A research agenda for childhood tuberculosis

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Improving the management of childhood tuberculosis within national tuberculosis programmes:

research priorities based on a literature review

World Health Organization

WHO

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[1] Organized under the auspices of the DOTS Expansion Working Group (one of the seven working groups of the Global Partnership to Stop TB). Its goal is to reduce the global burden of mortality and morbidity caused by TB in children.

Contents

Abbreviations

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ARTI	annual risk of tuberculous infection
BCG	Bacille Calmette-Guérin
CXR	chest X-ray
DOTS	"brand name" of the international TB control strategy
EMB	ethambutol
HIV	human immunodeficiency virus
INH	isoniazid
NTP	national tuberculosis programme
PAS	para-aminosalicylic acid
PCR	polymerase chain reaction
PPD	purified protein derivative
PZA	pyrazinamide
RMP	rifampicin
RTT	response to treatment
SM	streptomycin
TB	tuberculosis
TU	tuberculin unit
WHO	World Health Organization

Preface

"...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!"
Gaisford, 1946

"Physicians dealing with adults, either as individuals or in populations, knowing how great is the reservoir of infection in any given country and the implications of this for children, will want to spend as much of their resources as possible on problems relating to adults. But paediatricians are faced with the need to treat children and naturally wish to protect them from infection and so cannot avoid being concerned with these urgent human problems. Each must understand the other's position."

Miller, 1973

The new WHO Stop TB Strategy reflects the importance of the need to improve care for children with TB: the aim of the Strategy is to "ensure equitable access to care of international standards for all TB patients – infectious and non-infectious, adults and children, with and without HIV, with and without drug-resistant TB" (WHO, 2006a). The new Strategy also highlights the importance of research in the global campaign to Stop TB. The launch of the Stop TB Strategy therefore provides a timely opportunity to promote a prioritized research agenda for improving the management of childhood TB within national TB programmes (NTPs).

Summary

Childhood TB is a neglected aspect of the TB epidemic, despite constituting 20% or more of the TB case-load in many countries with high TB incidence. This "orphan disease" exists in the shadow of adult TB and is a significant child health problem, but is neglected because it is usually smear-negative and is thus considered to make a relatively minor contribution to the spread of TB. In order to redress this neglect and integrate childhood TB into the mainstream of TB control activities, research priorities are identified that will assist in improving the prevention and management of childhood TB as a part of national TB programmes (NTPs). The proposed research agenda seeks to better define childhood TB, to optimize the treatment of childhood TB and to identify the best management practices by which childhood TB can be accurately documented and recorded, and efficiently managed within NTPs.

At the outset it should also be recognized that HIV/AIDS is not only responsible for the exacerbation of the TB epidemic in many developing countries, but has also added another element of difficulty to the diagnosis and management of TB in young children.

The main elements of the proposed research agenda (*Fig. 1*) are:

1. Carry out a prospective evaluation of the incidence and burden of childhood TB in different communities, making use of the diagnostic criteria (as defined in line with WHO policy) for suspecting and diagnosing childhood TB. Evaluate trends in case detection of childhood TB making use of data already available within some NTPs. Study the annual risk of tuberculous infection (ARTI) in young children.

2. Evaluate new methodologies to aid the diagnosis of *Mycobacterium tuberculosis* infection and TB disease in children. Evaluate the Mantoux skin-test response in HIV-infected and non-infected children. Determine the proportion of children dying of suspected TB who do actually have TB, e.g. through postmortem studies.

3. Review existing published studies of the treatment of TB and the pharmacokinetics of antituberculosis agents in childhood. Evaluate the pharmacokinetics of the "first-line" and "second-line" antituberculosis agents under different conditions of nutrition across a range of ages, accompanied by studies of drug-drug interactions and drug toxicity, particularly in HIV-infected children who are receiving antiretroviral treatment. Evaluate rates of adherence, treatment failure, recurrence and relapse in children with and without HIV; and evaluate 3- and 4-month regimens of treatment in paucibacillary forms of childhood TB, and the necessity for longer treatment in HIV-infected children. Determine the most effective treatment of disease caused by resistant bacilli. Assess how best to promote compliance with treatment and the role of family members.

4. Determine the numbers of HIV-infected and non-infected children in contact with both sputum smear-positive and smear-negative adults, both HIV-infected and non-infected, that might qualify for chemoprophylaxis in different communities; and the value of conventional chemoprophylaxis with isoniazid compared to shorter, multidrug chemoprophylaxis in both HIV-infected and non-HIV-infected children. Explore different methodologies to ensure compliance with recommendations for chemoprophylaxis. Determine the use of chemoprophylaxis

for the close childhood contacts of adults with both sputum smear-positive and smear-negative drug-resistant TB. Evaluate TB chemoprophylaxis in sexually active adolescent with TB and HIV co-infection.

5. Evaluate the needs for and availability of qualified staff and different diagnostic investigations at the various levels of care under different circumstances. Evaluate the quality of routine NTP data and its value in documenting the community burden of childhood TB. Determine how best to promote the process of recording and reporting childhood TB and the integration of the data into the national reporting systems. Evaluate the accuracy of classification of individual cases. Evaluate the role of the private sector in the management of childhood TB. Evaluate family-centred services and clinics for the management of TB and the management of children with TB within a family-oriented approach.

6. Document the complications of BCG immunization in children and evaluate the most appropriate means of managing these complications. NTPs play a key role in the preparation of vaccine trial sites for the evaluation of new TB vaccines.

The value of these studies would be maximized if carried out at a number of centres throughout the world under a variety of different epidemiological conditions.

Fig. 1 Research priorities for childhood tuberculosis

The burden and diagnosis of childhood tuberculosis

Criteria for suspicion of childhood TB

Cough	Fever	Weight loss	TB contact

In all of the proposed studies the influence of HIV/AIDS must be taken into account

Determine the incidence of childhood TB using current diagnostic criteria. Evaluate new diagnostic methodologies. Use routine NTP data to assess trends in case detection.

Suspect TB

Not TB	Mantoux sputum/gastric aspirates	Chest radiograph HIV-testing		*M. tuberculosis* infected

TB

Disseminated TB	Pulmonary TB	Extrapulmonary TB

Document the incidence of these forms of TB among children. Study how to integrate diagnosis as part of routine NTP activities.

Treatment of childhood tuberculosis

Diagnostic category for treatment	I	II	III	IV	Chemo-prophylaxis
	2HRZE/4HR	2HRZSE 1HRZE 5HRE	2HRZ/4HR	Specifically designed regimens	6H

Review published studies of TB treatment and pharmacokinetics of anti-TB drugs in childhood. Evaluate the pharmacokinetics of TB drugs in children. Explore different options for chemoprophylaxis. Evaluate means of promoting adherence to treatment. Evaluate treatment outcomes.

Roles and responsibilities

Document the route followed to diagnose childhood TB under different epidemiological circumstances.
Evaluate the needs for and availability of staff and diagnostic investigations at different levels of care.
Document the role of the private sector in the management of childhood TB.
Evaluate the management of childhood TB within a family-oriented model of care.

Recording and reporting

Document the reporting and recording of childhood TB within national reporting systems and assist with the appropriate classification of cases utilizing existing data when available.

BCG vaccination in children

Evaluate the incidence and management of the complications of BCG vaccination.
NTPs play a role in developing vaccine trial sites for evaluation of new TB vaccines.

Introduction

The WHO policy document *Guidance for national tuberculosis programmes on the management of tuberculosis in children* provides guidance on the effective management of childhood TB as part of routine NTP activities (WHO, 2006b). 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 standardized 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 activities. The purpose of this document is to identify priorities for such research, based on a review of the literature relevant to the following six key areas of NTP activity (reflecting those set out in the WHO policy document mentioned above):

1. Epidemiology; programme monitoring and evaluation
2. Diagnosis
3. Treatment
4. Contact-screening and -management
5. Roles and responsibilities of health staff and family
6. BCG vaccination.

This document reviews the literature relating to these six key areas of NTP activity. The literature reviewed was derived from an electronic search using PubMed with the key words: tuberculosis, childhood, epidemiology, diagnosis, treatment and control in various combinations. The search produced more than 400 papers starting from 1950. Cross-referencing was also undertaken using a comprehensive library on childhood TB maintained by the the Denis Tutu Centre for Tuberculosis and the Department of Child Health and Paediatrics of Stellenbosch University (South Africa). Preference was given to papers based on substantial amounts of prospective data. "State of the art" reviews were also included as were policy statements by governmental and professional organizations when important practice or policy points were stated or debated.

With regard to four of the key areas of NTP activity (epidemiology and programme monitoring and evaluation; diagnosis; antituberculosis treatment; and BCG vaccination), the individual papers consulted are summarized in annexes, with a commentary, where appropriate.

1. Epidemiology; programme monitoring and evaluation (see *Annex 1*)

1.1 Epidemiology

Until the onset of the HIV/AIDS pandemic, TB was considered to be of declining importance for science and the health services. TB could be controlled with available treatments, and would in due course gradually disappear as a significant health problem. By 1993 it was all too evident that not only was TB not under control in many developing countries but that even in developed countries, mini-epidemics occurred involving migrants, drug-abusers and those with HIV/AIDS, also spilling over into the general population. The urgency of the situation led to the declaration that the TB situation was an international emergency and to the revitalization of the World Health Organization's TB activities. One of the first steps was the development and propagation of the DOTS strategy (DOTS is the "brand name" of this strategy, derived from " Directly Observed Treatment Short-course"). This strategy is composed of five essential elements:

(1) *Sustained political commitment* to increase human and financial resources and make TB control a nationwide priority integral to the national health system.

(2) *Access to quality-assured TB sputum microscopy* for case detection among persons presenting with symptoms of TB (most importantly, prolonged cough) or found through screening. Special attention is necessary for case detection among the HIV-infected and other high-risk groups, such as household contacts of infectious cases and persons in institutions.

(3) *Standardized short-course chemotherapy for all cases of TB* under proper case-management conditions, including direct observation of treatment. Proper case-management conditions imply technically sound and socially supportive treatment services.

(4) *Uninterrupted supply of quality-assured drugs* with reliable drug procurement and distribution systems.

(5) *Recording and reporting systems enabling outcome assessment of all patients and assessment of overall programme performance*. This is the basis for systematic programme monitoring and correction of identified problems.

This strategy emphasizes the finding and management of sputum microscopy smear-positive pulmonary TB patients as these are the main cause of the spread of infection and thus the maintenance of the tuberculosis epidemic. As childhood TB is seldom confirmed under programme conditions by culture of *Mycobacterium tuberculosis*, let alone sputum microscopy smear-positivity, it has tended to be a neglected aspect of national TB control programmes, despite the considerable number of children requiring treatment in high-incidence communities and high morbidity and mortality.

Childhood TB arises most often as a result of the inhalation of *M. tuberculosis* bacilli expectorated by sputum microscopy smear-positive adult pulmonary TB patients within aerosol droplets 5-10 µm in diameter and containing 1-3 bacilli. If infection is successfully established, a primary focus forms in the lung parenchyma, most often subpleural in location, and bacilli spread to the regional lymph nodes and later via the lymph and blood

to organs throughout the body. Depending upon age and the integrity of the immune system, and perhaps the virulence of the infecting organism, a majority of infections are contained, both at the site of the primary focus and the regional lymph nodes and at the extrapulmonary sites where the disseminated bacilli might have established themselves.

In young children, particularly those aged less than 2 years, progression of the various elements of the primary complex and overwhelming dissemination of TB are particularly likely to occur; at the other extreme of childhood, progression to adult-type pulmonary TB becomes much more frequent in adolescents, although there is a considerably reduced propensity to disseminated forms of disease. Childhood TB thus comprises a diversity of manifestations, both pulmonary and extrapulmonary, and it is not always possible to discern disease from infection.

Because of the uncertainty that surrounds the diagnosis of TB in childhood, it is not surprising that very few firm data are available to accurately quantify the burden of childhood TB worldwide. Most published figures are estimates, and these estimates also often do not reflect the diverse features of childhood TB, where the occurrence of extrapulmonary TB is much more common than in adult TB.

A considerable amount of published data is available from low-burden countries. This is reflected in the literature review, and suggests that childhood TB constitutes approximately 5% of the TB case-load. Incidence rates among children in these countries vary from < 1/100 000 to 10/100 000. As young children are rarely exposed to infection, serious disease that is more common in the very young is relatively unusual, and there may be some justification for considering childhood TB to be a relatively uncommon, often self-limiting condition that does not warrant too much attention. Even in low-burden countries however, higher rates are often encountered, rising to > 50/100 000 in some cities among subgroups within the socially disadvantaged and immigrant communities.

In developing underprivileged communities, the concurrence of a high TB annual risk of TB infection (ARTI), coupled with a broad-based population pyramid with more than 40% of the population under the age of 15 years, means that children are not only more often exposed to TB infection, but also become infected at a much younger age. This in turn results in a greater frequency of severe disseminated forms of TB, such as miliary TB and TB meningitis, and a higher incidence of lymphobronchial TB and its complications. In the case of high-burden countries, there are relatively few published data documenting the incidence of childhood TB. From what data there are, it emerges that in these high-burden communities, 20% or more of the TB case-load may be comprised of children, and childhood TB incidence rates in excess of 100/100 000, and more than 200/100 000 in some cases, may be encountered. In one estimate from developing countries with an overall TB incidence of 171/100 000, children represented 15% of the TB burden (Murray et al., 1990). In South Africa in 1993, the national incidence of TB was 224/1 000 000 and children constituted 20% of the TB case-load (Department of Health, 1995). In a community near Cape Town (South Africa) with a particularly high TB incidence of 1149/100 000, children constituted 39% of the case-load (Van Rie et al., 1999). These figures suggest that as the TB incidence rises under the influence of deteriorating socioeconomic circumstances, there is a disproportionate increase in the percentage of the TB case-load comprised of children. This is schematically illustrated in *Fig. 2* making use of the figures quoted above.

Fig. 2   Schematic illustration of the increasing proportion of the TB case-load comprising children as total TB incidence increases
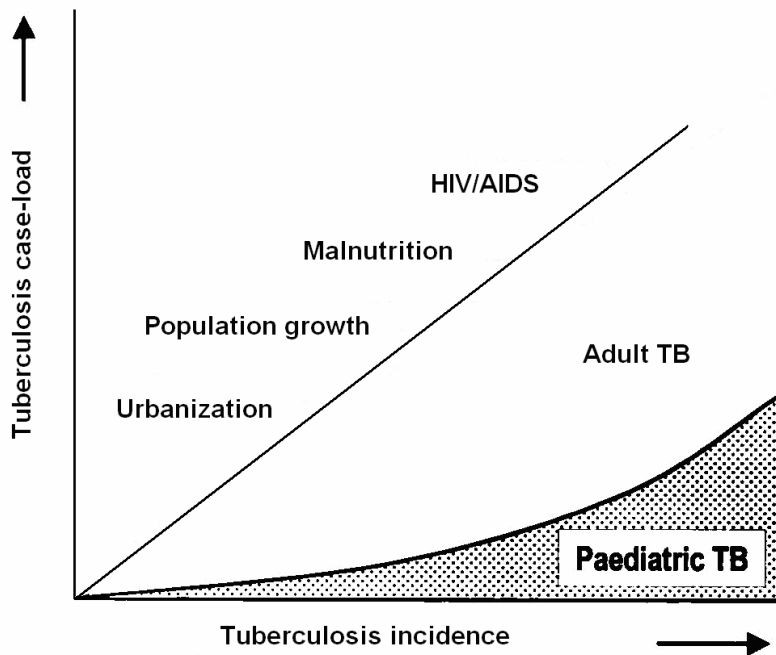
In certain countries, when the ARTI has been calculated and the population age structure is known, it may be possible to estimate the incidence of TB in children by drawing on historical data. Thus an ARTI of 1%-2% was encountered in the Netherlands between 1936-1940 and 1941-1945, at which time mortality from all forms of tuberculosis (but mainly TB meningitis and miliary TB) in children aged 0-4 years was between 32/100 000 and 34/100 000, and for children aged 5-14 years between 14/100 000 and 17/100 000 (Styblo & Sutherland, 1982).   In a number of developing countries, an ARTI of between 1% and 2% has been calculated within recent years suggesting that an epidemiological situation similar to that experienced in Europe between 1936 and 1945 prevails. Figures from the Western Cape Province of South Africa for the period 1985-1987 suggest that these figures still hold.   With an ARTI of approximately 2.5%, the incidence of TB meningitis in children aged 0-4 years was 24/100 000 (Berman et al., 1992).

