2 Hurwitz BJ. Analysis of current multiple sclerosis registries. *Neurology* 2011; 76: Suppl. 1, S7–S13.
3 Tantucci C, Massucci M, Piperno R, *et al.* Control of breathing and respiratory muscle strength in patients with multiple sclerosis. *Chest* 1994; 105: 1163–1170.
4 Buyse B, Demedts M, Meekers J, *et al.* Respiratory dysfunction in multiple sclerosis: a prospective analysis of 60 patients. *Eur Respir J* 1997; 10: 139–145.
5 Mutluay FK, Gürses HN, Saip S. Effects of multiple sclerosis on respiratory functions. *Clin Rehabil* 2005; 19: 426–432.
6 Smeltzer SC, Utell MJ, Rudick RA, *et al.* Pulmonary function and dysfunction in multiple sclerosis. *Arch Neurol* 1988; 45: 1245–1249.
7 Howard RS, Wiles CM, Hirsch NP, *et al.* Respiratory involvement in multiple sclerosis. *Brain* 1992; 115: 479–494.
8 Kuwahira I, Kondo T, Ohta Y, *et al.* Acute respiratory failure in multiple sclerosis. *Chest* 1990; 97: 246–248.
9 Benditt JO. Esophageal and gastric pressure measurements. *Respir Care* 2005; 50: 68–75.
10 Talmor D, Sarge T, Malhotra A, *et al.* Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359: 2095–2104.

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Multidrug-resistant tuberculosis in UK children: presentation, management and outcome

To the Editor:

Multidrug-resistant tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, is an increasing problem globally [1]. Children are not usually included in global surveys of MDR-TB incidence and prevalence [2] due to the diagnostic challenges of paucibacillary TB [3]. Data on the burden of MDR-TB in children are, therefore, lacking globally [1, 4, 5] and no published data from the UK exist. The current World Health Organization (WHO) [6] and National Institute for Clinical Excellence (NICE) [7] TB guidelines for the management of MDR-TB do not explicitly address paediatric disease. As a consequence, the complex management of this condition is left to individual clinicians' judgment. In general, childhood TB is paucibacillary, most cases are treated on clinical grounds without drug susceptibility testing [2], and correct and timely diagnosis of childhood MDR-TB is therefore challenging. There are limited data on the pharmacokinetics, dosing and safety of the many second-line drugs used to treat MDR-TB in children [5]. Our group is the first to review the management of a paediatric cohort with MDR-TB in the UK, and represents the largest available dataset from children with culture-confirmed MDR-TB from western Europe and North America published to date.

We conducted a retrospective audit of children diagnosed with culture confirmed MDR-TB between January 1, 2006 and December 31, 2010 and summarise presentation, management and outcome of this cohort. Data were included if the subjects were under 16 years old and had culture-confirmed MDR-TB reported to the Health Protection Agency (HPA). Additional, fully anonymised data, including HIV status, country of child and parents' birth, radiology, history of previous treatment for TB, symptoms, management, duration of therapy, use of directly observed therapy (DOT), duration of hospital admission and follow-up were obtained. Results of drug susceptibility testing for first- and second-line drugs, using the resistance ratio (proportion) method, were obtained from the UK Mycobacterial Surveillance Network [8, 9]. All second line antibiotic susceptibility testing was carried out by the supra-national laboratory. The period of follow-up was 2 years from the time of presentation.

The following definitions were used. Culture-confirmed MDR-TB cases: children who were symptomatic and had culture-confirmed *M. tuberculosis* resistant to rifampicin and isoniazid. Favourable treatment outcome: clinical and radiological resolution of symptoms and treatment completion 24 months post commencing MDR-TB treatment, as reported by the treating clinician. Treatment delay: the time from start of presentation to hospital to initiation of MDR-TB treatment.

17 children with culture-confirmed MDR-TB were notified between 2006–2010. The median age was 13 years (range 1–15 years) and the majority were female (13 out of 17). Details of the cases are presented in table 1.

There were few reported side-effects of treatment. Para-aminosalicylic acid was poorly tolerated by three of the four children who received it; two children had gastrostomy tubes inserted for treatment purposes and one developed hypothyroidism.

Since it was conducted as an audit, a limitation of our study is the retrospective nature of the collected data from multiple centres and HPA with some data gaps. Furthermore, due to the small sample size, caution should be exercised when generalising these results to a wider or future population of MDR-TB paediatric cases.

