Diagnosis of childhood tuberculosis in Pakistan: Are national guidelines used by private healthcare providers?

Aashifa Yaqoob[a,b,*], Sven Gudmund Hinderaker[b], Razia Fatima[a], Hemant D. Shewade[c,d], Nadia Nisar[e], Ahmed Wali[f]

[a] Common Management Unit (TB, HIV/AIDS and Malaria), Islamabad, Pakistan
[b] University of Bergen, Bergen, Norway
[c] Centre for Operational Research, International Union Against Tuberculosis and Lung Disease (The Union), Paris, France
[d] The Union South-East Asia Office, New Delhi, India
[e] Public Health England, Islamabad, Pakistan
[f] Provincial TB Control Program, Quetta, Pakistan

A R T I C L E   I N F O

A B S T R A C T

Background: The National Tuberculosis Control Program (NTP) in Pakistan developed, with the Pakistan Paediatric Association, a pediatric scoring chart to aid diagnosis of childhood tuberculosis (TB). Our study compared the diagnostic practice of private healthcare providers in Pakistan with the NTP guidelines.
Methods: A cross-sectional study comparing diagnosis of TB in children <15 years by Non-NTP private providers with the NTP's pediatric scoring chart. A generalized linear model was used to determine the difference in adherence by Non-NTP private providers to the NTP guidelines for childhood TB diagnosis by associated factors.
Results: A total of 5193 (79.7% of presumptive childhood TB cases identified in the selected districts during the study) children were diagnosed with TB by Non-NTP private providers. A strong clinical suspicion of TB was present in 17.3%, and chest x-ray was suggestive of TB in 34.3%. The Kappa score between Non-NTP private providers and the NTP guidelines for diagnosing TB was 0.152. Only 47.8% of cases were diagnosed in line with the NTP guidelines. Children <5 years old with a history of TB contact had a higher chance of being diagnosed according to the NTP guidelines.
Conclusion: This study indicates a low adherence of NTP guidelines for diagnosing childhood TB by private providers in Pakistan.

Introduction

Globally, nearly 600 children die of tuberculosis (TB) each day. Of the 1 million children estimated to have developed active TB in 2019, approximately 70% were either undetected or incorrectly diagnosed by healthcare providers (World Health Organization, 2020). The management of TB in children <15 years remains a challenge due to non-specific symptoms and difficult diagnosis. Despite advances in TB diagnosis, no diagnostic tool has been proven to be sufficiently sensitive and specific for childhood TB (Cartaxo et al., 2014; Coghlan et al., 2015; Detjen et al., 2018). The use of Xpert MTB/RIF© assay in stool samples has been explored to diagnose pulmonary TB in children (Kabir et al., 2020). Because of

the challenges in diagnosing childhood TB, different diagnostic approaches, such as point-scoring systems, diagnostic classifications and diagnostic algorithms, have also been used; however, none are used routinely (Cartaxo et al., 2014; Pearce et al., 2012).

The diagnosis of TB in children is more difficult and challenging in resource-constrained countries like Pakistan. It is primarily based on a history of contact with a TB case, in addition to clinical and radiological findings, often without microbiological confirmation. Challenges in diagnosis are compounded by under-reporting by private healthcare providers (Non-NTP private providers), with estimates that 78% of childhood TB cases are not reported to the National TB Control Program (NTP) by Non-NTP private providers (Fatima et al., 2019).

The present study aimed to evaluate the practices of Non-NTP private providers in 12 districts across Pakistan in the diagnosis of childhood TB against the diagnostic guidelines recommended by the NTP. Our objectives were to describe: (1) the proportion of diagnosed patients among presumptive cases; (2) the Pakistan

* Corresponding author at: Department of Global Public Health and Primary Care, University of Bergen, Norway.
E-mail address: Aashifa.Yaqoob@uib.no (A. Yaqoob).

Paediatric Association (PPA) scores in the presumptive cases; (3) the Non-NTP private providers adherence to the NTP guidelines for the diagnosis of childhood TB.

