Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

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Summary

Background **Paediatric multidrug-resistant (MDR) tuberculosis is a public health challenge of growing concern, accounting for an estimated 15% of all global cases of MDR tuberculosis. Clinical management is especially challenging, and recommendations are based on restricted evidence. We aimed to assess existing evidence for the treatment of MDR tuberculosis in children.**

Methods **We did a systematic review and meta-analysis of published and unpublished studies reporting treatment outcomes for children with MDR tuberculosis. We searched PubMed, Ovid, Embase, Cochrane Library, PsychINFO, and BioMedCentral databases up to Oct 31, 2011. Eligible studies included five or more children (aged ≤16 years) with MDR tuberculosis within a defined treatment cohort. The primary outcome was treatment success, defined as a composite of cure and treatment completion.**

Results **We identified eight studies, which reported treatment outcomes for a total of 315 patients. We recorded much variation in the characteristics of patients and programmes. Time to appropriate treatment varied from 2 days to 46 months. Average duration of treatment ranged from 6 months to 34 months, and duration of follow-up ranged from 12 months to 37 months. The pooled estimate for treatment success was 81·67% (95% CI 72·54–90·80). Across all studies, 5·9% (95% CI 1·3–10·5) died, 6·2% (2·3–10·2) defaulted, and 39·1% (28·7–49·4) had an adverse event. The most common drug-related adverse events were nausea and vomiting. Other serious adverse events were hearing loss, psychiatric effects, and hypothyroidism.**

Interpretation **The treatment of paediatric MDR tuberculosis has been neglected, but when children are treated outcomes can be achieved that are at least as good as those reported for adults. Programmes should be encouraged to report outcomes in children to improve the knowledge base for care, especially as new drugs become available.**

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Introduction

An estimated 12 million people worldwide have tuberculosis, of whom about 650 000 have multidrug-resistant (MDR) disease.[1] Childhood tuberculosis is estimated to account for 10–15% of the global tuberculosis burden,[2] and probably accounts for a similar proportion when considering only drug-resistant disease. The highest rates of paediatric MDR tuberculosis are reported in low-income countries,[2] and in some regions the incidence of MDR tuberculosis has risen sharply in the past two decades—eg, in the Western Cape, South Africa, the proportion of culture-confirmed cases of tuberculosis with multidrug-resistance has tripled in the past 15 years from 2·3% to 7·3%.[3]

MDR tuberculosis is underdetected in children. Diagnosis of drug resistance needs mycobacterial culture and drug susceptibility testing (DST),[4] but the difficulty in obtaining respiratory secretions, such as sputum or gastric aspirates, or specimens of extrapulmonary tuberculosis from young children,[5] along with the fact that up to half of all children with a clinical diagnosis of tuberculosis disease are smear-negative and culture-negative, makes microbiological confirmation challenging.[6] Strict programmatic requirements for microbiological confirmation of drug resistance combined with insufficient recognition of the importance of taking into account DST patterns from adult source cases can lead to substantial delays in diagnosis and initiation of appropriate treatment.[7] These delays could lead to progression of disease, increased risk of infectiousness of children, greater risk of disease complications such as tuberculous meningitis, and higher rates of morbidity and mortality.[8,9]

Paediatric drug-resistant tuberculosis is a neglected concern, with few children being treated relative to the estimated disease burden.[10] WHO guidelines for the treatment of drug-resistant tuberculosis in adults are based on evidence from meta-analyses of individual patients' data.[11] However, recommendations for children are based on expert opinion, drawing on data from case series and cohort studies,[12,13] often with small sample sizes. Consequently, variation exists in programmatic choices of treatment regimens, with the choice of drugs informed by previous drug exposure and DST results.[14] Because of uncertainties about diagnosis and the best treatment regimens, and concerns about the toxic effects associated with MDR tuberculosis treatment, health-care providers are cautious about treating paediatric MDR tuberculosis.

