MALAWI MEDICAL JOURNAL;17(4):119-124
December 2005

Childhood tuberculosis in Malawi: caseload, diagnostic practices and treatment outcomes

AD Harries, SM Graham, MM Weismuller, NJM Claessens, S Meijnen, NJ Hargreaves, C Mwansambo, PN Kazembe, F M Salaniponi

Abstract

There were 22,982 cases of TB registered in Malawi in 1998, of which 2739 (11.9%) were children. Children accounted for 11.3% of all case notifications with smear-positive pulmonary TB (PTB), 21.3% with smear-negative PTB and 15.9% with extrapulmonary TB (EPTB). A significantly higher proportion of TB cases were diagnosed in central hospitals. Only 45% of children completed treatment. There were high rates of death (17%), default (13%) and unknown treatment outcomes (21%). Treatment outcomes were worse in younger children and in children with smear-negative PTB. In 2001, all 44 non-private hospitals in Malawi that register and treat children with tuberculosis (TB) were surveyed to determine actual diagnostic practice. This cross-sectional study identified 150 children aged 14 years or below in hospital receiving anti-TB treatment, 98 with pulmonary TB (PTB) and 52 with extrapulmonary TB (EPTB). Median duration of illness was 8 weeks. Most patients had fever, no response to anti-malarial treatment and antibiotics, and 40% had a positive family history of TB. Nearly 45% had weight for age < 60%. Diagnosis was mainly based on clinical features and radiography, with less than 10% having tuberculin skin tests or HIV serology, and very few having other sophisticated investigations. Diagnostic difficulties make it difficult to accurately define the actual burden of childhood TB in Malawi. Diagnostic practices are poor and treatment outcomes unsatisfactory.

Introduction

In 1997, the sub-Saharan Africa region had the highest case notification rate of TB in the world at 259/ 100,000 population.[1] Malawi is one of the worst affected countries. The focus of National TB Control Programms (NTP) has been on adult TB because adults with smear-positive pulmonary TB (PTB) are the main transmitters of infection in the community. Childhood TB has been a lower priority because it is usually non-infectious and effective control of adult TB will prevent childhood TB. However, case notifications increase despite the implementation of good TB control programmes[2] and childhood TB is an important and increasing clinical problem as a consequence.[3-5] At Blantyre District TB Office, the number of children registered and treated with TB increased from 64 in 1986 to 507 in 1995.[3] Using the recording and reporting system of the Malawi NTP [6], a nation-wide study was undertaken to assess rates, pattern and treatment outcome of childhood TB in different age groups.

The diagnosis of TB in children is very difficult in resource-poor regions such as sub-Saharan Africa.[7] The diagnosis of childhood PTB is usually based on clinical features, a chest x-ray (CXR), a tuberculin skin test and sometimes through identification and/or culture of *Mycobacterium tuberculosis* obtained from sputum. Young children rarely expectorate sputum. Other methods of obtaining sputum have various limitations and are either not widely applied in hospitals in the region or are still limited to the research context.[7-11] Some forms of childhood EPTB are easier to recognise clinically e.g. scrofula or spinal gibbus, but are usually not confirmed microbiologically. The vast majority of childhood TB notifications are therefore not confirmed cases of TB. We conducted a cross-sectional study on a national basis of inpatient children being treated for TB to determine how the diagnosis of TB had been made and whether this varied between different types of hospital.

Methods

All non-private hospitals in Malawi (3 central, 22 districts and 18 missions) were visited in 2000. In each hospital, data were collected retrospectively on all TB patients (adults and children) registered at each hospital between January 1st and December 31st 1998. Children were defined as persons aged 14 years and below. Prior to the hospital visits, TB officers visited all health centres in their district in order to obtain treatment outcome data on childhood cases from health centre registers and treatment cards. These data were entered into the hospital TB registers. Treatment cards were also brought back to the hospital, and these cards along with the TB register were inspected in order to document treatment outcome. A record was made of the TB registration number and month of registration, type of TB, category of TB and final treatment outcome using standardized definitions. Where no treatment outcome was entered in the TB register as a result of no information being available in health centre registers or the treatment card being lost, the outcome was recorded as "unknown". Information was also collected on the type of hospital, and whether the hospital had a medically qualified doctor and/or a specialist paediatrician in 1998. Patient data were collected into structured proformas.

