Two sizes do not fit all: the terms infection and disease are inadequate for the description of children with tuberculosis

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The article by Loveday and colleagues published in this month's edition of *Archives of Disease in Childhood* provides an opportunity to review some very old and some very new literature on paediatric tuberculosis (TB). The authors describe 43 children who had been referred from primary and secondary care, during 2010 and 2011, to a specialist childhood drug-resistant TB hospital in South Africa with cultures that were positive for drug-resistant *Mycobacterium* (*M.*) *tuberculosis*.[1] The children were seen a median of 80 days after referral and a third of them had been given first-line TB treatment. The authors were unclear why these children had initially been investigated microbiologically for TB, but by the time they were seen in the specialist hospital, all had normal chest radiographs and had no symptoms or signs of TB. None had been given second-line TB treatment. Over the subsequent year or two, one child was started on treatment for drug-resistant TB disease, one children died and a few children were lost to follow-up. However, the majority remained well and free from TB disease.

So, what does this mean for us looking after children with TB and specifically drug-resistant TB? Traditionally, the term TB infection (or latent TB infection) suggests that a child is well, with no abnormal radiology, and that the child demonstrates immunological sensitisation to *M. tuberculosis*, as detectable through tuberculin skin testing or interferon-gamma release assay. For this to occur, organisms must be present, or must have been present, in the body. It is not inconceivable, therefore, that at some point during the course of their infection, it is possible to isolate mycobacteria from samples taken from the child. Studies from the early decades of the 20th century, before chemotherapy became available, suggest that organisms can often be transiently isolated from samples taken from well children soon after infection. In 1935, Arvid Wallgren wrote: "The presence or absence of bacilli obtained by means of washing out the stomach and the results of testing a guinea-pig with the water from the lavage must not be taken to have prognostic value".[2] In addition, many children, following infection, were described as developing hilar lymphadenopathy, detectable on chest radiograph, which then resolved without treatment.[3] So how can we know in a child with either positive cultures or an abnormal chest radiograph whether they have (a) primary infection, in which the mycobacteria will be contained immunologically, with the child remaining well, or (b) early disease which will progress to severe disease if left unchecked? It is a brave clinician who will leave a child with microbiological confirmation or chest radiograph changes without treatment, as has been done in this study.

However, in the study by Loveday and colleagues, the stakes were higher. Drug-resistant TB treatment is long and toxic with significant side effects. Children are separated from their families for often a year or more, are taken out of school and have to tolerate fist fulls of drugs on a daily basis, which frequently make them feel nauseous. A quarter to a half of children develop hearing loss, which for a child developing language, forming relationships and gaining education can have a significant impact on their chances in life. The children in this study had already waited a number of months prior to being evaluated at the specialist hospital without appropriate treatment and had remained well. In this situation, it seems entirely appropriate to adopt a cautious watch-and-wait approach. With hindsight, the clinicians evaluating the children when they arrived at the specialist hospital were probably right in concluding that these children only had TB 'infection'. But what does this term mean?

Our understanding of the pathophysiology of TB and the human immunological response to the organism is evolving and the classic division between infection and disease increasingly looks inadequate. Many commentators see a spectrum from transient infection to latent infection, to early, or subclinical disease, through to more severe disease.[4] The evolving field of transcriptomics, which tells us which genes are 'switched on' or 'switched off' in response to an infectious pathogen, is beginning to shed light onto what is taking place at a cellular level. This field also permits the identification of transcription signatures which might discriminate different clinical states. A recent study by Zak and colleagues followed over 6000 African adolescents who were infected with *M. tuberculosis*.[5] They were able to identify a 16-gene signature which predicted which of the adolescents would progress to overt disease in the subsequent 12 months. It is likely that the adolescents who exhibited this signature already had subclinical, or asymptomatic, disease. Is this infection or disease?

From a clinical perspective, investigators are considering whether shorter, less-intensive regimens can be used for children with less severe disease. The SHINE (Shorter Treatment for Minimal TB in Children) trial is soon to begin, which seeks to randomise children with limited drug-susceptible TB disease into 6 months or 4 months of therapy. In addition, WHO guidelines suggest that children with limited drug-resistant TB disease might be treated for shorter durations that are required for adults or children with extensive disease. This is supported by observational studies. If a child with recent exposure to an infectious case of TB has a chest radiograph demonstrating lymphadenopathy or limited pulmonary infiltrates, with or without subtle, early symptoms, what should we term this clinical state—infection, limited disease or disease?

As a clinician, the decision is always to evaluate the benefits and risks of an intervention against the benefits and risks of no intervention. As the authors have done in this study from South Africa, careful follow-up without treatment can be a pragmatic and safe approach that avoids significant risk. However, to make these decisions, children need to be evaluated on a case-by-case basis by experienced clinicians. From a programmatic perspective, this is challenging and it makes sense to limit the diagnostic, and consequently treatment, options available. However, it is clear that dividing all children into categories of either infection or disease does

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not tell the whole story. In the not too distant future, it is hoped that we will have a far more sophisticated, but at the same time widely available, approach to defining clinical states, based on symptoms, signs, functional radiology, microbiological assessments of bacillary load and host immune response. Treatment might then be tailored to what is required, saving resources and reducing the potential for adverse events. It is also hoped that as well as being able to categorise children accurately into a different clinical state, we will also be able to predict which asymptomatic children are likely to progress to TB disease. As Edith Lincoln stated 60 years ago: "So far we have been discussing the treatment of tuberculous children who have clinical evidence of disease. Probably we all agree that treatment of such children is always justifiable and sometimes mandatory. The point on which clinicians disagree is the desirability of treating tuberculous children who are without clinical symptoms or even without roentgen evidence of tuberculosis".[6] Let us hope that it is not another 60 years until we have a clearer understanding of how to manage these children.

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