Paediatric tuberculosis in Europe: lessons from Denmark and inclusive strategies to consider

Ben J. Marais[1], Marina Tadolini[2], Matteo Zignol[3] and Giovanni Battista Migliori[4]

Affiliations: [1]Marie Bashir Institute for Infectious Diseases and Biosecurity (MBI) and The Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Sydney, Australia. [2]Dept of Medical and Surgical Sciences Alma Mater Studiorum, University of Bologna, Bologna, and [4]World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy. [3]Global Tuberculosis Programme, World Health Organization, Geneva, Switzerland.

Correspondence: B.J. Marais, Clinical School, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW, 2145, Sydney, Australia. E-mail: ben.marais@health.nsw.gov.au

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European child TB data demonstrate need for accurate disease classification and new strategies to minimise transmission http://ow.ly/qvEgS

Background

Despite suffering high morbidity and mortality in tuberculosis (TB)-endemic areas, children with TB are generally less infectious than adult cases and are therefore low on the priority list of national tuberculosis control programmes [1]. Accurate disease burden assessment in children is hampered by diagnostic challenges [2], limited surveillance data and the poor quality of routinely collected programmatic data. In 2012, the World Health Organization (WHO) produced its first estimates of the TB disease burden suffered by children worldwide, which were updated in 2013: 530 000 cases and 74 000 child deaths were attributed to TB [3]. Many deficiencies were acknowledged and it probably is an underestimate given the conservative assumptions made [1]. However, it provided formal recognition of the plight of these children and supplemented the focus on paediatric TB during World TB Day commemorations in 2012. Despite improved awareness, pragmatic service delivery strategies are often lacking, with pronounced policy–practice gaps in TB-endemic areas with limited resources [3, 4].

This editorial puts recent paediatric TB trends in Denmark, as described by HATLEBERG *et al.* [5] in this issue of the *European Respiratory Journal*, into perspective; it explores study findings that may seem counterintuitive, advises on the importance of consistent and accurate classification of clinical syndromes in order for reports to be more informative, and argues for new strategies to reduce TB transmission to a minimum in low-burden settings.

The situation in Europe

Relatively good data exist on the paediatric TB disease burden in Europe. A descriptive analysis of European Union/European Economic Area surveillance data from 2000 to 2009 reported 39 695 paediatric cases, accounting for 4.3% of all notified TB cases [6]. Overall TB incidence rates in children <15 years of age dropped from 5.5 per 100 000 in 2000 to 4.2 per 100 000 in 2009, but rates were highly variable. Interestingly, epidemiological patterns described by the available adult and paediatric notification data do not necessarily overlap, as would be expected. This suggests different epidemic characteristics, case finding and prevention strategies, or case definitions used in various countries. Only 16.9% of paediatric cases were bacteriologically confirmed, highlighting diagnostic hurdles and the need for standardised approaches.

Received: Aug 01 2013 | Accepted after revision: Oct 13 2013

Conflict of interest: None declared.

Paediatric TB cases present with a wide spectrum of pathology and, therefore, accurate classification of clinical syndromes of disease is highly informative. The disease spectrum in Europe remains poorly characterized since most reports utilize standard adult reporting templates that recognize pulmonary and extrapulmonary TB but fail to differentiate important disease entities. This is illustrated by hilar lymph node enlargement, which is variably categorised as sputum smear-negative pulmonary TB or extrapulmonary TB, while associated complications are not considered or described (fig. 1) [1, 7]. Extrapulmonary disease as a category is similarly uninformative, ranging from life threatening manifestations such as tuberculous meningitis and miliary (disseminated) TB to uncomplicated peripheral adenitis [8]. Key differences between adult and paediatric TB are summarised in table 1. Given the level of sophistication and coordination that exists in Europe, it seems important for the European Centre for Disease Control and Prevention, in collaboration with existing paediatric networks like the Paediatric Tuberculosis Network European Trials Group [9], to develop and implement enhanced definition and reporting procedures for children diagnosed with TB, linked to strong advocacy to secure commitment from national TB programmes [10].