In all analyses from many countries, children infected at < 1 year of age have an excessively high TB morbidity and mortality.   Among children aged 1-4 years, considerable mortality and morbidity are still encountered before children enter the so-called "safe school age" of 5-10 years. From age 10 years onwards, an ever-increasing incidence of adult-type disease is found. In one calculation for the United States of America for 1940, mortality per 100 000 infected children aged < 1 year was 4920, falling to 123 for those aged 1-4 years and 18 for those aged 5-9 years (Rich, 1951).   A similar calculation for London during the period 1945-1949 found among those infected aged < 1 year a mortality of 5960/100 000, compared to 770 for those aged 1-4 years and 7 for those aged 5-9 years (Bentley et al., 1954).   The contrast between a hypothetical developed community and a developing community with regard to the age-related occurrence of TB in the absence of HIV infection is illustrated in *Fig. 3.*

Fig. 3 Age- and sex-related incidence of TB in hypothetical high-incidence (A) and low-incidence (B) communities in the absence of HIV/AIDS
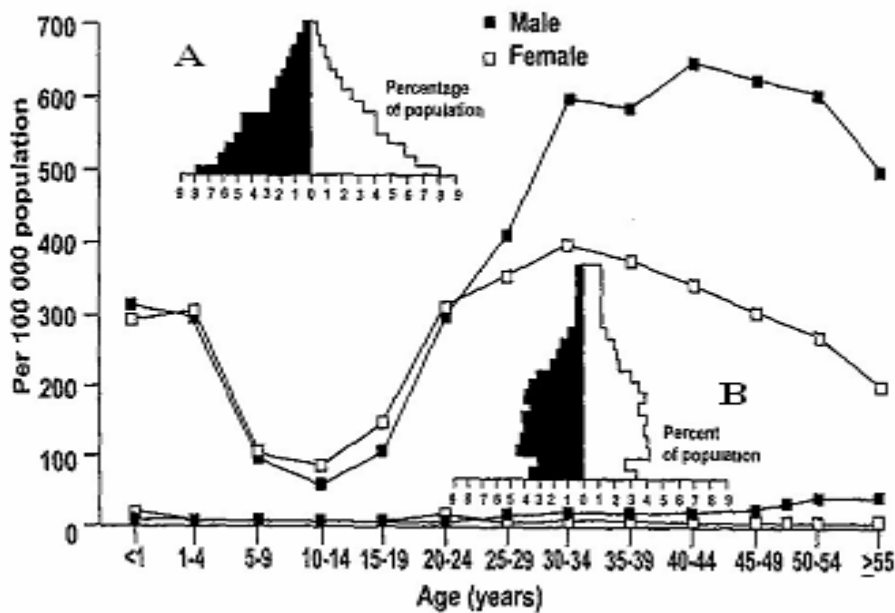
The epidemic spread of HIV/AIDS has added even more uncertainty to an already difficult situation. As is the case with adults, children with HIV/AIDS are exceptionally susceptible to *M. tuberculosis* infection and disease, and evidence of the interaction of HIV/AIDS and TB among children continues to accumulate, particularly from sub-Saharan Africa (Chintu et al., 1995). At the Queen Elizabeth Hospital, Blantyre (Malawi), the number of children admitted with a diagnosis of TB increased from 64 in 1986 to 525 in 1993; of 105 children HIV-tested in 1996, 64% were positive (Harries et al., 1997). In a further twist to this already desperate situation, TB linked to HIV/AIDS has been documented as a major non-obstetric cause of maternal death in South Africa and Zambia (Adhikari et al., 1997; Ahmed et al., 1999). Infants are thus not only exposed to HIV infection, but also to TB.

Finally, it should be pointed out that although children are usually the victims of *M. tuberculosis* infection, there are a number of well-documented cases of children as a source of infection, infecting not only other children, but also adults (Rabalais et al., 1991; Cardona et al., 1999; Curtis et al., 1999).

Tuberculosis in adolescents

With the onset of adolescence there is a striking rise in TB incidence (*Fig. 3*). Not only does TB incidence following infection increase, but it now often has the characteristics of adult-type TB with involvement of the apices of the lungs and a tendency for cavity formation. It is also of interest that more females than males tend to develop the characteristic features of apical infiltration and cavitation, and it has been calculated that the risk of developing adult-type pulmonary TB in adolescence is 2-6 times greater in females than males and that its occurrence is often associated with menarche (Grigg, 1958; Lincoln, 1960; Smith, 1967; Comstock et al., 1974; Comstock, 1975). At about the

same time large pleural effusions become a common phenomenon following infection however, more males than females develop these large straw-coloured effusions (Bentley et al., 1954). The reasons for the increased susceptibility to adult-type TB that accompanies adolescence are not understood, although a number of researchers have speculated that it must have an endocrinological foundation (Wallgren, 1938; Smith, 1967; Nemir, 1986; Donald et al., 1996). A greater understanding of the factors determining these well-established facts related to adolescent TB would greatly enhance knowledge of the pathogenesis of TB and contribute to its control.

Although the investigation of the reasons for the sudden appearance of adult-type forms of TB are of fundamental importance for the understanding of the pathogenesis of tuberculosis, there are equally cogent reasons for considering adolescents to be an important group for NTPs.These include:

- The fact that disease tends to follow infection more commonly in this group than in children aged 5-10 years. Edith Lincoln (1960) followed up more than 600 children who became infected during childhood, and 7% developed TB after an "average" interval of 5 years; most disease followed infection sustained after 7 years of age, while none developed in those infected as infants. Although adolescents are not usually considered for chemoprophylaxis, this could well prove to be a rewarding intervention in this group if the occurrence of infection can be demonstrated by tuberculin conversion or there has been close household contact with sputum smear-positive cases of pulmonary TB.

- Adolescence is also a time when sexual activity is likely to commence, and in communities with a high incidence of HIV and TB the co-incidence of these two formidable diseases creates the opportunity for dual interventions. Pregnant teenagers might be a suitable group where counselling and voluntary HIV-testing could well play an important preventive role.

- This is also an age group during which compliance with therapy is often problematic and during which the ground might well be laid for later problems of recurrence of TB disease or drug-resistance. Thus studies of the compliance with therapy among adolescents might be important.

1.2 Programme monitoring and evaluation

The documentation of childhood TB at local and national levels is more likely to be successful if it can be incorporated into existing reporting systems using the same broad groupings as are currently used for adult tuberculosis. WHO policy guidelines (WHO, 2006b) thus suggest that childhood TB should be classified as sputum smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. Those with both pulmonary and extrapulmonary disease should be classified as pulmonary disease. With this approach most children would fall into the category of smear-negative pulmonary disease and treatment success ("cure") would be considered in most cases as treatment completion. This would inevitably entail considerably more administrative work, again depending on the epidemiological situation. From the point of view of research, this process will need piloting in many communities before it can be applied nationally, and guidance will often be needed on the appropriate classification of individual cases.

Research priorities

Epidemiology
- Evaluate data already existing in some NTPs to assess how best to use these data to improve the documentation of the burden of childhood TB.

- Determine prospectively the incidence of childhood TB in different communities making use of the diagnostic criteria in the WHO policy document (WHO, 2006b). These studies should be carried out at a number of centres under a variety of epidemiological conditions to assess the burden and trends over time of TB in at least two different age groups (0-4 and 5-14 years), including the proportions of children with pulmonary (smear-positive and smear-negative) and extrapulmonary TB, and to assess the proportion of children with TB who are HIV-infected, and the proportion with drug-resistant TB.

- Study the annual risk of tuberculosis infection (ARTI) in children across a spectrum of communities in rural and urban areas.

Programme monitoring and evaluation
- Evaluate how NTPs can ensure that the reporting and recording of childhood TB is an integral part of the routine NTP recording and reporting system. Assess the accuracy of classification of cases as smear-positive pulmonary TB, smear-negative pulmonary TB and extrapulmonary TB, and the quality of management of cases.

- Evaluate trends in case detection of childhood TB making use of data already available within some NTPs.

- Assess NTP performance with reference to childhood TB using the standard indicators for case detection and treatment outocmes.

2. Diagnosis (see *Annex 2*)

"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 ..."
Myers & Kernkamp, 1930

It is clear from all the documents reviewed that the diagnosis of childhood TB is a critical aspect of the integration of childhood TB into national TB control programmes. Without the assurance of an accurate and consistent diagnosis, the precise burden of childhood TB and its importance will remain uncertain and controversial and many children who are treated for TB may not have TB. It is also clear that, in the short term, there is little prospect of achieving a widely available "gold standard" diagnosis of TB in children either by means of culture, microscopy, PCR or serology. Consequently one must fall back on clinical criteria, chest radiography and tuberculin-testing. It is therefore of the greatest importance that these criteria should be standardized as far as possible throughout the world, and that the proposals contained in the WHO policy document (WHO, 2006b) should be followed. It should also be recognized that the current diagnostic criteria relying as they do on history, chest radiography and tuberculin skin-testing are not totally accurate and that 15%-20% of children diagnosed using these criteria in high-incidence communities may not have TB (Schaaf et al., 1995). From a programme point of view, it could be argued that once a clinician has diagnosed TB in a child utilizing these criteria, that child becomes the responsibility of the programme and part of the burden imposed by the TB epidemic.

A further complicating factor is the confusion caused by HIV infection and AIDS in children. The manifestations of HIV/AIDS and the various infections and other conditions that complicate it have made the diagnosis of TB in young children even more difficult. These difficulties are graphically illustrated by the experience of Rennert et al. (2002), who undertook postmortem biopsies of lung and liver tissue from 93 children who died of HIV infection and its complications. TB was confirmed before death in only 4 children (4%), but a further 17 children (18%) had been empirically placed on TB treatment on the basis of history and clinical and radiological features, and this diagnosis could not be confirmed post mortem. Chest radiographs from these children were submitted for independent assessment, and a panel proved incapable of distinguishing TB from *Pneumocysis carinii* pneumonia, cytomegalovirus pneumonitis or interstitial lymphocytic pneumonitis.

2.1 History

2. 1.1 Contact with an adult with TB

This is the most frequently used aspect of history. Often however, it is not stated whether the adult was sputum microscopy smear-positive or not, whether there was close household contact or not, and over what time period in relation to the child's illness the contact existed. In the WHO policy document (WHO, 2006b) a close contact is defined as someone "living in the same household or in frequent contact with a source case (e.g. caregiver) with sputum smear-positive TB". The timely diagnosis of drug-resistant TB in a child could also be expedited by emphasizing the importance of a history of contact with

an adult with drug-resistant TB or a history of repeated treatment episodes of TB or poor compliance with TB treatment.

2.1.2 Symptoms of childhood TB

2.1.2.1 Chronic cough
A variety of durations of cough have been proposed as a significant sign of TB. The WHO policy document (WHO, 2006b) suggests that chronic cough should be defined as "an unremitting cough, that is not improving and has been present for more than 21 days (3 weeks) with or without wheezing being present".

2.1.2.2 Fever
Various definitions of fever with regard to both degree and duration of the fever are suggested by different investigators. The WHO policy document (WHO, 2006b) proposes that fever for the purpose of suspecting TB in a child should be defined as "a fever greater than 38^0C for 14 days after common causes like malaria or pneumonia have been excluded".

2.1.2.3 Loss of weight and failure to gain weight
When objectively documented, for example on a *Road to health* card, these often cause TB to be considered as the possible etiology and they are a frequent part of the various proposed scoring systems. The WHO policy document (WHO, 2006b) adds the important consideration that weight loss or failure to gain weight are of particular significance "…especially after being treated in a nutritional rehabilitation programme".

2.2 Investigations

There are inevitably communities where even the bare minimum of investigations to support the diagnosis of TB in childhood are not available. In developing a research programme to more accurately define the diagnostic criteria for childhood TB, tuberculin-testing and chest radiography should be an integral part of the elements to be evaluated.

2.2.1 Tuberculin skin-testing

The use of different PPD products is probably unavoidable but, even when the same product is used, different strengths are applied and different degrees of induration are accepted as significant. Thus both 1or 2 TU PPD RT 23 are used. The WHO policy document (WHO, 2006b) recommends that the tuberculin used should be standardized for each country "… using either 5 TU of tuberculin PPD-S or 2 TU of tuberculin PPD RT23". The Mantoux skin test should be regarded as positive if there is ≥ 5 mm induration in high-risk children such as those who are severely malnourished or HIV-infected, or ≥ 10 mm in all other children. As it is uncertain whether the use of 5 mm induration as a "decision point" in those children who are HIV-infected is justified in communities with a high prevalence of HIV infection, research should be directed at determining at which point along the course of HIV infection an induration of ≥ 10 mm after tuberculin skin-testing becomes an unreliable diagnostic criterion. Although tuberculin-testing is one of the cornerstones of the diagnosis of TB in childhood, its sensitivity and specificity may at times be inadequate and a certain percentage of TB-infected individuals may never react to tuberculin. Newer modalities such as assays for gamma-interferon or T-cell-based tests, that might separate infection from disease, should

be evaluated in parallel with tuberculin-testing (Lalvani et al., 2001; Taggart et al., 2004; Liebeschuetz et al., 2004; Ferrara et al., 2005; Zellweger, 2005).

2.2.2 Chest radiography

Chest radiography is probably the most frequently used method to support a diagnosis of probable childhood TB. Before the advent of HIV/AIDS, the presence of mediastinal adenopathy or a micronodular (miliary) appearance could be accepted as a reliable feature of childhood TB. This interpretation has now been confused by HIV/AIDS, and its complications and the value of chest radiology in the diagnostic process in areas of high HIV infection should be reassessed. Other problems relate to the difficulty of taking a chest radiograph of good quality in a fractious young child and interpreting the radiograph, in particular the hilar shadows on a radiograph of doubtful quality that may be subject to an overenthusiastic interpretation as hilar adenopathy by the inexperienced.

2.2.3 Culture of M. tuberculosis

Culture of *M. tuberculosis* is the gold standard by which the diagnosis of TB in an adult can be measured. As indicated in the literature reviewed, the frequency with which *M. tuberculosis* is cultured from children in whom TB is suspected varies considerably, depending on whether the child is investigated in hospital or in the community, the age of the child and the extent of disease. Gastric lavage has long been the standard investigation to obtain material for culture and microscopy from a child in whom tuberculosis is suspected. Although some investigators have performed the investigation with success in community clinics, it remains a labour-intensive technique and is frightening for a young child and in some instances for the parent. Sputum induction has been shown to equal gastric aspirate in yield, but it is also labour-intensive and not any less frightening for the parent and child, and may prove difficult to implement on a large scale in the community. Nasopharyngeal aspiration and laryngeal swabbing are alternatives that remain to be fully evaluated in a community clinic setting.

2.2.4 Smear microscopy for acid-fast bacilli

In many localities, sputum-smear microscopy is the sole means available to diagnose pulmonary TB in adults. Children, however, make up a small minority of those TB patients who are microscopy smear-positive in most communities, and this technique with its present low sensitivity and specificity cannot play a major role in the diagnosis of TB in childhood at a national level. Any evaluation of childhood TB should nonetheless document whether smear microscopy was attempted and the proportion of childhood TB cases that are microscopy smear–positive.

2.2.5 Polymerase chain reaction (PCR)

The introduction of nucleic acid amplification techniques raised hopes that this would provide a reliable alternative to culture for the diagnosis of TB in children (Pierre et al., 1993). Unfortunately this has not proved to be the case, and the various tests available have been described as "helpful" and at best have sensitivity and specificity comparable to gastric aspirate and culture (Smith et al., 1996; Montenegro et al., 2003). At the present stage of their development, PCR investigations probably have little to offer national programmes with regard to improving the management of childhood TB. Nonetheless a

research programme to evaluate the criteria for the diagnosis of childhood TB might provide a platform for a more intensive and comprehensive evaluation of these techniques and newer refinements and their predictive value under programmatic conditions than has hitherto been possible.

