Childhood Tuberculosis: Epidemiology and Natural History of Disease

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Abstract Despite previous misperceptions that childhood tuberculosis (TB) is less relevant, since children tend to develop mild disease, contribute little to transmission and do not impact epidemic control, awareness is growing that TB is an important preventable cause of disease and death among children in TB endemic areas. At an operational level there remains an urgent need for feasible and implementable policies to guide management in resource limited settings. This manuscript reviews the epidemiology and natural history of TB in children in order to improve understanding of the various disease entities encountered and to provide the rationale for different management approaches.

Keywords Childhood · Pediatric · Tuberculosis

Epidemiology

Tuberculosis (TB) is predominantly a disease of the poor and marginalized, although human immunodeficiency virus (HIV) infection is another major driver of the epidemic in certain areas [1]. Poor case ascertainment and limited surveillance data hampers the efforts to accurately quantify the disease burden associated with childhood TB [2]. No formal figures are currently available from the World Health Organization (WHO). They recently requested all National TB control Programmes (NTPs) to report future TB cases in 3 age categories; less than 5 years, 5–14 years and adult cases (≥15 years). Hopefully more accurate figures will become available in the near future, but this will be greatly dependant on improved access to care and more reliable diagnosis of TB in children.

Children develop TB in areas where infectious patients (usually adults and adolescents with cavitary lung disease) spread the infection. High rates of transmission are sustained in TB endemic areas due to high case density and prolonged diagnostic delay [3]. Since childhood TB reflects ongoing transmission, children are worst affected in areas where the adult epidemic is poorly controlled. Children rarely contribute to disease transmission, since they tend to develop pauci-bacillary disease and have reduced tussive force compared to adults [3, 4]. However, cavitary and/or sputum smear-positive disease frequently occur in older adolescent children (>8–10 years of age) and they constitute the same transmission risk as adults [4–6].

The only published estimates of the global pediatric TB disease burden are outdated and likely represent an underestimate of the current situation. Of the estimated 8.3 million new cases of TB diagnosed in 2000, 8,84,019 (11%) were children less than 15 years of age [7]. The most recent WHO figures estimate that 9.4 million new TB cases were diagnosed during 2008, with most cases living in Africa and Asia [1]. No pediatric estimates were included. In a prospective community-based survey performed in an area of South Africa little affected by the HIV-epidemic, children <13 years of age contributed 13.7% of the total disease burden with a calculated TB incidence of 408/100,000/year; the reported adult TB incidence in this community during the same time period was 840/100, 000/year [8]. It is estimated that with accurate diagnosis and good reporting systems children <15 years are likely to contribute 10–20% of the disease burden in TB endemic areas, with an TB incidence estimated at roughly 50% of that recorded in adults [9].
Under Detection of Child Cases

Apart from the few prospective surveillance studies reported there is convincing circumstantial evidence that childhood TB is grossly under detected in most TB endemic areas. 1) The child to adult case ratio is often less than 5%; far less than the 10–20% expected in areas with poor epidemic control. It is reasonable to observe low child to adult case ratio’s in developed countries where ongoing transmission is limited and preventive therapy is diligently provided. However, this would not be expected in developing countries with poorly controlled epidemics and non-functional preventive therapy programs. 2) Contrary to what one would expect from the natural history of disease [5], the age profile of child TB cases is often skewed towards older children (>5 year of age). This probably reflects diagnostic limitations in settings where TB case identification is sputum smear based, which is also supported by the disease spectrum observed. 3) The disease spectrum includes mainly children with sputum smear-positive disease (diagnosed at smear microscopy centres) and those with chronic and/or visible disease manifestations such as cervical adenitis or TB of the spine with gibbus formation. From the natural history of disease and from prospective studies conducted, sputum smear-negative intra-thoracic disease affecting young children should be the most common disease manifestation. Clearly, these are also the children that pose the greatest diagnostic challenge in areas with limited resources.

From these informal observations it is evident that children with TB are frequently misdiagnosed in TB endemic areas and that we are currently only seeing the “tip of the iceberg”, with the bulk of cases passing “below the radar screen”. The misperception that children with TB rarely develop serious disease was created by the experience in developed countries where diligent contact tracing and active case finding ensures that children are diagnosed early in their disease course. In stark contrast to the experience in developed countries, children who present with TB to health care facilities in endemic areas frequently demonstrate advanced disease [10] and TB is a major contributor to under-5 morbidity and mortality. A landmark autopsy study conducted in Zambia challenged many earlier assumptions, when it demonstrated that TB rivals bacterial pneumonia as a major cause of death from respiratory disease, both in human immunodeficiency virus (HIV)-infected and -uninfected children [11].