Nevertheless, although clinical practice showed considerable variability, our cohort seemed to have had favourable outcomes and few side-effects were reported. Most clinicians treating this cohort adhered to the WHO guidelines for programmatic management of drug-resistant tuberculosis, published in 2011 [6], which recommend (based on low quality evidence) the use of four second-line anti-tuberculous drugs that are likely to be effective, including a parenteral agent. However, many of the children were initially started on drugs that were found to be ineffective once drug sensitivity testing data became available. Of the children with available data regarding length of treatment, many received treatment for less than the 20 months recommended for adult patients.

TABLE 1 Details of the 17 cases of children with culture-confirmed multidrug-resistant tuberculosis (MDR-TB) notified between 2006–2010

Age years, Sex, Ethnicity	Country of birth	HIV Status	Contact	a) TST[#] b) IGRA c) prior TB treatment	CXR	a) Signs and symptoms b) site of disease	a) Smear[¶] b) culture[+]	Resistance profile	a) Treatment delay b) MDR regimen c) duration of MDR treatment	Outcome at 24 months post treatment start: a) clinical b) radiological
12, F, Black African	Somalia	Negative	Not known	a) Positive b) 1st negative, 2nd positive c) No	Abnormal	a) Cough, fever, weight loss, night sweats, lethargy, lymphadenopathy b) Pulmonary, extra pulmonary	a) Negative (x3 gastric washings) b) Positive (FNA of lymph node)	R, H	a) 9 weeks b) Z, E, Mfx, Pto, Amk c) Not known but Amk 4 weeks	a) No symptoms and signs b) Not known
13.5, F, Indian	India	Negative	Not known	a) Positive b) Positive c) No	Abnormal	a) Cough, fever, chest pain, b) Pulmonary	a) Positive b) Positive	R, H	a) 3 days b) Mfx, Amk, H, Z, E, Pto. H stopped after 9 days c) Not known	a) No symptoms and signs b) Normal CXR 1 year into treatment
10.2, M, Indian	UK	Negative	Not known	a) Positive b) Positive c) Yes	Abnormal	a) Cough, fever, weight loss, night sweats, lethargy b) Pulmonary	a) Positive b) Positive	R, H, E, S, Eto, Mfx, Ofx, Pto	a) 8 months b) Amk Pto, Mfx, Cs. PAS c) Not known	a) Not known b) Not known
14.8, F, Congolese	Not known	Negative	Close social[§]	a) Not known b) Not known c) No	Abnormal	a) Cough, fever, weight loss, night sweats, lethargy, lymphadenopathy b) Pulmonary	a) Positive b) Positive	R, H, Eto	a) 2 months b) Mfx, Amk, E, Z, PAS c) Minimum of 1 year	a) Not known b) Not known
10.6, F, Black African	Cote D'Ivoire	Positive	Not known	a) Negative b) Indeterminate c) No	Abnormal	a) Cough, fever, weight loss, night sweats, lethargy, lymphadenopathy b) Pulmonary, meningitis	a) Positive (broncho-alveolar lavage, lymph node, spleen) b) Positive	R, H, Eto, S, Pto	a) 6 weeks, b) Mfx, Clr, E, Z, PAS c) 2 years	a) Residual haemiplegia b) Hydrocephalus stable not shunted but died of acute hydrocephalus 10 months after stopping TB treatment (2 years 10 months after commencing treatment)
9, F, Somalian	Somalia	Not known	Not known	a) Positive b) Not known c) No	Normal	a) Fever and lymphadenopathy b) Extra pulmonary	a) Negative b) Positive (FNA of lymph node)	R, H	a) 6 weeks b) S, Pto, Cip, E c) Not known	a) No symptoms and signs b) Normal CXR.
15, F, Pakistani	UK	Not known	Not known	a) Not known b) Not known c) No	Not known	a) Not known b) Pulmonary	a) Negative b) Positive	R, H, E, Eto	a) Not known b) Mfx, Clr, Z, S then Z, Cs, Cm. Cip c) Not known	a) Not known b) Not known
13, F, Other	Afghanistan	Not known	Not known	a) Positive b) Positive c) Yes	Abnormal	a) Cough, haemoptysis b) Pulmonary	a) Positive b) Positive	R, H, E, Eto, S	a)1 month b) Amk,Clr, Mfx. Pto, PAS started, 4 months into treatment c) Not known	a) Had intermittent cough symptoms but repeat cultures negative b) Residual bronchiectasis on CXR
15, F, Pakistani	UK	Not known	Not known	a) Not known b) Not known c) No	Not known	a) Not known b) Pulmonary	a) Positive b) Positive	R, H, E, S	a) Not known b) Not Known c) Not known	a) Not known b) Not known
8, F, Indian	UK	Not known	Not known	a) Positive b) Not done c) No	Normal	a) Right sided facial swelling b) Extrathoracic lymph nodes	a) Not known b) Positive	R, H, Eto Pto, S	a)Not known b) Not known c) Not known	a) No symptoms and signs b) Not known
13, F, Black African	Netherlands	Not known	Not known	a) Not known b) Not known c) Yes	Not known	a) Not known b) Pulmonary and intrathoracic lymph node	a)Positive b) Positive	R, H, Eto, Pto, S	a) Not known b) E, Amk, Cs, Mfx, Z. Amk stopped after 6 months. c) Treatment only for 1 year.	a) Not known b) Not known
2, M, Black African	UK	Not known	Not known	a) Not known b) Not known c) No	Not known	a) Not known b) Intrathoracic lymph nodes	a) Negative b) Positive	R, H, E, Eto, Amk, Km, Cm	a) No delay b) Amk, Cs, Mfx, Pto along with H R E Z. 3/52 later H, E, R and AmK stopped as resistant. S added and then stopped after 1/52 c) 18 months	a) Not known b) Not known
8, M, Mixed/Other	UK	Not known	Not known	a) Not known b) Not known c) No	Not known	a) Not known b) Pulmonary	a) Not known b) Positive	R, H	a) Not known b) Not known c) 22 months	a) Not known b) Not known
13, F, Indian	India	Not known	Not known	a) Not known b) Not known c) No	Not known	a) Not known b) Pulmonary	a) Negative b) Positive	R, H, E, Z, S, Eto, Pto, Mfx	a) Not known b) First line drugs only. No changes recorded. c) 2.5 years (total treatment)	a) Not known b) Not known
15, M, Black African	Somalia	Not known	Not Known	a) Not known b) Not known c) Not known	Not known	a) Not known b) Pulmonary	a) Positive b) Positive	R, H, E, Z, S	a) Not known b) Not known c) 14 months	a) Not known b) Not known
15, F, Black African	Zambia	Not known	Not known	a) Not known b) Not known c) No	Not known	a) Not known b) Pulmonary	a) Negative b) Positive	R, H	a) Not known b) Not known c) Not known	a) Not known b) Not known
1, F, Black African	UK	Negative	Family	a) Not done b) Positive c) No	Abnormal	a) None b) Pulmonary	a) Not done b) Positive	R, H, E, Eto, Pto, S	a) No Delay b) Amk, Cs ,Z, Mfx c) 18 months but had Amk for 6 weeks only)	a) No symptoms or signs b) CXR normal