All non-private hospitals were visited again between April and June 2001. Private hospitals were not visited because of very few numbers of patients. All children aged 14 years and below who were registered with TB and were in hospital receiving treatment at the time of the visit were assessed. The following data was collected from the TB treatment card: type and category of TB, BCG vaccination status, age, and weight at the time of starting treatment, number of days on TB treatment and sputum smear results. Case note files were obtained, and a record made about whether an HIV test, tuberculin skin test, sputum induction, or nasopharyngeal/laryngeal/gastric aspiration had been performed. Clinical information was documented from the case note files and from interviewing the parent or guardian who was accompanying the child. Data were obtained on: BCG vaccination status, cough, duration of cough and illness, a positive family history of TB, fever or night sweats before TB treatment started, anti-malarial and/or antibiotic treatment and the response, nutritional treatment and response, results of any investigations and whether a score chart had been used in making the diagnosis. A physical examination of the child was performed. If a CXR was performed, the interpretation written in the case note files by the clinician was recorded. The CXR was obtained, whenever possible, and an independent assessment made by the study team to determine whether the x-ray was a) normal, b) abnormal not consistent with TB or c) abnormal consistent with TB. Radiographic features consistent with TB included:- hilar / mediastinal lymphadenopathy, cavitation, atelectasis, infiltration affecting one or more zones, particularly if bilateral and upper zone in distribution.

Results

Nation-wide survey of childhood TB

There were 22, 982 patients registered with all types of TB, of whom 2739 (11.9%) were children. There were 9462 patients with smear-positive PTB of whom 127 (1.3%) were children, 8453 with smear-negative PTB of whom 1804 (21.3%) were children, and 5067 with EPTB of whom 808 (15.9%) were children. Significantly higher proportions of childhood TB to all TB cases were diagnosed at central (14.5%) and mission (12.3%) hospitals compared with district hospitals (10.0%) and at hospitals where there was a specialist paediatrician (OR 1.66 [1.53-1.8]).

Of the 2739 cases of childhood TB, 2714 (99%) were new cases and 25 were recurrent cases (4 with smear-positive PTB, 17 with smear-negative PTB and 4 with EPTB). There were 1416 boys with TB: 36 (3%) with smear-positive PTB, 942 (67%) with smear-negative PTB and 438 (30%) with EPTB. There were 1323 girls: 91 (7%) with smear-positive PTB, 862 (65%) with smear-negative PTB and 370 (28%) with EPTB. The proportion of smear-positive PTB was significantly higher in girls than in boys. The pattern of EPTB was lymphadenopathy in 331 cases (41% of all EPTB cases), pleural effusion in 101 (12%), spinal disease in 83 (10%), pericardial disease in 60 (7%), ascites in 39 (5%), miliary in 34 (4%), meningitis in 30 (4%), and bone disease in 12 (1%). In 118 cases, the type of EPTB was not indicated in the TB register or the treatment card, and case files could not be found. The pattern of TB in relation to different age groups is shown in Table 1. As age increased there was a significant increase in the proportion of patients with smear-positive PTB ($p< 0.001$), a significant increase in the proportion of cases with EPTB and a significant decrease in the proportion of patients with smear-negative PTB ($p < 0.001$).

Table 1: Pattern of childhood TB in relation to age groups

Age Group:	Male: Female	Total TB	Smear-positive PTB	Smear-negative PTB	EPTB
Under 1 year	185: 151 (1.2:1)	336	0	265 (79%)	71 (21%)
1 - 4 years	688: 591 (1.2:1)	1279	4	919 (72%)	356 (28%)
5 - 14 years	542: 581 (0.9:1)	1124	123 (11%)	620 (55%)	381 (34%)
All age groups	1416: 1323 (1.1:1)	2739	127 (5%)	1804 (66%)	808 (29%)

The three most common types of EPTB in each age group were:

Less than 1 year:	lymphadenopathy in 25 (35%),	pleural effusion in 11 (15%), pericardial disease in 8 (11%)
1 - 4 years:	lymphadenopathy in 154 (43%),	pleural effusion in 40 (11%), spinal disease in 36 (10%)
5 - 14 years:	lymphadenopathy in 152 (40%),	pleural effusion in 50 (13%), spinal disease in 41 (11%)