Lessons from Denmark

A study by HATLEBERG *et al.* [5] presents long-term trend data from a 10-year survey conducted in Denmark. Similar to observations in Sweden [11], the majority of children diagnosed with TB were recent immigrants or refugees from TB-endemic countries, essentially providing ''a mirror to the world''. Clustering of cases within the first few years of arrival is consistent with the experience in most nonendemic areas. Identifying feasible TB screening and preventive therapy strategies that optimise the risk/benefit balance at the individual and community level remains an important ethics discussion and research priority.

Immigrant versus Danish cases

The interesting observation that Danish cases were, on average, younger than immigrant cases probably reflects selection bias, as most Danish cases were identified following active contact evaluation of young and vulnerable children. Selection bias is an important consideration when assessing variable TB disease rates in children and is often reflected in the disease spectrum identified [7, 12]. Active case finding among child contacts and the small number of Danish-born adult cases offers the most likely explanation for the counterintuitive observation that child/adult case notification ratios were higher among Danes compared with immigrants, rather than this being an indication of increased TB transmission within the Danish population. The fact that 13 ''immigrant children'' who developed TB were born in Denmark illustrate the importance of considering TB contact within the extended family and wider community, as well as visits to the parents' country of origin. It also emphasises the need to consider future TB exposure risk in children born to immigrant families when formulating bacille Calmette–Guérin vaccination policies [13, 14].

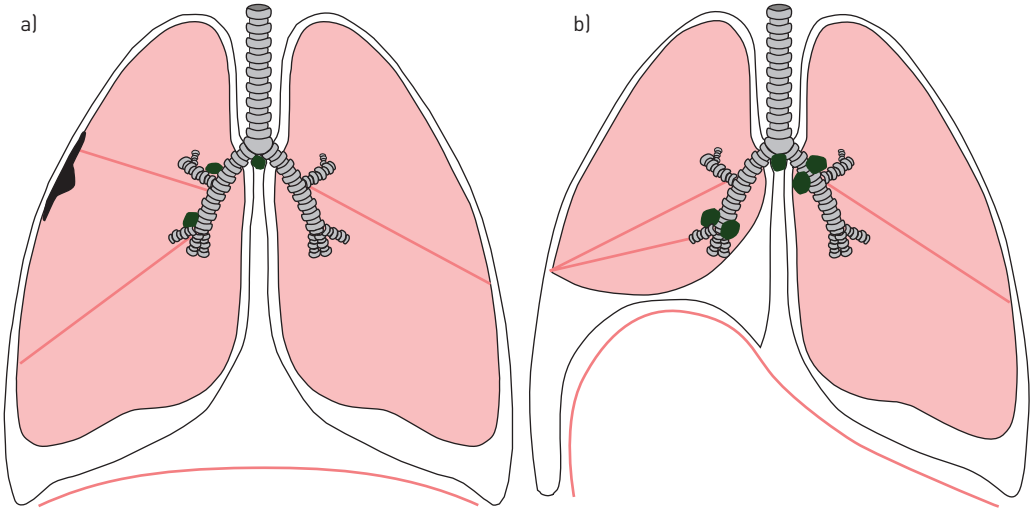

FIGURE 1 Schematic illustration of intrathoracic lymph node disease variably categorised as either sputum smear-negative pulmonary tuberculosis (TB) or extrapulmonary TB using standard adult classification. a) Uncomplicated lymph node disease may include radiologically visible Ghon foci with adjacent pleural reaction and/or regional lymph nodes. b) Complicated lymph node disease with complete airway obstruction and lobar collapse (right middle and right lower lobe collapse with bronchus intermedius obstruction, as illustrated for right lung) or partial obstruction with a ball-valve effect and hyperinflation (as illustrated for left lung). Reproduced and modified from [1] with permission from the publisher.

TABLE 1 Differences between adult and paediatric tuberculosis (TB)

