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Childhood TB, part 1

Childhood TB - the overlooked epidemic

This edition of HATIP is the first part of a two-part clinical review of the management of TB in children with HIV (the second half will appear later in December).

Childhood TB has been a long overlooked area of TB control, but childhood cases of TB contribute around 15% of the total burden of TB cases worldwide. Infants are at particularly high risk of dying quickly from TB,[1] and children with HIV have up to a tenfold greater risk of dying from TB than children with TB alone.

Most programmes seem to be poorly equipped to deal with most aspects of TB disease in children. There seems to be uncertainty about the size of the problem, which is directly related to problems diagnosing it — or how to distinguish an infection from a case of progressive active TB with limited diagnostic tools. How can programmes with limited resources find cases or act to prevent them; are the existing treatment regimens adequate and how should TB care and HIV care be coordinated for HIV-infected children?

There's a wealth of literature published about these problems, but relatively little reliable prospective clinical data to guide management of TB in children. With some notable exceptions, researchers and policy developers have mostly neglected the matter.

"At policy meetings, childhood TB just falls off the table," Mark Harrington of the Treatment Action Group told HATIP. "It's usually left until the end of the agenda, and then it's, 'oh sorry, we've run out of time.'"

Why has childhood TB been overlooked?

In a 2002 editorial in the International Journal of Tuberculosis and Lung Disease (IJTLD), Dr Jeffrey Starke of Texas Children's Hospital listed a number of reasons for childhood TB's low profile:[2]

• A degree of resignation about the inability to confidently diagnose young children with TB since routine inexpensive methods like smear microscopy are unreliable in children, especially those who are HIV-infected (to be discussed in part 2).

• Since younger children aren't usually smear-positive, they are considered to be rarely contagious and have thus been given a low priority by global tuberculosis control efforts and national programmes

• A misplaced faith in the effectiveness of BCG vaccines, which have had a mixed performance at preventing disease (and which studies show shouldn't be used in HIV-infected children, to be discussed in part 2)

• Limited interest from paediatricians, who have rarely been involved in developing tuberculosis control policies and setting priorities

• Research has been stymied by lack of funding and lack of interest from both investigators and funders; and:

• "Efforts have been crippled by the tired dogma that the best way—some say the only way—to prevent childhood tuberculosis is to treat and prevent tuberculosis in adults," Starke concluded.

When TB elimination seemed at hand — that is, before the HIV epidemic — that approach might have seemed more reasonable. But "today it's quite clear that we are going to have childhood tuberculosis with us as long as we have adult tuberculosis," said Professor Peter Donald, speaking at the Union World Conference on Lung Health in October 2008 in Paris. Professor Donald and his colleagues at the Desmond Tutu TB Centre at Stellenbosch University and Tygerberg Children's Hospital in the Western Cape in South Africa seem to have done the lion's share of paediatric TB research in the last decade or so.

Few others have shown so much interest in the issue, and as a result of the neglect, programmes fail to find TB-exposed children and take simple and effective measures to prevent disease. Children with active TB go undiagnosed, or only receive their diagnosis after being subjected to repeated and sometimes invasive

investigations or inappropriate treatments — if they survive that long. Conversely, in some settings, children may be over-diagnosed with TB —with the actual cause of their illness left untreated.[3] Programmes have not worked out how best to treat or manage difficult cases; for instance, most programmes appear to be completely unequipped when it comes to managing drug-resistant TB in children.

In addition, the entire process winds up putting a tremendous financial and social burden upon already impoverished families. Supportive and palliative measures to reduce the child and family's suffering often get lost in the shuffle or, in some cases have been sacrificed upon the altar of TB control (to be described in part 2). So it should come as little surprise that treatment outcomes are very poor. For instance, in a study in Malawi, only 45% of children completed treatment: 17% died, 13% defaulted and the treatment outcomes were unknown in 21%.[4]

HIV seems to increase the risk of these poor outcomes. For instance, a study in South Africa found that children coinfected with HIV and TB have between two to ten times the risk of early mortality than children with TB alone, while Mukadi et al reported that the risk of death in children with HIV and TB was six times higher than that in children with just TB.[5] [6] Finally, in a study in Ethiopia, 7% of the children with TB alone died, but 41% of those with TB and HIV died.[7]

