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REVIEW ARTICLE

# A research agenda to promote the management of childhood tuberculosis within national tuberculosis programmes

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SUMMARY

**Despite causing considerable mortality and morbidity, childhood tuberculosis (TB) is a neglected aspect of national tuberculosis programmes (NTPs), particularly in developing countries. A recently published World Health Organization (WHO) document, 'Guidance for national tuberculosis programmes on the management of tuberculosis in children', addresses the effective management of children within NTPs. Taking into account this document and following a literature review, research priorities are identified to promote the integration of childhood tuberculosis into NTPs. The implications of human immunodeficiency virus (HIV) infection apply to all aspects of this agenda.**

**The major priorities are:**

- **The prospective evaluation of the incidence of childhood TB and the monitoring of programme performance with regard to childhood TB. A lot of data are already available within many programmes that could inform this process.**
- **Study of the criteria to suspect and diagnose childhood TB using uniform criteria as defined in the Guidance document mentioned above. Evaluate new methodologies for this purpose.**
- **Study the pharmacokinetics and toxicity of antituberculosis drugs in children and the long-term outcome of the treatment of children.**
- **Determine how many childhood contacts of adult pulmonary TB qualify for chemoprophylaxis in different communities. Study chemoprophylaxis for drug-resistant TB and chemoprophylaxis among certain groups of adolescents.**
- **Document at what level children enter NTPs, the availability of qualified staff and their effectiveness in performing diagnostic investigations and ensuring quality care. Study the role of families as agents for DOTS, evaluate private sector participation in childhood TB management.**
- **Document bacille Calmette-Guérin (BCG) immunisation complications and study management strategies.**

**KEY WORDS**: TB; childhood; research; national programmes

*. . . a joint meeting of the Tuberculosis Association and the British Paediatric Association was held, and, in spite of the friendly spirit evident, it was clear that each party viewed the problem in an entirely different light. The Tuberculosis Association members quoted figures from their official returns, both of morbidity and mortality, which were at total variance with the clinical experience of the paediatricians, and in the main their conclusion was that 'childhood tuberculosis is not of great importance to the public health services', and their plea was for the paediatricians to preserve a sense of proportion!*
—W F Gaisford[1]

THE WORLD HEALTH ORGANIZATION (WHO) policy document 'Guidance for national tuberculosis programmes on the management of tuberculosis in children' provides guidance on the effective management of childhood tuberculosis (TB) as part of routine national tuberculosis programme (NTP) activities.[2] One of the ways to redress the chronic neglect of children with TB is to promote their diagnosis and treatment as part of routine NTP activities. This helps to ensure high-quality care (including diagnosis in line with international standards and treatment with recommended standardised regimens) and improved documentation of disease burden and treatment outcomes.

Research plays an important role in the implementation of recommended policies for effective management of childhood TB as part of routine NTP activi-

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ties. This article identifies the priorities for this research, based on a review of the literature relevant to the six key areas of activity (reflecting those set out in the WHO policy document):

- Epidemiology, programme monitoring and evaluation
- Diagnosis
- Anti-tuberculosis treatment
- Contact screening and management
- Health staff and family roles and responsibilities
- Bacille Calmette-Guérin (BCG) vaccination.

## METHODS

The literature reviewed was derived from an electronic search using PubMed with the key words tuberculosis, childhood, epidemiology, diagnosis, treatment and control. This search produced more than 400 papers dating from 1950. Cross-referencing was undertaken using a comprehensive paediatric TB literature library maintained by the Desmond Tutu Centre for Tuberculosis and the Department of Paediatrics and Child Health of Stellenbosch University. In conducting this review, preference was given to papers based on substantial amounts of prospective data. State of the Art reviews were included and policy statements by governmental and professional organisations when valuable or important policy points were stated or debated.

## EPIDEMIOLOGY: PROGRAMME MONITORING AND EVALUATION

The WHO declared TB a global emergency in 1993, and since then has promoted the strategy for global TB control known as DOTS. This strategy emphasises finding and curing patients with sputum microscopy smear-positive pulmonary tuberculosis (PTB), who are mainly responsible for spreading infection and maintaining the TB epidemic.[3] As children seldom have PTB that is sputum smear-positive, they have often been neglected by NTPs, despite significant numbers of children requiring treatment in high-incidence communities and considerable morbidity and mortality.

Childhood TB has diverse manifestations, pulmonary and extra-pulmonary, and the development of serious forms of disease is strongly influenced by age at infection. In young children, progression of the primary complex and dissemination of TB is particularly likely, leading to miliary TB and tuberculous meningitis (TBM). In all analyses, children infected when aged <1 year have excessively high morbidity and mortality, and those aged 1–4 years have considerable mortality and morbidity before entering the so-called 'safe' school age of 5–10 years, when morbidity and mortality are at their lowest. For example, in the United States the 1940 TB mortality rate (per 100 000 infected children) was 4920 for those aged <1 year, 123 for those aged 1–4 years and 18 for those aged 5–9 years.[4] A similar survey in London for 1945–1949 found a TB mortality rate (per 100 000 infected children) of 5960 for those aged <1 year, compared with 770 for those aged 1–4 years and 7 for those aged 5–9 years.[5] After 10 years of age an increasing incidence of adult-type disease is found.

In countries with low TB incidence, childhood TB constitutes approximately 5% of the TB case load. Incidence rates vary from <1 to 10/100 000. As young children are infrequently exposed to infection, serious forms of disease are unusual. However, higher rates may be encountered, rising to >50/100 000 among subgroups of socially disadvantaged, and immigrant, communities.[6]

In developing countries, with generally a high TB incidence, a high annual risk of infection (ARI) with *Mycobacterium tuberculosis*, combined with a proportion of the population aged <15 years that is close to 40%, leads to children being infected at a younger age, which in turn means a greater frequency of severe forms of TB. Because of the difficulty of confirming a diagnosis of TB in children and inadequate data recording, little accurate information regarding childhood TB is available from countries with a high TB incidence. Available data indicate that 20% or more of the case load may be childhood TB and incidence rates of childhood TB may be in excess of 200/100 000. In one estimate from developing countries with an overall TB incidence of 171/100 000, children comprised 15% of the TB burden.[7] In South Africa in 1993 the national incidence of TB was 224/100 000 and children constituted 20% of the case load.[8] In a community near Cape Town, South Africa, with a particularly high incidence of 1149/100 000, children constituted 39% of the case load.[9] As the TB incidence rises, so there will be a disproportionate rise in the percentage of the case load comprised by children.

