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Review

Imaging modalities for pulmonary tuberculosis in children: A systematic review

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HIGHLIGHTS

- A new diagnostic strategy for PTB in children in Western Europe is needed, due the rise in patients with TB following the current war in Ukraine.
- CT has a higher diagnostic accuracy for PTB findings than CXR, MRI and US.
- In cases of equivocal CXR or suspected PTB in children with normal CXR, CT should be considered for diagnostic imaging.

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ABSTRACT

Purpose: The optimal choice of protocol for diagnostic imaging in children with tuberculosis (TB) is a contemporary challenge due to the war in Ukraine, which potentially can create a steep rise in TB cases in Western Europe. We aimed to gather all primary research comparing imaging modalities and their diagnostic accuracies for pulmonary findings in children with suspected or confirmed pulmonary tuberculosis (PTB).

Method: We searched the databases PubMed and Embase using pre-specified search terms, for English- and non-English published and un-published reports from the period 1972 to 2022. We retrieved reports via citation search in excluded literature reviews and systematic reviews. Studies were eligible if most of the study population was between 0 and 18 years of age with confirmed or suspected PTB, and study participants had described diagnostic images from two or more different imaging modalities.

Results: A total of 15 studies investigated conventional chest X-Ray (CXR) and computed tomography (CT) in diagnosing PTB in children. Nine studies investigated the number of participants in where CT or CXR confirmed the diagnosis of TB, and all of them, including a total of 1244 patients, reported that findings compatible with TB were more frequently detected on CT than CXR. Only two studies did not include radiological findings as part of their diagnostic criteria for PTB, and combined they showed that CT diagnosed 54/54 (100 %) children with confirmed PTB, while CXR diagnosed 42/54 (78 %). Two studies compared magnetic resonance imaging (MRI) with CXR and showed that MRI diagnosed more children with PTB than CXR. One study reported a higher positive predictive value (PPV), sensitivity and specificity for PTB findings for MRI than CXR. One study compared CXR with high-kilovolt (high-kV) CXR, finding compatible sensitivity and specificity regarding confirmation of PTB. Two studies compared ultrasound (US) with CXR and found that US had a higher diagnostic yield and more often correctly identified consolidations, mediastinal LAP, and pleural effusion.

Conclusion: CT showed a higher diagnostic accuracy for PTB findings than CXR, MRI and US, and should be the imaging modality of first choice when available. MRI had a higher sensitivity and specificity than CXR for LAP, pleural effusion, and cavitation. US was complimentary in initial diagnostic work-up and follow up. A diagnostic

Abbreviations: TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; LAP, lymphadenopathy; CT, computed tomography; CXR, chest x-ray; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound; PPV, positive predictive value; NPV, negative predictive value; PCR, polymerase chain reaction; TST, tuberculin skin test; PPD, purified protein derivative.

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strategy for PTB in children according to local availability and expertise is proposed, as no evidence from this systematic review shows otherwise, in acknowledgement of the expertise in high TB-burdened countries. CT can be performed when in doubt, due to the higher diagnostic yield.

1. Introduction

Tuberculosis (TB) is currently regarded as the second leading cause of death from an infectious agent worldwide, right behind COVID-19, and the 13th leading universal cause of death. In 2020, TB resulted in 1.3 million deaths among HIV-negative people, including 208,000 children [1]. This is an alarming increase from 1.2 million deaths in 2019. According to the Global Tuberculosis Report 2021 by the World Health Organization (WHO), a fall in global spending on TB diagnostic, treatment, and prevention services, serves as a considerable impact on the fall. A pillar in WHO's strategy to reduce TB worldwide is early diagnosis. Diagnosing children with pulmonary TB (PTB), compared to the adults, remains a challenge. One of the reasons is that children have paucibacillary disease and few children can produce sputum for microscopy and bacterial culture [2]. The diagnosis is therefore primarily based on non-specific symptoms, history of TB exposure, clinical signs, tuberculin skin tests (TST), IGRA and radiological imaging [3].

Conventional chest X-ray (CXR) is the current radiological standard for initial evaluation of children with PTB [3–17]. However, radiological presentation of PTB is different in children compared to adults [7] and CXR has shown to have a lower diagnostic yield in detecting PTB findings compared to CT, e.g., lymphadenopathy (LAP) and pulmonary parenchymal lesions - key radiological lung manifestations in paediatric PTB [3–10,12–21]. Thus, in high-income settings, the use of computed tomography (CT) to evaluate suspected TB in paediatric cases is increasing [3].

The current war in Ukraine makes the issue pertinent due to the rise in number of patients with TB in Western Europe. These countries with low incidence of TB have typically had less experience in imaging of TB with CXR and a reconsideration of a new diagnostic approach may be required to accommodate the increasing number of suspected cases.

