreement on mediastinal lymphadenopathy ($\kappa = 0.56$).

DISCUSSION

Our study has shown that chest ultrasound may be useful to detect findings associated with PTB and for follow-up in children. At enrolment, pleural effusion was associated with confirmed PTB as were larger lymph nodes. Slower, or no resolution, of a consolidation at follow-up was associated with PTB and 4-drug TB treatment had a positive association on the disappearance of pleural effusions after three months of treatment. The inter-reader agreement was very high and good quality ultrasounds were obtained in most children.

Pleural effusion was more common in children with PTB, occurring in 30% of the confirmed PTB cases, and particularly in older children. This is consistent with prior reports documenting pleural effusion as a complication of PTB in 2-38% of pediatric cases, and more commonly in older children.[17] Pleural effusion may develop as an immune reaction to *Mycobacterium tuberculosis* but could also be caused by contiguous spread of PTB.[17] A pleural effusion is not diagnostic for PTB, as it may occur as a complication of pneumonia due to other bacteria or viruses.[18] Nevertheless, the occurrence of pleural effusion in an older child, in a TB-endemic setting, should be considered as possible PTB. Treatment with four TB drugs was associated with a better resolution of pleural effusion, possibly suggesting that four TB drugs could be the preferred choice of treatment in children with a pleural effusion.

Table 4. Chest ultrasound findings at follow-up

	Month 1			Month 3			Month 6	
	Confirmed PTB n = 33/40[a]	**Unconfirmed PTB n = 61/85**	**Unlikely PTB n = 35/45**	**Confirmed PTB n = 34/40**	**Unconfirmed PTB n = 64/85**	**Unlikely PTB n = 33/45**	**Confirmed PTB n = 24/40**	**Unconfirmed PTB n = 56/85**
Interrupted pleural line, n (%)	20 (61)	27 (42)	15 (47)	24 (71)	29 (43)	11 (37)	14 (58)	33 (59)
Consolidation, n (%)	15 (46)	11 (17)	5 (16)	15 (44)	7 (10)	5 (17)	7 (29)	7 (13)
Median size in cm [IQR]	2.48 [1.50-8.00]	1.87 [0.89-2.64]	1.64 [0.74-3.10]	2.48 [1.21-7.00]	3.00 [1.50-5.00]	0.88 [0.63-1.10]	1.49 [1.00-5.50]	2.00 [0.83-4.00]
Pleural gap, n (%)	20 (61)	27 (42)	15 (47)	14 (41)	27 (40)	7 (23)	10 (42)	30 (54)
Pleural effusion, n (%)	3 (9)	8 (13)	2 (6)	2 (7)	4 (6)	2 (6)	0 (0)	1 (2)
>3 B-lines, n (%)	7 (21)	11 (17)	4 (13)	4 (12)	5 (8)	3 (10)	1 (4)	2 (4)
Enlarged lymph nodes, n (%)	5/31[b] (16)	7/64 (11)	2/29 (7)	10/34 (29)	3/67 (5)	0/30 (0)	2/18 (11)	1/35 (3)
Median size in cm [IQR]	1.49 [1.30-1.50]	1.20 [1.11-1.68]	1.24 [1.2-1.27]	1.39 [1.00-1.50]	1.54 [1.00-2.00]	-	1.00 [1.00-1.00]	1.26 [1.26-1.26]

[a] enumerator = number of children returning for follow up per TB category per month; denominator = the total of children enrolled per TB category

[b] enumerator = number of children with enlarged lymph nodes on mediastinal ultrasound; denominator = number of children that had a mediastinal ultrasound of sufficient quality to be evaluated

Larger lymph nodes were associated with PTB (confirmed and unconfirmed PTB), although the proportion of enlarged lymph nodes was similar in all three categories. Therefore, the presence of enlarged lymph nodes per se is not useful for identifying PTB, but the size of the lymph nodes was helpful in discriminating children with PTB from those with other respiratory diseases. Further studies evaluating different size cut-offs stratified by age are needed.

Previous studies suggested that mediastinal ultrasound was useful to detect PTB cases that were missed by CXR,[9,10] and that if mediastinal ultrasound was negative, further radiographic investigation for PTB could be avoided.[10] However, we found that mediastinal ultrasound has a poor negative predictive value as the proportion of children with enlarged lymph nodes visualized by mediastinal ultrasound was very low in the confirmed (25%) and unconfirmed PTB category (15%). This was lower than in the study by Moseme et al.[11] who found enlarged lymph nodes in 40% of the children with confirmed or unconfirmed PTB.

As mediastinal lymph nodes ≥ 1 cm were also seen in children with other respiratory diseases, further studies should evaluate if it will be useful to included mediastinal ultrasound in routine lung ultrasound protocol for children with lower respiratory tract infection (LRTI). Enlarged lymph nodes were no longer seen in children with other respiratory infections at three months follow-up.

We found a moderate inter-reader agreement for enlarged mediastinal lymph nodes; this is similar to the overall inter-reader agreement for CXR findings consistent with PTB but higher than the inter-reader agreement for mediastinal lymphadenopathy on CXR ($\kappa = 0.3$).[3,4] However, enlarged mediastinal lymph nodes on ultrasound still needs to be interpreted with caution.

Consolidation was the most common finding detected by chest ultrasound. A study from Mozambique found that a consolidation was seen on CXR in 65% of TB cases (confirmed and unconfirmed TB) in young children,[19] slightly higher than we found on chest ultrasound, with 55% in the confirmed PTB category and 41% in the unconfirmed PTB category. An important finding from our study was that consolidation did not resolve, or resolved less quickly, with the least size reduction in the confirmed PTB category, even in children adhering to the correct treatment. Therefore, the speed of the reduction of a consolidation may be useful ancillary information for the diagnosis of PTB and for monitoring treatment response.

Comparison of our findings with previous studies[6-11] is limited, as previous studies evaluated paediatric patients with a positive Mantoux test[9-11] and not children with confirmed PTB, or evaluated adults[6-8] in whom PTB has a different pathophysiology.

A limitation of our study is that ultrasounds were performed and interpreted by a clinician without prior ultrasound experience but with bedside ultrasound training, which might have influenced the findings. However, bedside chest ultrasound is intended to be used by clinicians, and many other studies on chest ultrasound have been performed by inexperienced operators,[20-22] with the inter-reader agreement being high. The second clinician interpreted the clips taken by the first clinician, limiting a direct comparison of the two readers; comparing results from two interpreting sonographers would be desirable but was not feasible in this setting.

Another limitation is a small sample size for the confirmed and unlikely PTB categories, and for the follow-up findings; larger studies are needed. Nevertheless, our study has shown that there are key ultrasound findings that are associated with PTB.

Additionally, a third of mediastinal ultrasounds could not be evaluated due to low compliance or low-quality scans. Reasons for this might be that the window to the mediastinum is limited especially in young children, the technique to perform mediastinal ultrasound is more complex, and the detection of lymph nodes requires more experience.

We did not compare ultrasound findings with a gold standard imaging technique like low-dose CT chest or MRI chest, nor did we compare our findings with the commonest imaging technique for PTB, CXR. However, CXR is not the gold standard for the diagnosis of PTB and has many limitations with wide interobserver variability in interpretation.[3,4] However, comparing these two imaging modalities may be useful to investigate which is a better tool to use as a first-line imaging modality for the diagnosis of PTB.

Furthermore, only a small number of children received prednisone treatment, none of whom had enlarged lymph nodes on mediastinal ultrasound at enrolment. Therefore, we could not evaluate the influence of prednisone on

mediastinal lymph nodes. We also did not investigate the role of co-infection with other pathogens on chest ultrasound findings.

Strengths of our study are the categorization in three PTB categories, especially the confirmed PTB category and the control group of children with a lower respiratory tract infection not caused by TB, the prospective design and careful follow-up and documentation of treatment. A further advantage of ultrasound is that it can distinguish consolidation of the thymus which, on CXR, can be confused with pneumonia or other pathology.[23]

Chest ultrasound has the advantages of not exposing the child to ionizing radiation, bedside performance by the treating clinician, and the use to monitor treatment response. Therefore, chest ultrasound should be considered as a first line imaging modality in children with suspected PTB especially in settings were access to other imaging techniques is lacking.

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SUPPLEMENTARY MATERIAL

Supplementary tables

E-Table 1. Quality and compliance of chest and mediastinal ultrasound

	Quality chest ultrasound					Quality mediastinal ultrasound				
	Good	**Moderate**	**Poor**	**Compliance**	**No compliance**	**Good**	**Moderate**	**Poor**	**Compliance**	**No compliance**
Total	141 (83)	26 (16)	2 (1)	130 (78)	39 (23)	73 (51)	44 (31)	25 (18)	142 (83)	28 (17)
Confirmed PTB	34 (85)	6 (15)	-	30 (76)	10 (25)	14 (44)	10 (31)	8 (25)	32 (80)	8 (20)
Unconfirmed PTB	72 (82)	15 (17)	1 (1)	67 (76)	21 (24)	44 (59)	17 (23)	13 (18)	74 (84)	14 (16)
Unlikely PTB	36 (86)	5 (12)	1 (2)	34 (81)	8 (19)	15 (42)	17 (47)	4 (11)	36 (86)	6 (14)
Median age in months [IQR]	31.1 [18.2-63.7]	15.3 [11.2-31.0]	74.1 [22.0-126.1]	37.0 [19.5-66.9]	17.1 [11.9-22.0]	38.2 [23.7-67.2]	25.5 [18.2-60.2]	18.1 [10.7-31.0]	31.4 [18.5-62.0]	13.2 [10.5-23.4]

E-Table 2. Combination of chest ultrasound findings per TB category

	Confirmed PTB **n = 40**	***Unconfirmed PTB*** **n = 85**	***Unlikely PTB*** **n = 45**	**p-value *confirmed* vs *unlikely PTB***	**p-value *unconfirmed* vs *unlikely PTB***	**p-value *confirmed* and *unconfirmed* vs *unlikely PTB***
2 or more positive findings, n (%)	23 (58)	38 (45)	18 (40)	0.107	0.501	0.310
Consolidation + pleural gap, n (%)	11 (28)	22 (26)	11 (24)	0.748	0.775	0.797
Consolidation + pleural effusion, n (%)	9 (23)	3 (4)	2 (4)	**0.041**	1.000	0.517
Consolidation + >3B-lines, n (%)	12 (30)	14 (17)	8 (17)	0.283	0.916	0.747
Consolidation + enlarged lymph nodes, n (%)	6 (15)	4 (5)	7 (16)	0.943	**0.041**	0.147
Pleural gap + pleural effusion, n (%)	5 (13)	4 (5)	2 (4)	0.246	1.000	0.730
Pleural gap + >3B-lines, n (%)	6 (15)	13 (15)	8 (18)	0. 730	0.777	0.685
Pleural gap + enlarged lymph nodes, n (%)	4 (10)	3 (4)	4 (9)	1.000	0.243	0.484
Pleural effusion + >3B-lines, n (%)	6 (15)	5 (6)	2 (4)	0.140	1.000	0.517
Pleural effusion + enlarged lymph nodes, n (%)	2 (5)	0 (0)	0 (0)	0.218	-	1.000
>3B-lines + enlarged lymph nodes, n (%)	3 (8)	1 (1)	1 (2)	0.338	1.000	1.000

E-table 2. (continued)

	Confirmed PTB **n = 40**	***Unconfirmed PTB*** **n = 85**	***Unlikely PTB*** **n = 45**	**p-value *confirmed* vs *unlikely PTB***	**p-value *unconfirmed* vs *unlikely PTB***	**p-value *confirmed* and *unconfirmed* vs *unlikely PTB***
3 or more positive findings, n (%)	14 (35)	14 (16)	8 (18)	0.070	0.916	0.515
Consolidation + pleural gap + pleural effusion, n(%)	4 (10)	2 (2)	2 (4)	0.318	0.535	1.000
Consolidation + pleural gap + >3B-lines, n(%)	5 (13)	8 (9)	7 (16)	0.686	0.331	0.357
Consolidation + pleural gap + enlarged lymph nodes, n(%)	3 (8)	2 (2)	3 (7)	0.881	0.240	0.469
Consolidation + pleural effusion + enlarged lymph nodes, n(%)	2 (5)	0 (0)	0 (0)	0.218	-	1.000
Consolidation + pleural effusion + >3B-lines, n(%)	5 (13)	1 (1)	2 (4)	0.246	0.285	1.000
Consolidation + >3B-lines +enlarged lymph nodes, n(%)	3 (8)	1 (1)	2 (4)	0.663	0.285	0.656
Pleural gap + pleural effusion + >3B-lines, n(%)	2 (5)	3 (4)	2 (4)	1.000	1.000	1.000

E.table 2. (continued)

	Confirmed PTB **n = 40**	***Unconfirmed PTB*** **n = 85**	***Unlikely PTB*** **n = 45**	**p-value *confirmed* vs *unlikely PTB***	**p-value *unconfirmed* vs *unlikely PTB***	**p-value *confirmed* and *unconfirmed* vs *unlikely PTB***
Pleural gap + pleural effusion + enlarged lymph nodes, n(%)	2 (5)	0 (0)	0 (0)	0.218	-	1.000
Pleural effusion + >3B-lines +enlarged lymph nodes, n(%)	1 (3)	0 (0)	0 (0)	0.471	-	1.000
4 or more positive findings, n(%)	3 (8)	1 (1)	4 (9)	1.000	0.053	0.210
Consolidation + pleural gap + pleural effusion + enlarged lymph nodes, n(%)	2 (5)	0 (0)	0 (0)	0.218	-	1.000
Consolidation + pleural effusion + >3B-lines + enlarged lymph nodes, n(%)	1 (3)	0 (0)	0 (0)	0.471	-	1.000
Consolidation + pleural gap + pleural effusion + >3B-lines, n(%)	2 (5)	1 (1)	2 (4)	1.000	0.285	0.609

E-Table 3. Evolution of chest ultrasound findings related to treatment and HIV

		RHZ	RHZE	Poor adherence	Antibiotics	Prednisone	HIV infected
Month 1	**Resolved (n=30)[a]**	16/20 (80%)	4/20 (20%)	0/20 (0%)	23/30 (77%)	3/30 (10%)	6/30 (20%)
Consolidation	**Visible (n=26)[b]**	11/21 (52%)	10/21 (48%)	1/21 (5%)	23/26 (88%)	3/26 (12%)	6/26 (23%)
p-value		0.100	0.100	1.000	0.310	1.000	0.780
Month 3	**Resolved (n=37)[c]**	18/27 (67%)	9/27 (33%)	1/27 (4%)	31/37 (84%)	7/37 (19%)	6/37 (16%)
Consolidation	**Visible (n=23)[d]**	10/18 (56%)	8/18 (44%)	1/18 (6%)	19/23 (83%)	2/23 (9%)	5/23 (22%)
p-value		0.451	0.451	1.000	1.000	0.460	0.647
Month 6	**Resolved (n=25)**	15/25 (60%)	10/25 (40%)	1/25 (4%)	20/25 (80%)	5/25 (20%)	6/25 (24%)
Consolidation	**Visible (n=11)**	6/11 (55%)	5/11 (45%)	0/11 (0%)	9/11 (82%)	2/11 (18%)	4/11 (36%)
p-value		1.000	1.000	1.000	1.000	1.000	0.454
Month 1	**Resolved (n=6)**	2/6 (33%)	4/6 (67%)	1/6 (17%)	5/6 (83%)	0/6 (0%)	2/6 (33%)
Pleural effusion	**Visible (n=12)[e]**	7/10 (70%)	3/10 (30%)	0/10 (0%)	10/12 (83%)	1/12 (8%)	2/12 (17%)
p-value		0.302	0.302	0.375	1.000	1.000	0.569
Month 3	**Resolved (n=12)[f]**	3/10 (30%)	7/10 (70%)	1/10 (10%)	9/12 (75%)	1/12 (8%)	3/12 (25%)
Pleural effusion	**Visible (n=8)[g]**	6/6 (100%)	0/6 (0%)	0/6 (0%)	6/8 (75%)	0/8 (0%)	0/8 (0%)
p-value		**0.011**	**0.011**	1.000	1.000	1.000	0.242
Month 6	**Resolved (n=13)**	5/13 (38%)	8/13 (62%)	0/13 (0%)	10/13 (77)	2/13 (15%)	4/13 (31%)
Pleural effusion	**Visible (n=1)**	1/1 (100%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)
p-value		0.429	0.429	-	1.000	1.000	1.000
Month 1	**Resolved (n=12)[h]**	5/7 (71%)	2/7 (29%)	0/7 (0%)	9/12 (75%)	0/12 (0%)	2/12 (17%)
Enlarged LNs	**Visible (n=8)[i]**	4/7 (57%)	3/7 (43%)	0/7 (0%)	5/8 (63%)	0/8 (0%)	1/8 (13%)
p-value		1.000	1.000	-	0.642	-	1.000

