Original Article

Consensus Statement on Research Definitions for Drug-Resistant Tuberculosis in Children

James A. Seddon,[1,2] Carlos M. Perez-Velez,[3] H. Simon Schaaf,[1,4] Jennifer J. Furin,[5] Ben J. Marais,[6,7] Marc Tebruegge,[8,9,10] Anne Detjen,[11] Anneke C. Hesseling,[1] Sarita Shah,[12] Lisa V. Adams,[13] Jeffrey R. Starke,[14] Soumya Swaminathan,[15] and Mercedes C. Becerra;[16,17] on Behalf of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis

[1]Desmond Tutu TB Centre, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [2]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom; [3]Grupo Tuberculosis Valle-Colorado, and Clínica León XIII IPS Universidad de Antioquia, Medellín, Antioquia, Colombia; [4]Tygerberg Children's Hospital, Cape Town, South Africa; [5]Division of Infectious Diseases, TB Research Unit, Case Western Reserve University School of Medicine, Cleveland, Ohio; [6]Sydney Institute for Emerging Infectious Diseases and Biosecurity, and [7]The Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia; [8]Academic Unit of Clinical and Experimental Science, Faculty of Medicine, and [9]Institute for Life Sciences, University of Southampton, United Kingdom; [10]Department of Paediatrics, Faculty of Medicine, University of Melbourne, Australia; [11]The International Union Against Tuberculosis and Lung Disease, New York, and [12]Department of Medicine, Albert Einstein College of Medicine, Bronx, New York; [13]Section of Infectious Disease and International Health, Global Health Initiative, Dartmouth Medical School, Hanover, New Hampshire; [14]Department of Pediatrics, Baylor College of Medicine, Houston, Texas; [15]National Institute for Research in Tuberculosis, Chennai, India; [16]Department of Global Health and Social Medicine, Harvard Medical School, and [17]Partners In Health, Boston, Massachusetts

Corresponding Author: James Seddon, MBBS, MA, MRCPCH, DTM&H, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Clinical Building, Room 0085, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg, South Africa. E-mail: james.seddon@doctors.org.uk.

Received April 23, 2012; accepted February 7, 2013; electronically published April 10, 2013.

Few children with drug-resistant (DR) tuberculosis (TB) are identified, diagnosed, and given an appropriate treatment. The few studies that have described this vulnerable population have used inconsistent definitions. The World Health Organization (WHO) definitions used for adults with DR-TB and for children with drug-susceptible TB are not always appropriate for children with DR-TB. The Sentinel Project on Pediatric Drug-Resistant Tuberculosis was formed in 2011 as a network of experts and stakeholders in childhood DR-TB. An early priority was to establish standardized definitions for key parameters in order to facilitate study comparisons and the development of an evidence base to guide future clinical management. This consensus statement proposes standardized definitions to be used in research. In particular, it suggests consistent terminology, as well as definitions for measures of exposure, drug resistance testing, previous episodes and treatment, certainty of diagnosis, site and severity of disease, adverse events, and treatment outcome.

Key words. Pediatric; Children; Tuberculosis; Drug-Resistance; Definition; Consensus

The World Health Organization (WHO) estimated that 650 000 cases of multidrug-resistant (MDR) tuberculosis (TB) occurred globally in 2010 [1]. MDR-TB is caused by *Mycobacterium tuberculosis*, which is resistant to the 2 most effective first-line medications: rifampin and isoniazid [2]. In high-burden settings, pediatric TB comprises 15%–20% of the total disease burden [3-4]; this equates to a global estimate of up to 100 000 children with MDR-TB. Children traditionally have been neglected by both healthcare systems and research [5]. This is especially true for children with drug-resistant (DR)-TB, with fewer than 500 children with MDR-TB described in the medical literature to date [6]. With the imminent roll-out of newer molecular diagnostic tests [7-8], more children will be identified both as confirmed DR-TB cases, as well as presumed TB cases that have been in contact with a DR-TB source case. The limited number of studies to date and challenges evident in data collection highlight the need for improved coordination and standardization of data to ensure the development of an evidence base to inform the management of these children.

Journal of the Pediatric Infectious Diseases Society, Vol. 2, No. 2, pp. 100–9, 2013. DOI:10.1093/jpids/pit012
© The Author 2013. Published by Oxford University Press on behalf of the Pediatric Infectious Diseases Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by-nc/3.0/), which permits non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com.

The Sentinel Project on Pediatric Drug-Resistant Tuberculosis was formed in 2011 as a virtual community of experts and stakeholders who share the goal of preventing child deaths from DR-TB [9]. More than 200 researchers, healthcare providers, and advocates from over 40 countries are now collaborating in this global network. Task forces take on specific projects that seek to develop, deploy, and disseminate evidence-based strategies for improving the detection and treatment of children with DR-TB. One immediate priority for this network was to establish standardized definitions for key variables, terms, and outcomes, to facilitate study comparisons and research collaborations. The task force that developed this consensus statement has particular experience in carrying out research related to DR-TB in children. The proposed definitions were revised through meetings, conference calls, and written feedback to achieve clarity and consensus.

The current programmatic WHO definitions used to describe adults with DR-TB and children with drug-susceptible (DS) TB were considered to be inadequate for research studies of children with DR-TB. More rigorous definitions were required for use in research that records the epidemiology of exposure, infection and disease, as well as research into diagnosis, treatment, prevention, and outcome. Definitions were intended to be relevant for both prospective studies, in which comprehensive data can be collected, and for retrospective studies. The distinction between definitions used in clinical management, programmatic reporting, and research studies is complex; many research studies document clinical management or report programmatic data. Although we hope that the definitions suggested will strengthen programmatic reporting, this article proposes standardized consensus definitions intended for use in the research setting. These definitions are not intended for use by clinicians who make decisions regarding the management of children with DR-TB infection and disease.