TB transmission to children

The epidemiology of childhood TB mirrors that of TB in adults, associated with the same difficult socioeconomic and environmental conditions[8]. Children with TB often come from vulnerable populations or impoverished settings, live in crowded housing with inadequate ventilation (commonly in congested urban settlements) and are likely to have immune systems that have been weakened by malnutrition, HIV or other serious illnesses.[9, 10, 11, 12, 13]

Since children under 5 years tend to progress from infection to active disease quite rapidly, TB in a young child is a clear indication of deficiencies in the local TB programme since it represents recent and ongoing transmission of *mycobacterium tuberculosis* (m.TB) infection within the community.[14]

In young children (under 5 but especially under 2 years of age), most of the transmission comes from inhaling droplets produced by a coughing person with infectious smear-positive TB living in their own household.[15] However, in a rigorous review of the best of the pre-TB therapy research (up until the 1960s), Marais et al found substantial evidence demonstrating that "household exposure to a sputum smear-negative source case or non-household exposure to a sputum smear-positive source case posed a reduced, but still appreciable risk."[16] In fact, 30–40% of children exposed to someone with smear-negative TB became infected. A more recent study suggests that 17% of transmission is due to smear negative cases.[17]

Nevertheless, close contact with a highly infectious person poses the greatest risk. For instance, a study in the Gambia has reported that along with the severity of the source case (duration of cough, degree of lung involvement), the likelihood of infection is significantly related to the intensity of exposure to the source case (or intimacy), as measured by both the geographic proximity to the individual with TB at night-time (sleeping in the same bed) and the extent of activities shared with the individual with TB during the day-time[18]. This was linked with how closely the child was related to the source case — in other words, most young children get TB from their parents or caregiver.

Again, a proportion of transmission may come from other members of the household, such as grandparents, neighbours or visiting family or community members.[19] In addition, the definition of a household can vary, and multiple family dwellings are more common in some congested settings. A study of TB transmission in Uganda reported that most of the households included in the survey were part of multifamily housing units called 'muzigos'.[20] Each room in the muzigo contained a median of three persons— with typically only one window per house, while 22% had no windows. In such settings, the TB source cases may be among the neighbouring families — in the same house.

Another example of this comes from an oral poster presentation at this year's Union World Conference on Lung Health which described a household in a poor urban community in the Western Cape containing four families living in separate rooms but sharing the kitchen and bathroom.[21] Although there was one index TB case that had permitted access to the household, investigators discovered that there had been a history of at

least ten previous TB cases in the residence. All but one of the twelve children living there tested positive for TB exposure and at least three were diagnosed with active TB — and at least one of these came from a family without a previous history of TB.

Children who accompany their mother to health facilities where TB infection control practices are inadequate could also be at risk of TB exposure. Recently, in South Africa, there have been reports of transmission occurring within kangaroo care units (providing care to premature babies) due to exposure to other mothers with TB.[22] Presumably children with HIV and other health problems who repeatedly visit health facilities would also have an elevated risk of acquiring TB nosocomially.

Later, as children grow older and their social contacts broaden — when they start walking around, or go to school —the potential for exposure to TB within the community increases, and the annual risk of infection (ARI) becomes greater in older children.[23] There is also a risk of transmission within schools or children's homes[24]. For instance, at the first South African TB Conference this year, Dr David Moore described a TB outbreak in a children's home in Khayelitsha where 36 children lived in a four-room house.[25] After the index case was diagnosed, investigations within the home found that 46% of the children tested TST positive, while active disease was confirmed in four satellite cases.

Over time, more and more children become infected so that in some TB endemic settings, such as the townships and informal settlements in the Western Cape, 70-80% have been infected by the time they reach adulthood.[26, 27]

The burden of paediatric TB

But even though children have had less opportunity to be infected with TB than adults, they are more likely to progress to active TB if infected.[28] Even before the HIV epidemic, at least 40% of children under 1 year of age and 23% of those aged between 1 and 4 years who were infected with TB were at risk of progressing to active disease.[29]

So it should be expected that, in resource-limited settings where TB is endemic, children contribute a significant proportion of the disease burden and suffer severe tuberculosis-related morbidity and mortality.[30] Exactly how much is unclear despite all the surveys, because there isn't really an agreed case definition of active disease (see below), there are differences in case finding practices, differing abilities to accurately diagnose TB, and differences in registration and reporting of cases.