Research priorities

- Evaluate the use of the criteria as suggested and defined in the WHO policy document (WHO, 2006b) to suspect and diagnose childhood TB, and evaluate available new methodologies for assisting or confirming the diagnosis of TB in children.

- Evaluate new methodologies to aid the diagnosis of *M. tuberculosis* infection and TB disease in children.

- Evaluate Mantoux skin-test responses in HIV-infected and non-infected children to determine sensitivity, specificity and predictive value of the suggested "cut-points" to support a diagnosis of *M. tuberculosis* infection.

- Determine the proportion of children dying of suspected TB who do actually have TB, e.g. through postmortem studies.

3. Treatment (see *Annex 3*)

The lack of importance assigned to childhood TB has had a number of consequences in the field of treatment. Therapeutic trials have focused understandably on adults with TB where verifiable microbiological endpoints are available to accurately measure success. Relatively few studies have thus been undertaken in children and, contrary to accepted pharmacological principles, children tend to be given the same mg/kg body-weight dosages of antituberculosis drugs as adults. This approach can be summarized as "one size fits all". It is generally acknowleged that in considering the dosage of any drug for use in children, cognizance must be taken of the greater extravascular fluid volume of younger children and of the relatively greater liver mass in proportion to body mass (McCarver, 2004). Given that the definition of the precise relationship between serum concentrations of antituberculosis drugs and efficacy is often lacking even in adults, and often aims at a range of values, the use of a uniform dose for adults and children may be acceptable with regard to some agents. Evidence is emerging however that some caution is necessary (Zhu et al., 2004; Schaaf et al., 2005; Graham et al., 2006). In several instances it has been demonstrated that children receiving equivalent mg/kg body-weight doses of antituberculosis drugs are exposed to considerably lower serum concentrations than adults. In addition to the above problem, there are a number of different recommendations for the doses of all the antituberculosis drugs used in children.

Because of the diversity of disease in childhood, many studies of the treatment of childhood TB enrol children with a wide spectrum of disease. The natural history of these manifestations varies considerably, making it difficult to judge the success of treatment among subgroups of children. Despite these reservations, it would be valuable to review the existing literature relating to the treatment of childhood TB to establish a better understanding of the response to treatment, and of relapse and recurrence rates occurring in different forms of childhood TB. It is thus essential that in evaluating the success of the treatment of childhood TB, the spectrum of disease being treated is accurately defined. These studies should cover all the paediatric age groups (children aged < 2 years, 2-6 years and 7-14 years) and include children with HIV/AIDS.

There is now a considerable literature documenting poor absorption of antituberculosis drugs in adults with TB and HIV infection (Berning et al., 1992; Peloquin et al., 1996; Sahai et al., 1997) although not all studies have demonstrated poorer drug absorption in HIV-infected TB patients (Choudri et al., 1997; Taylor & Smith, 1998). Few data are currently available describing the absorption of antituberculosis drugs in children with TB and HIV infection, and this is obviously an important area for study.

The recurrence of TB, whether due to relapse or reinfection, has been documented in a significant number of children, particularly in the presence of HIV infection. Nonetheless relatively few studies of childhood TB record treatment success or failure, or relapse rates, in children followed up for a substantial length of time. Also, as with the criteria for diagnosis, the evaluation of treatment success or cure in children is seldom based on well-defined consistent criteria. There is little reason to doubt that the treatment regimens used in adults are also efficacious in children. It is even likely that several less severe forms of childhood TB could be treated with less intensive shorter regimens than is the practice in adults. In the management of adult TB there are very clear definitions of treatment outcome and failure. Because childhood TB is seldom microscopy smear-positive and infrequently culture-positive, the definitions of treatment success or failure tend to rely on

improvement in radiological findings and clinical features such as weight gain and the parent's impression of the child's well-being. Even when these definitions are applied, there are relatively few studies of the success of the treatment of childhood TB measured with the same degree of rigour as adult forms of TB.

Several studies have documented that 3- and 4-month regimens of treatment are successful in adults with culture-positive but smear-negative TB, and also with smear- and culture-negative TB (Hong Kong Chest Service/Tuberculosis Research Centre Madras/British Medical Research Council, 1989; Dutt et al., 1989). Such shorter regimens would be of considerable benefit to NTPs if shown 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.

Drug-resistance in childhood
Drug-resistance occurs with varying frequency in different parts of the world, but whatever the local situation, constitutes an ever-present threat to children. It is included under a separate heading at this point as it is often not considered as an important priority in drawing up national policy documents, and the importance of conducting ongoing operational research on the subject needs emphasizing. The most important aspect of the diagnosis of drug-resistance in childhood is that the possibility of the presence of drug-resistance in a child should be considered as early as possible. All too often a child's clinical condition will deteriorate before drug-resistance is considered as a possible cause.

The occurrence of drug-resistance among children was recognized not long after the introduction of antituberculosis chemotherapy, and the disastrous consequences of failure to recognize its presence were documented by several groups (Debré et al., 1959; Steiner & Cosio, 1966; Steiner et al., 1973). These authors also recognized the potential importance of resistance occurring among children. As this would nearly always be primary resistance, the findings in children would represent the current situation whereas the findings in adults would potentially be influenced by the endogenous reactivation of infection acquired as a child. There is now no doubt as to the pathogenicity of drug-resistant strains, and the transmission of a resistant strain from household contacts to children has been confirmed by several groups of researchers (Steiner et al., 1985; Schaaf et al., 1999; Schaaf et al., 2000; Schaaf et al., 2002). From a programme point of view, many of these clinical disasters could be prevented by a simple enquiry at the time of diagnosis as to possible contact of a child with either a known case of drug-resistant TB or contact with an adult who was known not to have complied with treatment, or to have been treated previously for TB (Mukherjee et al., 2003).

The research priorities that arise out of this brief review of drug-resistance in childhood TB are: (1) the regular quantification of the number of children who present following contact with an adult with drug-resistant TB; (2) the consequences of that contact and the best options for managing the children so exposed; and (3) surveillance of the incidence of drug-resistance among children as being one of the best means of determining the number of drug-resistant strains currently circulating in a community.

Research priorities

- Review existing literature relating to the treatment of childhood TB to establish the response to treatment and recurrence rates, and to identify already existing information regarding the pharmacokinetics of antituberculosis drugs in children.

- Undertake pharmacokinetic studies of each of the first-line antituberculosis drugs under different conditions of nutrition and HIV-infection status and across a range of ages.

- Undertake pharmacokinetic studies of second-line drugs. A literature review might reveal sufficient information to make well-founded assumptions with regard to agents such as the fluoroquinalones and aminoglycosides.

- Study drug-drug interactions, particularly in HIV-infected children who frequently receive multiple drugs other than antituberculosis agents. Study drug toxicity in this complex situation.

- Evaluate rates of treatment failure and recurrence, particularly in association with HIV/AIDS.

- Evaluate 3- and 4-month treatment regimens in paucibacillary forms of childhood TB and the necessity for longer periods of treatment in HIV-infected children.

- Evaluate the treatment of drug-resistant TB in children and determine the most effective regimens.

4. Contact-screening and management

The value of chemoprophylaxis among children in close contact with sputum smear-positive fully drug-sensitive adults with pulmonary TB, or in children known to be infected with *M. tuberculosis* (as judged by a positive tuberculin test), has been thoroughly studied and there is no doubt as to its value (Ferebee, 1970). The argument in the past has been rather about the priority of this intervention for NTPs in developing countries. Although many programmes recommend chemoprophylaxis, in particular for the very young, prophylactic treatment of children is not accorded a high priority and is not generally viewed as an essential element in TB control activities. Under certain circumstances this might be acceptable in view of the severe restrictions and personnel shortages under which many community clinics operate, nonetheless there are certain groups of children who would undoubtedly benefit from a more enthusiastic utilization of contact-tracing and chemoprophylaxis. Infants and very young children in contact with a sputum smear-positive adult would undoubtedly benefit from chemoprophylaxis to prevent TB meningitis and miliary TB. Conversely the occurrence of *M. tuberculosis* infection in a young child should lead to the evaluation of the child's household contacts for the source of infection.

The prevention of TB following infection became a practical possibility after the discovery of isoniazid (INH) and its introduction into clinical use in 1952. Shortly afterwards Edith Lincoln, the noted American paediatrician, observed that no children with miliary tuberculosis treated with INH developed TB meningitis, whereas such cases had been observed following treatment with streptomycin and PAS (Lincoln, 1954). A series of INH chemoprophylaxis trials were then organized (Ferebee, 1970) that led to the widespread adoption of INH as chemoprophylaxis for infected individuals. The WHO policy document (WHO, 2006b) recommends that chemoprophylaxis should be an integral part of programme activities.

Controversy remained with regard to the length of treatment (and this is still debated) and in 1982 the results of a large trial undertaken in eastern Europe under the auspices of the International Union against Tuberculosis were published (International Union Against Tuberculosis Committee on Prophylaxis, 1982). This trial evaluated daily INH taken by adults with radiographically visible fibrotic lesions for 12, 24 and 52 weeks and the results were compared to placebo. The follow-up period was 5 years, and at this point 24 weeks of INH prevented 65% of active cases of TB compared to 75% for 52 weeks of treatment. If however the results were restricted to those individuals taking $\geq 80\%$ of prescribed INH, the figures were 69% and 93% for 24 weeks and 52 weeks respectively.

More recently experience with chemoprophylaxis trials was reassessed by Comstock (1999) who concluded that among immunocompetent adults, 6 months of chemoprophylaxis did not provide optimal treatment, but that more than 12 months was unnecessary while 9-10 months appeared to be the optimal duration. To this he added that the total duration may be more important than its continuity.

The spread of HIV and the demonstration that INH chemoprophylaxis can prevent TB in these highly susceptible indivuals has given the debate surrounding INH chemoprophylaxis and chemoprophylaxis itself new urgency (Wilkinson et al., 1998; Bucher et al., 1999). Several studies have also shown that shorter regimens of multidrug prophylactic regimens in individuals with silicosis (Hong Kong Chest Service et al., 1992)

and HIV infection (Halsey et al., 1998; Gordin et al., 2000) gave results equivalent to INH monotherapy, but experience with hepatic toxicity from regimens containing pyrazinamide (PZA) has dampened enthusiasm for this approach (Whalen et al., 1997; Stout et al., 2003; Jasmer & Daley, 2003). There is evidence however that this approach may well be successful in children, without undue toxicity. Shorter regimens of two or three months of drug chemoprophylaxis warrant evaluation in children and could ease the task of chemoprophylaxis, particularly in areas where insufficient personnel are available to supervise this strategy (Magdorf et al., 1991; Graczyk et al., 1991; Ormerod, 1998). Research in this area should include an evaluation of the number of children that might qualify for chemoprophylaxis under different epidemiological circumstances and the workload that this might create, and the exploration of alternative shorter chemoprophylaxis regimens in children both with and without HIV infection.

Another aspect of prophylaxis related to HIV/AIDS is the fact that in developing countries with a high prevalence of HIV infection, children are increasingly exposed to sputum smear-negative cases of pulmonary TB and an accurate assessment of the impact of these contacts is needed to offer rational advice concerning chemoprophylaxis under these circumstances.

In an uncontrolled study, appropriate chemoprophylaxis has been demonstrated to reduce the incidence of disease among the childhood contacts of adults with multidrug-resistant TB (Schaaf et al., 2002) but a more precise delineation of the drugs, dosages and duration of chemoprophylaxis is needed. Because of the relatively small numbers of children that any individual researcher is likely to encounter, collaborative studies in this important area would be advantageous.

As discussed in chapter 1, adolescents are a vulnerable group both for the development of TB after infection, and for HIV infection if they are sexually active. Pregnant teenagers might well constitute an appropriate group for a targeted evaluation of the value of voluntary HIV-testing and -counselling, and tuberculin-testing and chemoprophylaxis.

Research priorities

- Carry out epidemiological studies to determine the numbers of HIV-infected and non-infected children in contact with both sputum smear-positive and smear-negative adults, both HIV-infected and non-infected, who might qualify for chemoprophylaxis in different communities.

- Assess the value of standard isoniazid prophylaxis and compare it to shorter multidrug chemoprophylaxis in both HIV-infected and non-infected children.

- Explore different methodologies to ensure adherence with recommendations for chemoprophylaxis.

- Study chemoprophylaxis for the childhood contacts of adults with sputum smear-negative and smear-positive drug-resistant TB.

- Study the concurrence of TB and HIV infection in pregnant teenagers and evaluate TB chemoprophylaxis in those infected.

5. Roles and responsiblities of health staff and families

The WHO policy document (WHO, 2006b) describes a structured hierarchy of case-management for children with possible TB, but acknowledges that the precise model adopted will vary from country to country depending on the epidemiological situation and the resources available.

Research related to this section of the recommendations should focus on the optimal approach to be followed under different circumstances. In different communities children may enter the NTP following various pathways. Research is needed to document these pathways as health service personnel need to be aware of the importance of these children being notified to the NTP, and of the protocols to be followed with regard to children.

In developing communities, children frequently present to the health system with symptoms which will then lead to the diagnosis of TB. In developed communities children are more often diagnosed following contact-tracing activities and often have less advanced forms of disease than in developing communities. When children are diagnosed as the result of contact-tracing activities, another family or household member often also has TB. It is uncertain how often this is the case when children present with disease symptoms. Research is necessary to evaluate the effectiveness of a family-oriented approach to contact-tracing, and of the mobilization of family members as treatment supporters (for directly observed treatment) regarding their own child's adherence to treatment or chemoprophylaxis (in addition to the counselling and advice that all parents or other child-carers should receive). The establishment and evaluation of family-centred clinics and services could make a valuable contribution in this respect.

The role of the private sector

In the past TB policies were often oriented towards the diagnosis and management of TB within government health facilities. It is however becoming apparent that a considerable number of TB patients are diagnosed and managed within the private health system. This is particularly true in Asia and South America, and it has been claimed that as many as 60% of TB patients are seen at some point by private practitioners in these countries (Newell, 2002). It has also been estimated that the private sector in India, which comprises 6.4 million of the 8 million registered Indian medical practitioners, handles approximately one-sixth of the world's TB cases (Uplekar, 1999). In Pakistan, as many as 80% of TB patients consult a private practitioner (Hussain et al., 2005).

On the one hand, shortcomings in the management of TB by the private sector include management inconsistent with NTP policy and deficiencies in both diagnosis and treatment prescription. On the other hand, it has been repeatedly demonstrated that patients often prefer to see a private practitioner and have their disease managed within the "privacy" of the private sector. This last factor may be particularly important in an age where HIV is becoming very closely associated with TB. With regard to childhood TB, there is almost no information as to the role of the private sector in its management. In view of the number of initiatives that are now being launched for private/public partnerships in TB control (Arora & Gupta, 2004; Rangan et al., 2004; Mantala, 2003; Newell et al., 2004) it is important that childhood TB be seen as an integral part of these plans and that evaluations of the epidemiology of childhood TB take into account the role of the private sector.

Research priorities

- Document the pathway followed to diagnose childhood TB 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 TB in children: is chest radiography or tuberculin-testing available?

- Study the effectiveness of a family-oriented approach to contact-tracing, and of the mobilization of family members as treatment supporters (for directly observed treatment) regarding their own child's adherence to treatment or chemoprophylaxis (in addition to the counselling and advice that all parents or other child-carers should receive).

- Evaluate the role of family-centred clinics and services in managing children with TB, including those with HIV co-infection.

- Document the role of the private sector in all aspects of the management of childhood TB and the extent to which existing public/private partnerships are aware of childhood TB and its particular problems.

