Dilemma of managing asymptomatic children referred with 'culture-confirmed' drug-resistant tuberculosis

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ABSTRACT

Background The diagnosis of drug-resistant tuberculosis (DR-TB) in children is challenging and treatment is associated with many adverse effects.

Objective We aimed to assess if careful observation, without initiation of second-line treatment, is safe in asymptomatic children referred with 'culture-confirmed' DR-TB.

Setting KwaZulu-Natal, South Africa—an area with high burdens of HIV, TB and DR-TB.

Design, intervention and main outcome measures

We performed an outcome review of children with 'culture-confirmed' DR-TB who were not initiated on second-line TB treatment, as they were asymptomatic with normal chest radiographs on examination at our specialist referral hospital. Children were followed up every other month for the first year, with a final outcome assessment at the end of the study.

Results In total, 43 asymptomatic children with normal chest radiographs were reviewed. The median length of follow-up until final evaluation was 549 days (IQR 259–722 days); most (34; 83%) children were HIV uninfected. Resistance patterns included 9 (21%) monoresistant and 34 (79%) multidrug-resistant (MDR) strains. Fifteen children (35%) had been treated with first-line TB treatment, prior to presentation at our referral hospital. At the final evaluation, 34 (80%) children were well, 7 (16%) were lost to follow-up, 1 (2%) received MDR-TB treatment and 1 (2%) died of unknown causes. The child who received MDR-TB treatment developed new symptoms at the 12-month review and responded well to second-line treatment.

Conclusions Bacteriological evaluation should not be performed in the absence of any clinical indication. If drug-resistant *Mycobacterium tuberculosis* is detected in an asymptomatic child with a normal chest radiograph, close observation may be an appropriate strategy, especially in settings where potential laboratory error and poor record keeping are constant challenges.

What is already known on this topic

- ▶ Diagnosing drug-resistant tuberculosis in children is challenging.
- ▶ Most clinicians regard culture confirmation as an indication for treatment, irrespective of clinical presentation or potential treatment-related adverse effects.

What this study adds

- ▶ Diagnostic certainty should be critically reviewed in children with 'culture-confirmed' drug-resistant tuberculosis.
- ▶ Asymptomatic children with 'culture-confirmed' drug-resistant tuberculosis with a normal chest radiograph may be carefully monitored without treatment.

therapy and lasts approximately 2 years. DR-TB treatment can have a significant negative physical, psychological and academic impact on children due to its duration, complexity and associated adverse effects.⁴ In addition, treatment places a significant financial burden on the child's family and the health system in general.^{4–6}

DR-TB is a laboratory diagnosis based on culture and drug-susceptibility testing (DST) or, more recently, rapid genotypic testing with Xpert MTB/RIF. However, false-positive DR-TB tests can occur due to specimen contamination and laboratory error.^{7–8} In addition, transient *Mycobacterium tuberculosis* (*M.tb*) excretion, detectable by culture or other sensitive tests, is not uncommon following recent primary infection, even in the absence of active disease.^{9–10} Given the high risk of irreversible hearing loss and other adverse effects associated with the use of second-line injectable drugs,¹¹ the clinical significance of a positive DR-TB test should be carefully considered. This has particular relevance in asymptomatic children with normal chest radiographs, in whom some practitioners may defer therapy and monitor closely for any suspicious symptoms or signs. The outcome and advisability of this practice, however, have not been evaluated. We aimed to assess if careful observation, without initiation of second-line treatment, is safe in asymptomatic children with 'culture-confirmed' DR-TB, under programmatic conditions.

INTRODUCTION

South Africa has a high burden of drug-resistant tuberculosis (DR-TB; resistance to one or more first-line TB drugs), which includes many children.^{1–2} Diagnosing DR-TB in young children is challenging, particularly in those co-infected with HIV, as the signs and symptoms are non-specific and the disease usually paucibacillary.^{2–3} DR-TB treatment requires the use of second-line drugs, which are less potent and more toxic than first-line medications. The treatment also includes a daily intramuscular injection for the first 4–8 months of

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METHODOLOGY

Study population and setting

King Dinuzulu Hospital (KDH) is the specialist referral hospital for DR-TB in KwaZulu-Natal Province, South Africa. Between January 2010 and December 2011, a number of children (≤ 14 years) were referred to KDH for initiation of multidrug-resistant-tuberculosis (MDR-TB) therapy. These children were referred by primary-level facilities, either clinics or district hospitals. At clinics, they would have been assessed and treated by a professional nurse and at district hospitals by a doctor. First-line TB drugs and antiretroviral therapy (ART) are available at both clinic and hospital level, but laboratories are usually hospital based. On presentation at KDH, despite having 'culture-confirmed' DR-TB, these children were clinically well with a normal chest radiograph and no signs or symptoms suggestive of active disease. Instead of being started on DR-TB treatment, a collective decision was taken at the weekly doctors meeting to enrol these children in an observation programme with monitoring every other month for a year.