E-table 3. (continued)

Month 3	**Resolved (n=54)**[j]	24/38 (63%)	14/38 (37%)	2/38 (5%)	41/54 (76%)	4/54 (7%)	4/54 (7%)
Enlarged LNs	**Visible (n=12)**	5/12 (42%)	7/12 (58%)	0/12 (0%)	9/12 (75%)	1/12 (8%)	3/12 (25%)
p-value		0.189	0.189	1.000	1.000	0.646	0.107
Month 6	**Resolved (n=19)**	10/19 (53%	9/19 (47%)	0/19 (0%)	12/19 (63%)	0/19 (0%)	4/19 (21%)
Enlarged LNs	**Visible (n=3)**	2/3 (67%)	1/3 (33%)	0/3 (0%)	2/3 (67%)	1/3 (33%)	0/3 (0%)
p-value		1.000	1.000	-	0.709	0.136	1.000

RHZ = 3-drug TB treatment with rifampicin, isoniazid and pyrazinamide

RHZE = 4-drug TB treatment with rifampicin, isoniazid, pyrazinamide and ethambutol or ethionamide

[a] 20/30 children with a resolved consolidation at month one of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[b] 21/26 children with a consolidation still visible at month one of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[c] 27/37 children with a resolved consolidation at month three of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[d] 18/23 children with a consolidation still visible at month three of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[e] 10/12 children with a pleural effusion still visible at month one of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[f] 10/12 children with a resolved pleural effusion at month three of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[g] 6/8 children with a pleural effusion still visible at month three of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[h] 7/12 children with resolved mediastinal lymph nodes at month one of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[i] 7/8 children with mediastinal lymph nodes still visible at month three of follow-up were in the confirmed and unconfirmed PTB category and received TB treatment

[j] 38/54 children with resolved mediastinal lymph nodes at month three of follow-up were in the confirmed and unconfirmed PTB category and received TB treatmen


8

chapter 8

CHEST ULTRASOUND COMPARED TO CHEST X-RAY FOR PAEDIATRIC PULMONARY TUBERCULOSIS

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ABSTRACT

Introduction

Chest ultrasound is increasingly used to radiologically diagnose childhood pneumonia, but there are limited data on its use for pulmonary tuberculosis (PTB).

Aim

Compare chest ultrasound with CXR findings.

Methods

Children (up to 13 years) with suspected PTB were enrolled. Bedside chest ultrasound findings were compared to CXR. Analysis was stratified by PTB category: confirmed PTB (microbiologically confirmed), unconfirmed PTB (clinical diagnosis with negative microbiological tests), or unlikely PTB (other respiratory diseases with improvement without TB treatment).

Results

159 children were enrolled (57% boys, median age 26.6 months [IQR 15.1-59.3]). Ultrasound detected abnormalities in 72% (n=114), CXR in 56% (n=89), p<0.001. Pleural effusion was detected on ultrasound in 15% (n=24) compared 9% (n=14) on CXR, p=0.004, more in confirmed PTB (33%, n=12 versus 8%, n=4 unlikely PTB, p=0.013). Ultrasound detected enlarged mediastinal lymph nodes more commonly (22%, n=25) than CXR (6%, n=10, p=0.001); the size of lymph nodes in the unlikely category (1.0 cm) was smaller than the other two PTB categories (1.4 cm and 1.5 cm, p=0.001). Inter-reader agreement (kappa Cohen) was higher for ultrasound than CXR for several findings (consolidation 0.67 versus 0.47, pleural effusion 0.86 versus 0.56, enlarged lymph nodes 0.56 versus 0.27).

Conclusion

Ultrasound detected abnormalities more frequently than CXR with higher inter-reader agreement; ultrasound abnormalities were most common in children with confirmed PTB. Ultrasound is a promising modality for detecting abnormalities in PTB. Further studies should evaluate the diagnostic accuracy of ultrasound against a gold standard.

INTRODUCTION

Tuberculosis (TB) remains a global major public health issue in children with an estimated one million incident cases in 2017.[1] Pulmonary TB (PTB) is the most common presentation but diagnosis can be challenging due to non-specific signs and symptoms, paucibacillary disease and difficulties in obtaining adequate samples.[2] Chest X-ray (CXR) is the imaging tool of choice, with perihilar or mediastinal lymphadenopathy being the most characteristic findings.[3-5] However, the intra- and inter-reader agreement for lymphadenopathy on CXR is poor (κ 0.00 – 0.40).[5-7] Other common CXR findings described in children with PTB are consolidation or pleural effusion,[3,5] but these are common findings in other respiratory infections as well.

Chest ultrasound is increasingly used for diagnosis of pediatric lung disease including pneumonia, bronchiolitis, or respiratory distress syndrome.[8] Advantages of chest ultrasound are that it is free of ionizing radiation; can be performed by the clinician at the bedside and is easily reproducible; making it a suitable tool for diagnosis, prompt management decisions and monitoring of treatment response. Training in chest ultrasound is relatively easy, and clinicians can be expected to perform good quality chest ultrasounds after 30 supervised examinations.[9] Furthermore, due to the recent development of portable, low-cost ultrasound machines, bedside chest ultrasound may become a cost-effective tool especially in resource-limited settings.

Data on the use of chest ultrasound for diagnosis of PTB in children are limited.[10-13] Previous studies showed that chest ultrasound demonstrated pleural effusion more commonly in children with microbiologically confirmed PTB than in children with other respiratory diseases.[13] Mediastinal ultrasound was feasible in visualizing lymphadenopathy,[10-12] and children with confirmed PTB had larger lymph nodes than children with other respiratory diseases.[13] Consolidation was as common in children diagnosed with PTB compared to those with other respiratory diseases, but resolution of consolidation was slower in children with confirmed PTB.[13]

The aim of this study was to compare chest ultrasound findings with CXR findings in children with suspected PTB.

METHODS

This was a prospective study of children hospitalized with suspected PTB at a tertiary children's hospital in Cape Town, South Africa from July 2014 until October 2015. Children from up to 13 years (the maximum age of children being admitted in our hospital) with suspected PTB were consecutively enrolled. Inclusion criteria were cough plus one of the following: 1) weight loss or failure to thrive over the last 3 months; 2) a positive tuberculin skin test; 3) a CXR suggestive of PTB; or 4) a household TB contact. Children on TB treatment or TB prophylaxis for more than 72 hours, those unable to provide an adequate sample, or when parents were unable to provide informed consent, were excluded. Children with exclusively extra-pulmonary TB (EPTB) or if the time between chest ultrasound and CXR was more than seven days were excluded from this analysis.

The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town. Written informed consent was obtained from a parent or legal guardian; assent was obtained in children older than 7 years.

Investigations

Two induced sputum samples were collected for liquid mycobacterial culture (BACTEC MGIT; Becton Dickinson, Sparks, MD, USA) and Xpert MTB/RIF (Xpert, Cepheid, Sunnyvale, CA, USA), HIV testing, chest ultrasound and CXR were performed on all enrolled children. Children were categorized into one of three PTB categories;[14] 1) confirmed PTB, *Mycobacterium tuberculosis* detected by either culture or GeneXpert; 2) unconfirmed PTB, clinically diagnosed but microbiological testing negative; or 3) unlikely PTB, not clinically or microbiologically diagnosed, and improvement of respiratory disease without TB treatment.[14]

All children underwent chest ultrasound, including mediastinal ultrasound, and had an anterior-posterior and lateral CXR.

Chest ultrasound

A portable, low-cost, grey scale ultrasound machine (Mindray DP10, Mindray, Shenzhen, China) with a 5-10 MHz linear probe was used to scan the chest. A clinician (CCH) without prior ultrasound experience, who attended 4-day ultrasound training prior the start of the study, performed the ultrasound scans. The children were scanned either sitting or supine plus in left and right lateral decubitus position, to examine the lungs and pleura. The chest was divided into 14 regions; the left and right, anterior, lateral and posterior, superior and inferior region, and the two apices. All regions were scanned in the longitudinal and transverse (intercostal) planes.[15] Additionally, mediastinal ultrasound was performed through the suprasternal notch with a 5.0 – 8.5 MHz micro-convex probe. The child was placed in the supine position with the neck slightly extended to improve access to the suprasternal notch: transverse and oblique views were obtained.[16] All cine clips were saved. The clinician performing the ultrasound recorded the findings 'consolidation <0.5 cm' (Image 1), 'consolidation ≥0.5 cm' (Image 2a), 'pleural effusion' (Image 3a), 'enlarged mediastinal lymph nodes ≥1.0 cm' (Image 4a) on a standardized reporting form. Another clinician (SB), with one year of pediatric ultrasound experience, reviewed the saved ultrasound cine clips and independently reported on these using the same standardized reporting form. In case the sonographer and the clinician reviewing the saved ultrasound cine clips disagreed on a chest ultrasound finding, the saved cine clips were reviewed by both clinicians again and their findings were discussed to come to an agreement. If no consensus was met the findings of the sonographer were used for comparison with CXR. A senior ultrasound specialist was consulted to resolve any disagreement on mediastinal ultrasound.

CXR

To ensure the highest achievable quality of CXR reports, the posterior-anterior and lateral CXRs were independently reviewed by two pediatric radiologists reporting on a standardized record sheet 'consolidation' (Image 2b), 'pleural effusion' (Image 3b), 'enlarged mediastinal lymph nodes' (Image 4b) and 'final diagnosis': TB or no TB. In case of disagreement on the final diagnosis, a third pediatric radiologist was consulted, and the final diagnosis was based on majority opinion. In case of disagreement for the other findings (consolidation, pleural effusion or enlarged mediastinal lymph nodes), the finding of the most experienced TB radiologist (SA) was used for comparison with ultrasound. The inter-reader agreement of clinicians analyzing the chest ultrasound was compared with the inter-reader agreement between the first two pediatric radiologists reporting on the CXRs.
The sonographer, the clinician reviewing the saved ultrasound clips, and the radiologists were blinded to each other's findings and clinical or microbiological data.

Image 1. Small consolidation (<0.5 cm) on chest ultrasound

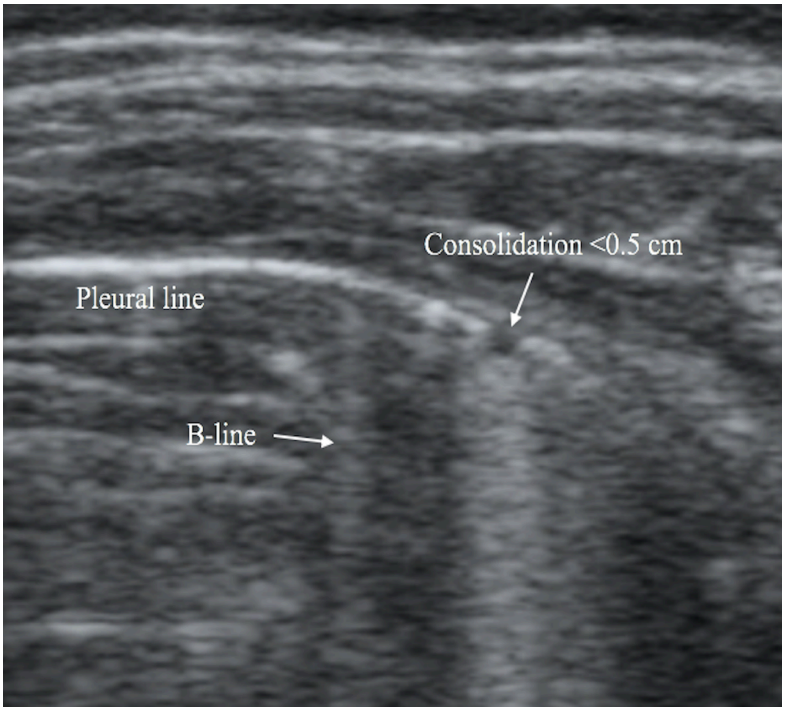
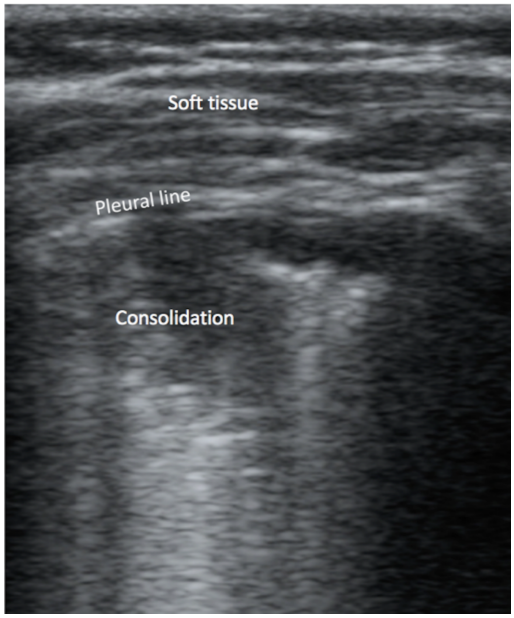


Image 2A and 2B. Large consolidation on chest ultrasound and on CXR



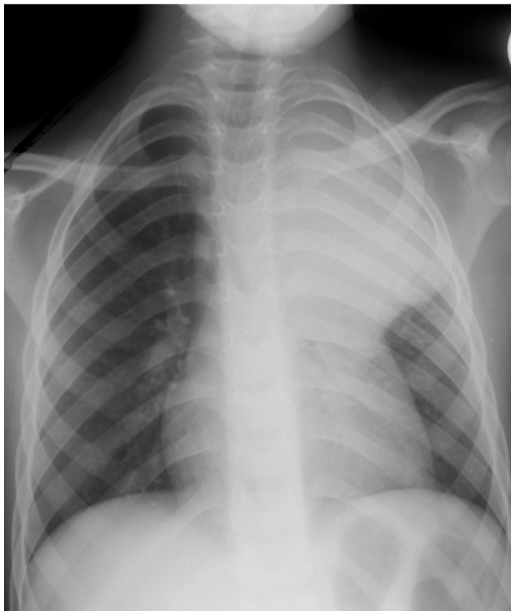
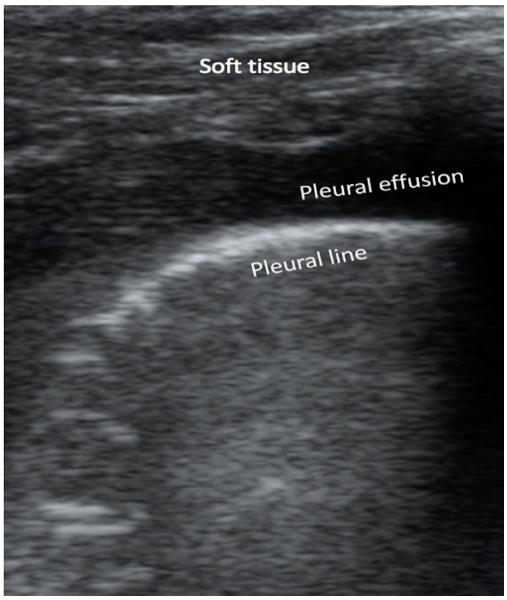