Methods

Study design

We undertook a cross-sectional descriptive study involving secondary data.

Study setting

General setting

Pakistan ranks 5th globally in countries with the highest TB burden. In 2018, Pakistan had approximately 562 000 active TB cases, and TB was the 9th leading cause of death in Pakistan (WHO, 2018). Approximately 361 000 TB cases (all ages, all forms) were notified in Pakistan in 2018, with 32% of notifications coming from the Non-NTP private providers. Administratively, Pakistan (population: 208 million in 2017) is divided into four provinces (Balochistan, Khyber Pakhtunkhwa, Punjab and Sindh) and two regions (Gilgit Baltistan and Azad Jammu, and Kashmir), which are subdivided into 144 districts (Pakistan Bureau of Statistics, 2017). The private healthcare sector is large and unregulated in Pakistan. The sector includes teaching hospitals and universities, general practitioner clinics, polyclinics, health facilities run by various charitable groups, and informal health providers. Less than 1% of Non-NTP private providers are engaged with the NTP.

Diagnostic tools for childhood tuberculosis in Pakistan

During 2006–7, the NTP developed its national childhood TB policy guidelines in collaboration with the PPA (National TB Control Program, 2007). The PPA scoring chart (see Table 1) aims to facilitate and standardize clinical decisions for screening children with presumptive TB. Scoring was based on clinical, histological and radiological features, categorized into TB unlikely, possible or probable. The NTP presented a diagnostic algorithm (revised 2019)

in the guidelines to facilitate the case management process (Figure 1).

Study population

For national representation, 12 districts in Pakistan were randomly selected based on probability proportional to population size of annual notified children per million population in the districts of all provinces and regions (Fatima et al., 2019). Districts with security concerns were excluded from the sampling frame. All private healthcare facilities that managed childhood TB in the 12 selected districts were included (Fatima et al., 2019); practitioners, including pediatric specialists, general practitioners, chest physicians and medical specialists, were mapped, and those in the consenting facilities were enrolled in the study.

The study period was April to June 2016, and the study population included all children <15 years in the 12 selected districts suspected of having TB after consulting with a PP. The data formed part of the national childhood TB inventory study (Fatima et al., 2019).

Data collection and variables

Under the national childhood TB inventory study (April–June 2016), a surveillance system was established among all PP facilities (Fatima et al., 2019).

To capture case history, investigation and management of presumptive TB cases by Non-NTP private providers, a register was introduced in health facilities diagnosing childhood TB to record information without changing their practices. All healthcare providers who participated in the study were trained to enter the required information in the provided registers. To reduce data entry errors, data from paper-based registers were captured through a mobile phone application developed by a mobile service provider (Yu et al., 2009). Field officers were asked to capture this data when visiting the health facilities every week. Data included PPA score, diagnosis by PP, district, and baseline characteristics of presumptive childhood TB cases. As shown in the Box 1, the PPA

Table 1
Scoring chart for the diagnosis of childhood tuberculosis (<15 y) recommended by the Pakistan Paediatric Association (PPA) & National TB programme.

Condition	Scores				
	1	2	3	4	5
Age	<5 years				
Close contact[a]	TB suggestive	Clinically positive	Bacteriological positive		
PEM/SAM[b]	Yes	Not responding to Nutritional rehabilitation for 02 months			
H/O Measles, Whooping Cough	3–6 months	<3 months			
HIV		Yes			
Immunocompromised[c]	Yes			Not improved	
Clinical Manifestation[d]		Suggestive		Strongly Suggestive	
Radio Diagnostic Imaging[e]	Non-specific	Suggestive	Strongly suggestive		
Tuberculin skin test	5–10 mm		>10 mm		
GeneXpert MTB/RIF					Positive
Microscope examination of tissue	Non-specific				Positive