Agreed criteria included a normal chest radiograph with no current signs or symptoms suggestive of intrathoracic or extrathoracic TB. Children who had commenced first-line TB treatment prior to enrolment continued until their course of treatment was complete. At follow-up visits, children were monitored for any suggestive TB signs or symptoms, a chest radiograph was performed and each child's weight was checked. If children remained well after 1 year, they were discharged from the programme. The duration of follow-up was measured in days from the date of entry into the observation programme to any of the following outcomes: death, initiation of MDR-TB treatment or date of last contact with the programme. Between July 2012 and June 2013, as a final outcome assessment, all children enrolled in the observation programme were contacted and asked to return to KDH for a final evaluation, irrespective of the time since enrolment.

Laboratory procedures

This study was undertaken before the introduction of the Xpert MTB/RIF assay (Cepheid, Sunnyvale, California, USA), in South Africa. Routine samples submitted to the centralised provincial diagnostic mycobacteriology laboratory in Durban included gastric aspirates collected from young children and sputum from older children who could expectorate. Smear microscopy for acid-fast bacilli was done using an auramine stain. Initial culture was performed in liquid media using mycobacteria growth indicator tubes MGIT 960 Mycobacteria Culture System (Becton, Dickinson and Co, Franklin Lakes, New Jersey, USA) and all positive cultures underwent line probe assay testing (Hain MTBDR_{plus}, Hain Lifescience, Nehren, Germany). Isolates demonstrating genotypic resistance to either isoniazid (INH) or rifampicin (RIF) then underwent first and second-line phenotypic DST using the 1% proportion method on Middlebrook 7H10 agar. Isolates were tested for susceptibility to INH (1 mg/L), RIF (2 mg/L), ethambutol (EMB) (5 mg/L), streptomycin (2 mg/L), kanamycin (16 mg/L) and ciprofloxacin (2 mg/L).

Data collection and analysis

We retrospectively reviewed hospital medical records and extracted the following information: baseline demographic and clinical characteristics, TB history, HIV status and treatment, laboratory data and chest radiographs. Unfortunately, we were unable to access clinical information at the referring facilities to assess the initial signs and symptoms that triggered the

microbiological evaluation. Weight was plotted on the USA Centers for Disease Control and Prevention weight-for-age percentile charts.¹² Malnutrition at baseline was classified as weight less than the third percentile for a given age in months.² Data were double-entered and checked for errors. Baseline characteristics and outcomes are presented as proportions, means or medians where appropriate.

Ethical approval

The study protocol was approved by the ethics committee of the South African Medical Research Council, the KwaZulu-Natal Department of Health and KDH (Ref: EC011-7/2013).

RESULTS

Between January 2010 and December 2011, 194 children with DR-TB were referred to KDH for initiation of DR-TB therapy. Of these children, 148 were initiated on second-line therapy and 46 (24%) asymptomatic children were enrolled in the observation programme. Three of the 46 children were excluded as they did not have 'culture-confirmed' DR-TB; 43 children were included in the outcome assessment (figure 1). Resistance patterns varied. Nine (21%) children had monoresistant *M.tb* bacilli; seven with RIF and two with INH monoresistance. The majority of the children (29/43; 68%) had MDR-TB (resistant to INH and RIF) with 62% (18/29) of the MDR isolates also displaying streptomycin resistance. Four children (9%) had extensively drug-resistant XDR-TB (MDR-TB with additional resistance to a fluoroquinolone and an aminoglycoside). One child (2%) had pre-XDR-TB (MDR-TB with added resistance to either the fluoroquinolones or a second-line injectable agent).