Image 3A and 3B. Pleural effusion on chest ultrasound and on CXR



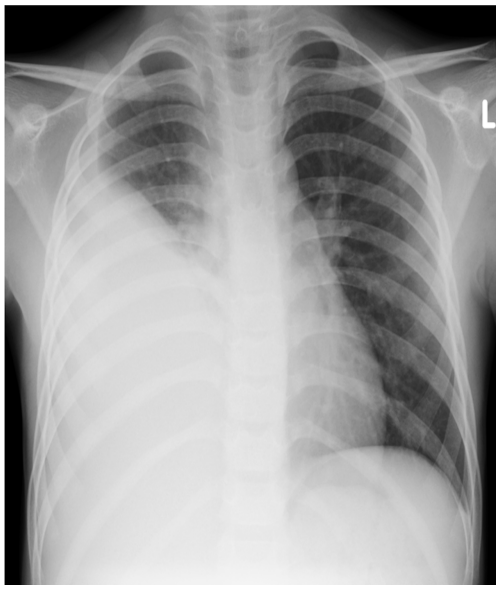
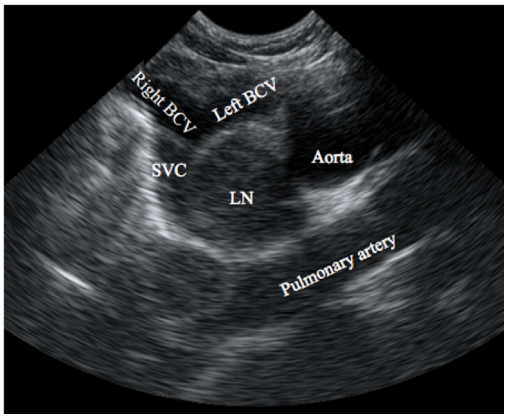
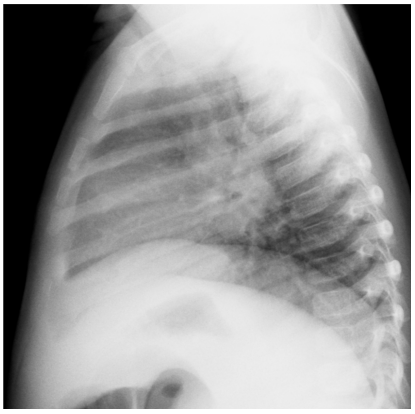


Image 4A and 4B. Enlarged mediastinal lymph node (LN) on chest ultrasound and CXR





Data Analysis

Ultrasound findings were compared to CXR findings for the presence of consolidation, pleural effusion or enlarged mediastinal lymph nodes. Descriptive statistics were used for participant characteristics; mean and standard deviation (sd) were used for normally distributed data, median and interquartile range [IQR] were used for non-normally distributed data. McNemar's test or x^2 test was used to calculate the p-value.

The Cohen's kappa coefficient (κ) was used to analyze the inter-reader agreement for chest ultrasound and for CXR. The following interpretation of the result was used: <0 no agreement, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1 almost perfect agreement.[17] STATA 14.2 (StataCorp; 2015, TX, US) was used for analysis.

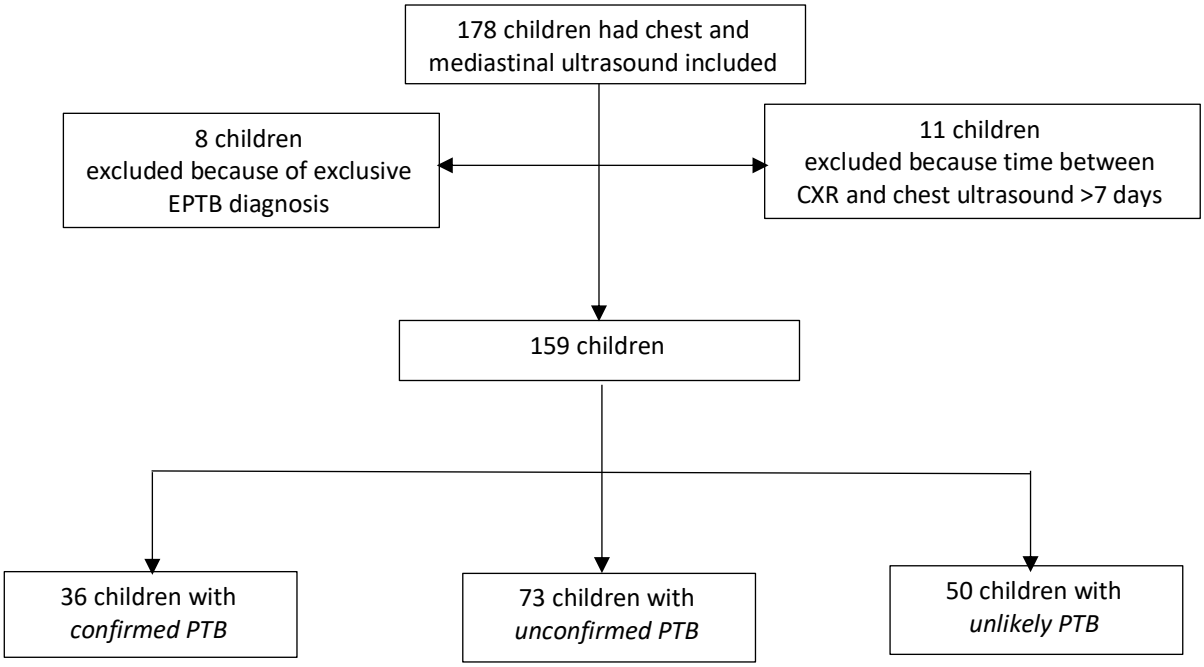
RESULTS

Demographics

One-hundred and seventy-eight children underwent chest ultrasound and CXR. Eight children were excluded from analysis because of an exclusive EPTB diagnosis, and a further 11 children were excluded because the interval between chest ultrasound and CXR was more than seven days. Of the 159 children remaining, 36 (23%) had confirmed PTB, 73 (46%) had unconfirmed PTB, and 50 (31%) had unlikely PTB, Figure 1.

Ninety children (57%) were boys; median age was 26.6 months [IQR = 15.1-58.1] and 14% (n = 22) were HIV-infected, Table 1. The mean time between chest ultrasound and CXR was 2.3 days (sd 1.7 days). The mean duration for performing chest ultrasound was six minutes [sd 5-8 minutes].

Figure 1. Flow diagram of participant enrolment



CXR = chest X-ray, EPTB = extrapulmonary tuberculosis, PTB = pulmonary tuberculosis

Table 1. Demographics

	Male, n (%)	**Median age [IQR],** *in months*	**HIV infected,** n (%)	**Mean interval chest US and CXR,** days (sd)
All enrolled patients, n = 159	90 (57)	26.6 [15.1 – 58.1]	22 (14)	2.3 (1.7)
Confirmed PTB, n = 36	23 (64)	48.6 [18.3 – 65.9]	6 (17)	2.3 (1.6)
Unconfirmed PTB, n = 73	42 (58)	25.0 [14.0 – 43.0]	10 (17)	2.4 (1.6)
Unlikely PTB, n = 50	25 (50)	23.9 [16.4 – 56.2]	6 (12)	2.1 (1.8)

CXR = chest X-ray, HIV = human immunodeficiency virus, IQR = interquartal range, n = number, PTB = pulmonary tuberculosis, sd = standard deviation, US = ultrasound

Chest ultrasound versus CXR findings

One-hundred and fourteen (72%) children had an abnormal finding (consolidation ≥0.5 cm, pleural effusion or enlarged mediastinal lymph node >1cm) on chest ultrasound versus 89 (56%) children who had an abnormal finding on CXR, $p < 0.001$. Children in the confirmed PTB category had the highest proportion with an abnormal finding on ultrasound (83%) compared to 72% in the unlikely PTB category, $p = 0.220$), Table 2.

Consolidation was the most common abnormal finding, with a consolidation ≥0.5 cm occurring in 75 (47%) children on chest ultrasound and in 83 (52%) on CXR, $p = 0.267$, Table 3. Consolidation was as common in children with confirmed PTB (56%) as in children with unlikely PTB (52%, $p = 0.744$). CXR and chest ultrasound performed similarly for detecting large consolidation (≥0.5 cm) across the three PTB categories, Table 3. In contrast, a small consolidation (<0.5cm) was reported on chest ultrasound in 78 (49%) children (15/36 confirmed PTB, 41/73 unconfirmed PTB, 22/50 unlikely PTB, $p = 0.250$). CXR reported a consolidation of any size in 44 (28%) of those children. In six (five unlikely PTB and one unconfirmed PTB) children a consolidation was reported on CXR but no consolidation (not ≥0.5 cm nor <0.5 cm) was seen on chest ultrasound. In three of those six children the radiologists did not agree on this finding, a third radiologist was consulted.

Pleural effusion was found on ultrasound in 24/159 (15%) children compared to 14/159 (9%) children on CXR, $p = 0.004$, Table 3. Both chest ultrasound and CXR detected pleural effusion in 13 children; chest ultrasound detected 11 (7%) additional children with a pleural effusion that was not seen on CXR, mainly in the confirmed PTB category where eight additional children were detected (in 7/8 children the pleural effusion was accompanied by a consolidation; in five of those seven children CXR reported only a consolidation; in the remaining children the CXR was reported to be normal). In one of the fourteen children with a reported pleural effusion on CXR, a large consolidation was reported on chest ultrasound rather than a pleural effusion.

Pleural effusion on ultrasound was significantly more commonly detected in children with confirmed PTB (33%) than in children with unlikely PTB (8%), $p = 0.013$. In the confirmed PTB category the pleural effusion was accompanied by a consolidation in 8/12 (75%) children, in the unconfirmed PTB category in 4/8 (50%) children and in the unlikely PTB category in 1/4 (25%) children. Mediastinal ultrasound could be evaluated in 112/159 (70%) children as the clips were of poor quality or ultrasound could not be performed due to poor compliance in 30%. Enlarged mediastinal lymph nodes were detected in 25/112 (22%) children on ultrasound (of whom ten were in the unlikely PTB category) and in 10/159 (6%) children on CXR, $p = 0.001$, Table 3. CXR did not detect any enlarged lymph nodes in the unlikely PTB category. The enlarged lymph nodes in the unlikely PTB category were significantly smaller than in the other two categories (median size enlarged lymph nodes unlikely PTB 1.0 cm [range 1.0 – 1.1 cm], unconfirmed PTB category 1.4 cm [range 1.0 – 2.8 cm], confirmed PTB category 1.5 cm [range 1.0 – 1.6 cm], $p = 0.001$). Twenty-two children were HIV infected; ultrasound detected abnormalities in similar numbers of HIV infected (73%) and uninfected children (58%), $p = 0.181$, Table 4.

Table 2. Abnormal chest ultrasound and chest X-ray findings by TB category

	Abnormal ultrasound[a] n/N (%)	**Abnormal CXR**[b] n/N (%)	**Abnormal CXR *or* ultrasound** n/N (%)	**p-value ultrasound versus CXR**
Total	114/159 (72)	89/159 (56)	130/159 (82)	<0.001
Confirmed PTB	30/36 (83)	22/36 (61)	32/36 (89)	0.021
Unconfirmed PTB	49/73 (67)	37/73 (51)	55/73 (75)	<0.001
Unlikely PTB	36/50 (72)	30/50 (60)	44/50 (88)	0.201

[a]Abnormal CXR means: consolidation, pleural effusion or enlarged mediastinal lymph nodes detected

[b]Abnormal chest ultrasound means: consolidation ≥0.5 cm, pleural effusion or enlarged mediastinal lymph nodes detected

CXR = chest X-ray, n = number of children with abnormal finding, N = number of children investigated, PTB = pulmonary tuberculosis

Table 3. Positive findings on chest ultrasound findings versus chest X-ray

Finding **PTB category**	**Positive chest ultrasound finding** n/N (%)	**Positive CXR finding** n/N (%)	**Agreement chest ultrasound *and* CXR positive** n/N (%)	**Positive chest ultrasound *or* CXR finding** n/N (%)	**p-value ultrasound versus CXR**
Consolidation (≥ 0.5 cm)	75/159 (47)	83/159 (52)	53/159 (33)	105/159 (66)	0.267
Confirmed PTB	20/36 (56)	20/36 (56)	15/36 (42)	25/36 (69)	1.000
Unconfirmed PTB	29/73 (40)	33/73 (45)	18/73 (25)	44/73 (60)	0.433
Unlikely PTB	26/50 (52)	30/50 (60)	20/50 (40)	36/50 (72)	0.317
Pleural effusion	24/159 (15)	14/159 (9)	13/159 (8)	25/159 (16)	0.004
Confirmed PTB	12/36 (33)	4/36 (11)	4/36 (11)	12/36 (33)	0.005
Unconfirmed PTB	8/73 (11)	7/73 (10)	6/73 (8)	9/73 (12)	0.564
Unlikely PTB	4/50 (8)	3/50 (6)	3/50 (6)	4/50 (8)	0.317
Enlarged mediastinal lymph nodes ≥ 1cm	25/112 (22)	10/159 (6)	3/112 (3)	29/159 (18)	0.001
Confirmed PTB	7/24 (29)	4/36 (11)	0/24 (0)	11/36 (31)	0.206
Unconfirmed PTB	8/51 (16)	6/73 (8)	3/51 (6)	8/73 (11)	0.257
Unlikely PTB	10/37 (27)	0/50 (0)	0/37 (0)	10/50 (20)	0.002

CXR = chest X-ray, n = number of children with a positive finding, N = number of children who underwent the investigation

Table 4. Positive chest ultrasound and CXR findings in HIV infected and non-infected children with suspected PTB

Imaging finding	HIV+ (n = 22)	HIV – (n = 137)	p-value
Abnormal chest ultrasound, n (%)	16 (73)	79 (58)	0.181
Consolidation ≥ 0.5 cm, n (%)	14 (64)	61 (45)	0.096
Pleural effusion, n (%)	5 (23)	19 (14)	0.281
Enlarged mediastinal lymph nodes, n/N (%)	3/16 (19)	22/96 (23)	0.711
Abnormal CXR, n (%)	14 (64)	75 (55)	0.435
Consolidation, n (%)	14 (64)	69 (50)	0.247
Pleural effusion, n (%)	1 (5)	13 (9)	0.448
Enlarged mediastinal lymph nodes, n (%)	0 (0)	10 (7)	0.191

Table 5. Inter-reader agreement of chest X-ray and chest ultrasound

Imaging finding	Kappa Cohen chest X-ray	Kappa Cohen chest ultrasound
Consolidation < 0.5 cm	-	0.39
Consolidation ≥ 0.5 cm	0.47	0.67
Pleural effusion	0.56	0.86
Enlarged mediastinal lymph nodes	0.27	0.56

Chest ultrasound had 'substantial' and 'almost perfect' inter-reader agreement for consolidation ≥0.5 cm (κ = 0.67) or pleural effusion (κ = 0.86) respectively, and a moderate agreement for enlarged mediastinal lymph nodes (κ = 0.56). The inter-reader agreement for a consolidation <0.5 cm on chest ultrasound was fair (κ = 0.39). The inter-reader agreement for CXR was fair to moderate for consolidation (κ = 0.47), pleural effusion (κ = 0.56) and enlarged mediastinal lymph nodes (κ = 0.27), Table 5.