We did a systematic review and meta-analysis of the available evidence for treatment outcomes in children

with MDR tuberculosis, and assessed the characteristics of patients and studies that could have affected treatment success.

Methods

Search strategy and selection criteria

We searched for publications in PubMed, Ovid, Embase, Cochrane Library, PsychINFO, and BioMedCentral databases up to Oct 31, 2011. We developed a highly sensitive search strategy, using a combination of the search terms "tuberculosis", "multidrug resistance", "multidrug-resistant", "treatment outcomes", and "children", both as exploded MESH headings and free-text terms. We reviewed the bibliographies of all retrieved articles. We also searched all electronically available conference abstracts from the International Union Against Tuberculosis and Lung Disease (2004–11). Authors of relevant studies were contacted for clarification and additional information when necessary. We applied no language restriction to our search of abstracts.

Two investigators (DE, NF) reviewed all abstracts and full-text articles, with final inclusion decided through consensus. In cases of disagreement, consensus was achieved through third-party arbitration (GSC), including verification with the study authors when needed. Studies were eligible if they included more than five children (aged ≤16 years) within a defined treatment cohort. In anticipation of a paucity of data, case series of five or more children were also included. Patients meeting the following criteria were viewed as having MDR tuberculosis: Patients meeting the following criteria were viewed as having MDR tuberculosis: the provision of second-line drugs together with either clinical evidence of tuberculosis and a known contact with MDR disease or confirmed MDR DST result from a *Mycobacterium tuberculosis* isolate.

