Assessment, diagnosis and management of pulmonary tuberculosis in children under five years of age in the Langeberg sub-district, Western Cape, South Africa.

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Declaration

I, **Dr Andrew Williams**, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree. I also declare that ethics approval for the study was obtained from the Health Research Ethics Committee of Stellenbosch University (Reference number: S19/08/160).

Signature: **Dr Andrew Williams**

Date: 31 May 2020

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ABSTRACT

Background: TB remains one of the top 10 leading causes of death worldwide as millions of people still contract the disease annually. It is estimated that TB caused between 1.2 and 1.4 million deaths globally in 2017. The incidence of TB in children is a reflection of the underlying factors that fuel the TB epidemic, as these infections reflect ongoing TB-transmission.

Aim: To describe how the diagnosis of Pulmonary Tuberculosis (PTB) in children under 5 years is made in the Langeberg sub-district.

Setting: The Langeberg sub-district includes Robertson and Montagu District Hospitals as well as their surrounding clinics. A total of nine primary healthcare (PHC) clinics as well as two mobile clinics serving the farm areas in the sub-district were included.

Methods: A retrospective descriptive study was conducted. The researcher obtained statistics from the information management department of the Langeberg sub-district and utilised information of all known and notified cases of tuberculosis in the district. All cases of PTB diagnosed from 1st January 2018 to 31st December 2018, in children under 5 years of age were included.

Results: A total sample of 166 folders were reviewed. A proven positive adult contact was identified in 39% of cases. A suggestive chest x-ray was found in 93,4% of cases although specific CXR findings were not documented. Gastric washings were done in 52 of the children and had a positive yield of 13%. A total of 4,7% had HIV/TB co-infection and 12% had comorbid malnutrition. 85,5% of children had a positive treatment outcome (treatment completed or cured).

Conclusion: The diagnosis of PTB in children primarily remains a radiological diagnosis, but clinical factors like symptoms and their duration, weight trends and the presence of an adult contact have also been considered. Microbiological confirmation was absent in the majority of cases started on TB treatment. Comorbid HIV infection, malnutrition or asthma did not contribute to increased risk for adverse outcomes. Contact tracing needs to be improved within the sub-district.

Keywords: Diagnosis, Pulmonary Tuberculosis (PTB), Children, Primary Health Care (PHC)

Introduction

According to the WHO, the annual global burden of TB in children during 2018 was estimated to be approximately 11% of the global TB burden. In high burden areas, around 10-20% of TB cases are expected to occur in children, with a high mortality rate especially in those children younger than five.[1]

A large component of TB morbidity and mortality occurs in the paediatric population with an estimated 239000 deaths due to TB in 2015, according to the most recent modelling studies.[2] Children are essentially the canaries in the coalmine of TB, as the incidence of TB in children is a reflection of the underlying factors that fuel a TB epidemic, as cases of PTB in children reflect ongoing TB-transmission.[3]

The disease often only gets diagnosed at an advanced stage due to difficulties in the process of diagnosing TB in children. The usual methods, such as sputum production in adults for Gene-Xpert or TB- smear and culture, are far more difficult in the younger population (under 5 years) and even when proper samples are obtained, they may give false negative results, due to the pauci-bacillary nature of the disease in children.[4]

As gaining microbiological evidence of TB is more difficult in younger children, clinicians have to rely on other methods of diagnosis namely; clinical suspicion, immunological tests like Mantoux tuberculin skin testing (TST), radiology (chest x-rays, ultrasounds, computed tomography), CSF evaluation or biopsies (in the case of extra-pulmonary TB). Even with all the above methods, there is room for error or missed diagnosis, as not all clinicians have the same experience with interpretation, especially of radiological investigations. Imaging studies like x-rays remain challenging as there is an array of presentations for primary and post-primary tuberculosis, which is further complicated by the two disease entities having overlapping radiological features.[5]

Early diagnosis of TB is of vital importance especially in those younger than five years of age, as this group is most at risk of rapid disease progression[3] and developing complicated, extra-pulmonary disease, such as tuberculous meningitis, miliary TB and TB pericarditis.[3] Thus, starting treatment as soon as possible could prevent prolonged morbidity, or mortality due to the aforementioned examples of complicated disease. The diagnosis is often based on non-specific symptoms, history of a TB contact and a variety of chest X-ray findings.[6] There is unfortunately no gold standard test yet to diagnose TB in the paediatric population.[7]