Impact of HIV and Drug Resistance

The HIV epidemic has had a major negative impact on TB control efforts, especially in sub-Saharan Africa [12]. In addition to increased absolute numbers of TB patients, HIV changed the epidemiology of TB by inducing a marked age and gender shift. More young adults and women of child bearing age started to develop TB, drastically increasing the exposure of young and vulnerable children in these communities [13]. Exceptionally high levels of TB exposure have been documented in infants born to HIV-infected mothers in hyperendemic areas. In a South African study, TB exposure was reported in 71/766 (10.1%) infants aged 3–4 months old and living in HIV-affected households [14].

Due to the paucibacillary nature of pediatric TB children are far less likely to acquire drug resistance and/or transmit drug-resistant organisms than adults, unless they have cavitary disease or extensive lung infiltration. Although children contribute very little to the creation of the drug-resistant epidemic, they are greatly affected by it. Ineffective treatment of drug-resistant cases permit ongoing TB transmission and since child TB cases reflect transmission, the drug resistance patterns observed among child TB cases provides an accurate estimate of primary/transmitted drug resistant TB within communities [15]. Globally, the emergence of the drug-resistant TB epidemic threatens the very fabric of TB control and unless effective measures are urgently implemented to limit transmission, the emergence of drug-resistant TB is likely to accelerate and affect greater numbers of children in the near future [16].

Natural History of Disease

Rontgen discovered X-rays in 1895 and chest radiographs became widely available in the Western world after the First World War, enabling the diagnosis of childhood TB. The first TB drugs only became available after the Second World War with more effective drugs following in the early 1950s. Therefore, the period from 1920 to 1950 represented a golden opportunity for accurate disease diagnosis and description; without effective treatment influencing the natural history of disease. Excellent observational studies were conducted during this time, characterized by the meticulous long-term follow-up of patients. Large cohorts of children were carefully monitored for the development of disease following primary infection with Mycobacterium tuberculosis, providing detailed descriptions of disease presentation and progression without the influence of chemotherapy or HIV infection [5]. Since the discovery of safe and effective TB treatment, conducting studies on the natural history of disease became unethical; therefore, these historic disease descriptions remain invaluable today. Critical review of the natural history of disease identified three central concepts that are important to consider when addressing current and/or future challenges in the field of childhood TB; 1) the need for accurate case definitions, 2)
the importance of risk stratification, and 3) the diverse spectrum of disease pathology, which necessitates accurate disease classification [4, 17].

Primary Infection

Primary infection is believed to occur when a previously uninfected child inhales a single infectious aerosol droplet (containing <5 bacilli) that penetrates into a terminal airway. A localized pneumonic process, referred to as the primary parenchymal (Ghon) focus, results at the site of organism deposition. Initially (for the first 4–6 week), unrestrained multiplication occurs within the Ghon focus and bacilli drain via local lymphatics to the regional lymph nodes and beyond.

The upper lobes drain to ipsilateral-paratracheal nodes, while the rest of the lung drains to peri-hilar and sub-carinal nodes, with dominant lymph flow from left to right. The Ghon complex is represented by both the Ghon focus, with or without some overlying pleural reaction, and the affected regional lymph nodes. Occult dissemination frequently occurs during this early proliferative phase before cell-mediated immunity is fully activated and bacteriologic cultures collected at this time may even be positive in the absence of clinical disease [18].

Case Definition Implications

Accurate case definition revolves mainly around the ability to differentiate primary infection from active disease. Uncomplicated hilar adenopathy remains the most common disease manifestation in children [19]. However, the pre-chemotherapy literature documented transient hilar adenopathy in the majority (50–60%) of children following recent primary pulmonary infection, of whom only a few progressed to disease [5]. The natural history of disease illustrates that progression to disease is indicated by the onset of persistent, non-remitting symptoms, referred to as the breakpoint of clinical significance, while the complete absence of symptoms usually indicates good organism containment [5]. By convention, asymptomatic hilar adenopathy is currently treated as active disease, although early experience (the U.S. Public Health Trials of the 1950’s and 1960’s) with isoniazid alone demonstrated that one drug therapy was sufficient in these cases. In terms of pathophysiology, microbiology and natural history, asymptomatic hilar adenopathy is more indicative of recent primary infection than active disease [5, 19].

This indicates that radiologic signs should be interpreted with caution in the absence of clinical data. The entity of so-called “asymptomatic TB”, where the case definition rests exclusively on radiographic criteria, is a case in point. High-resolution computed tomography (CT) is the most sensitive tool available to detect hilar adenopathy, but interpreting the relevance of the finding is highly problematic in the absence of symptoms suggestive of active disease [20]. The patient population studied and disease spectrum observed should always be carefully considered, since asymptomatic child contacts with visible hilar adenopathy may only reflect recent primary infection, while radiologic signs in symptomatic children indicate active disease. Inconsistent application of case definitions may confound the scientific interpretation and comparison of results [17].