DISCUSSION

In this study of children with suspected PTB, an abnormal finding was seen more frequently on chest ultrasound than on CXR for all three PTB categories. Children in the confirmed PTB category had an abnormal finding on chest ultrasound more frequently. Furthermore, ultrasound had a higher inter-reader agreement than CXR for consolidation ≥0.5 cm, pleural effusion or enlarged mediastinal lymph nodes. Ultrasound had the additional advantages in that it could be performed relatively easily as a bedside investigation, was quick to perform and was done by a clinician.

This is the first study comparing chest ultrasound findings with CXR findings in children with suspected PTB. A recent systematic review showed that there is limited data on the use of chest ultrasound in patients with PTB.[18] This review identified 12 small (1-87 participants) studies, of which 3 were pediatric (each with 30 – 57 participants), using mediastinal ultrasound.[10-12] We found that a large consolidation (≥0.5 cm) was nearly as commonly detected on ultrasound as on CXR and that a small consolidation (<0.5 cm) was predominantly identified on chest ultrasound. This is consistent with previous pneumonia studies,[19,20] in which a consolidation <1 cm was more commonly detected on chest ultrasound than CXR.[19,20] A study performed in adults with PTB

reported that sub-pleural nodules (consolidation <1 cm, close to the pleural line) were present in almost all patients;[21] however, a control group was lacking. In our study, a small consolidation was found on ultrasound in 49% of children, and was present in all three TB categories, including the unlikely PTB category. The clinical importance of small consolidation is unclear, as this may represent early disease, but has also been reported in healthy people. Further, the inter-reader agreement for a small consolidation was only fair. Further studies are needed to evaluate the clinical relevance and natural history of a small consolidation.

Pleural effusion was significantly more common on ultrasound than on CXR, especially in the confirmed PTB category. This is consistent with prior studies that have shown ultrasound to be superior to CXR for pleural effusion,[22,23] and for differentiating consolidation from pleural effusion.[24] In the confirmed PTB category, pleural effusion was often accompanied by a consolidation. Although pleural effusion and consolidation can occur in children with a pneumonia caused by other bacteria or viruses, PTB should be considered as a possible diagnosis when a pleural effusion is detected in the right setting and accompanied by a consolidation.

Enlarged mediastinal lymph nodes, the diagnostic hallmark for PTB in children,[3-5] were more commonly detected by ultrasound but were also found in the unlikely PTB category, but the size of nodes was smaller than in the other two categories. In contrast CXR did not detect enlarged lymph nodes in unlikely TB; as the size of lymph nodes in the unlikely PTB category ranged from 1.0 to 1.1 cm, these might have been too small to be detected on CXR. A previous study in children with a positive tuberculin skin test showed that mediastinal ultrasound detected enlarged lymph nodes in 67% of the children with a normal CXR.[10] It can be difficult to detect enlarged mediastinal lymph nodes on the posterior-anterior CXR as vascular and thymic structures might be confused for enlarged lymph nodes and vice versa. In addition, the wide inter-reader variability of reporting enlarged lymph nodes on CXR makes the interpretation difficult. Detection of enlarged mediastinal lymph nodes on ultrasound in the unlikely PTB category makes it difficult to distinguish PTB from other respiratory infections of other causes; based on the difference in size measured between the two PTB category and the unlikely PTB category, we recommend that future studies should determine the cut-off for enlarged lymph nodes in children with TB on ultrasound.

Chest ultrasound had a better inter-reader agreement for consolidation, pleural effusion or enlarged mediastinal lymph nodes than CXR. This is in line with previous studies showing poor inter-reader agreement for the detection of mediastinal lymphadenopathy on CXR[5-7] and a higher inter-reader agreement amongst chest ultrasound readers compared to CXR readers for the detection of consolidation in children with pneumonia.[25]

Limitations of this study include comparing chest ultrasound with CXR. We found a limited interreader agreement on CXR findings, therefore we considered CXR as an imperfect comparison to ultrasound, because of that we chose not to calculate the sensitivity or specificity of ultrasound versus CXR. Until advances in technology make CT or MRI a safe, ethical choice, we are limited to using CXR. A further limitation was the lack of prior ultrasound experience by the sonographer; previous chest ultrasound studies on children with pneumonia found that the diagnostic accuracy was higher when the sonographer was more experienced.[8]

Chest ultrasound is limited as only findings close to the pleural line can be detected, as the ultrasound beam will be scattered and impeded by the aerated lung. Therefore, abnormalities that do not reach the pleural line may be missed by ultrasound. Mediastinal ultrasound could not be evaluated in 30% of the children, due to low-quality imaging or non-compliance. This is a known limitation inherent in the use of mediastinal ultrasound especially in young children with short necks.

A further limitation is that a third radiologist was only consulted when there was a disagreement on the final diagnosis. Finally, ultrasound images were interpreted by clinicians, whereas CXR images were interpreted by pediatric radiologists; despite this, ultrasound revealed abnormalities more commonly and with a higher inter-reader agreement.

Further prospective, larger-scale, multi-center studies evaluating the diagnostic accuracy of chest ultrasound compared to a gold standard such as CT or MRI should be conducted, using experienced sonographers.

CONCLUSION

Chest ultrasound detected abnormalities more frequently than CXR, and ultrasound abnormalities were most common in the confirmed PTB category. Chest ultrasound also showed higher inter-reader agreement between clinicians for all categories of findings than CXR read by subspecialist pediatric radiologists. Chest ultrasound may therefore be useful to identify lung disease including PTB and other respiratory diseases. Lymph node size appears to differentiate PTB from other lower respiratory tract infections. However, microbiologic diagnosis remains important for confirming diagnosis. Further studies should evaluate if chest ultrasound detects enlarged mediastinal lymph nodes in children with other respiratory diseases, and evaluate the diagnostic accuracy and significance of chest ultrasound compared to a valid imaging gold standard, like chest CT or MRI.

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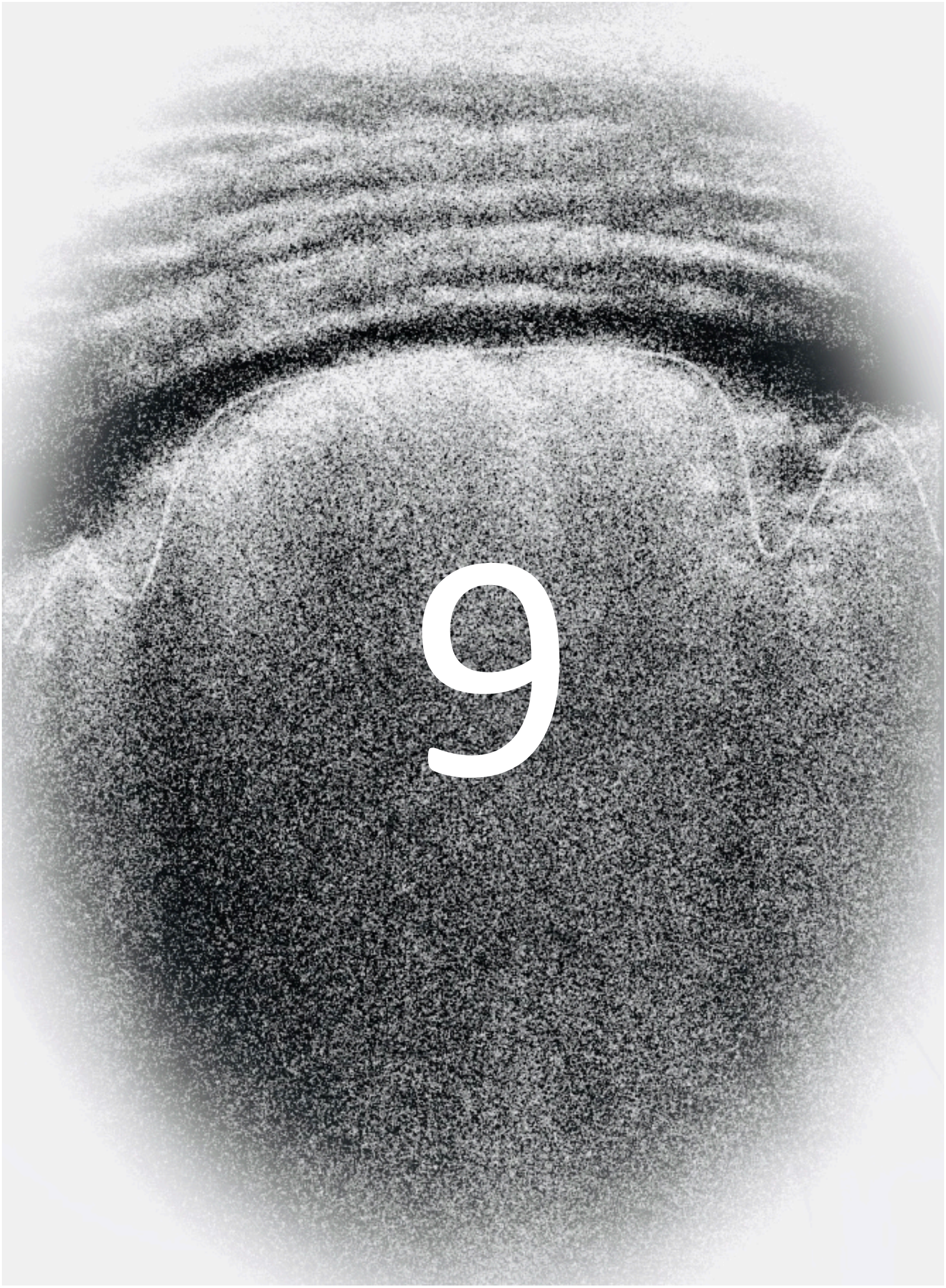
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chapter 9

CHEST ULTRASONOGRAPHY IN PATIENTS WITH HIV: A CASE SERIES AND REVIEW OF THE LITERATURE

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ABSTRACT

Introduction

Pulmonary disease is common in HIV infected patients. Diagnostic means, however, are often scarce in areas where most HIV patients are living. Chest ultrasonography has recently evolved as a highly sensitive and specific imaging tool for diagnosing chest conditions such as pneumothorax, pneumonia and pulmonary edema in critically ill patients. This article addresses the issue of imaging and differentiating common pulmonary conditions in HIV-infected patients by chest ultrasonography.

Methods

We report chest ultrasound features of five different common pulmonary diseases in HIV-infected patients (bacterial pneumonia, Pneumocystis jirovecii pneumonia, tuberculosis, cytomegalovirus pneumonia and non-Hodgkin lymphoma) and review the respective literature.

Conclusions

We observed characteristic ultrasound patterns especially in Pneumocystis jirovecii pneumonia and pulmonary lymphoma. Further exploration of chest ultrasonography in HIV-infected patients appears promising and may translate into new diagnostic approaches for pulmonary conditions in patients living with HIV.

INTRODUCTION

Ultrasonography has gained increasing interest during the past two decades. Various medical specialties have adopted focused ultrasound protocols, which are applied by physicians to immediately answer medically important questions, and to guide clinical management.[1] Portable ultrasound machines are available at reasonable cost. Hence, point-of-care ultrasonography is becoming a medical imaging modality suitable for resource-limited settings, where radiological equipment and expertise are scarce.

Chest ultrasonography is among the most recently emerging ultrasonography applications. For years the prevailing opinion was that ultrasound would be unsuitable for diagnosing lung pathologies due to air impeding transmission of sound waves. Today the value of ultrasound in visualizing lung pathologies arising close to the pleura is frequently documented. Assessment with ultrasound has proved sensitive for respiratory conditions such as pneumothorax,[2-4] pneumonia,[5-11] pleural effusion,[12,13] and pulmonary edema,[14,15] it also decreases time to diagnosis,[11] reduces costs,[11] and exposure to ionizing radiation.[16]

Ultrasound features representing healthy lungs or conversely indicating pathology are well described;[17] assessment of a few sonographic features (A-lines, B-lines, lung sliding, hepatization, anechogenicity) is usually enough to differentiate between healthy lung, consolidation, interstitial disease or pleural disease. In brief, A-lines are horizontal, hyperechoic reverberation artifacts from the pleural line and represent healthy lung parenchyma. B-lines are vertical, hyperechoic reverberation artifacts projecting from the pleural line to the bottom of the screen; occurrence of more than three B-lines in one intercostal space indicates interstitial pathologies of the lung tissue (sensitivity 97 %, specificity 95 %).[18] Pleural effusions are typically represented by anechoic collections between chest wall and lung. Lung consolidations present as subpleural hypoechoic areas, possibly with hyperechoic air bronchograms. As their echogenicity mimics liver tissue they are described as “hepatization” and can be a feature of infection, malignancy, pulmonary embolism or atelectasis.

Pulmonary diseases are common in HIV-infected patients.[19] Opportunistic infections, neoplastic diseases and other pulmonary pathology occur more frequently than in non-infected individuals.[20] Lung infection due to Pneumocystis jirovecii , (PJP , previously P. carinii pneumonia) was the first opportunistic infection described in HIV-infected patients and the striking increase in incidence furthered the description of the Acquired Immunodeficiency Syndrome (AIDS).[21] Increasing access to antiretroviral treatment (ART) has changed the global epidemiology of pulmonary manifestations in HIV, but pulmonary disease still accounts for about one-third of admissions of HIV patients.[19] The burden of pulmonary disease is underlined by the high incidence of pulmonary tuberculosis (PTB) in HIV patients in sub-Saharan Africa.[22]

The differential diagnosis of pulmonary disease in HIV infected patients is broad (see Table 1). History is helpful in the diagnostic process, as is the CD4 count as a marker of immunosuppression. Occurrence of opportunistic infections depends on the degree of immunosuppression; PJP and atypical mycobacterioses mainly occur when CD4 cell counts are <200 cells/ml; CMV and disseminated fungal infections are mainly seen when CD4 counts fall <100 cells/ml.[20] PTB is an infection affecting HIV patients at any stage of the disease with CD4 counts often still being >500/µL.

For a definitive diagnosis, identification of the pathogen or histo-pathological workup from bronchial secretions or diseased tissue is paramount. The majority of HIV-infected patients live in resource-limited settings, where sputum microscopy for acid-fast bacilli may be the only microbiological test available.

Imaging of the diseased lung can reveal patterns suggesting causative pathogens and processes. Chest radiographs and computed tomography (CT) showing consolidations, ground-glass opacity, cystic lesions or pulmonary nodules permit narrowing of differential diagnosis.[23] Many emergency departments in industrialized countries are equipped with CT, but access to even basic radiological imaging technology is often limited in countries where most HIV infected patients live.[24] This widespread shortage of imaging services in resource-limited settings significantly reduces health care quality and increases health care disparities.[25] Innovative imaging approaches such as clinician performed sonography may help to improve the situation,[26,27] provided that availability of ultrasound machines is matched by appropriate and sustained staff training.

Data on chest ultrasonographic findings in HIV-infected patients are very limited. However, as pulmonary diseases do significantly contribute to HIV-related morbidity and mortality, point-of-care chest sonography

recommends itself to quickly orient the clinician to differential diagnoses, required investigations and management decisions.

Here we present a case series of HIV-infected patients with typical pulmonary conditions undergoing chest ultrasound in Vicenza, Italy. The patients each had additional standard radiological workup. All ultrasound examinations were performed by MTG, a clinician specialized in infectious diseases and tropical medicine with over 20 years of experience in ultrasound in infectious diseases. Ultrasound examinations were performed using an Aplio XG Model SSA-790A (Toshiba, Tokyo, Japan), with a 3.5-MHz convex probe and an 8-MHz linear probe. The ultrasound studies were performed as point-of-care examination as part of routine clinical care. The convex probe was used first; in the case of superficial or pleural disease, scanning was also performed with the linear probe. Approval for publication was sought by the Ethics Committee for Clinical Research of the Vicenza Province (Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza, approval number 57/2014).