Table 1 shows the baseline characteristics of children enrolled in the observation programme; the median age at enrolment was 3 years (IQR 1.5–6.5 years). The majority (34/41; 83% tested) were HIV uninfected and 57% (4/7) of the HIV-infected children were on ART. The median length of time between referral and examination at KDH was 80 days (60–117 days). The positive fine needle aspiration biopsy was collected from a right axillary node that resolved by the time the patient was examined at KDH. Because the child was asymptomatic, MDR-TB treatment was not commenced and he was included in the observation programme. On presentation, 15 (35%) were on first-line TB treatment—an initial 2-month intensive phase of INH, RIF, pyrazinamide (PZA) and EMB, followed by 4 months continuation phase of INH and RIF. (Children <8 years did not receive EMB). Eight of the children presently on TB treatment had previously been treated for TB.

The median length of follow-up after evaluation was 549 days (IQR 259–722 days), with a minimum observation period of 109 days (table 2). At the final evaluation, 34 (80%) children were well, 7 (16%) had been lost to follow-up, 1 (2%) had been started on DR-TB treatment and 1 (2%) had died. The child started on treatment was 7 years old at the time of enrolment into the observation programme, and was HIV negative with no known close contact with a DR-TB source case. She was well up until the 10-month follow-up visit, but at the 12-month visit the chest radiograph, which had been clear, showed evidence of disease (infiltrates in the right lower lobe). In addition, she was coughing, presented with fatigue and had lost weight. Although sputum taken at this time was smear negative and culture negative, she was started on standard MDR-TB therapy—an initial 6-month regimen of kanamycin, PZA, EMB, ethionamide (Eth), ofloxacin (Ofx) and terizidone (TRD), followed by an 18-month

Figure 1 Schema of enrolment and drug-susceptibility patterns identified in asymptomatic children with culture-confirmed drug-resistant tuberculosis, Durban, South Africa. INH, isoniazid; MDR-TB, multidrug-resistant tuberculosis; Pre-XDR-TB, MDR-TB with resistance to either a fluoroquinolone or an aminoglycoside, but not both; RIF, rifampicin; Strep, streptomycin; XDR-TB, MDR-TB with resistance to both a fluoroquinolone and an aminoglycoside.

INH – isoniazid; RIF – rifampicin; Strep – streptomycin

* Pre-XDR-TB: MDR-TB with resistance to either a fluoroquinolone or an aminoglycoside, but not both.

**XDR-TB: MDR-TB with resistance to both a fluoroquinolone and an aminoglycoside.

continuation phase of PZA, EMB, Eth, Ofx and TRD. She responded well to treatment; completing a full 24-month course. The child who died was 12 months old and had severe cerebral palsy. No DR-TB contact was reported, and her isolate showed resistance to INH, RIF and streptomycin. She was HIV infected and not on ART until shortly before her death. She died from new onset seizures within 9 months of enrolment in the observation programme. No autopsy was performed and the possibility of central nervous system TB could not be ruled out.

DISCUSSION

In this observational study, the vast majority of children with ‘culture-confirmed’ DR-TB who were asymptomatic on presentation at our specialist referral hospital remained well and did not require TB treatment during follow-up. Two points require emphasis. First, the study findings apply to asymptomatic children without any physical or radiological signs suggestive of TB. Second, if a watchful waiting approach is adopted then careful follow-up for a period of at least 12 months should be ensured, and caregivers must be informed that onset of any suspicious symptoms require urgent re-evaluation.

We are uncertain as to why TB culture specimens were collected in these children, as they had no signs or symptoms suggestive of TB on presentation to the specialist hospital. Investigation at the referring facility may have been triggered by another infection such as acute viral or bacterial pneumonia, symptoms associated with recent primary *M.tb* infection (not disease), documented TB exposure or other risk factors.^{10–13} Although routine TB screening is advocated in children with close TB contact and in HIV-infected children, specimens should only be collected in the presence of signs or symptoms suggestive of possible active disease, even if these are of acute

onset.¹⁴ On presentation at KDH, more than a third of children were already on first-line TB treatment and, the possibility of mixed drug-susceptible and drug-resistant *M.tb* strains should be considered. However, mixed infections are highly unlikely in children given the paucibacillary nature of their disease, especially in the absence of visible chest radiograph abnormalities.¹⁵ Given the median delay of more than 2 months, those with monoresistant TB may have responded to first-line TB treatment as could MDR-TB cases with low-level INH resistance and susceptibility to EMB and PZA. Although this delay seems extremely long, delays of this length were not unusual prior to the introduction of Xpert MTB/RIF in South Africa, due to the slow culture process (4–8 weeks), as well as transport and laboratory reporting inefficiencies.^{16–17}

The possibility of inaccurate laboratory results arising from poor specimen labelling, administrative mistakes or specimen contamination should always be considered.^{7–8} Chances of specimen contamination increase in countries with high DR-TB disease burdens, due to the large number and high infectivity of specimens that laboratories process on a daily basis.¹⁸ The laboratory where these samples were processed serves as the provincial reference laboratory and has strict infection control measures. However, no specific protocols were in place to limit contamination of paediatric specimens, such as processing them in a separate room, use of a dedicated paucibacillary safety cabinet or workflow re-arrangement to ensure paediatric specimens are processed early in the morning before working with highly infectious adult specimens.