2. Methods

This systematic review has been reported in accordance with the 'Preferred Reporting Items for Systematic reviews and Meta-analysis' (The PRISMA 2020 statement [31]) and was registered May 17, 2022, on the 'International prospective register of systematic reviews PROSPERO' (ID: CRD42022330818).

2.1. Types of studies

We included meta-analyses, randomised controlled trials, clinical trials, cohort studies, cross-sectional studies, and case-control studies, but excluded ideas, editorial letters, opinions, comments, case reports, systematic reviews, and literature reviews in our search. We included only human studies.

2.2. Type of intervention

Intervention with imaging modalities and comparison of their pathological pulmonary findings in children with suspected or confirmed PTB.

2.3. Types of participants

Study participants between 0 and 18 years of age (including infants, children, and adolescents), with suspected or confirmed PTB.

2.4. Search method for eligibility

A search was conducted using the databases PubMed and Embase, covering all published results from January 1972 to the date of search; the first search date was September 30th, 2021, and the last search date was May 9th, 2022. We searched English- and non-English published and unpublished studies. One author (ET) designed a search strategy in cooperation with one information specialist under the supervision of all authors (AP, MF, LB, and UN). The search string was initially adjusted for PubMed and included controlled major MeSH subject headings and free text words from titles or abstracts (Fig. 1), and furthermore transposed for Embase. To avoid neglecting relevant and eligible studies, two authors searched the references of excluded reviews. In addition to the systematic search, we searched for other reports on all imaging modalities used in the diagnostic work-up for children with TB for perspective on their current practices in diagnostic imaging.

2.5. Inclusion criteria

Eligible studies had to compare at least two different imaging modalities, by evaluating imaging findings from each modality in the same study participant, or by calculating the specificity, sensitivity, positive predictive value (PPV) or negative predictive value (NPV) for each modality. Study participants had to be between 0 and 18 years of age and with suspected or confirmed PTB.

2.6. Exclusion criteria

We excluded studies with a majority or exclusively adult study population, as this systematic review focuses on paediatric medicine. Studies with study populations where the majority had HIV coinfection were excluded, to isolate the imaging findings for explicitly PTB patients.

2.7. Data extraction and management

Data extraction was done by two authors (MF and ET), that had to reach a consensus. Reported imaging findings, sensitivities, and specificities of imaging modalities, positive- and negative predictive values and interobserver agreement kappa-values were collected for this systematic review. Imaging findings are categorised by study and imaging modality and listed as the number of study participants with positive findings (n) per total number of participants (N). Collected findings are mediastinal LAP, hilar LAP, other thoracic LAP, LAP w/central necrosis or ring enhancement, consolidations, consolidation w/central low attenuation or necrosis, cavitation, granulomas, tree-in-bud pattern, calcification, ground glass opacity, bronchiectasis, bronchial thickening, bronchial narrowing, nodules, centrilobular nodules, military nodules, pleural nodules, pleural thickening, pleural effusion, air-trapping, airway compression, atelectasis, hyperinflation, fibrotic scar, reticulonodular opacity, infiltrates, overall PTB findings and the number of cases in which imaging confirmed PTB diagnosis were collected. If needed data was missing (i.e., study characteristics and radiological findings not reported in the article), corresponding authors were contacted to obtain the data.

2.8. Quality assessment

To assess the risk of bias, three authors (MF, LB, and ET) performed a quality assessment of included studies using the National Heart, Lung,

and Blood Institute's (NHLBI) "Quality Assessment of Case-Control Studies" and "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" (Appendix A, Table A.1).

3. Results

A total of 1176 records were identified in the latest PubMed search, and 1132 results were identified in Embase. One author (ET) used Covidence (https://www.covidence.org/) to screen 1924 articles firstly by title and abstract after Covidence removed duplicates. One hundred and ninety-four articles were screened in the full-text stage by two authors (MF and ET) that reached a consensus for inclusion of studies (Fig. 1). We identified 49 records through citation search, where two were found eligible. We included 19 studies in total (Fig. 1): 13 retrospective cohort studies, one retrospective control study, one retrospective cross-sectional study, three prospective cohort studies and one prospective cross-sectional study, with a total of 1368 study participants, including 498 with confirmed PTB and 746 with suspected PTB. Only results from participants with confirmed or suspected PTB were included in this systematic review, resulting in 1244 cases. The study setting was primarily tertiary level hospitals and one quaternary level hospital. Geographically the studies took place in Asian, European, North American, and African countries; four in South Africa, three in Turkey, two in Spain, two in Korea, two in India, two in Iran, one in Taiwan, one in Italy, one in Canada, and one in Portugal. All study characteristics are listed in Table 1.

Included imaging modalities were chest x-ray (CXR), High-kV CXR, magnetic resonance imaging (MRI), computed tomography (CT), high-resolution CT (HR-CT), and ultrasound (US). Most studies, 15 of 19, compared imaging findings in CXR and CT, 2 of 19 studies compared CXR and High-kV CXR, 2 of 19 studies compared CT and MRI, 1 of 19 studies compared CXR and MRI and 2 of 19 studies compared CXR and US. Three studies compared two or more modalities.

