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Rifampicin-mono-resistant *Mycobacterium tuberculosis* disease among children in Cape Town, South Africa

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SUMMARY

SETTING—Tygerberg Children's Hospital (TCH) and Brooklyn Chest Hospital (BCH), South Africa.

OBJECTIVES—To describe paediatric cases of rifampicin (RMP) mono-resistant tuberculosis (RMR-TB) disease.

DESIGN—Records of children with culture-confirmed RMR-TB between 1 March 2003 and 28 February 2009 were identified from a prospectively recorded database of drug-resistant TB at TCH and BCH. Mutation analysis was performed on available specimens.

RESULTS—Eighteen children with a median age of 6.9 years (range 2 months–12.8 years) were identified. Nine (50%) were human immunodeficiency virus (HIV) infected and four (22%) were HIV-exposed but non-infected. Eleven (61%) had had previous TB treatment or prophylaxis. Nine children (50%) had cavitary disease and five children (22%) had extra-pulmonary disease. Twelve (67%) had adult TB source cases, including five (42%) adults with known RMR-TB. Primary transmission occurred among 11 children (61%) and acquisition of RMR-TB was possible in seven (39%) with prior RMP exposure. Median delay to specific RMR-TB treatment was 70 days (range 23–188). One child died from RMR-TB meningitis. Gene mutations consistent with RMR-TB were confirmed in five available samples.

CONCLUSION—RMR-TB disease is increasingly encountered, particularly among HIV-infected and HIV-exposed non-infected children. Delay in commencing appropriate treatment for RMR-TB and high rates of cavitary disease could be a source of RMR-TB transmission.

Keywords

TB; HIV; rifampicin; rifampicin mono-resistance; drug-resistant TB

GLOBAL ESTIMATES suggest that 11% of tuberculosis (TB) disease occurs in children.¹ In South Africa, the TB incidence rate is approximately 600 cases per 100 000 children aged <2 years.² South Africa also faces the world's largest human immunodeficiency virus (HIV) epidemic,³ with an estimated 280 000 HIV-infected children, who are at increased risk of developing TB. The prevalence of childhood HIV infection is estimated at approximately 1% in the Western Cape Province.⁴ Among HIV-infected infants a 24-fold increased risk of TB disease is reported, with an incidence rate of 1596 cases/100 000 HIV-infected infants.⁵ Drug-resistant TB (DR-TB) disease in children is usually contracted by primary transmission from an adult DR source case;^{6,7} however, acquired TB drug resistance (as a result of inconsistent, inadequate or inappropriate TB drug exposure) may also occur. Global epidemiological trends in adults reflect a marked increase in prevalence of DR-TB strains. As a consequence of adult-to-child TB transmission, the drug susceptibility profile of paediatric TB disease is also evolving.

In Cape Town, Western Cape Province, most positive *Mycobacterium tuberculosis* culture specimens in children are collected from two referral hospitals, Tygerberg Children's Hospital (TCH) and Red Cross Children's Hospital. A review of culture-confirmed TB at these institutions from March 2003 to February 2005 yielded 596 culture-positive TB cases, with 67 (11.3%) DR isolates: 43 (7.3%) isoniazid (INH) monoresistant, 2 (0.3%) rifampicin (RMP) mono-resistant (RMR) and 22 (3.7%) multidrug-resistant (MDR).⁸ A more recent DR-TB survey at TCH only (March 2005 to February 2007) included 43 DR isolates among 291 culture-confirmed TB cases (15.1%), including 22 (7.7%) INH-monoresistant, 2 (0.7%) RMR and 19 (6.7%) MDR.⁷ HIV prevalence was respectively 22.3% and 26.6%, with no significant association of HIV infection with DR-TB disease in the latter survey. Two previous surveys of primary DR-TB from the Western Cape Province of South Africa revealed no cases of RMR-TB among children.^{6,9}

Prevalence estimates of RMR-TB among adult populations are limited, but case series of RMR-TB have been described in Burundi,¹⁰ Botswana,¹¹ Brazil¹² and the United States.¹³ Local surveillance data on RMR-TB prevalence reflecting the historical rarity of isolating this strain of DR-TB¹⁴ are minimal; however, a recent Western Cape survey reports a steady increase of RMR-TB disease in adults.¹⁵ To the best of our knowledge, no reports on the incidence, prevalence or clinical characteristics of RMR-TB in children have been published.