[a] Close contact: History of cough for more than 2 weeks among the household member of the child.
[b] PEM/SAM (Protein Energy Malnutrition/Severe acute malnutrition: Use WHO Recommended Z. scoring chart (1) & Not responding to Nutritional rehabilitation for 02 months (2).
[c] Immunocompromised status: Malignancies like leukemia or lymphomas etc, Immunodeficiency diseases like agammaglobunemiaetc. Chemotherapy /Immuno-suppressive therapy such as steroids for more than 2 weeks.
[d] Clinical Manifestation: Suggestive of TB: Pulmonary Findings (unilateral wheeze, dullness, weight loss, Hepato-splenomegaly, Lymphadenopathy, ascites etc. Strongly suggestive of TB: Matted lymph nodes, abdominal mass or doughy abdomen, sinus formation, gibbus formation, chronic mono arthritis, meningeal findings (bulging fontanel, irritability, choroid tubercle, papilloedema).
[e] Radio-Diagnostic/ imaging studies includes Chest X-ray, CT Chest/MRI. Non-specific signs: Ill-defined opacity or patchy infiltrates on chest X-Ray, Marked broncho-vacular marking. Signs suggestive of TB: Consolidation not responding to antibiotic therapy, Para-tracheal, or mediastinal Lymphadenopathy,Miliary Mottling, cavitation.
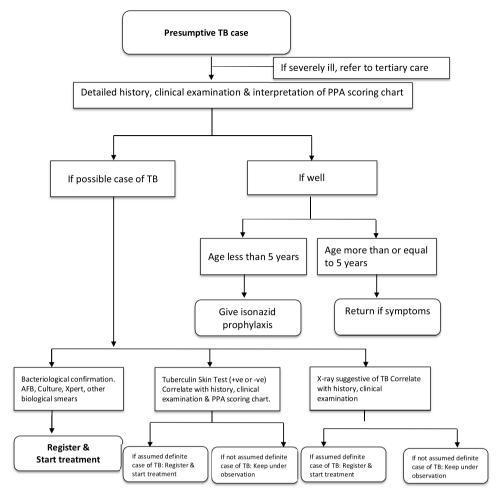
Figure 1. Flow chart for evaluation of a child (<15 y) with presumptive tuberculosis, recommended by the National TB programme.
TB = Tuberculosis; PPA = Pakistan Pediatric Association; CXR = chest radiograph; TST = tuberculin sensitivity testing.

Box 1. Interpretation of Pakistan Paediatric Association (PPA) scores for the diagnosis of childhood tuberculosis (<15 y).

Score	Interpretation	Suggested Actions
0–2	Unlikely TB	Investigate other reasons of illness
3–4	Possible TB	-Do not treat for TB
		-Manage the presenting symptom(s)
		-Monitor monthly the condition(s) for 3 months, using scoring chart
5–6	Possible TB	-Investigate and exclude other causes of illness
		-Investigation may justify therapy
7 or more	Probable TB	- Confirm (if possible)

score is based on various items, including levels of clinical suspicion. The district TB coordinators undertook monitoring visits with a provincial coordinator, supervisor and field officer to ensure the quality of data collected (completeness, correctness) for accurate record linkage and cross-checking of the NTP registration status.

Data analysis

We described the baseline characteristics of presumptive childhood TB cases and the proportion of those diagnosed as TB by Non-NTP private providers. PPA scores were compared with TB diagnosis by Non-NTP private providers. The kappa statistic was calculated to evaluate the agreement between diagnosis by the Non-NTP private providers and the NTP guidelines using PPA scoring (Landis and Koch, 1977). Analysis was done to describe the PPA scores to diagnose childhood TB. The diagnosis of the Non-NTP private providers was compared with the PPA scoring chart to measure the adherence to NTP guidelines for the diagnosis of childhood TB. The factors associated with non-adherence to the national guidelines were summarized using adjusted prevalence ratios (95% CI). Adjusted analysis was done using a generalized

Table 2
Children with presumptive and diagnosed tuberculosis identified by private health providers in 12 districts of Pakistan, 2016.