CASE SERIES

Case 1. Bacterial pneumonia (Haemophilus influenzae)

A 50-year-old HIV-infected man from Burkina Faso, who was non-compliant to ART, presented with fever, chills and chest pain. His CD4 count was 112 cells/μL. On admission, his chest radiograph (Online Resource 8) and CT (Figure 1) showed pneumonia with pleural effusion. Lung ultrasound performed on the same day revealed a large consolidation with hyperechoic air bronchograms and a small pleural effusion (Figure 2 and Online Resource 1). While cultures of bronchial secretions remained negative, blood cultures grew Haemophilus influenzae. The patient was successfully treated with antibiotics and ART was re-started after recovery.

Figure 1. Lung CT scan showing right basal consolidation and air bronchograms

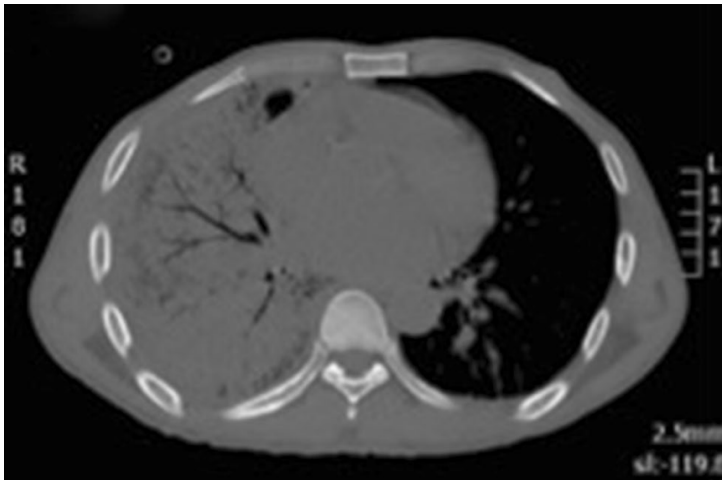


Figure 2. Transthoracic ultrasonography showing a hypoechoic consolidation with string-like echogenic reflexes due to remaining air in the bronchial system (sonographic air bronchogram). Additionally, a small pleural effusion is visible

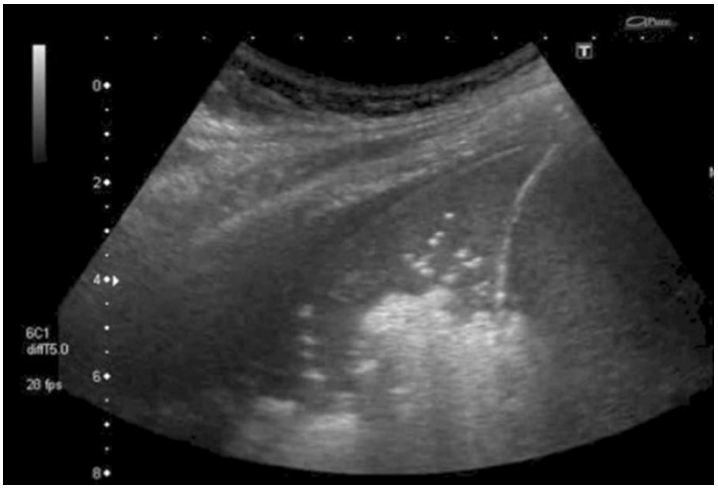


Table 1. Correlation of radiological patterns and ultrasound findings in pulmonary disease in patients with HIV infection (radiological pattern and possible etiology adapted and modified from Hoffman and Rockstroh[58])

Radiological pattern	Expected US pattern	Possible etiology
Without radiological changes	A-lines Pleural line moving normally	PJP Asthma KS of the trachea
Focal infiltrates	Subpleural hypoechoic region ± hyperechoic air bronchograms "Hepatization" of the lung	Bacterial pneumonia Mycobacteriosis Fungi Lymphoma Lung cancer
Interstitial pattern	B-lines Possible small subpleural hypoechoic regions	PJP CMV KS Lymphocytic interstitial pneumonia Interstitial lung diseases Cardiac insufficiency
Miliary pattern	Not reported	Mycobacteriosis Fungi
Pneumothorax	A-lines Absent lung sliding Identifiable 'lung point' In M-mode: "seashore sign"	PJP
Cavernous lesions	Not reported	Mycobacteriosis Bacterial abscess (Staphylococcus, Pseudomonas) Lung cancer
Cystic lesions	Multiple small echogenic gas containing lesions surrounded by hypoechoic solid lung	PJP Fungi PTB
Pleural effusion	Anechoic collection between chest wall and the lung Lung tissue may appear echogenic (compression atelectasis) Echogenic fibrin strands and septae possible	Bacterial pneumonia Mycobacteriosis KS Lymphoma Cardiac insufficiency

CMV = cytomegalovirus, KS = Kaposi's sarcoma, PJP = Pneumocystis jirovecii pneumonia, PTB = pulmonary tuberculosis, US = ultrasound

Case 2. Pneumocystis jirovecii pneumonia

A 35-year-old man from Italy with a history of syphilis presented with fever and weight loss. The patient tested HIV positive; his CD4 count was 34 cell/µL. Initially the patient denied experiencing any respiratory symptoms. His chest radiograph on admission was normal, but lung ultrasound performed on the same day showed multiple B-lines suggesting an "interstitial pattern" of lung injury. Additionally, small peripheral consolidated areas were noted, indicating subclinical lung pathology (Figure 3 and Online Resource 2). A subsequent chest radiograph (Online Resource 9) and CT scan (Figure 4) performed 4 days later suggested PJP; BAL microbiologically confirmed this. During the following 10 days he developed respiratory distress. The lung ultrasonography now showed large consolidated areas with bright, hyperechoic reflexes, suggesting gas and fluid trapping (Figure 5 and Online Resource 3). The patient deteriorated requiring mechanical ventilation, Pneumocystis jirovecii pneumonia (PJP) was treated with co-trimoxazole and he slowly recovered.

Figure 3. Transthoracic ultrasonography of the pleura shows an interstitial pattern with multiple B-lines. Additionally, small subpleural consolidations are present

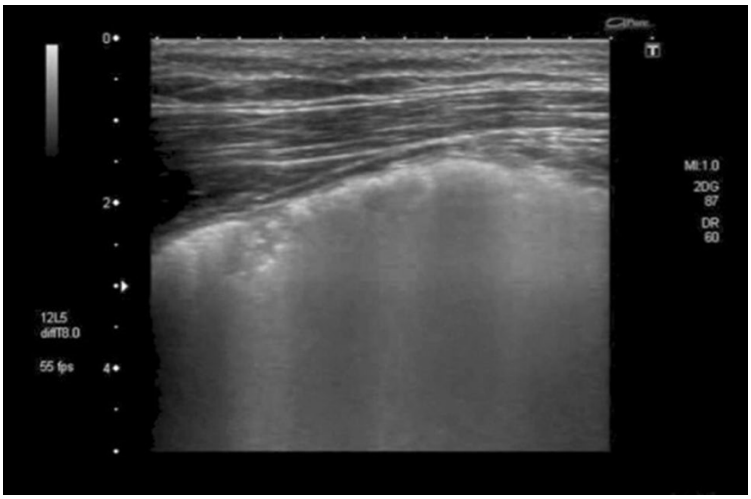


Figure 4. Chest CT after development of respiratory distress showing coarse interstitial thickening with cyst formation and areas of unaffected parenchyma suggestive of pneumocystis pneumonia, which was later microbiologically confirmed in BAL

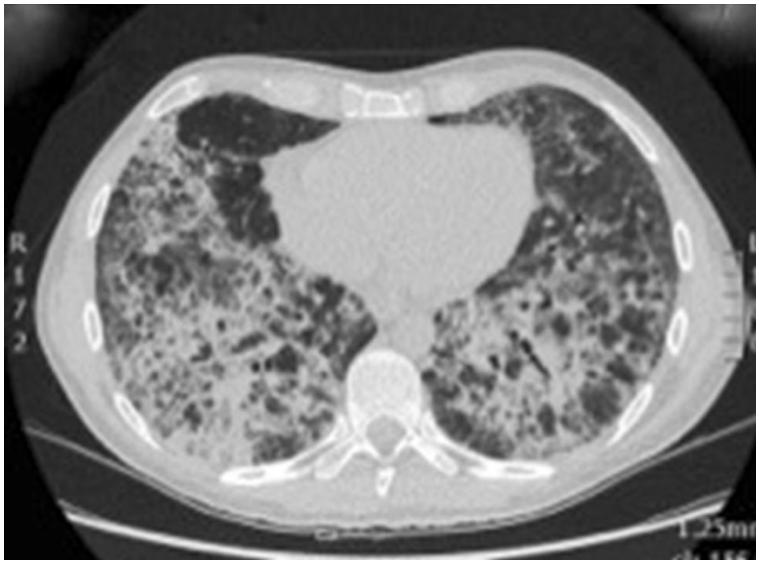
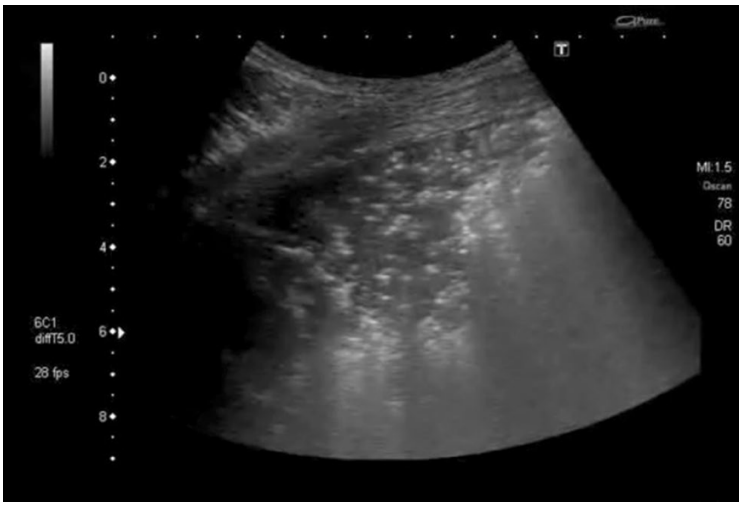


Figure 5. Transthoracic ultrasonography showing large consolidated areas with multiple bright artifacts suggesting gas inclusions. These represent both air bronchograms and cystic areas of the lung



Case 3. Tuberculosis

A 44-year-old Italian drug addict was admitted with fever. Abdominal ultrasound revealed enlarged hypoechoic abdominal lymph nodes and disseminated splenic hypoechoic lesions suggesting micro-abscesses; disseminated TB was suspected. The HIV test was positive and CD4 count was 173 cells/μL. Lung sonography at admission revealed a consolidation in the left lower lobe, resembling a “torn out” area of the lung (“shred sign”) (Figure 6 and Online Resource 4). This raised suspicion of infiltrative pulmonary involvement by TB disease, which a chest radiograph performed the same day confirmed (Figure 7); a subsequent BAL showed acid-fast bacilli. The patient received anti-tuberculous treatment and subsequently ART.

Figure 6. Transthoracic ultrasonography showing a subpleural hypoechoic consolidation. Due to the shredded, fractal boundary between the consolidation and the underlying aerated lung this is called “shred sign”

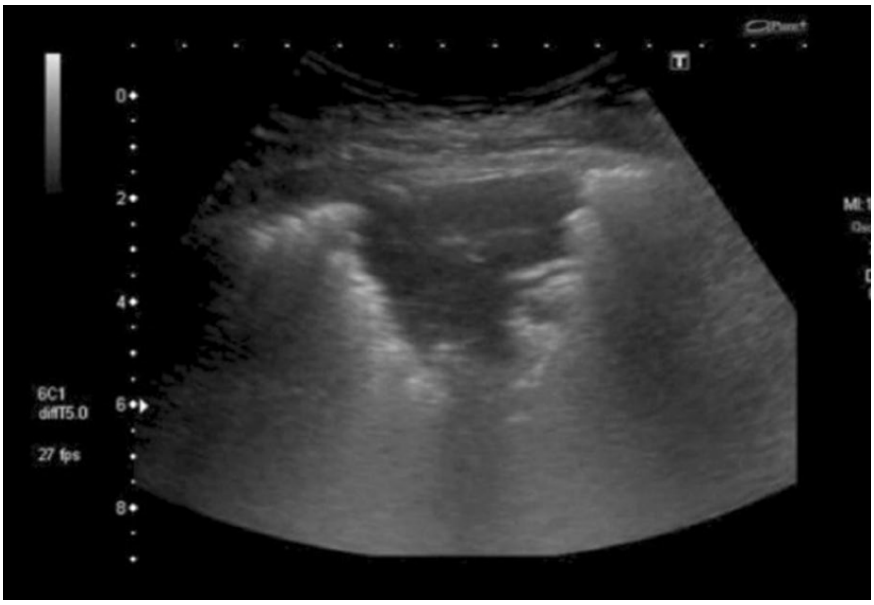
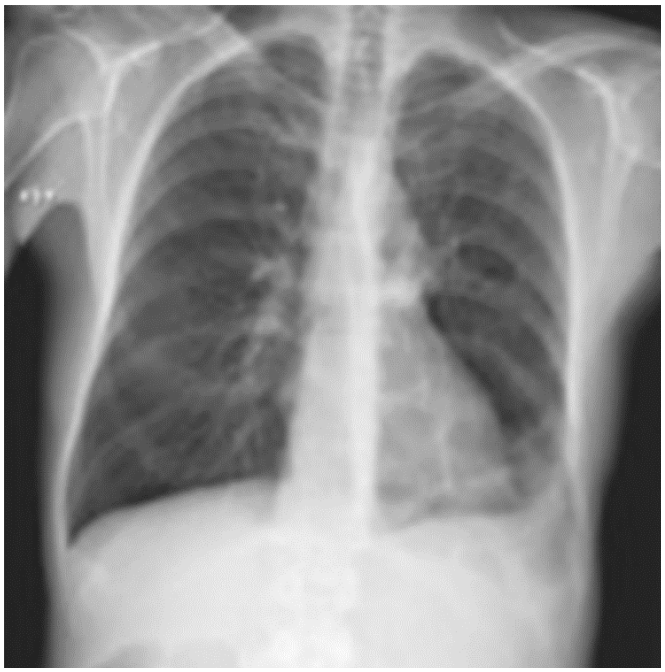


Figure 7. Chest radiograph of a febrile HIV-infected male (CD4 count 173 cells/µl) suggesting a left sided basal pneumonia



Case 4. Cytomegalovirus pneumonia

A 54-year-old HIV-infected man from Ivory Coast presented with fever, dyspnea, anemia and bloody stools. On admission his CD4 count was 15 cells/µ L. On admission a chest radiograph showed a diffuse interstitial pattern (Online Resource 10). Lung ultrasonography on the same day showed multiple B-lines originating from the pleura, which did not extend completely to the bottom of the screen (Figure 8 and Online Resource 5). These sonographic changes prompted the treating clinician to perform a chest CT scan that suggested interstitial pneumonia (Figure 9). A subsequent colonoscopy showed multiple bleeding ulcers and CMV-DNA was detected in serum. Treatment with gancyclovir was started with a good clinical response.