RMP is one of the most effective bactericidal and sterilising anti-tuberculosis drugs. Resistance to RMP is conferred by mutations in the *rpoB* gene, encoding the RNA polymerase beta subunit. Despite wide-spread use of RMP for treatment of TB, cases of RMR-TB remain rare. Possible explanations for the paucity of RMR-TB strains include the use of companion anti-tuberculosis drugs, such as INH,¹⁶ and the lowest rate of spontaneous drug resistance-conferring mutations of all the anti-tuberculosis agents (naturally occurring drug resistance mutation rates 1 in 10⁸ for RMP).¹⁷ RMP resistance usually follows INH

resistance as the protective effect of INH is lost. Another theory is that RMR strains readily develop further antibiotic resistance, representing an intermediate susceptibility pattern that is temporally difficult to isolate.¹⁶

Variable RMP dosing, impaired absorption, altered metabolism and HIV infection are independent risk factors for RMR-TB disease in adults.^{18,19} Intermittent (once- or twice-weekly) RMP-containing regimens have been shown to be associated with increased rates of RMR-TB,^{20,21} particularly in homozygous rapid INH acetylators, whereas daily RMP-containing treatment regimens protect against development of new RMR-TB strains.²² Drug malabsorption or poor bioavailability of some products may result in subtherapeutic RMP serum levels, with the risk of developing RMP resistance.²³ Intestinal uptake of RMP is also variable, as shown in animal models where the presence of efflux-mediators (p-glycoproteins) may result in poor drug bioavailability.²⁴ A rising incidence of RMR-TB strains among HIV-infected populations has been recognised,^{18,25–27} and may be a result of the permissive effect of immunosuppression, allowing persistence and proliferation of mycobacteria with reduced fitness.¹⁶ Risk factors associated with paediatric RMR-TB are unknown.

Although rare, RMR-TB poses a significant challenge to TB control programmes. A previous study of TB treatment outcomes found RMR-TB to be associated with extended treatment duration, elevated therapeutic cost and excessive mortality and failure rates.²⁸ Long periods of latency, the propensity for clinically silent infections and the lack of drug susceptibility testing (DST) facilities hamper recognition of RMR-TB cases in the developing world.

The aim of this study was to identify and describe all cases of paediatric RMR-TB managed over a 6-year period at a dedicated TB referral hospital and a paediatric referral hospital in the Western Cape Province of South Africa.

METHODS

Setting

The study was performed at TCH, a paediatric referral hospital and Brooklyn Chest Hospital (BCH), a TB referral centre in Cape Town, South Africa.

Laboratory testing

Smear microscopy for acid-fast bacilli (AFB) was performed on any lung fluid specimen (e.g., sputum and gastric aspirate). All paediatric TB diagnostic samples were submitted to the National Health Laboratory Service for DST. Initial screening was performed for INH and RMP resistance only. When resistance to INH and/or RMP was found, then DST for ethambutol (EMB), ethionamide (ETH) and other second-line anti-tuberculosis agents was performed.

