Longitudinal changes in clinical symptoms and signs in children with confirmed, unconfirmed, and unlikely pulmonary tuberculosis

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In partial fulfilment of the requirements for the degree:

Master of Philosophy (MPhil) in Paediatric Infectious Diseases

Department of Paediatrics
Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN

Student Dr Julie Copelyn
CPLJUL002

Supervisors Prof Brian Eley
Prof Heather Zar

Submission Date 13 July 2021

Table of contents

Declaration

I, *Julie Copelyn*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 13 July 2021

Abstract

Background: The paucibacillary nature of paediatric pulmonary tuberculosis (PTB) makes microbiological diagnosis difficult and limits the usefulness of microbiology for assessing treatment efficacy. Clinical response to treatment has thus been used by clinicians to monitor disease activity, as well as by researchers in clinical case definitions of intrathoracic TB to differentiate those with unconfirmed PTB from those with other lower respiratory tract infections (LRTIs). There is, however, limited data on the expected pattern and timing of resolution of symptoms and signs, and whether this does indeed differ between those with PTB and those without.

Objectives: To longitudinally investigate clinical response to TB treatment in children treated for PTB, to compare this to the clinical course of children with other LRTIs, and to identify factors associated with persistence of symptoms and signs.

Methods: This study is a secondary analysis of data collected prospectively in a TB diagnostic study from 1 February 2009 to 31 December 2018. We enrolled children ≤15 years with features suggestive of PTB. Study participants were categorized into 3 groups according to NIH consensus definitions; confirmed PTB, unconfirmed PTB and unlikely PTB. Children were followed at 1 and 3 months after enrolment. Those with confirmed or unconfirmed TB were also followed at 6 months. At enrolment and follow-up symptoms of PTB were recorded using a standardized questionnaire and physical examination was done including anthropometry and respiratory parameters. Data were analysed using STATA version 16.1. The effect of potential predictors of persistence of symptoms and signs was explored with univariable and multivariable logistic regression modelling.

Results: Two thousand and nineteen children were included in this analysis, 427 (21%) with confirmed PTB, 810 (40%) with unconfirmed PTB, and 782 (39%) with unlikely PTB. Symptoms resolved rapidly in the vast majority of participants. At 1 month, 9.2% (129/1402) of all participants who had a cough and 11.1% (111/999) of those with loss of appetite at baseline reported no improvement in these symptoms. At 3 months this declined to 2.0% (24/1222) and 2.6% (23/886) respectively, with no differences between the groups. Clinical signs persisted in a greater proportion of participants. At 3 months, tachypnoea persisted in 56.7% (410/723) of participants. Abnormal auscultatory findings (including wheeze,

crackles, reduced breath sounds or abnormal breath sounds) similarly persisted in almost a third of participants, with greater proportion in the confirmed group (37.1%) than unconfirmed (23.0%) and unlikely (26.2%) groups (p=0.002). Children living with HIV and those with abnormal baseline chest radiographs had greater odds of persistence of signs or symptoms (including cough, loss of appetite, abnormal auscultatory findings, or no weight improvement if underweight at baseline). No features of clinical response differentiated those with PTB from those without.

Conclusion: Symptoms resolved rapidly in the majority of children investigated for PTB whilst clinical signs took longer to resolve. The timing and pattern of resolution of symptoms and signs cannot differentiate those with PTB from those without – and is thus not a suitable parameter for confirming disease classification in paediatric TB research.

Acknowledgements

This work is a secondary analysis of data collected in large TB diagnostic studies. I would like to acknowledge and thank the children and their care-givers for participating in this research, as well as all the clinical and study staff involved in patient care and primary data collection.

I would further like to thank Lesley Workman and Prof. Helen Cox for their generous assistance and supervision with data extraction and statistical analysis.

Finally, I would like to thank my supervisors, Prof Brian Eley and Prof Heather Zar for their expert guidance and assistance, particularly in the writing of this manuscript.

List of Tables

List of Figures

Abbreviations

aOR	Adjusted odds ratio
CXR	Chest radiograph
DR	Drug resistant
HIV	Human Immunodeficiency Virus
PTB	Pulmonary Tuberculosis
NIH	National Institute of Health
NSH	New Somerset Hospital
RCWMCH	Red Cross War Memorial Children's Hospital
RR	Respiratory rate
TST	Tuberculin skin test
WAZ	Weight-for-age-z-score
WHO	World Health Organization

Chapter 1: Introduction

1.1 Context

The paucibacillary nature of paediatric pulmonary tuberculosis (PTB), and the difficulties in obtaining pulmonary specimens, greatly hinder microbiological confirmation of disease in children and limit the usefulness of microbiology in monitoring disease and treatment outcomes. Despite recent advancements in molecular diagnostics, rapid bacteriological confirmation is uncommon in children and diagnosis is thus predominantly still a clinical decision[1], based on a combination of history of exposure, clinical presentation, and results of tuberculin skin test and chest radiography (CXR) if available[2]. National and international guidelines also promote assessing treatment response on clinical parameters (such as resolution of symptoms and weight gain), and suggest actions to take for those responding poorly[2,3]. Furthermore, clinical response to treatment is used in research to assist in retrospectively differentiating those children with TB from those without[4]. However, very limited data exists on clinical response to treatment in children and recent data suggests it is an inappropriate diagnostic parameter for paediatric TB research[5]. Further evidence is thus urgently needed to define the expected clinical response to TB treatment and the factors affecting it, as well as to assess the diagnostic value of symptom resolution in children with pulmonary tuberculosis.

The National Institute of Health (NIH) consensus definitions of intrathoracic TB classify children into 3 categories for diagnostic studies– confirmed TB (microbiologically confirmed by culture or nucleic acid amplification test), unconfirmed TB (no bacteriological confirmation but at least two of: immunological evidence of infection, either a positive tuberculin skin test or interferon-γ release assay, suggestive signs/symptoms, consistent CXR, close TB exposure, positive clinical response to treatment) and unlikely TB (no bacteriological confirmation and criteria not met for unconfirmed TB)[4]. In clinical research it is thus primarily in the absence of a bacteriological diagnosis that treatment response becomes important as a factor in clinical case definitions[4]. Clinicians however use clinical treatment response in a much broader way. In patients with unconfirmed PTB, a good response to treatment is seen as supportive evidence of the diagnosis, whilst a poor response raises concerns of non-compliance to treatment, incorrect drug doses or poor drug absorption, drug resistant disease and incorrect diagnosis[2]. Increasingly children who fail to show a

clinical response whilst adherent to a drug sensitive TB regimen are suspected of having drug resistant (DR)TB[6]. Conversely, in children with lower respiratory tract infection who improve without TB therapy, the clinical response in the absence of TB treatment is used to classify children as having unlikely TB. Clinical treatment response could thus potentially be a key deciding factor in commencing increasing numbers of children on empiric DRTB therapy.

Despite the widespread use of clinical response to TB treatment, it is a poorly defined parameter[7]. For clinical research purposes, an attempt to standardize clinical case definitions by an expert panel suggested the response to anti-tuberculosis therapy be assessed at two months after initiation of therapy, and defined as: "clinical features suggestive of tuberculosis disease that were present at baseline have improved, and there is no new clinical feature suggestive of tuberculosis"[4]. Others have used more specific criteria defining a good clinical response as "complete symptom resolution and weight gain of ≥10% of body weight at diagnosis within 3 months of starting antituberculosis treatment"[8]. The variability in these case definitions highlights the lack of data on timing of expected symptom resolution. Furthermore, there are limited data on how variables such as co-infection with human immunodeficiency virus (HIV) or malnutrition may affect treatment response. While attempts have been made to define treatment response for research purposes, there is as yet insufficient data to assess the usefulness of these definitions in routine clinical care.

There are obvious limitations to the usefulness of clinical treatment response as a diagnostic parameter. Its specificity is limited by the fact that some children without TB infection will nevertheless improve whilst being treated for TB, either because of spontaneous resolution of symptoms over time, or because the TB therapy inadvertently treats other bacterial infections. The sensitivity is also poor as multiple factors such as poor drug adherence, incorrect drug doses and increasingly drug resistance can prevent a clinical response to treatment despite active TB disease. Nevertheless, there is data from the adult literature that suggests response to treatment could be a useful indicator[9–11].

In a prospective cohort study from Ethiopia, out of 804 adult patients diagnosed with PTB, rapid symptom reduction was reported, with 75% of participants having a clinical response by day 21 of treatment[10]. Clinical response was defined as resolution of initial signs and

symptoms, unfortunately it is unclear which signs and symptoms were specifically included, and furthermore the HIV status of the participants was not reported. A second study that reported rapid symptom resolution included almost 400 HIV-uninfected 18-60 year old patients with culture-confirmed TB in a multicentre clinical trial[11]. In this study, although the median time to complete symptom resolution was 117 days, within two months of commencing therapy the proportion of patients with fever, sweats and dyspnoea had reduced by 94%, 94% and 81% respectively. Other symptoms such as cough and chest pain resolved more slowly. At the end of treatment cough had not resolved in 13% of participants who reported cough at baseline. Finally, in a study of 147 adults living with HIV with smear-negative pulmonary and extra-pulmonary TB, 97.5% of participants with culture-confirmed tuberculosis (compared to 0% of those participants without TB) met two or more of the response to treatment criteria by 8 weeks of treatment[9]. This study used a combination of laboratory tests (C-reactive protein and haemoglobin) and clinical criteria (weight, symptom count ratio and quality of life measured by Karnofsky performance score) to define response to treatment (RTT). Although limited, this data from the adult literature suggests that there is a rapid clinical response to TB treatment and carefully selected criteria can be used to differentiate patients with TB from those without.

Data on response to TB treatment are even more limited in the paediatric literature. Only one recent study specifically addresses time to symptom resolution in this population. This study included 191 symptomatic HIV-uninfected children under 2 years of age treated for pulmonary TB[5]. The authors conclude that symptom resolution takes longer than 60 days from commencement of treatment in 56-68% of children with PTB depending on symptom, and therefore should not be used in diagnostic algorithms. Furthermore they found that having a CXR compatible with PTB was associated with prolonged time to symptom resolution for all three symptoms (cough, wheeze, and failure to thrive) on multivariate analysis. There are however a number of limitations to this study. The number of participants categorised as "TB cases" and included in the final analysis of symptom resolution was small. Resolution of cough, wheeze and failure to thrive could only be assessed in 24, 23 and 31 children respectively. The study design did not allow for detection of partial changes in symptom severity only the presence or absence of symptom, and follow-up visits were scheduled at 3 monthly intervals. The timing of follow-up visit may also be too insensitive to detect early resolution of symptoms. Finally the study excluded all children living with HIV and thus the findings may not be generalisable to children with TB and HIV coinfection.

Further data are thus required before conclusions can be made about the utility of treatment response for clinicians and researchers in paediatric PTB.

Despite the inherent issues with interpreting clinical response to TB therapy, the limitations of current diagnostic tools nevertheless make it an attractive outcome measure for clinicians and researchers in the field. Furthermore, if improvement or resolution of a specific sign or symptom was identified to correlate with good clinical outcomes, this could be used for treatment monitoring. Without significant improvements in microbiological or molecular diagnostic capabilities it is likely that clinical response will remain the primary tool for clinicians to monitor disease activity and treatment response, as well as in diagnostic algorithms for research purposes. This study thus aimed to characterize and gain greater insight into the spectrum of treatment response in children initiated on treatment for PTB, as well as the factors that affect such a response.

1.2 Ethical considerations

The study is a secondary analysis of previously collected data. De-identified data was extracted from the existing database for statistical analysis. There was thus no further interaction with study participants, no new data collection and consequently, no new ethical concerns for participants. Whilst the study participants themselves will not benefit from this sub-study, the study will generate much needed data on the clinical response to tuberculosis therapy in children with PTB.

The study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (HREC 827/2019) and by the research committee at Red Cross War Memorial Children's Hospital (Appendices 1 and 2).

1.3 Journal for publication

This research article will be submitted to the journal “Pediatric Pulmonology”. Pediatric Pulmonology is a well-respected journal with an impact factor of 2.534. The topic of this article fits well within the scope of the journal which focusses on the respiratory system of children at all phases of their development. See appendix 3 for author guidelines.