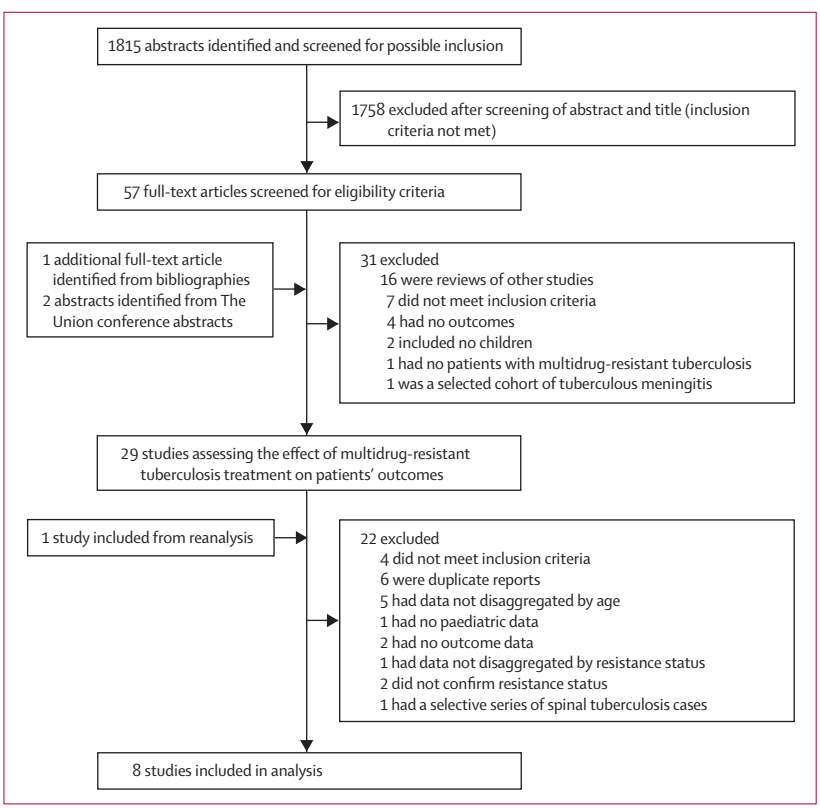

Figure 1: **Study selection process**

Data extraction

We extracted data from the eligible studies independently and in duplicate. Our primary outcome was treatment success. We recorded treatment outcomes according to WHO classifications of treatment success (cure, completion, or both), death, and default (defined as all patients lost to follow-up).[11] Success was defined as a composite of cure and treatment completion as defined by the studies. Intermediate outcomes were probable cure or failure according to the investigator's classification and were subsequently added to the success and failure categories, respectively. All patients transferred out of the reporting treatment facility were regarded as having defaulted treatment, consistent with other MDR tuberculosis outcome reviews.[15] Secondary outcomes were death, defaulting, and adverse events. For each study we collected information about the characteristics of patients (age, HIV status, previous treatment, and drug resistance), studies (setting, treatment protocols, average number of drugs in the regimen, treatment duration, length of follow-up, and whether the treatment was individualised or standardised), and study outcome definitions. We extracted the following information as determinants of study quality that could have affected treatment success: delivery of individualised treatment regimens guided by DST, use of injectable drugs, admission to hospital at the initiation of treatment, treatment completion rates, and provision of treatment support.

Statistical analysis

We calculated point estimates and 95% CIs for the proportion of patients achieving treatment success and the frequency of adverse outcomes. Treatment success was estimated conservatively, with all treatment defaults regarded as treatment failures. We stabilised the variance of the raw proportions using a Freeman-Tukey-type arcsine square-root transformation[16] and calculated pooled estimates using a DerSimonian and Laird random-effects model.[17] We ran a sensitivity analysis on our primary outcome using a Bayesian random-effects model with Monte Carlo Markov chain simulations of variability.[18] We calculated the τ^2 statistic to assess the proportion of overall variation attributable to between-study heterogeneity, because this measure is less sensitive to the number of studies,[19] and explored potential sources of heterogeneity with univariate

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sensitivity analyses with χ^2 to estabish the potential effect of the following covariates: DST confirmatory testing (≤50% or >50% of the cohort), treatment duration (≤ 18 months or >18 months), use of injectable drugs (≤80% or >80% of the cohort), age (≤ 5 years or >5 years), and HIV status (≤30% or >30% of the cohort). All p values are two-sided, and a p value of less than 0·05 was regarded as significant. We did analyses using Stata (version 12) and MetaAnalyst (version Beta 3.13).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The eight studies included in our analysis (figure 1) came from individual treatment programmes from five countries (Peru,[20] Spain,[21] the USA,[22,23] South Africa,[7,24,25] and Latvia[26]) and reported on treatment outcomes for a range of eight patients[21] to 111 patients.[24] One study was a conference abstract;[26] the rest were published as full text articles.

Studies were done in a range of settings, including countries with high[7,21,24,25] and low[17,22,23,26] MDR tuberculosis burdens. The median age of children ranged from 25 months[25] to 132 months[20] and HIV seropositivity ranged from 0%[22] to 54% (table 1).[25] In four studies, most children were reported to have been in contact with an adult with MDR tuberculosis (table 1).[7,20–22] The proportion of previously treated patients ranged from 0%[21] to 87%[20] (table 1).Duration of treatment ranged from 6 months to 34 months,[22] and in most studies treatment was provided for a minimum of 18 months, which is consistent with WHO recommendations (table 2).[7,20,22,24] Median duration of follow-up, reported by four studies, ranged from 12 months[25] to 36·7 months (table 2).[7] Time to appropriate treatment varied from 2 days[7] to 46 months.[20] All studies provided individualised treatment regimens guided by DST and reported high rates of treatment completion, and most studies[7,20–22,24–26] provided injectable drugs to most patients (table 2). For most patients, treatment was initiated in hospital (table 2).[7,20,21,23–25] Insufficient data were available for outcomes for treatment with extensively drug-resistant tuberculosis to be included in this review.