3.1. CT versus CXR

Of the 15 studies, nine studies reported the number of participants where CT or CXR confirmed the diagnosis of TB (Table 2). In all these studies, findings compatible with TB were more frequently detected on CT than CXR.

Only two of the 15 studies comparing CT and CXR, Bayhan [17], and Kim [8] did not include radiological findings as part of their diagnostic criteria for PTB. The two studies combined showed that CT diagnosed 54/54 (100 %) children with confirmed PTB, while CXR diagnosed 42/54 (78 %).

The key radiological features in PTB and the number of findings identified by CT versus CXR in each applicable study is presented in Table 3 and Appendix B, Table B.1.

In summary, 14 of 15 studies found both lymph node and pulmonary parenchymal findings significantly more frequently on CT compared to CXR.

3.2. MRI versus CXR

Two studies compared findings via MRI, CT and CXR [6,7] (Table 3), but only one study calculated and compared the sensitivity, specificity, PPV and NPV of MRI and CXR, using CT as the standard reference (Table 4) [5]. They found LAP, consolidations, cavitation, and pleural effusion to be equally prevalent in CT and MRI (Table 4) [5].

The interobserver agreement for MRI evaluations was higher compared to CXR (Table 4) [5].

3.3. High-kV CXR versus CXR

One study compared the diagnostic accuracy with High-kilovolt (High-kV) CXR compared to regular CXR [14]. No significant difference in the number of detected radiographic features consistent with PTB was demonstrated between the two imaging modalities (Table 4) [14].

3.4. US versus CXR

Two studies reported that US identified a higher percentage of patients with LAP than CXR (Table 3) [11,15], and US was found to have

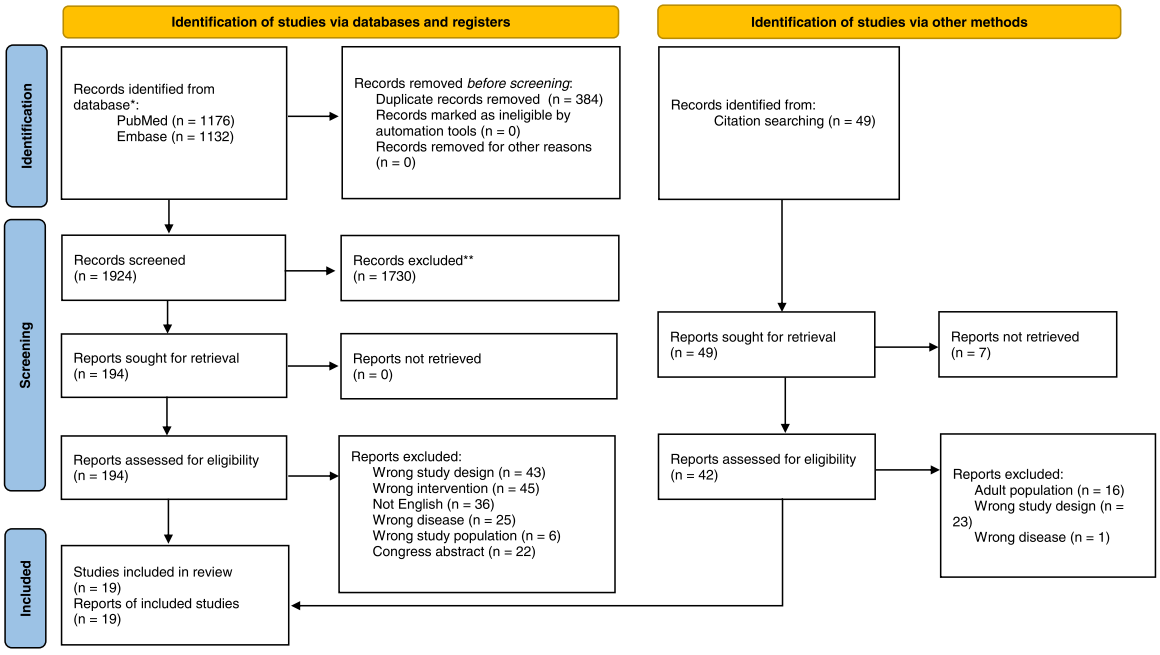

Fig. 1. PRISMA flow diagram. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 [31]. For more information, visit: http://www.prisma-statement.org/.

Table 1
Study characteristics of included studies.