It may also be possible to estimate the TB incidence in children by comparison with historical data. Between 1936–1940 and 1941–1945, the ARI was 1–2% in the Netherlands, and the mortality from all TB forms (but mainly TBM and miliary TB) in children aged 0–4 years was between 32 and 34/100 000 and for children aged 5–14 years between 14 and 17/100 000.[10] In a number of developing countries, an ARI of between 1% and 2% has been found recently, suggesting a situation similar to Europe between 1936 and 1945. In the Western Cape Province of South Africa for 1985–1987, an ARI of approximately 2.5% was found, and the TBM incidence in children 0–4 years was 24/100 000.[11]

Children with human immunodeficiency virus/acquired immune-deficiency syndrome (HIV/AIDS) are also exceptionally susceptible to TB. Evidence of the HIV/AIDS and TB interaction among children continues to accumulate, particularly from sub-Saharan Africa.[12] At Queen Elizabeth Central Hospital, Blantyre, Malawi, the number of children diagnosed with TB increased from 64 in 1986 to 525 in 1993; of 105 children with TB HIV-tested in 1996, 64% were positive.[13]

As HIV-related TB is common among women of childbearing age (HIV-related TB is one of the leading non-obstetric causes of maternal death in Zambia[14]), infants may often be exposed to HIV infection and TB.[15]

With adolescence there is a striking rise in the TB incidence, which now has adult-type characteristics with apical lung infiltration and cavity formation. More females than males develop these features and the risk of adult-type disease in adolescence is 2–6 times greater in females than males.[16] Disease follows infection more commonly in adolescents than in children aged 5–10 years. Among more than 600 children infected before adolescence, 7% developed adult-type TB after an 'average' of 5 years; most adult-type disease followed a primary infection that occurred after 7 years of age, and none developed in those infected as infants.[17] It is also during adolescence that sexual activity might commence in communities with a high HIV and TB incidence; this creates an opportunity for linked TB and HIV interventions. Thus counselling, voluntary HIV testing and TB chemoprophylaxis could play an important role in pregnant teenagers. This is also an age during which adherence to treatment is problematic and needs further study.

In routine NTP recording and reporting of children with TB, the standard international definitions for case categories and treatment outcomes apply. There are three important justifications for the recommended policy of routine NTP recording and reporting of children in the two age categories, 0–4 and 5–14 years.[2] First, accurate measurement of the TB disease burden in children and epidemiological trends is important, especially in developing countries where the great bulk of childhood TB is found. NTPs that may already collect this information can often make good use of it for these purposes. Second, it enables monitoring and evaluation of NTP performance specifically in relation to the standard of care for children. Third, monitoring and evaluation of disease trends in the 0–4 years age group can be useful in overall assessment of TB epidemiology, because disease in these young children usually reflects recent transmission.

Research priorities regarding the epidemiology of childhood TB and programme monitoring and evaluation are summarised in Table 1.

**Table 1** Proposed research priorities regarding the epidemiology of childhood tuberculosis and programme monitoring and evaluation

| |
|---|
| Epidemiology |
| • Evaluate how best to use data already existing in some NTPs to improve the documentation of the burden of childhood TB |
| • Determine prospectively the incidence of childhood TB, and its morbidity and mortality, making use of the internationally agreed-upon criteria and utilising the proposed definitions; carry out these studies at a number of centres under different epidemiological and social conditions and include children with and without HIV infection; quantify the burden of childhood TB in the age groups 0–4 and 5–14 years, and distinguish the burden of EPTB and the proportion of children with TB who are smear-positive and who are HIV-infected |
| • Carry out annual risk of infection studies across a spectrum of communities in rural and urban areas |
| Programme monitoring and evaluation |
| • Monitor and evaluate the management of childhood TB by NTPs using the routine NTP reporting and recording system, including treatment outcomes according to standard international definitions |
| • Evaluate the accuracy of classification of cases as smear-positive PTB, smear-negative PTB and EPTB |

NTP = National Tuberculosis Programme; TB = tuberculosis; EPTB = extra-pulmonary tuberculosis; HIV = human immunodeficiency virus; PTB = pulmonary tuberculosis.

## DIAGNOSIS OF TB

*It has been given many names, such as juvenile tuberculosis, puerile tuberculosis, infantile tuberculosis, Ranke's primary complex, hilum tuberculosis, tracheobronchial node tuberculosis, primary and secondary tuberculosis . . .*
—J A Myers, L M Kernkamp[18]

Accurate, consistent diagnosis is critical not only to the effective management of children with TB but also to measuring the precise burden of childhood TB. In the short-term there is little prospect of a widely available 'gold standard' diagnosis of TB in children by the current techniques of microbiological detection (microscopy and culture) or by new diagnostic techniques (including nucleic acid amplification techniques and serology). Until the introduction of improved means of diagnosis, standardised approaches to diagnosis continue to rely on clinical criteria, chest radiography (CXR) and tuberculin skin testing (TST).[2]

### *History and symptoms*

Table 2 lists history and symptoms used by various authors to diagnose childhood TB. Of 27 papers, 21 (78%) use contact with an adult with TB, 19 (70%) cough, 16 (52%) fever and 14 (59%) failure to thrive or loss of weight. A smaller number of papers suggest failure to respond to antibiotics (9, 33%) or the presence of superficial nodes (6, 22%). In 5 (19%) papers, reference is made to a 'symptom complex' compatible with childhood TB. Other symptoms include abdominal distension, difficulty walking, sputum production, chest pain, haemoptysis, anorexia, malaise/fatigue and bone deformities. Some of these are obviously intended to accommodate extra-pulmonary forms of TB. One interesting criterion in the scoring system of Stegen et al. is age $<2$ years, thus accommodating the higher mortality and morbidity of the young.[19]

For each criterion there are varying definitions; as an example of this diversity some definitions relating to contact with an adult with TB are summarised in Table 3. Only three definitions link duration to the contact. The WHO policy document recommends that

**Table 2** History and symptoms leading to the diagnosis of tuberculosis in children

| Authors | Contact | Failure to thrive/ weight loss | Cough | Fever | Response to antibiotics | Palpable nodes | Symptom complex |
|---|---|---|---|---|---|---|---|
| Stegen et al. (1969)[19] | + | | | | | | |
| Aderele (1979)[20] | + | | + | + | + | | |
| Ghidey and Habte (1983)[21] | + | + | + | + | | + | |
| Cundall (1986)[22] | + | | | | | | |
| Kumar et al. (1990)[23] | | + | + | + | | + | |
| Reis et al. (1990)[24] | + | + | + | + | | | |
| Migliori et al. (1992)[25] | + | | + | | | | |
| Pineda et al. (1993)[26] | + | | + | + | + | | |
| Seth et al. (1993)[27] | + | + | + | + | | | |
| Luo et al. (1994)[28] | + | | | | | | + |
| Chintu et al. (1995)[29] | + | | | | | | + |
| Schaaf et al. (1995)[30] | + | + | + | | + | | |
| Espinal et al. (1996)[31] | | + | + | + | | + | |
| Jeena et al. (1996)[32] | + | | | | + | | + |
| Garay (1997)[33] | | + | + | + | + | | |
| Mukadi et al. (1997)[34] | | | + | + | + | | |
| Fourie et al. (1998)[35] | + | + | + | + | | | |
| Houwert et al. (1998)[36] | + | + | + | | | | |
| van Beekhuizen (1998)[37] | | + | | + | | + | |
| Mahdi et al. (2000)[38] | + | | | | | | + |
| Kiwanuka et al. (2001)[39] | | + | + | | + | | |
| Salazar et al. (2001)[40] | + | | + | + | | | |
| Blussé van Oud-Alblas et al. (2002)[41] | + | | | | | | |
| Palme et al. (2002)[42] | + | + | + | + | | | |
| van Reenen (2002)[43] | + | + | + | + | | | |
| Weismuller et al. (2002)[44] | + | | + | + | + | + | + |
| Indian Academy of Pediatrics (2004)[45] | + | + | + | + | + | + | |
| Total, *n* (%) | 21 (78) | 14 (52) | 19 (70) | 16 (59) | 9 (33) | 6 (22) | 5(19) |