Province	District	Presumptive TB	Diagnosed TB	
		N	n	(%)[a]
All sites		6519	5193	(79.7)
Punjab	Attock	497	442	(88.9)
	Chiniot	671	337	(50.2)
	Hafizabad	874	555	(63.5)
	Vehari	376	333	(88.6)
Sindh	Shikarpur	623	394	(63.2)
	Hyderabad	838	838	(100)
	Karachi	1041	942	(90.5)
KPK	Buner	232	148	(63.8)
	Peshawar	1034	999	(96.6)
AJK	Pallundary	118	114	(96.6)
Balochistan	Jhal Magsi	44	27	(61.4)
GB	Ghizer	171	64	(37.4)

KPK = Khyber Pakhtunkhwa, AJK = Azad Jammu & Kashmir, GB = Gilgit Baltistan.
[a] "Diagnosed TB" with proportion out of all presumptive patients.

linear model. Age, gender, district and being a close contact of a TB patient were included in the model. With our large sample size, we assessed for programmatic significance (≥ 1.5 or ≤ 0.7) and interpreting statistical significance ($P < 0.05$) (Fonseca Martinez et al., 2017). Analysis was done in STATA version 14.

Results

Table 2 shows that among 6519 presumptive childhood TB cases were identified by Non-NTP private providers in our study area during the study period, 5193 (79.7%) were diagnosed as TB by the Non-NTP private providers; this varied from 37.4%–100% across districts. Characteristics of children suspected of having TB who were assessed with the PPA scoring chart are given in Table 3. Of 6519 presumptive childhood TB cases, 32.1% were <5 years of age. Strong clinical suspicion of TB was present in 17.3%; chest x-ray was suggestive of TB in 34.3%. Table 4 shows the comparison of the PPA score categories and the diagnosis set by Non-NTP private providers indicating 30% of children were highly possible or probable TB cases according to their PPA score. A large proportion of those with a PPA score of 1–4 were diagnosed with TB. Table 5 presents a comparison of diagnostic practices of Non-NTP private providers with the PPA scoring chart. According to the PPA scoring chart, 1910 (36.8%) were categorized as TB cases. The Kappa score between the Non-NTP private providers diagnoses and PPA-scored diagnoses was 0.152 (95% CI 0.140–0.165). Table 6 describes some factors associated with adherence to the NTP guidelines. Only 47.8% of the Non-NTP private providers followed the guidelines. Children <5 years old with a history of TB contact had a higher chance of being diagnosed according to the NTP guidelines.

Discussion

This study documents practices among Non-NTP private providers of childhood TB diagnosis, highlighting low adherence to the NTP guidelines in Pakistan. Results indicated that a strong clinical suspicion of TB was present in 17.3% of the children, and chest x-ray was suggestive of TB in 34.3%. According to the PPA score, 30% of the children were suspected as highly possible or probable TB cases. Only 47.8% of the Non-NTP private providers diagnosed childhood TB in accordance with the PPA scoring chart. Children <5 years old with a history of TB contact had a higher chance of being diagnosed according to the national guidelines.

In 2006, the NTP, in collaboration with PPA, prepared guidelines for early diagnosis and management of TB in children. A few studies in Pakistan provide evidence on the effectiveness of the PPA

Table 3
Baseline assessment and PPA score of children with presumptive tuberculosis identified by private health providers in 12 districts of Pakistan, 2016.