Figure 8. Transthoracic ultrasonography of the pleura. Multiple B-lines are visible suggesting an interstitial pattern of lung injury; as these are not penetrating the complete image, nor do they extinguish the A-lines completely which are visible towards the right side of the screen, these should be referred to as “lung rockets”

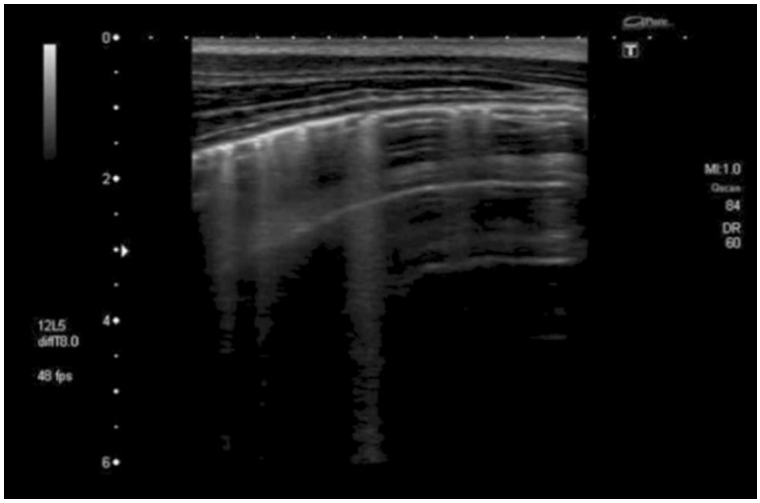
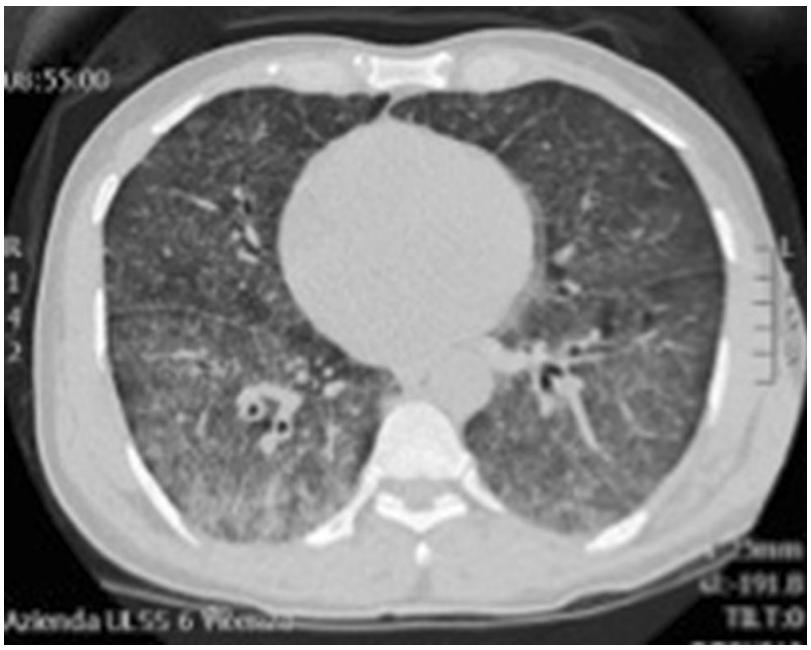


Figure 9. Chest CT scan showing ground-glass appearance and interstitial thickening due to interstitial pneumonia caused by the underlying generalized CMV infection



Case 5. Non-Hodgkin lymphoma

A 56-year-old Italian man recently diagnosed with HIV, presented with fever, dyspnea and weight loss. He was non-smoker and worked in the chemical industry. On admission his CD4 count was 53 cells/μL. The chest radiograph performed 8 days after admission showed a dense opacity in the right lower field (Figure 10); pneumonia and malignancy were suggested as differential diagnoses. Lung ultrasonography performed on the same day showed a consolidation of the right lower lobe (Figure 11a and Online Resources 6 and 7). This was not homogenous, suggesting focal parenchymal abnormalities surrounding the vascular structures on color-Doppler (Figure 11b). Air bronchograms were scarce and only present in the peripheral parts of the consolidation. Retrospectively, the hypoechoic areas were interpreted as lymphoma nodules. A CT-guided lung biopsy (Online Resource 11) revealed an HIV-related diffuse large B cell lymphoma. The patient was treated with poly-chemotherapy (CHOP) and ART and improved.

Figure 10. Chest radiograph with consolidation adjacent to the right hemi-diaphragm

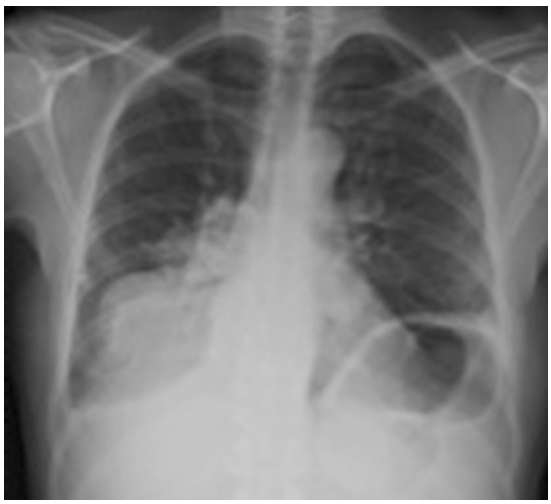
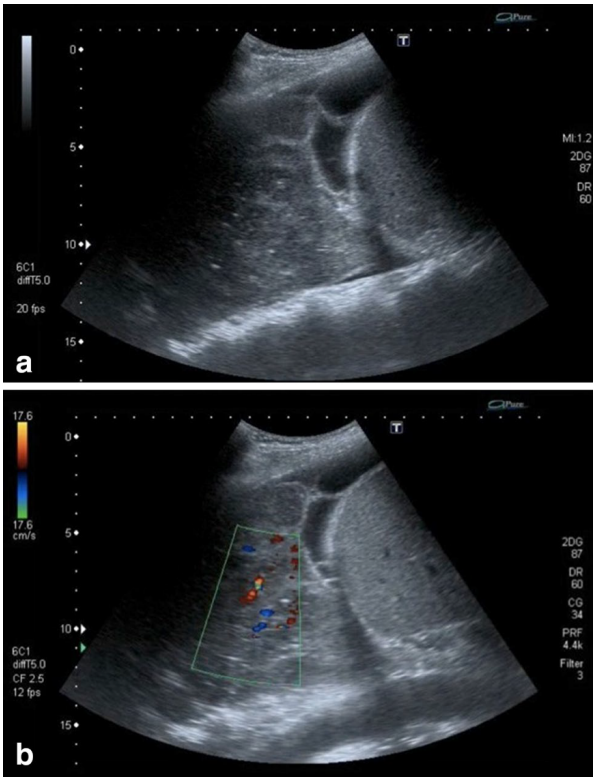


Figure 11. a) Sonographic image of a right-sided consolidation. The consolidation shows areas of lower echogenicity suggesting lymphoma infiltration. Additionally a pleural effusion with fibrin strands is present. b) Using color-Doppler the hypoechoic areas surround the vasculature (see Online Resources 6 and 7)



DISCUSSION

The cases above describe five HIV-infected patients with different HIV-related pulmonary diseases where clinician-performed chest ultrasound proved useful in the diagnostic workup. The following paragraphs discuss the diseases and the associated radiological and ultrasound patterns (Table 1) and review the literature currently available.

Bacterial pneumonia

Bacterial pneumonia, predominantly due to Streptococcus pneumoniae, Staphylococcus aureus and Haemophilus influenzae remains a major cause of morbidity and mortality in HIV-infected people.[28-30] Since this condition can present with minimal symptoms in patients with low CD4 cell counts, pneumonia is more likely to be misdiagnosed. Recently, the use of chest ultrasonography for the diagnosis of pneumonia in adults and children has been studied extensively.[5-7,9-11,31] Several studies showed that chest ultrasonography was as sensitive (93–98 %) and specific (95–97 %) as chest radiography in diagnosing pneumonia.[5-7,10,11,31] Hyperechoic air bronchograms in a hypoechoic consolidated area with ill-defined margins are typical sonographic findings in patients with pneumonia (70–97 %).[7-9] On ultrasonography, affected lung areas appear as a “solid” structure, referred to as hepatization of the lung, which may be accompanied by pleural line attenuation over the affected area. In 34–61 % of the cases these findings are accompanied by pleural effusion, which presents as an anechoic area surrounding the lung tissue.[6-9] To maximize sensitivity with chest ultrasound the whole thorax needs to be scanned by ultrasound circumferentially but still pneumonic lung areas may be missed if ventilated lung parenchyma is interposed; retrocardial or bronchopneumonia thus cannot be ruled out by means of ultrasound.

Our patient’s chest ultrasound findings are similar to those previously described in immune competent patients with a hypoechoic area with air bronchograms and an accompanying pleural effusion.

Pneumocystis jirovecci pneumonia

PJP remains one of the most prevalent opportunistic infection in patients infected with HIV. Patients with CD4 cell counts below 200 cells/µL not receiving prophylaxis are particularly at risk.[32] Common presentation of PJP includes progressive dyspnea, non-productive cough, and fever.[33] Increasing hypoxemia may lead to respiratory insufficiency requiring mechanical ventilation; acute deterioration with chest pain may indicate the development of pneumothorax. PJP may be difficult to diagnose due to non-specific symptoms and signs, which overlap with those of other infections.

PJP causes bilateral interstitial infiltrates. On chest radiography, ground-glass opacity due to fluid, debris and cells in the interstitium and alveoli is present in the majority of patients.[34] Ten to 40 % of PJP patients develop thin walled cystic lesions within the lung. Little data concerning the use of ultrasound in the diagnosis of PJP exists. In a case description bilateral presence of B-lines is reported, while A-lines remained visible.35 A small case series of six PJP cases from Brazil found bilateral symmetric B-lines without pleural effusion in all six cases, contrasting with the asymmetric distribution of findings in TB and community acquired pneumonias.[36]

We saw B-lines at the margins of the diseased lung parts; additionally, lung ultrasound at a later stage showed a high number of hyperechoic areas within the consolidated lung, which cannot be explained by air bronchograms alone. These echogenic areas did not show shadows. Correlating these focal findings with changes seen in CT scan performed at the same time, we are drawn to conclude that they most likely represent the cystic changes typical for PJP; cystic changes possibly filled with material consisting in gas and fluid. This pattern of consolidation with hyperechoic foci has not been previously described, its frequency and specificity for PJP should be investigated in further prospective studies.

Tuberculosis

TB remains the most common opportunistic infection in HIV patients worldwide and mortality rates remain high. In 2012 1.1 million HIV-infected patients were newly diagnosed with TB.[37] Patients typically present with cough, weight loss and night sweats/fever, but a significant fraction of patients show mainly constitutional symptoms and less pronounced pulmonary findings, possibly due to accompanying extrapulmonary disease. Diagnosis of pulmonary tuberculosis by sputum smear microscopy is less sensitive in HIV patients; similarly characteristic cavitary lesions are less commonly seen on chest radiography.

Ultrasonography is an excellent diagnostic tool for extrapulmonary TB in HIV-infected patients, which mostly presents as pleural effusion, pericardial effusion or abdominal TB.[38] Mediastinal ultrasonography for mediastinal tuberculous lymphadenopathy has also been reported.[39-41] Pleural effusions, which appear “complex” on ultrasound, in that they are septated, have fibrin strands or contain echogenic material, are likely to be exudates. TB is the most common cause for exudative effusion in high-prevalence settings.[42] The use of chest ultrasonography to evaluate PTB has not been systematically studied yet; the main radiological features of PTB seen on other imaging modalities such as CT are focal opacities, nodules, cavities and collapsed lung segments or lobes,[43] which are potentially visible features on chest ultrasonography as well. The initial abdominal ultrasound of our patient showed two sonographic features highly suggestive of abdominal TB: abdominal lymphadenopathy and splenic microabscesses. In this context our patient’s pulmonary changes on chest ultrasonography pointed towards pulmonary involvement of TB, which was confirmed by BAL. Consolidations and pleural effusions seen on chest ultrasonography should always include TB in the differential diagnosis.

Cytomegalovirus pneumonia

Global seroprevalence of CMV is high and reactivation of CMV leading to CMV viremia and disseminated CMV disease is frequent in patients with advanced HIV.[44] CMV retinitis is the most commonly reported CMV localization in HIV-infected patients, but other end-organ diseases such as CMV pneumonitis or CMV colitis are also common and are probably underreported due to difficulties in confirming the diagnosis.[45] Diagnosis of CMV pneumonitis is challenging, but a timely diagnosis and effective treatment are crucial to yield favorable outcomes, especially in severely immunosuppressed HIV patients. While imaging features of CMV pneumonitis have been described for chest radiography studies and CT scanning, we are not aware of any report on lung ultrasound features of CMV lung disease having been published to date. Findings on chest radiographs and CT are usually non-specific and

diverse and include ground-glass opacities, small pulmonary nodules with bilateral distribution involving all zones; confluent consolidation may be more marked towards the lower lobes;[46-50] the differential diagnosis includes other viral pneumonias and PJP.[51] Chest ultrasound features seen in our patient with CMV pneumonitis are in line with the expected patterns of interstitial alteration represented by B-lines. In our patient with CMV pneumonitis the B-lines were narrower and did fade in the deeper regions on the screen, making them less pronounced than the B-lines seen in the patient with PJP; furthermore, the interstitial pattern seen in CMV pneumonitis did not show any air inclusions or consolidations observed in the PJP pattern. Whether these differences in interstitial lung ultrasound pattern represent sufficiently typical characteristics of PJP and CMV lung disease, respectively, and may therefore serve as diagnostic differentiators, needs to be addressed in further studies.

AIDS-related lymphoma (ARL)

ARL is the second most common neoplastic disease associated with HIV infection; the risk of developing non-Hodgkin lymphoma within 3 years of AIDS diagnosis is 165- fold higher than in people without AIDS.[52] Most ARL are high-grade B cell lymphomas and a role of Epstein-Barr-Virus infection in the pathogenesis is hypothesized.[53] ARL tends to be highly aggressive, presents at a late stage and extra-nodal involvement is seen in up to 90 %.[54] The central nervous system, gastrointestinal tract and liver are commonly affected sites. Lung involvement is not uncommon, in autopsy series the lung was the most frequent extra-nodal site of ARL disease.[55] Patients with pulmonary ARL present most commonly with cough and dyspnea;[55] additionally, constitutional B-symptoms are prevalent. Most patients present with hilar lymphadenopathy or enlarged lymph nodes elsewhere; primary pulmonary ARL exists but is rare.[23] Pulmonary nodules, lobar infiltrates and lung masses are the most common parenchymal abnormalities.[55] Unilateral or bilateral effusions are found in around 50 % of cases and may be the only manifestation of pulmonary ARL. To our knowledge, data on the sonographic appearance of pulmonary ARL has not been reported so far, while ultrasound findings of abdominal ARL have been well described. On ultrasonography most ARL cases affecting solid organs like liver or spleen, present as hypoechoic nodules, which are normally multiple and range in size from 0.5 to 10 cm.[56] A special pattern of lymphoma involvement in the liver is periportal infiltration; in these cases, ARL appears as hypoechoic confluent masses, which are localized around intrahepatic vessels.[57] In our patient sonographic hypoechoic nodules can be distinguished within echogenic, consolidated lung. Similar to hepatic cases the masses appear to encase or 'follow' the vasculature of the lung. This nodularity observed in our case suggests a sonographic pattern slightly different from more homogenous pneumonic infiltrates; the specificity of this pattern cannot be commented on from this single case and further cases need to be studied.

CONCLUSION

Chest ultrasonography is a valuable diagnostic tool for a variety of respiratory infections and diseases as demonstrated here in HIV-infected patients. The five cases described represent common respiratory conditions in HIV-infected patients and sonographic patterns suggestive of the conditions were identified. However, at this point the specificity of the ultrasound findings cannot be generalized and further systematic studies in patients with these pulmonary conditions are needed. Among the many benefits related to ultrasound are its low costs, radiation-free imaging, realtime imaging, its mobility, repeatability and suitability for remote settings, where many patients with severe conditions are seen but imaging modalities are lacking. The minimal technical requirements of the equipment needed for lung assessment should be further studied, although in our opinion and experience basic portable ultrasound machines with both, convex and linear probes seem adequate. Albeit ultrasonography can only identify pathological tissue patterns and not the underlying etiology, differential diagnosis can be narrowed, allowing more focused action, reduced time to diagnosis, reduced costs and ultimately better outcomes.