close contact be defined as 'living in the same household as or in frequent contact with a source case (e.g., the child's caregiver) with sputum smear-positive PTB'. In the literature reviewed, cough is either mentioned without any duration or the duration varies from >2 weeks[25,34,36,42] to >3 weeks,[45] 4 weeks or >4 weeks.[39,46] Expert consensus recommends a definition of chronic cough as 'an unremitting cough, that is not improving and has been present for more than 21 days'.[2] Fever is recommended as a criterion in 16 papers, but its degree and duration are seldom defined. A definition of fever as a feature of suspected childhood TB based on expert consensus is 'body temperature >38°C for 14 days after common causes such as malaria or pneumonia have been excluded'.[2] Malnutrition, in one form or another, featured in 52% of the criteria. This might be stated merely as 'loss of weight',[21] 'weight loss',[23,25] 'weight loss of >10%',[34] or 'malnutrition'.[37] Expert consensus draws particular attention to the significance of weight loss or failure to gain weight 'especially after being treated in a nutritional rehabilitation programme'.[2]

Stegen et al. draw a distinction between signs or symptoms that bring children to our attention, as opposed to those that are specific for TB.[19]

**Table 3** Definitions of a child's contact with an adult with pulmonary tuberculosis

- Living in the same household or in frequent contact with a source case (e.g., caregiver) with sputum smear-positive pulmonary TB[2]
- History of close contact with cases of tuberculosis[20]
- A person in the immediate household of the child had confirmed or probable tuberculosis[22]
- Household contact with a tuberculous adult[25]
- Family history of tuberculosis[27]
- History of close contact with a case of tuberculosis[28]
- Close household contact with a recently diagnosed adult case of pulmonary tuberculosis[30]
- Recent known exposure to an active case of tuberculosis[31]
- Close household contact with an adult with active pulmonary tuberculosis diagnosed within the previous 12 months[35]
- Family history of TB[37]
- An adult contact with active TB and/or who had received treatment within the previous 6 months[38]
- Recent close household contact with an adult with sputum microscopy smear-positive pulmonary TB[41]
- Living in a household with an adult taking anti-tuberculosis therapy or who has taken such therapy in the past 2 years[45]

### *Clinical signs and investigations*

Table 4 summarises clinical signs and investigations used to diagnose childhood TB. The almost total reliance on CXR and Mantoux testing is noteworthy. Thirty-one (94%) of 33 papers refer to the use of CXR

**Table 4** Signs and investigations utilised in the diagnosis of childhood tuberculosis

| Authors | Culture | AFB | Histology | PCR | TST | CXR | Mal-nutrition | Clinical features | Response to treatment |
|---|---|---|---|---|---|---|---|---|---|
| Stegen et al. (1969)[19] | | + | + | | + | + | | + | |
| Aderele (1979)[20] | + | | + | | + | + | | + | |
| Ghidey and Habte (1983)[21] | + | | + | | + | + | | | |
| Cundall (1986)[22] | | + | | | + | + | | | |
| Starke and Taylor-Watts (1989)[47] | + | | | | + | | | + | + |
| Kumar et al. (1990)[23] | + | + | + | | + | + | | | |
| Reis et al. (1990)[24] | | + | + | | + | + | | | |
| Migliori et al. (1992)[25] | | + | + | | + | + | | | + |
| Goodyear et al. (1993)[48] | + | | | | + | + | | + | |
| Pineda et al. (1993)[26] | + | + | | | + | + | | | + |
| Seth et al. (1993)[27] | | | | | + | + | + | | |
| Luo et al. (1994)[28] | | + | + | | + | + | | | + |
| Chintu et al. (1995)[29] | | + | | | + | + | | + | + |
| Schaaf et al. (1995)[30] | + | | | | + | + | + | | + |
| Espinal et al. (1996)[31] | + | + | | | + | + | | | + |
| Jeena et al. (1996)[32] | | | + | | + | + | | | + |
| Garay (1997)[33] | + | + | | | + | + | | | + |
| Mukadi et al. (1977)[34] | + | | | | | + | | | + |
| Fourie et al. (1998)[35] | + | | + | | + | + | + | | |
| Houwert et al. (1998)[36] | + | | | | + | + | | | |
| van Beekhuizen (1998)[37] | + | | | | + | | + | | |
| Neu et al. (1999)[49] | + | + | + | + | + | + (CT) | | + | |
| Mahdi et al. (2000)[38] | + | + | + | | + | + | | + | |
| Ibadin and Oviawe (2001)[46] | | + | | | + | + | | | |
| Kiwanuka et al. (2001)[39] | + | + | | | + | + | | | |
| Salazar et al. (2001)[40] | + | + | | + | + | + | | | |
| Wong et al. (2001)[50] | + | | + | | | + | | | |
| Blussé van Oud-Alblas et al. (2002)[41] | + | + | + | | + | + | | | |
| Palme et al. (2002)[42] | | + | + | | + | + | | | |
| Sánchez-Albisua et al. (2002)[51] | + | + | | | + | + | | + | |
| van Reenen (2002)[43] | + | + | + | + | + | + | + | | |
| Kabra et al. (2004)[52] | | + | + | | + | + | | | |
| Indian Academy of Pediatrics (2004)[45] | + | + | + | | + | + | | | |
| Total, *n* (%) | 22 (66) | 21(64) | 17 (52) | 3 (9) | 31 (94) | 31 (94) | 5 (15) | 8 (24) | 10 (30) |

AFB = acid-fast bacilli; PCR = polymerase chain reaction; TST = tuberculin skin testing; CXR = chest X-ray; CT = computerised tomography.

and 31 (94%) papers to Mantoux TST. With reference to the first, it should be noted that the assessment of children's CXRs is complicated by technical factors (variation in inspiration penetration and rotation) and inter-observer variation.