Terminology and Measures of Exposure

To facilitate comparisons between different studies it is vital that key terms be standardized. Table 1 provides a summary of the suggested consensus definitions regarding epidemiologic terms, disease classification, type of treatment, and categories of drug resistance.

Exposure is a continuum, with no documented exposure at one extreme and extensive exposure at the other. Although any exposure to a DR-TB source case could potentially result in a child becoming infected, in reality this exposure must reach a *significant* threshold for the child to be deemed a contact. This necessitates the use of a binary definition. The issue is complex and incorporates elements of the infectiousness of the source case, the proximity and intensity of interaction between source case and contact, the daily duration of exposure, the length of exposure over time, as well as environmental factors such as air exchange [10-11]. Different definitions will provide different degrees of sensitivity and specificity, and it is important that definitions are consistent and well described. Recent interactions are more likely to result in disease in the child compared with interactions that took place more than 1 year ago [12-15].

This task force came to the consensus that a "DR-TB contact" should be defined as a child exposed to an infectious DR-TB source case who, in the last 12 months, had either slept in the same household or had daily interaction with the child [16]. We propose that, if possible, a set of 10 questions be answered to provide an exposure "score" (see Table 1), where the sum of binary responses valued at 0 (no) or 1 (yes) result in a contact score ranging from 0 to 10. This concept comprises 4 unique aspects of TB exposure, which provide a more precise and comprehensive description of the likely infection risk and correlates well with tests of *M tuberculosis* infection [11].

In the same way that exposure is a gradient, so too is the spectrum from exposure through infection to disease [17]. Despite this continuum, it is necessary to assign children into distinct categories for research studies. The terminology used in the literature for children who demonstrate immunological evidence of infection with *M tuberculosis,* in the absence of clinical symptoms, is confusing. Latent TB infection, latent TB, *M tuberculosis* infection, and TB infection have all been used. The word "tuberculosis" implies a disease state, and therefore we thought that TB infection should not be used for a well child. For children who have been recently infected by *M tuberculosis*, the use of the word latency is incongruous because it implies an established immunological equilibrium, which may not have been achieved. We suggest that a child with a positive immunological test (eg, tuberculin skin test or interferon-γ release assay) should be classified as having "*M tuberculosis* infection" to cover both recent and latent infection. This is consistent with other consensus definitions [18]. In order for a child to be classified as having "DR *M tuberculosis* infection," the child must have a positive immunological test result as well as being a DR-TB contact. The terminology used for children with clinical, radiological, or microbiological pathology is similarly inconsistent across the published literature. "Active disease" is a term used widely to denote an ill child, but "inactive disease" was not felt to be a useful concept. For consistency, we suggest that the term "TB disease" be used.

Table 1. Proposed Terminology for Drug-Resistant Tuberculosis in Children and the Assessment of Drug-Resistant Tuberculosis Exposure

	Recommended Term	Definitions
Epidemiological terms	DR-TB index case	The first identified, confirmed DR-TB case in a social group (eg, a household) during an investigation or outbreak (which may be the child)
	DR-TB source case	An infectious (sputum-smear microscopy or culture positive) DR-TB case who could have infected the contact
	DR-TB contact	A child exposed to an infectious DR-TB source case who, in the last 12 months, had either slept in the same household or had daily interaction with the child [16]
	DR-TB exposure score	Ten points to be used for exposure score [11] • Is the source case the child's mother? • Is the source case the child's primary caregiver? • Does the source case sleep in the same bed as the child? • Does the source case sleep in the same room as the child? • Does the source case live in the same household as the child?[a] • Does the source case see the child every day?[a] • Is the source case coughing? • Does the source case have pulmonary TB? • Is the source case sputum-smear microscopy positive? • Is there more than one source case in the child's household?
Infection and disease	*M tuberculosis* infection	A positive immunological test of infection (eg, tuberculin skin test or interferon-γ release assay), in the absence of symptoms and physical signs (both acute and chronic) [18]
	DR *M tuberculosis* infection	A positive immunological test of infection, in the absence of symptoms and physical signs (both acute and chronic), but in combination with being a DR-TB contact
	TB disease	Clinical, radiological, or microbiological pathology
	DR-TB disease	Clinical, radiological, or microbiological pathology, in combination with diagnosis of confirmed, probable, or possible DR-TB disease (see Table 2)
Type of treatment	DR-TB treatment	The treatment of DR-TB disease
	DR-TB preventive therapy	Includes DR-TB pre-exposure (primary) prophylaxis, DR-TB post-exposure prophylaxis (including window prophylaxis), DR-TB secondary prophylaxis, and treatment of DR *M tuberculosis* infection
Drug resistance categories	Monoresistant	Resistance to a single TB drug
	Polyresistant	Resistance to 2 or more TB drugs other than both rifampin and isoniazid
	MDR	Resistant to at least both rifampin and isoniazid
	Pre-extensively DR	MDR-TB with resistance to either a fluoroquinolone, or at least 1 of 3 injectable second-line TB drugs,[b] but not both
	Extensively DR	MDR-TB with resistance to both a fluoroquinolone and at least 1 of 3 injectable second-line TB drugs[b]
	Primary resistance	DR-TB that results from transmission of a DR *M tuberculosis* strain. This could be any of the after clinical situations in a child newly diagnosed with confirmed or probable DR-TB: (a) never treated: a child without previous TB treatment who has not yet received any TB treatment; or (b) previously treated: a child who was previously treated with first-line drugs who was either cured or completed that treatment regimen; or (c) currently receiving treatment: a child who is receiving first-line drugs for presumed DS-TB disease.
	Acquired resistance	A child previously diagnosed with confirmed DS-TB disease who developed DR-TB disease (or resistance to additional drugs) during TB treatment.