TST: tuberculin skin test; IGRA: interferon gamma release assay; CXR: chest radiograph; Not known: data unavailable from contributing centre; FNA: fine needle aspirate; R: Rifampicin; H: Isoniazid; Z: Pyrazinamide; E: Ethambutol; Mfx: Moxifloxacin; Pto: Prothionamide; Amk: Amikacin; S: Streptomycin; Eto: Ethionamide; Ofx: Ofloxacin; Cs: Cycloserine; PAS: Para-aminosalicyclic acid; Clr: Clarithromycin; Cip: Ciprofloxacin; Cm: Capreomycin; Km: Kanamycin. [#]: a positive TST result is defined as induration $\geqslant$15 mm if there was a previous history of BCG vaccination, otherwise $\geqslant$6 mm is interpreted as positive [7]; [¶]: microscopy for acid fast bacilli on sputum samples; [+]: culture growth of *M. tuberculosis* from diagnostic samples, including samples not derived from sputum; [§]: Close social contact defined as non-family member with culture positive MDR-TB with more than 8 h of close contact with case.

Whether the same length of treatment is indeed needed for children is currently unknown and represents an important knowledge gap, requiring further research. South African guidelines on the management of MDR-TB in children [10] recommend using daily treatment with DOT. The NICE guidelines [7] for the UK and the WHO [6] guidelines for management of drug resistant TB do not explicitly address DOT, and only four children in our culture confirmed MDR-TB cohort were known to have received DOT.