#	Study ID	Location	Setting	Study period	Study design	No. of participants, N	Age of participants	Diagnostic criteria for PTB	Participants w/confirmed PTB, n/N	Participants w/suspected PTB, n/N	Limitations	NHLBI score*
1	Kakalia, 2020, *Journal of the Paediatric Infectious Diseases Society*	Canada	Secondary, tertiary, and quaternary level hospital	January 1st, 2002, to September 30th, 2018	Retrospective cohort study	26	Median: 15 years (range: 14–16 years)	≥ 1 of the following: 1) Respiratory specimen culture or NAAT positive for M. tuberculosis 2) Abnormal CXR consistent with TB w/ positive culture or NAAT from another site. 3) Culture-negative: Abnormal CXR consistent with TB and > 2 of: Immunologic evidence of TB infection, close contact with infectious source, or positive response to anti-TB treatment.	26/26	``	Radiological imaging is part of diagnostic criteria.	Fair
2	Heuvelings, 2019, *Paediatric Pulmonology by Wiley Periodicals Inc.*	South Africa	Tertiary level hospital	July 2014 to October 2015	Prospective cohort study	159	Median: 26.6 months (range: 15.1–59.3 months)	M. tuberculosis detected by culture or GeneXpert.	36/159	73/159	Mediastinal US evaluated in 112/159, CXR evaluated in 159/159	Good
3	Sodhi, 2017, *Indian Journal of Paediatrics*	India	Tertiary level hospital	August 2013 to February 2016	Prospective cohort study	40	Range: 5–15 years	≥ 1 of the following: 1) Persistence of fever or cough or both for > 2 weeks 2) Documented weight loss > 5% or failure to gain weight > 3 months 3) Contact with infectious case of TB	``	40/40	``	Fair
4	Peprah, 2012, *Journal of Thoracic Imaging*	South Africa	Tertiary level hospital	2006–2009	Prospective cohort study	6	Range: 7–13 years	Airway symptoms and bronchoscopic biopsy of subcarinal nodes positive for TB.	6/6	``	Small study population	Fair
5	Garrido, 2012, *Paediatric Pulmonology*	Spain	Tertiary and secondary level hospital	jun.-09	Retrospective cohort study	28	< 4 years of age	Children with positive TST (> 5 mm) and pathological CXR and/or TCT.	28/116	0/116	Radiological imaging is part of diagnostic criteria.	Good
6	Peng, 2011, *Journal of the Formosan Medical Association*	Taiwan	Tertiary level hospital	Unknown	Retrospective control study	26	Range: 1–14 years	≥ 1 of the following: 1) M. tuberculosis cultured from sputum 2) PTB decided by consensus of expert meetings	26/26	``	Unspecific diagnostic criteria	Good
7	Bayhan, 2011, *Journal of Turkish Association of Tuberculosis and Thorax*	Turkey	Tertiary level hospital	February 2007 to May 2009	Retrospective cohort study	13	Mean: 5.6 months (range: 1.5–12 months)	≥ 1 of the following: 1) Positive culture of gastric aspirates for M. tuberculosis 2) > 2 of the following: positive TST, family member with TB, subsequent clinical or radiologic improvement from anti-TB treatment	13/13	``	Small study population	Fair
8	Boloursaz, 2009, *Acta Medica Iranica*	Iran	Tertiary hospital	2001–2006	Retrospective cohort study	70	Range: 5 months-15 years	≥ 1 of the following: 1) Clinical features 2) History of contact with	70/70	``	Radiological imaging is part of diagnostic criteria.	Fair

(*continued on next page*)

Table 1 (*continued*)