Laboratory procedures for determining drug resistance were as follows: Middlebrook 7H12 (BACTEC, BD Biosciences, Sparks, MD, USA) culture medium was used for selective primary isolation of mycobacterial strains. The niacin production test or polymerase chain

reaction was used to identify *M. tuberculosis*. Prior to August 2008, DST was performed using the indirect proportion method. The susceptibility of a strain was interpreted as susceptible or resistant by determining the proportion of bacilli resistant to a specific drug in comparison with growth on a specific control using international criteria. Resistance was defined as $\geq 1\%$ bacterial growth. Quality assurance for DST was done locally with every batch, and quarterly by the national tuberculosis reference laboratory. After August 2008, DST of positive mycobacterial cultures was performed using the genotypic line-probe assay (LPA; GenoType® MTBDR_{plus}, Hain Lifesciences, Nehren, Germany). Phenotypic INH DST was performed on isolates showing RMR on LPA to confirm INH susceptibility. Where clinical samples from this retrospective cohort were available, gene sequencing was also performed to confirm presence of the *rpoB* gene mutation, indicative of RMP resistance, and absence of INH resistance mutations, *inhA* and *katG*.

Clinical data

All DR-TB cases have been prospectively recorded in a database at TCH since the year 2000. All children with culture-confirmed RMR-TB disease referred to TCH and BCH between 1 March 2003 and 28 February 2009 were retrospectively identified from this database. The clinical records of children with RMR-TB were retrieved and data extracted on demographics, contact with an adult with smear- or culture-positive pulmonary TB, history of previous TB chemoprophylaxis or treatment, clinical features and weight at presentation, Mantoux tuberculin skin test (TST) results, chest radiograph (CXR) appearance, HIV status and antiretroviral treatment (ART) status, TB disease manifestations and final outcome. All children included were observed for at least 6 months following initiation of treatment for RMR-TB disease. TST (per-formed with 2 tuberculin units of purified protein derivative RT23), with induration diameter of ≥ 10 mm (≥ 5 mm in HIV-infected children) was interpreted as a positive reaction. Delays were defined as follows: time to culture positivity as time from specimen collection to culture positivity; time to specific RMR treatment as time from specimen collection to starting RMR treatment; and time to first negative culture (usually performed monthly) as time from starting RMR-specific treatment to first culture-negative result, whereafter cultures remained negative.

Statistical analysis

A database of categorical and numerical variables was created using Microsoft Excel spreadsheets (Microsoft, Redwoods, WA, USA). Frequency distributions, and parametric and non-parametric measures of central tendency were calculated using the STATA 10 statistical software package (Stata Corp, College Station, TX, USA).

Ethical approval

The study was approved by the Faculty of Health Sciences Committee for Human Research at Stellenbosch University (Project Number N08/10/297).

RESULTS

Culture-confirmed RMR-TB disease was identified in 18 children, with 16 (89%) identified in the second half of the 6-year study period (Figure). The median age at TB diagnosis was

6.9 years (range 2 months to 12.8 years). Nine children (50%) were HIV-infected, of whom 1 was already receiving ART and 8 were commenced on ART after TB diagnosis. TST was reactive in 5 (38%) of the 13 children in whom it was performed. Demographic, clinical and laboratory data are summarised in Tables 1 and 2.

History of TB contact and previous TB treatment

Of the 18 children, 12 (67%) had known exposure to an adult TB case; in all 12, the adult case was the child's primary care giver. In 5/12 (42%) children, the DST from the adult source case also showed RMR-TB. Of the 12 adult source cases, 7 (58%) had a history of previous TB treatment, and 7 (58%) adult cases were known to be HIV-infected. Four of the 12 (25%) adult source cases had died from TB disease (1 with RMR-TB, 1 with drug-susceptible TB [DS-TB] and 2 with unknown DST) at the time of the child's diagnosis.

Of the 18 children, 9 had received previous treatment for presumed DS-TB, 1 had received MDR prophylaxis, 1 had received INH+RMP prophylaxis and 7 had no history of prior TB treatment or prophylaxis. Of the 9 children previously treated for TB, 3 (33%) had received more than 1 course of prior TB treatment. In 8/9 children (89%), TB treatment for presumed DS-TB was completed less than 6 months before RMR-TB diagnosis was confirmed. Two of the nine children had a history of defaulting from a previous course of TB treatment. The child who had received MDR chemoprophylaxis for 2 months (with INH, ofloxacin [OFX] and EMB) was converted to RMR-TB treatment after the DST results became available. Another child had received 3 months of INH+RMP chemoprophylaxis from birth (mother died from DS-TB) before being diagnosed a year later with RMR-TB.