Across all studies that used second-line drugs in individualised protocols (315 children), most children had

	Location	Tuberculosis prevalence in country (2010)[1]	Total confirmed MDR cases in country (2010)[1]	Setting	Median age (months [range])	Sample size	HIV positive	Culture-positive tuberculousis	Pulmonary tuberculosis	Extra-pulmonary tuberculosis	Number previously treated	Number in contact with an adult with MDR tuberculosis
Schaaf et al (2003)[7]	Western Cape, South Africa	400 000	7386	Hospital and clinic	74·4 (4·8–194·4)	39	6 (15%)	39 (100%)	37 (95%)	18 (46%)	17 (44%)	27 (54%)
Drobac et al (2006)[20]	Lima, Peru	34 000	1048	Ambulatory care (after initiation)	132 (24–168)	38	2 (5%)	30 (79%)	NS	5 (13%)	34 (87%)	27 (71%)
Granich et al (2005)[23]*	California, USA	15 000	92	NA		10	NA	NA	NA	NA	NA	NA
Mendez Echevarria et al (2007)[21]	Madrid, Spain	8400	49	Ambulatory care (after initiation)	48 (6–180)	8	1 (13%)	5 (63%)	7 (88%)	1 (13%)	0	4 (50%)
Feja et al (2008)[22]	New York, USA	15 000	92	Chest clinics (Department of Health sites, municipal hospital clinics, private doctors)	32·4 (0–178)	20	0%†	6 (30%)	16 (80%)	4 (20%)	NS	13 (65%)
Leimane et al (2009)[26]	Latvia	970	87	NS	NS	76	0	NS	NS	NS	NS	NS
Fairlie et al (2011)[25]	Johannesburg, South Africa	400 000	7386	Hospital	25 (5–84)	13	7 (54%)	13 (100%)	NS	NS	2 (15%)	0
Seddon et al (2011)[24]	Western Cape, South Africa	400 000	7386	Hospital and clinic	50 (IQR 19–108)	111	43 of 100 (43%)	111 (100%)	99 (89%)	38 (34%)	28 (25%)	45 (41%)

Data are number or number (%) unless otherwise stated. MDR=multidrug-resistant. NA=not applicable. NS=not stated. *Additional data provided by authors. †Data available for only three patients.

Table 1: **Characteristics of included studies**

	Time to appropriate treatment	Median (range) number of drugs given	Main drugs used	Duration of treatment	Duration of follow-up	Individualised treatment guided by DST	Number (%) of injectable drugs in regimen	Number (%) admitted to hospital at initiation	Provider of directly observed treatment	Treatment support provided	Definition of cure
Schaaf et al (2003)[7]	2 days if contact with MDR tuberculosis; 246 days if drug susceptibility of source unknown; 283 days if no known source	NS	Am, Cfz, Cs, E, Eto, H, Km, Ofx, S, Thz, Z	9–12 months after the last positive culture, depending on disease severity	Median 14·8 months (range 0–36·7) for individuals not lost to follow-up before end of treatment	Yes (34)	20 (56%)	23 (64%)	Health-care providers or community volunteers	NS	All children followed up clinically and radiologically for as long as possible; follow-up cultures during and towards end of treatment to confirm cure
Drobac et al (2006)[20]	Median 6·5 months (range 0–46)	6·5 (5–9)	First-line drugs, injectables, fluoroquinolones	18–24 months with at least 12 consecutive months of negative cultures	NS	Yes (28 of 38)	38 (100%)	17 (45%)	Nurse or community health worker	Nutritional and economic support	Minimum of 12 months with negative cultures and sustained radiographical and clinical improvement (weight gain and resolution of presenting symptoms)
Granich et al (2005)[23]*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Mendez Echevarria et al (2007)[21]	NS	NS	Am, Cfx, Cs, E, Eto, H, Lfx, PAS, Z	15·1 months (range 12–18)	Minimum 18 months after diagnosis	Yes (five from the child patients and three from the source case)	5 (63%)	All patients admitted to hospital for 3 weeks	Nurse	Social support	All patients followed up for at least 18 months with clinical examinations
Feja et al (2008)[22]	NS	5 (1–12)	Cs, Eto, quinolones, Z	18·8 (range 5·7–33·6)	NS	Yes (19 of 20)	7 (35%)	NS	Health-care provider or outreach worker	NS	NS
Leimane et al (2009)[23]	NS	5 (4–7)	NS	12·5 (range 10–20)	NS	Yes (18 of 76)	74 (97%)	76 (100%)	NS	NS	NS
Fairlie et al (2011)[25]	2·5 months (range 0·3–15)	NS	Am, E, Eto, Km, Ofx, Z	NS	12 months after initial investigation	Yes (10 of 13)	NS	7 (54%)	NS	NS	Culture-negative by 12 months (treatment continued to end of study)
Seddon et al 2011)[24]	Median 91 days (IQR 51–166); 58 days if MDR tuberculosis index cases; 123 days without index case	7 (4–13; for patients successfully treated)	Am, Cs, E, Eto, H, Ofx, Trd, Z	18 months (range 8–26) for patients successfully treated	All patients followed up for 1 year after the completion of treatment	Yes (103 of 111)	105 (95%)	Almost all treated initially in hospital	NS	NS	Negative results of three consecutive respiratory cultures obtained at least 1 month apart, with no positive culture results after the first negative result