Aspect	Adults	Children
Epidemiology/awareness	Massive global disease burden that is well quantified; excellent awareness	Massive global disease burden that is poorly quantified; increasing awareness
Control	Main focus of TB control programmes	Not a TB control priority
Pathology	Usually ''adult-type'' cavitary lung disease	Usually intrathoracic lymph node disease
Bacterial load/transmission/infection control	Multibacillary Highly infectious; strict infection control measures required to limit airborne aerosol transmission	Paucibacillary Low infection risk, but may be infectious if extensive lung involvement with/without cavities; epidemiological marker of transmission
Drug resistance	Difficult to differentiate acquired from transmitted (primary) drug resistance	Usually transmitted (primary) drug resistance indicating recent transmission
Exposure history	Important, but often neglected	Essential part of diagnostic work-up
Risk of progression to disease after infection	Relatively low risk, unless immunocompromised or relevant comorbidities	Highly variable risk: greatest in the very young and/or immune compromised; time dependent: greatest within the first year after infection
Preventive therapy	Limited individual benefit, except in immunocompromised; may assist to sterilise the ''pool of latent infection'' in areas with limited transmission according to the principle of TB elimination	Definite individual benefit, especially in very young (<5 years of age) and/or immunocompromised children
Imaging studies	CXR mainly performed to evaluate the extent of lung involvement or to exclude active disease	CXR (both PA and lateral views) are the most informative study to perform for diagnostic/screening purposes
Disease classification	Traditional pulmonary *versus* extrapulmonary distinction; the term ''post-primary TB'' is confusing and should best be replaced[#]	Diverse spectrum of pathology requires accurate disease classification; for reporting purposes, intrathoracic lymph node disease best classified as sputum smear-negative pulmonary TB
Microbiological studies	Easy to collect adequate respiratory specimen Bacteriological confirmation usually achieved	Difficult to collect adequate specimen (young children cannot expectorate); bacteriological confirmation frequently absent; use of culture and Xpert MTB/RIF[¶] improve yield, but highly dependent on disease manifestation
Treatment	⩾4 drugs	⩾3 drugs, depending on likely organism load and severity of disease
Prognosis	Excellent outcomes achievable with timely and appropriate treatment Rapid disease progression rare	Excellent outcomes achievable with timely and appropriate treatment Rapid disease progression not uncommon in very young or immunocompromised children Potentially grave outcome with delayed diagnosis

CXR: chest radiography; PA: posteroanterior. [#]: the term ''post-primary'' TB obscures the fact that adult-type TB frequently results from recent re-infection or documented primary infection (particularly in adolescents) and not necessarily from re-activation of a distant infection; [¶]: Cepheid, Sunnyvale, CA, USA. Reproduced from [1] with permission from the publisher.

Robust case definitions

The inclusion of a positive tuberculin skin test and/or interferon-γ release assay result as a ''verifying test'' is confusing, since neither differentiates *Mycobacterium tuberculosis* infection from TB disease [1, 15]. European Union standards of TB care acknowledge the role of these tests in screening for *M. tuberculosis* infection, but a positive result offers only ancillary evidence for TB disease while a negative result cannot be used as a rule-out test [16]. Although roll-out of the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) test offers the prospect of rapid molecular diagnosis [17], yields in children remain suboptimal (~70% of culture-positive cases, which represents the minority of children treated for TB). This emphasises the difficulty of establishing robust case definitions for use in research. To offer clear guidance for diagnostic research, a consensus document was developed following a US National Institutes of Health-sponsored workshop in Washington, DC, USA, that defines standard case definitions for use in clinical research [18]. Table 2 provides a summary of the disease categories proposed. The fact that diagnostic yields varied widely depending on specimen type in the Danish study probably reflects differences in the disease spectrum and age profile of patients in whom these specimens were collected [19], though variations in the quality, quantity, and technique of sample collection and processing can also have a significant impact. Improved

DOI: 10.1183/09031936.00133613

TABLE 2 Clinical case definitions for consideration, derived from consensus intrathoracic tuberculosis (TB) case definitions proposed by the US National Institutes of Health expert group for use in clinical paediatric research

Category	Definition
Confirmed TB	Present with relevant signs and symptoms and microbiological confirmation[#]
Probable TB	Present with relevant signs and symptoms and chest radiography consistent with intrathoracic TB and/or other imaging consistent with extra-thoracic TB and ⩾1 of the following: documented TB exposure; immunological evidence of *Mycobacterium tuberculosis* infection; clinical response to TB treatment
Possible TB	Present with relevant signs and symptoms and CXR is consistent with intrathoracic TB and/or other imaging consistent with extrathoracic TB or ⩾1 of the following: documented TB exposure; immunological evidence of *M. tuberculosis* infection; clinical response to TB treatment
TB unlikely	Not fitting the above definitions and no alternative diagnosis established
Not TB	Not fitting the above definitions and alternative diagnosis established

It is acknowledged that clinical research, routine patient care and epidemiological surveillance may require different diagnostic thresholds; the case definitions proposed should be widely applicable and encourage more consist reporting irrespective of the resources available. CXR: chest radiography. [#]: includes microscopy, culture or the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). Reproduced from [18] with permission from the author.

specimen collection methods and diagnostic tests with enhanced sensitivity in children with paucibacillary disease remain key research priorities [2].