References

1. Frigati L, Maskew M, Workman L, et al. Clinical Predictors of Culture-confirmed Pulmonary Tuberculosis in Children in a High Tuberculosis and HIV Prevalence Area. *Pediatr Infect Dis J*. 2015;34(9):e206-e210. doi:10.1097/INF.0000000000000792
2. South African National Department of Health. Guidelines for the Management of Tuberculosis in Children. 2013. http://www.kznhealth.gov.za/family/National-Childhood-TB-Guidelines-2013-ZA.pdf.
3. World Health Organization (WHO). *Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, Second Edition*.; 2014. doi:10.1016/0025-5408(96)80018-3
4. Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update. *Clin Infect Dis*. 2015;61(Suppl 3):S179-S187. doi:10.1093/cid/civ581
5. Mpofu N, Moyo S, Mulenga H, et al. Time to symptom resolution in young children treated for pulmonary tuberculosis. *Pediatr Infect Dis J*. 2014;33(12):1226-1230. doi:10.1097/INF.0000000000000523
6. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatr Respir Rev*. 2011;12(1):31-38. doi:10.1016/J.PRRV.2010.09.010
7. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *Int J Tuberc Lung Dis*. 2002;6(12):1038-1045. http://www.ncbi.nlm.nih.gov/pubmed/12546110.
8. Marais BJ, Gie RP, Hesseling AC, et al. A Refined Symptom-Based Approach to Diagnose Pulmonary Tuberculosis in Children. *Pediatrics*. 2006;118(5):e1350-e1359. doi:10.1542/peds.2006-0519
9. Wilson D, Nachega J, Morroni C, Chaisson R, Maartens G. Diagnosing smear-negative tuberculosis using case definitions and treatment response in HIV-infected adults. *Int J Tuberc Lung Dis*. 2006;10(1):31-38.
10. Feleke BE, Alene GD, Feleke TE, Motebaynore Y, Biadglegne F. Clinical response of tuberculosis patients, a prospective cohort study. *PLoS One*. 2018;13(1):1-11. doi:10.1371/journal.pone.0190207
11. Bark CM, Dietze R, Okwera A, Quelapio MI, Thiel BA, Johnson JL. Clinical

symptoms and microbiological outcomes in tuberculosis treatment trials. *Tuberculosis*. 2011;91(6):601-604. doi:10.1016/J.TUBE.2011.05.007

12. Nicol MP, 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(11):819-824. doi:10.1016/S1473-3099(11)70167-0.Accuracy
13. Zar HJ, Workman LJ, Prins M, et al. Tuberculosis diagnosis in children using Xpert Ultra on different respiratory specimens. *Am J Respir Crit Care Med*. 2019;200(12):1531-1538. doi:10.1164/rccm.201904-0772OC
14. Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W, Nicol MP. Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: A prospective study. *Lancet Glob Heal*. 2013;1(2):e97-e104. doi:10.1016/S2214-109X(13)70036-6
15. Nicol MP, Workman L, Prins M, et al. Accuracy of Xpert MTB/RIF Ultra for the Diagnosis of Pulmonary Tuberculosis in Children. *Pediatr Infect Dis J*. 2018:1. doi:10.1097/INF.0000000000001960
16. World Health Organization (WHO). *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses, 2nd Edition*. Vol second edi.; 2013. doi:10.1111/j.1553-2712.1996.tb03308.x
17. World Health Organization (WHO). WHO growth reference data for 5-19 years. Geneva. https://www.who.int/growthref/en/. Accessed November 11, 2020.
18. World Health Organization (WHO). WHO Child Growth Standards. Geneva. doi:10.1111/j.1469-8749.2009.03503.x
19. World Health Organization. WHO Case Definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. *World Heal Organ*. 2007:52. http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf.
20. Moyo S, Verver S, Hawkridge A, et al. Tuberculosis case finding for vaccine trials in young children in high-incidence settings: A randomised trial. *Int J Tuberc Lung Dis*. 2012;16(2):185-191. doi:10.5588/ijtld.11.0348
21. Turner RD, Bothamley GH. Cough and the transmission of tuberculosis. *J Infect Dis*. 2015;211(9):1367-1372. doi:10.1093/infdis/jiu625
22. Heslop R, Bojang AL, Jarju S, et al. Changes in host cytokine patterns of TB patients with different bacterial loads detected using16 S rRNA analysis. *PLoS One*.

2016;11(12):1-11. doi:10.1371/journal.pone.0168272

23. Hai HT, Vinh DN, Thu DDA, et al. Comparison of the Mycobacterium tuberculosis molecular bacterial load assay, microscopy and GeneXpert versus liquid culture for viable bacterial load quantification before and after starting pulmonary tuberculosis treatment. *Tuberculosis*. 2019;119:101864. doi:10.1016/j.tube.2019.101864
24. Sabiiti W, Azam K, Farmer ECW, et al. Tuberculosis bacillary load, an early marker of disease severity: The utility of tuberculosis Molecular Bacterial Load Assay. *Thorax*. 2020:606-608. doi:10.1136/thoraxjnl-2019-214238
25. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: From epidemiology to pathophysiology. *Eur Respir Rev*. 2018;27(147). doi:10.1183/16000617.0077-2017
26. Madhi SA, Huebner RE, Doedens L, Aduc T, Wesley D, Cooper PA. HIV-1 co-infection in children hospitalised with tuberculosis in South Africa. *Int J Tuberc Lung Dis*. 2000;4(5):448-454.
27. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. *BMC Infect Dis*. 2014;14 (Supp 1.
28. Belay GM, Wubneh CA. Childhood tuberculosis treatment outcome and its association with HIV co-infection in Ethiopia: A systematic review and meta-analysis. *Trop Med Health*. 2020;48(1):1-10. doi:10.1186/s41182-020-00195-x

Chapter 2: Publication-ready manuscript

Title page

Treatment response in paediatric pulmonary tuberculosis – a prospective longitudinal study

J.Copelyn, MMed[1,2]; B.Eley, MBChB[1,2]; H.Cox, PhD[3]; L.Workman, MPH[2,4]; K. Dheda, PhD[5]; M. Nicol, PhD[6]; H.Zar, PhD[2,4]

[1] Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital

[2] Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town, South Africa

[3]Division of Medical Microbiology, Wellcome Centre for Infectious Disease Research and Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa

[4] South African Medical Research Council unit on Child & Adolescent Health, University of Cape Town, South Africa

[5] Department of Medicine, University of Cape Town, South Africa

[6] Division of Medical Microbiology, University of Cape Town & Division of Infection and Immunity, Department of Biomedical Sciences, University of Western Australia

Financial support

Funded by the Regional Prospective Observational Research in Tuberculosis (RePORT TB) Consortium which is co-funded by the Medical Research Council of South Africa and the US Office of AIDS Research of the National Institutes of Health of the USA. Additional funding was received from the Medical Research Council of South Africa, from the National Institutes of Health, USA (RO1HD058971) and EDCTP (TB-NEAT; IP.2009.32040.009).

Corresponding author: J. Copelyn: julie.copelyn@gmail.com

Keywords: clinical resolution, pulmonary tuberculosis, child

Abbreviated title: Treatment response in paediatric PTB

Word count

Abstract: 249

Article: 3500

Abstract

Background: Data are limited on the resolution of symptoms and signs in children treated for pulmonary tuberculosis (PTB) and whether this differs from other lower respiratory tract infections (LRTI).

Objectives: To longitudinally investigate treatment responses in children with PTB, compare to those with other LRTI, and identify factors associated with persistence of symptoms or signs.

Methods: Children aged ≤15 with features suggestive of PTB were categorized into 3 groups, confirmed PTB, unconfirmed PTB and unlikely PTB. At enrolment and follow-up (1, 3 and 6 months) symptoms and signs of PTB were recorded using a standardized questionnaire. Univariable and multivariable logistic regression modelling was done to investigate predictors of persistence of symptoms or signs.

Results: Included were 427 (21%) with confirmed, 810 (40%) with unconfirmed and 782 (39%) with unlikely PTB. Of those with cough or loss of appetite at baseline, persistence at 3 months was reported in 2.0% (24/1222) and 2.6% (23/886) respectively. Of those with tachypnoea or abnormal auscultatory findings at baseline, persistence at 3 months occurred in 56.7% (410/723) and 27.8% (216/778) respectively. HIV infection and abnormal baseline chest radiography were associated with persistence of signs or symptoms at month 3 [aOR 1.6 (IQR 1.1, 2.3) and aOR 2.3 (IQR 1.5, 3.3) respectively]. No clinical features distinguished those with PTB from those with other LRTI.

Conclusion: Symptoms resolved rapidly in most children with PTB, but signs resolved more slowly. The timing and pattern of resolution of symptoms and signs was similar in PTB compared to other LRTI.

Introduction

Diagnosis of PTB in children is usually made clinically, based on history of exposure, symptoms, signs, tuberculin skin test (TST) results and chest radiography (CXR) if available[2]. Challenges in obtaining samples for microbiological confirmation limit the usefulness of microbiology in diagnosis, monitoring disease and treatment outcomes. Clinical response to treatment is used as an additional factor for disease classification to differentiate those with PTB from those with other lower respiratory tract infection[4] (LRTI). Clinicians also rely on resolution of symptoms and weight gain for assessment of treatment effectiveness[2,3].

Despite the widespread use of clinical response to TB treatment there is a lack of data on the expected pattern and timing of resolution of symptoms and signs, and the impact of factors such as co-infection with human immunodeficiency virus (HIV) or malnutrition. Evidence from studies of adults with PTB suggest clinical symptoms improve in most patients within 4-8 weeks after treatment initiation[9–11] and can be used in diagnostic algorithms to distinguish those with PTB from those without[9]. The very limited paediatric data however, suggest symptom resolution in young children takes longer than 8 weeks, and that the timing of symptom resolution cannot differentiate those with PTB from those without[5].

Clinical case definitions of intrathoracic TB, developed by a National Institutes of Health (NIH) expert consensus panel, recommend assessment of response 2 months after treatment initiation[4]. However, one study suggests that a substantial proportion of children treated for PTB only had symptom resolution after 2 months, suggesting that the 2 month time point may be too early to assess response to treatment in clinical practice[5]. Improved understanding of the pattern and timing of treatment response in children initiated on treatment for PTB is thus needed.

The aim of this study was to longitudinally investigate treatment responses in children treated for PTB, to compare these to the clinical course of children with other LRTI, and to identify factors associated with persistence of symptoms and signs.

Methods

Study design & participants

This study was a secondary analysis of data collected prospectively in large TB diagnostic

studies from 1 February 2009 to 31 December 2018[12–15]. Study participants were enrolled at Red Cross War Memorial Children's Hospital, a tertiary referral centre, New Somerset Hospital, a secondary level hospital, and Nolungile primary health care clinic in Cape Town. Children were eligible for enrolment if they were 15 years of age or younger and had features suggestive of PTB, defined as a cough or difficulty breathing and one of the following: a household contact with TB in the preceding 3 months, weight loss or failure to thrive in preceding 3 months, a positive tuberculin skin test (TST), or a CXR suggestive of PTB. Children were excluded if they had received TB therapy or prophylaxis for 72 hours or more prior to enrolment, were unable to attend follow-up, informed consent was not available, or if a pulmonary specimen could not be obtained. For this study, children without at least one follow-up visit were excluded.

At enrolment, a history and physical examination were done including anthropometry. Tachypnoea was classified according to World Health Organization (WHO) age specific criteria (<2 months, respiratory rate (RR) ≥60 breaths per minute (bpm); 2–12 months, RR ≥50 bpm; 12–59 months, RR ≥40 bpm; and ≥60 months, RR ≥20)[16]. WHO 2007 growth standards were used to calculate weight-for-age z scores (WAZ)[17,18]. Comprehensive investigations for microbiological confirmation were done including 2 induced sputum specimens for Xpert MTB/RIF (Cepheid, USA) testing and culture, or from February 2018 onwards Xpert MTB/RIF Ultra, and liquid culture (Mycobacterium Growth Indicator Tube, BACTEC MGIT. Becton Dickinson, MD, USA). All children had a TST. A positive skin test was defined as transverse induration of ≥5mm in participants with HIV infection, and ≥10mm in those without HIV infection[3]. Children whose HIV status was unknown had HIV testing done. Children living with HIV were classified as having advanced or severe immunodeficiency based on the WHO immunological classification for established HIV infection (<11 months, CD4% <30%; 12-35 months, CD4% <25%; 36-59 months, CD4%<20%; >5 years, CD4 <350cells/μL or CD4%<15%)[19].

Baseline CXRs were reported by a radiologist experienced in paediatric radiographs, using a standardized reporting tool and categorized as normal or abnormal, as well as 'consistent with TB disease', 'not consistent with TB disease' or 'inconclusive'. Features suggestive of TB included lymphadenopathy, airway compression, miliary pattern, pleural effusion or cavitary disease. Decisions regarding initiation of TB therapy were made by the attending

clinician, who prescribed TB drug regimens in accordance with national TB protocols[2].

Study participants were categorized into 3 groups according to NIH consensus definitions[4]; confirmed PTB (*Mycobacterium tuberculosis (M.tb*) confirmed on a pulmonary specimen by Xpert / Xpert Ultra or culture), unconfirmed PTB (no bacteriological confirmation with at least 2 of the following: consistent signs and symptoms, compatible CXR, close TB exposure or immunological evidence of exposure, or a positive clinical response to treatment), and unlikely PTB (no bacteriological confirmation and criteria not met for unconfirmed PTB).

Children were followed at 1 and 3 months after enrolment; participants with confirmed or unconfirmed PTB were also followed up at 6 months. At follow-up visits, symptoms and signs of PTB were recorded using a standardized questionnaire and a clinical examination including anthropometry was done.

This study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (HREC 827/2019).

Statistical analysis

Data were analysed using STATA version 16.1 (Stata Corp, College Station, Texas, USA). Baseline characteristics were summarized as medians (inter-quartile range) or means (standard deviation) for continuous data, and as number (percentages) for categorical data. Differences between groups were explored with chi-squared test for categorical data, and one-way ANOVA and Kruskal Wallis tests for normally and non-normally distributed numeric data respectively.

Data for follow-up visits were regarded as missing if the timing was not within the specified range of 15 - 59 days for month 1, 60-149 days for month 3 and 150-240 days for month 6. Persistence of symptoms and signs were calculated for those participants with the specific symptom or sign at baseline and who had been assessed for persistence or resolution at all preceding time points. Symptoms and signs that developed during the follow-up period, or that recurred after previous resolution were not included in the analysis.

