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Pediatric and adolescent tuberculosis in Latvia, 2011–2014: case detection, diagnosis and treatment

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SUMMARY

OBJECTIVE: To perform a comprehensive analysis of case detection, diagnosis and treatment of tuberculosis (TB) in children and adolescents in Latvia, and to evaluate the utility of the current approach.

DESIGN: A retrospective study of all Latvian children and adolescents diagnosed with TB from 1 January 2011 to 31 December 2014.

RESULTS: Of 3081 patients diagnosed with TB during 2011–2014, 250 (8%) were aged <18 years, and 80% were identified through contact investigation. Pulmonary TB was diagnosed in 77% of the patients. TB was confirmed bacteriologically in 21% of patients; chest X-ray (CXR) was consistent with TB in 42% of study participants, while 58% of cases were diagnosed with subclinical TB using low-dose computed tomography (CT) after being missed by CXR. Patients with visible abnormalities on CXR had a higher rate of bacteriological confirmation and were more often clinically symptomatic, which indicates active disease. Early diagnosis had a treatment success rate of 100% for drug-resistant and 99% for drug-susceptible TB.

CONCLUSION: TB case detection through contact investigation provided early diagnosis and excellent treatment outcomes in children and adolescents in Latvia. CT was able to identify pathology consistent with subclinical TB in children with a history of exposure.

KEY WORDS: computed tomography scan; Mantoux test; TB; chest X-ray; paediatric

OF THE ESTIMATED 9.6 MILLION new cases of tuberculosis (TB) worldwide in 2014, one million (10.4%) were children aged <15 years.[1] In industrialised countries, children make up ⩽5% of the TB caseload. In communities with the highest incidence of TB, children represent up to 40% of all TB patients.[2] Discrepancies in the expected values and the proportions of reported cases or cases with confirmed diagnoses may give an indication of how well childhood TB is being diagnosed and reported in particular settings. These data may also alert health care providers to the extent of over- and under-diagnosis.[3]

Accurate diagnosis of childhood TB can be challenging. Bacteriological confirmation in children is less frequent than in adults, ranging from 16.9% to 62%.[4–10] In the absence of bacteriological confirmation, diagnosis is based on a combination of criteria such as clinical symptoms, contact history, positive immunological diagnosis of *Mycobacterium tuberculosis* infection and radiological abnormalities consistent with TB.[10–14]

Clinical symptoms and abnormalities visible on chest radiograph (CXR) may not be present during subclinical disease and may lead to under-detection of TB in children. Computed tomography (CT) is a corroborative imaging modality used to study TB.[15–17] The use of CT for the examination of asymptomatic children is not common practice, and has not been suggested in clinical guidelines. However, CT is more sensitive than CXR in the detection of localised and disseminated disease and mediastinal lymphadenopathy.[15–17]

Despite a steady decline in TB incidence since 2001 in Latvia (located in the Baltic region of Northern Europe), the TB notification rate in 2014 was as high as 31.6 per 100 000 population. The rate of multidrug-resistant and extensively drug-resistant TB (MDR/XDR-TB) among previously treated adult patients was 29.3–27.5% in 2011–2014. Latvia also has a high human immunodeficiency virus (HIV) burden; in 2014, 11.6% of all newly diagnosed TB patients were HIV-infected. However, the number of HIV-infected children and adolescents aged <18 years is relatively low (72/345 837, 0.02% in 2014).[18] Given this unfavourable situation, children are expected to constitute some of the TB cases, although the exact rate of childhood TB depends on

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the overall TB burden and the diagnostic approach used.

The present study evaluated the current approach to the diagnosis and treatment of TB in children and adolescents in Latvia, with a focus on the value of CT for early diagnosis in asymptomatic children with normal or inconclusive CXR results in an appropriate clinical setting.

METHODS

Setting and patient population

The Department of Paediatric Tuberculosis, Riga East Clinical University Hospital (RECUH), Riga, Latvia, is a stand-alone paediatric TB department for all Latvian children and nearly all adolescents, where a full range of TB diagnostics is performed and anti-tuberculosis treatment is initiated. We conducted a retrospective study of case detection, diagnosis and treatment for all children and adolescents aged <18 years who were diagnosed and treated for TB from 1 January 2011 to 31 December 2014 in Latvia.

Data collection

Using medical records from the RECUH, data on demographics, medical history, presenting symptoms, physical examinations, laboratory results, treatment regimens and immunological, radiological, bacteriological, histopathological results for each participant were extracted from the patient files using a standardised coding system. All available radiological images were specifically reviewed by researchers for the study. Medical records on radiological findings were used if the images for review were not available. Data on treatment outcomes were obtained from the National TB Registry database. All data were de-identified, and only a study identification number was used.

Approach to tuberculosis diagnosis and treatment

The routine patient examination included a physical assessment, blood count analysis and blood biochemistry, immunological diagnosis for *M. tuberculosis* infection (Mantoux test and/or the T-SPOT®.*TB* test [T-SPOT, Oxford Immunotec, Abingdon, UK]), and radiological and bacteriological studies. The Mantoux test using two tuberculin units of purified protein derivative RT 23 (Statens Serum Institut, Copenhagen, Denmark) was administered intracutaneously, read at 72 h and interpreted according to World Health Organization (WHO) recommendations.[19] T-SPOT was performed according to the manufacturer's instructions.