With regard to Mantoux TST, varying doses of tuberculin are used and different criteria proposed to define reactions indicating *M. tuberculosis* infection. The precise manner of measurement is seldom stated. The use of different purified protein derivative (PPD) products is probably unavoidable, but even with the same product, different strengths are applied and different degrees of induration accepted as significant. The recommendation by expert consensus is for the standardisation for each country with either 5 tuberculin units (TU) of tuberculin PPD-S or 2 TU of tuberculin PPD RT23.[2] The Mantoux skin test should be regarded as positive if ⩾5 mm induration in high-risk children (those severely malnourished or HIV-infected), or ⩾10 mm in other children. Research should, however, evaluate whether the use of a 5 mm induration 'decision point' in HIV-infected children is justified and at which point in the HIV/AIDS cycle an induration of ⩾10 mm after TST becomes unreliable. Although TST is a cornerstone of diagnosis in childhood TB, its sensitivity and specificity may at times be inadequate, and some individuals never react. Newer modalities such as interferon-gamma or T-cell based tests that might distinguish infection from disease should also be evaluated and may be particularly valuable in HIV-infected or severely malnourished children.

The success of *M. tuberculosis* culture from children will vary depending upon whether the child is investigated in hospital or the community, the child's age and the extent of disease. Gastric lavage/aspirate has long been the standard investigation for obtaining material for culture and microscopy. Although some investigators have used this procedure successfully in community clinics, it remains labour intensive. Sputum induction has a similar yield to gastric lavage, but is labour intensive and may prove difficult to implement on a large scale in the community. Naso-pharyngeal

aspiration and laryngeal swabbing are alternatives that remain to be fully evaluated in a community setting.

Some countries rely on sputum smear microscopy as the main means of diagnosis of TB. Children, however, represent a small minority of microscopy smear-positive patients, and this technique has low sensitivity and specificity, which precludes a major role in childhood TB. Any evaluation of childhood TB should nonetheless document smear microscopy results.

Nucleic acid amplification techniques have been described as 'helpful', but at best have sensitivity and specificity comparable to gastric aspirate and culture.[53,54] At their present stage of development such investigations have little to offer national programmes with regard to the management of childhood TB. Nonetheless, a programme to study the diagnosis of childhood TB might provide a platform for a more comprehensive evaluation of these techniques and their predictive value under programmatic conditions.

A significant prevalence of HIV infection creates problems with all approaches to TB diagnosis in children.[33,39,43] HIV-infected children will frequently be malnourished, immunosuppressed and have a negative TST, and will have frequent respiratory infections and lymphadenopathy for other reasons. The problems created by HIV/AIDS are graphically illustrated by Rennert et al., who took post mortem lung and liver biopsies from 93 HIV-infected children.[55] TB was confirmed in only four children (4%); a further 17 (18%) were empirically placed on TB treatment on the basis of history and clinical and radiological features. This diagnosis was not confirmed post mortem. The children's CXRs were assessed independently and a panel proved incapable of distinguishing TB from *Pneumocystis jirovecii* pneumonia, cytomegalovirus pneumonitis or interstitial lymphocytic pneumonitis.

The paper by Iriso et al. is an example of the studies required to place the diagnosis of childhood TB on a more scientific foundation.[56] This study, from an HIV-endemic area, enrolled a considerable number of children as 'suspect' cases and used culture-proven cases as a 'gold standard'. The study provides sensitivity and specificity for various criteria and determines their predictive value. Although a sensitivity of 94% was found for cough of >2 weeks, 92% for fever, 81% for a history of weight loss and 86% for the WHO scoring system, the specificity of these criteria was 0%, 3%, 12% and 22%, respectively, and the positive predictive values 32%, 31%, 31% and 35%.

Taking into consideration the above findings, Table 5 summarises research priorities regarding the diagnosis of childhood TB.

**Table 5** Research priorities regarding the diagnosis of childhood tuberculosis

- Evaluate the use of the criteria defined in the WHO policy document 'Guidance for national tuberculosis programmes on the management of tuberculosis in children'[2] to suspect childhood TB and evaluate available new methodologies for assisting or confirming the diagnosis of TB in children
- Evaluate new methodologies for establishing the presence of tuberculosis infection and/or disease in children
- Study Mantoux skin test responses in HIV-infected and non-infected children to determine sensitivity, specificity and predictive value of suggested 'cut-off points' to support a diagnosis of TB infection
- Carry out post mortem studies in children dying of suspected tuberculosis, particularly if HIV-infected, to determine the diagnostic accuracy of the various suggested criteria

WHO = World Health Organization; TB = tuberculosis; HIV = human immunodeficiency virus.

## ANTI-TUBERCULOSIS TREATMENT

The standard WHO definitions of treatment outcome apply to childhood TB.[2] As childhood TB is seldom microscopy smear-positive and infrequently culture-positive, the outcome defined as 'cure' rarely applies because this is a microbiological outcome. Even using the standard definitions, there are few studies of treatment outcomes among children with TB using the same degree of rigour as studies of TB in adults. Assessing response to treatment may also be difficult among subgroups of children because the natural history of the diverse manifestations of childhood TB varies considerably.

Studies have documented that 3- and 4-month treatment regimens give satisfactory results in adult culture-positive, smear-negative TB and also in smear- and culture-negative TB.[57] It would be of considerable benefit to NTPs if such shorter regimens were found to be efficacious in children both with and without HIV infection, with paucibacillary forms of disease such as hilar lymphadenopathy with no or limited lung infiltration, or with cervical adenopathy.

There are few pharmacokinetic studies of anti-tuberculosis agents in children, and contrary to accepted pharmacological principles, children tend to receive the same mg/kg body weight dosages of anti-tuberculosis drugs as adults. This approach can be summarised as 'one size fits all.' As we often lack definition of the precise relationship between serum concentrations of anti-tuberculosis agents and efficacy in adults, and aim at a range of values, this may be acceptable, but there is evidence that caution is necessary. In considering drug doses for children, cognisance must be taken of the greater extra-vascular fluid volume of younger children and the greater liver mass in proportion to body mass. Children receiving equivalent mg/kg body weight doses of some anti-tuberculosis agents have been shown to have lower serum concentrations than adults.[58–60] There are also varying recommendations for the doses of anti-tuberculosis agents for children. Few studies are yet available describing the absorption of anti-tuberculosis agents in children with TB and HIV-infection;[61] this is an

**Table 6** Research priorities regarding the treatment of childhood tuberculosis

- Review existing literature relating to the treatment of childhood tuberculosis to establish the response to treatment, relapse rates and what information already exists regarding the pharmacokinetics of anti-tuberculosis agents in children
- Undertake pharmacokinetic studies of each of the first-line anti-tuberculosis agents under different conditions of nutrition and HIV infection status and across a range of ages; where possible utilise sparse sampling techniques
- Undertake pharmacokinetic studies of second-line agents; a literature review might reveal sufficient information to make well-founded assumptions with regard to agents such as the fluoroquinolones and aminoglycosides
- Study drug-drug interactions, particularly in HIV-infected children, who will frequently be receiving multiple drugs other than the anti-tuberculosis agents; study drug toxicity in this complex situation
- Evaluate rates of treatment failure, recrudescence and relapse, particularly in association with HIV/AIDS
- Evaluate 3- and 4-month treatment regimens in paucibacillary forms of childhood tuberculosis and the necessity for longer treatment in HIV-infected children
- Study the treatment of drug-resistant tuberculosis in children

HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome.

important area for study. Pharmacokinetic studies should cover all paediatric age groups (e.g., children aged <2 years, 2–4 years and 5–14 years) and include children with HIV/AIDS.