Results of treatment in all patients and according to age group and type of TB are shown in Table 2. Outcome improved as age increased with 25% of children aged less than one year completing treatment compared with 43% of those aged 1 - 4 years and 54% of those aged 5 years and above ($p < 0.001$). Death rates ($p <0.001$), default rates ($p <0.05$) and unknown outcomes ($p<0.05$) also declined with advancing age. The best outcomes were found in children with smear-positive PTB with treatment completion rates of 76%. The worst treatment outcomes were for patients with smear-negative PTB, while those with EPTB had an intermediate result. In children with EPTB, the proportion of those who completed treatment was 56% for those with TB lymphadenitis, 55% with spinal disease, 48% with pleural effusion, 47% with pericardial effusion, 50% with miliary disease, 44% with ascites and 23% with meningitis. Treatment outcomes improved with increasing age for each type of TB.

Table 2: Treatment outcome for childhood TB

	Smear-positive PTB	Smear-negative PTB	EPTB	Total
All age groups:				
No. registered	127	1804	808	2739
Treatment complete	97 (76%) [a]	750 (42%)	393 (49%)	1239 (45%)
Died	14 (11%)	343 (19%)	119 (15%)	476 (17%)
Defaulted	12 (9%)	246 (14%)	95 (12%)	353 (13%)
Transfer Out	0	68 (4%)	51 (1%)	119 (4%)
Unknown	4 (4%)	397 (21%)	150 (23%)	551 (21%)
Age < 1 year				
No. registered	0	265	71	336
Treatment complete		63 (24%)	20 (28%)	83 (25%)
Died		88 (33%)	19 (27%)	107 (32%)

Defaulted		43 (16%)	14 (20%)	57 (17%)
Transfer Out		13 (5%)	1 (1%)	14 (4%)
Unknown		58 (22%)	17 (24%)	75 (22%)
Age 1 - 4 years				
No. registered	4	919	356	1279
Treatment complete	3 (75%)	383 (42%)	166 (47%)	552 (43%)
Died	0	180 (20%)	56 (16%)	236 (18%)
Defaulted	0	115 (13%)	49 (14%)	164 (13%)
Transfer Out	0	30 (3%)	23 (6%)	53 (4%)
Unknown	1 (25%)	211 (22%)	62 (17%)	274 (22%)
Age 5-14 years				
No. registered	123	620	381	1124
Treatment complete	94 (76%) [a]	304 (49%)	207 (54%)	604 (54%)
Died	14 (11%)	75 (12%)	44 (12%)	133 (12%)
Defaulted	12 (10%)	88 (14%)	32 (8%)	132 (12%)
Transfer Out	0	25 (4%)	27 (7%)	52 (5%)
Unknown	3 (3%)	128 (21%)	71 (19%)	202 (17%)

Treatment complete = completed a full course of treatment; Died = a patient who has died on anti-TB treatment from any cause; Defaulted = not collected drugs for two months or longer; Transfer Out = transferred to another registration unit and the treatment outcome is not known; Unknown = there is no information about treatment outcome.

Cross-sectional study of diagnostic practice

There were 150 inpatient children receiving TB treatment, 72 boys and 78 girls, with a median age of 3 years. 10 children were aged less than one year, 81 aged 1- 4 years, and 59 aged 5 - 14 years. One hundred and eleven (74%) children had received BCG vaccination, 26 (17%) had not received vaccination and in the remainder there was no reliable information. There were 98 children with PTB (all with either no smears done or negative sputum smears) and 52 with EPTB. The 3 most common types of EPTB were - lymphadenopathy in 18 (35%), pericardial effusion in 7 (14%) and spinal disease in 6 (12%). 146 children had new TB and 4 had recurrent disease. The median number of days in hospital on anti-TB treatment was 17.