The diagnosis of tuberculosis in a child is only the tip of an iceberg. In any notified case of paediatric TB, active case finding should be done as other studies have shown that there is likely to be a close adult contact with active disease in over a third of the cases identified.[7] If a household contact is not

identified, a contact should be actively sought as the infection risk within the community persists and poses a public health threat.[7]

Co-morbid diseases play a significant role in the development of TB in children as much as it does in adults. It is estimated that about 45% of deaths in children under five years of age is due to under-/malnutrition.[8,9] Conversely, we also know that severe infections in children also affects the nutritional status of children,[8]although the exact mechanism is still poorly understood and there are limited studies to explain the association between these two entities.[10] Some authors have suggested a predisposition to respiratory infections due to impaired innate immunity due to malnutrition, which can in turn, contribute to progression of disease from TB infection through altered gene expression and impaired cell-mediated immunity.[10] The inflammation caused by the abovementioned process further worsens the nutritional status of the child.[11] HIV co-infection further complicates this by also causing impaired child growth, recovery from malnutrition, and directly affecting the frequency and severity of infectious diseases that the affected children develop.[10]

Within a PHC setting in a rural area like the Langeberg sub-district, with significantly high morbidity rates for respiratory tract infections as reflected by our admission statistics, the question we should ask is are we doing enough to confirm a diagnosis of PTB. We should also consider the risks and benefits of starting treatment empirically as two of the greatest barriers to starting treatment in children are the difficulties in confirming the diagnosis and the concerns around adverse effects of medications,[12] especially potentially fatal hepatotoxicity.[13]

In answering the question of making this challenging diagnosis, an initial step would be to determine how the diagnosis of TB is currently made in children in this geographic area. The results of this research may assist in identifying areas which could improve the detection and diagnosis of TB in children, as well as identify whether other strategies are needed to improve the management of PTB in children.

Aim:

To describe how the diagnosis of PTB in children under 5 years is made in the Langeberg sub-district.

Objectives:

1. To determine how the diagnosis of PTB was made in all notified cases of paediatric TB.

2. To determine whether any microbiological evidence was found in those children on treatment.

3. To establish whether further contact tracing was done in cases of confirmed paediatric PTB.

4. To determine whether there were any comorbid diseases in the cases of confirmed PTB.

Methods

A retrospective descriptive study was conducted. The researcher obtained statistics from the information management department of the Langeberg sub-district and utilized the information of all notified cases of TB in the district. All cases of PTB diagnosed from January 2018 to December 2018, in children under 5 years of age were included. These included notified cases, whether diagnosis took place at one of the district hospitals or one of the PHC clinics in the district. Information collected included clinical history, examination findings, results of relevant investigations done, epidemiological information, the presence of any comorbid diseases like HIV/AIDS, malnutrition or lung diseases like Asthma and the outcome of each case was noted. All of the above-mentioned information was found either in their hospital or clinic patient folders. Information regarding contact tracing was also obtained from the TB-stationery in the patient folders.

The NHLS Labtrak system was used to determine whether any samples for microbiological evidence were sent off for any of the diagnosed cases to confirm a diagnosis of TB. The patient folder numbers or demographic details were used to obtain results.

Study setting: This research was conducted in the Langeberg sub-district, which includes Robertson and Montagu District Hospitals as well as their surrounding clinics. A total of nine PHC clinics were included, as well as two mobile clinics serving the farm areas in the sub-district.

Study population: All children under five years of age diagnosed with PTB were included.

Pilot study

A small pilot study was performed using 5-10 patient records from 1st January 2018 to 31st December 2018 to check the quality of the checklist for ambiguity, ease of use and to make overall improvements and changes where necessary on the quality of data collected.

Data collection: See appendix 1 for the checklist used to collect relevant information for analysis from all reviewed patient folders.

Data analysis: All data was captured on an excel spreadsheet and analysed for the method of diagnosis, microbiological proof of infection, whether contact tracing was done, the presence of comorbidity and outcome of cases.

Data was reviewed, cleaned and coded on a spreadsheet prior to data analysis. Data was then analysed with assistance from the Centre of Evidence-based Health Care at the Faculty of Health Sciences, Stellenbosch University, using descriptive and inferential statistics where appropriate. A P value of 0.05 was considered statistically significant. Both categorical and continuous data were analysed.