Risk Stratification

The natural history of disease demonstrates that age is the most important variable that determines the risk to progress to disease following primary *M. tuberculosis* infection in immune competent children. (Table 1) Children with HIV infection and/or other forms of immune compromise, such as severe malnutrition seem to experience a similar high risk as very young immune immature children [5]. The vast majority (>95%) of children who progress to disease, do so within 12 months of primary infection [5], and therefore it seems prudent to categorize all children <3 years of age and immune compromised children of any age as high-risk. In these high risk children the provision of preventive therapy is warranted following documented TB exposure and/or infection, once active disease has been excluded [21].

Immune competent children ≥3 years of age are at low risk of progression to disease following primary infection.

### Table 1 Age-specific risk to develop tuberculosis following primary *M. tuberculosis* infection

<table>
<thead>
<tr>
<th>Age at primary infection</th>
<th>Risk of tuberculosis in immune competent children</th>
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<tbody>
<tr>
<td>&lt;2 years</td>
<td>No disease 50–70%</td>
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<tr>
<td></td>
<td>Pulmonary disease 10–30%</td>
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<tr>
<td></td>
<td>TBM or miliary disease 2–10%</td>
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<tr>
<td>2–10 years</td>
<td>No disease 95–98%</td>
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<tr>
<td></td>
<td>Pulmonary disease 2–5%</td>
</tr>
<tr>
<td></td>
<td>TBM or miliary disease &lt;0.5%</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>No disease 80–90%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease 10–20%</td>
</tr>
<tr>
<td></td>
<td>TBM or miliary disease &lt;0.5%</td>
</tr>
</tbody>
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Adapted from: The natural history of childhood intra-thoracic tuberculosis—A critical review of the pre-chemotherapy literature [5].

*TBM* tuberculous meningitis

*More than 95% of disease progression occurs in the first year after infection, which explains why all children <3 year are regarded as high-risk.*
However, since the vast majority of children become infected after 2–3 years of age, these low-risk children still contribute a significant percentage of the total disease burden [10]. In this group disease progression is slow and usually accompanied by persistent, non-remitting symptoms, which allows symptom-based passive case finding [22].

**Disease Diversity**

Childhood TB is often reported as a single disease entity, although it represents a diverse spectrum of pathology [19, 23]. Accurate disease classification is important, because of its prognostic significance and also to facilitate scientific communication and ensure optimal case management. The various disease manifestations show clear patterns related to; 1) the age at the time of primary infection (Figs. 1 and 2) the time since infection occurred (Fig. 2) [23]. The disease manifestations observed in immune compromised children seem to correlate with those seen in very young (<3 year of age) children.

**Intra-thoracic Lymph Node Disease**

Involvement of the regional lymph nodes (peri-hilar or paratracheal) is considered the radiological hallmark of primary infection (Figs. 3 and 4), and it is most common in children <5 years of age, probably due to exuberant lymph node responses and the small calibre of their airways. Both antero-posterior (AP) and lateral views are required for optimal lymph node visualization, since the lateral view allows better visualization of perihilar, especially subcarinal, lymph nodes.

Apart from uncomplicated lymph node enlargement a whole range of lympho-bronchial pathology and/or involvement of adjacent anatomical structures are possible. Airway compression is an important and fairly pathonomonic sign, which is best visualized on a high kilovolt (KV) chest radiograph. Partial airway obstruction may cause a check-valve effect with distal hyperinflation, while total airway obstruction results in the resorption of distal air with alveolar collapse. When a caseated lymph node erupts into an airway, caseous material may be aspirated and the resulting pathology may range from caseating pneumonia to hypersensitivity induced inflammation depending on the bacterial load and viability of the bacilli aspirated. Caseating pneumonia causes progressive parenchymal destruction; affected segments/lobes often become expansile (bulging against their anatomical boundaries) and areas of parenchymal breakdown (cavitation) may be visible on the chest radiograph. (Fig. 5) Anatomical structures that are rarely involved include; the phrenic nerve with unilateral diaphragmatic palsy, the oesophagus with the formation of a broncho- or tracheo-oesophageal fistula, and/or the thoracic duct with the formation of a unilateral chylothorax.