The effect of potential predictors of persistence of symptoms and signs was explored with

univariable and multivariable logistic regression modelling. Multivariable models were run for individual symptoms (cough and loss of appetite), signs (tachypnoea and abnormal auscultatory findings) as well as for a combined variable including any of: persistent cough, loss of appetite, abnormal auscultatory findings, or no weight improvement if underweight (WAZ <-2) at baseline. Variables included in all models included sex, HIV status, age category (<1year, 1-5 years, >5 years), PTB category (confirmed, unconfirmed, unlikely) and CXR findings at baseline. Variables with a p-value of <0.15 in univariable analysis were also included in the multivariable models.

Subset analyses investigated variables associated with persistence of symptoms and signs in the unlikely PTB group, in those living with HIV infection, as well as in the whole cohort excluding those participants with EPTB. A sensitivity analysis was done excluding 117 participants whose inclusion in the unconfirmed PTB group was contingent on a positive clinical response to treatment.

Results

Cohort description

Between 1 February 2009 and 31 December 2018, 2389 participants were enrolled. 370 children were excluded (figure 1), predominantly for no follow-up visits (n=226) or only extra-pulmonary TB (103). Two participants who met criteria for unconfirmed PTB did not have confirmation on respiratory samples but had *M. tuberculosis* identified on extra-pulmonary samples and were included in the confirmed PTB category. This analysis therefore included 427 (21%) participants with confirmed PTB, 810 (40%) with unconfirmed PTB, and 782 (39%) with unlikely TB. No participants in the unconfirmed group were treated for PTB.

Baseline characteristics are summarized in table 1. Of the cohort, 50.8% (1026/2019) were male and 16.1% (325/2015) were living with HIV, with no differences between the groups. Amongst those with HIV, the median CD4% was 17.5 (IQR 10.1, 24.7) and 88.5% (269/304) were receiving antiretroviral therapy (ART). Participants with confirmed PTB were older than the unconfirmed or unlikely PTB groups, [median age 40.0 months (IQR 17.5, 85.8) vs 30.9 months (IQR 14.6, 58.9) vs 30.4 months (IQR 15.2, 61.5)] respectively (p<0.001) and had lower WAZ scores. A greater proportion of those with confirmed PTB than unconfirmed

TB had extrapulmonary disease in addition to PTB (39.8% vs 16.2%, p<0.001). Of those with extrapulmonary TB 108 (35.9%) had a pleural effusion, 70 (23.3%) had abdominal TB, 69 (22.9%) had TB lymphadenitis and 37 (12.3%) had TB meningitis. In the confirmed group 7/427 (1.6%) participants had documented resistance to Isoniazid and Rifampicin.

Reported baseline symptoms differed between the confirmed, unconfirmed and unlikely groups for weight loss: 78.2%, 70.6% and 65.2% (p<0.001); malaise: 55.6%, 42.3% and 33.3% (p<0.001), and night sweats: 55.7%, 55.0% and 45.0% (p=0.001). Similarly, the reported duration of weight loss was longer in the confirmed or unconfirmed TB groups than in the unlikely TB group: median number of days 21 (IQR 7, 31) and 21 (IQR: 10, 31) vs 14 (IQR 7, 31) p=0.005.

Clinical signs also differed between the confirmed, unconfirmed and unlikely groups. Abnormal respiratory examination was found in 61.0% (260/426), 49.6% (400/807) and 45.5% (353/776) (p<0.001); tachypnoea in 58.0% (233/402), 47.8% (366/765), and 46.7% (335/717) (p=0.001), and subcostal recession in 19.3% (81/420), 13.6% (108/792) and 14.6% (111/761) respectively (p=0.028). Changes on baseline CXR occurred in 87.6% (283/323), 70.9% (422/595) and 57.8% (384/664) in the confirmed, unconfirmed and unlikely PTB groups respectively (p<0.001).

Time to follow-up was similar between the groups; median time to month 1 follow-up was 30 (IQR 28, 35), 31 (IQR 28, 35) and 32 days (IQR 29, 36) in the confirmed, unconfirmed and unlikely groups respectively. Median time to month 3 follow-up visit was 91 days (IQR 87, 97) in all groups, and 181 (IQR 174, 186) days for the month 6 follow-up visit in those treated for TB.

Resolution of signs and symptoms

Table 2 shows the proportion of participants with persistence of a baseline symptom or sign. For the vast majority, symptoms of cough and loss of appetite resolved rapidly. At the 1-month visit only 9.2% (129/1402) of all participants who had a cough at baseline reported no improvement. This was lower in the confirmed and unconfirmed TB groups than in the unlikely TB group; 8.6% (24/278) and 6.9% (39/564) vs. 11.8% (66/560) respectively (p=0.017). At 3 and 6 months this had declined to 2.0% (24/1222) and 0.6% (4/697) respectively, with no significant difference between groups. Similarly, of all those reporting

loss of appetite at baseline, 11.1% (111/999) reported non-resolution of this symptom at month 1, 2.6% (23/886) at month 3, and 0.6% (3/471) at month 6, with no differences between the groups.

In contrast, abnormal signs persisted in greater proportions of participants at months 3 and 6. While subcostal recession resolved in all participants by month 3, tachypnoea and abnormal auscultatory findings (wheeze, crackles, reduced breath sounds or abnormal breath sounds) persisted in a high proportion. Among 723 participants with baseline tachypnoea, 56.7% (n=410) remained tachypnoeic at month 3. At month 6, 45.0% (171/380) remained tachypnoeic. Similarly, among 778 participants with baseline abnormal auscultatory findings, 27.8% (n=216) had persistence at month 3, with a greater proportion in the confirmed group (37.1%, 75/202) than unconfirmed (23.0%, 71/309) and unlikely (26.2%, 70/267) groups (p=0.002). In the confirmed group, 79.7% (161/202) of those seen at month 3 were seen at month 6, of whom 15.5% (n=25) had persistent abnormal auscultatory findings. In the unconfirmed group, 85.1% (263/309) of those seen at month 3 were seen at month 6, and 7.2% (n=19) had persistent abnormal auscultatory findings.

Median WAZ score was lowest in the confirmed and highest in the unlikely PTB groups at all time points. However, the median increase in WAZ was higher in the confirmed and unconfirmed PTB groups than in the unlikely PTB group at month 3. In those who were underweight at baseline, the median (IQR) increase in WAZ at month 3 was 0.9 (0.5, 1.8), 0.9 (0.5, 1.5), and 0.7 (0.4, 1.2) in the confirmed, unconfirmed and unlikely groups respectively (p=0.037).

Factors associated with persistence of symptoms or signs

Table 3 presents factors associated with persistence of any symptom or sign (cough, loss of appetite, abnormal auscultatory findings, or no weight improvement if underweight at baseline) at 3 months in univariable and multivariable logistic regression models. After adjustment for other variables, only HIV infection or abnormal baseline CXR were significantly associated with persistence of signs or symptoms. This association was unchanged in the sensitivity analysis (supplementary data).

HIV infection increased the adjusted odds of persistence of symptoms or signs at month 3 by 1.6 times (95%CI: 1.1, 2.3, p=0.011). In models of each individual sign or symptom, HIV

infection was associated with persistence at 3 months for tachypnoea (aOR 2.2, 95%CI: 1.2, 4.0, p=0.009) and abnormal auscultatory findings (aOR 1.6, 95%CI: 1.1, 2.5, p=0.025). The association between HIV and persistence of symptoms or signs was evident in all subset analyses with the exception of those with unlikely TB, where HIV infection was not associated with increased odds of symptom or sign persistence at 3 months (aOR 1.3, 95%CI: 0.7, 2.4, p=0.461).

Abnormal baseline CXR was the strongest predictor of persistent symptoms or signs, increasing the adjusted odds by 2.3 times (95%CI: 1.5, 3.3, p<0.001) in comparison to normal baseline CXR. This association remained statistically significant in subset analyses excluding those with EPTB (aOR 2.0, 95%CI: 1.4, 3.0, p<0.001) and in those with unlikely TB (aOR 2.7, 95%CI: 1.6, 4.5). In models of individual signs and symptoms, abnormal CXR increased the adjusted odds for persistent abnormal auscultatory findings (aOR: 2.7, 95%CI: 1.3, 5.4) but not for tachypnoea (aOR:1.2, 95%CI: 0.6, 2.1). There was no association between baseline CXR abnormality and persistence of either cough or loss of appetite at month 3.

In models evaluating predictors of persistence of tachypnoea at 3 months, only age greater than 5 years was a predictor in all subset analyses. Age greater than 5 years compared to less than 1 year was associated with an increased odds of tachypnoea in the entire cohort (aOR 13.6, 95%CI: 6.9, 27.0, p<0.001), when those with EPTB were excluded (aOR 15.4 95%CI: 7.3, 32.5, p<0.001), and in those with unlikely TB (aOR 15.7, 95%CI: 5.0, 49.7, p<0.001).

Discussion

In this large prospective study of over 2000 children presenting with symptoms of PTB, including 21% with microbiologically confirmed disease, symptoms resolved within one month in most, but of those with baseline clinical signs (abnormal auscultatory findings or tachypnoea) more than half had persistence at 3 months. The timing of resolution of symptoms and signs was similar for those with confirmed PTB, unconfirmed PTB and other LRTI, but confirmed cases had greater persistence of abnormal auscultatory findings and lower weight-for-age at 3 months. Living with HIV infection and an abnormal baseline CXR were the only factors independently associated with increased odds of persistence of symptoms or signs at 3 months.

The finding of rapid symptom resolution is consistent with data from adults treated for PTB[9,10], but not with the limited paediatric data. In a study of 191 young children treated for PTB, the median time to resolution of cough was 63 days, with only 42% (10/24) of children with 'definite' or 'probable' TB[20] having resolution of baseline cough 60 days after treatment initiation[5]. The study population differed from ours in being of younger age (median age 12 months), low numbers of participants with confirmed PTB (5%, 9/191), and exclusion of children living with HIV infection. Differences in timing of symptom resolution may also reflect differences in study design. Our study was much larger, the median time to first follow-up visit was 31 days vs 61 days, and we reported improvement of symptoms, not just complete resolution. It is likely that our study, with its shorter interval to first follow-up and recording of improvement not only resolution, had greater sensitivity to pick up earlier improvement of symptoms.

Our study found no differences in the timing of resolution of symptoms or signs that could be used to distinguish those children with PTB from those without. Small differences occurred between groups but were too small to be clinically useful. Furthermore, whilst there was a statistically significant difference between the groups in resolution of abnormal auscultatory findings at 3 months, this was not the case for the unconfirmed compared to unlikely category, the exact distinction that clinical case definitions are designed to make. Our data indicate that clinical response to treatment may not be useful as an endpoint in clinical case definitions.

Whilst symptoms resolved rapidly for most children, a small percentage reported persistence of cough (2.0%) and loss of appetite (2.6%) at 3 months. In a clinical trial of almost 400 adults with culture confirmed PTB, 13% reported persistent cough at 6 months, after completion of PTB therapy[11]. To account for the persistence of cough, the authors highlight not only the poor specificity of cough for active PTB infection, but also complications such as bronchiectasis, that could cause chronic cough. In our study, cough persisted in a similar proportion of those with unlikely PTB as with PTB. Undiagnosed chronic respiratory disease such as asthma or post infectious bronchiectasis (from TB or other pathogens) may account for persistence of cough.

Whilst the exact mechanism of cough in PTB has not been definitively elucidated, it may be due to the presence of mycobacteria, substances they release, or host immune responses[21]. *M.tb* bacillary load declines rapidly following initiation of effective anti-tuberculosis therapy[22–24], and thus rapid improvement with reduction in bacillary load would be expected, especially in children who usually have a low mycobacterial load. Clinical signs may reflect the results of the complex host immune response and resultant lung impairment[25]. This may at least partially explain the high proportion of persistent abnormal auscultatory findings at month 3. The higher proportion of persistent abnormal auscultatory findings in the confirmed PTB group, as well as the strong association between abnormal baseline CXR findings and persistence of abnormal auscultatory findings, indicate that extent of pulmonary involvement influences the timing of resolution of clinical signs.

Tachypnoea was also found to persist in an unexpectedly high proportion of participants with baseline tachypnoea, especially in children older than 5 years of age. This finding may be due to the use of WHO-recommended age specific cut-off values which were used to define tachypnoea (respiratory rate of 20 or above in those 5 years or older vs 40 in children 1 to 5 years or 50 in infants).

HIV infection was associated with persistent signs and symptoms at 3 months in those treated for TB. While most children living with HIV in this cohort were receiving ART, a high proportion were still classified as having advanced or severe immunodeficiency, and thus may not represent children established on ART with good immune function. This finding is nevertheless important as HIV infection is a common comorbidity in areas of high TB prevalence. Interestingly, the same association was not found in those with unlikely PTB. The association between HIV co-infection and poorer outcomes of TB treatment has been shown previously[26–28], and our findings reiterate this vulnerability.