Microscopy, culture and gene sequencing results

Thirteen children (72%) had smear-positive pulmonary TB disease (Table 2); of these, six had cavities present on CXR and eight were HIV-infected.

DST was performed on one or more samples from each of the 18 children. All initial samples were RMP-resistant and INH-susceptible. In three cases, DST was repeated on a second sample, confirming RMR. In further efforts to validate RMR-TB diagnoses, five available samples were submitted for gene sequencing, confirming the presence of the *rrpB* gene mutation and the absence of *inhA* and *katG* gene mutations.

DST changed on multiple follow-up isolates for two patients. One HIV-infected child previously had confirmed DS-TB and was treated with a 6-month first-line regimen, but ART was not started. Despite adherence to treatment, she returned 3 months later with RMR-TB and a CD4 count of 0.8% (total count 16 cells/ μ l). She was also found to be a fast acetylator of INH (not a routinely performed test). The combination of advanced HIV disease and rapid break-down of INH could have led to the development of RMR-TB. Another child was non-HIV-infected, but defaulted from TB treatment several times over a period of 3 years, eventually evolving from RMR-TB to MDR-TB.

Time to RMR-TB confirmation, duration of hospitalisation and RMR treatment regimen

While empirically started on DS-TB treatment, the cohort's median time to RMR culture positivity was 45 days (interquartile range [IQR] 28–62). The median time delay to starting RMR-specific treatment from TB diagnosis was 70 days (IQR 23–188). Children were hospitalised for a median of 175 days (IQR 54–282). In addition to 4 months of an injectable aminoglycoside (amikacin), the cohort typically received INH, EMB, ETH, pyrazinamide and OFX. In four cases, terizidone was added for extensive cavitory disease on CXR or pre-existing chronic lung disease. RMR-TB treatment was continued for a minimum of 18 months, initially in hospital and then as out-patient directly observed therapy. The median time to first negative culture result was 75 days (IQR 25–79). Four children culture-converted prior to initiation of the RMR-specific TB treatment regimen; however, no child continued on DS-TB regimens after identification of an RMR-TB isolate.

Possible risk factors for the development of RMR-TB disease

Of the 18 children, 5 (28%) had contact with an adult RMR-TB case, 2 (11%) had contact with an adult TB case who died with unknown DST, 13 (72%) resided in an HIV-affected household (includes HIV-infected and HIV-exposed non-infected children); 4/9 (44%) HIV-infected children had severe immunosuppression ($CD4 < 15\%$), and 2/9 (22%) children with previous TB had a history of malabsorption, vomiting or diarrhoea during past treatment.

Treatment outcome

Sixteen children were cured (with at least two consecutive negative TB cultures prior to treatment completion), one child was transferred to another hospital before treatment completion, and one non-HIV-infected child died from complications of TB meningitis. Of the 16 children who were cured, 5 (28%) had residual chronic lung disease.

DISCUSSION

Data in adults have demonstrated a steady increase in RMR-TB disease in the Western Cape¹⁵ and elsewhere,^{10,12,13} particularly among HIV-infected populations. This previously rare form of DR-TB is increasingly being isolated among children in Cape Town, with almost 90% of RMR cases identified in the latter half of the study period. Our paper reports the first published series of paediatric RMR-TB disease in an HIV- and TB-endemic region.