Abbreviations: DR, drug-resistant; DS, drug-susceptible; MDR, multidrug-resistant; *M tuberculosis, Mycobacterium tuberculosis;* TB, tuberculosis.

[a]Either of these 2 components will classify the child as being a DR-TB contact if occurring in the preceding 12 months.

[b]Amikacin, kanamycin, capreomycin [2].

Terms used for the treatment given to those with TB disease include "curative treatment," "disease treatment," "anti-TB treatment," and "TB treatment." To avoid ambiguity, we suggest using the term "TB treatment." In the existing literature, there is also inconsistency surrounding the terminology used to describe other forms of chemotherapy. Pre-exposure prophylaxis refers to treatment given to a child without known exposure to an infectious TB case. Postexposure (including window) prophylaxis refers to treatment given to a child after documented TB exposure. Treatment of latent TB infection refers to drugs given after a positive immunological test result indicating previous or current *M tuberculosis* infection. Posttreatment prophylaxis refers to treatment given to a child after a course of TB treatment. For consistency, we suggest the use of the summative term "TB preventive therapy" to cover all of these circumstances.

Definitions of Drug Resistance and Testing Methodology

Although drug resistance is generally divided into the discrete categories of mono-, poly-, MDR-TB or extensively DR-TB [2] (see Table 1), it is more useful to view drug resistance as a continuum. For research into pediatric DR-TB, it is important to describe the precise drug-susceptibility test (DST) pattern. It is also important to record the DST pattern of the likely source case(s), rather than their DST category, when the child has been diagnosed presumptively.

Due to the wide variety of testing methodologies available to determine drug resistance, at a minimum, researchers should clearly state the laboratory techniques used in determining drug resistance. It should be documented to which drugs DST was performed and which techniques were used for each of the drugs. If DST is determined by phenotypic testing, the Clinical and Laboratory Standards Institute standards should be used [19]. It is anticipated that more DST will be carried out using genotypic methods in the future. More than 10 genotypic tests exist using nucleic acid amplification to determine drug resistance [20]. Some assays only determine whether the organism belongs to the *M tuberculosis* complex and whether mutations in the *rpoB* gene are present (associated with rifampin resistance in >95% cases). The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) is one such test, which is currently being rolled out widely [7]. If this test is used and the *rpoB* mutation result is positive, the sample should be recorded as having resistance to rifampin, because this test cannot confirm or rule out resistance to isoniazid. The frequency of rifampin-monoresistant strains is increasing in some settings [21], and samples found to be rifampin-resistant should therefore not be assumed to also be resistant to isoniazid. Conversely, isoniazid-monoresistant TB is common in many regions; if a sample is found not to have an *rpoB* gene mutation, it should not be assumed to be fully DS. Consequently, it is important to follow up results from nucleic acid amplification tests that only detect rifampin resistance with additional testing for isoniazid resistance.

The genotypic testing of resistance to isoniazid usually involves testing for mutations in the *inhA* promoter region and the *katG* gene [22]. A molecular line probe assay (eg, GenoType MTBDR*plus*; Hain Lifescience, Nehren, Germany) is frequently used for this purpose. As well as recording the presence of genotypic resistance to isoniazid, it is desirable to also record the mutation conferring resistance, because this has clinical and epidemiological significance [23]. Other molecular tests are under development and in the future, genotypic testing to the second-line drugs is likely to become more widespread, because drug resistance to these agents is associated with known gene mutations [24].

Certainty of Diagnosis of Disease

When treating children for DR-TB disease, the decision is binary – the child is treated or not. For the clinician, this diagnosis is either confirmed or presumed. Either of these diagnoses may be sufficient for clinical management and for recording and reporting purposes. For research purposes, however, it is important to document the degree of certainty for both the diagnosis of TB and the diagnosis of drug resistance (see Table 2). For the diagnosis of TB disease in children, the WHO first proposed categories of suspect, probable, and confirmed TB for reporting and for research [25]. This classification has recently been refined by a National Institutes of Health expert panel, focusing specifically on intrathoracic disease [18]. For extrathoracic TB, a similar system should be adopted; one has been proposed for TB meningitis [26]. As with the definitions advised by Graham et al [18], at least 1 sign or symptom of TB is required for the research definition of TB disease. Children without clinical manifestations consistent with TB disease will therefore not meet the strict research criteria, even though in clinical practice a physician may initiate treatment.

A definition of "confirmed DR-TB disease" requires clinical evidence of TB disease together with the detection of *M tuberculosis* from a specimen collected from the child with resistance demonstrated. We strongly support all specimens from children being submitted for culture and DST. A definition of "probable DR-TB disease" should be used when a diagnosis of probable TB disease has been made and the child is a DR-TB contact. Cases should be classified as "possible DR-TB disease" if a diagnosis of probable TB disease has been made and either the child

fails adherent first-line TB treatment or has been exposed to a source case with risk factors for drug resistance (failed therapy, death, or default with no known DST).