As regards formulations, particular problems are experienced among children weighing <10 kg. Because very few childhood formulations are available, among these very young children tablets formulated for adults must be broken, leading to very inaccurate dosing.

The recurrence of TB, whether due to relapse or reinfection, has been documented in children, particularly in those who are HIV-infected. Nonetheless, few paediatric studies record treatment success or failure or relapse rates in children followed up for a substantial time.

Table 6 summarises the research priorities relating to the treatment of childhood TB.

## CONTACT SCREENING AND MANAGEMENT

There is no doubt as to the value of chemoprophylaxis for children in close contact with adults with sputum smear-positive, fully drug-susceptible, PTB or for children infected with *M. tuberculosis* (as judged by positive TST). The argument has been about the priority of chemoprophylaxis for NTPs in developing countries. Although many NTPs recommend chemoprophylaxis, especially for children aged <5 years, prophylactic treatment is not accorded a high priority, nor is it viewed as an essential element in TB control. Despite severe financial restrictions and personnel shortages, there are nonetheless groups of children, particularly the very young, who would benefit from contact tracing and chemoprophylaxis. New strategies for chemoprophylaxis should also be explored with assessment of simplified approaches to contacts that do not use TST or CXR.

The spread of HIV/AIDS and the use of isoniazid (INH) chemoprophylaxis in these highly susceptible individuals has given the debate surrounding chemoprophylaxis new urgency. Shorter regimens of multidrug prophylactic regimens in individuals with HIV infection give results equivalent to INH monotherapy.[61] This approach may be successful in children, without undue toxicity, and shorter regimens of 2 or 3 months of two- or three-drug chemoprophylaxis warrant evaluation, particularly where insufficient personnel are available to supervise chemoprophylaxis.[62] Research should include evaluation of the number of children who qualify for chemoprophylaxis under different circumstances and the workload that this would create, and exploration of alternative shorter chemoprophylaxis regimens in children with and without HIV infection. In countries with a high prevalence of HIV infection, children are increasingly exposed to sputum smear-negative cases of PTB; accurate assessment of the impact of these contacts is needed to offer advice as regards chemoprophylaxis under these circumstances.

Expert consensus recommends that chemoprophylaxis for susceptible children should be an integral part of NTP activities.[2]

There is no doubt as to the pathogenicity of drug-resistant strains and transmission of resistant strains from household contacts to children. At the time of diagnosis of TB in a child, clinicians should enquire about risk factors for drug-resistant TB, for example, contact with a known case of drug-resistant TB or with an adult known not to have complied with treatment or to have been treated previously for TB. The main research priorities regarding drug-resistant TB are 1) quantification of the number of children with TB who present following contact with an adult with drug-resistant TB, 2) evaluation of the consequences of that contact and the best options for managing those children exposed and 3) surveillance of the incidence of drug resistance among children as a means of determining the number of drug-resistant strains currently circulating in a community. An uncontrolled study of appropriate chemoprophylaxis found reduced disease incidence among childhood contacts of adults with multidrug-resistant (MDR) TB,[63] but more precise delineation of drugs, dosages and duration of chemoprophylaxis is needed. The relatively small numbers of children encountered by an individual researcher would necessitate collaborative studies.

As discussed above, adolescents are a vulnerable group, both for development of TB disease and for HIV infection, if they are sexually active. Pregnant teenagers are an appropriate group for targeted evalua-

**Table 7** Research priorities regarding childhood contact screening and management

- Determine the numbers of HIV-infected and non-infected children in contact with fully drug-sensitive smear-positive and smear-negative adults, and who might qualify for chemoprophylaxis in different communities
- Determine the numbers of HIV-infected and non-infected children in contact with drug-resistant smear-positive and smear-negative adults and who might qualify for chemoprophylaxis in different communities
- Evaluate the morbidity and mortality of children, HIV-infected and non-infected, arising out of contact with adults with pulmonary tuberculosis, both smear-negative and smear-positive
- Assess the value of shorter, multidrug chemoprophylaxis in both HIV-infected and non-HIV-infected children
- Study the management of childhood contacts of adults with sputum smear-positive drug-resistant tuberculosis
- Evaluate the value of the surveillance of drug resistance in childhood as a means of determining the numbers of resistant strains currently circulating in a community

HIV = human immunodeficiency virus.

tion of voluntary HIV testing and counselling, TST and chemoprophylaxis.

Table 7 summarises proposed research priorities arising from the above discussion relating to contact screening and management.

## HEALTH STAFF AND FAMILY ROLES AND RESPONSIBILITIES

Based on expert consensus, a structured case management hierarchy is proposed for children with suspected TB, with flexible implementation depending on the epidemiological situation and resources available in a particular country.[2] Research should focus on documenting the different pathways children follow in different communities to enter the NTP and evaluating the optimal approach that should be adopted under different circumstances.

In communities with high TB incidence, children frequently present with symptoms that lead to the diagnosis of TB. In communities with low TB incidence, children are more often diagnosed following contact tracing, often have less advanced forms of disease and will often be asymptomatic. When children are diagnosed following contact tracing, another family or household member will often have TB. It is, however, uncertain how often other family members will also have TB when children present with symptoms. Questions thus arise as to the possible effectiveness of a family-oriented approach in this situation. How often will other TB cases be identified in the child's family when the child presents with or without symptoms? What is the effectiveness of a family-oriented approach to contact tracing? How best can parents or other child caregivers receive the necessary counselling and advice? In addition, what is the role of family members in observing and recording treatment or chemoprophylaxis?

**Table 8** Research priorities regarding health staff and family roles and responsibilities

- Document the pathway followed to diagnose childhood tuberculosis under different epidemiological and social circumstances and the personnel responsible for this process
- Evaluate the availability of qualified staff and different investigations at various levels of care under different circumstances and the accuracy of the diagnosis of tuberculosis in children. Are chest radiography or tuberculin testing available?
- Evaluate how best children can be successfully managed within a family-oriented approach. How best can parents and other caregivers receive the necessary counselling and support to help ensure completion of treatment? Assess the effectiveness of family members in observing and recording treatment. Are there other innovative ways in which children can be treated under the DOTS strategy?
- Document the role of the private sector in all aspects of the diagnosis and management of childhood tuberculosis. To what extent have existing public/private partnerships taken cognisance of childhood tuberculosis and its particular problems?