We documented significant TB exposure, with 67% of primary care givers receiving anti-tuberculosis treatment at the time of the child's diagnosis. There was concordance with the adult source case and the child's DST in 42% of cases, suggesting primary transmission of the RMR strain. In these five children and an additional six children without previous RMP exposure, primary transmission of RMR-TB is likely (11/18, 61% of cohort.) This is in contrast to RMR-TB in adults, which usually reflects acquired drug resistance. The remaining 7/18 children (39%) had failed previous TB treatment or RMP-containing prophylaxis and may possibly have had acquired RMR-TB disease. Six cases had completed a previous TB treatment regimen, with full adherence, less than 6 months before RMR-TB diagnosis. In these cases, undiagnosed RMR-TB and receipt of inadequate treatment is a more likely explanation than reinfection, as has been shown in other cohorts.⁸

As this is a retrospective case series, it is difficult to comment on missed opportunities for TB prophylaxis, as many children were initially managed at community level. In previous studies at the same institution, missed opportunities for chemoprophylaxis were present in 117/182 (64.3%) children aged <5 years.⁸ It is likely that the same may be true for this cohort of children in whom there were 12 known adult TB source cases.

A high frequency of cavitation (50%) was noted on CXRs in this cohort. As documented in earlier studies,⁸ cavitory disease was more common among immunocompromised children (7/9; 78% were HIV-infected or HIV-exposed, non-infected). The ages of children with or without cavitory disease were similar. The higher rate of cavitation in HIV-infected children may be due to uncontained progressive disease that is not effectively managed or other concomitant lung pathology.

Mortality in this cohort was low, which may be partly explained by the universal ART coverage after RMR-TB diagnosis among the nine HIV-infected children. Other reports of childhood MDR-TB have demonstrated good outcomes with appropriate treatment regimens.^{6,29} Morbidity, however, was substantial, with 5/18 (28%) having residual chronic lung disease despite cure of RMR-TB. This may have been complicated by pre-existing lung disease in three children with underlying HIV infection.

Significant delays in the identification of RMR by DST and transition to an appropriate RMR-TB treatment regimen were identified in this case series. These delays occurred despite a well-functioning health system and an efficient laboratory service, highlighting the difficulty of identifying DR-TB in children. The affected children had prolonged hospitalisation and treatment, with implications of increased costs to health care and opportunity costs to their families. The availability of rapid diagnostic tests for DST may improve the time to diagnosis of DR-TB.

Understanding of the factors that promote development of RMR-TB is limited, and the only available data come from adult studies in HIV-infected populations. Although limited by the small numbers reported in this series, the major risk factor for children appears to be residence in an HIV-affected household (with consequent high exposure to DR-TB infected adults).

This study has several limitations, including possible selection bias (only children treated at BCH and TBH were included; however, the majority of DR-TB would be managed at these two institutions), interobserver variability (data were collected by different physicians in different hospitals), lack of a comparator/control group of DS-TB and limited generalisability owing to the small sample size and limited time period.

Despite these limitations, we believe that several important learning points are illustrated by these cases. Clinicians should always attempt to establish the DST of an adult source case, so as to reduce delay in commencing appropriate treatment in potentially DR child TB cases. DST should be routinely requested in children from TB-and HIV-endemic settings in view of the rising rates of DR-TB. Clinicians should be aware of the greater risk of DR-TB, especially among children from HIV-affected households. New modalities for rapid DST,

such as the genotypic LPA, should be made more accessible to reduce delays in starting appropriate treatment in DR cases.

The apparent increase in RMR-TB warrants on going local and national surveillance. Larger, prospective studies are required to inform best practice of RMR-TB treatment for children. The possible role of HIV in promoting the evolution of RMR-TB and other forms of DR-TB should be explored.

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Figure.

Timeline of RMR-TB cases. RMR-TB = rifampicin-monoresistant TB.

Table 1Demographic, clinical and laboratory data of paediatric RMR-TB cases ($n = 18$)

Feature	<i>n</i> (%)
Male sex	11 (61)
Age at initial TB diagnosis, years	
0–<5	8 (44)
5–<10	4 (22)
10–<15	6 (34)
HIV status	
Positive	9 (50)
Exposed, non-infected	4 (22)
Negative	5 (28)
Nutritional status (WAZ score)	
>0	1 (6)
0 to –2	8 (44)
>–2	9 (50)
Common presenting symptoms	
Loss of weight/failure to thrive	12 (66.7)
Cough >2 weeks	12 (66.7)
Fever	9 (50)
Radiographic features	
Hilar lymphadenopathy	14 (78)
Lobar opacification	14 (78)
Cavitation	9 (50)
Pleural effusion	5 (28)
Large airway compression	5 (28)
Miliary pattern	3 (17)

RMR-TB = rifampicin-mono-resistant TB; TB = tuberculosis; HIV = human immunodeficiency virus; WAZ = weight-for-age Z-score.