Previous Episodes and Treatment

A distinction should be made between a previous episode of disease and any previous treatment given, because this will have implications both for research aimed at improving clinical management of individual patients and for research aimed at improving programmatic strategies. Definitions have been previously proposed for classifying patients who are newly diagnosed, previously treated with first-line drugs, and previously treated with second-line drugs [2]. However, no definitions have been proposed for a previous TB disease episode or for a previous DR-TB disease episode. We propose definitions to classify both of these types of disease episode (see Table 2). One recent study used a 6-month symptom-free period after the completion of at least 1 month of previous treatment as a pragmatic differentiator of disease episodes [27].

For a child newly diagnosed with confirmed or probable DR-TB disease, it is important to distinguish among several clinical scenarios. The first 3 scenarios are examples of transmitted or primary resistance, whereas the fourth is an example of acquired resistance (Table 1):

(1) A child without previous TB treatment who has not yet received any TB treatment (*primary resistance in a never treated child*);
(2) A child who was previously treated with first-line drugs who was either cured or completed that treatment regimen (*primary resistance in a previously treated child*);
(3) A child who is currently receiving first-line drugs for presumed DS-TB disease (*primary resistance in a child currently receiving treatment*); and
(4) A child previously diagnosed with confirmed DS-TB disease who developed DR-TB disease during treatment with first-line drugs.

Although clinically it is sensible to suspect the development of resistance in a child if treatment has been poorly adhered to or incorrectly prescribed or supplied, for this conclusion to be reached in a research context, it is necessary to have had an initial DS isolate. Most children with DR-TB disease, however, have transmitted resistance [28].

To document treatment delay, a standard definition of when the DR-TB episode began should be used to determine the interval from the assumed start of the disease episode to the start of DR-TB treatment. Published studies have defined a DR-TB episode as beginning (in the event that DR-TB was subsequently confirmed) at either the child's initial documented presentation to the healthcare system, when a specimen was obtained that eventually confirmed DR-TB, or alternatively, when the child commenced TB treatment for the current episode, based on whichever was the first documented event [27].

Site of Disease and Disease Severity

Site and severity of disease can have an impact on the choice and duration of treatment as well as treatment outcome. Disease severity, for example, has been shown to correlate with bacterial yield in children and culture conversion [27, 29-30]. TB programs usually report disease site using ICD-10 codes [31], and this task force came to the consensus that these codes should be used for reporting disease site in children with DR-TB. Defining the severity of disease in children is challenging and existing approaches are limited. Radiological findings can be used to describe the spectrum of intrathoracic disease and can be an indicator of severity [32]. A recently proposed classification system divides different types of both intra- and extrathoracic childhood TB into severe and nonsevere disease based on known host-pathogen interaction and pathophysiology of disease [29]. Future studies need to ensure the accuracy of this classification system across pediatric TB populations. Furthermore, this classification system should be evaluated prospectively in children with DR-TB disease, because its correlation with treatment response, disease progression, and outcome is still unknown. Where possible, we propose that this classification should be used for research purposes.

Adverse Events

Second-line TB drugs are associated with increased risk of adverse events [33]. For research, it is important to determine the type of adverse event, the severity, the relationship to the medications being given, any action taken and any associated risk factors [34]. The Division of Microbiology and Infectious Diseases within the US National Institute of Allergy and Infectious Diseases has published tables to allow the grading of adverse events [35]. These tables are specific for children and we recommend their use for research on pediatric DR-TB. However, a number of adverse events that are frequently encountered in the treatment of children with DR-TB disease and DR *M tuberculosis* infection are not adequately covered in this classification system [36]. These include thyroid dysfunction, hearing loss, arthralgia, and arthritis. Proposed criteria for grading these adverse events are included in Table 3.

It is important to note the action taken when an adverse event occurs [37]. For each adverse event, we recommend that data be collected documenting whether any action was taken and, if so, what type. Where possible, other factors that may be associated with the adverse event should be recorded. These include comorbidities such as

Table 2. Classification According to Previous Disease Episodes, Diagnostic Certainty, and Description of Drug-Resistant Tuberculosis Disease in Children

	Recommended Term	Definition
Certainty of diagnosis of TB disease [18]	Confirmed TB disease	At least 1 of the signs and symptoms suggestive of TB disease[a] and microbiological confirmation of *M tuberculosis*
	Probable TB disease	At least 1 of the signs and symptoms suggestive of TB disease[a] and the CR is consistent with intrathoracic TB disease[b] and presence of 1 of the following: (a) a positive clinical response to TB treatment, (b) documented exposure to a source case with TB disease, or (c) immunological evidence of TB infection
	Possible TB disease	At least 1 of the signs and symptoms suggestive of TB disease[a] and either (a) a clinical response to TB treatment, documented exposure to a source case with TB disease or immunological evidence of TB infection, or (b) CR consistent with intrathoracic TB disease[b]
Certainty of diagnosis of DR-TB disease	Confirmed DR-TB disease	At least 1 of the signs and symptoms suggestive of TB disease[a] and detection of *M tuberculosis* from the child with demonstration of genotypic or phenotypic resistance
	Probable DR-TB disease	DR-TB contact and diagnosis of probable TB disease
	Possible DR-TB disease	Diagnosis of probable TB disease together with either (a) contact of a source case with TB disease who has risk factors for drug resistance[c] or (b) failure of first-line TB treatment
Previous episodes and treatment	Previous TB disease episode	An episode of TB disease in which treatment was given for at least 1 month, after which there was a reported symptom-free period of $\geq$6 months before the start of the current DR-TB disease episode
	DR-TB disease episode	If DR-TB disease is subsequently confirmed, a TB disease episode that began when the child is first documented to have presented to the healthcare system, when the specimen was obtained that eventually confirmed DR-TB disease, or when the child commenced any TB treatment, whichever is the first available documented event [27]
	Previously treated with first-line TB drugs	Treatment for 1 month or more with any drug in Drug Group 1 [2]
	Previously treated with second-line TB drugs	Treatment for 1 month or more with any drug in Drug Groups 2-5 [2]
Site of TB and disease severity	ICD-10 code	Code to be recorded [31]
	Severe disease	A clinical syndrome classified as uncontrolled,[d] disseminated,[e] or complicated[f] [29]
	Nonsevere disease	A clinical syndrome classified as controlled (limited), non-disseminated, and uncomplicated [29]