Am=amikacin. Cfx=ciprofloxacin. Cfz=clofazimine. Cs=cycloserine. E=ethambutol. Eto=ethionamide. DST=drug susceptibility testing. H=isoniazid (given at high dose [15–20 mg/kg bodyweight]). Km=kanamycin. Lfx=levofloxacin. MDR=multidrug-resistant tuberculosis. NS=not stated. Ofx=ofloxacin. PAS=para-aminosalicylic acid. S=streptomycin. Thz=thiacetazone. Trd=terizidone. Z=pyrazinamide. *Additional data provided by authors.

***Table 2*: Details of treatment provided**

successful treatment (τ^2 200·7; figure 2). Our pooled estimate changed little when we used a Bayesian approach (successful treatment in 80·1% of patients, 95% credible intervals 67·0–92·0). In subgroup analysis, treatment success was higher for studies in which most patients were treated with injectable drugs (87·2%, 95% CI

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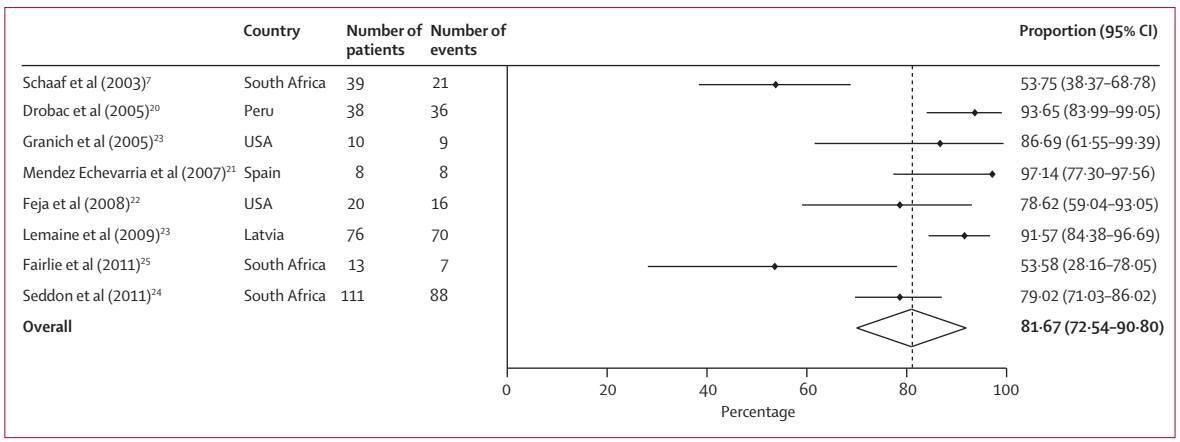

Figure 2: **Proportion of patients achieving treatment success**
Weighted according to random-effects analysis.