#	Study ID	Location	Setting	Study period	Study design	No. of participants, N	Age of participants	Diagnostic criteria for PTB	Participants w/confirmed PTB, n/N	Participants w/suspected PTB, n/N	Limitations	NHLBI score*
								smear positive TB patient 3) Positive TST 4) Radiologic manifestation and laboratory investigations (smear or gastric lavage).				
9	Kim, 2006, *American Journal of Roentgenology*	Korea	Tertiary level hospital	1991–2003	Retrospective cohort study	25	Mean: 5.9 months (range: 2–12 months)	≥ 1 of the following: 1) Positive culture of gastric aspirates for AFB 2) Positive PCR for M. tuberculosis 3) Positive culture of ascites for M. tuberculosis 4) Positive biopsy for M. tuberculosis 5) > 2 of the following: positive TST, clinical or radiologic improvement from anti-TB treatment, or ≥ 1 family member with contagious TB.	25/25	``	25/25 participants underwent CXR, only 17/25 underwent CT.	Good
10	Swingler, 2005, *Archives of Disease in Childhood*	South Africa	Tertiary level hospital	March 5th, 2001, to August 14th, 2001	Prospective cross-sectional study	100	Median: 21.5 months (range: 16–31 months)	Pulmonary infiltrates on CXR and > 1 of the following: 1) Positive TST 2) Significant TB contact 3) Failure to gain weight over the previous 2 months. 4) Chronic cough for > 1 month	``	100/100	No criteria for the detection of nodes were prescribed. Radiological imaging is part of diagnostic criteria.	Fair
11	Bosch-Marcet, 2004, *Paediatric Radiology*	Spain	Tertiary level hospital	1994–2000	Retrospective cohort study	32	Mean: 6 years (range: 4 months-17 years)	Positive TST (≥ 9 mm)	``	32/32	6/32 participants underwent CT and 32/32 underwent CXR and US.	Poor
12	De Villiers, 2004, *Australasian Radiology*	South Africa	Tertiary level hospital	1992–1997	Retrospective cohort study	61	Mean: 20.9 months (range: 2–69 months)	Gastric aspirate positive for TB	18/61	27/61	Small study population	Poor
13	Kim, 1997, *American Roentgen Ray Society*	Korea	Tertiary level hospital	1989–1994	Retrospective cohort study	41	Mean: 6 years (range: 3 months-14 years)	≥ 1 of tests positive for M. tuberculosis or AFB: 1) Culture 2) Staining of sputum 3) Gastric aspirates 4) Pleural/bronchoscopic/ surgical biopsy or ≥ 2 of the following: 1) Positive TST 2) Other diseases ruled out and clinical course consistent with TB 3) Known adult, contagious TB contact	41/41	``	41/41 participants underwent CXR, only 31/41 patients underwent CT. 14/41 participants underwent HR-CT, and 10/41 participants had access to High-kV CXR (not specified no. of scans)	Fair
14	Buonsenso, 2021,	Italy	Tertiary level hospital	January 2006 to December 2015	Retrospective cohort study	41	Median: 4.68 years (range: 0–16)	(Confirmed PTB) ≥ 1 of the following: 1) Clinical specimen culture	34/41	7/41	CT was not performed in 4/41 participants due to	Good

(*continued on next page*)

Table 1 (*continued*)

#	Study ID	Location	Setting	Study period	Study design	No. of participants, N	Age of participants	Diagnostic criteria for PTB	Participants w/confirmed PTB, n/N	Participants w/suspected PTB, n/N	Limitations	NHLBI score*
	Frontiers in Paediatrics							positive for M. tuberculosis 2) Positive AFB smear microscopy 3) PCR positive for M. tuberculosis (Probable TB) $\geq$ 3 of the following: 1) CXR findings consistent with active TB 2) Typical symptoms (fever/cough/weight loss) 3) Radiological mark of active TB w/symptoms 4) Exposure to case with active, infectious TB 5) Response to appropriate anti-TB therapy			lack of consent. Radiological imaging is part of diagnostic criteria.	
15	Durmus, 2016, *Indian Journal of Paediatrics*	Turkey	Tertiary level hospital	2006–2011	Retrospective cohort study	326	Mean: 9.0 (range: 1–17 years)	Suspected PTB: Positive TST (> 15 mm)	``	326/326	No participants with normal CXR findings underwent CT, while all participants underwent CXR.	Poor
16	Silva, 2021, *Anales de Pediatría: Elsevier Espana*	Portugal	Tertiary level hospital	January 2007 to June 2017	Retrospective cross-sectional study	46	Median: 5 years (range: 0–18 years)	Definitions of the European Centre for Disease Prevention and Control (ECDC)	12/46	Probable TB: 7/46 Possible TB: 27/46	No explanation for why CT scan was performed in only 82.2 % of study participants, while 100 % received a CXR.	Poor
17	Bayhan, 2015, *The Turkish Journal of Paediatrics*	Turkey	Tertiary level hospital	January 2005 to December 2012	Retrospective cohort study	144	Mean: 76.3 months	(Confirmed TB) $\geq$ 1 positive clinical sample (AFS/culture/PCR tests) or detection of caseating granuloma or AFS in a single histopathologic specimen. (Probable TB) $\geq$ 3 of the following: 1) Non-specific TB symptoms (fever/cough/weight loss) 2) CXR or CT suggesting active TB 3) Active EPTB findings on other radiologic examinations 4) Contact history with adult index case 5) TST positivity 6) Good response to anti-TB therapy	15/144	Probable PTB: 107/144	Single centre hospital-based study design. 116/122 PTB patients underwent CT, while 122/122 PTB patients underwent CXR. Radiological imaging is part of diagnostic criteria.	Fair
18	Chunawala, 2021, *Journal of Tropical Paediatrics*	India	Tertiary level hospital	January 2015 to March 2018	Retrospective cohort study	58	Mean: 7.1 $\pm$ 4.3 years (range: 3 months to 16years)	Clinical diagnosis: Necrotic and caseous mediastinal nodes on imaging w/ symptoms suggestive of TB	Mediastinal TB: 58/58 Associated PTB: 22/58	``	58/58 with mediastinal TB underwent CXR,	Poor

(*continued on next page*)

Table 1 (*continued*)