6. BCG vaccination (see *Annex 4*)

BCG is a most successfully administered vaccine and is given to close to 90% of the world's children. Although there is considerable doubt as to its effect on the occurrence of adult forms of TB, it plays a key role in the prevention of disseminated forms of TB in young children. While vaccine development does not fall within the ambit of this review, the occurrence and management of the complications of BCG vaccination, in particular as they affect HIV-infected children, are certainly of importance to an NTP. NTPs also have an important role in collaborating in the establishment of vaccine trial sites. In the past, disseminated BCG disease was relatively unusual and nearly always associated with severe forms of immunosuppression (Lotte et al., 1988). There was therefore understandable concern regarding the possibility of the susceptibility of the newborn HIV-infected infant to disseminated BCG disease (Von Reyn et al., 1987; Reichman,1989). Although case reports have indicated that some degree of caution is needed (Talbot et al., 1997; Hesseling et al., 2003), prospective evaluation of immunization practices has suggested that HIV infection is not associated with an increased incidence of BCG disease (Ryder et al., 1993). In a study in Zambia, the occurrence of bacteraemia caused by mycobacteria was documented in HIV-infected adults and children (Waddel et al., 2001). Among 387 children (median age 15 months) hospitalized with symptomatic HIV disease, only 1 child (0.26%) had a blood culture positive for *M. bovis* BCG. Although the authors claimed that this illustrated that bacteraemia caused by BCG was a rare event, this translates into an incidence of 258/100 000, a not inconsiderable incidence for a potentially lethal complication of vaccination. More recently the acquisition of resistance in *M. bovis* BCG Danish strain has also been described in a child with disseminated disease, together with inherent resistance to INH (Hesseling et al., 2004).

Current WHO policy recommends that BCG vaccine should be given to children as soon after birth as possible, and that it should also 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 incidence of tuberculosis should receive the vaccine. Prospective surveillance of the occurrence of BCG disease is urgently needed to inform both national and international policies concerning the use of BCG in populations with a high prevalence of HIV. There is also a need for systematic evaluation of the most appropriate treatment for BCG-related disease.

Research priorities

- Carry out a prospective evaluation of the incidence of BCG disease and the drug-sensitivities of the BCG organisms for the various antituberculosis agents.

- Evaluate the management of BCG disease to assist decision-making in those countries with a significant prevalence of HIV infection.

- NTPs to collaborate in the establishment of vaccine trial sites for the evaluation of new TB vaccines.

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Wilkinson D et al. (1998) Effect of preventive treatment of tuberculosis in adults infected with HIV: a systematic review of randomized placebo conrolled trials. *British Medical Journal*, 317:625-629.

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Zhu M et al. (2004). Pharmacokinetics of ethambutol in children and adults with tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:1360-1367.

Annexes

Literature summaries

Annex 1
Epidemiology; programme monitoring and evaluation

Summary of findings from the papers reviewed

The following conclusions can be drawn from the literature reviewed below.

In low-burden countries, childhood tuberculosis constitutes approximately 5% of the tuberculosis case-load. Incidence rates among children in these countries varies from < 1/100 000 to 10/100 000. Rates among subgroups of the socially disadvantaged, and among immigrant communities, may be higher, rising to > 50/100 000 in some cities.

In high-burden countries, childhood tuberculosis constitutes approximately 20% of the case-load and 40% in certain communities, with incidence rates in excess of 100/100 000 and more than 200/100 000 in some cases. Because many more younger children are likely to be involved in these countries, more serious forms of disseminated tuberculosis and extrapulmonary tuberculosis are also encountered more frequently.

In certain countries, when the ARTI has been calculated and the population age structure is known, estimation of tuberculosis incidence in children may be possible using historical data. Thus the ARTI was 1%-2% in the Netherlands between 1936-1940 and 1941-1945, at which time mortality from all forms of tuberculosis 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.

In all analyses from many countries, morbidity and mortality are excessively high among children < 1 year, and are still considerable among children aged 1-4 years before children enter the so-called "safe school age" of 5-10 years. From age 10 years onwards, an ever-increasing incidence of adult-type disease is found.

The occurrence of drug resistance among children probably reflects the situation among adults, and might provide a more accurate picture of the sensitivities of bacilli currently in circulation in a community than data from previously untreated adults.

Summary of each paper reviewed

Illingworth RS (1955). The epidemiology of tuberculosis in childhood. *Medical Illustrated*, 9:561-563.

This paper describes the consequences of *M. tuberculosis* infection and summarizes childhood tuberculosis incidence in several countries during the middle of the previous century, illustrating the dramatic falls in incidence that antedated the chemotherapy era.

Country	Year	Incidence/100 000
Norway	1930	52
	1949	8
	1951	4.3
Denmark	1930	36.4
	1952	0.9
England & Wales	1947	21.4
	1951	8.5

Myers JA (1964). Eradication of tuberculosis from the schools of America. *Journal of School Health*, 34:458-463.

The purpose of this paper was to promote steps to eradicate tuberculosis from American schools, but its interest with regard to the burden of childhood tuberculosis lies in some of the data provided concerning tuberculosis in childhood. These data are tabulated below and show the abrupt decline in tuberculosis mortality that started even before the availability of chemotherapy. It also illustrates, once again, the greater vulnerability of the infant (< 1 year of age) and the rise in mortality associated with puberty.

Age-related mortality in the United States of America, 1900-1960

Age group (years)	1900	1934	Age group (years)	1960
All	194.4	56.7	All	5.1
<1	311.6	37.2	<1	1.0
1-4	101.4	18.4	1-4	0.5
			5-9	0.2
5-14	36.2	8.2	10-14	0.1
			15-19	0.2
15-24	205	52.1	20-24	0.4

Myers also gives figures in this paper for the follow-up of children found to be tuberculin-positive. Thus 1886 children reacted to tuberculin between the ages of 6-12 years from 1921-1941 and were observed for 51 005 person years; of 1585 traced recently (i.e. 1964), 4.2% developed clinical disease whereas of 1127 who reacted to tuberculin when aged 13-17 years between 1921-1941, 899 were followed up for 30 099 person-years and 11.9% developed clinical disease. This again suggests a relative protection from disease following infection enjoyed between the ages of 5-12 years.

Härö AS, Mäkipaja J (1966). Factors decreasing the tuberculosis mortality of children in Finland, 1936-1961. *Scandinavian Journal of Respiratory Diseases*, 47:37-52.

This study reflects events described in other similar reports from developed countries. An interesting variation is that the decline in childhood mortality did not appear to be adversely affected by the war years. In 1936-1940, infant mortality resulting from tuberculosis was 258.8/100 000 per year and decreased to 4.2/100 000 by 1960. In 1960, no death occurred as a result of tuberculosis in any child < 10 years of age.

McGeorge M, Taylor AJ (1967). Childhood tuberculosis in Otago. *New Zealand Medical Journal*, 66:526-530.

The authors describe the circumstances under which 65 children with tuberculosis in Otago were diagnosed in the period 1961-1965. No incidence is given, although the description of incidence is claimed as one of the aims of the paper.

Forty of the children (62%) presented as contacts of known cases of tuberculosis, 19 (29%) were referred because of symptoms and 6 (9%) were detected through routine screening. A more detailed description of the circumstances surrounding the transmission

of infection is given, and one is impressed by the relatively brief nature of the contact in some cases. A source was identified in 51 cases (78%) and all of the discovered source cases were domiciliary in one way or another.

Styblo K, Sutherland I **(1982)**. Epidemiology of tuberculosis in children. *Bulletin of the International Union against Tuberculosis and Lung Disease*, 57:133-139.

In this review the authors made use of historical data to evaluate the relationship between the incidence of childhood tuberculosis and annual risk of infection (ARI), and also the proportion of childhood tuberculosis that is smear-positive or that constitutes an infection risk.

In the prechemotherapy era, mortality caused by tuberculosis in children 0-4 years of age was very high: 600/100 000 in England and Wales in the second half of the 19th century, falling to 300/100 000 by 1900 and 100/100 000 by the late 1920s and <50/100 000 by 1936-1940. Accurate data from the Netherlands permitted the calculation of a rough relationship between the ARI and tuberculosis mortality in children. For an ARI of 1%- 2.5%, mortality in those aged 0-4 years, mainly as a result of tuberculous meningitis, was 18-19/100 000, and total tuberculosis mortality 32-34/100 000. In those aged 5-14 years, it was 14-17/100 000 and 7/100 000 respectively. Figures from the Western Cape Province of South Africa for the period 1985-1987 suggest that these figures still hold: with an ARI of approximately 2.5%, the incidence of TBM in children aged 0-4 years was 24/100 000 (Berman et al., 1992).

The percentage of infectious tuberculosis cases (smear-positive) occurring among children was calculated from Norwegian data for the period 1936-1955 at approximately 8% for children aged 0-4 years, 5% for those 5-9 years, and 10% for those 10-14 years.

Powell KE, Meador MP, Farer LS **(1984)**. Recent trends in tuberculosis in children. *JAMA*, 251:1289-1292.

This paper antedates the full impact of the HIV epidemic on the tuberculosis situation in the United States of America, and documents the incidence of tuberculosis in children aged 0-14 years for the period 1976-1981. During this period, the incidence of tuberculosis in children did not decline and rates ranged from 3.4/100 000 in1976 to 3.0/100 000 in 1978. The authors also noted that the failure of the incidence rates to decline appeared to be due to high rates of disease among Indochinese refugees and Hispanic children, although this assumption did not fully explain their findings.

Paul FM (1987). Mortality and morbidity of childhood tuberculosis in Singapore. *Journal of the Singapore Paediatric Society*, 29:80-86.

In this paper the author reviews the control of childhood tuberculosis in Singapore over a period of nearly 30 years. In 1948, tuberculosis accounted for 14% of all deaths in Singapore and by 1965 this had fallen to 5.1% and in 1985 1%. In 1955 the Paediatric Unit of the Singapore General Hospital admitted 112 cases of tuberculous meningitis in children aged ≤ 12 years and in 1976 only 2 cases. A similar dramatic fall in admissions to the hospital for various other forms of childhood tuberculosis is also documented. The author ascribes the improvement to:

        the introduction of BCG vaccination

the improved nutritional status of the children
a good tuberculosis case-finding system
an improvement in housing conditions
good medical services for treatment
the availability of good antituberculosis drugs.

Snider DE et al. **(1988)**. Tuberculosis in children. *Pediatric Infectious Disease Journal*, 7:271-278.

The authors note that the case rates of tuberculosis in children aged < 5 years in the United States of America declined from 10/100 000 in 1962 to 2.4/100 000 in 1985. The largest number of cases (19%) was in the group < 1 year of age, and 60% of childhood cases occurred in those aged < 5 years. In 1985, the case rate for children 0-4 years (4.4/100 000) was three times that in children aged 5-14 years (1.4/100 000). It is also pointed out that childhood tuberculosis was increasingly focused in certain areas and was reported in only 11.6% of the country's 3138 counties. Four states (California, South Carolina, New York and Texas) accounted for half of the childhood cases.

Mortensen J et al. **(1989)**. Childhood tuberculosis in a developed country. *European Respiratory Journal*, 2:985-987.

Between 1975 and 1985, 65 children with tuberculosis were diagnosed in Copenhagen: 25 were of Danish extraction and the remainder the children of immigrants. In Denmark in 1987, the incidence of tuberculosis among children < 15 years of age was 1/100 000; in Copenhagen the incidence among Danish children was 5/100 000, but among immigrant children it varied from 68 to 200/100 000, depending on the country of origin. Several differences were noted between the Danish children and the immigrant children. Although there was no difference between the two groups of children as regards sex or age, none of the Danish children had extrapulmonary tuberculosis, whereas 68% of the immigrant children had respiratory tuberculosis only. In 44 children, *M. tuberculosis* was cultured (48% of the Danish children and 80% of the immigrant children). Symptoms led to the diagnosis in 45% of cases, contact-screening in 39%, and routine screening in 16%.

As in a number of developed countries, this paper illustrates again that among subgroups in low-incidence countries remarkably high incidence rates of tuberculosis may be found.

Mulholland EK, Gilbert GL, Kempster RE **(1989)**. Childhood tuberculosis in Victoria, 1970-1986. *Australian Pediatric Journal*, 25:31-34.

During the 17-year period that the authors review, the incidence of childhood tuberculosis in the Australian state of Victoria declined from 3.84/100 000 to 1.94/100 000. During the study period, the number of cases notified was 460 of whom 170 (37%) were born outside Australia, mainly in South-East Asia. The 84 notifications from Sout-East Asian children represented a mean crude incidence of 158/100 000 among this group. Primary pulmonary disease was present in 356 patients (77%), more advanced pulmonary disease in another 25 (5.4%), and non-pulmonary disease in 79 (17%). In contrast to the fall in the incidence of pulmonary disease, the incidence of non-pulmonary disease remained constant throughout the period reviewed.

Tuberculosis was confirmed by culture of *M. tuberculosis* in 134 children (29%), and this percentage varied from 41% and 43% in children aged < 2 years and 15-16 years respectively to 26% in those aged 2-14 years. This variation most probably mirrors the more serious forms of tuberculosis seen at the extremes of the childhood spectrum.

Uke BT, Seth V **(1991)**. National tuberculosis programme in India: lacunae in relation to childhood tuberculosis. *Indian Pediatrics*, 28:239-241.

This paper reviews the development of the Indian National Tuberculosis Programme up to the point of publication. Problems in relation to childhood tuberculosis are pointed out. The annual "incidence of infection" is given as 0.8% at age < 5 years, 1.1%, at 5-9 years, 1.3% at 10-14 years, and 1.6% for all ages. The authors plead for urgent attention to the following:

7. "Uniform diagnostic criteria for common forms of childhood tuberculosis.
8. Dosage and regimens as for short-course antituberculosis treatment.
9. Children of sputum-positive patients must be considered as high risk for the disease and need at least a tuberculin test and an X-ray test.
10. Pharmacokinetic studies in children should be done at referral centres so that proper dosages can be recommended."

This programme is not very different to that now being promoted to advance the integration of childhood tuberculosis into national tuberculosis programmes.

Styblo K (1991). Epidemiology-III: Global Scenario. In: Puri RK, Sachdev HP, eds. *Tuberculosis in children*. New Delhi, Indian Academy of Pediatrics:53-61.

In this book chapter, Karel Styblo provides an estimate of the number of "… infected, diseased and at-risk children aged 0-14 years in a general population of 10 million exposed to a risk of infection of 1% in a developing country ...".

General population	10 000 000
Children aged 0-14 years	4 500 000
1% infected annually	45 000
Active tuberculosis (10%)	4 500

A similar calculation is often used to estimate the burden of childhood tuberculosis in the developing world.

Starke JR, Jacobs RF, Jereb J **(1992)**. Resurgence of tuberculosis in children. *Journal of Pediatrics*, 120:839-853

This extensive review of a number of aspects of the epidemiology of childhood tuberculosis does not give case rates in the USA, but does record that the number of cases of tuberculosis in children < 5 years of age increased by 39% between 1987 and 1990.

Barazzone C et al. **(1993)**. Childhood tuberculosis at a Swiss university hospital: a 2-year study. *European Journal of Pediatrics*, 152:805-809.

This paper describes the incidence of tuberculosis seen at the University Hospital of Geneva, Switzerland during the period October 1989 to October 1991. Of the 43 cases

identified during this period, 42% had active disease or clinical evidence of organ involvement, while the remainder were asymptomatic. It was noted that all the children were from families originating from countries outside Switzerland.

Okot-Nwang M, Wabwire-Mangen F, Kagezi VB **(1993)**. Increasing prevalence of tuberculosis among Mulago Hospital admissions, Kampala, Uganda (1985-1989). *Tubercle and Lung Disease*, 74:121-125.

The authors describe the prevalence of tuberculosis among admissions to Mulago Hospital, Uganda during the period 1985-1989. During these years the number of cases of tuberculosis doubled from 835 in 1985 to 1614 in 1989. Unfortunately the precise numbers of children are not given, but interestingly the percentage of cases with pulmonary tuberculosis falling in the age group 0-14 years increased from 25% in 1985 to 44% in 1989. The authors do not comment upon this, but children with HIV infection often have pulmonary involvement. HIV-positivity among all tuberculosis patients at the hospital increased from 37% in 1985 to 68% in 1988. Extrapulmonary disease was most frequent among children aged 0-14 years, accounting for close to 60% of such disease seen, but again the actual numbers are not given.

Medical Research Council Cardiothoracic Epidemiology Group (1994). Tuberculosis in children: a national survey of notifications in England and Wales in 1988. *Archives of Disease in Childhood*, 70:497-500.

This paper reports the notification of childhood tuberculosis in England and Wales in 1988. That year 294 children aged < 15 years were notified, representing an annual rate of 3.1/100 000. The rate for children of Indian subcontinent ethnic origin born outside the United Kingdom was 53/100 000 and for those born in the United Kingdom 26/100 000. By 1988, the risk of disease among white children in the United Kingdom was < 2/100 000.