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10

chapter 10

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

In this thesis, we discussed TB diagnostics and management in low-incidence settings, like the European Union, and in children in a high-incidence setting, South Africa. In the first part we focussed on the barriers of TB service uptake as well as effective interventions to improve TB identification and management in hard-to-reach populations in low- and middle-incidence countries. The European Centre of Disease Prevention and Control (ECDC) asked us to perform a systematic review on TB identification and management in hard-to-reach populations in order to set up guidelines to improve TB control among those groups and reduce the number of TB cases in Europe. In 2015, ECDC published a scientific evidence report titled 'Guidance on tuberculosis control in vulnerable and hard-to-reach populations'[1] and we published three systematic reviews on this topic (**Chapter 2, Chapter 3** and **Chapter 4**).[2-4]

In the second part, we focussed on the use of chest ultrasound for the diagnosis of pulmonary TB and other respiratory diseases in children. We conducted a systematic review on the use of chest ultrasound for the diagnosis of paediatric pulmonary diseases, mainly focussing on childhood pneumonia (**Chapter 5**).[5] We presented the technical aspects of mediastinal ultrasound for the detection of enlarged mediastinal lymph nodes to assist in diagnosing paediatric TB (**Chapter 6**).[6] We reported chest ultrasound findings in South African children with suspected pulmonary TB (**Chapter 7**),[7] and compared those findings with CXR findings (**Chapter 8**).[8] In **Chapter 9**, we presented a case series of ultrasound findings in HIV infected individuals, including a chest ultrasound in a patient co-infected with HIV and TB.[9]

Part I: TB in hard-to-reach populations

Chapters 2, 3 and **4,** constitute three systematic reviews focussing on TB services in in hard-to-reach populations in a low-incidence setting.[2-4] In the first review we found that stigma and access to health care are the main barriers for TB screening uptake and treatment adherence especially in the migrant and homeless populations.[10-21] Community sensitisation targeting TB stigmatisation actions and attitudes can reduce stigma and therefore can improve TB screening uptake and treatment adherence. Access to health care is challenging for those hard-to-reach populations, therefore countries should reflect on their access to health care for those vulnerable populations.

In the second and third review we found that TB screening by chest radiography is effective and cost-effective in the migrant population.[22-28] Another systematic review reported similar findings in the homeless population.[29] A further finding was that mobile radiography units make access to TB screening easier and improve TB identification.[30-33] An important advantage of chest radiography over a tuberculin skin test is that it can be read instantly, with a rapid result being essential as follow-up attendance for hard-to-reach populations may be low.
Including sputum culture in the pre-migration TB screening program can increase TB identification and reduce the importation of TB in the host country.[34-37] A disadvantage of sputum culture is that it takes about four weeks for the results to return. Therefore, sputum culture is only a useful tool for pre-migration screening, as migrants will only receive a visa when the results are reported back. The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) could be a useful microbiological alternative, it has a higher sensitivity than sputum smear, provides results within 2 hours, and is cheaper than sputum culture.[38]

The effective and cost-effective tool, chest radiography is widely used. A majority of countries uses chest radiography as the preferred screening tool to screen migrants for active TB, but it is not universally adopted. A 2016 survey performed by the World Health Organization (European region) found that two countries (Serbia and the Republic of Macedonia) did not perform screening for active TB on refugees at all. Three countries (Italy, Monaco and Portugal) did not systematically screen refugees for active TB; instead, only symptomatic refugees were screened. The majority of the European countries performed chest radiography, some countries screened by symptom-based questionnaire or bacteriological tests. TB screening among refugees was mainly performed at refugee centres.[39]

For legal migrants obtaining a valid visa, TB screening is part of the visa application process. Some countries request TB screening from migrants of all countries, other countries only ask migrants from high-incidence countries to get screened for active TB. Some countries, like the United States, ask legal migrants to be screened before entering the host country,[34-37] in other countries, like the Netherlands, migrants are invited for

TB screening after arrival in the host country.[40] In our systematic review we found that active referral, like a scheduled appointment or a direct phone number to a TB clinic, improves screening uptake among migrants and drug users.[41-44] For example, in the Netherlands migrants are referred directly to the Public Health service for screening.

Regarding TB management interventions, we found that enhanced case management was a cost-effective tool[32] to improve treatment completion and outcome.[32,45-47]

Directly observed therapy (DOT) improves treatment outcomes and adherence.[48-50] Partial DOT, only during the first 2 months of treatment, can be as effective as full DOT.[51] It does not matter at what location or by whom DOT is applied, DOT at a TB clinic versus DOT as social outreach had similar treatment outcomes.[51] The same accounts for DOT administered by a family member compared to regular monthly check-ups.[52] DOT is still the cornerstone of TB control but the best way to administer DOT and the effectiveness varies in several studies. A study conducted in Bangkok showed that family-based DOT had a higher treatment success rate than a centre-based DOT, yet the highest treatment success rate was found in a combined centre- and family-based DOT.[53] In contrast, a randomised controlled trial in Pakistan found no difference in cure rate or adherence when DOT was administered by a health care worker, a family member or self-administration.[54] An Indian study found similar cure rates between patients who received DOT and patients that self-administrated treatment, but the adherence was better in the DOT group.[55]

Combining TB care with other care can improve TB outcome, like TB care integrated in the methadone clinic. In our review we discussed that integrated TB and HIV care can reduce TB-related mortality.[56] Combined HIV and TB care is already happening in developing countries. In 2004, the World Health Organization published a plan for collaborative TB/HIV activities.[57] The activities include HIV testing for TB patients, TB screening for patients living with HIV, ensure HIV prevention for TB patients, and integration of TB/HIV care in primary care clinics for example.[57] The European countries have not made a lot of progress in the integration of TB and HIV care; even though strengthening of combined TB/HIV care programmes was requested at the 2007 Berlin declaration on tuberculosis.[58]

We discussed that incentives can improve TB screening uptake, screening completion, and treatment adherence among homeless people and drug users.[59-62] A systematic review published in 2015 found that incentives can be effective for short term use. However, there is not sufficient evidence to know if it can be an effective tool to improve treatment adherence in TB patients.[63]

Limited studies focus on services models and organisational structures for TB identification and management, we found that the involvement of community health workers and outreach teams can improve TB screening uptake and TB treatment completion.[64-67] Good collaboration between all the involved parties (health care workers, peers, communities and patients) can improve treatment outcome. [64-67]

Part II: Chest ultrasound for the diagnosis of pulmonary TB and other respiratory diseases

In the second part of this thesis we discussed the use of chest ultrasound for the diagnosis of TB and other respiratory diseases and we mainly focussed on children.

In **Chapter 5** we presented the findings of our systematic review and meta-analysis on chest ultrasound for the diagnosis of paediatric pulmonary diseases. We found that chest ultrasound has a very high sensitivity (95.0%) and specificity (96.1%) for the diagnosis of childhood pneumonia, chest ultrasound was superior to chest radiography in detection of small consolidations.[68-71] The diagnostic accuracy for other respiratory diseases like pneumothorax, respiratory distress syndrome, atelectasis and bronchiolitis were also high but due to a limited amount of available, included studies, a meta-analysis could not be performed.

Another important finding of our systematic review was that chest ultrasound performed by an experienced operator had a higher diagnostic accuracy than when it was performed by an inexperienced operator; however the skills needed to learn and do chest ultrasound can be rapidly gained .[72]

It is difficult to radiologically differentiate TB from pneumonia. The radiological hallmark of TB diagnosis is enlarged mediastinal and hilar lymph nodes.[73] A few South African groups evaluated the use of mediastinal ultrasound in children with pulmonary TB.[74-76] Those studies found enlarged mediastinal lymph nodes in 40% of the children with suspected or confirmed pulmonary TB[74] and ultrasound detected mediastinal lymphadenopathy

more often than chest radiography in children with a positive tuberculin skin test.[75-76] However, a formal mediastinal ultrasound protocol has not been drafted. In **Chapter 6,** we described the technical aspects of mediastinal ultrasound for the diagnosis of paediatric pulmonary TB and included schematics and ultrasound images of the mediastinal landmarks and pathology. Since the publication of this protocol, we published two studies (represented in **Chapters 7** and **8**) including mediastinal ultrasound, accessing the mediastinum through the suprasternal notch, for the diagnosis of TB. Most mediastinal ultrasound studies focus on endobronchial ultrasound, which is a more invasive technique but has the advantage of taking a sample for culture if needed.

In **Chapter 7**, we reported chest ultrasound findings in children with suspected pulmonary TB. We discussed that in the right context and setting, chest ultrasound may be a useful tool to detect changes associated with pulmonary TB. Pleural effusion was associated with confirmed pulmonary TB. Pleural effusion is a known complication of pulmonary TB especially in older children. However, a pleural effusion is not diagnostic for pulmonary TB, as it may occur as a complication of pneumonia as well. Nevertheless, the occurrence of pleural effusion in an older child, in a TB-endemic setting, should be considered as possible pulmonary TB, when available, further microbiological testing should be considered to confirm the diagnosis.

Additionally, chest ultrasound may be a useful tool to monitor treatment response in children with pulmonary TB. We found that at 1-month follow-up chest ultrasound, a consolidation reduced in size or disappeared more frequently in children with other respiratory diseases than in children with confirmed pulmonary TB. So, if a consolidation increases in size, the clinician should consider TB and investigate and change management accordingly. However a consolidation that resolves slowly in a child treated for pulmonary TB, is consistent with TB, as we found that no resolution or a minimal reduction of a consolidation was seen at 1- and 3-month follow-up chest ultrasound.

On mediastinal ultrasound we found that enlarged mediastinal lymph nodes were seen in children with pulmonary TB but also in children with other respiratory diseases. However Children with microbiologically confirmed pulmonary TB had significant larger mediastinal lymph nodes (median size 1.5 cm) compared to children with other respiratory diseases. Enlarged lymph nodes were no longer seen at 3-month follow-up in children with other respiratory diseases, but it could still be seen in children treated for pulmonary TB. Therefore, if large nodes are present at enrolment or enlarged lymph nodes are still seen after three months, TB should be considered.
Another finding was that, compared to a 3-drug regimen, a 4-drug TB treatment regimen had a better effect on the disappearance of pleural effusion after three months of treatment. Therefore, we concluded that children with a pleural effusion should be treated with four TB drugs.

Another advantage of chest ultrasound was the very high inter-reader agreement. It is known that chest radiography has a poor inter-reader agreement for the diagnosis of pulmonary TB[77-78] but also for pneumonia,[79-80] for example. A previous pneumonia study found a higher inter-reader agreement for chest ultrasound compared to chest radiography.[81]

In **Chapter 8,** we compared chest ultrasound findings with chest radiography findings in children with suspected pulmonary TB. To the best of our knowledge, this was the first study published comparing chest ultrasound findings with chest radiography. Abnormal findings were seen more frequently on chest ultrasound than on chest radiography. Pleural effusion or enlarged mediastinal lymph nodes were more frequently detected on US. Previous pneumonia studies showed that chest ultrasound was superior over chest radiography in detecting consolidations, especially small consolidations.[68,71] and that chest ultrasound is better in detecting pleural effusion, especially small effusions, than chest radiography.[82] Abnormal findings, especially pleural effusions, were more frequently seen in children with confirmed pulmonary TB than in children with other respiratory diseases. Furthermore, ultrasound had a higher inter-reader agreement than CXR for consolidation ≥0.5 cm, pleural effusion or enlarged mediastinal lymph nodes.

In **Chapter 9**, we presented a case series on the use of chest ultrasound in HIV infected individuals. FASH has been introduced for the diagnosis of extrapulmonary TB in HIV infected individuals[83-85] and has been widely used in low-and-middle income countries. However, chest ultrasound to diagnose pulmonary TB is still in its early days. One out of the five cases in our case series was about pulmonary TB. In this case, chest ultrasound showed a large consolidation. A consolidation was also seen on the chest ultrasound of the patient with a bacterial pneumonia, underpinning the point that it is difficult to differentiate TB from pneumonia on chest ultrasound but

this is also the case for chest radiography. Therefore, the question is whether chest ultrasound has a higher diagnostic accuracy in finding radiological signs of TB, like consolidation, pleural effusion, enlarged lymph nodes, than chest radiography. Several pneumonia studies have proven that chest ultrasound has a similar or even better diagnostic accuracy than chest radiography.[86-87]

IMPACT OF THIS RESEARCH AND FUTURE PERSPECTIVES

Our three systematic reviews on barriers to uptake of TB services and interventions to improve TB identification and management were the framework for the development of the ECDC guidelines to improve TB control in hard-to-reach populations in Europe. To date, those guidelines are used by national policymakers, national TB programmes and non-governmental organisations (NGO's), to improve early TB diagnosis and treatment completion among hard-to-reach populations in European countries. Due to the war in Syria there has been an increased influx of refugees from Syria but also from African countries. Despite this increased number of (illegal) migrants, the TB incidence rate and TB mortality rate are still declining in the European region and the treatment coverage is improving.[88] Unfortunately there is no data that shows if the identification and treatment completion of the several hard-to-reach populations improved since the publication of the guidelines.

Even though there is an increasing interest of chest ultrasound for the diagnosis of childhood pulmonary diseases, our studies have been the first paediatric studies of chest ultrasound for the diagnosis of pulmonary TB. Although our studies show promising findings, further, large-scale studies comparing chest ultrasound with a valid good standard are needed to show the diagnostic accuracy of chest ultrasound. Future studies should also evaluate the duration of chest ultrasound training and the duration of post-training supervised ultrasound scanning, including the value of remote supervision like telemedicine. The (cost-) effectiveness of chest ultrasound for the diagnosis of TB in low-, middle- and high-income countries should be evaluated. However, our findings suggest that US is a promising entity as an aid to diagnosing PTB in childen and should be considered as a first line imaging modality in children with suspected pulmonary TB and where follow-up imaging is needed.

During this PhD project, several other chest ultrasound studies have been published, mainly focussing on pulmonary TB in adult patients.[89,90] Those studies did not address the diagnostic accuracy but described their ultrasound findings. The South African study described the findings of adult patients with miliary TB, B-lines and comet-tail artifacts in multiple lung fields and a subpleural granularity were seen on chest ultrasound of those patients.[89] The other study, conducted in a rural African setting, found that the most frequent ultrasound finding in TB patients was the presence of subpleural nodules.[90] Other findings were consolidation, cavitation, miliary patterns presenting as miniature subpleural nodules, pleural effusion and pericardial effusion. However, this study did not include a comparison group.[90] An Italian group presented their preliminary findings on the European Society of Thoracic Imaging (ESTI) conference in 2019, comparing ultrasound findings with chest CT findings.[91] Their conclusion was that most of the ultrasound findings were non-specific and did not differentiate TB from other pulmonary diseases, but chest ultrasound could be a useful tool to monitor follow-up in TB patients.[91] Currently, there is a point-of-care ultrasound study running in South Sudan and Guinea Bissau, those studies are coordinated by Médicines Sans Frontières. The primary aim is to identify the diagnostic test accuracy of chest ultrasound in children with TB. There is no preliminary data available yet (personal communication with Laura Moreto, principal investigator, MSF Spain).

This thesis shows that chest ultrasound should be added as a new imaging tool to TB diagnostic tools especially in countries with limited resources (part II of the thesis), and that the available tools should be used in an effective way in low incidence settings (part I of the thesis) to allow us as a global community to move on closer towards the ultimate goal of attaining TB control globally.

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&Appendices

SUMMARY

SAMENVATTING

AUTHORS AND AFFILIATIONS

PORTFOLIO

ABOUT THE AUTHOR

WORD OF THANK

SUMMARY

In the first part of this thesis we discussed the findings of our three systematic reviews (**Chapters 2, 3 and 4**) on the barriers and facilitators of uptake of TB services and on TB identification and management in hard-to-reach populations in low-incidence settings, like the European Union. In the first review we found that stigma and access to health care are the main barriers for uptake of TB services for people living in hard-to-reach populations, especially among migrants and homeless people. In the second and third review we found that chest radiography is an effective and cost-effective tool to screen migrants and that a mobile radiography unit improves access to TB screening. Active referral to a TB clinic, by means of a scheduled appointment or a direct phone number, improves screening uptake among migrants and drug users. Involvement of community health workers or outreach teams as well as incentives can improve TB identification and treatment completion among homeless people and drug users. Enhanced case management improves TB adherence and outcome and combining TB and HIV care can reduce TB related mortality.