Detection of *M.tb* in respiratory specimens from asymptomatic children could have different explanations. First, it could be explained by the natural history of infection, since children may transiently excrete live bacilli in the absence of active disease

Table 1 Baseline characteristics of asymptomatic children with 'culture-confirmed' drug-resistant tuberculosis (DR-TB) in Durban, South Africa

Characteristic	Number (%) N=43
Referred from primary clinic	5 (12)
Referred from district hospital	38 (88)
Female	17 (40)
Median age; years (IQR)	3 (1.5–6.5)
Children ≤1 year	4 (16)
Weight <3rd percentile for age	9 (21)
Days from DR-TB diagnosis to KDH examination; median (IQR)	80 (60–117)
<i>TB-related findings</i>	
Signs or symptoms suggestive of TB	0
Abnormal chest radiograph	0
Previous TB treatment*	18 (42)
Presently on TB treatment	15 (35)
Previous TB treatment and presently on TB treatment	8 (19)
Reported contact with infectious MDR-TB source case	3 (7)
Respiratory specimen <i>Mycobacterium tuberculosis</i> positive	42 (98)
Extrapulmonary specimen (FNAB) <i>M. tuberculosis</i> positive	1 (2)
<i>HIV status</i>	
HIV unknown	2 (5)
HIV infected	7/41 (17)
On antiretroviral therapy	4/7 (57)
<i>Drug-resistance profile</i>	
Monoresistant	9 (21)
Isoniazid monoresistant	2 (5)
Rifampicin monoresistant	7 (16)
MDR	29 (68)
Pre-XDR	1 (2)
XDR	4 (9)

*Previous TB treatment refers to any TB episode for which the child received treatment during the course of their life (excluding the current episode). FNAB, fine needle aspiration biopsy; KDH, King Dinuzulu Hospital (specialist TB hospital); MDR, multidrug resistance; resistance to isoniazid and rifampicin; Pre-XDR-TB, MDR-TB with resistance to either a fluoroquinolone or an aminoglycoside, but not both; TB, tuberculosis; XDR-TB, MDR-TB with resistance to both a fluoroquinolone and an aminoglycoside.

following recent primary infection. This phenomenon was first documented in the 1930s when Wallgren recovered *M.tb* from recently infected children who were not clinically diseased.^{10 19} Second, current evidence suggests that latent TB infection is not a single state, but encompasses a spectrum ranging from inactive (latent) *M.tb* infection to periods of subclinical growth that is insufficient to cause lung damage.^{20 21} Third, spontaneous cure is a remote possibility and has been well documented in the pre-chemotherapy era. A recent study from Cape Town traced 17 children with 'culture-confirmed' TB who were discharged from the hospital without TB treatment initiation.¹³ Eight of these children were found in good health, four were lost to follow-up, one died of likely TB bronchopneumonia and two were subsequently started on TB preventive therapy by their local clinic. Whether a completely asymptomatic person with 'culture-confirmed TB', who has no clinical or radiological signs suggestive of active disease, represents a true case of TB, remains open for debate.²² We believe that such children (if laboratory contamination has been ruled out) should be categorised as latent TB infection, rather than TB disease, as has been suggested in a consensus statement on research definitions for DR-TB in children.²³ In TB endemic areas where both primary infection and

Table 2 Clinical course and final outcome of asymptomatic children with 'culture-confirmed' drug-resistant tuberculosis in Durban, South Africa

Clinical course/outcome	Number (%) N=43
<i>Management</i>	
Length of follow-up in days; median (IQR)	549 (259–722)
Minimum period of follow-up (days)	109
<i>Change in weight</i>	
Crossed centile line/s upwards	21 (49)
Same centile line	10 (23)
Crossed centile line/s downwards	4 (9)
No follow-up weight recorded as lost to follow-up or died	8 (19)
<i>Outcome*</i>	
Well	34 (80)
Lost to follow-up	7 (16)
Doing well at 365 days, subsequently lost to follow-up	4 (9)
Started on MDR-TB treatment	1 (2)
Died	1 (2)

*Outcome at final evaluation.