Table 2

Clinical and laboratory characteristics of 18 children with RMR-TB disease

No.	Sex	Age months	HIV status	Absolute CD4 count	Source case DST	Source case HIV status	Type of TB disease	Site of EPTB	AFB smear	Cavities on CXR	Previous TB treatment or prophylaxis	Previous regimen(s)	Compliance with previous treatment or prophylaxis	Treatment completion to RMR diagnosis, months	Suspected source of RMR-TB disease	Final outcome
1	M	41	Positive	310	DS	Positive	PTB		Positive	Yes	Treatment	RHZ	Unknown	4	ACQ	RES
2	M	121	Negative			Negative	PTB		Negative	No	None				PRIM	CLD
3	M	122	Negative				PTB		Positive	Yes	Treatment	RHZ /2 then RHZE	Poor	0	ACQ	RES
4	F	14	HEU		MDR	Positive	PTB		Positive	No	MDR prophylaxis	HEO	Good		PRIM	RES
5	M	2	HEU		RMR	Positive	PTB		Positive	No	None				PRIM	RES
6	M	80	Positive	589	RMR	Positive	PTB		Positive	No	Treatment	RHZ	Good	3	PRIM	RES
7	M	8	Negative		RMR	Unknown	PTB		Negative	No	None				PRIM	RES
8	F	154	Positive	31	Unknown	Unknown	PTB-EPTB	ABD	Positive	Yes	None				PRIM	RES
9	M	118	Positive	—	RMR	Unknown	PTB		Positive	No	Treatment	RHZE	Good	5	PRIM	CLD
10	M	4	Negative				PTB		Positive	No	None				PRIM	TFO
11	F	124	Positive	455			PTB		Positive	Yes	Treatment	RHZ /2	Unknown	5	ACQ	RES
12	M	121	Positive	—	Unknown	Unknown	PTB-EPTB	ABD LAD	Negative	Yes	None				PRIM	CLD
13	M	96	HEU		Unknown	Positive	PTB-EPTB	MIL	Positive	No	None				PRIM	RES
14	F	10	Positive	477			PTB		Positive	Yes	Treatment	RHZ	Unknown	16	ACQ	CLD
15	M	112	Positive	22	RMR	Positive	PTB-EPTB	PERIMIL	Positive	No	Treatment	RHZ	Good	5	PRIM	RES
16	F	21	Positive	16			PTB		Positive	Yes	Treatment	RHZE then RHZ	Poor	3	ACQ	RES
17	F	81	HEU		DS	Positive	PTB-EPTB	TBMMIL BM	Not performed	Yes	Prophylaxis	RH	Good		ACQ	Died
18	F	13	Negative		Unknown	Unknown	PTB		Negative	Yes	Treatment	RHZ	Good	5	ACQ	CLD

RMR-TB = rifampicin-mono-resistant TB; HIV = human immunodeficiency virus; DST = drug susceptibility testing; TB = tuberculosis; EPTB = extra-pulmonary TB; AFB = acid-fast bacilli; CXR = chest X-ray; M = male; PTB = pulmonary TB; R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; ACQ = acquired; RES = full resolution; PRIM = primary; CLD = chronic lung disease; HEU = HIV-exposed non-infected; MDR = multidrug-resistant; 0 = ofloxacin; ABD = abdominal; LAD = lymphadenitis; TFO = transferred out before treatment completion; MIL = miliary; PERI = pericarditis; TBM = TB meningitis; BM = bone marrow.