Ethical considerations

The researcher applied for a waiver of consent as this retrospective descriptive study carried minimal to no risk for the patients whose folders were reviewed. There was no need for patient contact and no interventions were implemented during this research project.

The challenge of the diagnosis of TB in the paediatric population, is that in most cases it happens very late in the disease process. This under-5 age group was chosen as they are a very high-risk group for rapid disease progression and thus high mortality rates.

This research project posed minimal risk to those involved as it was only the patient files and statistics that were investigated. All folders and information were handled strictly confidentially by the researcher.

Ethics approval was obtained from Stellenbosch University Health Research Ethics Committee. (HREC) Reference number: S19/08/160. Permission was obtained from the Western Cape Department of Health to enter facilities and review folders.

Results

A total of 181 children under the age of 5 years were identified on ETR.net that were started on TB treatment during the period of 1 January 2018 to 31 December 2018. Of these patients, one had extra pulmonary TB (TB-Knee) and was thus excluded as this study focused on PTB. Of the remaining 180 folders, twelve had missing data as either their clinic notes/TB notes were not available or they were present but no notes concerning the episode of TB in question were made. Outcomes were not documented in two files, which were also excluded. The total sample for this study was therefore 166 (figure 1).

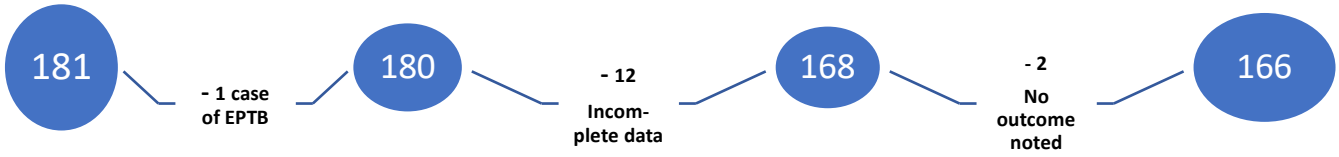

Figure 1. The process of record selection

In 39% of cases where PTB was identified, a proven adult contact with TB was traced. The remaining 61% either had incomplete data i.e. minimal details was recorded for contacts like their age and whether they were already on TB treatment and a possible infection risk or none were noted at all. Further contact tracing of at-risk individuals, i.e. individuals in the same household environment was done in 50,6% of cases (table 1).

The diagnosis of paediatric PTB relied on a combination of findings. In 31,9% of cases symptoms were present for more than a month compared to 22,9% who reported symptoms for less than a month. The remaining 45,2% had no symptoms noted in their files. A decrease or plateau in weight was reported in 53,6% of cases. In terms of clinical examination findings, 25% had adventitious breath sounds on auscultation, in 19% of cases respiratory distress was noted and only 5,4% had lymphadenopathy documented. These clinical examination findings were well documented mostly in the files of children who were seen and diagnosed at district or secondary healthcare levels. The lack of data recorded in files were mostly seen in the PHC folders of patients.

Table 1. Documented contact tracing findings

Contact Tracing		
	n	*% of sample*
Proven contact	64	38,60%
Unsure contact	52	31,30%
No contact traced	50	30,10%
Other household contacts traced	84	50,60%

In 93,4% of cases the CXR was found to be suggestive of PTB, however no note was made of the specific radiological signs seen on the chest x-ray of most patients. A TST was only done in 4,8% of cases due to the fact that it was out of stock for quite some time during the year in review. Of the TST's that were done, 37,5% were positive. Gastric washings were done in 52 of the children and had a positive yield of 13% (figure 2).

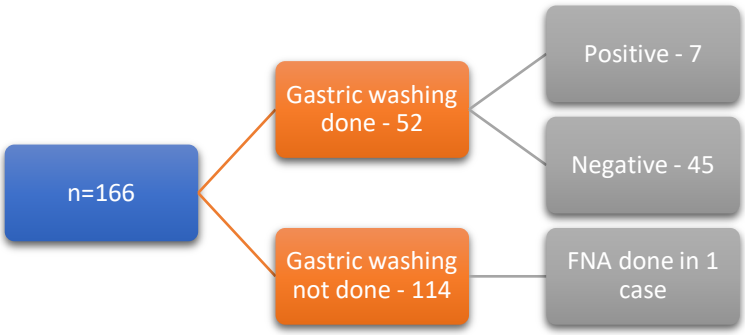

Figure 2. Gastric washings performed in patient sample.