Radiological examinations were performed using digital CXR in the posterior-anterior position and continued in the lateral view if pathology was suspected retrocardially and/or in the hilar lymph nodes. The decision to use low-dose CT was made on an individual basis after considering the risks of non-diagnosed subclinical disease: the major indication was normal or inconclusive CXR results in children who had a significant possibility of subclinical disease due to close contact with a TB patient and/or a positive immunological test result for tuberculous infection. CT was also performed to better document the extent of CXR-visualised abnormalities. The radiologist was not blinded to the child's clinical information.

Up to three biological samples were obtained for bacteriological examination from the majority of patients before treatment. Each sample was examined by fluorescence microscopy using auramine-rhodamine staining and cultured on solid Löwenstein-Jensen medium. One sample from each patient was cultured on liquid medium (Middlebrook 7H9 broth, BACTEC™ MGIT™ [Mycobacteria Growth Indicator Tubes; BD, Forest Lake, NJ, USA]). In more than half of the patients, at least one sample was tested using Xpert®MTB/RIF (Cepheid, Sunnyvale, CA, USA). All positive cultures were subjected to drug susceptibility testing (DST).

HIV testing was performed at the discretion of the attending physician and was provided for cases with a history of HIV exposure during pregnancy and/or clinical indications.

Needle pleural biopsy was performed to obtain histological and/or bacteriological confirmation of TB in patients for whom additional information was considered necessary for a confident diagnosis; the procedure was considered as safe.

The diagnosis was established after three physicians experienced in childhood TB reached an agreement. Treatment was initiated according to DST results of either the child's own isolates or the isolates of the infectious source case (the index case) if bacteriological confirmation was absent. WHO-recommended treatment regimens were used. For patients with drug-susceptible TB, this consisted of 2 months of isoniazid (INH, H), rifampicin (RMP, R), ethambutol and pyrazinamide followed by 4 months of INH and RMP. Standardised or individualised treatment was prescribed for cases with MDR/XDR-TB. For cases with INH resistance and polyresistance, INH was replaced by ofloxacin and treatment was extended up to 9 months.[19]

Treatment outcomes were evaluated according to WHO recommendations.[19] Statistical analysis was performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics, version 22.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were computed to characterise the study sample. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine associations between different characteristics. All *P* values were two-sided and calculated

Table 1 Baseline characteristics for 250 children and adolescents diagnosed with TB

Characteristics	All *n* (%)	0–4 years *n* (%)	5–9 years *n* (%)	10–14 years *n* (%)	15–17 years *n* (%)	*P* value
Total	250 (100)	73 (29)	82 (33)	45 (18)	50 (20)	
Female sex	118 (47)	37 (51)	39 (48)	22 (49)	20 (40)	0.696
Information on BCG status ($n = 232$, 92%)						
Vaccinated (presence of scar)	194 (84)	65 (89)	72 (89)	37 (82)	20 (61)	0.001
Vaccinated (absence of scar)	31 (12)	1 (1)	9 (11)	8 (18)	13 (39)	<0.001
Not vaccinated	7 (3)	7 (10)	—	—	—	0.002
Reason for examination for TB						
Positive Mantoux test	12 (5)	6 (8)	1 (1)	3 (7)	2 (4)	<0.001
Radiographic manifestation consistent with TB	17 (7)	2 (3)	1 (1)	3 (7)	11 (22)	<0.001
Chronic symptoms attributable to TB	20 (8)	7 (10)	2 (2)	6 (13)	5 (10)	0.084
TB contact history	201 (80)	58 (80)	78 (95)	33 (73)	32 (64)	<0.001
Type of contact with TB patient ($n = 201$, 80%)						
Household contact, AFB-positive, culture-positive	117 (58)	39 (67)	42 (54)	20 (60)	16 (50)	0.019
Household contact, AFB-negative, culture-positive	27 (13)	9 (16)	7 (9)	6 (18)	5 (16)	0.176
Close contact, AFB-positive, culture-positive	44 (22)	5 (9)	23 (29)	5 (15)	11 (34)	0.019
Close contact, AFB-negative, culture-positive	8 (4)	3 (5)	5 (6)	—	—	0.176
Casual contact, AFB-positive, culture-positive	5 (3)	2 (3)	1 (1)	2 (6)	—	0.015
DST results of the index cases' *M. tuberculosis* isolates ($n = 199$, 99%)						
Drug-susceptible	155 (78)	43 (75)	63 (81)	24 (75)	25 (78)	0.874
Drug-resistant (including resistance to isoniazid)	44 (22)	14 (25)	15 (19)	8 (25)	7 (22)	

TB = tuberculosis; BCG = bacille Calmette-Guérin; AFB = acid-fast bacilli; DST = drug susceptibility testing.

using Pearson's χ^2 test or Fisher's exact test. $P \leqslant 0.05$ was considered statistically significant.

The study was approved by the Ethics Committee of Riga Stradiņš University, Riga, Latvia. Written consent was not obtained as this was a retrospective study.

Definitions used

Bacteriologically confirmed TB: biological specimen was positive for *M. tuberculosis* using smear, culture or Xpert.