This study has several limitations. Firstly, we were only able to analyse a few symptoms and signs, (cough, poor appetite, abnormal auscultatory findings and weight gain), however these are key factors used in diagnosis and assessing response to treatment. Secondly, symptoms and signs were assessed at a series of pre-determined time points, thus it is not possible to differentiate persistence from recurrence. However, follow up occurred at 1 and 3 months, relatively soon after initial illness as well as at 6 months in those treated for TB. Although the consensus clinical case definitions suggest response to treatment be assessed at 2 months,

our follow-up increased the number of time points, optimised cohort retention and enabled assessment of rapid resolution of symptoms in most children at a 1 month timepoint. Strengths are the large study population, careful follow-up, high cohort retention, standardised assessment, and comprehensive microbiological investigations for TB as well as the inclusion of children across a broad range of ages, and those living with HIV, enabling us to assess the impact of these factors on resolution. Future research considerations include designing and evaluating better diagnostic criteria or algorithms particularly for the category of unconfirmed TB in resource-limited settings.

Conclusion

Differentiating children with PTB from those with other LRTI remains a challenge, but resolution of symptoms and signs does not reliably distinguish these groups. This study provides much needed information on the timing of the resolution of symptoms and signs in children treated for PTB compared to those with other LRTI. Clinicians should be aware of the limitations and use caution in the interpretation of response to treatment. Finally, this study raises the issue of whether clinical response to treatment should be included in clinical case definitions for PTB.

References

1. Frigati L, Maskew M, Workman L, et al. Clinical Predictors of Culture-confirmed Pulmonary Tuberculosis in Children in a High Tuberculosis and HIV Prevalence Area. *Pediatr Infect Dis J*. 2015;34(9):e206-e210. doi:10.1097/INF.0000000000000792
2. South African National Department of Health. Guidelines for the Management of Tuberculosis in Children. 2013. http://www.kznhealth.gov.za/family/National-Childhood-TB-Guidelines-2013-ZA.pdf.
3. World Health Organization (WHO). *Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, Second Edition*.; 2014. doi:10.1016/0025-5408(96)80018-3
4. Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update. *Clin Infect Dis*. 2015;61(Suppl 3):S179-S187. doi:10.1093/cid/civ581
5. Mpofu N, Moyo S, Mulenga H, et al. Time to symptom resolution in young children treated for pulmonary tuberculosis. *Pediatr Infect Dis J*. 2014;33(12):1226-1230.

doi:10.1097/INF.0000000000000523

6. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatr Respir Rev*. 2011;12(1):31-38. doi:10.1016/J.PRRV.2010.09.010
7. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *Int J Tuberc Lung Dis*. 2002;6(12):1038-1045. http://www.ncbi.nlm.nih.gov/pubmed/12546110.
8. Marais BJ, Gie RP, Hesseling AC, et al. A Refined Symptom-Based Approach to Diagnose Pulmonary Tuberculosis in Children. *Pediatrics*. 2006;118(5):e1350-e1359. doi:10.1542/peds.2006-0519
9. Wilson D, Nachega J, Morroni C, Chaisson R, Maartens G. Diagnosing smear-negative tuberculosis using case definitions and treatment response in HIV-infected adults. *Int J Tuberc Lung Dis*. 2006;10(1):31-38.
10. Feleke BE, Alene GD, Feleke TE, Motebaynore Y, Biadglegne F. Clinical response of tuberculosis patients, a prospective cohort study. *PLoS One*. 2018;13(1):1-11. doi:10.1371/journal.pone.0190207
11. Bark CM, Dietze R, Okwera A, Quelapio MI, Thiel BA, Johnson JL. Clinical symptoms and microbiological outcomes in tuberculosis treatment trials. *Tuberculosis*. 2011;91(6):601-604. doi:10.1016/J.TUBE.2011.05.007
12. Nicol MP, 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(11):819-824. doi:10.1016/S1473-3099(11)70167-0.Accuracy
13. Zar HJ, Workman LJ, Prins M, et al. Tuberculosis diagnosis in children using Xpert Ultra on different respiratory specimens. *Am J Respir Crit Care Med*. 2019;200(12):1531-1538. doi:10.1164/rccm.201904-0772OC
14. Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W, Nicol MP. Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: A prospective study. *Lancet Glob Heal*. 2013;1(2):e97-e104. doi:10.1016/S2214-109X(13)70036-6
15. Nicol MP, Workman L, Prins M, et al. Accuracy of Xpert MTB/RIF Ultra for the Diagnosis of Pulmonary Tuberculosis in Children. *Pediatr Infect Dis J*. 2018:1. doi:10.1097/INF.0000000000001960
16. World Health Organization (WHO). *Pocket Book of Hospital Care for Children:*

Guidelines for the Management of Common Childhood Illnesses, 2nd Edition. Vol second edi.; 2013. doi:10.1111/j.1553-2712.1996.tb03308.x

17. World Health Organization (WHO). WHO growth reference data for 5-19 years. Geneva. https://www.who.int/growthref/en/. Accessed November 11, 2020.
18. World Health Organization (WHO). WHO Child Growth Standards. Geneva. doi:10.1111/j.1469-8749.2009.03503.x
19. World Health Organization. WHO Case Definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. *World Heal Organ*. 2007:52. http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf.
20. Moyo S, Verver S, Hawkridge A, et al. Tuberculosis case finding for vaccine trials in young children in high-incidence settings: A randomised trial. *Int J Tuberc Lung Dis*. 2012;16(2):185-191. doi:10.5588/ijtld.11.0348
21. Turner RD, Bothamley GH. Cough and the transmission of tuberculosis. *J Infect Dis*. 2015;211(9):1367-1372. doi:10.1093/infdis/jiu625
22. Heslop R, Bojang AL, Jarju S, et al. Changes in host cytokine patterns of TB patients with different bacterial loads detected using16 S rRNA analysis. *PLoS One*. 2016;11(12):1-11. doi:10.1371/journal.pone.0168272
23. Hai HT, Vinh DN, Thu DDA, et al. Comparison of the Mycobacterium tuberculosis molecular bacterial load assay, microscopy and GeneXpert versus liquid culture for viable bacterial load quantification before and after starting pulmonary tuberculosis treatment. *Tuberculosis*. 2019;119:101864. doi:10.1016/j.tube.2019.101864
24. Sabiiti W, Azam K, Farmer ECW, et al. Tuberculosis bacillary load, an early marker of disease severity: The utility of tuberculosis Molecular Bacterial Load Assay. *Thorax*. 2020:606-608. doi:10.1136/thoraxjnl-2019-214238
25. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: From epidemiology to pathophysiology. *Eur Respir Rev*. 2018;27(147). doi:10.1183/16000617.0077-2017
26. Madhi SA, Huebner RE, Doedens L, Aduc T, Wesley D, Cooper PA. HIV-1 co-infection in children hospitalised with tuberculosis in South Africa. *Int J Tuberc Lung Dis*. 2000;4(5):448-454.
27. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. *BMC Infect Dis*. 2014;14 (Supp 1.
28. Belay GM, Wubneh CA. Childhood tuberculosis treatment outcome and its association

with HIV co-infection in Ethiopia: A systematic review and meta-analysis. *Trop Med Health*. 2020;48(1):1-10. doi:10.1186/s41182-020-00195-x

Table I: Baseline characteristics of cohort by TB categorization [a]

	Total (n=2019)	Confirmed PTB (n=427)	Unconfirmed PTB (n=810)	Unlikely PTB (n=782)	P-value
			n (%) or median [IQR]		
Sociodemographics					
Male sex	1026 (50.8)	229 (53.6)	418 (51.6)	379 (48.5)	0.194
Age category					
<1 years	368 (18.2)	64 (15.0)	157 (19.4)	147 (18.8)	0.000
1-5 years	1099 (54.4)	209 (49.0)	457 (56.4)	433 (55.4)	
>5 years	552 (27.3)	154 (36.1)	196 (24.2)	202 (25.8)	
Age in months, median	31.8 [15.2, 63.0]	40.0 [17.5, 85.8]	30.9 [14.6, 58.9]	30.4 [15.2, 61.5]	0.000
HIV infected	325 (16.1)	73 (17.2)	143 (17.7)	109 (14.0)	0.110
CD4 count (cells/μL)	541 [245,1073]	466 [235, 878]	543 [253, 1096]	552 [245, 1005]	0.831
CD4%	17.6 [10.1, 24.7]	17.0 [9.9, 26.4]	16.0 [9.6, 24.0]	19.0 [11.8, 24.7]	0.521
Advanced or severe immunodeficiency[b]	163 (62.5)	37 (57.8)	74 (66.1)	52 (61.2)	0.529
Caregiver reported symptoms					
Cough	1693 (84.3)	341 (80.2)	669 (83.0)	683 (87.9)	0.001
Fever	1217 (60.9)	258 (61.0)	495 (61.6)	464 (60.1)	0.837
Weight loss	1371 (70.1)	326 (78.2)	553 (70.6)	492 (65.2)	0.000
Malaise	817 (41.7)	234 (55.6)	331 (42.3)	252 (33.3)	0.000
Night sweats	762/1472 (51.8)	216/388 (55.7)	322/586 (55.0)	224/498 (45.0)	0.001
Poor appetite	1157 (58.0)	253 (59.7)	472 (58.8)	432 (56.1)	0.403
Reported symptom duration (days)					
Cough	14 [6, 21]	14 [7, 21]	14 [6, 21]	14 [5,21]	0.610
Fever	7 [3, 14]	7 [4,14]	7 [3,14]	7 [3,14]	0.156
Weight Loss	21 [7,31]	21 [7,31]	21 [10,31]	14 [7,31]	0.005
Malaise	7 [4,14]	10 [5,21]	7 [4,14]	7 [3, 10]	0.000
Night Sweats	14 [7,30]	14 [7,30]	14 [7,30]	14 [7,30]	0.931
Poor appetite	14 [5,21]	14 [6,21]	14 [6,21]	8.5 [5,14]	0.004
Clinical signs					
Abnormal respiratory exam	1013 (50.4)	260 (61.0)	400 (49.6)	353 (45.5)	0.000
Subcostal recession	300 (15.2)	81 (19.3)	108 (13.6)	111 (14.6)	0.028
Abnormal Breath sounds	357 (18.7)	105 (25.3)	132 (17.1)	120 (16.6)	0.000
Crackles	578 (29.0)	130 (30.9)	222 (27.7)	226 (29.4)	0.492
Wheeze	271 (13.7)	54 (12.8)	105 (13.2)	112 (14.6)	0.628
Dullness to percussion	229 (11.5)	69 (19.4)	104 (13.1)	56 (7.3)	0.000
Lymphadenopathy	596 (30.5)	186 (44.4)	238 (30.6)	172 (22.7)	0.000
Tachypnoea	934 (49.6)	233 (58.0)	366 (47.8)	335 (46.7)	0.001
Anthropometry					
WAZ	-0.9 [-1.8, 0.1]	-1.2 [-2.1, -0.3]	-0.9 [-1.8, 0.0]	-0.6 [-1.6, 0.2]	0.000
WAZ < -2	428/2003 (21.4)	117/425 (27.5)	177/808 (21.9)	134/770 (17.4)	0.000
Investigations					
Mantoux -positive	1022 (55.0)	286/372 (76.9)	524 (68.4)	212 (29.4)	0.000
CXR – abnormal	1089/1582 (68.8)	283/323 (87.6)	422/595 (70.9)	384/664 (57.8)	0.000
CXR -consistent PTB	447/1539 (29.0)	165/323 (51.1)	182/562 (32.4)	100/654 (15.3)	0.000
Extrapulmonary disease					
PTB & EPTB	301 (14.9)	170 (39.8)	131 (16.2)	0 (0)	0.000

[a] Denominator shown if >10% of cohort missing data

[b] Defined according to WHO immunological classification for established HIV infection (<11 months, CD4% <30%; 12-35 months, CD4% <25%; 36-59months, CD4%<20%; >5 years, CD4 <350cells/μL or CD4%<15%)

Abbreviations: HIV= Human immunodeficiency virus; WAZ= weight-for-age z-score; CXR= Chest radiography; PTB=pulmonary tuberculosis; EPTB= extrapulmonary tuberculosis