Abbreviations: CR, chest radiograph; DR, drug-resistant; *M tuberculosis*, *Mycobacterium tuberculosis*; TB, tuberculosis; WHO, World Health Organization.

[a]Persistent cough, weight loss, or failure to thrive; persistent unexplained fever; persistent unexplained lethargy or reduced playfulness; or the presence of any of the following in the neonate: pneumonia, unexplained hepatosplenomegaly, or sepsis-like illness [18].

[b]For extrathoracic TB disease, alternative appropriate radiological imaging should be substituted.

[c]Risk factors for DR-TB include: treatment failure, death during TB treatment, treatment default or nonadherence, previous treatment, exposure to a known DR-TB case, as well as having resided in or traveled to an area with high prevalence of DR-TB [2].

[d]Disease resulting in significant local or peripheral tissue damage and caseous necrosis.

[e]Disease resulting from hematogenous bacillary spread, such as miliary TB, meningitis, bone marrow disease, or renal, hepatic, or splenic TB granulomata.

[f]Disease resulting in infiltration or compression of adjacent bronchial, vascular, cardiac, nervous, or osseous tissue, resulting in functional impairment. Often involves severe sequelae, with the exceptions of peripheral lymph node disease, pleural effusion without emphysema, and skin disease.

Table 3. Classification of Adverse Events in Children With Drug-Resistant Tuberculosis

	Recommended Term	Definition
Adverse drug events	Clinical	DMID grading scale 0–4 [35]
	Laboratory	DMID grading scale 0–4 [35]
	Arthralgia/arthritis	Not covered but parallels with DMID • Grade 0 – No pain • Grade 1 – Pain, but no interference with function or movement • Grade 2 – Moderate pain affecting function, but able to carry out normal activities • Grade 3 – Severe pain limiting activities • Grade 4 – Disabling pain and unable to carry out normal activities
	Thyroid function	Abnormal considered if TSH raised above and T4 below the threshold of normal, using the reference ranges that have been specified by the laboratory with consideration of the analyzer used and the age of the child
	Hearing	ASHA criteria for hearing loss [50-52] using pure tone audiometry. Hearing loss defined as a change from baseline of the following: • 20 decibel decrease at any 1 frequency or • 10 decibel decrease at any 2 adjacent frequencies or • Loss of response at 3 consecutive test frequencies where responses were previously obtained.

Abbreviations: ASHA, American Speech and Hearing Association; DMID, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, US National Institutes of Health; TSH, thyroid-stimulating hormone.

human immunodeficiency virus infection (HIV), diabetes, and asthma, as well as the nutritional status and the type and severity of TB disease.

Disease Outcome

Adult guidelines typically use microbiological parameters to determine response to treatment. The outcome definitions currently recommended by WHO for adults with DR-TB disease were first proposed by an expert consensus group for use in the analysis of retrospective data. Cure was defined as "five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment" [2, 38]. For children with DS-TB disease, cure has been defined as a child who is "sputum smear-negative in the last month of treatment and at least one previous occasion" [39]. This task force reasoned that neither of these definitions was appropriate for children with DR-TB disease. Instead, we propose to define "cure" as the completion of treatment, with attainment of clinical (resolution of symptoms and physical signs), radiological (improvement of imaging abnormalities), and microbiological (conversion of cultures) criteria (Table 4).

Because only a relatively small proportion of children will have a confirmed diagnosis at the beginning of their treatment [40-42], and because microbiological investigations are frequently not repeated during follow-up, the majority of children will not fulfill the definition for cure. We chose to define "probable cure" as the presence of the same constellation of features, but without the microbiological component. The proposed definitions for treatment outcome are described in detail in Table 4. One consideration in using this approach relates to the natural history of TB: in some patients, disease involutes without treatment [15]. However, it is impossible to predict which children will respond in this manner and if the research terminology is consistently applied across settings to facilitate comparisons, this should not undermine the value of such definitions.