Clinically diagnosed TB: the patient did not fulfil the criteria for bacteriological confirmation but was diagnosed with active TB on the basis of CXR and/or CT abnormalities and histopathological findings consistent with TB. Alternative pathology as a reason for radiological abnormality was excluded.

Active TB disease: TB either bacteriologically confirmed or clinically diagnosed and abnormality identified on CXR.

Subclinical TB disease: TB either bacteriologically confirmed or clinically diagnosed and abnormality visualised only on CT.

Index care: a person diagnosed with pulmonary and/or laryngeal TB (smear- and/or culture-positive).

Household and close contacts were defined according to WHO recommendations.[20] Casual contacts were those who had met the index case several times in a confined space.

RESULTS

Demographics and clinical characteristics

Of the 3081 TB patients diagnosed in 2011–2014 in Latvia, 250 (8%) were children and adolescents aged <18 years (Table 1). All children were born and resided in Latvia at the time of diagnosis; most were bacille Calmette-Guérin vaccinated and developed a scar after vaccination (84%) (Table 1). The main reason for TB examination (201/250, 80%) was history of contact with a TB patient; DST results of the *M. tuberculosis* isolates of the index case were available for all but two patients (199/201, 99%); 22% of these isolates showed resistance to anti-tuberculosis drugs (44/199). Only 8% (20/250) of the study participants had sought medical attention due to chronic symptoms.[19] Overall, 68% (169/250) of the patients did not report any health-related complaints on admission (Table 2). In 90% of the patients (199/222), the Mantoux test induration was $\geqslant$10 mm. However, T-SPOT was negative in 28% (43/155) of patients diagnosed with TB. Abnormalities consistent with TB were clearly visible on CXR in 42% of the patients (105/250). In those 241 patients with both CXR and CT images available, CT scans in addition to CXR revealed pulmonary nodules in 41%, calcification in lymph nodes and lung parenchyma in 42%, inthrathoracic lymphadenopathy in 29%, consolidation in 13% and cavitation in 4% of patients (Table 3). In total, 58% (145/250) of cases were diagnosed as subclinical TB using CT after being missed by CXR (Table 2).

TB was bacteriologically confirmed in 7/145 (5%) patients with subclinical TB disease. Pleural biopsy samples were obtained in 17 patients who had pleural involvement, and histopathology consistent with TB was identified in 59% (10/17) (Table 2). Pulmonary TB was diagnosed in 192/250 (77%) study participants, with TB pneumonia being the most common form of disease (Table 4). Extra-pulmonary TB with

Table 2 Results of diagnostic studies for 250 children and adolescents diagnosed with TB

	All *n* (%)	0–4 years *n* (%)	5–9 years *n* (%)	10–14 years *n* (%)	15–17 years *n* (%)	*P* value
Symptoms reported at time of diagnosis, ($n = 250$, 100%)						
Chronic symptoms*	20 (8)	7 (10)	2 (2)	6 (13)	5 (10)	0.084
Mild symptoms†	61 (24)	16 (22)	24 (29)	10 (22)	11 (22)	0.915
Mantoux test induration size, mm ($n = 222$, 89%)						
⩾10	199 (90)	53 (80)	75 (96)	40 (91)	31 (91)	0.042
⩾5<10	13 (6)	7 (11)	3 (4)	2 (5)	1 (3)	
<5	10 (5)	6 (9)	—	2 (5)	2 (6)	
T-SPOT.*TB* test results ($n = 155$, 62%)						
Positive	112 (72)	38 (68)	39 (85)	20 (67)	15 (65)	0.159
Negative	43 (28)	18 (32)	7 (15)	10 (33)	8 (35)	
Negative in bacteriologically confirmed TB ($n = 35$)	11 (31)	3 (43)	2 (29)	2 (29)	4 (29)	0.956
CXR ($n = 250$, 100%)‡						
Abnormalities consistent with TB	105 (42)	24 (33)	20 (27)	20 (44)	39 (78)	<0.001
Normal	131 (52)	38 (52)	57 (70)	25 (56)	11 (22)	<0.001
Doubtful or not interpretable	14 (6)	11 (15)	3 (4)	—	—	<0.001
Chest CT ($n = 248$, 99%)§						
Abnormalities consistent with TB	248 (100)	73 (100)	82 (100)	45 (100)	48 (100)	—
Histopathological studies of pleural biopsy sample ($n = 17$)						
Histopathology consistent with TB	10 (59)	—	1 (10)	3 (30)	6 (60)	0.044
HIV test results ($n = 19$, 8%)						
HIV-infected	2 (11)	1 (11)	1 (50)	—	—	0.298
Non-HIV-infected	17 (89)	8 (89)	1 (50)	1 (100)	7 (100)	
Microbiological studies ($n = 238$, 95%)						
Bacteriological confirmation obtained	52 (22)	7 (11)	8 (10)	9 (20)	28 (56)	<0.001
Expectorated sputum	9 (18)	—	1 (13)	—	8 (29)	0.146
Induced sputum	26 (51)	—	5 (63)	7 (78)	14 (50)	0.013
Gastric aspirante/lavage	6 (12)	6 (86)	—	—	—	<0.001
Bronchoalveolar aspirate	5 (10)	—	1 (13)	1 (11)	3 (11)	1.000
Cerebrospinal fluid	1 (2)	1 (17)	—	—	—	0.135
Pleural fluid, pleural biopsy	5 (10)	—	1 (13)	1 (11)	3 (11)	1.000
Smear-positive¶	10 (4)	—	2 (3)	1 (2)	7 (14)	0.003
Culture-positive#	48 (20)	6 (10)	7 (9)	9 (20)	26 (52)	<0.001
Xpert-positive** ($n = 143$)	23 (16)	3 (7)	1 (3)	2 (8)	17 (37)	<0.001
DST results ($n = 48$, 19%)						
Drug-susceptible	35 (73)	3/6 (50)	5 (71)	7 (78)	20 (77)	0.614
Monoresistance to H	5 (10)	—	1 (14)	1 (11)	3 (12)	1.000
Polyresistance to S+H	6 (13)	2 (33)	1 (14)		3 (12)	0.249
Polyresistance to S+H+Eth	1 (2)	1 (17)	—	—	—	0.125
Multidrug-resistance to S+H+R+Cpm+PAS+Eth	1 (2)	—	—	1 (11)	—	0.458
Bacteriologically confirmed TB ($n = 52$, 21%)						
Active TB disease (visible on CXR and CT)††	45 (87)	5 (71)	5 (63)	8 (89)	27 (96)	0.025
Subclinical TB disease (visualised only on CT)‡‡	7 (14)	2 (29)	3 (38)	1 (11)	1 (4)	0.025
Clinically diagnosed TB ($n = 198$, 79%)						
Active TB disease (visible on CXR and CT)††	60 (30)	19 (29)	17 (23)	12 (33)	12 (55)	0.041
Subclinical TB disease (visualised only on CT)‡‡	138 (70)	47 (71)	57 (77)	24 (67)	10 (46)	0.041