Table II: Persistence of symptoms and signs at follow-up by TB categorization

		Total (n=2019)	Confirmed PTB (n=427)	Unconfirmed PTB (n=810)	Unlikely PTB (782)	P-value
		n (%) or median [IQR]				
Symptoms						
Cough	Baseline	1693/2008 (84.3)	341/425 (80.2)	669/806 (83.0)	683/777 (87.9)	0.001
Cough non-improvement	M1	129/1402 (9.2)	24/278 (8.6)	39/564 (6.9)	66/560 (11.8)	0.017
	M3	24/1222 (2.0)	4/240 (1.7)	5/495 (1.0)	15/487 (3.1)	0.061
	M6	4/697 (0.6)	2/219 (0.9)	2/478 (0.4)		0.422
Loss of appetite	Baseline	1157/1997 (57.9)	253/424 (59.7)	472/803 (58.8)	432/770 (56.1)	0.403
	M1	111/999 (11.1)	21/220 (9.6)	50/412 (12.1)	40/367 (10.9)	0.606
	M3	23/886 (2.6)	4/195 (2.1)	12/371 (3.2)	7/320 (2.2)	0.595
	M6	3/471 (0.6)	2/164 (1.2)	1/307 (0.3)		0.245
Signs						
Tachypnoea	Baseline	934/1884 (49.6)	233/402 (58.0)	366/765 (47.8)	335/717 (46.7)	0.001
	M3	410/723 (56.7)	116/182 (63.7)	163/298 (54.7)	131/243 (53.9)	0.085
	M6	171/380 (45.0)	72/140 (51.4)	99/240 (41.2)		0.054
Subcostal Recession	Baseline	300/1973 (15.2)	81/420 (19.3)	108/792 (13.6)	111/761 (14.6)	0.028
	M3	0/229 (0.0)	0/61 (0.0)	0/88 (0.0)	0/80 (0.0)	
Abnormal Auscultation	Baseline	947/1999 (47.4)	246/424 (58.0)	366/803 (45.6)	335/772 (43.4)	0.000
	M3	216/778 (27.8)	75/202 (37.1)	71/309 (23.0)	70/267 (26.2)	0.002
	M6	44/424 (10.4)	25/161 (15.5)	19/263 (7.2)		0.007
Combination score						
	Baseline	1944/2012 (96.6)	407/426 (95.5)	780/807 (96.7)	7575/779 (97.2)	0.323
	M3	295/1750 (16.9)	90/364 (24.7)	100/708 (14.1)	105/678 (15.5)	0.000
Anthropometry						
WAZ	Baseline	-0.9 [-1.8, 0.1]	-1.2 [-2.1, -0.3]	-0.9 [-1.8, 0.0]	-0.6 [-1.6, 0.2]	0.000
	M1	-0.5 [-1.4, 0.3]	-0.7 [-1.7, -0.0]	-0.5 [-1.4, 0.3]	-0.4 [-1.2, 0.5]	0.000
	M3	-0.4 [-1.3, 0.4]	-0.6 [-1.5, 0.2]	-0.4 [-1.3, 0.4]	-0.3 [-1.2, 0.5]	0.001
	M6	-0.3 [-1.1, 0.5]	-0.4 [-1.2, 0.2]	-03 [-1.0, 0.6]		0.030
Change in WAZ if underweight at baseline	M1	0.5 (0.2, 1.0)	0.5 (0.2, 1.3)	0.6 (0.2, 1.1)	0.5 (0.2, 0.9)	0.585
	M3	0.8 (0.4, 1.4)	0.9 (0.5, 1.8)	0.9 (0.5, 1.5)	0.7 (0.4, 1.2)	0.037

Combination score includes any of: cough, loss of appetite, abnormal auscultation or no weight gain if underweight at baseline
Abbreviations: WAZ= weight-for-age z-score; PTB=pulmonary tuberculosis

Table III: Prevalence and predictors of sign or symptom persistence at 3 months[a]

		Prevalence	Univariable Predictors		Multivariable Predictors	
		% (n/total)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Sociodemographics						
HIV status	Uninfected	15.3 (223/1461)	1.0		1.0	
	Infected	25.2 (72/286)	1.9 (1.4, 2.5)	0.000	1.6 (1.1, 2.3)	0.011
Gender	Male	17.6 (158/898)	1.0		1.0	
	Female	16.1 (137/852)	0.9 (0.7, 1.2)	0.398	0.9 (0.7, 1.2)	0.392
Age category	<1 year	19.1 (62/324)	1.0		1.0	
	1-5	14.7 (139/947)	0.7 (0.5, 1.0)	0.058	0.7 (0.5, 1.0)	0.061
	>5 years	19.6 (94/479)	1.0 (0.7, 1.5)	0.864	0.9 (0.6, 1.4)	0.798
PTB disease classification						
	Unlikely	15.5 (105/678)	1.0		1.0	
	Confirmed	24.7 (90/364)	1.8 (1.3, 2.5)	0.000	1.3 (0.9, 1.9)	0.156
	Unconfirmed	14.1 (100/708)	0.9 (0.7, 1.2)	0.475	0.7 (0.5, 1.0)	0.086
Chest Radiography findings						
CXR normal	Yes	8.9 (37/417)	1.0		1.0	
	No	19.7 (189/962)	2.5 (1.7, 3.6)	0.000	2.3 (1.5, 3.3)	0.000

[a] Symptom and sign persistence includes any of: cough, loss of appetite, abnormal auscultatory findings, or no weight improvement if underweight at baseline

Abbreviations: OR=Odds Ration; aOR=adjusted odds ration; HIV=human immunodeficiency virus; PTB=pulmonary tuberculosis; CXR= chest radiography

Supplementary data

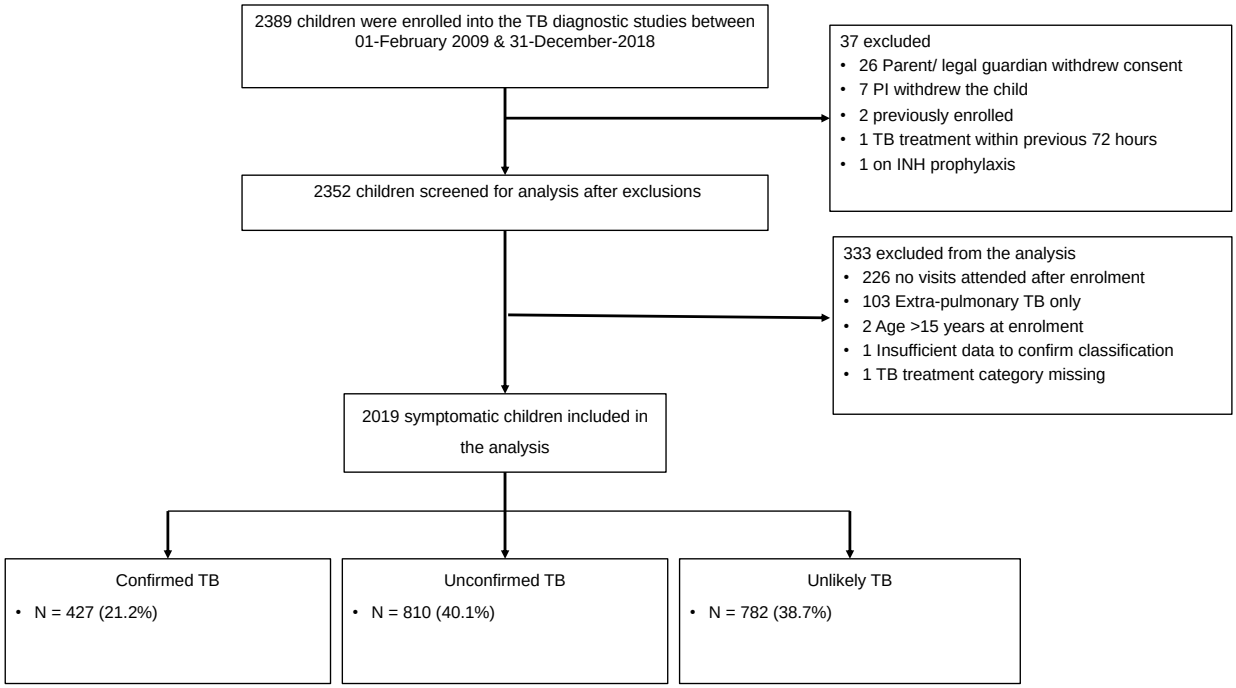
Table IV: Prevalence and predictors of sign or symptom persistence at 3 months: Sensitivity cohort[a]

		Prevalence	Univariable Predictors		Multivariable Predictor	
		% (n/total)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Sociodemographics						
HIV status	Uninfected	15.4 (215/1399)	1.0		1.0	
	Infected	26.5 (63/238)	2.0 (1.4, 2.7)	0.000	1.7 (1.1, 2.4)	0.008
Gender	Male	18.0 (150/835)	1.0		1.0	
	Female	15.9 (128/805)	0.9 (0.7, 1.1)	0.266	0.9 (0.7, 1.2)	0.481
Age category	<1 year	19.4 (62/315)	1.0		1.0	
	1-5	14.9 (131/879)	0.7 (0.5, 1.0)	0.065	0.7 (0.5, 1.0)	0.071
	>5 years	19.3 (86/446)	1.0 (0.7, 1.4)	0.977	0.9 (0.6, 1.4)	0.748
PTB disease classification						
	Unlikely	15.5 (105/678)	1.0		1.0	
	Confirmed	24.7 (90/364)	1.8 (1.3, 2.5)	0.000	1.3 (0.9, 1.9)	0.177
	Unconfirmed	13.9 (83/598)	0.9 (0.6, 1.2)	0.419	0.7 (0.5, 1.1)	0.100
Chest Radiography findings						
CXR normal	Yes	8.5 (33/390)	1.0		1.0	
	No	20.0 (183/914)	2.7 (1.8, 4.0)	0.000	2.4 (1.6, 3.7)	0.000

[a] Symptom and sign persistence includes any of: cough, loss of appetite, abnormal auscultatory findings, or no weight improvement if underweight at baseline.
Sensitivity cohort excludes 117 participants from unconfirmed PTB group whose disease classification depended on resolution of baseline symptoms in response to anti-tuberculosis therapy

Abbreviations: OR=Odds Ration; aOR=adjusted odds ration; HIV=human immunodeficiency virus; PTB=pulmonary tuberculosis; CXR= chest radiography

Figure I: Study profile



Appendices

1. Human Research Ethics Committee approval & renewal

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 January 2020

HREC REF:827/2019

Prof B Eley
Division of Paediatrics
Room 520, 5th floor
ICH Building
Red Cross Children's Hospital

Dear Prof Eley

PROJECT TITLE: LONGITUDINAL CHANGES IN CLINICAL SYMPTOMS AND SIGNS IN CHILDREN WITH CONFIRMED, UNCONFIRMED, AND UNLIKELY PULMONARY TUBERCULOSIS. (SUB-STUDY 045/2008) (MPHIL DEGREE - DR JULIE COPELYN)

Thank you for submitting your study to the Faculty Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 January 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Julie Copelyn will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 827/2019sa

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
HEALTH SCIENCES FACULTY

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signature Removed	Date Signed	20/1/2021

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	19 January 2021		
HREC REF Number	827/2019	Current Ethics Approval was granted until	30 January 2021
Protocol title	Longitudinal changes in clinical symptoms and signs in children with confirmed, unconfirmed and unlikely pulmonary tuberculosis		
Principal Investigator	Brian Eley		
Department / Office Internal Mail Address	Room 520, 5th floor ICH building, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7700		

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
✓	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		2019
Total number of records or specimens collected, reviewed or stored since last progress report		2019
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	✓ No

4. Signature

2. Hospital Research Review Committee approval

Western Cape Government
Health

DR AN PARBHOO
Manager: Medical Services
Red Cross War Memorial Children's Hospital
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

17 June 2020

Prof B Eley
Paediatric Infectious Diseases

Dear Prof Eley,

RESEARCH: RXH: RCC 232 / WC_202006_011

PROJECT TITLE: Longitudinal changes in clinical symptoms and signs in children with confirmed, unconfirmed, and unlikely pulmonary tuberculosis

It is a pleasure to inform you that the hospital Research Review Committee has approved your application to conduct above-mentioned study in the Department at Red Cross War Memorial Children's Hospital.

Kindly note that this approval is subject to strict adherence to the HREC recommendations regarding research involving participants during COVID-19, dated 17 March 2020 (UCT HREC notice attached).

Yours sincerely,

Signature Removed

DR AN PARBHOO
MANAGER: MEDICAL SERVICES

3. Author Instructions: Pediatric Pulmonology

Author guidelines accessed 26 May 2021 at:
https://onlinelibrary.wiley.com/page/journal/10990496/homepage/forauthors.html

Please note new author guidelines for *Reporting of Race and Ethnicity* in section 9.

1. SCOPE OF JOURNAL

Pediatric Pulmonology publishes the results of original clinical or laboratory research, state of the art reviews, exceptionally instructive or unique case reports, and letters to the Editor (and responses), pertaining to the specialty.

Reports on meetings, conferences and symposia may be published after consultation with the Publisher and the Editor-in-Chief.

Preliminary brief communications will be considered if the articles contain information which would be considered a major breakthrough in the field.

We do not publish research funded by tobacco companies.

As the field is continually evolving, our Journal has seen an increase in the number of submissions over the past few years, and, as a result, our rejection rate is climbing.

2. PERMISSIONS

No material published in Pediatric Pulmonology may be reproduced or published elsewhere without the written permission of the publisher and the author. To request permission to reproduce an article, in part, or in whole, click here to for the Permissions Page

3. AUTHOR RESOURCES

For additional tools visit Author Services - an enhanced suite of online tools for WileyOnlineLibary journal authors, featuring Article Tracking, E-mail Publication Alerts and Customized Research Tools.

4. ENGLISH LANGUAGE SERVICES

Article Preparation Support

The Editors reserve the right to return any manuscript that is not in acceptable English. Translations from another language will not be provided by the Editorial Office. Authors from countries in which English is not the primary language should have their manuscript reviewed and corrected by an English language service before submission.

Wiley Editing Services offers expert help with English Language Editing, as well as translation, manuscript formatting, figure illustration, figure formatting, and graphical abstract design – so you can submit your manuscript with confidence.

Also, check out our resources for Preparing Your Article for general guidance about writing and preparing your manuscript.

GUIDELINES FOR COVER SUBMISSIONS
If you would like to send suggestions for artwork related to your manuscript to be considered to appear on the cover of the journal, please follow these general guidelines.

5. ELECTRONIC SUBMISSION OF MANUSCRIPTS

If you are familiar with our guidelines, click here to login to your ScholarOne account to submit your manuscript. If you do not have an account, click on "Register Here" to establish one.