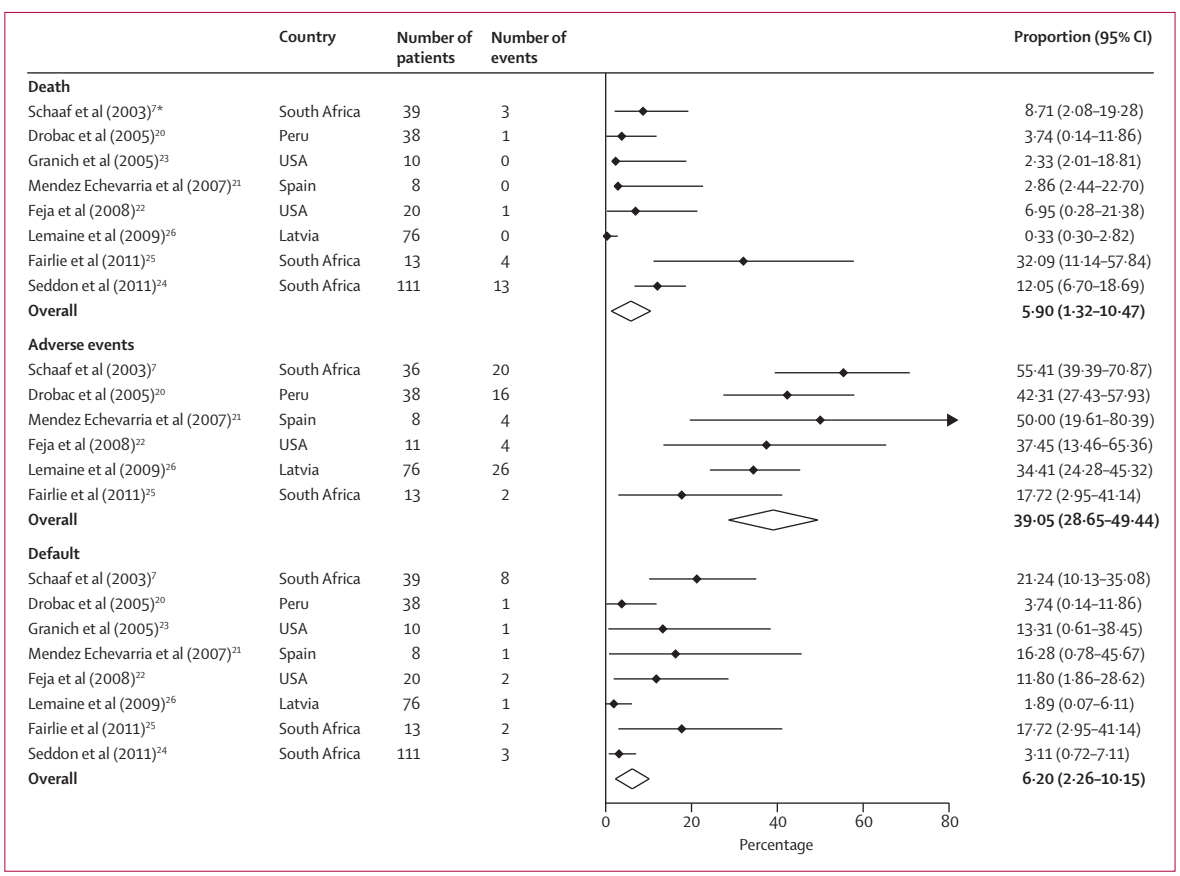

Figure 3: **Secondary outcomes**
Weighted according to random-effects analysis. *Study reported one additional death unrelated to tuberculosis.

74·7–99·8%) compared with studies in which injectable drugs were used rarely (62·6%, 45·3–80·0%; p=0·02)—the effect of all other covariates (DST confirmatory testing, treatment duration, age, and HIV status) on treatment success were non-significant, but the small sample size prevents us from making any firm conclusions.