Goldman JM et al. **(1994)**. Childhood tuberculosis in Leeds, 1982-1990: social and ethnic factors and the role of the contact clinic in diagnosis. *Thorax*, 49:184-185.

The tuberculosis incidence rate for children 0-14 years in Leeds for the period 1982-1990 was 5.5/100 000.

Drucker E et al. **(1994)**. Childhood tuberculosis in the Bronx, New York. *Lancet*, 343:1482-1485.

This paper gives a detailed evaluation of cases of childhood tuberculosis reported from the New York suburb of the Bronx for the period 1986-1992. A total of 75 cases of tuberculosis in children < 5 years of age was evaluated with regard to a number of factors. Those most closely associated contemporaneously with the increase in tuberculosis rates in adults and children were crowding and the increase in AIDS cases. The population of children aged < 5 years in 1990 was 102 906 and a total of 75 cases of tuberculosis were recorded for the period investigated, representing an incidence of 73/100 000. Taking into account crowding, the incidence of childhood TB cases varied from 1.47 to 8 cases per 10 000 children as crowding increased.

Villabí JR et al. **(1994)**. The evolution of tuberculosis infection among schoolchildren in Barcelona and the HIV epidemic. *Tubercle and Lung Disease*, 75:105-109.

This paper analyses the prevalence of tuberculosis infection among first-grade students in schools in Barcelona. In common with other cities in the developed world, although the overall rate was fairly low at 0.87%, it varied among the different districts of the city from a low of 0.13% to a high of 3.03%. Review of the results of previous studies indicated that the rates were not declining as previously and this is ascribed to immigration from countries with a higher rate of tuberculosis combined with poverty and the effects of HIV.

WHO (1995). *Tuberculosis*. Fact sheet No. 93. Geneva, World Health Organization.

This document states that tuberculosis kills "… almost 300 000 children" every year.

Kimerling ME, Vaughn ES, Dunlap NE **(1995)**. Childhood tuberculosis in Alabama: epidemiology of disease and indicators of program effectiveness, 1983-1993. *Pediatric Infectious Disease*, 14:678-684.

This 11-year review of childhood tuberculosis in the American state of Alabama gives details of 171 cases occurring in children aged < 15 years. The case rates varied from 3.3 to 1.0/100 000 for children aged 0-4 and 5-14 years, and from 0.7 to 3.8 for white and black children respectively. *M. tuberculosis* was isolated from 25% of cases, but from 52% of those where isolation was attempted. It is relevant that the authors discuss the problems that arise from the presence of hilar adenopathy without pulmonary infiltration, and whether these cases should be classified as extrapulmonary tuberculosis.

Eriksson M, Bennet R, Danielsson N **(1997)**. Clinical manifestations of tuberculosis and epidemiology of childhood tuberculosis in Stockholm 1976-1995. *Scandinavian Journal of Infectious Diseases*, 29:569-572.

In 1975 the incidence of childhood tuberculosis in Sweden was 0.8/100 000, and 1.1 and 1.5/100 000 in 1984 and 1994 respectively. Within the catchment area of St Goran's Children's Hospital (Stockholm), incidence varied from 5.9/100 000 for the whole childhood population to 4.2 for Swedish-born children, 0 for children both of whose parents were Swedish, and 20/100 000 for children from a suburb with a very high proportion of immigrant families coming mainly from countries with high tuberculosis incidence.

Reinhard C, Paul WS, McAuley JB **(1997)**. Epidemiology of pediatric tuberculosis in Chicago, 1974 to 1994: a continuing public health problem. *American Journal of the Medical Sciences*, 313:336-340.

During the period 1974-1994, the overall mean rate of tuberculosis in children aged < 15 years was 5.13/100 000; and from 1982 to 1994, 6.29/100 000. Within some communities however, rates of > 15/100 000 were recorded. Tuberculosis in children aged < 15 years was responsible for 3.8% of all tuberculosis notifications.

Bibi H et al. **(1997)**. Epidemiology of childhood tuberculosis in the Ashkelon region in Israel, 1958-1994. *Acta Paediatrica*, 183:183-186.

Between 1958 and 1994, 250 cases of childhood tuberculosis (children aged 0-18 years) were reported for the Ashkelon region of Israel. Incidence rates for the whole period are not given, but in 1958-1964 a total of 1075 tuberculosis cases were recorded, of which 7.26% occurred among children. During the period 1975-1979, the total number of cases had fallen to 251, of which 16% were children. For subsequent years, childhood incidence rates are given and in the most recent period of 1990-1994 the rate among children 0-14 years was 10.1/100 000. The figures were influenced at different periods by immigration from North Africa and later from Ethiopia. During the years 1985-1994, Ethiopian children constituted the majority of the children diagnosed, and cases were coming to the fore even 9 years after the arrival of the immigrants.

Felten MK et al. **(1998)**. Childhood tuberculosis in Germany between 1985 and 1994: comparison of three selected patient groups. *International Journal of Tuberculosis and Lung Disease*, 2:797-803.

The incidence of tuberculosis in children < 15 years of age increased from 3.8/100 000 in 1991 to 5.0 in 1993, and fell again to 4.0/100 000 in 1994.

Lobato M et al. **(1998)**. Tuberculosis in children and adolescents: California, 1985-1995. *Pediatric Infectious Disease Journal*, 17:407-412.

The authors describe the epidemiology of tuberculosis among children aged 0-14 years in California from 1985 to end-1995. Case rates among children aged 0-4 years were 13/100 000. The peak incidence rates were encountered in 1991-1992 and were 13/100 000 for children 0-4 years and 5/100 000 for those aged 5-14 years. These rates were 8 and 4 respectively in 1995. As in other studies and other countries, there was considerable variation among different population subgroups, so that rates in 1995 for white, black, Hispanic and Asian/Pacific islander children aged 0-4 years were 1.0, 11.6, 12.8 and 12.2 respectively; and for children aged 5-14 years 0.2, 4.1, 6.8 and 6.2.

Makristathis A et al. **(1998)**. Infant tuberculosis in Austria – trend reversal since 1990. *Infection,* 26:46-48.

The authors of this paper describe an increase in the number of cases of tuberculosis in children aged 0-4 years seen in Austria during the period 1986 (9 cases) to 1996 (33 cases), with 52 cases reported in 1995. No incidence rate is given. Of the 85 cases recorded in 1995-1996, 66 (78%) were respiratory tuberculosis and in 45 cases (53%) the diagnosis was proven by culture of *M. tuberculosis*. Approximately half of the cases (52% in 1995 and 53% in 1996) arose among "foreign citizens".

Kalaajieh WK (1999). Epidemiology of tuberculosis in Lebanon. *International Journal of Tuberculosis and Lung Disease*, 3:774-777.

Of 1111 recorded cases of tuberculosis occurring from January 1995 to December 1996, 5% were < 5 years of age and 19% < 15 years. The author notes that these proportions have been constant since 1963.

Odhiambo JA et al. **(1999)**. Tuberculosis and the HIV epidemic: increasing annual risk of tuberculous infection in Kenya. *American Journal of Public Health*, 89:1078-1082.

This study documents an ARI of 1.1% in Kenya between 1994 and 1996. This was higher than that found earlier between 1986 and 1990. The greatest increases in the ARI were found in areas where tuberculosis notification rates had increased prior to 1994. These were also the districts with high HIV prevalence rates. In the urban district of Nairobi, the ARI was 2.9%.

Scholten JN, Fujiwara PI, Frieden TR **(1999)**. Prevalence and factors associated with tuberculosis infection among new school entrants, New York City, 1991-1993. *International Journal of Tuberculosis and Lung Disease*, 3:31-41.

This study enabled the calculation of the ARI for US-born 5-year-old children resident in New York entering school for the first time, and this was 0.058% for 1991 and 0.075% for 1993.

Suryanarayana L, Suryanarayana HV, Jagannatha PS **(1999)**. Prevalence of pulmonary tuberculosis among children in a South Indian community. *Indian Journal of Tuberculosis*, 46:171-178.

This is one of the few studies to have attempted a tuberculosis prevalence survey among children. The survey was linked to an annual risk of infection survey carried out in the periphery of the city of Bangalore, and a positive tuberculin test constituted one of the entry points into the study. The other criteria for inclusion in further investigations were malnutrition, a history of contact with an adult case of tuberculosis and lymph node enlargement. The further investigation included chest radiography (carried out in 30% of the children < 5 years of age) and in addition bacteriological evaluation in those ≥ 5 years of age. Fifty "radiological" cases were identified and 17 "bacteriological" cases. The prevalence rate of bacteriological cases in children aged 5-14-years was 0.15%, and that of radiological cases in children 0-14-years, 0.3%. The authors state that these rates were identical to those found among slum children in Bangalore 30 years previously. Although they state that these rates are low, they translate into rates of 150 and 300/100 000, rates that are not by any means negligible.

Van Rie A et al. **(1999)**. Childhood tuberculosis in South Africa: burden and risk factor. *Archives of Disease in Childhood*, 80:433-437.

This study described the epidemiology of childhood tuberculosis in two South African socioeconomically poor urban communities. The case notification rate in these suburbs was 3588/100 000 for children 0-5 years of age and 332/100 000 for those 6-14 years. Children < 14 years of age represented 39% of the total tuberculosis case-load.

Schaaf HS et al. **(2000)**. Primary drug-resistant tuberculosis in children. *International Journal of Tuberculosis and Lung Disease*, 4:1149-1155.

Part of the burden of tuberculosis is the presence of drug-resistant tuberculosis in a community. In the case of childhood tuberculosis, this is not often quantified and reliance is placed on data obtained from adult patients. This study is one of the few attempts to quantify the burden of drug resistance among children. Although hospital-based, this study

from the Western Cape Province of South Africa reported data from 300 children obtained over two years in an area with a very high incidence of tuberculosis. The incidence of INH resistance was 5.6% and that of MDR 1%. These figures were similar to those obtained in the same area for adults with primary resistance, and suggest that the incidence of drug resistance among children in a community may provide a reliable reflection of the strains currently being transmitted in that community.

Parslow R et al. **(2001)**. Tuberculosis, deprivation, and ethnicity in Leeds, UK, 1982-1997. *Archives of Disease in Childhood*, 84:109-113.

This paper gives details of the incidence of childhood tuberculosis in Leeds. As in a number of other studies from developed countries, the overall rate during the study period was low (3.9/100 000 per year), but was higher in certain subgroups of the population. Among children of southern Asian origin, the rate was 25.7/100 000. Children aged 0-4 years comprised 24% of the 107 notifications, and those aged 5-9 years, 36%. Respiratory tuberculosis was diagnosed in 82.2% of cases.

Tanzania Tuberculin Survey Collaboration (2001). Tuberculosis control in the era of the HIV epidemic: risk of tuberculous infection Tanzania, 1983-1998. *International Journal of Tuberculosis and Lung Disease*, 5:103-112.

Between 1988 and 1992, the ARI was 1%, but was 0.9% during this study, conducted during the period 1993-1998. Despite the stable ARI, higher rates were found in those regions with high tuberculosis notification rates. Thus in Dar es Salam (notification rate for smear-positive tuberculosis 266/100 000), the ARI was 1.7% and 1.9% in Mtwara with a smear-positive notification rate of 115/100 000.

San Gabriel P et al. **(2003)**. Completeness of pediatric TB reporting in New York City. *Public Health Reports*, 118:144-153.

This paper describes an attempt to improve the completeness of the reporting of paediatric tuberculosis in New York by a survey of alternative sources of information. Making use of hospital-based sources of information, 25 cases of childhood tuberculosis were found. Of these, 4 had never been reported to the New York Department of Health and 3 had not previously fulfilled the criteria for diagnosis. By this means the number of cases of paediatric tuberculosis identified was increased by 21%. This paper highlights the well-known fallability of the notification system and one manner of addressing its deficiencies.

Arora VK, Gupta R **(2003)**. Directly observed treatment for tuberculosis. *Indian Journal of Pediatrics,* 70:885-889.

This paper summarizes the rationale behind the adoption of the DOTS strategy and its expansion in India. At the same time the paper gives a number of details from other sources that reflect the current tuberculosis situation among children in India. Thus a study among 20 063 children from the south of India found a 0.3% incidence of tuberculosis on chest radiology and 0.15% among children aged 0-14 on bacteriology in the age group 5-14 years (Sryanarayana et al., 1999). Another study from Mumbai found tuberculosis to be the most common infection among hospitalized children (Dharnidharka & Kandoth, 1999).

Enarson DA (2004). Children and the global tuberculosis situation. *Paediatric Respiratory Reviews*, 5 (supplA):S143-145.

This paper highlights the development of the current strategies for the control of tuberculosis, and with regard to childhood tuberculosis draws attention to the lesson provided by experience in China, where the Beijing Municipality started to implement DOTS in 1978. Since then tuberculous meningitis has virtually disappeared from the community, and the prevalence of tuberculosis has declined to a very low level. "The ability of the DOTS strategy to prevent tuberculosis infection in children is the key to reducing the burden of tuberculosis in the long term and of eventually eliminating the microbe from our society."

De Pontual L et al. **(2004)**. Childhood tuberculosis in a low-income Paris suburb : lessons from a resurgence brought under control. *International Journal of Tuberculosis and Lung Disease*, 8:976-981.

The overall incidence of tuberculosis in children in France in 1997 was 6.2/100 000; in the low-income Paris suburb of Seine-St Denis it was 10.2/100 000 in 1998.

Chadha VK et al. **(2004)**. The annual risk of tuberculous infection in the eastern zone of India. *International Journal of Tuberculosis and Lung Disease*, 8:537-544.

Shashdhara AN et al. **(2004)**. The annual risk of tuberculous infection in Orissa State, India. *International Journal of Tuberculosis and Lung Disease*, 8:545-551.

These two articles in conjunction with two earlier papers document the ARI over a large area of India. Rates varied from 1.3% for the eastern zone, 1.7%-1.8% for Orissa state to 1.9% in the northern zone and 1.1% in the southern zone. In all of these studies, rates were higher within urban areas than rural areas and in coastal areas than in inland areas. -------

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Kassa-Kelembho E et al. **(2004)**. Surveillance of drug-resistant childhood tuberculosis in Bangui, Central African Republic. *International Journal of Tuberculosis and Lung Disease*, 8:574-578.

In 1998 the overall prevalence of drug resistance among new adult tuberculosis cases in Bangui, the capital of the Central African Republic, was 16.4% and for MDR, 1.1%. This study determined the prevalence of drug resistance among 165 children during the period April 1998 to June 2000. The prevalence of drug resistance overall and MDR were 15.2% and 0.6% respectively. This study, as that of Schaaf et al. (2000), suggests that the prevalence of drug resistance among children is a fairly accurate reflection of the situation among adults.

It could be argued that the data obtained from children might be even more accurate than that from adults as it is likely to reflect the situation among organisms currently in circulation.

Nascimento LF (2004). Childhood tuberculosis incidence in Southeast Brazil, 1996. *Cadernos de Saude Publica*, 20:1749-1752.

This paper describes the incidence of childhood tuberculosis during 1996 in an area with a population of 1.8 million situated between the cities of São Paulo and Rio de Janeiro, including cases up to 15 years of age. In this age group, the incidence was 10.4/100 000. In Brazil in 2000, the overall tuberculosis incidence rates were 60.7/100 000 and 11.3 in children aged < 5 years and 5.8/100 000 in those aged 5-9 years. The two groups together represented only 2.7% of all tuberculosis cases in 2000. Other fragments of information are also provided: between 1989 and 1993, the incidence of paediatric tuberculosis in Rio de Janeiro was 27/100 000, and for all age groups in 1993, 151/100 000. In São Paulo in 1996, overall tuberculosis incidence was 51/100 000 with approximately 4% of cases occurring in children. During the period evaluated there was only one case of meningeal tuberculosis and cavities were present in only 1.6% of the childhood cases.

The picture sketched is thus one of a country with a tuberculosis incidence fast approaching that of a developed country.

Nelson LJ, Wells CD **(2004)**. Global epidemiology of childhood tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:636-647.