According to guidance for national TB programmes, put out in 2006 by the WHO and the Stop TB Partnership Childhood TB Subgroup, roughly one million (or 11%) of the 9 million annual cases of active TB occur in children under the age of 15 years of age. These estimates are very close to those reported by Corbett and colleagues, who took the reported number of smear-positive cases by age in 2000 and then calculated overall disease burden based upon the proportion of cases that are usually smear-positive in each age group (for instance, the vast majority of TB cases in children under 12 years of age are smear-negative). [31, 32]

According to these calculations about 75% of the global burden of paediatric TB is found in the 22 countries with the highest burden of TB. But the rates do vary greatly. Children with TB make up about 2.7% of the total TB cases in Thailand, around 16.9% of the cases in South Africa and up to 25.3% of cases in Afghanistan and Pakistan. However, these proportions may be influenced by how well each country performs at case finding, diagnosing and registering these TB cases in children, along with other variables (the proportion of children to adults in the population, etc).

For instance, in a survey of childhood TB in Malawi, a significantly higher ratio of childhood TB to all TB cases were diagnosed at central and mission hospitals compared with district hospitals; while hospitals with a specialist paediatrician found that 15.7% of TB cases were in children, in hospitals without a specialist only 10.1% of TB cases were found in children.[33]

"The general rule of thumb is that children represent approximately 15% of the TB burden in the developing world," wrote the authors of a report on a Workshop on Childhood TB, at the Union World Conference on Lung Health in 2002."[34]

However, "incidence differs widely between countries as well as communities," said Dr Robert Gie of the Desmond Tutu Tuberculosis Centre at the Union World Conference in Paris. For instance, according to a study in 1996, cases were distributed very unevenly through Ravensmead and Uitsig, two periurban areas near Cape Town[35]. At the time, the two communities, covering an area of 2.42 km^2, had a high overall case rate of TB (over 1000 per 100,000) but the case rate by subdistrict varied from 78 to 3,150/100,000. However the increased burden of active disease in children in such a setting could be disproportionately higher, since in many low-income areas, the population is often younger (and, again, children are more likely to rapidly progress to active disease than adults).

"As the TB incidence rises in deprived communities, so too does the proportion of the caseload caused by children," Professor Donald wrote in one review paper.[36] There are at least a couple of studies supporting this. One reported that between 1985 and 1995, the TB case rate quadrupled in Blantyre, Malawi, but the rise was steepest among children, from 64 per 100,000 in 1985 to 507 per 100,000 in 1995.[37] In another, van Rie et al reported that children made up 39% of the caseload in an urban community with a high incidence of TB in the Western Cape.

On the other hand, an increasing HIV epidemic could alter this balance, since HIV makes active disease much more common among adults as well.

The net impact of HIV upon the risk of TB exposure and infection

The effects of the HIV pandemic (and the related surge in TB throughout sub-Saharan Africa) upon the TB epidemic in children are quite complex. Perhaps counter-intuitively, the HIV epidemic does not seem to have had a clear and dramatic impact on the rate of new TB infections in children — at least at the population level. In fact, data from Tanzania and Uganda suggest that there has been a stable or slightly decreasing annual rate of infection among children since the HIV epidemic, though a study in Kenya has reported an increase.[38,39,40]

A recently published cross-sectional study by Middelkoop et al, that looked at TST results in 831 children between the ages of 5–17 years at one school in a community near Cape Town with a high (and increasing) prevalence of HIV among adults, reported a very high annual rate of TB infection, at 4.1% per year — a rate about four to five times higher than seen in most other countries in Africa.[41] And yet, looking at already published data from the same community, the authors conclude that there hasn't been a major increase in TB transmission since the spread of HIV and explosion in TB in the community which has only happened within the last seven or eight years. Nor did they observe an increase in active TB case notification rates among children in the community, although they acknowledged that TB case notification is quite low and that the TB control programme may be missing cases.

"It appears that HIV infection–associated TB is not the major determinant of the [the annual risk of TB infection] in this community," the authors conclude.