#	Study ID	Location	Setting	Study period	Study design	No. of participants, N	Age of participants	Diagnostic criteria for PTB	Participants w/confirmed PTB, n/N	Participants w/suspected PTB, n/N	Limitations	NHLBI score*
								(fever or cough >15 days) w/ positive TST Bacteriological diagnosis: GeneXpert and growth of M. tuberculosis on lymph node biopsy, gastric lavage, or sputum analysis			while 54/58 underwent HR-CT.	
19	Khalilzadeh, 2009, *The Tanaffos Journal*	Iran	Tertiary level hospital	Timespan 4 years (dates not reported)	Retrospective cohort study	126	3 groups: 0–5 years, 6–10 years, and 11–15 years	≥ 3 of the following: 1) Presence of clinical symptom 2) History of contact with a TB patient 3) TB compatible radiological features 4) Positive pathologic/ bacteriologic findings 5) Positive PPD	126/126	``	Radiological imaging is part of diagnostic criteria.	Fair

*Quality assessment score from the NHLBI quality assessment tool (Appendix A, Table A.1).

Table 2
Children radiologically diagnosed with PTB by CT versus CXR.

Study ID	CT confirms PTB diagnosis, n/N (%)	CXR confirms PTB diagnosis, n/N (%)
Chunawala and Shah [22]	54/54 (100)	31/58 (53.4)
Buonsenso [3]	26/37 (70.3)	15/41 (36.6)
Bayhan [21]	116/166 (100)	92/122 (75.4)
Garrido [12]	27/28 (96.4)	11/28 (39.3)
Bayhan [17]	13/13 (100)	9/13 (69.2)
Peng [7]	21/26 (80.8)	13/26 (50)
Boloursaz [16]	70/70 (100)	48/70 (69)
Khalilzadeh [19]	119/126 (94.4)	82/126 (65.1)
Kim [8]	41/41 (100)	33/41 (80.5)

N: number of study participants with evaluated imaging, n: number of study participants with positive findings on imaging.

Table 3
Radiological findings for PTB identified by MRI, CT, CXR and US.

Radiological findings	Study ID	MRI, n/N (%)	CT, n/N (%)	CXR, n/N (%)	US, n/N (%)
Imaging confirms PTB diagnosis	Bosch-Marcet [15]			21/32 (65.6)	26/32 (82.3)
Overall PTB findings	Heuvelings [11]			59/109 (54)	79/109 (72.5)
	Bosch-Marcet [15]			21/32 (65.6)	27/32 (59.4)
LAP	Sodhi [5]	15/40 (37.5)	15/40 (37.5)	5/40 (12.5)	
	Peprah [6]	6/6 (100)	6/6 (100)	N/A	
	Heuvelings [11]			10/109 (9.2)	15/75 (20)
	Bosch-Marcet [15]			N/A	27/32 (84)
Consolidation	Sodhi [5]	26/40 (65)	26/40 (65)	14/40 (35)	
	Peprah [6]	6/6 (100)	6/6 (100)		
	Heuvelings [11]			53/109 (48.6)	49/109 (45)
Cavitation	Sodhi [5]	12/40 (30)	12/40 (30)	6/40 (15)	
Bronchiectasis	Sodhi [5]	7/40 (17.5)	8/40 (20)	4/40 (10)	
Nodule	Sodhi [5]	15/40 (37.5)	17/40 (42.5)	7/40 (17.5)	
	Peprah [6]	2/6 (33.3)	2/6 (33.3)		
Pleural effusion	Sodhi [5]	7/40 (17.5)	7/40 (17.5)	6/40 (15)	
	Heuvelings [11]			11/109 (10.1)	20/109 (18.3)

N: number of study participants with evaluated imaging, n: number of study participants with positive findings on imaging, N/A: not applicable

higher interobserver agreement than CXR in identifying consolidations $\geq$ 0.5 cm and pleural effusion, equal for LAP and slightly lower in US for consolidations $\leq$ 0.5 cm (Table 4) [11].

3.5. Risk of bias across studies

In 8 of 19 included studies the diagnostic reference standard for TB included radiological findings, which may introduce bias in the

Table 4
Specificity, sensitivity, PPV, NPV, and interobserver agreement for CT, MRI, CXR High-kV CXR and US.

Study ID	Imaging finding	Specificity, %	Sensitivity, %	PPV, %	NPV, %	Interobserver agreement, kappa-value*
CT						
Buonsenso [3]	Probable PTB			70.3		
MRI						
Sodhi [5]	Nodules	95.7	88.2	93.8	91.7	
	Consolidations	92.9	100	96.3	100	
	LAP	100	100	100	100	
	Bronchiectasis	100	87.5	100	97	
	Pleural effusion	100	100	100	100	
	Cavitation	100	100	100	100	
	All PTB findings					0.963
CXR						
Buonsenso [3]	Probable PTB			36.6		
Sodhi [5]	Nodules	91.3	41.2	77.8	67.7	
	Consolidations	85.7	53.8	87.5	50	
	LAP	92	33.3	71.4	69.7	
	Bronchiectasis	96.9	50	80	88.6	
	Pleural effusion	93.9	85.7	75	96.9	
	Cavitation	96.4	50	85.7	81.8	
	All PTB findings					0.440
Swingler [4]	LAP	59	67			0.300
DeVilliers [14]	PTB diagnosis	74.4	38.8			
Heuvelings [11]	Consolidations					0.47
	LAP					0.27
	Pleural effusion					0.56
HIGH-KV CXR						
DeVilliers [14]	PTB diagnosis	86	38.8			
US						
Heuvelings [11]	Consolidations $\geq$ 0.5 cm					0.67
	Consolidations $\leq$ 0.5 cm					0.39
	LAP					0.56
	Pleural effusion					0.86