* Grounds for seeking medical help, including chronic unremitting symptoms persisting >2 weeks without sustained improvement or resolution following appropriate treatment for other potential diagnoses (cough, fever, anorexia, weight loss or failure to thrive, fatigue, reduced playfulness or decreased activity).
† Not a reason for seeking medical help (periodic low-grade temperature, cough, headache, loss of appetite and chest pain).
‡ Performed in all patients; CXR images not available for review in 6 patients.
§ Two patients with pleural effusion did not undergo CT examinations; one patient did not have a CT image available for review.
¶ One child had only an AFB-positive sample without a positive Xpert result and culture.
# Four children had no culture data available; of these, three had only Xpert-positive results, and one had only an AFB-positive sample.
** Xpert RMP resistance was detected in one patient.
†† Abnormality visible on CXR and CT.
‡‡ Abnormality visualised only on CT.
TB = tuberculosis; CXR = chest X-ray; CT = computed tomography; HIV = human immunodeficiency virus; DST = drug susceptibility testing; H = isoniazid; Eth = ethionamide; R, RMP = rifampicin; Cpm = capreomycin; PAS = para-aminosalicylic acid; AFB = acid-fast bacilli.

isolated involvement of inthrathoracic lymph nodes was diagnosed in 58/250 (23%) patients.[19] Severe forms of TB (central nervous system and miliary TB) were diagnosed in two children aged <4 years, one of whom was co-infected with HIV.

Bacteriologically confirmed TB

Samples for bacteriological examination were collected from 95% (238/250) of the patients (Table 2). Bacteriological confirmation was obtained in 22% (52/238) of these. Only 10 patients had acid-fast bacilli-positive sputum smears. Xpert analysis was performed in 60% (143/238) of the samples and in 85% (41/48) of patients with subsequent culture confirmation. Xpert testing was positive in 53% (20/38) of the culture-confirmed cases. Pan-drug-suscep-

Table 3 Comparison of radiological abnormality revealed on CXR and CT in 241 children and adolescents who had both examinations available for review

	All *n* (%)	0–4 years *n* (%)	5–9 years *n* (%)	10–14 years *n* (%)	15–17 years *n* (%)	*P* value
Radiological abnormality						
Any abnormality visible on CXR	97 (40)	23 (32)	22 (27)	17 (42)	35 (76)	<0.001
Any abnormality visible on CT	241 (100)	72 (100)	82 (100)	41 (100)	46 (100)	—
Inthrathoracic adenopathy						
Visible on CXR	20 (8)	12 (17)	7 (9)	—	1 (2)	0.004
Visible on CT	88 (37)	36 (50)	32 (39)	8 (20)	12 (26)	0.004
Calcifications in lymph nodes and lungs						
Visible on CXR	5 (2)	—	4 (5)	1 (2)	—	0.140
Visible on CT	106 (44)	30 (42)	44 (54)	17 (42)	15 (33)	0.143
Nodules and micronodules						
Visible on CXR	56 (23)	10 (14)	11 (13)	10 (24)	25 (54)	<0.001
Visible on CT	155 (64)	31 (43)	54 (66)	30 (73)	40 (87)	<0.001
Miliary pattern						
Visible on CXR	1 (0.4)	1 (1)	—	—	—	1.000
Visible on CT	1 (0.4)	1 (1)	—	—	—	1.000
Consolidation						
Visible on CXR	37 (15)	9 (13)	5 (6)	6 (15)	17 (37)	<0.001
Visible on CT	67 (28)	20 (28)	16 (20)	14 (34)	17 (37)	0.136
Cavitation						
Visible on CXR	15 (6)	—	2 (2)	4 (10)	9 (20)	<0.001
Visible on CT	24 (10)	—	2 (2)	8 (20)	14 (30)	<0001
Dissemination (both lungs, all lobes)						
Visible on CXR	1 (0.4)	—	1 (1)	—	—	1.000
Visible on CT	8 (3)	—	1 (1)	2 (5)	5 (11)	0.004
Pleural effusion						
Visible on CXR	14 (6)	—	3 (4)	5 (12)	6 (13)	0.002
Visible on CT*	12 (5)	—	1 (1)	5 (12)	6 (13)	<0.001
Pleural thickening						
Visible on CXR	14 (6)	—	3 (4)	5 (12)	6 (13)	0.002
Visible on CT	32 (13)	7 (10)	6 (7)	8 (20)	11 (24)	0.025
Fibrosis (parenchymal band)						
Visible on CXR	2 (0.8)	—	—	1 (2)	1 (2)	0.129
Visible on CT	15 (6)	2 (3)	5 (6)	5 (12)	3 (7)	0.271