22 deaths were reported across all studies, giving an overall pooled proportion of 5·9% (1·3–10·5). 19 children were reported to have defaulted from care across all studies, giving a pooled proportion of 6·2% (2·3–10·2).

Adverse events, reported by six studies (182 patients),[7,20–22,24,26] were common, with a pooled

	Adverse events (n [%])	Drugs potentially implicated
Schaaf et al (2003)[7]	Nausea (4 [3%]) Vomiting (17 [44%]) Gastrointestinal discomfort (14 [4·1%])	Ethambutol, ethionamide Ethambutol, ofloxacin Ethionamide
Drobac et al (2006)[20]	Gastritis (12 [31·6%]) Loss of high frequency hearing (2 [6·7%]) Nephrotoxicity (asymptomatic creatinine rise; 1 [2·6%]) Psychiatric effects (depression, anxiety, and hallucinations; 4 [10·5%]) Hypothyroidism (3 [7·9%]) Hypersensitivity rash (1 [2·6%]) Hypokalaemia (1 [2·6%])	Ethionamide Streptomycin Streptomycin Cycloserine Ethionamide Not stated Streptomycin
Mendez Echevarria et al (2007)[21]	Raised creatine kinase (1 [12·5%]) Temporary achilles tendinitis (1 [12·5%]) Abnormality of visual evoked potential without clinical repercussion (1 [12·5%]) Transitory psychosis (1 [12·5%])	Amikacin Levofloxacin Ethambutol Cycloserine
Feja et al (2008)[22]	Hypothyroidism (1 [9·1%]) Blurred vision (1 [9·1%]) Hearing loss (1 [9·1%]) Muscle pain (1 [9·1%]) Raised liver function test results (1 [9·1%]) Gastrointestinal upset (1 [9·1%]) Loss of appetite and abdominal pain (1 [9·1%])	Ethionamide, para-aminosalicylic acid Cycloserine Capreomycin Capreomycin Not stated Not stated Not stated
Leimane et al (2009)[26]	Not stated	..
Fairlie et al (2011)[25]	Angioedema (1 [10·0%]) Hearing loss (1 [10·0%])	Rifampicin Amikacin
Seddon et al (2011)[24]	Not stated	..

Table 3: **Adverse events**

proportion of children having an adverse event of 39·05% (28·7–49·4; figure 3). In most studies, children were screened clinically on a regular basis (of varying regularity in the different studies), with investigations requested if any concerns were raised. The most frequently reported drug-related adverse event was nausea (table 3). Other serious adverse events were hearing loss, psychiatric effects, and hypothyroidism. For minor adverse events, treatment could largely be continued without the need to stop any drugs. For the more severe adverse events, treatment with the drug thought to be causing the adverse effect was discontinued, and the patient was switched to an alternative treatment.

Discussion

Our systematic review suggests that MDR tuberculosis can be successfully treated in children, with the overall proportion of children achieving treatment success as good as, if not better than, that reported for adults receiving individualised treatment regimens (64%).[15] Mortality and defaulting seemed to be lower for children than for adults, but these differences were not statistically significant.

Detailed data for adverse events were absent from some studies, and adverse events were not systematically recorded in most studies. Nevertheless, more than a third of children had adverse events. This finding draws attention to the urgent need for more effective drugs, paediatric formulations of drugs, and a better understanding of the best possible dosing in children. Previous studies have reported a lower incidence of adverse events to second-line drugs in children than in adults.[27] In one study,[28] investigators compared incidences of adverse events between adults and children, recording rates of gastritis and psychiatric effects in adults to be about three times that of children who received similarly aggressive individualised regimens within the same series. We were unable to compare the prevalence of adverse events for children and adults because summary estimates were not available for adults.[15,29]