6. MANUSCRIPT GUIDELINES

We accept submissions of the following types of articles. Please note the specific guidelines for each type:

Original Research Articles

Original Research Articles should follow the standard structure of abstract, introduction, methods, results, discussion, and references, and may include up to six tables and/or images when appropriate. Original Research Articles should be limited to 3,500 words (not including the abstract or references). The abstract should not exceed 250 words, and references should be limited to 40. There should be no more than 6 figures/tables in any combination. The Methods section must state that the paper has IRB approval or explain why the study is exempt.

Reviews/State of the Art Papers

Editors generally commission Reviews and State of the Art papers, but uninvited submissions are also welcome, particularly if the submission outlines an important and topical subject with a focus on recent advances. Reviews should be limited to 4,000 words, while State of the Art papers should be limited to 5,000 words (not including the abstract or references). We ask that the abstracts for these manuscript types do not exceed 250 words. There is no set limit on images, tables, or references for these types of manuscripts. We would encourage a PRISMA statement to be provided with these submissions.

Editorials and Commentaries

Editors and members of the Editorial Board may make editorial comments on individual articles or on a group of articles published in the same issue. Editorials (including pro/con debates) from authors who are not part of the editorial team are also welcome as submissions to the Journal. These narrowly focused articles should discuss an article that was recently published, or that is soon to be published. The commentary should discuss

specific issues within a subject area rather than the whole field, while explaining the implications of the article and putting it in context. Opinions must be factually based. These types of manuscripts should be limited to 1,500 words (not including the abstract or references). There is no limitation on the number of tables, images or references for these types of manuscripts.

Reports, Letters to the Editors and General Interest

We encourage letters that offer criticism of published material in an objective, constructive, and educational manner conducive to further exchanges. Such letters will only be considered if they are in reference to an article published within the previous six months. Letters may also discuss matters of general interest pertaining to the field of pediatric pulmonology, or may consist of brief reports of truly unique cases. Note that we do not publish original, previously unpublished data as letters. If appropriate, a copy will be sent to the author(s) referred to in the letter, so that they may respond. Letters to the Editor should not exceed 1,000 words (not including the abstract or references). Letters should contain no more than 5 references. There should be no more than 1 image or table in any combination.

7. PRIOR TO SUBMITTING

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/ppul

Click here for more details on how to use ScholarOne.

Author Contributions

For all articles, the journal mandates the CRediT (Contribution Roles Taxonomy), for more information please see Author Services.

Data protection

By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com/statements/data-protection-policy.html.

Preprint policy

Please find the Wiley preprint policy here.

This journal accepts articles previously published on preprint servers.

Pediatric Pulmonology will consider for review articles previously available as preprints. Authors may also post the submitted version of a manuscript to a preprint server at any time. Authors are requested to update any pre-publication versions with a link to the final published article.

Preprint your manuscript while it's under review

Beginning in early 2020, *Pediatric Pulmonology* is participating in a pilot of the under review service, Wiley's new initiative to streamline the early sharing of research and open up the peer review process. Authors can now opt to preprint their manuscript during the submission process and showcase their work to the global research community as a preprint, before it is accepted or published.

The under review service is powered by Authorea, an open research platform for all your research outputs, including data, figures, and preprints. By opting-in authors can:

- Seamlessly preprint at the same time you submit your research for publication
- Share your work early, while indicating it is being considered at a specific journal
- Track the peer review process openly in real time
- Immediately make their work citable, discoverable, and easily shareable
- Get additional community feedback that can be used to improve your manuscript

Learn more about the benefits of the under review service.

For help with submissions, please contact the Editorial Office: ppuledoffice@wiley.com

8. COMPONENTS OF ARTICLE/FILE PREPARATION

Please make note of the following when preparing your submission:

Main Document

All manuscript types must include a title page, abstract, text and references in the Main Document. Standard, double-spaced manuscript format, in 12 point font is requested. Number all pages consecutively.

Title page: The title should be brief (no more than 100 words in length including spaces) and useful for indexing. All authors' names with highest academic degree, affiliation of each, but no position or rank, should be listed. For cooperative studies, the institution where research was primarily done should be indicated. In a separate paragraph, specify grants, other financial support received, and the granting institutions (grant number(s) and contact name(s) should be indicated on the title page). If support from manufacturers of products used is listed, assurances about the absence of bias by the sponsor and principal author must be given. Identify meetings, if any, at which the paper was presented. The name, complete mailing address, telephone number, fax number, and e-mail address of the person to whom correspondence and reprint requests are to be sent must be included. Keywords should also be noted on the title page. For

usage as a running head, provide an abbreviated title (maximum 50 characters) on the bottom of the title page.

Summary/Abstract: In accordance with the structure of the article, with or without separate headings, outline the objectives, working hypothesis, study design, patient-subject selection, methodology, results (including numerical findings) and conclusions. The Summary should not exceed the word counts outlined above. If abbreviations are used several times, spell out the words followed by the abbreviations in parentheses.

Acknowledgements: Technical assistance, advice, referral of patients, etc. may be briefly acknowledged at the end of the text under "Acknowledgements."

Informed Consent: Informed consent statements, if applicable, should be included in the Methods section.

References/citations: References may be included at the end of your text, or uploaded as a separate file. Ensure your references are up to date, and include a critical selection from the world literature. References should be prepared according to CSE (Council of Science Editors) citation-sequence style. Refer to the *Scientific Style and Format: The CSE Manual for Authors, Editors, and Publishers*, 8th edition (University of Chicago Press). Start the listing on a new page, double-spaced throughout.

Number the references in the sequence in which they first appear in the text, listing each only once even though it may be cited repeatedly.

When citing a reference in the text, the style advocated by CSE suggests numbers appear in superscript, and appear before punctuation marks (commas or periods). In the **citation-sequence** system, sources are numbered by order of reference so that the first reference cited in the paper is [1], the second [2], and so on. If the numbers are not in a continuous sequence, use commas (with no spaces) between numbers. If you have more than two numbers in a continuous sequence, use the first and last number of the sequence joined by a hyphen, for example [2,4,6-10].

In the references, list the first ten authors of the cited paper. If there are more than ten authors, list the first 10 authors followed by 'et al'.

Journals' names should be shown by their abbreviated title in *Index Medicus*.

Manuscripts in preparation or submitted for publication are not acceptable references. If a manuscript "in press" is used as a reference, a copy of it must be provided with your submission.

Sample references:

Standard journal article

Landau IL, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. Pediatr Pulmonol 1993;16:31-35.

Book with authors

Voet D, Voet JG. 1990. Biochemistry. New York: John Wiley & Sons. 1223 p.

Book with editors

Coutinho A, Kazatch Kine MD, editors. Autoimmunity physiology and disease. New York. Wiley-Liss; 1994. 459 p.

Chapter from a book

Hausdorf G. Late effects of anthracycline therapy in childhood: evaluation and current therapy. In: Bricker JT, Green DM, D'Angio GJ, editors. Cardiac toxicology after treatment for childhood cancer. New York: Wiley-Liss; 1993. p 73-86.

For a book reference only include the page numbers that have direct bearing on the work described.

Keywords: On the title page, supply a minimum of 3 to 5 keywords, exclusive of words in the title of the manuscript. A guide to medical subject heading terms used by PubMed is available at http://www.nlm.nih.gov/mesh/MBrowser.html

Abbreviations: Define abbreviations when they first occur in the manuscript and from there on use only the abbreviation. Whenever standardized abbreviations are available use those. Use standard symbols with subscripts and superscripts in their proper place.

Drug names: Use generic names. If identification of a brand name is required, insert it in parentheses together with the manufacturer's name and address after the first mention of the generic name.

Eponyms: Eponyms (diseases or biologic entities named for persons) should not be used when standard descriptive terminology is available. Examples include club cells (formerly known as Clara cells); and granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis). It is permissible to use the eponym in parenthesis at the first mention of the term in cases in which the eponym is still in common use.

Formatting Specific to Original Research Articles: Divide article into: Title Page, Summary/Abstract, Introduction, Materials and Methods, Results, Discussion, and References, starting each section on a new page. All methodology and description of experimental subjects should be under Materials and Methods; results should not be included in the Introduction. Please ensure the following appears in the appropriate section of your manuscript:

- a concise introductory statement outlining the specific aims of the study and providing a discussion of how each aim was fulfilled;
- a succinct description of the working hypothesis;
- a detailed explanation of assumptions and choices made regarding study design and methodology;
- a description of the reasons for choosing the type and number of experimental subjects (patients, animals, controls) and individual measurements; if applicable, information about how and why the numbers may differ from an ideal design (e.g., the number required for achieving 90% confidence in eliminating Type II error);
- specifics about statistical principles, techniques and calculations employed and, if applicable, methods for rejecting the null hypothesis;
- a concise comparison of the results with those of conflicting or confirmatory studies in the literature;
- a brief summary of the limitations of the scientific methods and results; and
- a brief discussion of the implications of the findings for the field and for future studies.

- **Tables**

Tables should not be included in the Main Document, but submitted as a separate DOC or RTF file. Number tables with Arabic numbers consecutively and in order of appearance. Type each table double-spaced on a separate page, captions typed above the tabular material. Symbols for units should be used only in column headings. Do not use internal horizontal or vertical lines; place horizontal lines between table caption and column heading, under column headings, and at the bottom of the table (above the footnotes if any). Use footnote letters (a, b, c, etc.) in consistent order in each table. All tables should be referred to in the text. Do not submit tables as photographs and do not separate legends from tables.

- **Images**

Image files must be submitted in TIF or EPS (with preview) formats. Do not embed images in the Main Document. Number images with Arabic numbers and refer to each image in the text. The preferred form is 5 X 7 inches (12.5 X 17.5 cm). Print reproduction requires files for full color images to be in a CMYK color space.

Please note authors are encouraged to supply color images regardless of whether or not they are amenable to paying the color reproduction fees. Color images will be published online, while greyscale versions will appear in print at no charge to the author. See Author Charges below.

Journal quality reproduction requires grey scale and color files at resolutions yielding approximately 300 ppi. Bitmapped line art should be submitted at resolutions yielding 600-1200 ppi. These resolutions refer to the output size of the file; if you anticipate that your images will be enlarged or reduced, resolutions should be adjusted accordingly.

Lettering on images should be of a size and weight appropriate to the content and the clarity of printing must allow for legibility after reduction to final size. Labeling and arrows on images must be done professionally. Spelling, abbreviations, and symbols should precisely correspond to those used in the text. Indicate the stain and magnification of each photomicrograph. Photographs of recognizable subjects must be accompanied by signed

consent of the subject of publication. Images previously published must be accompanied by the author's and publisher's permission.

Image legends should be brief, and included as a separate DOC file under the heading: "Image Legends." When borrowed material is used, the source of the image should be shown in parentheses after its legend, either by a reference number or in full if not listed under References.

Online Supporting Information

Additional non-essential material such as text, appendices, tables, images, video, and soundtrack files may be submitted for posting as supporting information to an article. The scientific value of such material should be evident. The material should be submitted simultaneously with the manuscript so that it may undergo peer review. In naming these files, please note the file names should be preceded by the letter "E." For example "E-table 1,"E-image 1," "E-text," etc.

Note that supporting online material is not typeset, nor proofread following the review process, so please ensure the material is accurate and free of typographical errors. Supporting material should be prepared in the same manner as the print material.

While supporting information does not appear in the print version, a notation is made that supporting material is available online.

9. POLICIES/DISCLOSURE STATEMENTS

We recognize the importance of developing the highest ethical standards and we are committed to ethical publication practice. For more information on the publisher's policies, please see Wiley-Blackwell Guidelines on Publication Ethics and Best Practices www.wiley.com/bw/publicationethics. Of particular importance is the section on Research Misconduct, which includes data fabrication, falsification, plagiarism, and inappropriate image manipulation.

Authors who submit to Pediatric Pulmonology should take heed of the following:

Conflict of Interest: Authors must indicate at the time of submission any potential conflict of interest (particularly of a fiscal nature) that may have a perceived influence on the results of the research. The existence of such does not automatically preclude publication. A conflict of interest statement should appear in the Acknowledgment section. For further information on Conflict of Interest please visit www.icjme.org

Experimental and Publication Ethics: Studies involving human subjects must conform to the guiding principles of the World Medical Association Declaration of Helsinki. Human subjects must have given informed consent and the study must have been approved by the Committee on Human Research at the author(s) institution(s) and a statement to this effect must appear in the Methods section of the submitted article. It is also important to document in the Methods section that consent has been obtained from older children and adolescents. Similarly, animal studies must be approved by an Institutional Animal Research Review Board and a statement to this effect must appear in the Methods section. In addition, details of anesthesia and euthanasia must appear in the Methods section.