Clinical features of patients are shown in table 3. The median duration of illness prior to diagnosis was 8 weeks in PTB and 9 weeks in EPTB patients. The median number of days between hospital admission and diagnosis of TB was 8 (range 1 - 87): a median of 8 for central hospitals, 10 for district hospitals and 7 for mission hospitals. Diagnostic investigations in patients with PTB and EPTB in relation to type of hospital are shown in table 4. In children with PTB, the majority had a chest x-ray, but other investigations were rarely performed. Four hospitals only had access to tuberculin skin test reagents, explaining the low percentage of children having such an investigation. In children with EPTB, a higher percentage had tuberculin skin testing. Lymphadenopathy was investigated by needle aspiration and/or biopsy in one third of cases. In all those with pericardial effusion, spinal disease, miliary TB and pleural effusion chest x-rays were done. HIV testing was performed in less than 10% of patients with either PTB or EPTB. Only 4 children who were malnourished prior to the diagnosis of TB were treated in hospital with nutritional supplementation: their failure to respond was an indication for anti-TB treatment. A WHO or slightly modified score chart was used by hospital staff in 13 (9%) patients in 4 mission hospitals.

Of the 93 patients with PTB who had CXR's performed, 7 were lost or of poor quality and could not be assessed by the study team. Of the remaining 86 CXRs, 4 (5%) were judged to be normal, 9 (10%) were abnormal but not consistent with TB, 72 (84%) were consistent with PTB and one CXR was consistent with EPTB. 13 patients with miliary disease, pericardial or pleural effusions had CXRs assessed. 1 (8%) was abnormal but not consistent with TB, 8 (62%) were consistent with EPTB and 4 (30%) CXRs were consistent with PTB.

Table 3: Clinical features in children registered with pulmonary and extra pulmonary tuberculosis

Clinical feature	Pulmonary TB		Extrapulmonary TB	
	Number assessed[a]	No. (%) with clinical feature	Number assessed[a]	No. (%) with clinical feature
Symptoms:				
Cough	98	93 (95%)	52	27 (52%)
Fever / night sweats	98	95 (97%)	52	47 (90%)
Anti-malarial treatment	98	88 (90%)	52	35 (67%)
No Response	88	79 (90%)	35	32 (91%)
Antibiotic treatment	98	98 (100%)	52	47 (90%)
No response	98	93 (95%)	47	45 (96%)
Positive family history of TB	98	40 (41%)	51	18 (36%)

Physical signs:				
Weight for age:	97		50	
< 60%		45 (46%)		21 (42%)
60 - 80%		42 (43%)		25 (50%)
> 80%		10 (11%)		4 (8%)
Lymphadenopathy suggestive of TB	98	5 (5%)	52	20 (38%)
Ascites	98	4 (4%)	52	7 (14%)
Abdominal swelling	98	0	52	2 (4%)
Joint/bone swelling	98	1 (1%)	52	2 (4%)
Spinal deformity	98	0	52	5 (10%)

[a] not all patients had a full assessment

Table 4: Diagnostic practice in TB patients according to type of hospital

	Number (%) of patients	Number (%) in each type of hospital		
		Central	District	Mission
All TB	150	36	74	40
PTB:	98	21	51	26
diagnosis by paediatrician	24 (24%)	21 (100%)	0	3 (12%)
chest x-ray	93 (95%)	20 (95%)	49 (96%)	24 (92%)
tuberculin test	6 (6%)	4 (19%)	1 (2%)	1 (4%)
sputum submission for smears	6 (6%)	0	5 (10%)	1 (4%)
sputum induction	0	0	0	0
nasopharyngeal aspirate	0	0	0	0
gastric aspirate	2 (2%)	0	0	2 (8%)
HIV serology	6 (6%)	1 (5%)	3 (6%)	2 (8%)
EPTB:	52	15	23	14
diagnosis by paediatrician	15 (29%)	15 (100%)	0	0
tuberculin test	6 (12%)	6 (40%)	0	0
sputum submission for smears	3 (6%)	1 (7%)	0	2 (14%)
HIV serology	4 (8%)	2 (13%)	1 (4%)	1 (7%)

percentages refer to percentage of patients with PTB or EPTB in total and within each type of hospital