Treatment response can be divided into clinical, radiological, and microbiological responses. A key component of clinical response is nutritional status, with poor status being a risk for both the development of TB disease as well as poor treatment outcome [43-46]. Nutritional variables that require monitoring, at a minimum, include height and weight. These parameters should be assessed at treatment initiation and then monthly and should then be plotted on standardized growth charts (see Table 4). We propose that an improvement in nutritional status (ie, resolution of failure to thrive) should be included among the criteria used to define "probable cure." Radiological improvement encompasses partial or complete resolution of chest radiographic features. However, it is important to consider that

Table 4. Classification of Treatment Outcome in Children With Drug-Resistant Tuberculosis

	Recommended Term	Definition
Treatment outcome	Cure	Completion of prescribed treatment[a] with attainment of clinical (resolution of symptoms and physical signs[b]), radiological (improvement of imaging abnormalities[c]), and microbiological (conversion of cultures[d]) criteria.
	Probable cure	Completion of prescribed treatment[a] with attainment of clinical[b] and radiological[c] improvement
	Treatment completed	Completion of prescribed treatment[a]
	Default	Treatment interruption for 2 months or more
	Primary default	Never started on DR-TB treatment
	Death	Death for any reason while on DR-TB treatment
	Primary death	Death before starting DR-TB treatment
	Treatment failure	Ongoing sputum culture positivity, or does not meet criteria for both clinical[b] and radiological[c] improvement, after more than 6 months of the child receiving an appropriate DR-TB regimen (with adherence >80%) in the absence of IRIS

Abbreviations: DR, drug-resistant; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis.

[a]Treatment completion criterion: The duration of prescribed DR-TB treatment will vary according to the study setting and may vary based on the drug-resistance profile and the clinical severity.

[b]Clinical criterion: Resolution of all acute and chronic clinical manifestations (symptoms and physical signs) of TB disease, including both those that are constitutional and those that are specific to the affected anatomical sites. Constitutional manifestations: TB can cause decreased activity level, decreased appetite, failure to thrive, fever, and night sweats. The resolution of failure to thrive should be objectively demonstrated by a weight gain equal or greater than that required to follow the child's baseline weight-for-age percentile (on the WHO Child Growth Chart [53–54]) over the treatment period. For consistency, we suggest use of the current (pretreatment) percentile, because predisease measurements may not be available in all children. Manifestations specific to the affected anatomical site(s): TB has myriad manifestations given that necrotic lymph node infiltration into contiguous structures and lymphohematogenous spread of *Mycobacterium tuberculosis* can lead to disease in virtually any tissue of the body. An exhaustive list of manifestations is therefore not possible. The following is a list of examples of common tuberculous clinical syndromes, organized by organ systems: pulmonary/pleural (eg, pneumonia; pleural effusion); cardiovascular (eg, pericarditis; vasculitis); digestive (eg, enteritis; pancreatitis; hepatitis); urinary (eg, nephritis); endocrine (eg, adrenal insufficiency; thyroiditis); hematologic (eg, anemia); lymphatic (eg, lymphadenitis; splenic abscess); nervous (eg, meningitis; parenchymal granuloma); musculoskeletal (eg, arthritis; osteomyelitis); integumentary (eg, nodular skin disease); and reproductive (eg, salpingitis; tubo-ovarian mass; epididymitis). All manifestations of persisting disease activity should be resolved by the completion of TB treatment. However, manifestations associated with sequelae (ie, secondary complications after healing of TB disease) such as permanent lung scarring (eg, bronchiectasis), neurological deficits (eg, cognitive impairment; cranial nerve palsy), and joint/bone deformities (eg, gibbus) should be excluded from this criterion.

[c]Radiological criterion: Improvement of imaging abnormalities of all of the following: (a) lymph nodes (after effective DR-TB treatment, the enlarged lymph nodes of the majority of children will have normalized in size; however, a small minority may have mildly enlarged lymph nodes or have developed calcifications); (b) lung parenchyma (after effective DR-TB treatment, the parenchymal lesions of the majority of children will have resolved; however, a minority may only present improvement [reduction in size and/or intensity of lesions], or have developed calcifications or fibrotic lesions); and (c) pleural space (after effective DR-TB treatment, the pleural lesions of the majority of children will have resolved; however, some may have residual pleural thickening or calcifications).

[d]Microbiological criterion: In those children with bacteriologically confirmed disease, at least 3 consecutive negative mycobacterial cultures of respiratory specimens (eg, sputum; gastric aspirate/lavage) during the treatment course, with at least 1 in the last 12 months of treatment, and no positive cultures during the minimum length of treatment after culture conversion.

some children with HIV infection who are started on antiretroviral therapy may experience a radiological deterioration despite clinical improvement due to immune reconstitution inflammatory syndrome (IRIS) [47-49]. Nevertheless, this phenomenon is unlikely to influence classification of final disease outcome, because IRIS typically presents early in the treatment course and resolves before final outcome is determined.

We propose that other treatment outcomes which should be recorded are primary death and primary default. The first term would apply in a child who is diagnosed with DR-TB disease but dies before receiving DR-TB treatment; the second term would apply in a child who refuses treatment or is not given treatment or is lost to follow-up before DR-TB treatment is initiated. Finally, for the purpose of assigning classification of final disease outcome, we propose that the outcome of treatment failure be assigned if a child has had ongoing sputum culture positivity or does not meet criteria for both clinical and radiological improvement (Table 4), after more than 6 months of receiving an appropriate DR-TB treatment regimen in the absence of IRIS. It should be noted that this definition is intended for research use such as analyzing outcomes in treatment cohorts, and it is not intended to guide clinical decisions about individual patients. More research is needed to identify the optimal durations of the intensive and continuation phases for children with DR-TB, as well as to identify optimal cutoffs for assigning final treatment outcomes specifically for children with DR-TB.

CONCLUSIONS

Currently, there is a concerning paucity of data regarding childhood DR-TB and inconsistent use of classifications for cases, treatment, and outcome. More pediatric studies are urgently needed. Overall, the study of children with DR-TB requires similar approaches to research in adults. However, many existing adult tools require adaptation for the specific requirements of studies of childhood DR-TB. The standard definitions and terminology proposed here will allow improvements in data collection for clinical research and reporting of study findings, thereby facilitating comparison across different settings and populations, as well as promoting a stronger evidence base for policymakers and guideline development.