### *The role of the private sector*

The emphasis of many NTPs has often been on the diagnosis and treatment of TB within the public sector health system. However, a considerable number of TB patients are diagnosed and managed in the private sector. This is particularly true in Asia and South America, where the majority of TB patients may be seen by private practitioners. It is also estimated that the private sector in India, which comprises 6 400 000 of the 8 000 000 registered medical practitioners, handles approximately a sixth of the world's TB cases.[64] In Pakistan as many as 80% of TB patients consult a private practitioner.[65]

Shortcomings in private sector TB care have been documented, including management inconsistent with NTP policies and deficiencies in the accuracy of diagnoses and the treatment prescribed. However, it has also been shown that patients may prefer to consult a private practitioner and have their disease managed within the 'privacy' of the private sector. This is particularly so where HIV is closely associated with TB. There is little information regarding the private sector role in managing childhood TB. In view of initiatives for private/public partnerships in TB control,[66] it is important that childhood TB should be an integral part of these plans so that the private sector can be fully engaged in delivering high quality care for children with TB.

Table 8 summarises the research priorities regarding health staff roles and responsibilities.

## BCG VACCINATION

Although in countries with high TB incidence the impact of BCG on adult TB is doubtful, the impact of BCG is well documented in reducing the risk of disseminated forms of TB (mainly miliary and meningeal) in children. The provision of BCG vaccination is the responsibility of the Extended Programme on

**Table 9** Research priorities regarding BCG vaccination

- Evaluate prospectively the incidence of BCG disease and drug sensitivities of the BCG organisms
- How best can BCG disease be managed in those countries with a high prevalence of HIV infection?

BCG = bacille Calmette-Guérin; HIV = human immunodeficiency virus.

Immunization, and the focus of this review is on the prevention and control of childhood TB in relation to NTPs. The main consideration in this context is thus the occurrence and management of complications of BCG vaccination, in particular in HIV-infected children. In the past, disseminated BCG disease was unusual and nearly always associated with severe immunosuppression. There was therefore understandable concern regarding the potential risk of BCG in newborn HIV-infected infants.[67] Prospective evaluation of immunisation practices has suggested that HIV infection is not associated with an increased incidence of BCG disease,[68] but case reports suggest the need for some caution.[69] More recently, the acquisition of resistance by the *M. bovis* BCG Danish strain has been described in a child with disseminated disease, together with inherent resistance to INH.[70]

Current WHO policy recommends vaccination of children with BCG as soon after birth as possible, and that it should be used in asymptomatic HIV-infected infants, but not in those who are symptomatic. This in effect means that all newborns in countries with a high TB incidence should be vaccinated. Prospective surveillance of BCG disease is needed to inform policies regarding BCG use in populations with a high HIV prevalence. There is also a need for a systematic evaluation of the treatment of BCG-related disease.

The research priorities for childhood BCG vaccination summarised in Table 9 therefore include the prospective evaluation of the incidence of BCG-related disease and the determination of the drug sensitivities of BCG organisms and the study of different means of managing BCG disease.

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### *References*

1 Gaisford W F. Primary tuberculosis in childhood. Br Med J 1946; 1: 84–86.
2 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO/HTM/TB/2006.371. Geneva, Switzerland: WHO, 2006.
3 World Health Organization. WHO Tuberculosis programme. Framework for effective tuberculosis control. WHO/TB/94.179. Geneva, Switzerland: WHO, 1994.
4 Rich A R. Native resistance. Individual resistance. The influence of sex and age. In: The pathogenesis of tuberculosis. Springfield, IL, USA: Charles C Thomas, 1951: pp 182–251.
5 Bentley F J, Grzybowski S, Benjamin B. Infection and fatality. In: Tuberculosis in childhood and adolescence. London, UK: National Association for the Prevention of Tuberculosis, 1954: pp 232–234.
6 Nelson L J, Wells C D. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004; 8: 636–647.
7 Murray C J L, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. Bull Int Union Tuberc Lung Dis 1990; 65: 6–24.
8 South African Department of Health, Directorate Epidemiology. Tuberculosis update. Epidemiol Comments 1995; 22: 13–17.
9 Van Rie A, Beyers N, Gie R P, Kunneke M, Zietsman L, Donald P R. Childhood tuberculosis in South Africa: burden and risk factor. Arch Dis Child 1999; 80: 433–437.
10 Styblo K, Sutherland I. Epidemiology of tuberculosis in children. Bull Int Union Tuberc 1982; 57: 133–139.
11 Berman S, Kibel M A, Fourie P B, Strebel P M. Childhood tuberculosis and tuberculous meningitis: high incidence rates in the western Cape Province of South Africa. Tubercle Lung Dis 1992; 73: 349–355.
12 Chintu C, Zumla A. Childhood tuberculosis and infection with the human immunodeficiency virus. J Royal Coll Physicians Lond 1995; 29: 92–95.
13 Harries A D, Parry C, Mbewe L N, et al. The pattern of tuberculosis in Queen Elizabeth Central Hospital, Blantyre, Malawi: 1986–1995. Int J Tuberc Lung Dis 1997; 1: 346–351.
14 Ahmed Y, Mwaba P, Chintu C, Grange J M, Ustianowski A, Zumla A. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. Int J Tuberc Lung Dis 1999; 3: 675–680.
15 Adhikari M, Pillay T, Pillay D G. Tuberculosis in the newborn: an emerging disease. Pediatr Infect Dis J 1997; 16: 1108–1112.
16 Smith M H D. Tuberculosis in adolescence. Characteristics, recognition, management. Clin Pediatr 1967; 6: 9–15.
17 Lincoln E M, Gilbert L, Morales S M. Chronic pulmonary tuberculosis in individuals with known previous primary tuberculosis. Dis Chest 1960; 38: 473–482.
18 Myers J A, Kernkamp L M. Tuberculosis infection in infancy. Am Rev Tuberc 1930; 21: 423–478.
19 Stegen G, Jones K, Kaplan P. Criteria for guidance in the diagnosis of tuberculosis. Pediatrics 1969; 43: 260–263.
20 Aderele WI. Pulmonary tuberculosis in childhood. Trop Geogr Med 1979; 31: 41–51.
21 Ghidey Y, Habte D. Tuberculosis in childhood: an analysis of 412 cases. Ethiop Med J 1983; 21: 161–167.
22 Cundall D B. The diagnosis of pulmonary tuberculosis in malnourished Kenyan children. Ann Trop Paediatr 1986; 6: 249–255.
23 Kumar L, Dhand R, Singhi P D, Tao K L N, Katariy S. A randomized trial of fully intermittent vs. daily followed by intermittent short course chemotherapy for childhood tuberculosis. Pediatr Infect Dis J 1990; 9: 802–806.
24 Reis F J C, Bedran M B M, Moura J A R, Assis I, Rodrigues M E S M. Six-month isoniazid-rifampin treatment for pulmonary tuberculosis in children. Am Rev Respir Dis 1990; 142: 996–999.
25 Migliori G B, Borghesi A, Rossanigo P, et al. Proposal of an improved score method for the diagnosis of pulmonary tuberculosis in childhood in developing countries. Tubercle Lung Dis 1992; 73: 145–149.
26 Pineda P R, Leung A, Muller N L, Allen E A, Black W A, Fitzgerald J M. Intrathoracic tuberculosis: a report of 202 cases. Tubercle Lung Dis 1993; 74: 261–266.
27 Seth V, Singhal P K, Semwal O P, Kabra S K, Jain Y. Childhood tuberculosis in a referral centre: clinical profile and risk. Indian Pediatr 1993; 30: 479–485.
28 Luo C, Chintu C, Bhat G, et al. Human immunodeficiency