Reporting of Race and Ethnicity: *Pediatric Pulmonology* is committed to scientific rigor and reproducibility, equity in science and medicine, and publishing articles from the global community of physicians and scientists who study childhood-onset respiratory and sleep disorders. These principles require appropriate terminology to accurately describe and differentiate race and ethnicity while not approximating either for ancestry or genetic variation. Race and ethnicity are social constructs that reflect societal acculturation, influence and personal identity, and that create inequalities in access, resources and privilege. Race and ethnicity have significant consequences on health and in society. Reporting of race and ethnicity is strongly encouraged because 1) studying structural and systemic inequities, and their effects on health, remains important; 2) transparency in research participation and respect for screened as well as enrolled participants is an ethical mandate; and 3) generalizability of findings requires inclusion of representative populations. Ancestry is an imprecise category of geographic origin. Inherited disorders may be more prevalent based on ancestry at the population level (for example, gene mutations resulting in cystic fibrosis in populations of northern European ancestry and sickle cell disease in populations of west African ancestry). Therefore, studies may appropriately report ancestral genetic markers in assessments of population health. In contrast, race is not a proxy for genetic variation and should not be inferred to predict

disease risk in individuals. For manuscripts submitted to *Pediatric Pulmonology*, the methods should include the source of race and ethnicity data (such as medical records or, preferably, self/family-report) and how race and ethnicity were categorized. Authors should note, in the methods section, whether laws or policies of a country or institution forbid the ascertainment of race and ethnicity data. Otherwise, results should include the distribution of race and ethnicity in the study population. The guidance used to describe race and ethnicity should be noted. For example, authors from the United States could note that the US Census Bureau guidelines or National Institutes of Health policy was used. In reporting, race and ethnicity should be used as adjectives rather than nouns. Race and ethnicity terms should be capitalized. Expect updates to this guidance as required in accordance with publisher policies. Questions or comments are welcome and should be addressed to the Editor-in-Chief, Susanna A. McColley, MD smccolley@northwestern.edu

Plagiarism: It should be noted that Pediatric Pulmonology employs a plagiarism detection system. By submitting your manuscript to this journal you accept that your manuscript may be screened for plagiarism against previously published works. CrossCheck is a multi-publisher initiative to screen published and submitted content for originality. Pediatric Pulmonology uses iThenticate software to detect instances of overlapping and similar text in submitted manuscripts. To find out more about CrossCheck visit http://www.crossref.org/crosscheck.html.

Prior Publication: Manuscripts submitted to Pediatric Pulmonology may not have been published in any part or form in another publication of any type, professional or lay, including electronic publications, the exception being abstracts of no more than 400 words. Any material available via PubMed or other electronic sources is considered to have been published. When a question arises, the Editor-in-Chief will determine what constitutes duplicate publication. If duplicate publication is confirmed, the Editor-in-Chief will initiate a discussion with the sponsoring institution and the authors.

It is the responsibility of submitting authors to inform the Editor-in-Chief of potentially overlapping or related data either in submitted manuscripts or papers in press, and such manuscripts should be appended to the submission. If there is significant overlap in data with previously published articles this should be addressed by the author in the "Authors Comments" section during the submission process. In particular, giving reasons why the

new submission should be published. The editors reserve the right to determine whether or not publication is warranted.

For further information on redundant or duplicate publication, please visit http://www.icmje.org

Clinical Trials: We endorse the Consolidated Statement of Reporting Trials (CONSORT Statement) Lancet 2002;357:1191-1194 which may be accessed at www.consort-statement.org. In accordance with ICMJE standards, all clinical trials must be registered with a database that is publicly accessible such as http://clinicaltrials.gov/ However, other free of charge public registries are acceptable. For further information, please visit http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

Expects Data Sharing

Please review Wiley's policy here. This journal expects and peer review data sharing.

The journal expects that data supporting the results in the paper will be archived in an appropriate public repository. Authors are required to provide a data availability statement to describe the availability or the absence of shared data. When data have been shared, authors are required to include in their data availability statement a link to the repository they have used, and to cite the data they have shared. Whenever possible the scripts and other artefacts used to generate the analyses presented in the paper should also be publicly archived. If sharing data compromises ethical standards or legal requirements then authors are not expected to share it.

See the Standard Templates for Author Use section to select an appropriate data availability statement for your dataset.

10. PEER REVIEW AND FAST TRACK REVIEW

Upon submission, authors are encouraged to submit names of experts who they deem appropriate to review their paper, but should avoid suggesting reviewers from their own institution. Authors may also indicate persons to whom they do not wish the manuscript sent for review. In most cases, articles will be reviewed by at least two authorities as well as the editorial staff to determine validity, significance, novelty, and potential impact on the field of

contents and conclusions. The reviewers will be selected by the Editor-in-Chief, Associate Editors, and/or Editorial Board members. The selection will be made on the basis of expertise, impartiality, and equal distribution among the available experts, regardless of geographic origin of the manuscript or locations of the reviewers. Authors will be advised within the shortest possible time whether their paper is accepted, requires major or minor revisions, or is rejected. All necessary efforts will be made to ensure a timely review process.

Authors should note the time from submission to final decision can be shortened by a timely return of a revised manuscript when revision has been requested.

The Editor-in-Chief reserves the right to reject any submission deemed not suitable for the journal after an in-house review.

FAST TRACK REVIEW

If circumstances so warrant, a fast-track review of a paper may be requested in the cover letter. At the Editor-in-Chief's discretion, a fast-track review will be undertaken to expedite manuscripts that deserve rapid review and publication. Expedited peer review and publication is rare and is reserved for timely presentation of significant data. If fast-track review is requested in the cover letter, the corresponding author will be informed if expedited review has been granted or not.

11. SUBMISSIONS FROM EDITORS AND EDITORIAL BOARD MEMBERS

Pediatric Pulmonology strives to ensure that any submission from the Editor-in-Chief, Deputy Editor, the Associate Editors, or from a member of the journal's Editorial Board receives an objective and unbiased evaluation. This is achieved by assigning any research article submitted by the Editor-in-Chief, Deputy or Associate Editors to an impartial referee who can maintain the integrity of the review process. When appropriate, Pediatric Pulmonology may also utilize the services of Guest Editors who are familiar with the peer review processes and policies of the journal. Articles submitted by Editorial Board members undergo a blinded peer review process that is as stringent as for those authors who are not on the Board. All submitting authors are automatically blinded to all aspects of the review process.

12. AUTHOR CHARGES

Should authors wish for manuscript images appear in color in the print edition, color reproduction fees will be charged to the authors. Current color reproduction fees are $800 per figure. Authors do, however, have the option of submitting color images for online publication, and greyscale images for the print edition at no charge, and we encourage authors to do so. For information on color charges, please contact Production Editor, at ppulprod @wwiley.com Color figures may be published online free of charge; however, the journal charges for publishing figures in colour in print. If the author supplies colour figures at Early View publication, they will be invited to complete a colour charge agreement in RightsLink for Author Services. The author will have the option of paying immediately with a credit or debit card, or they can request an invoice. If the author chooses not to purchase color printing, the figures will be converted to black and white for the print issue of the journal.

13. MANUSCRIPTS ACCEPTED FOR PUBLICATION

The author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services where via the Wiley Author Licensing Service (WALS) they will be able to complete a license agreement on behalf of all authors on the paper:

Article Promotion Support

Wiley Editing Services offers professional video, design, and writing services to create shareable video abstracts, infographics, conference posters, lay summaries, and research news stories for your research – so you can help your research get the attention it deserves.

Open Access

Open access fulfills RCUK, Wellcome Trust, NIH, and other funder mandates. Authors can choose open access to make their article freely available to all on Wiley Online Library. Wiley also immediately deposits open access articles in PubMed Central and PMC mirror sites. In addition, authors of open access articles are permitted to post the final, published PDF of their article on a website, institutional repository or other free public server, immediately on publication.

With open access, the author, the author's funding agency, or the author's institution pays a fee to ensure that the article is freely available.

If the open access option is selected the corresponding author will have a choice of the following Creative Commons License Open Access Agreements (OAA):

Creative Commons Attribution License OAA

- Creative Commons Attribution Non-Commercial -NoDerivs License OAA

If you select open access option and your research is funded by The Wellcome Trust and members of the Research Councils UK (RCUK) you will be given the opportunity to publish your article under a CC-BY license supporting you in complying with Wellcome Trust and Research Councils UK requirements. For more information on this policy and the Journal's compliant self-archiving policy please visit: http://www.wiley.com/go/funderstatement

For RCUK and Wellcome Trust authors click on the link below to preview the terms and conditions of this license:

Creative Commons Attribution License OAA

Note to NIH Grantees: Pursuant to the NIH mandate, Wiley Blackwell will post the accepted version of contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 12 months after publication. For further information, see Wiley Blackwell's NIH Policy Statement.

Copyright Transfer Agreement

If open access option is not selected, the corresponding author will be presented with the copyright transfer agreement (CTA) to sign on behalf of all authors.

To preview the terms and conditions of the open access agreements, or the copyright transfer agreement, please visit the FAQs hosted on Wiley Author Services. See http://authorservices.wiley.com/bauthor/faqs_copyright.asp and http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright--License.html.

Accepted Articles

The journal offers Wiley's Accepted Articles service for all manuscripts. Manuscripts accepted 'in press' are published online shortly after acceptance, prior to copy-editing or typesetting and appear in PDF format only. After the final version article is published (the article of record), the DOI remains valid and can still be used to cite and access the article.

Accepted Articles will be indexed by PubMed; submitting authors should carefully check the names and affiliations of all authors provided in the cover page of the manuscript so it is accurate for indexing. The final copyedited and proofed articles will appear in an issue on Wiley Online Library; the link to the article in PubMed will update automatically.

Proofs

Following acceptance, the corresponding author will be alerted by e-mail to access galley proofs in web-based proofing system. Corrections should be returned within 48 hours of receipt, as delays in returning galley proofs cause delays in publication. Alterations should be kept to a minimum. Costs of extensive alterations to the galley proof will be billed to the authors. All statements in (or omissions from) published manuscripts are the responsibility of the authors who are asked to carefully review proofs prior to publication.

Reprints

Reprints may be ordered at: https://caesar.sheridan.com/reprints/eorder/order

Appeal Requests

Authors who wish to request reconsideration of a rejected manuscript should direct their query to the Editor in Chief, Susanna McColley, smccolley@luriechildrens.org or the PPUL editorial office, ppuledoffice@wiley.com. Requests must include the manuscript ID and a detailed description of why the authors believe the paper should be reconsidered.

Appeal requests will be evaluated by the Editor-in-Chief to determine if an appeal will be permitted. These appeals will be approved on a very limited basis. If the appeal is allowed, instructions will be provided on how to resubmit your paper. Authors should not resubmit their rejected paper without prior approval from the Editors and the Editorial Office. Requests that are sent elsewhere will not be considered.

14. EDITOR-IN-CHIEF CONTACT/QUESTIONS CONTACT

Contact the Editor-in-Chief

Susanna McColley, smccolley@luriechildrens.org

Production Questions

Contact Production Editor at ppulprod@wiley.com

Questions About Your Submission

Contact the PPUL editorial office at ppuledoffice@wiley.com

Transferable Review: *Health Science Reports*

This journal works together with Wiley's Open Access Journal, *Health Science Reports* to enable rapid publication of good quality research that is unable to be accepted for publication by our journal. Authors may be offered the option of having the paper, along with any related peer reviews, automatically transferred for consideration by the Editor of *Health Science Reports*. Authors will not need to reformat or rewrite their manuscript at this stage, and publication decisions will be made a short time after the transfer takes place. The Editor of *Health Science Reports* will accept submissions that report well-conducted research that reaches the standard acceptable for publication. *Health Science Reports* is a Wiley Open Access journal which is indexed on PubMed/MEDLINE and Scopus. For more information please go to **www.healthsciencereports.org**.

We look forward to your submission.

4. Chest radiography reporting tool

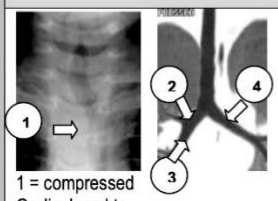
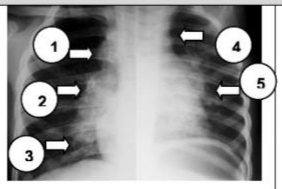
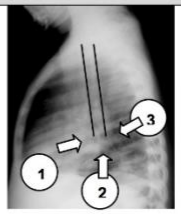
INFORMATION:

• Reader initials: …….. • Case number: ……..

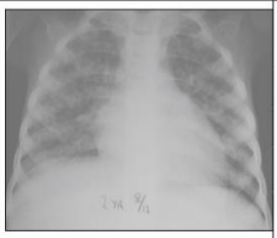
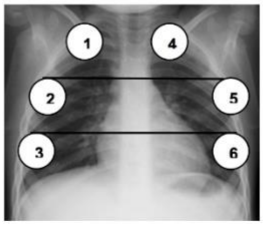
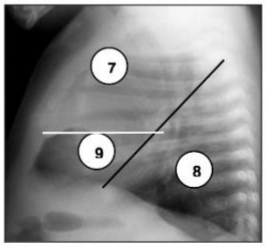
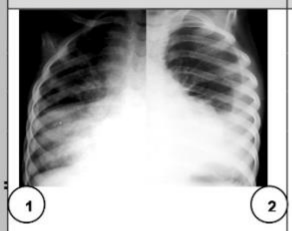
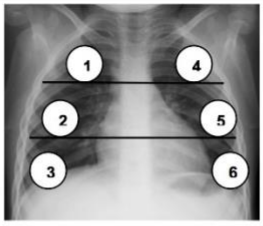
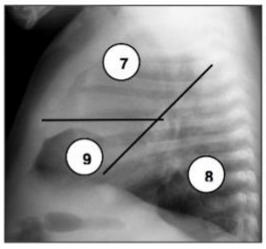
Instructions to tick-sheet:

Please mark clearly on the circled number only when you believe **confidently** that a finding is present. Please complete the overal decision below each box and the final decision on TB below. Do not complete the 'post process' block! Any abnormalities not listed **can** contribute to 'inconclusive' category.