Characteristics of children	n	(%)*
Total	6519	(100)
Age (year)		
0–4	2090	(32.1)
5–14	4429	(67.9)
Close contact of TB patient in last 2 years		
TB patients Bacteriological positive	778	(11.9)
TB patients Bacteriological Negative	709	(10.9)
No TB contact	2611	(40.1)
Missing	2421	(37.1)
Loss of body weight		
Yes	504	(7.7)
Missing	6015	(92.3)
H/O Measles, Whooping Cough		
Missing	6519	(100)
HIV		
Missing	6519	(100)
Immunocompromised		
Missing	6519	(100)
Clinical Manifestation		
Suggestive	3352	(51.4)
Strongly suggestive	1128	(17.3)
Not suggestive	2039	(31.3)
Radio Diagnostic imaging		
Suggestive of TB	2235	(34.3)
Non-TB specific	770	(11.8)
Missing	3514	(53.9)
Tuberculin skin test		
5–10 mm	155	(2.4)
More than 10 mm	64	(1.0)
Missing	6300	(96.6)
Sputum (or induced sputum or gastric lavage) smear microscopy		
Positive	545	(8.4)
Negative	1330	(20.4)
Missing	4644	(71.2)
Xpert MTB/RIF		
NAAT MTB detected	130	(2.1)
Not detected	194	(3.1)
Missing/not applicable	6195	(95.0)
Culture		
Positive	36	(0.6)
Negative	116	(1.8)
Missing / not applicable	6367	(97.7)
Histopathology Examination		
Non-TB specific	296	(4.5)
Consistent with TB (microscope examination of tissue)	541	(8.3)
Missing / not applicable	5682	(87.2)
PPA score		
Unlikely TB (0–2)	3068	(47.1)
Possibly TB (3–4)	1443	(22.1)
Highly Possibly TB (5–6)	839	(12.9)
Probably TB (≥ 7)	1169	(17.9)

NAAT = Nucleic Acid Amplification Testing.

scoring chart to identify cases of childhood TB at an early stage (Ayesha Mehnaz, 2006; Mehnaz and Arif, 2005; Safdar et al., 2010). In the public health sector, these guidelines were implemented; however, in Pakistan, almost 90% of patients initiate care in the private sector. Less than 5% of Non-NTP private providers are effectively engaged with the NTP, accounting for only 15% of the facilities with capacity for TB diagnosis and treatment (Fatima et al., 2017). The current study revealed that utilization of the national guidelines was low nationally. There is an urgent need to improve linkages between the NTP and the private sector through engaging, training and capacity building on the national guidelines for managing childhood TB cases to improve TB care in Pakistan.

An important finding of the study was that Non-NTP private providers often diagnosed childhood TB but were not following the NTP guidelines. Reasons for this non-adherence were not identified

Table 4
Diagnosis by private health care providers and the corresponding PPA scores for children (0–15 y) with presumptive tuberculosis in 12 districts of Pakistan, 2016.

Diagnosis by private providers	PPA score				Total
	Unlikely TB (0–2)	Possible TB (3–4)	Highly possible TB (5–6)	Probable TB (>6)	
Childhood TB case	2,122 (69.5)	1,161 (81.2)	769 (91.7)	1,141 (97.6)	5193
Not a TB case	931 (30.5)	269 (18.8)	70 (8.3)	27 (2.4)	1297
Total	3,053 (100)	1,430 (100)	839 (100)	1,168 (100)	6,519

Table 5
Diagnosis recorded by private providers versus diagnosis based on PPA score on children with presumptive tuberculosis identified in 12 districts of Pakistan, 2016.

TB diagnosis	TB based on PPA score		Total
	Yes (≥5)	No (0–4)	
Yes	1910 (95.2)[c] (36.8)[r]	3,283 (73.2)[c] (63.2)[r]	5,193 (X%) (100)
No	97 (4.8)[c] (7.5)[r]	1,200 (26.8)[c] (92.5)[r]	1297 (x%) (100)
Total	2007 (100) (Y%)	4483 (100) (Y%)	6519

[c] column percentage.
[r] row percentage.

in this study; however, we speculate that a lack of awareness and a weak partnership/collaboration between the Non-NTP private providers and the NTP are potential reasons. A misdiagnosis of childhood TB could be challenging for the individuals and their community. At an individual level, there may be adverse impacts from treating patients and taking the drugs every day is a burden for the family. At the community level, a misdiagnosis could increase the financial burden and stigma due to unnecessary investigation and traveling to healthcare facilities for investigation and/or treatment. Communication between the NTP and Non-NTP private providers needs to be improved in both directions: guidelines and training for childhood TB need to reach all

stakeholders, and providers outside the NTP need to implement the guidelines and report childhood TB cases to the program. It may be included in the regular visits of the District TB coordinators to facilities that report TB cases for discussion with the responsible person.