Discussion

This nation-wide survey shows that nearly 12% of all registered TB cases in Malawi in 1998 were in children. We believe that the results provide an accurate picture of childhood TB notifications and treatment outcomes. However, due to difficulties of diagnosis in children and lack of resources, there is likely to be a significant discrepancy between registered notifications and actual numbers of children with TB. A critical question is whether the findings of this survey represent an under-estimate or over-estimate of the real burden of TB in Malawian children. We reported a marked increase in childhood TB notifications in urban Blantyre from 1986 to 1995 following an increase in cases of adult PTB as the HIV epidemic worsened.[4] Childhood TB case notifications rose proportionately to the total case load and accounted for 24% of all 19,377 TB case notifications, double the rate found in this study. Higher rates in urban populations may reflect increased TB transmission compared to rural regions because of more crowded living conditions. Other important differences include better diagnostic facilities and the presence of paediatricians in the central hospitals, based in Malawi's major cities. Central hospitals recorded significantly higher rates than the district hospitals. Studies of childhood household contacts in Malawi and South Africa have found higher rates of childhood TB.[12,13] Thus, the lack of adequate clinical and diagnostic services throughout Malawi is likely to reduce case detection rates of childhood TB.

Higher rates of TB notifications and poorer outcome occurred in infants and children aged less than 5 years. Early studies of TB epidemiology showed that young age is associated with an increased susceptibility to disease and is an important risk factor for death.[14-16] There is now the additional impact of HIV infection to consider.[17,18] The greatest impact of HIV infection in African children is in children under 5 years of age and as seen in this study, confirmation of PTB cases is very rare in this age group. An unknown but a considerable proportion of cases registered as smear-negative PTB may not have had TB but another HIV-related pneumonia. The epidemiological and clinical overlap of PTB and HIV therefore can lead to an over-diagnosis of TB, particularly by misdiagnosing cases of smear-negative PTB.[18,19].

There is evidence nevertheless that TB is common and increasing in Malawian children rather than simply a rise in cases misdiagnosed as smear negative PTB in a region where childhood HIV and malnutrition are endemic. The predominant types of childhood TB were smear-negative PTB followed by EPTB, with smear-positive PTB being the least common. This would be expected because of acknowledged difficulties in confirming PTB in children too young to expectorate sputum.[7,8] As EPTB is

usually a more straightforward diagnosis than PTB, it has been suggested that the rate of EPTB compared to PTB can be a useful indicator of the real burden of childhood TB.[8] EPTB cases were 29% of all childhood TB notifications in this study, compared to a proportion of EPTB being 17.5% in North American children with TB[20] and 18 -20% in Blantyre from 1986 to 1995.[4] This suggests that PTB is being under-diagnosed in Malawian children. A rise in childhood TB would be expected following an increase in smear-positive adults, such as has occurred in Malawi. Further, the peak prevalence of smear-positive TB is in young adults as a consequence of the HIV epidemic. This further increases the risk to children because of increased exposure as the contact is now often the child's mother.[19,21,22] Indeed, the diagnosis of PTB in young children can be a useful means of identifying smear-positive adults.[23]

The treatment outcome of children with TB for all age groups combined was poor. Only 45% of children completed treatment, and there were high rates of death, default and unknown treatment outcome. Treatment outcomes were worse the younger the child, and worse for patients with smear-negative PTB followed by EPTB. For the small proportion of children with smear-positive PTB, the majority of whom were aged 5 – 14 years, the rate of treatment completion was good and superior to the national rate of 66% in adults registered with smear-positive PTB in 1998 (source: Malawi NTP). Poor treatment outcomes in children with smear-negative PTB and EPTB may relate to younger age, severe disease or to higher HIV prevalence in these groups. HIV infection results in poorer outcomes to TB treatment due to immune suppression, poorer compliance and the fact that many HIV-infected children may not have TB but another HIV-related lung disease.[18,19,21]

This study also highlights the inadequacy of childhood TB diagnosis in Malawi. The majority of children had clinical features suggestive of TB but further investigation was usually limited to the use of CXR which lacks specificity and sensitivity.[7,8]. Tuberculin skin testing was performed in just over 5% of patients, with the majority of hospitals having no reagents. Sputum examination was unusual. Needle aspiration and/or biopsy were only performed in one third of patients with lymphadenopathy. Despite the strong association between a diagnosis of suspected childhood TB and HIV in the region, HIV testing was performed in only 10 patients. A higher proportion of children underwent tuberculin skin testing or lymph node aspiration/biopsy for lymphadenopathy in central hospitals. This partly reflects the fact that central hospitals have better access to diagnostic services, particularly if there is research activity in the department. Such diagnostic services are not routinely available in Malawi.