* CT was usually performed after thoracocentesis and liquid removal.
CXR = chest X-ray; CT = computed tomography.

tible isolates were identified in 35/48 (73%) patients with culture-confirmed TB.

Patients with abnormalities visible on CXR had higher rates of bacteriological confirmation than those with normal or inconclusive CXR (43% vs. 5%, $P < 0.001$) (Table 5). In addition, patients who were identified due to clinical symptoms were more often bacteriologically confirmed (60% vs. 17%, $P < 0.001$).

Clinically diagnosed TB

In the absence of bacteriological confirmation, diagnosis was based on the combined diagnostic approach, including clinical symptoms, contact his-

Table 4 Disease classification for 250 children and adolescents diagnosed with TB

Clinical form of TB	All *n* (%)	0–4 years *n* (%)	5–9 years *n* (%)	10–14 years *n* (%)	15–17 years *n* (%)	*P* value
Pulmonary TB						
Total	192 (77)	45 (62)	65 (79)	36 (80)	46 (92)	0.001
TB pneumonia	82 (43)	7 (16)	16 (25)	19 (53)	40 (87)	<0.001
Primary complex	39 (20)	10 (22)	19 (29)	9 (25)	1 (2)	<0.001
Inthrathoracic lymph node TB and pulmonary lesion	60 (31)	26 (58)	29 (45)	4 (11)	1 (2)	<0.001
Other cases*	11 (6)	2 (4)	1 (2)	4 (12)	4 (8)	0.151
Extra-pulmonary TB						
Total	58 (23)	28 (38)	17 (21)	9 (20)	4 (8)	0.001
Isolated inthrathoracic lymph node TB	48 (83)	28 (100)	14 (82)	5 (56)	1 (25)	<0.001
Isolated TB pleurisy	7 (12)	—	2 (12)	3 (33)	2 (50)	0.002
Inthrathoracic lymph node TB and pleural TB	3 (5)	—	1 (6)	1 (11)	1 (25)	0.075

* Miliary pulmonary and extra-pulmonary TB; primary complex and TB meningitis; primary complex and pleural TB; TB pneumonia and pleural TB ($n = 4$); primary complex and extrathoracic lymph node TB; inthrathoracic lymph node TB and pulmonary lesion and pleural TB ($n = 2$); pulmonary TB and bowel TB.
TB = tuberculosis.

Table 5 Bacteriological confirmation by type of case detection, CXR abnormality and disease location for 250 children and adolescents diagnosed with TB

Characteristic	Bacteriologically confirmed *n* (%)	Not bacteriologically confirmed *n* (%)	OR (95%CI)	*P* value
Identified based on contact history				
Yes ($n = 201$)	31 (15)	170 (85)	0.24 (0.12–0.48)	<0.001
No ($n = 49$)	21 (43)	28 (57)		
Identified due to clinical manifestation suggestive of TB				
Yes ($n = 20$)	12 (60)	8 (40)	7.13 (2.74–18.56)	<0.001
No ($n = 230$)	40 (17)	190 (83)		
Identified due to positive Mantoux test				
Yes ($n = 12$)	1 (8)	11 (92)	0.33 (0.04–2.64)	0.469
No ($n = 238$)	51 (21)	187 (79)		
Identified due to radiological abnormality consistent with TB				
Yes ($n = 17$)	8 (47)	9 (53)	3.82 (1.39–11.46)	0.011
No ($n = 233$)	44 (19)	189 (81)		
Pulmonary TB				
Yes ($n = 192$)	45 (23)	147 (77)	2.23 (0.95–5.26)	0.067
No ($n = 58$)	7 (12)	51 (88)		
Abnormality consistent with TB visible on CXR				
Yes ($n = 105$)	45 (43)	60 (57)	14.79 (6.31–34.67)	<0.001
No ($n = 145$)	7 (5)	138 (79)		

CXR = chest X-ray; TB = tuberculosis; OR = odds ratio; CI = confidence interval.

tory, Mantoux test, T-SPOT test, CXR and CT findings (198/250, 79%).