In line with expert opinion[30] and reviews,[31] our subgroup analysis suggested that the use of injectable drugs was associated with improved treatment outcomes for paediatric MDR tuberculosis. The best possible duration of treatment for MDR tuberculosis is not established, and recommendations are largely based on expert opinion.[30] The duration of treatment reported for children in this review was on average less than that reported for adults.[15,27] The paucibacillary nature of MDR tuberculosis in many children implies that bacillary clearance can be faster in children than in adults,[7] although one of the studies included in this study had very high rates of smear-positive disease, most likely because of progression of disease before MDR tuberculosis was diagnosed.[24] Shortening treatment duration is an important goal for MDR tuberculosis management programmes,[32] and fewer drugs and shorter treatment durations (12 months compared with 18 months for adults) can potentially suffice in early, non-extensive childhood disease.[33] Future research should further assess the potential for shorter treatment as a method to limit costs and adverse events,

especially because improvements in diagnostics might increase the number of individuals needing treatment.[34]

The average time to initiation of appropriate treatment ranged from 2·5 months to 9·2 months, with the long delays probably caused by challenges in the confirmation of diagnosis. Such delays before appropriate treatment draw attention to the need to develop rapid, reliable, and affordable tuberculosis diagnostics for children.[35] If programmes were to treat more children and need less stringent proof of MDR tuberculosis, then treatment could be started earlier for children, which might improve outcomes. For this to happen, substantial changes in treatment practices would be needed, whereby children with clinical tuberculosis and an MDR contact would be initiated on MDR tuberculosis treatment while awaiting microbiological test results with the assumption that the disease is likely to be MDR tuberculosis. At present, such children are started on first-line treatment while waiting for microbiological drug-resistant confirmation or clinical failure. However, because available drugs are associated with a high frequency of adverse events, such a strategy might become more feasible when new, less toxic drugs become available.

Our study has several strengths and limitations. We used a random-effects analysis and subgroup analyses in anticipation of heterogeneity. We also used a broad and inclusive search strategy, but cannot rule out the risk of publication bias. Several limitations also exist in the available evidence base. All studies included in our analysis were observational, and thus subject to potential bias as a result of unmeasured variables that could have affected outcomes, such as level of health-care provider, and programme inputs (eg, such as material and social support for patients). Another limitation is that we were able to do a meta-analysis of only aggregate data; a meta-analysis of individual patients' data could be expected to provide further information about clinical determinants of treatment success.[36] The small amount of data from a few published paediatric cohorts leads to poor precision of overall estimates and limits the generalisability of findings. Nevertheless, the decision to pool data through meta-analysis was based on the value of the provision of a more precise estimate for treatment success compared with that reported by individual studies.[37] Programmes should be encouraged to report outcomes to improve the knowledge base for care, especially because new drugs will become available. Although major adverse events are likely to be well recorded,[38] under-reporting of minor toxic effects in observational studies might lead to underestimation in our meta-analysis. Generally, however, estimates of the frequency of adverse events derived from observational studies are equivalent to those reported from trials.[38] Another limitation is the difficulty in identifying the drug that causes a particular adverse event, because children were treated with multiple drugs with overlapping toxicities.

Our findings draw attention to the urgent need to encourage more reporting of outcomes for children with MDR tuberculosis. We identified several reports that had to be excluded because data were not clearly disaggregated by age, which was a missed opportunity.[39,40] Furthermore, the discrepancies in the recording of study characteristics for paediatric treatment regimens draws attention to the need for the standardisation of the data collection process and reporting in programmes of childhood tuberculosis.[41] Although substantial progress has been made in the harmonisation of the definitions of cure for adult MDR tuberculosis during the period covering the included studies,[42] the definition is not suitable for paediatric disease. The absence of this definition means that study comparisons need to be interpreted with caution and that a standardised definition is needed to improve the comparability of the results of future research and programme assessments. Nevertheless, the results of our study should provide encouragement to health-care providers treating children with MDR tuberculosis that successful outcomes can be achieved, possibly with greater frequency than for adults.

Contributors

NF had the idea for the study and analysed the data. DE, NF, JAS, and HSS collected the data. All authors drafted and revised the paper, and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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