Lymphadenopathy

Airway compressed and / or tracheal displacement	Soft tissue density = nodal mass	Post process: Lymph-adenopathy
 1 = compressed Or displaced to **left only** 2-4=compression	  Lines indicate the trachea	Yes No
Yes No	Yes No	Yes No

Parenchymal and pleural

Nodular = Milliary or larger widespread and bilateral	Airspace consolidation	Post process: Overall Lung disease
	 	Yes No
Yes No	Yes No	Yes No
Pleural effusion/thickening	**Cavities**	**Post process: Overall Pleura**
	 	Yes No
Yes No	Yes No	Yes No

Tick one box on the right on your TB Decision	Yes = Lymphadenopathy or Milliary	Inconclusive = abnormal **but** no lymphadenopathy or milliary	Normal	Unreadbale quality

5. Data capture sheet

STUDY	TB RePORT: COMMON PROTOCOL	STUDY NUMBER	
DEMOGRAPHIC AND CLINICAL INFORMATION			
Recruitment site			
PATIENT DETAILS			
Date of Birth	|__|__|-|__|__|__|- |__|__|__|__|	**Sex**	☐ M ☐ F
	Y	**N**	

CAREGIVER DETAILS					
	Gender		**Age**		
	☐ M	☐ F	_____Years		
Relationship to child					
☐ Mother	☐ Father	☐ Grandmother	☐ Aunt	☐ Other_____	
Have you ever been to school?		**If yes, highest level achieved**			**Number of years of education**
☐ Yes	☐ No	☐ Primary	☐ Secondary	☐ Tertiary	
SMOKING IN HOUSEHOLD					
Does the caregiver smoke		**If Yes, number of cigarettes smoked per day**			**Number of Household smokers**
☐ Yes	☐ No	☐ <10	☐ <20	☐ <30	☐ >30
TB HISTORY OF THE CAREGIVER					
Have you ever been treated for TB?		**If yes, how many times?**			**When did you start the most recent TB treatment**	**How many months were you on TB trt during the recent episode**
☐ Yes	☐ No	☐ 1x	☐ 2x	☐ >2x		
IMMUNISATION					
Was BCG given		**BCG date OR**	☐ **Date DK**	**BCG scar visible**	
☐ Yes	☐ No		|__|__|-|__|__|__|-|__|__|__|__|	☐ Yes	☐ No	☐ Unsure/DK
EPI Schedule up to date?			**If no, what is missing**		
☐ Yes	☐ No	☐ Card not available			
Has the child been vaccinated against TB with BCG at any-time in their life			**Approximately when was the most recent BCG vaccination provided?**		

☐ Yes	☐ No	☐ <1yr ago	☐ 1-<5yrs ago	☐ 5-10yrs ago	☐ >10yrs ago

CLINICAL HISTORY						
		Yes	**If yes, duration (days)**	**N**	**DK**	**Comment**
Night Sweats		☐		☐	☐	
Fever		☐		☐	☐	
Malaise, fatigue or lethargy		☐		☐	☐	
Cough		☐		☐	☐	
If yes to cough, coughing up blood		☐		☐	☐	
Pleuritic chest pain		☐		☐	☐	
Loss of Appetite		☐		☐	☐	
Unintended weight loss		☐		☐	☐	
Failure to thrive		☐		☐	☐	
Vomiting		☐		☐	☐	
Diarrhoea		☐		☐	☐	
Other 1	**specify**	☐		☐	☐	
Other 2	**specify**	☐		☐	☐	
Other 3	**specify**	☐		☐	☐	

PAST MEDICAL HISTORY				
Is this a new case of TB or a previously treated case?		☐ New	☐ Previously treated	
Complete for previously treated TB episode				
Where was the child previously treated for TB	**When was the child previously treated for TB**	**How many times has the child been treated for TB**		
Did the child require hospital admission during the last 3 months?		☐ Yes	☐ No	☐ DK
IF Yes, give details: Principal Admission Diagnosis		**Date of Admission**		
1.		|__|__|-|__|__|__|-|__|__|__|__|		
2.		|__|__|-|__|__|__|-|__|__|__|__|		
3.		|__|__|-|__|__|__|-|__|__|__|__|		

TB CONTACT HISTORY						
Has anyone in your household or close family, including those who have died, *EVER* been treated for TB				☐ Yes	☐ No	☐ DK
If YES, was he/she a:	☐ Parent	☐ Sibling	☐ Visitor	☐ Other	Other specify	
Was the Contact	☐ MDR	☐ XDR	☐ Mono-R		☐ Unknown	☐ Drug-R
When was the contact treated for TB?		☐ Current	☐ <12 mths		☐ > 1 yr	

HIV EXPOSURE				
Mother HIV infected during pregnancy?	☐ Yes	☐ No	☐ DK	
Was mother part of the PMTCT programme?	☐ Yes	☐ No	☐ DK	
Early infant feeding (First 6 months)?	☐ Excl breast	☐ Mxd	☐ Excl bottle	☐ DK
Was the child previously diagnosed with HIV?	☐ Yes	☐ No	☐ DK	
Child tested for HIV?	☐ Yes	☐ No	☐ DK	
Date of HIV diagnosis	|__|__|-|__|__|__|-|__|__|__|__|			
Is the Participant currently on ART?		**If yes, start date of current ART regimen**		
☐ Yes ☐ No		|__|__|-|__|__|__|-|__|__|__|__|		
HIV Status?	☐ Exposed	☐ Infected	☐ Uninfected	☐ DK

CLINICAL EXAMINATION					
Weight (kg)	**Height (cm)**	**Comment**			
|__|__|.|__| **OR** ☐ ND	|__|__|.|__| **OR** ☐ ND				
Oxygen saturation (%)	☐ Room air	☐ Supplemental oxygen			
Pulse (beats/min)	**Temperature (^{o}C)**	**Respiratory rate (breaths/min)**			
|__|__|__| **OR** ☐ ND	|__|__|.|__| **OR** ☐ ND	|__|__|__| **OR** ☐ ND			
Are there any of the following present?			**Yes**	**No**	**DK**
Phlyctenular Conjunctivitis			☐	☐	☐
Erythema Nodosum			☐	☐	☐
Oedema			☐	☐	☐

Clubbing	☐	☐	☐

Lymphadenopathy	**Yes**	**No**	**DK**
Are there any generalised enlarged Lymph nodes?	☐	☐	☐
IF YES, please give the size	**Small**	**Medium**	**Large**
	☐	☐	☐

Respiratory				
Subcostal Recession			☐ Yes	☐No
	No	**Rt**	**Lt**	**Bilat**
Dullness to percussion	☐	☐	☐	☐
Crackles	☐	☐	☐	☐
Wheeze	☐	☐	☐	☐
Reduced Normal Sounds	☐	☐	☐	☐
Abnormal Breath Sounds	☐	☐	☐	☐

RESULTS SECTION:		
CXR result		
Date Done	**Result**	
|__|__|-|__|__|__|-|__|__|__|__|	Compatible with TB ☐ Incompatible with TB ☐	Lymphadenopathy only ☐ Limited disease ☐ Extensive disease ☐

MANTOUX RESULT								
Was mantoux done		**If NO, give reason**			**Was mantoux read**		**Results Available**	
☐ **Yes**	☐ **No**	☐ **Prev TB**	☐ **No mx avail.**	☐ **Other** _____	☐ **Yes**	☐ **No**	☐ **Yes**	☐ **No**
TST Result (mm)								
Induration transverse diameter				**Was there blistering**		**Was there ulceration**		
_ _ mm				☐ **Yes**	☐ **No**	☐ **Yes**	☐ **No**	

HIV results	Specimen Number	Date Done	Result		
			Pos	Neg	Indeterminate
HIV Determine		___/ ___/ ____	☐	☐	☐
HIV Elisa		___/ ___/ ____	☐	☐	☐
HIV DNA PCR		___/ ___/ ____	☐	☐	☐
Final HIV Diagnosis	EXPOSED	INFECTED	UNINFECTED		UNKNOWN

Test	Specimen Number	Date Done	CD4 Result	CD4 %
CD4		___/ ___/ ____		
	Specimen Number	Date Done	Viral Load Result	
Viral load		___/ ___/ ____		
Is the Patient receiving ARV's?	☐ Yes	☐ No	☐ DK	

TB DIAGNOSIS RESULTS

☐ **TB Micro not done**

Spec type	Date taken	Smear result			Gene Xpert or Gene Xpert ultra					RIF S		Culture						INH S		RIF S	
		Pos	Neg	ND	Pos	Neg	Indeterminate Trace Call	Invalid	ND	S	R	Pos	MTB	Neg	ND	Cont	Days	S	R	S	R
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		☐	☐	☐	☐

TB TREATMENT			
Has TB treatment been prescribed	☐ **Yes**	☐ **No**	
Date TB treatment started	|__|__|-|__|__|__|-|__|__|__|__|		
Date TB treatment stopped	|__|__|-|__|__|__|-|__|__|__|__|		

Name of TB drug	Tablet or MG	Dosage
☐ **RIF**		
☐ **INH**		
☐ **PZA**		
☐ **ETHAM**		
☐ **ETHION**		
☐ **Pyridoxine**		
☐ **Other _____**		

Other medication	Yes	No	If yes, give name
Antibiotics	☐ **Yes**	☐ **No**	
Bronchodilators	☐ **Yes**	☐ **No**	
Prednisone	☐ **Yes**	☐ **No**	
Iron Tablets	☐ **Yes**	☐ **No**	

FOLLOW-UP VISITS								
Visit Date	|__|__|-|__|__|__|-|__|__|__|__|							
Visit Type	☐ 1M	☐ 3M	☐ 6M	☐ End RX	☐ 6 M post-RX	☐ TX F/R/W	☐ Other	Comment:
Was contact and evaluation of participant possible?							☐ Yes	☐ No
This visit was conducted	☐ In person	☐ By phone	☐ By email	☐ Other	Specify other:			

VISIT						
		Place of Interview			**Other comment**	
	☐ B11	☐ OPD	☐ Home	☐ Other		
Who came with the child today?	☐ Mother	☐ Father	☐ Grandparent	☐ Sibling	☐ Other	Other comment
Are you the main person who gives the child the TB/ARV RX		☐ Yes	☐ No	☐ NA	If no, who usually gives the medicine?	
Has the participant missed any TB RX doses since last visit? (if DOT card not available, ask participant directly				☐ Yes	☐ Dot card	☐ Self report
				☐ No	☐ Dot card	☐ Self report
How many treatment doses were supposed to be taken since the last visit? (based on the participants regimen)						
How many TB treatment doses were actually taken (Only count full doses, a partial dose = missed dose)						
Did the participant have an HIV test within the protocol specified period?				☐ Yes	☐ No[1]	☐ NA
Status of TB signs and symptoms since previous visit				☐ Improved, but signs/symptoms still present		
				☐ Improved, no signs/symptoms present		
				☐ Worsened		
				☐ No change		

CLINICAL EXAMINATION					
Nutritional Status					
Weight (kg)	**Height (cm)**	**Oedema**			**Comment**
|__|__|.|__| **OR** ☐ ND	|__|__|.|__| **OR** ☐ ND	☐ Yes	☐ No		
General examination		**Yes**	**No**	**DK**	**NA**	**Comment**

Has the child improved since discharge	☐	☐	☐	☐	
Unintended weight loss	☐	☐	☐	☐	
Failure to thrive	☐	☐	☐	☐	
Has the cough/respiratory symptoms such as wheeze etc. improved since last visit?	☐	☐	☐	☐	
Cough	☐	☐	☐	☐	
Has the child developed a cough since last visit	☐	☐	☐	☐	
LOA	☐	☐	☐	☐	
Vomiting	☐	☐	☐	☐	
Fever	☐	☐	☐	☐	
Night sweats	☐	☐	☐	☐	
Fatigue/lethargy	☐	☐	☐	☐	
Pleuritic pain	☐	☐	☐	☐	
Other	☐	Other, specify			

Respiratory examination				
Respiratory rate	|__|__|__| **OR** ☐ ND			
Findings	**Yes**	**No**	**DK**	**Side**
Subcostal recession	☐	☐	☐	
Dullness to percussion	☐	☐	☐	☐ **L** ☐ **R** ☐ **B**
Crackles	☐	☐	☐	☐ **L** ☐ **R** ☐ **B**
Wheeze	☐	☐	☐	☐ **L** ☐ **R** ☐ **B**
Reduced breath sounds	☐	☐	☐	☐ **L** ☐ **R** ☐ **B**
Abnormal breath sounds	☐	☐	☐	☐ **L** ☐ **R** ☐ **B**

Adherence	**Yes**	**No**	**DK**	**Comment**
Is the child on TB treatment[2]?	☐	☐	☐	
If yes, is treatment taken as prescribed?	☐	☐	☐	If no explain

Is the child on ARVs?	☐	☐	☐	
If yes, are ARVs taken as prescribed?	☐	☐	☐	If no explain
Is the child on steroids?	☐	☐	☐	

CXR	**Y**	**N**	**Comment/Accession number if yes**
Has a CXR been taken at this visit	☐	☐	
Date of Xray |__|__|-|__|__|__|-|__|__|__|__|	Compatible with TB ☐ Incompatible with TB ☐	Lymphadenopathy only ☐ Limited disease ☐ Extensive disease ☐	

Final Outcome Status

Confirmed TB	☐	**Confirmed by:** Gene Xpert ☐ Gene Xpert Ultra ☐ Culture ☐
Unconfirmed TB	☐	
Unlikely TB	☐	