There is a clear need to improve the diagnosis of childhood TB in Malawi and elsewhere, especially of PTB, preferably with methods that can be applied on a country-wide scale. Alternative methods to gastric aspiration such as induced sputum and laryngeal swabs have been tested to attain sputum from young Malawian children with mixed results, the former showing greater yield than the latter.[9,19] These methods and nasopharyngeal aspiration[11] have shown promise elsewhere, could be adapted at relatively low cost and do not suffer the same constraints that make gastric aspiration difficult to apply as a routine diagnostic procedure. However, there is still the problem of uncertain sensitivity and diminished practical usefulness because such tests tend to identify *M.tuberculosis* on stain much less frequently than by culture.

Should efforts be made to re-introduce tuberculin skin testing on a country-wide basis? Tuberculin reactivity is significantly reduced in HIV-positive children with TB.[18,19,21] Nevertheless, it remains a useful diagnostic technique. In a recent study of Malawian children with suspected PTB, the tuberculin test was positive in 19% of 72 HIV-infected children compared to 50% of 30 HIV-uninfected children. However, almost half of these positive reactions were in HIV-infected children[19]. A non-reactive test does not exclude TB but a positive test is still very useful in the setting of such limited diagnostic options. The majority of PTB patients in this study had undergone a CXR, and in over 80% CXR abnormalities were thought by the study team to be consistent with TB. However, the CXR in childhood TB is non-specific.[8] This is compounded by HIV infection, which predisposes to diseases such as LIP that may easily be mistaken for TB.18 Up to 10% of children with culture-positive PTB may also have a normal chest x-ray.[8] Thus, undue reliance on CXR as a diagnostic tool in an HIV endemic region will lead to misdiagnosis.

It is reasonable to consider that HIV testing be an integral part of the diagnostic work-up of children with suspected TB living in HIV endemic regions. Trials of treatment should not be used as a diagnostic aid, and NTP policy in Malawi, understandably, does not allow early cessation of TB treatment. It is also recognised that some HIV-infected children with confirmed TB have a poor response to TB treatment[18,19,21], and so treatment may be stopped inappropriately. Some types of EPTB could be diagnosed with more precision. Needle aspiration and biopsy of enlarged lymph nodes are useful adjunctive investigations in children presenting with lymphadenopathy[21]. These diagnostic procedures should be used more frequently even in peripheral hospitals.

In high TB burden countries, the focus of TB control efforts has been on the adult with infectious TB, and there is little doubt that this is the best means of preventing TB in childhood. Childhood TB will continue to tax both the clinician and the NTP and efforts need to be made now to improve diagnostic practices. The added difficulties of diagnosis in HIV endemic regions should not detract from this challenge. Why are treatment outcomes in children so poor? Operational research should determine whether this is due to poor compliance or poor treatment response. The potential of chemoprophylaxis in select groups of children demands a much more active approach. Identification and management of childhood contacts should be part of routine management of smear-positive PTB cases and incorporated into the DOTS approach.

Acknowledgements

We thank all the TB officers, clinical officers and nurses from around the country that assisted with interviews of children and their parents or guardians. We also thank the Department for International Development (DFID), UK, the Norwegian Agency for Development Cooperation (NORAD) and the Royal Dutch Tuberculosis Association (KNCV) for financial support. The study received the support of the TB Programme Steering Group and ethical approval from the Malawi Health Science Research Committee.

SM Graham, AD Harries, MM Weismuller, NJM Claessens, S Meijnen, NJ Hargreaves, F M Salaniponi

Wellcome Trust Research Laboratories and Department of Paediatrics,

College of Medicine, Blantyre, Malawi (SM Graham FRACP); National Tuberculosis Control Programme, Community Health Science Unit, Private Bag 65, Lilongwe, Malawi (Prof AD Harries FRCP, NJ Hargreaves MRCP, FM Salaniponi PhD).

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