In this sample, 4,7% were TB-HIV co-infected and a further 12% were malnourished. There was minimal overlap of HIV and malnutrition as it was found that only two of the HIV positive children were malnourished. Of the 8 that were HIV positive, 6 were on treatment at the time of diagnosis of PTB. The severity of malnutrition was not noted in many of the cases.

The majority of notified cases (67%) were diagnosed at PHC level. Those patients started on treatment at the PHC facility, were started mostly due to the presence of a suggestive chest x-ray and rarely with any bacteriological confirmation. Those patients who required admission for instance children with Severe Acute Malnutrition or respiratory distress, were more likely to be worked up for PTB as an in-patient and subsequently diagnosed at district health services or at secondary or tertiary levels of care. In terms of treatment outcomes, the majority (n=141) completed treatment (84%), one (0.6%) died, one (0,6%) were cured, 11 (6%) were transferred out to other facilities/health districts, seven (4,2%) defaulted and six (3.6%) were not evaluated (figure 3).

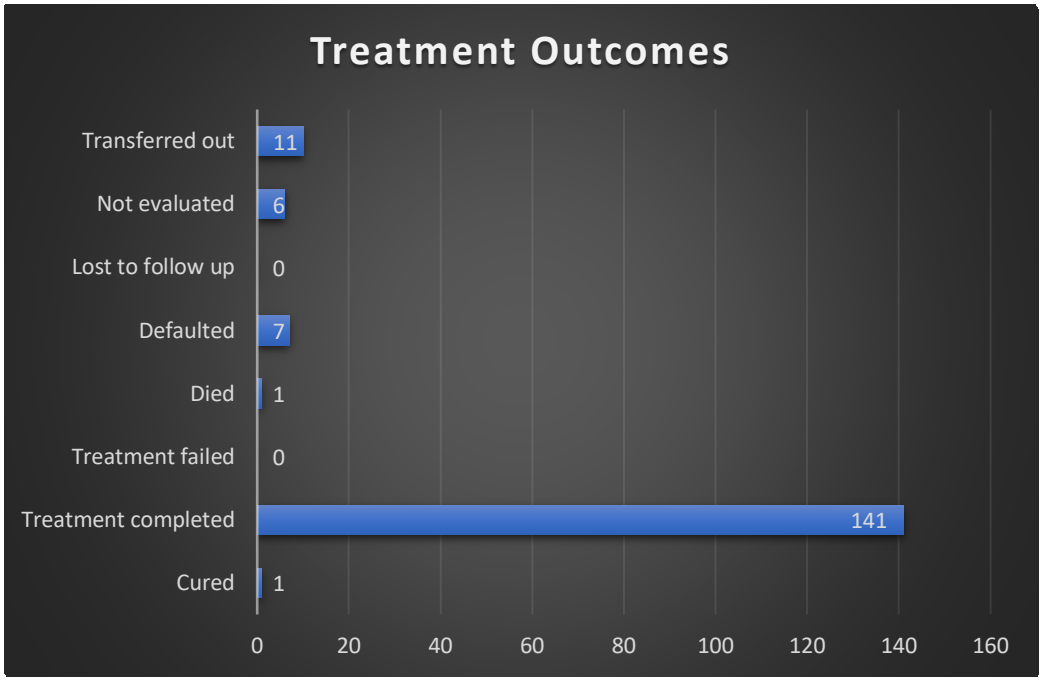

Figure 3. Treatment outcomes in the sample of patients.

Seven cases were microbiologically confirmed yet only one case outcome was noted as cured where the rest were noted as treatment completed.

Discussion

The diagnosis of PTB in children remains a difficult challenge. It is often not possible to obtain microbiological confirmation of infection thus other methods to rely on are clinical history and examination, evidence of being in contact with a confirmed TB case as well as radiological findings on chest x-rays.