Our study indicates that adherence to the NTP guidelines in the diagnosis of childhood TB cases varied and was generally inadequate in the study area, which may be due to a lack of knowledge. A systematic review of the management of TB by healthcare practitioners in Pakistan (Braham et al., 2018) also suggested poor standards of care and knowledge. Another reason for variation in adherence to the guidelines across the different districts is that treatment facilities available at health centers, especially in the rural areas, are limited and ineffective. There are inherent problems with the system of patient referral to a facility with directly observed treatment short-course services (DOTS), and the private sector is not fully involved in the implementation of these services. However, many private practitioners and government health workers are poorly trained in diagnosing and treating TB and lack the communication skills required to motivate patients towards increased compliance (Mushtaq et al., 2011). We believe the shortcomings shown in this study represent the whole country and improvement could be achieved through better training of practitioners, greater availability of recommended diagnostic tools and PPA scoring charts, and expansion of public-private partnerships.

The study had several strengths. The study area was reasonably representative of Pakistan, involving all provinces, and included all children with presumptive TB who approached Non-NTP private providers for diagnosis and treatment. To improve the study's validity, data quality was audited, removing inconsistencies by

Table 6
Generalized linear model for factors associated with adherence to national guidelines for the diagnosis of childhood TB by private health providers in 12 districts of Pakistan, 2016.

Variables		Presumptive childhood TB	Adherence of guidelines n (%)	Adjusted prevalence ratio	(95% CI)
Overall		**6519**	**3110 (47.8)**		
Sex	Male	4199	1903 (45.3)	Ref.	
	Female	2320	1207 (52.0)	1.10	(1.04–1.15)
Age group	0–4	1691	1020 (60.3)	1.23	(1.15–1.31)
	5–11	3214	1341 (41.7)	0.95	(0.89–1.00)
	12–14	1614	749 (41.7)	Ref.	
Area					
Punjab	Attock	497	118 (23.7)	0.75	(0.64–0.88)
	Chiniot	671	448 (66.8)	1.81	(1.64–1.98) *
	Hafizabad	874	363 (41.5)	1.12	(1.00–1.25)
	Vehari	376	149 (39.6)	0.99	(0.85–1.16)
Sindh	Shikarpur	623	484 (77.7)	1.92	(1.74–2.12) *
	Hyderabad	838	100 (11.9)	0.30	(0.25–0.37) *
	Karachi	1041	728 (69.9)	1.75	(1.59–1.92) *
KPK	Buner	232	165 (71.1)	1.94	(1.73–2.18) *
	Peshawar	1034	330 (31.9)	Ref.	
AJK	Pallundary	118	71 (60.2)	1.58	(1.34–1.86) *
Baloschistan	Jhal Magsi	44	35 (79.6)	2.18	(1.88–2.53) *
GB	Ghizer	171	119 (69.6)	1.80	(1.58–2.05) *
Close contact of TB patient	TB patient	1487	992 (66.7)	1.39	(1.32–1.47)
	No TB contact	5032	2118 (42.1)	Ref.	

cross-checking every record from the hard copies; a mobile phone application was used for data entry to avoid input errors. The study also has several limitations. All demographic, clinical and radiographic data of presumptive childhood TB patients were collected from registers, and diagnostic practices of Non-NTP private providers were retrospectively assessed so that the accuracy and completeness of the data could not be ensured. The proportion of examinees diagnosed with TB (79.7%) in this study was high compared to other settings, where they ranged from 2.1% to 19% (Bonnet et al., 2017; Fairlie et al., 2014; Jaganath et al., 2013; Tadesse et al., 2016). One possible reason for this high yield is that Non-NTP private providers may have recorded most cases on the provided registers post x-ray or when there was already a strong suspicion of childhood TB; this may have missed an unknown number of other presumptive TB cases. The proportion of TB among examined patients varied among the districts, which may reflect a variation in the completeness of reporting of "suspects". Future research is recommended to further assess and verify these findings in the field. Further research is also required into treatment practices, including the drug dosages being prescribed by practitioners.