**Pleural Effusion**

Pleural effusions are unusual in children <3 years of age and tend to develop within the first 3–9 months after primary infection. A persistent loculated fluid collection may indicate caseating TB empyema, but this is rare. The accumulation of the typical lymphocyte-rich, straw-coloured fluid, containing very few organisms represents a hypersensitivity response. The amount of pleural fluid typically obliterates 30–60% of the affected hemithorax, although massive fluid collections may cause mediastinal shift and cardiovascular compromise. (Fig. 6)

**Pericardial Effusion**

Pericardial effusion usually develops when a subcarinal lymph node erupts into the pericardial space, but hematogenous spread is also a possibility. On chest radiograph the heart shadow is often enlarged with a suggestive globular appearance, although cardiac ultrasound is the most sensitive way to confirm the presence of a pericardial effusion. Short term complications include atrial collapse with signs of heart

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**Fig. 1** Schematic time-line, indicating the average time when different disease manifestations occur, following primary infection with *M. tuberculosis*
failure, while long term sequelae include constrictive pericarditis.

Disseminated (Miliary) Disease

Dissemination represents a condition of infinite gradation. Although occult dissemination is common following primary infection, it rarely progresses to disseminated disease except in very young (<2–3 years of age) and immune compromised children [5]. The typical radiologic signs include the presence of even sized miliary lesions (<2 mm) that are distributed bilaterally into the very periphery of the lung. (Fig. 7) Diagnostic confusion often exists in HIV-infected children in whom lymphocytic interstitial pneumonitis (LIP), malignancies and opportunistic infections such as *Pneumocystic jiroveci* may present with a similar radiological picture [13].

Adult-Type Disease

Adult-type disease is a phenomenon that suddenly appears around puberty and is distinguished by cavitation that occurs predominantly in the lung apices. (Fig. 8) Although the apices are especially vulnerable, the posterior segments of the upper lobes and the superior segments of the lower lobes are also frequently involved. The natural history of disease indicates that adult-type disease may follow rapidly (within 6–12 months) after primary infection (as documented by tuberculin skin test conversion), and the majority of adolescents who develop adult-type disease do so within 2 years after primary infection [5, 23]. This implies that adult-type disease in adolescents, most frequently follows inappropriate containment of a recent primary infection rather than reactivation of an old, well-contained infection. Two hypotheses, summarized as preferential organism deposition and preferential organism growth, have been proposed to explain the typical anatomical distribution and the particular vulnerability of the lung apices.

On inhalation, airflow is directed towards the dependent lung zones, which should favour organism deposition in the lung bases. However, it has been postulated that preferential deposition of tubercle bacilli in the lung apices may be facilitated by air trapping that occurs with coughing or due to preferential hematogenous spread (so called Simon foci) [23]. Radiographically visible Ghon foci in children and

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Fig. 2: Schematic age-line, indicating the age profile of different disease manifestations following primary infection with *M. tuberculosis*

Fig. 3: Right hilar lymph node enlargement (antero-posterior view)—adapted from [19]

Fig. 4: Lateral chest radiograph confirming enlarged hilar nodes—adapted from [19]
those seen at autopsy show no predilection for the upper lobes and the dependant zones of the right lung (middle and lower lobes) seem most frequently involved [5]. Thus the hypothesis of preferential deposition is not supported by clinical observation and most importantly, it does not explain the distinct absence of adult-type disease until puberty.

The alternative hypothesis of preferential organism growth also fails to explain the absence of adult-type disease until puberty; however, it may do so when viewed in conjunction with the changes that occur in the immune response around puberty. Major changes relating to the effective containment of primary *M. tuberculosis* infection seem to occur around 2 years of age, and around puberty (>8–10 year of age) when hormonal changes may be an important factor in the altered pathogenesis [24]. It seems reasonable to deduce from clinical observation that a change towards more aggressive containment, often accompanied by tissue necrosis, occurs around puberty. This destructive immune response may allow the organism to take full advantage of a favourable micro-environment. The oxygen tension is highest in the lung apices due to high ventilation/perfusion (V/Q) ratio’s, which may encourage more vigorous growth and multiplication of *M. tuberculosis* in these areas. Apart from the relatively high oxygen tension; poor blood flow and decreased lymph formation may also contribute to the vulnerability of the lung apices. Thus, the combination of destructive attempts at organism containment together with increased organism survival and multiplication in the lung apices, may initiate a positive feed-back loop that results in a vicious circle of escalating parenchymal destruction [23]. This hypothesis would explain the sudden emergence of adult-type tuberculosis around puberty, as well as its anatomical localization.

**Conclusions**

Awareness regarding the importance of childhood TB as a cause of serious disease and death in TB endemic areas is growing. WHO has compiled a formal guidance for the management of TB in children [25], and the Global Drug Facility recently made quality assured child friendly drug formulations available to poor countries [26]. However, many barriers to service delivery remain in place.
A thorough understanding of the natural history of disease and disease diversity in children is essential, since it has relevance for TB research [17], pragmatic diagnosis [22] and optimal management [27]. The vulnerability of pregnant women and young children to develop TB also emphasizes the important contribution that TB control should play to promote maternal and child health, especially in TB endemic areas such as India [28].

**Conflict of Interest** None.

**References**