Radiological evidence plays a vital role in making the diagnosis of PTB. The presence of abnormalities suggestive of PTB on chest x-ray remains one of the main reasons for starting TB-treatment. Findings like alveolar opacities, lymphadenopathy, nodular opacities or the presence of a miliary pattern were all associated with a diagnosis of TB.[6] In this sample, 93% of cases had a chest x-ray suggestive of PTB. Although it was indicated that the chest x-rays that were done were suggestive, the clinician reviewing the x-rays rarely indicated what was seen on the chest x-ray. Chest x-rays might be the primary screening tool, but evidence shows that there is high intra- and inter-observer variability with regards to assessing radiographs and only showed 74% specificity and 39% sensitivity.[15] A high specificity indicates the ability of a test to correctly diagnose a patient as not having a disease. In this case if a child has a normal CXR, that would mean they are highly unlikely to have pulmonary TB. 93% of the sample had a CXR suggestive of PTB. Of the remaining 7% TB was diagnosed due to the presence of symptoms, whether present for more than a month or less, coupled with the history of a TB contact in 7 of those 8 cases and a clear weight decrease trend noted.

In the cases where a diagnosis was made at a PHC facility, one doctor who is a senior medical officer working at a TB hospital in the district reviewed the x-rays and made the final decision. In the 29% of cases where the diagnosis of PTB was made at the district hospital, other less experienced clinicians made the decision to treat. The decision to treat a child for PTB remains difficult and with

the significant inter-observer variability, it is important to note that diagnosis requires a more comprehensive approach than just a review of the CXR, i.e. clinical, microbiological and radiological findings.

A thorough clinical history and examination is vital. It is an essential part of the evidence that leads to a diagnosis of PTB in a child. Common symptoms include failure to thrive/growth faltering, intermittent fever, coughing and/or wheezing. These symptoms are relatively non-specific, but in light of other suggestive information on further history taking and radiological findings, could indicate likely TB infection. The presence of symptoms was documented in 54,8% of patients. The remaining 45,2% had no note indicating symptoms, but it does not mean symptoms were not present. Because this is a retrospective study, it would be difficult to determine whether symptoms were present at that point. The presence of other findings i.e. radiological, contact history could have been enough grounds for a specific clinician to start their TB treatment.

An important finding was that there was a proven TB contact in 39% of cases. An alarmingly low figure when one takes into consideration that children infected with TB reflects ongoing transmission in the community as they cannot transmit the infection to each other due to the pauci-bacillary nature of the disease.[4] This study also looked at how long symptoms were present. In 31,9% of the cases symptoms were present for more than a month. A further 22,9% had symptoms for less than a month before diagnosis. This is a slightly lower figure than that noted from a study done by Cano APG et al in 2017,[7] however it is not an entirely true reflection as almost half the cases had no comment on the duration of symptoms in their files.

The majority of cases (67%) were diagnosed at PHC facilities. Diagnosis at this level would in these cases only require the probable history of a TB contact, symptoms suggestive of PTB and a suggestive CXR. A suggestive CXR was noted in 93% of the cases reviewed. Staff at the PHC facilities have no means to obtain specimens for microbiological evidence at the PHC facilities in the Langeberg sub-district. Gastric washings were the primary method of specimen collection, but was done in only 31% of diagnosed cases. Of those, only 13,5% of the specimens had a culture positive result, once again showing the low yield that this specific test has. Dunn et al[16] suggests that a possible method of ensuring a better yield for diagnostic tests would be to use induced sputum by nebulising children as young as one month old with hypertonic saline. The induction procedure would also not require the patient to be hospitalised, unlike with obtaining gastric washings where ideally two or three consecutive early morning samples are necessary.[16] Obtaining bacteriological proof is much more challenging in younger children compared to adolescents or adults. In adults the standard method of specimen collection would be the expectoration of sputum, preferably an early morning sample. Gastric washings are regarded as the standard specimen in children, although the yield is much lower than would be found in sputum.[14] Induction of sputum by means of nebulisation with hypertonic saline is a possible method of obtaining samples, but could not be done due to the fact that the facilities in question do not have hypertonic saline. Urinary LAM tests have not been used in this sample. At the facilities in question, these tests are usually reserved for HIV positive patients where possible extra-pulmonary TB is suspected. Studies on the use of urinary LAM tests in children are limited.[17]

Tracing adult contacts with active TB infection is of utmost importance when PTB is diagnosed in a child. This study showed that a proven TB contact was found in 39% of notified cases of paediatric TB. This means the other 61% had no traced contact with possible TB which is unlikely, as a TB diagnosis in a child is usually a reflection of actively spreading infection in a community whether it be at home or any other social setting.[7]

By definition, a cured case is one which tested positive i.e. was confirmed microbiologically and subsequently became negative on their treatment. In this sample, seven cases had microbiological confirmation of the diagnosis. After successful treatment their outcomes should have been noted as cured and not just as treatment completed.