This valuable review provides estimates of the numbers and rates of tuberculosis occurring in children throughout the world. The analysis estimated that there were 884 019 new cases of tuberculosis in children aged < 15 years in 2000, and that they represented 10.7% of all tuberculosis cases; 75% of childhood cases occurred in 22 high-burden countries. The proportion of tuberculosis that occurred in children varied from 2.7% in Thailand to > 20% in Afghanistan, Brazil and Pakistan. Case rates for childhood tuberculosis in the 22 high-burden countries varied from 15/100 000 in Thailand to 237/100 000 in South Africa.

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Summary of findings from the papers reviewed

The use of standardized criteria for the diagnosis of childhood tuberculosis is crucial in mainstreaming the care of children with tuberculosis as part of routine NTP activities, and in assessing the burden of childhood tuberculosis. *Table 1* lists the features suggested in some of the papers reviewed below for the diagnosis of tuberculosis in childhood.

Table 1. History and symptoms leading to the diagnosis of tuberculosis childhood

Authors	Contact	FTT/WL*	Cough	Fever	Response to antibiotics	Palpable nodes	Symptom complex
Stegen et al. (1969)	+						
Aderele (1979)	+		+	+	+		
Ghidey & Habte (1983)	+	+	+	+		+	
Cundall (1986)	+						
Kumar et al. (1990)		+	+	+		+	
Reiss et al. (1990)	+	+	+	+			
Migliori et al. (1992)	+	+	+				
Pineda et al. (1993)	+		+	+	+		
Seth et al. (1993)	+	+	+	+			
Luo et al. (1994)	+						+
Chintu et al. (1995)	+						+
Schaaf et al. (1996)	+	+	+		+		
Espinal et al. (1996)		+	+	+		+	
Jeena et al. (1996)	+				+		+
Garay (1997)		+	+	+	+		
Mukadi et al. (1997)			+	+	+		
Fourie et al. (1998)	+	+	+	+			
Houwert et al. (1998)	+	+	+				
VanBeekhuizen (1998)		+		+		+	
Mahdi et al. (2000)	+						+
Kiwanuka et al. (2001)		+	+		+		
Salazar et al. (2001)	+		+	+			
Blussévan Oudblas et al. (2002)	+						
Palme et al. (2002)	+	+	+	+			
van Reenen (2002)	+	+	+	+			
Weismuller et al. (2002)	+		+	+	+	+	+
Indian Acad Ped (2004)	+	+	+		+	+	
	21 (78%)	14 (52%	19 (70%)	16 (59%)	9 (33%)	6 (22%)	5 (19%0

* FTT = failure to thrive; WL = weight loss.

With regard to symptoms, of the 27 papers summarized in *Table 1*, 21 (78%) use contact with a case of adult tuberculosis, 19 (70%) cough, 16 (59%) fever and 14 (52%) failure to thrive or loss of weight. A relatively small number of papers (9, 33%) used, or suggested, failure to respond to a course of antibiotics or the presence of superficial nodes (6, 22%). In 5 papers (19%), reference was made to a "symptom complex" compatible with childhood tuberculosis without defining what this was. Other symptoms infrequently used included abdominal distension, difficulty in walking, sputum production, chest pain, haemoptysis, anorexia, malaise/fatigue and bone deformities. The inclusion of some of these is obviously intended to accommodate extrapulmonary forms of tuberculosis. One interesting criterion in the scoring system of Stegen et al. (1969) − the so-called Jones criteria − is age < 2 years, thus accommodating the considerably higher mortality and morbidity seen in the very young.

For each of the criteria, there is also considerable variation in how it is defined. Thus contact with an adult case of tuberculosis might be:

- "… a tuberculous adult or a person with chronic cough" (Ghidey & Habte, 1983)
- "A person in the immediate household of the child had confirmed or probable tuberculosis" (Cundall, 1986)
- "… household contact with a tuberculous adult …" (Migliori et al., 1992)
- "… a family history of tuberculosis …" (Seth et al., 1993)
- "History of close contact with a case of tuberculosis" (Luo et al., 1994)
- Tuberculosis contact differentiated as "close", "sputum positive" or a "sputum positive mother" (Bergman, 1995)
- "… close household contact with a recently diagnosed adult case of pulmonary tuberculosis" (Schaaf et al., 1995)
- "Recent known exposure to an active case of tuberculosis" (Espinal et al., 1996)
- "Contact with a diagnosed TB case" (Jeena et al., 1996)
- "Household contact with diagnosed PTB" (Garay, 1997)
- "Close household contact with an adult with active pulmonary tuberculosis diagnosed within the previous 12 months" (Houwert et al., 1998)
- "Family history of TB" (Van Beekhuizen,1998)
- "An adult with active tuberculosis and/or who had received treatment within the previous 6 months" (Mahdi et al., 2000)
- "A smear-positive household TB contact" (Kiwanuka et al., 2001)
- "…recent close household contact with an adult with sputum microscopy smear-positive pulmonary TB" (Blussé van Oudblas et al., 2002)
- "… household contact with proved TB or symptoms highly suggestive of TB" (Palme et al., 2002)
- "Contact is defined as any child who lives in a household with an adult taking anti-TB therapy or who has taken such therapy in the past 2 years" (Indian Academy of Pediatrics, 2004).

Aside from a number of possibly minor variations upon a theme and the fact that many are very vague, only three definitions link a duration to the contact.

Similarly *cough* is either mentioned as a criterion without any duration or the duration varies from > 2 weeks (Migliori et al., 1992; Mukadi et al., 1997; Houwert et al., 1998;

Palme et al., 2002), to > 3 weeks (Indian Academy of Pediatrics, 2004), 3 or 4 weeks (Bergman, 1995), 4 weeks or > 4 weeks (Ibadin & Oviawe, 2001; Kiwanuka et al., 2001).

Fever is recommended as a criterion in 11 papers (48%), but neither its degree nor duration is defined in most cases.

Malnutrition, in one form or another, featured in 61% of the proposed criteria. This might be stated merely as "loss of weight" (Ghidey & Habte, 1983), "weight loss" (Kumar et al., 1990; Migliori et al., 1992), "no weight gain for 4 months" or "objective loss of weight for 3 months" (Bergman, 1995), "weight loss of >10%" (Garay, 1997) or "malnutrition" (Van Beekhuizen, 1998).

Stegen et al. (1969) make the important point that one should distinguish between those features, whether signs or symptoms, that bring children to our attention and those that are specific for tuberculosis.

Table 2 summarizes clinical signs and investigations in diagnosing childhood tuberculosis.

Firstly, the almost total reliance on chest radiography and Mantoux testing should be noted. Of the 33 papers reviewed, 31(94%) made use of chest radiology, as did 31 (94%) of tuberculin-testing in the form of the Mantoux test. As in the case of symptomatology there is a lack of uniformity, particularly with regard to the interpretation of the Mantoux test. Varying doses of tuberculin are used (1 or 2 units of RT23 tuberculin), and different criteria are used to define a reaction indicative of *M. tuberculosis* infection. Most frequently, 10 mm or 15 mm induration are suggested, but 5 mm is also recommended even without reference to HIV infection. The precise manner in which the induration following a Mantoux test is measured is almost never stated.

Secondly, HIV poses particular problems for all the suggested approaches to the diagnosis of tuberculosis in children (Garay, 1997; Kiwanuka et al., 2001; Van Rheenen, 2002). HIV-infected children are often malnourished and immunosuppressed, leading to a negative tuberculin test. They often have respiratory infections other than tuberculosis and may have lymphadenopathy for a variety of other reasons. *Table 3* summarizes common diagnostic features of children with tuberculosis, with and without HIV infection. Definitions across these studies are not uniform but without applying a statistical analysis, it would appear that fever and clubbing are more common in children with HIV infection, and that HIV-infected children are less likely to respond to tuberculin skin-testing.

Table 2. Signs and investigations used in the diagnosis of childhood tuberculosis

Authors	Culture	Acid-fast bacilli	Histology	PCR*	Tuberculin skin-test	Chest radiograph	Malnutrition	Clinical features	Response to treatment
Stegen et al. (1969)		+	+		+	+		+	
Aderele (1979)	+	+	+		+	+	+	+	
Ghidey & Habte (1983)	+		+		+	+			
Cundall (1986)		+			+	+			
Starke&T-Watts (1989)	+				+			+	+
Kumar et al. (1990)	+	+	+		+	+			
Reis et al. (1990)		+	+		+	+			
Migliori et al. (1992)		+	+		+	+			+
Goodyear et al. (1993)	+				+	+		+	
Pineda et al. (1993)	+	+			+	+			+
Seth et al. (1993)					+	+	+		
Luo et al. (1994)		+	+		+	+			+
Chintu et al. (1995)		+			+	+		+	+
Schaaf et al. (1995)	+				+	+	+		+
Espinal et al. (1996)	+	+			+	+			+
Jeena et al. (1996)			+		+	+			+
Garay (1997)	+	+			+	+			+
Mukadi et al. (1977)	+					+			+
Fourie et al. (1998)	+		+		+	+	+		
Houwert et al. (1998)	+				+	+			
Van Beekhuizen (1998)	+				+		+		
Neu et al. 1999)	+	+	+	+		+ (CT)*		+	
Mahdi et al. (2000)	+	+	+		+	+		+	
Ibadin & Oviawe (2001)		+			+	+			
Kiwanuka et al. (2001)	+	+			+	+			
Salazar et al. (2001)	+	+		+	+	+			
Wong et al. (2001)	+		+			+			
Blussé van Oudblas et al. (2002)	+	+	+		+	+			
Palme et al. (2002)		+	+		+	+			
S-Albisua et al. (2002)	+	+			+	+		+	
Van Reenen (2002)	+	+	+	+	+	+	+		
Kabra et al. (2004)		+	+	+	+	+			
Indian Acad Ped (2004)	+	+				+	+		
	22 (66%)	21 (64%)	17 (52%)	4 (12%)	31 (94%)	31 (94%)	5 (15%)	8 (24%)	10 (30%)

* PCR = polymerase chain reaction; CT = computerized tomography.

Table 3. Presenting symptoms and clinical features in children with tuberculosis (%) with (+) and without (-) HIV infection

Author	HIV+ No.	TST pos*	Cough	Fever	Weight loss	PTB contact*	Adenop	Clubbing
Espinal et al. (1996)	+ 26	20	77	85	65	-	-	-
	-178	70	73	82	74	-	-	-
Garay (1997)	+ 25	-	52	40	20	-	-	-
	- 25	-	98	8	20	-	-	-
Mahdi et al. (2000)	+ 68	12	52	73	61	37	-	-
	-93	Data not given	38	61	36	37	-	-
Kiwanuka et al. (2001)	+ 26	54	96	92	88	88	65	35
	- 19	79	84	63	68	63	47	0
Jeena et al. (2002)	+ 57	18	-	-	-	28	63	19
	- 44	48	-	-	-	36	7	2
Palme (2002)	+ 58	21	93	93	79	69	-	-
	- 459	80	69	79	78	52	-	-
Van Rheenen (2002)	+23	9	-	48	-	43	87	-
	-52	31	-	38	-	27	71	-
Iriso et al. (2005)	+62	24	98	95	89	37	33	26
	-64	68	94	95	78	44	34	8

* TST pos = tuberculin skin-test positive; PTB = pulmonary tuberculosis.

In a critical review of various diagnostic approaches to childhood tuberculosis, Hesseling et al. (2002) identified a number of criteria, including many of those discussed above, where lack of uniformity hindered any attempts at comparison. They argued for standardization of definitions and for multicentre studies to validate the different approaches and determine the sensitivity, specificity and predictive value of the various criteria.

The recent paper of Iriso et al. (2005) is an example of the sort of study that is required to place the diagnosis of childhood tuberculosis on a more scientific foundation. Conducted in an HIV-endemic area, this study not only enrolled a considerable number of children as "suspect" cases, but was able to use culture-proven cases as a "gold standard", and to provide both sensitivity and specificity of the various criteria and determine 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%.

Finally, further evaluation of sputum induction as opposed to gastric aspirate, particularly in a primary care setting, is necessary.

Summary of each paper reviewed

Stegen G, Jones K, Kaplan P **(1969)**. Criteria for guidance in the diagnosis of tuberculosis. *Pediatrics*, 43:260-263.

This was one of the first attempts to place the diagnosis of childhood tuberculosis on a firm systematic basis.

Methodology. This descriptive paper outlines the use of a point scoring system for the diagnosis of childhood tuberculosis based on experience in Chile. The system is intended to give one of four possible answers: (1) tuberculosis unlikely; (2) tuberculosis possible, requires further investigation; (3) tuberculosis probable, may justify therapy; (4) tuberculosis appears unquestionable.

"Jones criteria" for guidance in the diagnosis of tuberculosis in childhood

Finding	Points
Acid-resistant bacilli	+3
Tuberculous granuloma	+3
Positive tuberculin test > 10 mm	+3
Suggestive X-ray	+2
Suggestive physical examination	+2
Positive tuberculin test > 5-9 mm	+2
Conversion of negative to positive TST*	+2
Known contact with positive sputum	+2
Non-specific X-ray	+1
Compatible physical examination	+1
History of contact with tuberculosis	+1
Non-specific granuloma	+1
< 2 years of age	+1
BCG during the last 2 years	-1

* TST = tuberculin skin-test.

The authors then give several examples of applying these criteria to clinical cases. They note: "We do not take into account signs and symptoms such as fever, cough, erythrocyte sedimentation rate, etc. because we consider these non-specific and only useful in determining activity. They are no help in the differential diagnosis".

This last point of the authors is perhaps helpful in that it again emphasizes that one should distinguish between those features, whether signs or symptoms, that bring children to our attention and those features with the greatest specificity for tuberculosis.

Mathur HC, Saxena S, Bhardwaj RM **(1974)**. Evaluation of Kenneth Jones criteria for diagnosis of childhood tuberculosis. *Indian Journal of Pediatrics*, 41:349-355.

Summary. "The aim of the present study was to determine the utility of this point system in diagnosing children suffering from tuberculosis …". This study was undertaken in Jaipur (India) and the authors applied the point scoring system of Kenneth Jones to 100 children during the period June 1969−March 1970.

Without going into the precise results, the authors' conclusions contain some relevant remarks. They considered that the system clarifies dubious diagnoses based on "vague X-rays and doubtful Mantoux tests" but that "the evaluation has to be very rigid" and "there

is a long cumbersome list". Applying the system to their patients, they found it to have a sensitivity of 73%; if, however, they added one point for marasmus the sensitivity became 93%, but this would make the list of criteria even longer. One finds it difficult to imagine busy primary care staff finding the time and energy to fill in the list of 14 findings every time a child needs to be evaluated for possible tuberculosis.

Laven GT (1977). Diagnosis of tuberculosis in children using fluorescence microscopic examination of gastric washings. *American Review of Respiratory Diseases*, 115:743-749.

Population and methodology. This study was carried out in Lima (Peru) on "a select group of patients chosen by pediatricians for many clinical reasons". Also it should be noted that "the study group does not include the vast majority of children (usually outpatients) in whom tuberculosis was diagnosed during the study period on the basis of reaction to a skin-test using purified protein derivative and chest roentgenogram alone". In this study the use of fluorescent microscopy was compared with culture of gastric aspirate in 191 patients aged 2 months to 14 years. The children were severely ill and 18 deaths were recorded. Pulmonary tuberculosis was diagnosed in 107 children.

Results. Tuberculosis was confirmed in 63 children by culture of gastric washings (61 children) or sputum or by autopsy in one child each. The results were then classified according to the extent of disease seen on chest radiographs, summarized in the table below. Among the children with less severe disease, the number of specimens per child was 2.7, and 2.9 among those with more severe disease. The results are interesting from several points of view. Firstly the percentage of positive smears is exceeded in the literature only by the results of Migliori et al. (1992). This suggests that the success of smear-microscopy in childhood is probably linked to the time and care taken to examine the smear. Secondly the sensitivity of the examination for both smear and culture increased with the severity of the disease, while the opposite effect was seen with regard to the tuberculin test results.

Clinical and radiographic diagnosis	No. of children	Positive FM* (%)	Positive GW* culture (%)	Positive TST* (%)
Miliary TB*	13	54	69	31
Far-advanced cavitary TB	13	62	69	62
Far advanced non-cavitary TB	26	73	65	54
Moderately advanced TB	21	14	43	57
Minimal TB or negative CR*	24	21	17	75
Total with TB	97	43	50	58
Total without TB	81	1	5	8
Total number patients	178	24	30	35

* TB = tuberculosis; FM = fluorescent microscopy; GW = gastric washing; CR = chest radiography; TST = tuberculin skin-test.