Treatment regimens and treatment outcomes

Treatment was prescribed based on DST of either the child's own isolates or the index case's isolates immediately after diagnosis in all but two patients (Table 6). Among those 44 patients for whom the index case's DST showed resistance, six were bacteriologically confirmed. MDR/XDR-TB was diagnosed in 23 (9%) patients, 22 of whom received treatment based on the DST results of the index case. The treatment success rate was 100% for MDR/XDR-TB and 99% for drug-susceptible TB.

DISCUSSION

We investigated case detection, diagnosis and treatment of TB in children and adolescents in Latvia. Our approach resulted in a relatively high proportion of TB in those aged <18 years. Two major reasons could potentially influence this caseload: aggressive diagnosis using a combined approach including low-dose CT examination aimed to detect both clinical and subclinical disease, and active contact screening.

Contact investigation is an active case-finding strategy that contributes to early identification of active TB. The estimated TB prevalence in all contacts in low-middle-income and high-income countries has been reported to be respectively 3.1% and 1.4%.[21]

Table 6 Treatment regimens and treatment outcomes for 250 children and adolescents diagnosed with TB

Treatment regimens and treatment outcomes	All *n* (%)	0–4 years *n* (%)	5–9 years *n* (%)	10–14 years *n* (%)	15–17 years *n* (%)	*P* value
Standard treatment regimen for drug-susceptible TB ($n = 199$, 80%)						
Bacteriologically confirmed	39 (20)	4 (7)	6 (9)	7 (20)	22 (54)	< 0.001
Clinically diagnosed	160 (80)	52 (93)	61 (91)	28 (80)	19 (46)	
Treatment regimen for isoniazid-resistant and polyresistant TB, ($n = 28$, 11%)						
Bacteriologically confirmed	12 (43)	3 (43)	2 (33)	1 (14)	6 (75)	0.121
Clinically diagnosed	16 (57)	4 (57)	4 (67)	6 (86)	2 (25)	
Treatment regimen for MDR/XDR-TB ($n = 23$, 9%)						
Bacteriologically confirmed	1 (4)	—	—	1 (33)	—	0.174
Clinically diagnosed	22 (96)	10 (100)	9 (100)	2 (67)	1 (100)	
Treatment outcomes for drug-susceptible, isoniazid-resistant and polyresistant TB						
Cured	39 (17)	3 (5)	7 (10)	7 (17)	22 (45)	< 0.05
Treatment completed	186 (82)	60 (95)	66 (90)	34 (81)	26 (53)	
Lost to follow-up*	2 (1)	—	—	1 (2)	1 (2)	
Treatment outcomes for MDR/XDR-TB						
Cured	1 (4)	—	—	1 (33)	—	0.174
Treatment completed	22 (96)	10 (100)	9 (100)	2 (67)	1 (100)	

* Treatment was permanently interrupted in one patient due to development of Grade 4 toxic hepatitis to first-line drugs and in one patient due to refusal to receive treatment.
TB = tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

The proportion of TB cases identified during contact investigation in children aged <10 years was as high as 19.5% in a study by Ottmani et al.[22] In our study, 80% of all new cases were identified during contact investigation. These patients had lower bacteriological confirmation rates than clinically symptomatic patients (15% vs. 43%, $P < 0.001$), and had less advanced disease on radiological examination. In total, 21% of patients had bacteriologically confirmed TB, and the confirmation rate was probably related to the extent of disease and clinical presentation.[23–25] Xpert testing was positive in 53% of culture-confirmed cases, which was lower than results reported by other studies.[24] Children presenting with chronic symptoms had higher rates of bacteriological confirmation than asymptomatic children (60% vs. 17%), which was possibly associated with more advanced disease.

It has been shown that CXR can have low sensitivity and specificity in detecting TB abnormalities due to inter-observer and intra-observer variations.[15,26] Chest CT is superior to CXR in the visualisation of intrathoracic lymphadenopathy, mild parenchymal abnormality and early cavitation. Abnormal thoracic CT was found in 92.8% of children with positive Mantoux test results, contact history and normal CXR in a study by Garrido et al.[15] In a study by Baghaie et al., pathological findings on CT were identified in 45.5% of children with normal CXR.[27] Another recent study showed that high-resolution imaging identified pathology consistent with symptom-free, subclinical but active TB in 10 of 35 HIV-infected adult patients.[28]

However, controversy exists as to the need to use thoracic CT systematically to differentiate between tuberculous infection and TB disease in children.[14,16,17,29] The interpretation of CT findings as tuberculous infection or TB disease is complicated by low specificity and the absence of credible reference standards for the assessment of intrathoracic lymphadenopathy.[30]

Transient parenchymal consolidation and/or hilar adenopathy may occur during the natural course of primary infection, and the clinical relevance of CT findings is not clear.[31,32] Routine use of CT may thus lead to overdiagnosis of TB and unnecessary treatment. In our study, subclinical TB disease was additionally diagnosed using CT in 58% of children who had normal or inconclusive CXR results (Table 2). The proportion of the TB caseload represented by children and adolescents would be much lower (~3%) without CT investigation. Which is true: is the TB caseload in children and adolescents in Latvia 3% or is it 8%? On the one hand, CT can discover disease before the appearance of clinical symptoms and bacteriological confirmation. In some patients, TB disease that is not visible on CXR can progress further and result in advanced disease. On the other hand, in some patients, incipient disease can spontaneously resolve on its own, without treatment, and those patients could be considered as over-diagnosed and over-treated.