There could be a number of possible explanations for this. "It may well be the case that the sheer magnitude of the epidemic in Cape Town dwarfs any age-specific difference in infection at any given time," Dr Hans Rieder wrote in an accompanying editorial.[42]

Another possibility is that improvements in healthcare delivery and TB case management, or changes in the population, or better nutrition and housing since 1999 could have offset or masked the impact of the HIV/TB epidemic on transmission in this particular community. In fact, it may be a mistake to make too much of one study in just one school. In Paris, Dr Gie presented the results of slightly earlier TST surveys of school children in the Ravensmead and Uitsig communities, which noted a slightly decreased incidence in Ravensmead between 1999 and 2005 (from 3.5% to a 3.1% annual risk of infection) but an increased incidence in Uitsig (from 4.1% to 5.5%) over the same period. Uitsig and Ravensmead are neighbouring communities but the pattern of TB transmission among the children who live there seems to be diverging.

But HIV may not affect the rate of transmission as much as one might expect because a significant proportion of people coinfected with HIV/TB may have smear-negative disease (are less infectious) and may have a much shorter survival time during which to transmit the infection. Moreover a survey of school-aged

children will miss a significant proportion of the TB-exposed children who do not survive the first few years of life — especially those who are HIV-infected and more likely to die of TB or other illnesses (see below).

Despite the effects at the population level, "there is evidence that HIV-infected children are more likely to be exposed to parents with smear-positive TB than non-HIV-infected children," wrote Mukadi and De Cock in 1997.[43] This is at least partly because HIV has resulted in a shift towards more people of child-bearing age developing TB.

A recent study by Dr Mark Cotton of Tygerberg Children's Hospital and colleagues reported very high rates of MTB exposure among HIV-exposed infants being screened for entry into PACTG 1041, an isoniazid preventive therapy (IPT) study in South Africa.[44] Out of 766 infants aged three to four months old, seventy-seven had had a documented contact with a TB source case. According to the authors' calculations, "the maximum incidence of TB exposure was 10,026/100,000, predicting a possible infection rate of 5013/100,000 and a rate of disease of 2005/100,000. The potential for drug-resistant TB disease from those detected at formal screening was 213/100,000."

There are some limitations in the study, such as the fact that not all the TB contacts may have been highly infectious; but on other hand, referring clinics had been specifically instructed not to send *any* TB-exposed infants to the trial investigators (since children known to be TB-exposed were excluded from the trial and put directly on IPT) — so the fact that so many showed up would seem to indicate an even bigger problem in the community. In addition, these infants were only a few months old so the annual risk of exposure can be expected to be even higher.

Indeed, the estimated case rates at Tygerberg Hospital are lower that what was actually found in another IPT study by Dr Heather Zar and Dr Cotton and colleagues, where 23.4/100 HIV-infected children developed TB per year.[45] The children in that study had a median age of about 2 years and most were not on ART. Speaking at a symposium at the 2007 Union World Conference on Lung Health, Dr Cotton stressed that "this was fairly well diagnosed TB that's gone through a peer review process" (as opposed to the majority of reports of childhood TB in the literature, which are often unconfirmed cases).

The case rate is similar to that observed in a retrospective record review including 980 children with HIV at four different hospitals in South Africa (three in Johannesburg, one in Cape Town).[46] The median age was older in this cohort, at 6.8 years. There was an incidence of 16.3 cases per 100 child years in all the children not on ART (which reduced the incidence by 60%), though few of the cases were confirmed by microscopy or culture (an indication that clinicians often don't bother to pursue further investigation of TB in many children with HIV).

The incidence is significantly higher than what is reported for the general population of children in South Africa. For instance, in 1999, van Rie et al reported an incidence of 3588 per 100,000 children between 0 – 5 years old from a retrospective analysis looking at 10 years of TB case notification data in the Western Cape (while the HIV prevalence was still low in that province). Several years later Marais et al reported a case rate of 441 per 100,000 children years in children under the age of 13 in a 21 month prospective study.[47]

Thus, one of HIV's greatest effects on childhood TB is to increase the risk of progression from TB infection to active disease.