In the second part of this thesis, we discussed the use of chest ultrasound for the diagnosis of TB and other respiratory diseases. We first presented a systematic review and meta-analysis on the use of chest ultrasound for the diagnosis of paediatric pulmonary diseases (**Chapter 5**). The majority of the studies focussed on childhood pneumonia but chest ultrasound had a very high diagnostic accuracy for the diagnosis of respiratory distress syndrome, atelectasis and bronchiolitis as well. We only considered it useful to perform a meta-analysis on pneumonia, the sensitivity of chest-ultrasound for the diagnosis of pneumonia was 95% and the specificity was 96%. Another important finding was that chest ultrasound was superior over chest radiography for the detection of small consolidations (<1.0 cm). Chest ultrasound has a very steep learning curve but the diagnostic accuracy was better when the chest ultrasound was performed by an experience sonographer.

In **Chapter 6**, we described the technical aspects of mediastinal ultrasound supported by schematics and ultrasound images. Mediastinal ultrasound has been used to demonstrated enlarged mediastinal lymph nodes but a formal protocol has never been drafted before.

In **Chapter 7,** we described the chest ultrasound findings, including the mediastinal ultrasound findings, of children with suspected pulmonary TB. We concluded that the occurrence of pleural effusion in an older child, in a TB-endemic setting, should be considered as possible pulmonary TB as pleural effusions were associated with confirmed pulmonary TB. Additionally, we concluded that children with pleural effusion should be treated with 4 drugs as it had a positive effect in the disappearance of pleural effusion. At one-month follow-up, children with other respiratory diseases more often had a reduction in size or complete resolution of consolidations, therefore we concluded that when a consolidation increased in size at follow-up, pulmonary TB should be considered. On mediastinal ultrasound we found that enlarged mediastinal lymph nodes were significantly larger in children with confirmed pulmonary TB (median 1.5 cm) than in children with other respiratory diseases (median 1.0 cm), and enlarged lymph nodes were no longer seen after 3 months in children with other respiratory diseases.

The chest ultrasound findings were compared with the chest radiography findings in children with suspected pulmonary TB in **Chapter 8**. Chest ultrasound picked up abnormal findings more frequently than chest radiography, especially enlarged mediastinal lymph nodes and pleural effusions. Abnormal findings were more commonly seen in children with confirmed pulmonary TB. Additionally, chest ultrasound had a higher inter-reader agreement than chest radiography.

In **Chapter 9,** we presented the ultrasound findings 5 HIV infected individuals, one case had HIV associated TB. The ultrasound finding of this case showed a large consolidation.

In conclusion, chest ultrasound is a promising tool to diagnose pulmonary TB, and in settings were other imaging techniques are lacking chest ultrasound should be considered for the diagnosis of pulmonary TB and other respiratory diseases. However, further, large-scale studies comparing chest ultrasound to a valid gold standard are needed to calculate the true diagnostics accuracy. Future studies should also focus on the duration of chest ultrasound training, the need of post-training supervised scanning and the use of telemedicine. The (cost-) effectiveness should be evaluated in different settings, like low-, middle- and high-income countries.

SAMENVATTING

In het eerste deel van dit proefschrift presenteerden we de bevinding van onze drie systematische reviews (**Hoofdstukken 2, 3 en 4**). Deze reviews richtten zich op de herkenning en begeleiding van tuberculose (TBC) patiënten in populaties die moeilijk te bereiken zijn voor de behandelaar. De studies die geïncludeerd waren in deze drie reviews concentreerden zich vooral op patiënten die leven in landen waar TBC weinig voorkomt, zogeheten landen met een lage incidentie. De eerste review liet zien dat stigma en toegang tot gezondheidszorg de belangrijkste barrières waren voor deze groep patiënten om gebruik te maken van TBC services. In het tweede en derde review zagen we dat het maken van een röntgenfoto van de longen een effectief en kosteneffectief middel is om migranten te screenen voor TBC en dat een 'mobiele röntgen bus' de toegang tot TBC screening verbetert. Een doorverwijzing naar een TBC kliniek, door middel van een ingeplande afspraak of een direct telefoonnummer, verbetert de screening opkomst bij migranten en drugsverslaafden. Het betrekken van wijkverpleegkundigen en sociale werkers, alsmede een (financiële) beloning, kunnen ertoe bijdragen dat TBC vaker herkend wordt en dat de therapietrouw en de behandelingsuitkomst verbetert bij daklozen en drugsverslaafden. Zorg op maat verbetert therapietrouw en gecombineerde zorg voor HIV en TBC zorgt voor een lagere TBC gerelateerde sterfte.

In het tweede gedeelte van dit proefschrift bediscussieerden we het gebruik van long echo's om TBC en andere longziekten te kunnen diagnosticeren. Als eerste presenteerden we een systematische review en meta-analyse, deze review besprak het gebruik van long echo's om longziekten bij kinderen te diagnosticeren (**Hoofdstuk 5**). Het merendeel van de geïncludeerde artikelen concentreerde zich op longontstekingen maar long echo had ook een hoge sensitiviteit en specificiteit voor andere longziekten zoals acute respiratory distress syndrome, atelectase en bronchiolitis. We achtten het alleen zinvol een meta-analyse van longontsteking te ondernemen, de sensitiviteit voor long echo's voor het diagnosticeren van een longontsteking was 95% en de specificiteit was 96%. Long echo was beter in het detecteren van kleine ontstekingen (<1.0 cm) in de long dan röntgen. Long echo heeft een steile leercurve, als een long echo werd uitgevoerd door iemand met ervaring in het maken van long echo's verhoogde dat de diagnostieke juistheid.

In **Hoofdstuk 6** bespraken we de technische aspecten van mediastinale echo's, tevens presenteerden wij schematische tekeningen en foto's van de echo's. Mediastinale echo werd eerder al gebruikt om vergrote mediastinale lymfeklieren aan te tonen maar nooit eerder werd er een formeel protocol opgesteld.

In **Hoofdstuk 7** beschreven we de bevindingen van long echo's, inclusief mediastinale echo, in kinderen met een verdenking op pulmonale TBC. We concludeerden dat als de long echo pleuraal vocht demonstreert in een ouder kind dat woont in een TBC endemisch gebied, pulmonale TBC serieus overwogen moet worden. Pleuraal vocht werd geassocieerd met microbiologisch bewezen TBC. Verder concludeerden we dat als er pleuraal vocht wordt geconstateerd, de patiënt behandeld zou moeten worden met vier verschillende TBC medicijnen omdat dat een beter behandelingsresultaat opleverde dan behandeling met drie TBC medicijnen. De long echo's van kinderen met andere longziekten dan TBC toonden vaker een reductie in de omvang of een complete remissie van een consolidatie. Daarom concludeerden we dat als tijdens de controle echo, een maand na de start van de behandeling, de consolidatie toeneemt in grootte, TBC overwogen moet worden. Mediastinale echo's demonstreerden dat lymfeklieren significant groter zijn in kinderen met microbiologisch bewezen TBC dan in kinderen met andere longziekten en kinderen met andere longziekten hadden echografisch geen vergrote lymfeklieren meer bij de controle echo drie maanden later.

De long echo's werden vergeleken met de röntgenfoto's van de kinderen met een verdenking op pulmonale TBC in **Hoofdstuk 8**. Abnormale bevindingen werden vaker geconstateerd op de long echo dan op de röntgenfoto, vooral vergrote lymfeklieren en pleuraal vocht. Abnormale bevindingen kwamen vaker voor bij kinderen met microbiologisch bewezen TBC. Verder had long echo een hogere inter-rater overeenkomst dan röntgen.

In het laatste hoofdstuk, **Hoofdstuk 9**, presenteerden we de echo bevindingen van vijf HIV geïnfecteerde personen, een van die personen was gediagnostiseerd met HIV geassocieerde TBC. De echo bevindingen van deze HIV/TBC patiënt demonstreerde een grote consolidatie.

Concluderend, long echo is een veel belovend diagnostisch middel om pulmonale TBC aan te tonen. Long echo zou overwogen moeten worden als geprefereerde beeldvormende diagnostiek voor pulmonale TBC en andere

longinfecties in een omgeving waar andere beeldvormende diagnostiek ontbreekt. Desalniettemin, verder onderzoek zou een grotere onderzoekspopulatie moeten includeren, long echo's zouden vergeleken moeten worden met een valide gouden standaard, om de diagnostische nauwkeurigheid van long echo te kunnen bepalen. Toekomstige onderzoeken zouden zich ook moet richten op de inhoud en de duur van de training voor long echo, of long echo's onder supervisie gemaakt zouden moeten worden na de training en of het gebruik van "telemedicine" nuttig zou kunnen zijn. De kosten efficiëntie per economische situatie, bijvoorbeeld derde wereld landen en landen in de westerse wereld, zou ook onderzocht moeten worden.

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COURSES

2014 Ultrasound Course, Munich, Germany

2014 Good Clinical Practice, Cape Town, South Africa

2015 Ultrasound Imaging: What is inside? University of Twente, the Netherlands

2015 PubMed Basics, Academic Medical Center Amsterdam, The Netherlands

2015 Ebola: Essential Knowledge for Health Professionals, University of Amsterdam and University of Utrecht, the Netherlands

2016 Preventing the Zika virus: understanding and controlling the aedes mosquito, London School of Hygiene and Tropical Medicine, United Kingdom

2019 Medical Literature: Zoeken voor een CAT, Academic Medical Center Amsterdam, The Netherlands

2019 Correct citation, Amsterdam UMC, the Netherlands

2020 Covid-19, London School of Hygiene and Tropical Medicine, United Kingdom

PRESENTATIONS

2014 Chest ultrasound for HIV-infected patients: preliminary findings. *Poster presentation at ASTMH the 63rd Annual Meeting.* November 2014, New Orleans, LA, USA

2015 Focused point-of-care ultrasound (FASH) at diagnosis and follow-up of children with pulmonary tuberculosis - preliminary results . *Oral Presentation at the 46th Union World Conference on Lung Health*. December 2015, Cape Town, South Africa

2017 Technical aspect of Point-of-Care Mediastinal Ultrasound for the diagnosis of Pediatric Pulmonary Tuberculosis - A new standardized method. *Poster presentation at SPR 2017 Annual Meeting and Categorical Course.* May 2017, Vancouver, Canada

2017 Mediastinal Ultrasound versus Chest Radiograph for the detection of Lymphadenopathy in Children with suspected Pulmonary Tuberculosis. *Poster presentation at SPR 2017 Annual Meeting and Categorical Course.* May 2017, Vancouver, Canada

2017 Point-of-care chest ultrasound in South African children with suspected pulmonary tuberculosis. *Oral Presentation at the 10th European Congress on Tropical Medicine and International Health.* October 2017, Antwerp, Belgium

2017 Chest Ultrasound versus X-ray for Pulmonary Tuberculosis in South African Children. *Oral Presentation at the ASTMH 66th Annual Meeting.* November 2017, Baltimore, ML, USA

2017 Chest Ultrasound versus X-ray for Pulmonary Tuberculosis in South African Children. *Poster Presentation at the ASTMH Young Investigator Award.* November 2017, Baltimore, ML, USA

2017 Chest Ultrasound versus X-ray for Pulmonary Tuberculosis in South African Children. *Oral Presentation at the ASTMH Young Investigator Award.* November 2017, Baltimore, ML, USA

2017 Chest Ultrasound versus X-ray for Pulmonary Tuberculosis in South African Children. *Oral Presentation at the ASTMH Elsevier Clinical Research Award.* November 2017, Baltimore, ML, USA

2020 Point-of-Care Chest Ultrasound for the diagnosis of Pulmonary Tuberculosis in Children. *Invited speaker at Pediatric Academic Societies Meeting*. May 2020, Philadelphia, PA, USA (*cancelled because of Covid-19*)

CONFERENCES

2014 International Conference of Infectious Diseases, Cape Town, South Africa

2015 The Union World Conference on Lung Health, Cape Town, South Africa

2017 The European Congress on Tropical Medicine and International Health, Antwerp, Belgium

2017 American Society of Tropical Medicine and Hygiene Annual Meeting, Baltimore, ML, USA

OTHERS

2014 Instructor point-of-care ultrasound training at Red Cross War Memorial Children's Hospital, Cape Town, South Africa

2015 Supervision medical student AMC, Amsterdam, the Netherlands (4 months)

2015 Supervision medical student from Berlin, Germany (2 months)

2014-2015 Weekly morning lectures at Red Cross War Memorial Children's Hospital, Cape Town, South Africa

2019-2020 Expert reviewer of point-of-care studies by Médicins Sans Frontières in Guinea-Bissau and South Sudan

2020 Board member of the Dutch School in Cape Town, South Africa

Ongoing Regular manuscript review for several medical journals, including *Pediatric Pulmonology, BMJ Open, Infection, American Society of Tropical Medicine and Hygiene, Transactions of the Royal Society of Tropical Medicine and Hygiene, International Journal of STD and AIDS, Globalization and Health, Patient Preference and Adherence*

AWARDS

2015 Marie Curie People Grant

2017 ASTMH Young Investigator Award - First-tier mention

2017 ASTMH Elsevier Clinical Research Award - Third place

LIST OF PUPLICATIONS

Belard, S; **Heuvelings, CC**; Janssen, S; Grobusch, MP. Bedaquiline for the treatment of drug-resistant tuberculosis. *Expert Rev Anti Infect Ther.* 2015;13(5):535-53.

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ABOUT THE AUTHOR

Charlotte Carina Heuvelings was born on the 9th of May 1983 in Tegelen, the Netherlands. After graduation at the Valuascollege in Venlo (2001), she first enrolled in Health Science at the University of Maastricht. In 2002 she moved to Amsterdam to start her medical training at the University of Amsterdam. During her study she lived in South Africa for a 4-month research internship at Tygerberg Hospital, Stellenbosch University (2006) and in Tanzania for a 4-month Tropical medicine internship (2009). After graduating in 2009 she moved to London to work as a Senior House Officer in several NHS hospitals (2009-2013). In 2011-2012 she enrolled at the London School of Hygiene and Tropical Medicine for a Master degree in Tropical Medicine and International Health, including a Diploma in Tropical Medicine and Hygiene. During this period, she undertook a 3-month research internship at the Medical Research Centre (MRC) in Fajara, the Gambia.

In 2014 Charlotte started her PhD project at the Centre of Tropical Medicine and Travel Medicine at the Academic Medical Center (AMC) in Amsterdam, now known as Amsterdam UMC, under the supervision of Prof. Dr. Martin P. Grobusch. The fieldwork for her PhD was conducted at the Red Cross War Memorial Children's Hospital/University of Cape Town under the supervision of Prof. Dr. Heather J. Zar.

In her spare time Charlotte is a very active hockey player, during her school period she used to play for the Dutch national youth teams; under 16 and under 18. During her medical training she used play for the Dutch national team under 21 and during her internships she played at the Olympic qualifying tournament in Kazan, Russia with the national team of the Dutch Antilles. In the Netherlands she used to play for the first ladies teams of Venlo, Oranje-Zwart and Amsterdam Hockey and Bandy Club (AH&BC), in London she used play for the First Ladies Team of Hampstead and Westminster Hockey Club and in Singapore she played for the "Hollandse Club". During her PhD project, Charlotte and her partner, Derk Jan, became parents of two beautiful boys, Beau (2015, Cape Town) and Charlie (2018, Singapore).

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