To date, few papers [4, 5] have reported descriptively on paediatric MDR-TB cohorts with largely favourable outcomes. A systematic review and meta-analysis of treatment outcomes for children with MDR-TB [5] described a pooled treatment success, defined as a ''composite of cure and treatment completion as defined by the studies'', of 81.7%, with a mortality of 5.9% and 6.2% default of treatment, which is similar to that seen in our study, which however, did not have any defaulters.

All but three (17%) of our culture-confirmed MDR-TB children lacked a known index case, unlike the 45% with an identified index case reported by SEDDON *et al.* [4], who cite absence of a known MDR-TB source case as a factor leading to delay in starting appropriate treatment. This highlights the importance of improved reverse contact tracing to identify a source case, especially in the absence of an isolate from the child. Few children had a previous diagnosis of TB, suggesting that most children acquire an already-resistant strain from their index case, rather than developing resistance through poor adherence to treatment.

Our work has highlighted that no prospective data collection tool currently exists in the UK able to collate information on children managed for MDR-TB, exposure, infection or disease, making it difficult to establish an evidence base for management guidelines. Currently, each case will need to be assessed, preferably by a team of experts, on an individual basis. We propose the creation of such a data collection tool in order to form a resource for assessment of management and outcomes of children with MDR-TB. Such data should include active cases, as well as management of latent TB infection with presumed MDR-TB strains, and MDR-TB-exposed children of various age groups, since evidence-based guidance is urgently needed for all of these groups potentially affected by MDR-TB.

Bhanu Williams*, Shiva Ramroop[#], Pooja Shah[¶], Laura Anderson[+], Sreena Das[§], Anna Riddell[§], Sue Liebeschuetz[§], Robin Basu Roy[ƒ], Maria O'Callaghan[§], Katherine Sloper, Jolanta Bernatoniene[##], Delane Shingadia[#] and Beate Kampmann[ƒ,¶¶]**

*North West London Hospitals NHS Trust, London, [#]Great Ormond Street Hospital, London, [¶]Imperial Healthcare NHS Trust, London, [+]Health Protection Agency, London, [§]Barts Health NHS Trust, London, [ƒ]Imperial College London, London, **Ealing NHS Trust, London, and [##]Bristol Royal Hospital for Children, Bristol, UK. [¶¶]MRC Unit, Fajara, The Gambia.

Correspondence: B. Williams, Northwick Park Hospital, NWLH NHS Trust, Watford Road, Harrow, HA1 3UJ, UK. E-mail: bhanu.williams@nhs.net

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REFERENCES

1 Gandhi NR, Nunn P, Dheda K, *et al.* Multi-drug resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet* 2010; 375: 1830–1843.
2 Sandgren A, Cuevas LE, Dara, *et al.* Childhood tuberculosis: progress requires an advocacy strategy now. *Eur Respir J* 2012; 40: 294–297.
3 Marais BJ, Hesseling AC, Gie RP, *et al.* The bacteriological yield in children with intrathoracic tuberculosis. *Clin Infect Dis* 2006; 42: e69–e71.
4 Seddon JA, Hesseling AC, Willemse M, *et al.* Culture-confirmed multi-drug resistant tuberculosis in children: clinical features, treatment and outcome. *Clin Infect Dis* 2012; 54: 157–166.
5 Ettehad D, Schaaf HS, Seddon JA, *et al.* Treatment outcomes for children with multi-drug resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; 12: 449–456.
6 Falzon D, Jaramillo E, Schünemann HJ, *et al.* WHO Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011; 38: 516–528.
7 National Institute for Health and Clinical Excellence. CG117. Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for its Prevention and Control. http://publications.nice.org.uk/tuberculosis-cg117/guidance Date last accessed: December 19, 2012. Date last updated: March 23, 2011.
8 Drobniewski FA, Caws M, Gibson A, *et al.* Modern laboratory diagnosis of tuberculosis. *Lancet Infect Dis* 2003; 3: 141–147.
9 Pedrazzoli D, Kruijshaar M, Anderson L, *et al.* Tuberculosis in the UK: 2011 Report. London, Health Protection Agency, 2011. Available from: www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1317131784267 Date last accessed: December 19, 2012. Date last updated: December 16, 2011.
10 Al-Dabbagh M, Lapphra K, McGloin R, *et al.* Drug-resistant Tuberculosis: Pediatric Guidelines. *Pediatr Infect Dis J* 2011; 30: 501–505.

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