Acknowledgments

S. S. and M. C. B. are joint senior authors.

Financial support. J. A. S. was supported by the Sir Halley Stewart Trust. H. S. S. was supported by the South African National Research Foundation. M. T. was supported by a Fellowship award by the European Society for Paediatric Infectious Diseases.

Disclaimer. The funding agencies had no role in the preparation, review, or approval of the manuscript.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization, Geneva, Switzerland. Global tuberculosis control. WHO/HTM/TB/201116 2011. Available at: http://www.who.int/tb/publications/global_report/2011/gtbr11_full.pdf. Accessed March 26, 2013.
2. World Health Organization, Geneva, Switzerland. Guidelines for the programmatic management of drug-resistant tuberculosis - Emergency update. WHO/HTM/TB/2008402 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf. Accessed March 26, 2013.
3. Marais BJ, Hesseling AC, Gie RP, et al. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. Int J Tuberc Lung Dis **2006**; 10:259–63.
4. van Rie A, Beyers N, Gie RP, et al. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. Arch Dis Child **1999**; 80:433–7.
5. Marais BJ, Schaaf HS. Childhood tuberculosis: an emerging and previously neglected problem. Infect Dis Clin North Am **2010**; 24:727–49.
6. Ettehad D, Schaaf HS, Seddon JA, et al. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis **2012**; 12:449–56.
7. World Health Organization, Geneva, Switzerland. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. Available at: http://www.who.int/tb/laboratory/roadmap_xpert_mtb_rif.pdf. Accessed March 26, 2013.
8. World Health Organization, Geneva, Switzerland. Molecular line probe assays for the rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Policy Statement. **2008**: Available at: http://www.who.int/tb/features_archive/policy_statement.pdf. Accessed March 26, 2013.
9. The Sentinel Project on Pediatric Drug-Resistant Tuberculosis. Available at: www.sentinel-project.org. Accessed March 26, 2013.
10. Rieder HL. Epidemiologic Basis of Tuberculosis Control. 1st ed. International Union Against Tuberculosis and Lung Disease. Paris, France; **1999**.
11. Mandalakas AM, Kirchner HL, Lombard C, et al. Well-quantified tuberculosis exposure is a reliable surrogate measure of tuberculosis infection. Int J Tuberc Lung Dis **2012**; 16:1033–9.
12. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibl Tuberc **1970**; 26:28–106.
13. Davies PD. The natural history of tuberculosis in children. A study of child contacts in the Brompton Hospital Child Contact Clinic from 1930 to 1952. Tubercle **1961;** 42(Suppl):1–40.
14. Gedde-Dahl T. Tuberculous infection in the light of tuberculin matriculation. Am J Hyg **1952**; 56:139–214.
15. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis **2004**; 8: 392–402.
16. Van Wyk SS, Mandalakas AM, Enarson DA, et al. Tuberculosis contact investigation in a high-burden setting: house or household? Int J Tuberc Lung Dis **2012**; 16:157–62.