Drug-resistant TB

Relatively few children with drug-resistant TB were detected in Denmark (18 out of 159, 11.3%), but as in Sweden [11], the majority of cases originated in sub-Saharan Africa and figures were highly dependent on immigration patterns. Globally, the ominous rise of drug-resistant TB threatens the very fabric of traditional TB control efforts [20]. Although levels of multidrug (isoniazid and rifampicin)-resistant (MDR)-TB in children are highly variable among countries, the proportion of MDR-TB in children and adults is similar in many settings, and there is no indication that children have lower risk of MDR-TB than adults [21]. In Europe, high rates of drug-resistant TB in conflict areas around the globe pose particular threats among the refugee population, while many eastern European states struggle with high rates of ''indigenous'' drug-resistant TB. In Moldova, up to 60% of children diagnosed with culture-confirmed TB have MDR-TB, demonstrating on-going MDR-TB transmission within the country [22]. In general, the outcome of MDR-TB treatment in children is excellent, if the diagnosis is timely and access to second-line drugs can be secured [8, 23]. Since the management of children with MDR-TB can be daunting, the European Respiratory Society/WHO Consilium has been established to support clinicians with the management of difficult cases [24]. The provision of preventive therapy to young and vulnerable contacts of MDR-TB cases remains controversial due to a lack of rigorous evidence [25]; however, the available evidence suggests benefit and more TB clinicians are considering its use [26].

Inclusive strategies to consider

The rise of drug-resistant TB and the long-term objective of global TB elimination demand increased efforts to reduce vulnerability at the community level, optimise early case detection and explore novel ways of reducing ongoing transmission within communities.

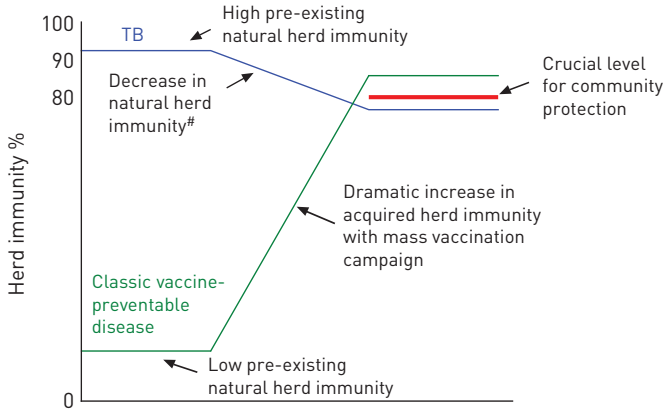

FIGURE 2 Applying the concept of "natural herd immunity" to illustrate key differences between tuberculosis (TB) and classic vaccine-preventable diseases. #: decrease in natural herd immunity influenced by the social determinants of disease; the effects of an ageing global population and the rapid rise in noncommunicable diseases may also contribute. Reproduced and modified from [31] with permission from the publisher.

Targeted active case finding and wide-scale use of preventive therapy

TB elimination is defined as the point at which less than one infectious (sputum smear positive) case per 1 000 000 inhabitants emerges annually in the general population or when the prevalence of TB in the general population is <1% and continues to decrease. Working towards this goal requires multiple areas of action, including enhanced case finding and careful reassessment of TB prevention strategies [27, 28]. Targeted active case finding is important, since delayed diagnosis facilitates on-going TB transmission. Accurate programmatic data, consideration of local circumstances and operational research should guide active case finding efforts. Massive policy–practice gaps in the provision of TB preventive therapy to young and vulnerable children in TB-endemic areas should be addressed [2, 4], while wide-scale use of preventive therapy to reduce the "pool of latent infection" requires consideration in nonendemic areas with limited transmission [28, 29].