Aderele WI (1979). Pulmonary tuberculosis in childhood. *Tropical and Geographical Medicine*, 31:41-51.

Site and population. Children referred to the author at a childhood tuberculosis clinic in Ibadan (Nigeria) from January 1972 to December 1976; 263 children aged 3 months to 13 years with pulmonary tuberculosis were diagnosed and treated.

Diagnostic criteria. Criteria for inclusion in the study included any of the following:
  (1) Isolation of *M. tuberculosis* from sputum or gastric aspirate, plus CXR changes.
  (2) Histological diagnosis of tuberculosis by biopsy of gland, bone or skin plus CXR features.
  (3) Miliary shadowing on CXR plus features of tuberculosis elsewhere in the body.
  (4) Phlyctenular kerato-conjunctivitis plus a positive tuberculin skin-test of at least grade 2 and radiological changes.
  (5) CXR changes which persisted despite adequate antibiotic therapy plus a positive tuberculin test.
  (6) History of close contact with cases of tuberculosis plus positive skin test and radiological changes.
  (7) Necropsy confirmation of pulmonary tuberculosis.

The major presenting symptoms in this study were cough, fever and weight loss. The duration of cough (present in 180 children, 68%) varied from 2 weeks to 30 months with a mean of 2 months. Fever which is not defined was present in 149 children (57%) and had lasted for 2 weeks to 24 months (mean 3 months). Loss of weight was a symptom in 136 children (52%). In only 46 cases (17%) was there a history of contact with a case or a possible case of pulmonary tuberculosis. Of 224 children who were tuberculin-tested, 57 (25%) had a negative test, but most had a Heaf test done and it is difficult to compare the results with those after Mantoux testing. Bacteriological or histological confirmation was obtained in 60 children (23%): in 17 following lymph node biopsy and in 12 and 8 respectively from gastric aspirate and sputum culture.

Outcome. Of the 219 children whose outcome could be analysed by the time of publication, 24 (11%) were known to have died.

The author comments specifically on the clinical value of the finding of supraclavicular nodes (found in 56 cases, 25%) for the diagnosis of childhood tuberculosis.

Ghidey Y, Habte D (**1983**). Tuberculosis in childhood: an analysis of 412 cases. *Ethiopian Medical Journal*, 21:161-167.

Site and population. Children presenting to the chest clinic of the Ethio-Swedish Paediatric Clinic, Addis Ababa during the period May 1979 to April 1981. During this period 412 children were registered as suffering from tuberculosis.

Diagnostic criteria. The presence of two or more of the criteria was required for the diagnosis of tuberculosis in children 4-6 years of age and at least three criteria for children > 6 years of age. Response to treatment was not utilized as a criterion.

  (1) History of contact with a tuberculous adult.
  (2) Suggestive symptom complex. In a footnote this is summarized "… includes non-specific symptoms such as fever, night sweats and loss of weight and specific symptoms related to the site invaded, e.g. cough, swelling of lymph nodes, abdominal distension, difficulty walking …".
  (3) Radiological findings compatible with tuberculosis.
  (4) 2TU PPD reaction (positive): 10 mm or greater induration in a non-BCG-vaccinated patient, or 15 mm or greater induration in a BCG-vaccinated patient.
  (5) Bacteriological or histological proof.

From table 4 in the paper, it appears that a sedimentation rate of > 20 mm/hour was also used as a criterion. In this table the tuberculosis symptom complex was found in 335 children (86%), contact with a tuberculous adult or *a person with chronic cough* in 212 (51%), a positive Mantoux test in 299 (73%) and a compatible X-ray in 339 (83%).

Outcome. As with several other studies from developing countries, a very high rate of attrition was experienced during treatment. Of the 339 children who remained under the care of the clinic, 202 (60%) attended regularly, but 137 (40%) were lost to follow-up. There were 3 deaths.

This is one of the few papers to distinguish between children by age, at least three criteria (rather than two) being required for the diagnosis in children > 6 years of age.

Cundall DB (1986). The diagnosis of pulmonary tuberculosis in malnourished Kenyan children. *Annals of Tropical Paediatrics*, 6:249-255.

Site and population. This is a prospective study that records how the diagnosis of pulmonary tuberculosis was made in Maua Hospital (Kenya) during the 2-year period December 1981 to November 1983. "The aim of the study was to record how the diagnosis of pulmonary tuberculosis was made in order to define an appropriate diagnostic process for use in similar areas." The 144 children, aged from 6 weeks to 12 years, represented 4% of all paediatric admissions during the study period.

Diagnostic criteria
 (1) AFB positive: AFB identified on direct microscopy of sputum or gastric washings.
 (2) Mantoux positive: induration of 6 mm or more after the injection of 1 TU PPD RT23. In children who had received BCG, an induration of $\geq$ 10 mm was positive.
 (3) Contact positive: a person in the immediate household of the child had confirmed or probable tuberculosis.
 (4) Diagnostic X-ray: the CXR was strongly indicative of tuberculosis, showing for example miliary shadowing or segmental lesions and hilar enlargement consistent with a primary complex.
 (5) Suspicious X-ray: the appearance of the X-ray was suggestive, but not diagnostic, of tuberculosis

Results. This study shows that children with pulmonary tuberculosis divided into confirmed, probable and suspect cases. As the author states, this represents "a hierarchy of diagnostic reliability, which may be used in a rational approach to suspected cases".

No. of children		Diagnostic criterion	No. of children with other criteria	Final classification
144	6	AFB positive	2 contact 1 X-ray	Confirmed TB
138	19	Mantoux positive	6 contact 2 contact & X-ray 4 X-ray	Probable TB
119	34	Contact positive	13 X-ray	
85	22	Diagnostic X-ray		
63	23	Suspicious X-ray		
40				Suspected TB

This study, as with the WHO criteria (WHO, 1983), reflects the certainty with which the diagnosis of childhood tuberculosis is made in areas of high tuberculosis incidence. From a more practical point of view, once the decision has been made to institute antituberculosis therapy the children, whether confirmed, probable or only suspect cases of tuberculosis, become part of the burden imposed upon the health services by tuberculosis. What is not clear in this study is how the children entered the diagnostic process and became suspect cases.

Zimmerman BL et al. **(1987)**. Children with AIDS – Is pathologic diagnosis possible based on chest radiographs? *Pediatric Radiology*, 17:303-307.

The authors review their experience with the interpretation of the chest radiographs of children with AIDS. Among 36 patients, 29 had pulmonary infections that, on either autopsy or biopsy, were shown to be lymphocytic interstitial pneumonitis, bronchus-associated lymphoid tissue, chronic interstitial pneumonitis, desquamative interstitial pneumonitis and immunoblastic sarcoma. The chest radiographs were not predictive in making a specific diagnosis.

Miliary tuberculosis was not one of the diseases found by these authors, but the number of diagnoses made when the histology was evaluated illustrates some of the confusion caused by HIV/AIDS in areas where tuberculosis and HIV/AIDS are common.

Starke JR, Taylor-Watts KT **(1989)**. Tuberculosis in the pediatric population of Houston, Texas. *Pediatrics*, 84:28-35.

Population evaluated. 110 children with a median age of 24 months seen at the Children's Tuberculosis Clinic, Houston (Texas) between September 1984 and December 1987.

Diagnostic criteria. The diagnosis of tuberculosis was confirmed if *M. tuberculosis* was isolated from any body site, or if the clinical findings were consistent with tuberculosis and at least two of the following criteria were also met:
    (1) a Mantoux 5-TU skin-test result of >10 mm induration;
    (2) other disease entities were ruled out and the subsequent course was consistent with tuberculosis;
    (3) an adult source-case with contagious disease was discovered.

These criteria are fairly simple and do not rely on symptomatology at all. The tuberculin used is not stated and "contagious" is presumed to mean sputum smear-positive. A culture of *M. tuberculosis* was obtained from 39% of children with pulmonary involvement and this rose to 75% in those aged < 1 year. At the time of diagnosis, 10 children had a negative TST, but in 8 of these children this converted to positive when repeated within 3 months of commencing treatment.

Treatment regimens. Initially the then-standard regimen of 12-18 months of INH and RMP was used, the duration of treatment later being reduced to 9 months, and then 6-9 months with pyrazinamide for the first two months of treatment.

Drug dosages: INH, 10-15 mg/kg/day; RMP, 10-20 mg/kg/day; PZA, 25-35 mg/kg/day. If given twice weekly, then INH 20-25 mg/kg/dose and RMP 10-20 mg/kg/dose.

Compliance with treatment was judged by self-report, parents' knowledge of the medicines, pill counts, clinical improvement and compliance with clinic visits. In the event of suspected non-compliance, patients were given twice-weekly supervised medications by a nurse or outreach worker after initial daily therapy for two months. Compliance was recognized to be a major problem and 39% of patients were considered significantly non-compliant. The ability to supervise treatment twice weekly enabled completion rates to reach 94%. Disease in those treated twice weekly resolved as quickly and completely as in those treated with daily regimens. In the entire series only two children relapsed and this was associated with drug-resistance in both cases.

Other points of interest
Although 58 children had pulmonary parenchymal disease, only 20 (35%) had respiratory tract symptoms and 14 of these children were < 1 year of age. The fact that children with significant radiological findings may be asymptomatic needs to be considered in drawing up algorithms or scoring systems for the diagnosis of childhood tuberculosis.

Kumar L et al. **(1990)**. A randomized trial of fully intermittent vs. daily followed by intermittent short course chemotherapy for childhood tuberculosis. *Pediatric Infectious Disease Journal*, 9:802-806.

Population evaluated. 76 newly-diagnosed children aged 1-15 years from Chandigarh (India).

Diagnostic criteria. For the purpose of evaluating two therapeutic regimens the authors had to define tuberculosis in their subjects. "A diagnosis of tuberculosis was considered when at least 3 of the following criteria were met":
   (1) tuberculous lymphadenopathy
   (2) pulmonary tuberculosis
   (3) disseminated tuberculosis.
Criteria are then further provided for each of these different categories.

Tuberculous lymphadenopathy
   (a) enlargement of lymph nodes either regionally or generalized;
   (b) positive Mantoux reaction (10 mm or more induration at 72 hours after 1 TU unit of PPD);
   (c) caseous granulomata on histopathology;
   (d) acid-fast bacilli (AFB) in histopathological sections or smears from lymph node aspirates or cultured on Lowenstein-Jensen slants.

Pulmonary tuberculosis
   (a) history of fever, cough, sputum production (older children), chest pain or haemoptysis, malaise, fatigue, weakness and weight loss;
   (b) CXR evidence of consolidation, cavitation, collapse, pleural effusion or pneumothorax;
   (c) positive Mantoux test;
   (d) gastric lavage, deep laryngeal swab or sputum positive for AFB in smears or on culture.

Disseminated tuberculosis
   (a) involvement of multiple organs;

(b) miliary mottling on chest roentgenogram either alone or with other radiological features;

(c) histopathological evidence of tuberculosis as caseous granulomata in biopsies of lymph nodes or the liver;

(d) demonstration of AFB in gastric lavage, sputum or tissue biopsies and/or positive culture.

A positive Mantoux test was not included in the last group because of the frequency of a negative test in the presence of malnutrition and the frequency of malnutrition in disseminated tuberculosis.

These are fairly comprehensive criteria, but it is uncertain how many of the children actually had the different features. The Mantoux test was positive in 94% of children, and a positive culture was obtained in 9%, compatible histopathology in 38% and a positive smear in 36%, but it is not clear in how many cases these findings overlapped in the same children.

What is valuable in this paper is that the authors also gave criteria for assessment of efficacy of therapy:

- *General improvement* was defined as normalization of body temperature, improvement in appetite and weight gain.
- Improvement in *pulmonary tuberculosis* was graded according to general improvement and the regression of radiological lesions or conversely the appearance of new lesions. In the case of *lymphadenitis* the size of the nodes was relied upon, while for disseminated tuberculosis the criteria were similar to the other classes but included a decrease in the size of enlarged organs. Improvement in these various features should have taken place within 3-4 months.

Reis FJ et al. **(1990)**. Six-month isoniazid-rifampin treatment for pulmonary tuberculosis in children. *American Review of Respiratory Diseases*, 142:996-999.

Population evaluated. For the purpose of a therapeutic trial 152 children diagnosed as having pulmonary tuberculosis in Minas Gerais (Brazil) were enrolled.

The *diagnosis* was based on a chest roentgenogram that showed parenchymal changes or mediastinal lymph nodes suggestive of tuberculosis, plus two or more of the following criteria:

(1) suggestive symptoms and clinical signs;

(2) direct contact with a tuberculous adult, bacillary-positive or -negative;

(3) tuberculin test (PPD RT23 2TU) positive ($\geq$ 5 mm induration);

(4) acid-fast bacilli in the sputum or gastric washings, or the presence of granulomata in any histology specimen.

The most frequent symptoms were cough (59%), fever (28%) and weight loss (27%), and 55% had contact with a sputum smear-positive adult. All the children had radiological changes suggestive of tuberculosis, but none had miliary tuberculosis or cavitation. In this study the criteria for improvement are not clearly defined, but it is stated that at the end of treatment there was radiological improvement in all patients, and weight gain with no recurrence in those patients followed up. HIV/AIDS was not evaluated and was probably not yet a significant factor in this community.

Migliori GB et al. **(1992)**. Proposal of an improved score method for the diagnosis of pulmonary tuberculosis in childhood in developing countries. *Tubercle and Lung Disease*, 73:145-149.

Site and population evaluated. Children aged < 5 years referred for suspected pulmonary tuberculosis to the Regional Antituberculosis Centre Arua Hospital (northern Uganda) from June 1987 to August 1989.

Methodology. In this study the authors considered the clinical criteria used by Ghidey & Habte (1983) to provide the "gold standard" diagnosis of pulmonary tuberculosis in childhood, and then evaluated against this standard gastric aspirate for acid-fast bacilli and response to treatment (RTT). At least two of the criteria of Ghidey & Hapte were required for the diagnosis of pulmonary tuberculosis.

Diagnostic criteria
   (1) Medical history was considered "sufficient" if the child had household contact with a tuberculous adult.
   (2) Cough persisting for more than two consecutive weeks was considered suspicious of tuberculosis. Weight loss, fever and sweats were looked on as non-specific symptoms.
   (3) Chest radiograph was performed "on all the children when a consistent suspicion of pulmonary tuberculosis was present after clinical examination".
   (4) A Mantoux test with 2 TU of PPD RT23 was regarded as positive if the induration was ≥ 10 mm in those without a BCG scar or ≥ 15 mm in those with BCG scars.
   (5) Bacteriological or histological proof: three early-morning nasogastric aspirations were performed; further, in the event of negative results three new aspirations were performed.
   (6) In those children placed on treatment, RTT was evaluated and this was defined as clinical improvement (body-weight increase of more than 10% of the starting weight and not less than 0.7 kg, and cough and non-specific symptoms disappearing after two months of treatment).

Results. On the basis of the clinical score the children were classified as:
   (a) Pulmonary tuberculosis cases (31 children, 15%) ... more than 2 points with or without a positive gastric washing or positive RTT.
   (b) Highly suspected pulmonary tuberculosis (23 children, 11%) …1 point and in addition a positive gastric washing or RTT.
   (c) Suspected pulmonary tuberculosis (156 children, 74%) …1 point allocated but GW negative and RTT not evaluated as the children were not treated.

One is left wondering what would have been found if the children in group (c) had been placed on treatment: would some of them not have gained in weight and could they then have been classified as cases?

One of the features of this paper is the very high incidence with which acid-fast bacilli were found in the gastric aspirate and equally the enthusiasm with which this was pursued, three new aspirations being undertaken if the first three were negative. Of the 31 children diagnosed with pulmonary tuberculosis, 30 (97%) had a positive gastric aspirate for AFB; and 14 of the 23 suspected cases (61%). By contrast the percentage of children with a

positive Mantoux result is relatively low, overall only 37%. What is valuable is the existence of a group thought not to have tuberculosis, although not many of their details are given. It is stated that 13 of 40 non-tuberculosis children had a chest radiograph considered compatible with tuberculosis, but that all of them improved after antibiotic treatment.