*Definition of interobserver agreement from Heuvelings [11] & Sodhi [5]: Slight ($k < 0.20$), Fair ($k = 0.21–0.40$), Moderate ($k = 0.41–0.60$), Substantial ($k = 0.61–0.80$), Almost perfect ($k = 0.81–1.00$)
Data are from Buonsenso [3], Sodhi [5], Swingler [4], DeVilliers [14] and Heuvelings [11].

assessment of diagnostic efficacy of each modality as the standard reference for diagnosis varies.

In Durmus [13], only children with abnormal CXR underwent CT, while all participants underwent CXR, hence creating a bias towards the diagnostic effect of CXR [13]. Buonsenso [3] chose a selective reporting of imaging findings and excluded CXR findings from the article [3]. CXR findings from this study are therefore non-published Supplementary material, and the data was obtained through e-mail correspondence with the corresponding author. Selection bias is declared in Sodhi [5] because the authors only included children who could cooperate for MRI [6].

4. Discussion

To our knowledge, this is the first systematic review to create an overview of all primary research comparing imaging modalities and their radiographic findings in children with suspected or confirmed pulmonary TB. The present war in Ukraine has led to millions of Ukrainian refugees entering the western part of Europe. As Ukraine is known to be one of 16 high multi-drug resistant TB (MDR-TB) burdened countries [1], the situation can challenge Western European health systems that have had less experience with this disease. Educating health care systems on new, more accurate diagnostic methods is a responsibility that particularly lies with high-income countries that have the resources and access to high-cost diagnostic imaging.

WHO's Global Tuberculosis Report for 2021 estimated the biggest impact on TB deaths was in year 2021, and that the incidence increase would lead to a higher TB mortality compared to pre-2020 trends [1]. In Ukraine, the estimated impact of the COVID-19 pandemic on TB incidence in 2022 is modelled to be a 5–10 % increase relative to 2020 [1].

We highly acknowledge the competence in TB burdened countries and their diagnostic methodology for TB. This systematic review is based on small, primarily retrospective studies with methodical shortcomings and inherent limitations. There is need for larger, prospective, standardised studies with well-defined diagnostic references to accurately assess the diagnostic value of each imaging modality.

4.1. CT

In 14 of 15 included studies, CT more frequently detected pulmonary parenchymal lesions and LAP compared to CXR [3–9,12,13,15,16,19–21], and four studies concluded that CT should be used when CXR scans are inconclusive or complications of TB are suspected [8,9,16,17]. When excluding studies where radiological findings were included in the diagnostic reference standard, the two remaining studies revealed that CT and CXR diagnosed 100 % versus 77.8 % children with confirmed PTB, respectively.

Necrotic LAP has previously been associated with radiological TB findings - changes in the lung parenchyma, bronchial compression, and positive TB culture [22] - but is rarely found on CXR and regularly seen on CT and HR-CT [4,6–9,12,13]. In this systematic review, LAP w/central necrosis and ring enhancement was not found on any CXR image across all applicable studies, while it was identified by CT in all studies [3,7–9,12,22].

Although CT may have superior sensitivity in comparison with CXR, the radiation dose is also substantially larger. For a diagnostic CT scan of the thorax, estimated radiation dose for a child aged 5–15 is between 0.91 and 1.96 mSv [23]. In contrast, the radiation dose from CXR is approximately 0.01 mSv, if performed on new generation equipment [23]. Therefore, CT is generally only recommended in cases of uncertainty [24].

4.2. US

The results from this systematic review prove US to be useful in diagnosing mediastinal LAP and pleural effusion in children with PTB and can be of value in the follow-up of children receiving anti-tuberculosis treatment [14,15,23]. Sensitivity and specificity are calculated in [18] based on data from one study included in this review [11]. Sensitivity was 46 % for consolidations and 19 % for enlarged lymph nodes, with a coherent specificity of 53 % and 72 %, respectively [11,18]. US is operator-dependent hence the results can easier be compromised by the applied technique and experience of the examinator. However, interobserver agreement for consolidations $\geq$ 0.5 cm and pleural effusion was higher for US than CXR, equal for LAP and slightly lower in US for consolidations $\leq$ 0.5 cm [11]. It is nevertheless regarded as an important imaging method especially for paediatric patients, attributable to being radiation-free, bed-side applicable and non-invasive.