CONCLUSION

Active contact investigation and early TB diagnosis using chest CT in addition to standard CXR has provided excellent treatment outcomes in both drug-susceptible and drug-resistant TB. Although the clinical relevance of CT findings in subclinical TB disease is not clear, and interpretation of tuberculous infection or TB disease is subjective, CT is currently the only method of identifying abnormalities earlier than CXR. Until reliable biomarkers that enable the discrimination of active TB vs. tuberculous infection and predict the risk of developing active TB in individuals with tuberculous infection become available,[33,34] the use of low-dose chest CT can be justified for early TB diagnosis in children after a careful consideration of the risk-benefit ratio.

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References

1 World Health Organization. Global tuberculosis report, 2015. WHO/HTM/TB/2015.22. Geneva, Switzerland: WHO, 2015.
2 Donald P R. Childhood tuberculosis: out of control? Curr Opin Pulm Med 2002; 8: 178–182.
3 Seddon J A, Jenkins H E, Liu L, et al. Counting children with tuberculosis: why numbers matter. Int J Tuberc Lung Dis 2015; 19 (Suppl 1): 9–16.
4 Sandgren A, Hollo V, Quinten C, Manissero D. Childhood tuberculosis in the European Union/European Economic Area, 2000 to 2009. Euro Surveill 2011; 16: 8–15.
5 Blount R J, Tran B, Jarlsberg L G, et al. Childhood tuberculosis in Northern Viet Nam: a review of 103 cases. PLOS ONE 2014; 9: e97267.
6 Erkens C G, de Vries G, Keizer S T, Slump E, van den Hof S. The epidemiology of childhood tuberculosis in the Netherlands: still room for prevention. BMC Infect Dis 2014; 14: 295.
7 Mor Z, Cedar N, Pinsker G, Bibi H, Grotto I. Childhood tuberculosis in Israel: epidemiological trends and treatment outcomes, 1999–2010. Eur Respir J 2013; 41: 1157–1162.
8 Del Castillo-Barrientos H, Centeno-Luque G, Untiveros-Tello A, et al. Clinical presentation of children with pulmonary tuberculosis: 25 years of experience in Lima, Peru. Int J Tuberc Lung Dis 2014; 18: 1066–1073.
9 Abubakar I, Laundy M T, French C E, Shingadia D. Epidemiology and treatment outcome of childhood tuberculosis in England and Wales: 1999–2006. Arch Dis Child 2008; 93: 1017–1021.
10 Marais B J, Graham S M, Cotton M F, Beyers N. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. J Infect Dis 2007; 196 (Suppl 1): 76–85.
11 Lalvani A, Thillaii M. Diagnosis of tuberculosis: principles and practises of using interferon-γ release assays (IGRAs). Breathe 2009; 5: 303–309.

12 Rangaka M X, Wilkinson K A, Glynn J R, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systemic review and meta-analysis. Lancet Infect Dis 2012; 12: 45–55.
13 European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm, Sweden: ECDC, 2011.
14 Gomez-Pastrana D. Diagnosis of pulmonary tuberculosis in children. J Infect Dis 2013; 1: 17–24.
15 Garrido J B, Alias Hernández I, Bonillo Perales A, et al. Usefulness of thoracic CT to diagnose tuberculosis disease in patients younger than 4 years of age. Pediatr Pulm 2012; 47: 895–902.
16 Piccazzo R, Paparo F, Garlaschi G. Diagnostic accuracy of chest radiography for the diagnosis of tuberculosis (TB) and its role in the detection of latent TB infection: a systemic review. J Rheumatol Suppl 2014; 91: 32–40.
17 Amado C A, Ferrer D J, Agüero R, Ocejo-Vinyals J G. Clinical, radiological and immunological features in children with pulmonary tuberculosis: a review. Mycobac Dis 2014; 4: 159.
18 Centre for Disease Prevention and Control of Latvia. Valsts statistikas pārskati. Riga, Latvia: Centre for Disease Prevention and Control, 2015. www.spkc.gov.lv Accessed April 2017. [Latvian]
19 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO/HTM/TB/2014.03. Geneva, Switzerland: WHO, 2014.
20 World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. WHO/HTM/TB/2012.9. Geneva, Switzerland: WHO, 2012.
21 Fox G J, Barry S E, Warwick J B, Marks G B. Contact investigation for tuberculosis: a systemic review and meta-analysis. Eur Respir J 2013; 41: 140–156.
22 Ottmani S, Zignol M, Bencheikh N, Laâsri L, Blank L, Mahjour J. TB contact investigations: 12 years of experience in the National TB programme, Morocco 1993–2004. East Mediterr Health J 2009; 15: 494–503.
23 Wiseman C A, Mandalakas A M, Kirchner H L, et al. Novel application of NIH case definitions in a paediatric tuberculosis contact investigation study. Int J Tuberc Lung Dis 2015; 19: 446–453.
24 Nicol M P, Workman L, Isaacs W, et al. Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infect Dis 2011; 11: 819–824.
25 Rachow A, Clowes P, Saathoff E, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. Clin Infect Dis 2012; 54: 1388–1396.
26 Swaminathan S, Datta M, Radhamani M P, et al. A profile of bacteriologically confirmed pulmonary tuberculosis in children. Indian Pediatrics 2008; 45: 743–747.
27 Baghaie N, Karam M B, Khalilzadeh S, Arami S, Masjedi M R, Velayati A A. Diagnostic value of lung CT scan in childhood tuberculosis. Tanaffos 2005; 4: 57–62.
28 Esmail H, Lai R P, Lesocky M, et al. Characterisation of progressive HIV-associated tuberculosis using 2-deoxy-2-[^{18}F]fluro-D-glucose positron emission and computed tomography. Nat Med 2016; 22: 1090–1093.
29 Hamzaoui A, Yaalaoui S, Cherif F T, Saidi L S, Berraies A. Childhood tuberculosis: a concern of the modern world. Eur Resp Rev 2014; 23: 278–291.
30 Swingler G H, du Toit G, Andronicou S, van der Merwe L, Zar H J. Diagnostic accuracy of chest radiography in detecting mediastinal lymphadenopathy in suspected pulmonary tuberculosis. Arch Dis Child 2005; 90: 1153–1156.
31 Marais B J, Gie R P, Schaaf H S, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc lung Dis 2004; 8: 392–402.
32 Marais B J, Schaaf H S, Gie R P, Donald P R. TB contact screening: which way to go? Int J Tuberc Lung Dis 2009; 13: 1576–1577; author reply 1577–1578.
33 Portevin D, Moukambi F, Clowes P, et al. Assessment of the novel T-cell activation marker-tuberculosis assay for diagnosis of active tuberculosis in children; a prospective proof-of-concept study. Lancet Infect Dis 2014; 14: 931–938.
34 Maertzdorf J, Weiner J, Kaufmann S H. Enabling biomarkers for tuberculosis control. Int J Tuberc Lung Dis 2012; 16: 1140–1148.