Although scoring systems with a moderate case yield are less prone to extreme diagnostic error, in the absence of a gold standard, the predictive value of any one system cannot be determined (Hatherill et al., 2010; The Union, 2016). However, the findings of this study should not undermine confidence in existing national guidelines using the PPA scoring chart. Instead, innovative research and critical analysis should be encouraged to search for improved diagnostics for childhood TB.

Conclusion

This study highlights the low utilization of the NTP guidelines by Non-NTP private providers for the diagnosis of childhood TB in Pakistan. There is an urgent need to focus on advocacy at all levels and strengthen the public-private partnership. The NTP should regularly conduct training on the national guidelines and engage with the private sector to address specific gaps in diagnosis and treatment.

Funding source

World Health Organization's headquartersfunded the main survey. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript. No specific funding was available or obtained from any organization for this study. The publication fee for publication in an international journal is covered by the University of Bergen.

Conflict of interest

None to declare

Ethics

Ethical clearance (registration # NBC 192 given in 2015) was obtained from the Pakistan Medical and Research Council, as well as the World Health Organization Ethics Committee for the East-Mediterranean region, from the ethics committee in Norway (2018/56/REK vest), and local ethical clearance was also obtained from Institutional Review Board ethics committee, common management unit (HIV, TB and Malaria). Informed consent was waived by the ethics committee, as all data used had been previously collected during the child inventory study and did not pose any additional risks to the patients.

References

Mehnaz Ayesha. Tuberculosis in children. JPMA 2006;56:390–1, doi:http://dx.doi.org/10.1016/j.pcl.2017.03.010.

Bonnet M, Kyakwera C, Kyomugasho N, Atwine D, Mugabe F, Nansumba M, et al. Prospective cohort study of the feasibility and yield of household child tuberculosis contact screening in Uganda. Int J Tuberc Lung Dis 2017;21:862–8, doi:http://dx.doi.org/10.5588/ijtld.16.0889.

Braham CA, White PJ, Arinaminpathy N. Management of tuberculosis by healthcare practitioners in Pakistan: a systematic review. PLoS One 2018;13:, doi:http://dx.doi.org/10.1371/journal.pone.0199413.

Cartaxo CGB, Rodrigues LC, Braga CP, Ximenes RA de A. Measuring the accuracy of a point system to diagnose tuberculosis in children with a negative smear or with no smear or culture. J Epidemiol Glob Health 2014;4:29–34, doi:http://dx.doi.org/10.1016/j.jegh.2013.10.002.

Coghlan R, Gardiner E, Amanullah F, Ihekweazu C. Understanding market size and reporting gaps for paediatric TB in Indonesia, Nigeria and Pakistan: supporting improved treatment of childhood TB in the advent of new medicines. PLoS One 2015;10:1–12, doi:http://dx.doi.org/10.1371/journal.pone.0138323.

Detjen A, M G, Sm G, C S. Improving the estimates of childhood TB disease burden and assessing childhood TB activities at country level. Geneva, Switzerland: WHO; 2018.

Fairlie L, Muchiri E, Beylis CN, Meyers T, Moultrie H. Microbiological investigation for tuberculosis among HIV-infected children in Soweto, South Africa. Int J Tuberc Lung Dis 2014;18:676–81, doi:http://dx.doi.org/10.5588/ijtld.13.0839.

Fatima R, Haq MU, Yaqoob A, Mahmood N, Ahmad KL, Osberg M, et al. Delivering patient-centered care in a fragile state: using patient-pathway analysis to understand tuberculosis-related care seeking in Pakistan. J Infect Dis 2017;216:S733–9, doi:http://dx.doi.org/10.1093/infdis/jix380.