Routine TB risk assessment for all children admitted with malnutrition should be standard protocol, especially in a high burden country like South Africa.[8] Since these children are routinely referred to the district hospitals in the sub-district for further management and investigations, a full work-up as an inpatient gets done as noted in the hospital folders of those diagnosed in a district hospital. Unfavourable outcomes like defaulting treatment, treatment failure and death were more likely in HIV/TB co-infected patients as well as those cases complicated by malnutrition.[11] In this study sample, 4% were HIV positive and on treatment, 12% were malnourished and only two (1,2%) children had underlying Asthma. There was only one paediatric death noted in the sample but this case had underlying hepatitis A infection and developed hepatotoxicity after initiation of tuberculosis treatment. There were no adverse outcomes of cases who had comorbid diseases that were assessed as part of this study namely HIV infection, lung disease and malnutrition, although many studies show that these are some of the factors which predispose individuals to unfavourable outcomes.[8,11,18]

Limitations

The primary limitation was that this was a retrospective study and the researcher had to rely on notes made either in the TB records of each notified TB-patient or in their clinic or hospital files. This proved to be a challenge in many cases as notes were incomplete especially data relevant to this study.

In clinic files the following were identified:

1) Symptoms were not noted in many cases although there is a clear space provided in the records/stationery. Where symptoms were documented, the duration of symptoms were rarely indicated.
2) Clinical signs were not noted as most diagnoses at clinics were made based on the CXR picture of a patient.
3) The responsible clinician reading the CXR would indicate that the person has a suggestive CXR, but the exact findings were not communicated or documented in the records.
4) Treatment outcomes were not always assessed.

The tracing of files was largely dependent on whether cases were coded correctly with the ICD-10 coding system and also notified by the diagnosing doctor/nursing personnel.

Recommendations

Further training of clinicians in the assessment of paediatric chest x-rays should be considered. Poor note keeping limited the amount and quality of information collected during this study. Better note keeping would be advised especially in terms of clinical history and examination, chest x-ray findings and TB contact tracing. Improving the TB records used could perhaps assist in this regard.

Since children cannot transmit the disease to each other due to the pauci-bacillary nature of the disease, one should do more especially at PHC level by including all possible resources like community health workers to assist in tracing adult contacts to curb further community spread to at-risk individuals.

Conclusion

Diagnosis of tuberculosis in children in the Langeberg sub-district remains mainly a radiological diagnosis, but other factors such as history and examination also need to be taken into account to support the diagnosis. The assessment of these radiographs is also clinician dependent and were mostly seen by an experienced TB-clinician. The low number of positive results on gastric washings as the standard investigation also brings into question the need for bacteriological proof of infection. No specific comorbidities were linked to adverse outcomes in this study sample. TB contact tracing remains an area of concern in the management of paediatric PTB cases. The presence of comorbid diseases especially HIV could possibly place a child at higher risk of unfavourable outcomes like defaulting medicines, thus close follow-up of these individuals would be needed.

To reduce the amount of deaths due to TB, more children need to be reached, diagnosed and treated, but without a gold standard test this would prove to be difficult. If children are treated empirically without the need for need for confirmation of disease, we run the risk of treating children unnecessarily for TB. Current investigations either have a low positive yield like gastric washings or a low sensitivity like CXR. The current approach of using a combination of findings to support a PTB diagnosis should thus remain in place until a gold standard test can be developed.

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Appendix: 1

Checklist for Paediatric Pulmonary Tuberculosis File Review

Folder number: Age:		
Criteria		
TB Contact	Proven	
	Unsure	
	None	
Further contact tracing done?		
Constitutional symptoms	>1 month	
(cough, LOW, LOA, fever)	<1month	
Weight trend prior to diagnosis	Noted decrease or plateau	
Clinical signs	Respiratory distress	
	Lymphadenopathy	
	Adventitious breath sounds	
Mantoux done?		
CXR	Suggestive	
	Not suggestive	
Previous TB treatment		
Comorbid diseases	HIV	

	Malnutrition	
	Asthma or other lung diseases	
Facility where diagnosis was made?	Regional Hospital	
	District hospital	
	Primary Healthcare Clinic	
Case outcome	Cured	
	Treatment completed	
	Treatment failed	
	Died	
	Lost to follow up	
	Not evaluated	
	Transferred out	
If HIV+	On treatment?	
	Viral load	
	CD4	