MDR-TB, multidrug-resistant tuberculosis.

reinfection are common,²⁴ a reappraisal of TB case definitions seems warranted.²² The INH monoresistant isolate collected from an axillary lymph node probably was *M. bovis* BCG, only partially identified as *M.tb* complex. Some BCG strains exhibit INH resistance, and BCG vaccination is commonly associated with transient lymphadenitis.

Potential adverse effects should be carefully considered as part of the risk–benefit analysis before second-line TB therapy is commenced in an asymptomatic individual.^{22 25} One of the main reasons for enrolling study participants in an observation programme was the reluctance to use toxic second-line drugs without adequate justification. Serious drug-related adverse effects associated with DR-TB therapy include irreversible hearing loss, hypokalaemia, renal damage, hypothyroidism, depression and psychosis, while unpleasant effects include tinnitus, nausea and vomiting, joint pain, vertigo, peripheral neuropathy, anxiety and confusion.²⁶ In patients with HIV co-infection, adverse events do not appear to be more common, but can be more difficult to diagnose and manage, due to overlapping drug toxicities with ART.^{25 27} While adverse effects associated with DR-TB therapy have been well documented in adults,²⁶ they have been underinvestigated in young children,^{28–30} although treatment appears to be better tolerated than in adults. TB-associated stigma,³¹ prolonged hospitalisation and repeated painful injections may also leave psychological scars. Additionally, because most MDR-TB medications do not have adequate paediatric formulations, adult pills have to be split, crushed or ground up resulting in inaccurate dosing with potentially subtherapeutic or toxic drug levels.^{30 32} Finally, the pill burden in a MDR-TB/HIV co-infected child is excessive and children often experience vomiting and/or diarrhoea, leading to further uncertainty about the actual ingested dose and potentially detrimental impacts on HIV care.³³

Few studies have assessed the management of asymptomatic DR-TB child contacts.²⁸ South African guidelines recommend high-dose INH preventive therapy for DR-TB child contacts ≤5 years; however, the value of this intervention is uncertain²⁸ and adherence to unsupervised preventive therapy is poor.^{34 35} International guidelines and practices vary greatly, from advocating follow-up without medication^{36 37} to the provision of two

drugs to which the source case's strain is susceptible.³⁸ Although preventive therapy based on the likely source case's susceptibility pattern seems logical and its value has been demonstrated in observational studies,^{39–40} the efficacy of MDR-TB prophylaxis has not been confirmed in any randomised control trials.²⁹ Guidelines unanimously advise against the provision of preventive therapy until active disease has been ruled out, which is why we elected to closely monitor these children instead of providing preventive therapy. We acknowledge that preventive therapy may have been appropriate in children with proven *M.tb* infection once active disease was ruled out with certainty.

Our study was limited by its small size and the fact that it was implemented as a pragmatic observational trial in the public sector, a sector with human resource constraints. Although the intention was to monitor children every other month, follow-up was at times inadequate and parents/caregivers were not contacted if a child failed to attend his or her appointment. We used data routinely collected by health workers, which was, at times, incomplete. In addition to the one child who died, three (7%) children were lost to follow-up before 1 year and we were unable to verify if these children had developed DR-TB or died. Nevertheless, a major strength of the study is that it reflects 'real-life' dilemmas, which may not be apparent in a carefully controlled trial setting. We could not secure access to records from referring facilities and were unable to compare specimens collected at the referring centre to those collected at KDH. Only three children were known contacts of MDR-TB cases, but unknown exposure to DR-TB is common in this high burden setting. A detailed assessment of potential laboratory cross-contamination was impossible, due to the time delay and large numbers of samples handled daily at the reference laboratory. The study highlights the importance of meticulous infection and quality control procedures in all TB laboratories, especially in high volume reference laboratories in TB endemic areas.

CONCLUSION

Our findings suggest that careful clinical assessment and close observation is a justifiable option in completely asymptomatic children with a bacteriological diagnosis of DR-TB. They also highlight the need for accurate disease description in the referral letter. It is critically important that practitioners and policy-makers remain aware that a laboratory diagnosis in the absence of a consistent clinical picture may reflect laboratory error, cross-contamination or recent infection (primary or re-infection) in the absence of active disease. In such cases, the risk and cost of unnecessary treatment should be taken into consideration.

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