Moving towards zero TB transmission

An interesting opportunity is presented by the situation in Denmark, where TB is essentially an imported disease and local transmission is minimal, reflecting the reality in many low-burden countries. Providing a formal definition of being "TB transmission free" and challenging nonendemic countries to aspire to this goal may galvanise national action and encourage the incorporation of cutting-edge molecular tools into routine TB control activities together with the development of active response systems [30]. Benefits of new molecular tools such as whole-genome sequencing include rapid detection of known drug-resistance mutations (allowing for earlier initiation of effective medications, thereby cutting transmission) and accurate identification of transmission clusters to guide outbreak investigation and public health responses. It also allows TB control to join the genomic revolution and provides an important vehicle to engage low-burden countries. Achieving and maintaining the status of being TB transmission free provide a strong focus for national and regional action in nonendemic areas, similar to the focus provided by the "Roll Back Polio" campaign for global poliomyelitis eradication. Minimising local transmission also has important benefits for children.

Considering "natural herd immunity"

The observation that only a small minority of those infected with *M. tuberculosis* ever progress to TB disease remains intriguing; however, it is rarely appreciated that this important characteristic differentiates TB from classic vaccine-preventable diseases. The fact that >90% of immune-competent individuals are inherently "resistant" to TB provides a high level of natural herd immunity. The natural herd immunity concept underlies the importance of population factors that may erode this herd immunity effect to below the crucial level required for community protection (fig. 2) [31]. At a population level, natural herd immunity is significantly reduced by the social determinants of disease, such as malnutrition, HIV infection, age-related immune immaturity, diabetes mellitus, chronic lung disease and cigarette or biofuel smoke exposure [32]. It is important to recognise that both natural and acquired, induced by a protective vaccine, immunity contribute to herd immunity. Acknowledging the natural herd immunity concept does not detract from the urgency to explore novel vaccination approaches, but it emphasises the need to consider inclusive strategies to reduce relevant comorbidities and address the social determinants of disease.

Better integration with maternal and child health programmes

Children are poorly served by traditional TB control efforts and service delivery channels, especially in resource-limited settings. This calls for better integration of TB care into maternal and child health

DOI: 10.1183/09031936.00133613

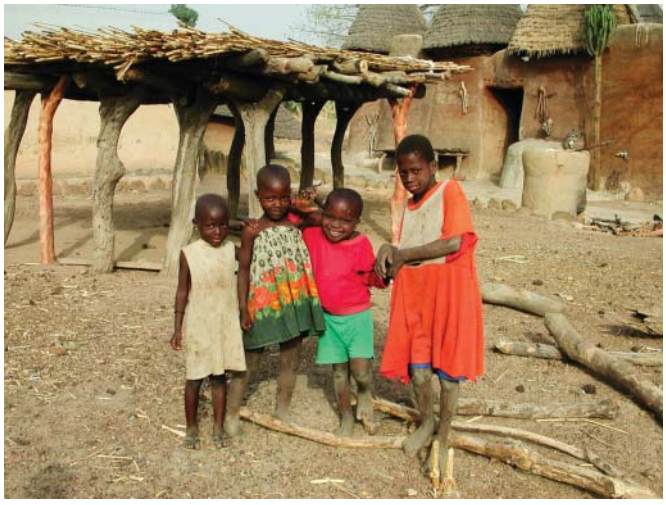

FIGURE 3 Children in Benin. Copyright© MatthieuZellweger (with AIDSpartners.org)/ matthieuzellweger.com

programmes [33]. Despite well-recognised benefits and latent synergies, practical service integration remains a major challenge, given existing funding channels and performance assessment formats [34, 35]. There have been numerous calls to reassess the way that global health support programmes to ''do business''. A recent paper by the president of the World Bank, Jim Kim, emphasised the urgent need to redefine global healthcare delivery models [36].

Conclusions

The report by HATLEBERG *et al.* [5] presents interesting longitudinal data and demonstrates the value of good quality surveillance data, which would be enhanced by better disease classification. Paediatric cases encourage a renewed focus on strategies to reduce TB transmission. Approaches that incorporate rapid whole-genome sequencing into routine surveillance may in future guide targeted public health interventions and assist European countries to become TB transmission free. It also encourages TB control agencies to reconsider the role of treating latently infected individuals, and to identify integrated strategies that will reduce vulnerability at the population level and improve service delivery to children in TB-endemic areas (fig. 3).

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DOI: 10.1183/09031936.00133613