Fatima R, Yaqoob A, Qadeer E, Hinderaker SG, Ikram A, Sismanidis C. Measuring and addressing the childhood tuberculosis reporting gaps in Pakistan: the first ever national inventory study among children. PLoS One 2019;14:e0227186, doi:http://dx.doi.org/10.1371/journal.pone.0227186.

Fonseca Martinez BA, Leotti VB, Silva G de Se, Nunes LN, Machado G, Corbellini LG. Odds ratio or prevalence ratio? An overview of reported statistical methods and appropriateness of interpretations in cross-sectional studies with dichotomous outcomes in veterinary medicine. Front Vet Sci 2017;4:, doi:http://dx.doi.org/10.3389/fvets.2017.00193.

Hatherill M, Hanslo M, Hawkridge T, Little F, Workman L, Mahomed H, et al. Sistemas estructurados de cribado y diagnóstico de la tuberculosis infantil en una región de alta prevalencia de Sudáfrica. Bull World Health Organ 2010;88:312–20, doi:http://dx.doi.org/10.2471/BLT.09.062893.

Jaganath D, Zalwango S, Okware B, Nsereko M, Kisingo H, Malone LS, et al. Contact investigation for active tuberculosis among child contacts in Uganda. Clin Infect Dis 2013;57:1685–92, doi:http://dx.doi.org/10.1093/cid/cit645.

Kabir S, Rahman SMM, Shakil Ahmed, Islam MS, Banu RS, Shewade HD, et al. Xpert ultra assay on stool to diagnose pulmonary tuberculosis in children. Clin Infect Dis 2020;, doi:http://dx.doi.org/10.1093/cid/ciaa583.

Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159, doi:http://dx.doi.org/10.2307/2529310.

Mehnaz A, Arif F. Applicability of scoring chart in the early detection of tuberculosis in children. J Coll Physicians Surg Pakistan 2005;15:543–6 https://doi.org/09.2005/JCPSP.543546.

Mushtaq MU, Shahid U, Abdullah HM, Saeed A, Omer F, Shad MA, et al. Urban-rural inequities in knowledge, attitudes and practices regarding tuberculosis in two districts of Pakistan's Punjab province. Int J Equity Health 2011;10:, doi:http://dx.doi.org/10.1186/1475-9276-10-8.

National TB Control Program. National guidelines for diagnosis and management of tuberculosis in children 2006-07 Islamabad, Pakistan. 2007.

Pakistan Bureau of Statistics. 6th population and housing census 2017. Islamabad, Pakistan: Government of Pakistan; 2017.

Pearce EC, Woodward JF, Nyandiko WM, Vreeman RC, Ayaya SO. A systematic review of clinical diagnostic systems used in the diagnosis of tuberculosis in children. AIDS Res Treat 2012;2012:, doi:http://dx.doi.org/10.1155/2012/401896.

Safdar N, Hinderaker SG, Baloch NA, Enarson DA, Khan MA, Morkve O. Are children with tuberculosis in Pakistan managed according to National programme policy guidelines? A study from 3 districts in Punjab. BMC Res Notes 2010;3:324, doi: http://dx.doi.org/10.1186/1756-0500-3-324.

Tadesse Y, Gebre N, Daba S, Gashu Z, Habte D, Hiruy N, et al. Uptake of isoniazid preventive therapy among under-five children: TB contact investigation as an entry point. PLoS One 2016;11:1–11, doi:http://dx.doi.org/10.1371/journal.pone.0155525.

The Union. The union's desk guide for diagnosis and management of TB in children. third edition 2016 Paris, France: 2016.

WHO. Global tuberculosis report 2018. Geneva: World Health Organization; 2018 2018. Licence: CC BY-NC-SA 3.0 IGO.

World Health Organization. Global Tuberculosis Report 2020. Geneva, Switzerland: WHO; 2020.

Yu P, de Courten M, Pan E, Galea G, Pryor J. The development and evaluation of a PDA-based method for public health surveillance data collection in developing countries. Int J Med Inform 2009;78:532–42, doi:http://dx.doi.org/10.1016/j.ijmedinf.2009.03.002.