17. Lin PL, Flynn JL. Understanding latent tuberculosis: a moving target. J Immunol **2010**; 185:15–22.
18. Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. J Infect Dis **2012**; 205(Suppl 2):S199–208.
19. Clinical and Laboratory Standards Institute (CLSI). Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard - Second Edition: CLSI document M24-A2 (ISBN 1-56238-746-4). Clinical and Laboratory Standards Insitutue, Wayne, PA.
20. Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med **2012**; 367:348–61.
21. Mukinda FK, Theron D, van der Spuy GD, et al. Rise in rifampicin-monoresistant tuberculosis in Western Cape, South Africa. Int J Tuberc Lung Dis **2012**; 16:196–202.
22. Hazbon MH, Brimacombe M, del Valle M Bobadilla, et al. Population genetics study of isoniazid resistance mutations and evolution of multidrug-resistant *Mycobacterium tuberculosis*. Antimicrob Agents Chemother **2006**; 50:2640–9.
23. Muller B, Streicher EM, Hoek KG, et al. inhA promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa? Int J Tuberc Lung Dis **2011**; 15:344–51.
24. Sandgren A, Strong M, Muthukrishnan P, et al. Tuberculosis drug resistance mutation database. PLoS Med **2009**; 6:e2.
25. World Health Organization, Geneva, Switzerland. Provisional guidelines for the diagnosis and classification of the EPI target diseases for primary health care, surveillance and special studies. EPI/GEN/83/4 1986. Available at: http://whqlibdoc.who.int/euro/-1993/ICP_EPI_012_12.pdf. Accessed March 26, 2013.
26. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis **2010**; 10:803–12.
27. Seddon JA, Hesseling AC, Willemse M, et al. Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. Clin Infect Dis **2012**; 54:157–66.
28. Schaaf HS, Marais BJ, Hesseling AC, et al. Surveillance of antituberculosis drug resistance among children from the Western Cape Province of South Africa–an upward trend. Am J Public Health **2009**; 99:1486–90.
29. Wiseman CA, Gie RP, Starke JR, et al. A proposed comprehensive classification of tuberculosis disease severity in children. Pediatr Infect Dis J **2012**; 31:347–52.
30. Marais BJ, Hesseling AC, Gie RP, et al. The bacteriologic yield in children with intrathoracic tuberculosis. Clin Infect Dis **2006**; 42:e69–71.
31. World Health Organization, Geneva, Switzerland. International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Available at: http://apps.who.int/classifications/icd10/browse/2010/en. Accessed March 26, 2013.
32. Marais BJ, Gie RP, Schaaf HS, et al. A proposed radiological classification of childhood intra-thoracic tuberculosis. Pediatr Radiol **2004**; 34:886–94.
33. Bloss E, Kuksa L, Holtz TH, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. Int J Tuberc Lung Dis **2010**; 14:275–81.
34. Papastavros T, Dolovich LR, Holbrook A, et al. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ **2002**; 167:131–6.
35. Division of Microbiology and Infectious Diseases. Pediatric Toxicity Tables. November 2007 DRAFT. Available at: http://www.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/Documents/dmidpedtox.pdf. Accessed March 26, 2013.
36. Drobac PC, Mukherjee JS, Joseph JK, et al. Community-based therapy for children with multidrug-resistant tuberculosis. Pediatrics **2006**; 117:2022–9.
37. Marra F, Marra CA, Moadebi S, et al. Levofloxacin treatment of active tuberculosis and the risk of adverse events. Chest **2005**; 128:1406–13.
38. Laserson KF, Thorpe LE, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2005**; 9:640–5.
39. World Health Organization, Geneva, Switzerland. Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. WHO/HTM/TB/2006371, WHO/FCH/CAH/20067 2006. Available at: http://www.who.int/maternal_child_adolescent/documents/htm_tb_2006_371/en/index.html. Accessed March 26, 2013.
40. Starke JR. Pediatric tuberculosis: time for a new approach. Tuberculosis (Edinb) **2003**; 83:208–12.
41. Marais BJ, Gie RP, Schaaf HS, et al. Childhood pulmonary tuberculosis: old wisdom and new challenges. Am J Respir Crit Care Med **2006**; 173:1078–90.
42. Zar HJ, Hanslo D, Apolles P, et al. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet **2005**; 365:130–4.
43. Chisti MJ, Tebruegge M, La Vincente S, et al. Pneumonia in severely malnourished children in developing countries - mortality risk, aetiology and validity of WHO clinical signs: a systematic review. Trop Med Int Health **2009**; 14:1173–89.
44. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis **2004**; 8: 286–98.
45. Hesseling AC, Westra AE, Werschkull H, et al. Outcome of HIV infected children with culture confirmed tuberculosis. Arch Dis Child **2005**; 90:1171–4.
46. Soeters M, de Vries AM, Kimpen JL, et al. Clinical features and outcome in children admitted to a TB hospital in the Western Cape–the influence of HIV infection and drug resistance. S Afr Med J **2005**; 95:602–6.
47. Walters E, Cotton MF, Rabie H, et al. Clinical presentation and outcome of tuberculosis in human immunodeficiency virus infected children on anti-retroviral therapy. BMC Pediatr **2008**; 8:1.
48. Orikiiriza J, Bakeera-Kitaka S, Musiime V, et al. The clinical pattern, prevalence, and factors associated with immune reconstitution inflammatory syndrome in Ugandan children. AIDS **2010**; 24:2009–17.
49. Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. Int J Tuberc Lung Dis **2007**; 11:417–23.
50. American Speech-Language-Hearing Association. Guidelines for Audiologic Screening (Guideline). Available at http://www.asha.org/docs/pdf/GL1997-00199.pdf. Accessed March 26, 2013.
51. American Speech-Language-Hearing Association. Audiologic Management of Inidividuals Receiving Cochleotoxic Drug Therapy (Guideline). Available at http://www.asha.org/docs/pdf/GL1994-00003.pdf. Accessed March 26, 2013.
52. American Speech-Language-Hearing Association. Audiologic Screening (Technical Report). Available at http://www.asha.org/docs/pdf/TR1994-00238.pdf. Accessed March 26, 2013.
53. World Health Organization, Geneva, Switzerland. WHO child growth standards: Weight for age. Available at: http://www.who.int/childgrowth/standards/weight_for_age/en/index.html. Accessed March 26, 2013.
54. World Health Organization, United Nations Children's Fund. WHO child growth standards and the identification of severe acute malnutrition in infants and children, 2009. Available at: http://www.who.int/nutrition/publications/severemalnutrition/9789241598163/en/index.html. Accessed March 26, 2013.

University Library

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Seddon, JA;Perez-Velez, CM;Schaaf, HS;Furin, JJ;Marais, BJ;Tebruegge, M;Detjen, A;Hesseling, AC;Shah, S;Adams, LV;Starke, JR;Swaminathan, S;Becerra, MC;Sentinel Project on Pediatric Drug-Resistant Tuberculosis,

Title:
Consensus Statement on Research Definitions for Drug-Resistant Tuberculosis in Children.

Date:
2013-06

Citation:
Seddon, J. A., Perez-Velez, C. M., Schaaf, H. S., Furin, J. J., Marais, B. J., Tebruegge, M., Detjen, A., Hesseling, A. C., Shah, S., Adams, L. V., Starke, J. R., Swaminathan, S., Becerra, M. C. & Sentinel Project on Pediatric Drug-Resistant Tuberculosis, (2013). Consensus Statement on Research Definitions for Drug-Resistant Tuberculosis in Children.. J Pediatric Infect Dis Soc, 2 (2), pp.100-109. https://doi.org/10.1093/jpids/pit012.

Persistent Link:
http://hdl.handle.net/11343/264969

License:
CC BY-NC