Active TB in children - the influence of HIV

This was recently demonstrated quite clearly by another study presented by Dr David Moore at the South African TB Conference.[48] The study looked at the burden of TB in a cohort of 39,836 children participating in a placebo-controlled pneumococcal vaccine trial in Soweto, South Africa from 1998 to 2000. An estimated 6.5% of the children were HIV-infected (based upon antenatal seroprevalence data and expected vertical transmission rates).

Both the study and the ancillary hospital (Chris Hani Baragwanath (CHB)) databases were reviewed to identify participants with or suspected of having TB. TB was classified as confirmed TB (with culture or microscopy confirmation), probable pulmonary TB (clinical and radiological evidence without microbiological

confirmation) and probable extrapulmonary TB (clinical, radiological or histological evidence without culture confirmation). Children were stratified by age and HIV-status.

Looking just at the CHB database, there were 2654 study participants admitted to the general paediatric wards, with a total of 4164 admissions (693 children had recurrent admissions — and most were HIV positive). Overall, 39.5% of HIV positive children from the study were admitted to CBH, compared to just 3.9% of the HIV-negative children (OR 16.3; 95% CI, 14.8 – 17.9), p<0.001. Of the admissions, 423 (15.9%) were due to TB, 273 (64.5%) of these were in the small subset of HIV-positive children. Children with HIV were also more likely to have recurrent TB.

Including just the first episode of TB from the study participants admitted to CBH, children with HIV had an incidence rate of 2223 per 100,000 child-years for all forms of TB, and 708 per 100 000 child-years for confirmed TB, compared to 394 per 100,000 child-years and 105 per 100,000 child-years respectively for the HIV-negative children. The risk ratios for TB between HIV positive and –negative, hospitalised children were 5.6 (95% CI, 5.1 – 6.3), p<0.001 for all forms of TB, 5.7 (95% CI, 5.0 – 6.5), p<0.001 for probable pulmonary TB and 6.7 (95% CI, 5.5 – 8.3), p<0.001 for microbiologically-confirmed TB.

In the trial database there were 1062 cases per 100,000 for all forms of TB and 231 for culture-confirmed TB overall. This yielded a crude incidence rate of 10,594 per 100,000 for all forms of TB and 2406 per 100,000 for culture-confirmed disease for the HIV-positive children, and 384 per 100,000 and 81 per 100,000 respectively for the HIV-negative children. The risk ratio for a child with HIV compared to a child without HIV was 27.6 (95% CI, 22.6 – 33.7), p<0.001 for developing any form of TB and 29.9 (95% CI, 19.4 – 46.4), p<0.001 for culture-confirmed tuberculosis.

While TB incidence rates in children are lower in countries with a lower annual risk of TB infection, the incidence among children with HIV can still be quite elevated. For instance, in one study in Abidjan, 7 new cases of TB were identified in 98 children with HIV, yielding a case rate of 8.5 per 100 patient years (in children not on ART).[49]

In a necropsy study from Zambia, Chintu et al found evidence of tuberculosis in 32 (18%) of 180 HIV-positive and 22 (26%) of 84 HIV-negative children who died of a respiratory disease.[50] TB was actually the third most common cause of respiratory infection found in autopsies in the HIV positive children — and of note, although miliary TB was detected in some children, by design, these autopsies, which did not include death from other causes, would not detect the contribution of extrapulmonary TB to childhood mortality.

The risk of TB appears to be greatest in the children with HIV with more advanced disease and immune suppression. For instance, in ANRS 1278, an observational cohort study of 282 HIV-infected children in Abidjan, Côte d'Ivoire, there was a cumulative incidence of tuberculosis of 2500/100,000 at one year.[51] But the incidence of TB in children with CD4 <15% was almost 4 times higher, while, the incidence of TB was 30 times higher in children with high viral loads (over 5 log/ml) than in children with lower viral loads.

"Recent disease descriptions in HIV-infected children indicate that immune-compromised children behave in a similar fashion to immune immature children (less than 2 years of age)," wrote Marais et al in another review paper addressing the natural history of intra-thoracic TB in children[52]. And the younger a child when infected with TB, the more likely he or she is to rapidly develop active TB.

The second part of this article, due to be published later this month will discuss the natural history of TB in children with HIV, and its diagnosis and management.

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