RESUME

OBJECTIF : Réaliser une analyse complète de la détection, du diagnostic et du traitement des cas de tuberculose (TB) chez les enfants et les adolescents en Lettonie et évaluer l'utilité de l'approche actuellement utilisée.

SCHEMA : Étude rétrospective de tous les enfants et adolescents de Lettonie ayant eu un diagnostic de TB du 1 janvier 2011 au 31 décembre 2014.

RESULTATS : Sur les 3081 patients ayant eu un diagnostic de TB entre 2011 et 2014, 250 (8%) avaient <18 ans et 80% ont été identifiés grâce à une recherche de contacts. Une TB pulmonaire a été diagnostiquée chez 77% des patients. La TB a été confirmée par bactériologie chez 21% des patients. La radiographie pulmonaire (CXR) a été en accord avec une TB chez 42% des participants à l'étude, tandis que 58% des cas ont eu un diagnostic de TB infraclinique grâce à une tomographie numérisée à faible dose (CT) après avoir été manqués par la CXR. Les patients qui ont eu des anomalies visibles à la CXR ont eu un taux plus élevé de confirmation bactériologique et ont été plus souvent cliniquement symptomatiques, ce qui témoigne d'une maladie active. Un diagnostic récent a abouti à un taux de succès du traitement de 100% pour la TB pharmacorésistante et de 99% pour la TB pharmacosensible.

CONCLUSION : Le taux de détection des cas de TB grâce à la recherche des contacts a permis un diagnostic précoce et un excellent résultat du traitement chez les enfants et les adolescents en Lettonie. La CT a permis d'identifier des pathologies compatibles avec une TB infraclinique chez les enfants qui ont été exposés.

RESUMEN

OBJETIVO: Realizar un análisis exhaustivo de la búsqueda de casos, el diagnóstico y el tratamiento de la tuberculosis (TB) en los niños y los adolescentes en Latvia y evaluar la utilidad de la estrategia que se aplica en la actualidad.

MÉTODOS: Fue este un estudio retrospectivo de todos los niños y adolescentes de Latvia en quienes se diagnosticó la TB del 1 de enero del 2011 al 31 de diciembre del 2014.

RESULTADOS: De los 3081 pacientes diagnosticados con TB del 2011 al 2014, 250 eran <18 años de edad (8%) y el 80% se detectó por conducto de la investigación de contactos. Se diagnosticó la TB pulmonar en el 77% de los pacientes. Se obtuvo confirmación bacteriológica en el 21% de los pacientes. Las imágenes de la radiografía de tórax (CXR) fueron indicativas de TB en el 42% de los participantes y en el 58% de los casos, el diagnóstico de TB asintomática se asignó a partir del resultado de la tomografía computarizada (CT) en bajas dosis, después de haberse pasado por alto en la CXR. Los pacientes cuya CXR comportaba imágenes anormales presentaron una tasa más alta de confirmación bacteriológica y fueron con mayor frecuencia sintomáticos, lo cual sugiere la presencia de una enfermedad activa. El diagnóstico temprano permitió una tasa de éxito terapéutico de 100% en los casos de TB farmacorresistente y de 99% en los casos de TB normosensible.

CONCLUSIÓN: La detección de casos de TB por conducto de la investigación de contactos dio lugar a un diagnóstico temprano y a excelente desenlaces terapéuticos en los niños y adolescentes de Latvia. La CT permitió el reconocimiento de cambios patológicos infraclínicos, indicativos de TB asintomática en los niños con antecedente de exposición.