virus type-1 infection in Zambian children with tuberculosis: changing seroprevalence and evaluation of a thioacetazone-free regimen. Tubercle Lung Dis 1994; 75: 110–115.
29 Chintu C, Bhat G, DuPont H L, Mwansa-Salamu P, Kabika M, Zumla A. Impact of human immunodeficiency virus type-1 on common pediatric illnesses in Zambia. J Trop Pediatr 1995; 41: 348–353.
30 Schaaf H S, Beyers N, Gie R P, et al. Respiratory tuberculosis in childhood: the diagnostic value of clinical features and special investigations. Pediatr Infect Dis J 1995; 14: 189–194.
31 Espinal M A, Reingold A L, Pérez G, et al. Human immunodeficiency virus infection in children with tuberculosis in Santa Domingo, Dominican Republic: prevalence, clinical findings, and response to antituberculosis treatment. J Acquired Imm Def Syndr Human Retrovir 1996; 13: 155–159.
32 Jeena P M, Mitha T, Bamber S, Wesley A, Coutsoudis A, Coovadia H M. Effects of the human immunodeficiency virus on tuberculosis in children. Tubercle Lung Dis 1996; 77: 437–443.
33 Garay J E. Clinical presentation of pulmonary tuberculosis in under 10s and differences in AIDS-related cases: a cohort study of 115 patients. Trop Doct 1997; 27: 139–142.
34 Mukadi Y D, Wiktor S, Coulibaly I-M, et al. Impact of HIV infection on the development, clinical presentation, and outcome of tuberculosis among children in Abidjan, Côte d'Ivoire. AIDS 1997; 11: 1151–1158.
35 Fourie P B, Becker P J, Festenstein F, et al. Procedures for developing a simple scoring method based on unsophisticated criteria for screening children for tuberculosis. Int J Tuberc Lung Dis 1998; 2: 116–123.
36 Houwert K A F, Borggreven P A, Schaaf H S, Nel E, Donald P R, Stolk J. Prospective evaluation of World Health Organization criteria to assist diagnosis of tuberculosis in children. Eur Respir J 1998; 11: 1116–1120.
37 van Beekhuizen H J. Tuberculosis score chart in children in Aitape, Papua New Guinea. Trop Doct 1998; 29: 155–160.
38 Mahdi S A, Huebner R E, Doedens L, Aduc T, Wesley D, Cooper P A. HIV-1 co-infection in children hospitalized with tuberculosis in South Africa. Int J Tuberc Lung Dis 2000; 4: 448–454.
39 Kiwanuka J, Graham S M, Coulter J B S, et al. Diagnosis of pulmonary tuberculosis in children in an HIV-endemic area, Malawi. Ann Trop Paediatr 2001; 21: 5–14.
40 Salazar G E, Schmitz T L, Cama R, et al. Pulmonary tuberculosis in children in a developing country. Pediatrics 2001; 108: 448–453.
41 Blussé van Oud-Alblas H J, Van Vliet M E, Kimpen J L L, De Villiers G S, Schaaf H S, Donald P R. Human immunodeficiency virus infection in children hospitalized with tuberculosis. Ann Trop Paediatr 2002; 22: 115–123.
42 Palme I B, Gudetta B, Bruchfeld J, Muhe L, Gieseke J. Impact of human immunodeficiency virus 1 infection on the clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. Pediatr Infect Dis J 2002; 21: 1053–1061.
43 van Rheenen P. The use of the paediatric tuberculosis score chart in an HIV-endemic area. Trop Med Intern Hlth 2002; 7: 434–441.
44 Weismuller M M, Graham S M, Claessens N J M, Meijnen S, Salaniponi F M, Harries A D. Diagnosis of childhood tuberculosis in Malawi: an audit of hospital practice. Int J Tuberc Lung Dis 2002; 6: 432–438.
45 Indian Academy of Pediatrics. Consensus statement of IAP Working Group: status report on diagnosis of childhood tuberculosis. Indian Pediatr 2004; 41: 146–155.
46 Ibadin M O, Oviawe O. Trend in childhood tuberculosis in Benin City, Nigeria. Ann Trop Paediatr 2001; 21: 141–145.
47 Starke J R, Taylor-Watts K T. Tuberculosis in the pediatric population of Houston, Texas. Pediatrics 1989; 84: 28–35.
48 Goodyear H M, Moore-Gillon J C, Price E H, Larcher V F, Savage M O, Wood C B S. Mycobacterial infection in an inner city children's hospital. Arch Dis Child 1993; 69: 229–231.
49 Neu N, Saiman L, San Gabriel P, et al. Diagnosis of pediatric tuberculosis in the modern era. Pediatr Infect Dis J 1999; 18: 122–126.
50 Wong K S, Chiu C H, Huang Y C, Lin T Y. Childhood and adolescent tuberculosis in northern Taiwan: an institutional experience during 1994–1999. Acta Paediatr 2001; 90: 943–947.
51 Sánchez-Albisua I, Baquero-Artigao F, del Castillo F, Borque C, García-Miguel M J, Vidal M L. Twenty years of pulmonary tuberculosis in children: what has changed? Pediatr Infect Dis J 2002; 21: 49–53.
52 Kabra S K, Lodha R, Seth V. Category based treatment of tuberculosis in children. Indian Pediatr 2004; 41: 927–937.
53 Smith K C, Starke J R, Eisenach K, Ong L T, Denby M. Detection of *Mycobacterium tuberculosis* in clinical specimens from children using a polymerase chain reaction. Pediatrics 1996; 87: 155–160.
54 Montenegro S H, Gilman R H, Shen P, et al. Improved detection of *Mycobacterium tuberculosis* in Peruvian children by use of a heminested IS6110 polymerase chain reaction assay. Clin Infect Dis 2003; 36: 16–23.
55 Rennert W P, Kilner D, Hale M, Stevens G, Stevens W, Crewe-Brown H. Tuberculosis in children dying from HIV-related lung disease: clinical-pathological correlations. Int J Tuberc Lung Dis 2002; 6: 806–813.
56 Iriso R, Mudido P M, Karamagi C, Whalen C. The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. Int J Tuberc Lung Dis 2005; 9: 716–726.
57 Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum smear-negative pulmonary tuberculosis. Am Rev Respir Dis 1989; 130: 23–28.
58 Zhu M, Burman W J, Syarke J R, et al. Pharmacokinetics of ethambutol in children and adults with tuberculosis. Int J Tuberc Lung Dis 2004; 8: 1360–1367.
59 Schaaf H S, Parkin D P, Seifart H I, et al. Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. Arch Dis Child 2005; 90: 614–618.
60 Graham S M, Bell D J, Nyirongo S, Hartkoorn R, Ward S A, Molyneux E M. Low levels of pyrazinamide and ethambutol in children with tuberculosis and impact of age, nutritional status, and human immunodeficiency virus infection. Antimicrob Agents Chemother 2006; 50: 407–413.
61 Gordin F M, Chaisson R E, Matts J P, et al. An international randomized trial of rifampin and pyrazinamide versus isoniazid for prevention of tuberculosis in HIV-infected persons. JAMA 2000; 283: 1445–1450.
62 Magdorf K, Rusche A F, Geiter L J, O'Brien R J, Wahn U. Short-course preventive therapy for tuberculosis: a pilot study of rifampin and rifampin-pyrazinamide regimens in children. Am Rev Respir Dis 1991; 143 (Suppl): A119.
63 Schaaf H S, Gie R P, Kennedy M, Beyers N, Hesseling P B, Donald P R. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. Pediatrics 2002; 109: 765–771.
64 Uplekar M. Involving the private medical sector in tuberculosis control: practical aspects. In: Porter J D H, Grange J D, eds. Tuberculosis: an international perspective. London, UK: Imperial College Press, 1999: pp 193–212.
65 Hussain A, Mirza Z, Qureshi F A, Hafeez A. Adherence of private practitioners with the National Tuberculosis Treatment Guidelines in Pakistan: a survey report. J Pak Med Assoc 2005; 55: 17–19.
66 World Health Organization. Public-private mix for DOTS. Towards scaling up. WHO/HTM/TB/2005.356. Geneva, Switzerland: WHO, 2005.