4.3. MRI

MRI can identify PTB findings without radiation exposure, and even though it cannot detect ground glass opacities, small nodules, and calcified nodules with the same sensitivity as CT, it shows high sensitivity and specificity in detecting LAP, pleural effusion and/or cavitation [5,23]. Sodhi [5] promote MRI as part of the diagnostic work-up in children with complicated or equivocal tuberculosis. According to their study, the interobserver agreement between two radiologists is "almost perfect" for MRI evaluations compared to "moderate" in CXR [5]. CT cannot distinguish caseating necrosis related to TB from other bacterial necrosis, while areas of lung necrosis may show a low signal on T2/STIR MRI [6].

The limitations of MRI for paediatric examinations include challenges involving patient cooperation. For ensuring the child holds still and achieving optimal imaging quality, sedation/general anaesthesia is most often needed in younger children. Furthermore, in many parts of the world, the availability of MRI is not sufficient to accommodate the clinical need.

4.4. PET/CT

No studies compared positron emission tomography (PET) to other imaging modalities. However, complimentary research for perspective in this review state that PET can potentially aid in the detection of TB and discrimination between active and latent TB [25,26]. For a PET/CT the average effective radiation dose for a child aged 1–15 is around 10 mSV [27]. A recent development in PET/CT is the large field-of-view scanner Quadra (Siemens Healthineers, Erlangen, Germany) in which a whole-body scan is possible with a radiation dose of $<$ 1 mSv or an examination time $<$ 2 min [28]. This can significantly reduce the need for anaesthesia for paediatric patients [29]. It can identify foci of intrathoracic and extrapulmonary TB in one scan alone, compared to exposing children to several different imaging modalities [25]. On the other hand, it is costly and unavailable in most countries [3–17,19–22], and the added value compared to other modalities still needs to be verified in paediatric patients.

4.5. Artificial intelligence

Artificial intelligence (AI) applications for an automated detection of TB on CXR images are increasing [30]. None of the present applications are specifically designed for children. However, the application named CAD4TB is a certified AI protocol that can be used in children aged $>$ 4 years [30].

5. Conclusion

We highly acknowledge the expertise in high TB burdened countries, and a diagnostic strategy for PTB in children according to local availability is proposed. No strong evidence from this systematic review shows otherwise. Based on the scarce available data, CT seems to have superior diagnostic accuracy compared to CXR. However, due to higher cost, lower availability, and higher radiation dose of CT, CXR is used in the diagnostics of children evaluated for TB. In cases of equivocal CXR or suspected PTB in children with normal CXR, CT can be considered.

US has the advantage of low cost and no radiation and seems promising in skilled hands especially for detection of thoracic lymphadenopathy. For high-income countries without solid competencies in the diagnosis of PTB in children, and where CT, PET/CT or MRI are available, these modalities could be an alternative in children with suspicion of TB. Additionally, PET/CT also allows for the diagnosis of extrapulmonary disease and possible discrepancy between active and latent disease. In the current situation with the Ukrainian refugee flow, an AI algorithm could assist the interpretation of screening children with CXR to accommodate the increasing demand.

6. Limitations

Most studies were unable to provide statistical data between the different imaging modalities, due to the limited number of patients. Additionally, 6 of 19 studies did not have an equal number of study participants undergoing both modalities. Fifteen of 19 were retrospective studies, which can reduce the quality of data due to lack of standardisation in patient recruitment, clinical management, imaging procedures and interpretation. In some of the included studies comparison of modalities was not the primary objective, which led to inadequate reporting of imaging findings. We included the studies in the systematic review, but with incomplete data.

CRediT authorship contribution statement

All authors had access to the data and accept the responsibility to submit it for publication. **Erle Opdahl Tonne (ET):** Development of protocol, screening of studies, development of tables, development of all sections of the manuscript. **Marie Øbro Fosbøl (MF):** Development of protocol, screening of studies, development of tables, development of all sections of the manuscript. **Anja Poulsen (AP):** Development of protocol, development of all sections of the manuscript. **Ulrikka Nygaard (UN):** Development of protocol, development of all sections of the manuscript. **Liselotte Højgaard (LH):** Development of protocol, development of all sections of the manuscript. **Lise Borgwardt (LB):** Development of protocol, development of tables, development of all sections of the manuscript.

Ethical statement

All procedures performed in the systematic review were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Patient and public involvement

There was no involvement from either patients or the public in this systematic review.

Declarations of interest

There are no conflicts of interest in this systematic review.

Data sharing statement

Data will be made available to the public with publication in the scientific literature. Data will be shared after the approval of a proposal.

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All data included is supplied by the PubMed- and Embase databases.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejro.2022.100472.

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