67 von Reyn C F, Clements C J, Mann J M. Human immunodeficiency virus infection and routine childhood immunization. Lancet 1987; 2: 669–672.
68 Ryder R W, Oxtoby M J, Mvula M, et al. Safety and immunogenicity of bacille Calmette-Guérin, diphtheria-tetanus-pertussis and oral polio vaccines in newborn children in Zaire infected with human immunodeficiency virus type 1. J Pediatr 1993; 122: 697–702.
69 Hesseling A C, Schaaf H S, Hanekom W A, et al. Danish bacille Calmette-Guérin vaccine-induced disease in human immunodeficiency virus-infected children. Clin Infect Dis 2003; 37: 1226–1233.
70 Hesseling A C, Schaaf H S, Victor T, et al. Resistant *Mycobacterium bovis* bacillus Calmette-Guérin disease in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2004; 23: 476–479.

**RÉSUMÉ**

**La tuberculose (TB) infantile est un aspect négligé des programmes nationaux antituberculeux (PNT) en dépit de la mortalité et de la morbidité considérables qu'elle provoque, particulièrement dans les pays en développement. Un document récemment publié par l'Organisation Mondiale de la Santé, « Directives pour les programmes nationaux de la tuberculose sur la prise en charge de la tuberculose infantile », répond à la question d'une prise en charge effective des enfants au sein des programmes nationaux antituberculeux. Des priorités de recherche sont identifiées par ce document et par une revue de la littérature afin de promouvoir l'intégration de la TB de l'enfant au sein des PNT. Les implications de l'infection VIH s'appliquent à tous les aspects de cet agenda.**

**Les priorités principales sont :**

- **Evaluation prospective de l'incidence de la TB infantile et suivi des performances du programme en ce qui concerne la TB des enfants. Beaucoup de données sont déjà disponibles au sein de nombreux programmes et pourraient fournir des informations pour ce processus.**
- **Etude des critères de suspicion et de diagnostic de la TB infantile par l'utilisation de critères uniformes définis dans le document sur les directives cité ci-dessus. Evaluation de nouvelles méthodologies à cet égard.**
- **Etude de la pharmacocinétique et de la toxicité des médicaments antituberculeux chez les enfants et des résultats au long terme du traitement des enfants.**
- **Détermination du nombre de contacts infantiles avec cas adultes de TB pulmonaire constituant une indication pour la chimioprophylaxie dans diverses collectivités. Etude de la chimioprohylaxie pour la TB à germes résistants aux médicaments et de la chimioprophylaxie dans certains groupes d'adolescents.**
- **Détermination du niveau auquel ces enfants accèdent au PNT, de la disponibilité d'un personnel qualifié et de son efficience dans l'exécution des investigations de diagnostic et dans la réalisation de soins de qualité. Etude du rôle des familles comme agents du DOTS. Evaluation de la participation du secteur privé dans la prise en charge de la TB infantile.**
- **Documentation des complications de l'immunisation par le bacille Calmette-Guérin et les stratégies de gestion de cette étude.**

**RESUMEN**

**La tuberculosis (TB) de los niños constituye un aspecto olvidado de los Programas Nacionales de Tuberculosis (PNT), pese a que causa mortalidad y morbilidad considerable, en particular en los países en desarrollo. El documento 'Normas para los programas nacionales de control de la tuberculosis sobre el tratamiento de la tuberculosis infantil' publicado recientemente por la Organización Mundial de la Salud presenta el tratamiento eficaz de los niños dentro de los PNT. Teniendo en cuenta este documento y los resultados de una investigación bibliográfica realizada, se pusieron en evidencia las prioridades de la promoción de la integración de la TB de la infancia en los PNT. Las implicaciones de la infección por el virus de la inmunodeficiencia humana (VIH) conciernen a todos los aspectos de este programa de trabajo.**

**Las principales prioridades son :**

- **Estimar en forma prospectiva la incidencia de TB infantil y supervisar la eficacia del programa con respecto a la misma. Numerosos PNT cuentan ya con múltiples datos que pueden documentar esta labor.**
- **Estudiar los criterios de presunción y confirmación del diagnóstico de TB en los niños utilizando criterios uniformes, según se definen en el documento sobre las normas citado susodicho. Evaluar nuevos métodos con este propósito.**
- **Estudiar la farmacocinética y la toxicidad de los medicamentos antituberculosos y el desenlace terapéutico a largo plazo de los niños.**
- **Determinar la cantidad de contactos pediátricos de los casos de TB pulmonar del adulto elegibles para quimioprofilaxis en las diferentes comunidades. Estudiar la quimioprofilaxis de la TB farmacorresistente y la quimioprofilaxis en determinados grupos de adolescentes.**
- **Verificar el nivel por conducto del cual entran los niños al PNT, la existencia de personal calificado y su eficacia real en la realización de pruebas diagnósticas y en la provisión de atención sanitaria de buena calidad. Estudiar la función de las familias en la ejecución de la estrategia DOTS. Evaluar la participación del sector privado en el manejo de la TB de los niños.**
- **Verificar las complicaciones de la vacuna antituberculosa y estudiar las estrategias de manejo de las mismas.**