Starke JR, Jacobs RF, Jereb J **(1992)**. Resurgence of tuberculosis in children. *Journal of Pediatrics*, 120:839-855.

This is a conventional review article discussing the current "state of the art". There are, however several potentially valuable definitions.

Tuberculous infection without disease. This is the preclinical stage of infection with *M. tuberculosis.* The tuberculin-test reaction is positive, but the chest radiograph is normal and the child is free of signs or symptoms. (But how does one classify the case should the culture of gastric aspirate be positive for *M. tuberculosis*?)

Tuberculous disease. This occurs when clinical manifestations of pulmonary or extrapulmonary tuberculosis become apparent, either by chest radiograph or by clinical signs and symptoms. In general an infected child with any radiographic or clinical manifestations consistent with tuberculosis is considered to have disease, even if no symptoms are present.

Several studies have demonstrated that if chest radiographs are taken shortly after infection, a majority of children have evident radiological changes, especially mediastinal lymphadenopathy. This could be described as a diagnostic "grey area" and leads to a discussion of whether these children have infection or disease. This becomes important in deciding if these children need chemoprophylaxis or treatment.

Goodyear HM et al. **(1993)**. Mycobacterial infection in an inner city children's hospital. *Archives of Disease in Childhood*, 69:229-231.

Population evaluated. Children with tuberculosis admitted to the Queen Elizabeth Hospital for Children, Hackney, London (England).

Diagnostic criteria. "The diagnosis of mycobacterial infection was based on a positive culture, or clinical and radiological features suggestive of tuberculosis, in the presence of a positive tuberculin test". No further description of the criteria is given. The most common complaints were cough, night fever and weight loss, but the number of children with these complaints is not given.

Treatment regimens. "Conventional regimens" were applied, but details are not given.

Results. 64 cases of mycobacterial disease were encountered, but 11 were due to atypical mycobacteria. A culture of *M. tuberculosis* was obtained in 20 cases (38%). The principal sites of disease were pulmonary in 39 children (74%) and in 9 (17%) cervical lymph nodes.

Oviawe O, Ojemudia E **(1993)**. The problem of non-attendance at a paediatric tuberculosis outpatient clinic. *Annals of Tropical Paediatrics*, 13:243-247.

The authors relate their experience with clinic non-attendance in a group of 146 children receiving treatment for pulmonary tuberculosis. There were 70 (48%) non-attenders and the mean time to non-attendance was 20 weeks. Low maternal education, disruptive family events and the perception that the disappearance of symptoms indicated cure were associated with non-attendance. Of the 70 non-attenders, 19 (27%) were found still to have major health problems when they were traced. The authors state that financial constraints and the enormous scale of the tuberculosis problem mitigate against routine home visits.

The findings of this study are of interest in that with modern short-course chemotherapy that includes rifampicin, pyrazinamide and isoniazid, a majority of paucibacillary patients might be cured by 20 weeks of treatment.

Seth V et al. **(1993)**. Childhood tuberculosis in a referral centre: clinical profile and risk. *Indian Pediatrics*, 30:479-485.

This paper gives clinical details of 196 children diagnosed with pulmonary tuberculosis attending the Pediatric Tuberculosis Clinic at the All India Institute of Medical Sciences (New Delhi) between January 1988 and December 1989. The Mantoux test in this study was considered positive if an induration of more than 10 mm was found using 1 TU of PPD RT 23. Of the children, 61% were severely malnourished, the Mantoux test was positive in 77% and 34% of children had family contact with tuberculosis. The chest radiograph showed parenchymal infiltration in 51% of cases, infiltration and mediastinal adenopathy in a further 17%, and adenopathy alone in 32%.

Pineda PR et al. **(1993)**. Intrathoracic tuberculosis: a report of 202 cases. *Tubercle and Lung Disease*, 74:261-266.

This paper describes experience with paediatric intrathoracic tuberculosis in British Columbia during the period 1979-1988. Notification is centralized in British Columbia so that the authors were aware of all cases reported. Nonetheless a rate is not given in the paper. Data from 202 cases were analysed.

Diagnostic criteria. Demonstration of *M. tuberculosis* either by smear or culture or following a positive response to 5 TU of PPD (> 5 mm), a history of contact, with appropriate chest X-rays and a favourable response to treatment. Contact investigation led to diagnosis in 154 children (76%) and 48 were referred because of symptoms. On questioning, 40% of patients had symptoms, the most frequent of which were cough (51%) and fever (28%). In 45 patients (22%) sputum was positive for smear and/or culture, and gastric washings done in 72 cases were positive in 24%.

Gutman LT et al. **(1994)**. Tuberculosis in human immunodeficiency virus-exposed or -infected United States children. *Pediatric Infectious Disease Journal*, 13:963-968.

Population evaluated. This retrospective study was undertaken to document the occurrence of tuberculosis among HIV-infected or -exposed children aged under 12 years between 1991 and 1992 in the United States of America. A survey by questionnaire was conducted among HIV-referral centres that were participating in the Pediatric Acquired

Immunodeficiency Syndrome Clinical Trials Group (PACTG); 75 cumulative cases of tuberculosis were identified among 14 038 children.

Diagnostic criteria. The study defined children with tuberculosis disease as those who were treated with two or more drugs since the PACGT site was established and who were clinically symptomatic with known or presumed *M. tuberculosis* infection.

Relevant findings. An isolate of *M. tuberculosis* was obtained from 34 (45%) of the 75 children. Of these isolates, 5 of 25 (20%) were resistant to both INH and RMP; 11 of the children (15%) failed to respond to therapy. Treatment regimens are not discussed.

Luo C et al. **(1994)**. Human immunodeficiency virus type-1 infection in Zambian children with tuberculosis: changing seroprevalence and evaluation of a thioacetazone-free regimen. *Tubercle and Lung Disease*, 74:110-115.

Population evaluated. All consecutively seen, newly-diagnosed cases of tuberculosis in children aged 1 month to 15 years admitted to the Paediatric Department of the University Teaching Hospital, Lusaka (Zambia) between October 1991 and May 1992. These patients were compared with children aged 1 month to 15 years admitted to the same hospital with traumatic injuries.

Diagnostic criteria. The diagnosis of tuberculosis was defined as the presence of three of the following:
    (1) symptoms and signs suggestive of tuberculosis;
    (2) sputum smear or gastric washings positive for acid-fast bacilli;
    (3) lymph node or other tissue biopsy revealing acid-fast bacilli or suggestive of tuberculosis;
    (4) radiological features suggestive of tuberculosis;
    (5) response to antituberculosis treatment;
    (6) history of close contact with a case of tuberculosis;
    (7) positive skin reaction to PPD.
Details of suggestive symptoms and signs are not given, nor is it stated what were regarded as suggestive radiological features on chest radiography. Certain clinical features are tabulated in the results.

Treatment regimen. Zambian national guidelines were followed:
    • SM 20 mg/kg for 2 months
    • INH 10 mg/kg for 6 months
    • RMP 15 mg/kg for 6 months
    • PZA 35 mg/kg for 6 months
It is not stated whether the drugs were given daily or intermittently.

Relevant results. The main thrust of this paper was the increased HIV-positive seroprevalence among Zambian children. Of the 120 children enrolled, 67 (57%) were HIV-seropositive compared to 16 (10%) among the 167 controls. While a satisfactory response to treatment was noted among all the HIV-negative children with tuberculosis, 16 (24%) of the HIV-positive children died within an average of 60 days from the time of diagnosis.

Although one might quibble about the accuracy with which tuberculosis was identified in this study, the paper was one of the first to draw widespread attention to the various problems caused by the interaction of HIV and tuberculosis among children.

Bergman N (1995). A "treatment score" for primary and pulmonary tuberculosis. *Central African Medical Journal*, 41:1-6.

Summary. This paper presents another proposal for a "scoring" system to diagnose childhood tuberculosis. The difficulty of arriving at a diagnosis of tuberculosis in childhood is discussed and it is pointed out that it is the "total picture" that is important and not only certain specific findings, and also that certain findings are often given more credence than others and therefore are "weighted". No data on the use of the score is presented, but there is reference to cases that did not qualify for treatment, but then had a positive culture of *M. tuberculosis*. On follow-up, some of these children remained well and it is assumed that they represent "the natural history of healing of a primary focus."

Diagnostic feature*	Score	Diagnostic feature*	Score
GL AFB positive	8	Cough 4 or 3 weeks	1
Cult >5 col	8	Previous TB	2
Cult 3-4 col	5	Close TB contact	1
Cult 1-2 col	3	Contact sputum positive	2
Pleural cult >3 col	8	Sputum positive mother	4
Pleural cult 1-2 col	5	LOW subjective	1
Any repeat cult	2X	No weight gain 4 months	2
Biopsy positive	8	Objective LOW 3 months	3
Biopsy compatible	7	FTT on ward diet	3
		Hypersensitivity	3
		Hypomelanosis	1
Cavity	6	Accelerated BCG response	2
Miliary	7	Hb <8 G/L	2
Hilar nodes	3	Hb <9 G/L	1
Pneum not responding	6	Mantoux<10mm	1
Ghon complex	5	Mantoux >10mm	2
		Mantoux blistering	4
		HIV+	1

* Cult = culture; CXR = chest radiograph; FTT = failure to thrive; GL = gastric lavage; LOW = loss of weight; col = colonies; pneum = pneumonia.

This is a very complex chart and, again, it is difficult to imagine it being completed regularly by primary health care personnel who are responsible for much of the day-to-day administration of a tuberculosis control programme in a developing community.

Chintu C et al. **(1995)**. Impact of human immunodeficiency virus type-1 on common pediatric illnesses in Zambia. *Journal of Tropical Pediatrics*, 41:348-353.

Study site. This study was undertaken at the University Teaching Hospital, Lusaka (Zambia) and documents the impact of HIV infection on the admissions profile of the hospital for the period October 1990 to July 1991.

Diagnostic criteria. The criteria used previously by the Lusaka group of researchers were applied in this study. The presence of three of the following was used to make a clinical diagnosis of tuberculosis:

- symptoms and signs suggestive of tuberculosis;

- sputum-smear or gastric washings positive for acid-fast bacilli;
- lymph node or other tissue biopsy revealing acid-fast bacilli or suggestive of tuberculosis;
- radiological features suggestive of tuberculosis;
- response to antituberculous treatment;
- history of close contact with a case of tuberculosis;
- positive skin reaction to PPD.

No further description of the criteria is provided, but the main thrust of the paper was the burden of disease and not tuberculosis per se.

From the point of view of tuberculosis control, this study quantified the burden of childhood tuberculosis at a Zambian hospital and found it to be the fifth most common diagnosis, and responsible for 5% of all admissions to the Department of Paediatrics and Child Health.

Schaaf HS et al. (**1995**). Respiratory tuberculosis in childhood: the diagnostic value of clinical features and special investigations. *Pediatric Infectious Disease Journal*, 14:189-194.

Site and population evaluated. Children presenting to a paediatric outpatient facility in the Western Cape Province of South Africa with suspected tuberculosis were investigated, followed up and finally classified on the basis of results of investigations and clinical course as probable, confirmed tuberculosis or not tuberculosis.

Results. Of the 258 children admitted to the study, 109 children (42%) were eventually confirmed to have tuberculosis by positive culture for *M. tuberculosis* from one or more sources, 86 children (33%) were considered to have probable tuberculosis, whereas 63 (24%) children were, after follow-up, thought not to have tuberculosis. Household contact with adult pulmonary tuberculosis was found in 43% of the confirmed tuberculosis cases and 56% of the probable cases, but also in 21% of the not-tuberculosis cases (P < 0.01). There was however no difference in the prevalence of weight loss, cough or other respiratory symptoms or the duration of any symptoms between the different diagnostic groups. As in some of the other papers reviewed above, 10% of the children with confirmed tuberculosis had a normal chest radiograph.

This study was carried out at a time when the prevalence of HIV infection in the area was very low. In the presence of a significant incidence of HIV infection among children, the diagnostic utility of signs and symptoms such as prolonged cough or loss of weight will be even more compromised.

Espinal MA et al. (**1996**). Human immunodeficiency virus infection in children with tuberculosis in Santa Domingo, Dominican Republic: prevalence, clinical findings, and response to antituberculosis treatment. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirus*, 13:155-159.

Population evaluated. All newly-diagnosed cases of tuberculosis in children aged 18 months to 5 years residing in Santo Domingo (Dominican Republic) and examined at the

Pulmonary Department of the Robert Reid Children's Hospital and the Santa Socorro Tuberculosis Sanatorium between September 1991 and July 1994. In all, 204 children were enrolled; 26 (13%) were HIV-infected.

Diagnostic criteria. An active case of tuberculosis fulfilled the following criteria:
(1) three or more signs and symptoms suggestive of active tuberculosis (fever, cough, weight loss, sweating, anorexia and node enlargement);
(2) and either laboratory evidence of disease caused by *M. tuberculosis* as manifested by a positive culture or acid-fast bacillus smear of a clinical specimen;
(3) or all of the following: chest radiograph findings suggestive of active tuberculosis, evidence of prior contact with *M. tuberculosis* documented by recent known exposure to an active case of tuberculosis or by a positive PPD skin-test, and clinical response to antituberculosis treatment.

The criteria for a positive TST are not given, although in the results mention is made of the proportions of children responding with an induration $\geq$ 5 mm. Radiographic features regarded as suggestive of tuberculosis are not given.

Treatment regimen. The children were treated with a standard short-term regimen of 6 months of daily INH and RMP, together with SM and PZA for the first 2 months. "Treatment doses were in accord with WHO recommendations."

Other relevant results. Only 2 (9%) of 23 HIV-infected children from whom specimens were submitted were positive on AFB smear, and none was culture-positive compared with 20 (11%) of 175 HIV-negative children, who were culture-positive. Four HIV-positive children died and no HIV-negative children; 6 (29%) of HIV-positive children were treatment failures, but only 5 (3%) of HIV-negative children.

Jeena PM et al. (**1996**). Effects of the human immunodeficiency virus on tuberculosis in children. *Tubercle and Lung Disease*, 77:437-443.

Population evaluated. Systematically selected cases and controls with and without HIV infection were prospectively enrolled between 1992 and 1994 at King George V Tuberculosis Hospital, Durban (South Africa); 40 children with HIV infection (mean age 25 months) were compared to 40 children with tuberculosis only (mean age 31 months).

Diagnostic criteria. The diagnosis of probable tuberculosis was made in the presence of three or more of the following:
(1) history compatible with the symptoms and signs of tuberculosis;
(2) history of contact with a diagnosed tuberculosis case;
(3) suggestive radiological findings;
(4) lymph node or other biopsy tissue with caseation;
(5) non-response to a 2-week course of antibiotic treatment;
(6) response to antituberculosis treatment;
(7) a positive tuberculin skin-test.

Although precise details of the radiological findings in the two groups are given, the criteria used for diagnosing tuberculosis on chest radiography are not discussed. Similarly the symptoms and signs are not given.

Tuberculin skin-testing was with 2 TU of RT23 tuberculin and was regarded as positive if ≥ 14 mm in those children who had received BCG immunization, ≥ 10 mm without BCG immunization, and ≥ 5 mm in all of those HIV-infected.

Significant results. Significantly more of the HIV-infected children had symptoms and signs of tuberculosis (97% vs 70%). The TST was more frequently non-reactive among the HIV-infected children (63% vs 13%). No differences in radiological features were found between the two groups. There were 6 deaths (15%) among the HIV-infected children and none among the non-HIV-infected children, and the response to treatment of the HIV-infected children, measured by weight gain, radiological response and clinical signs, was slower.

Munyard P, Bush A **(1996)**. How much coughing is normal? *Archives of Disease in Childhood*, 74:531-534.

Persistent cough is one of the most common symptoms used to raise suspicion of tuberculosis in a child. This paper is of interest in that it provides, perhaps for the first time, an objective measure of the frequency of coughing in a normal population of children. The frequency of cough was determined with the aid of a multiparametric apparatus employing a number of electronic leads and a recording device: 44 children aged 8-12 years were studied and had a cough frequency of 11.3/24 hours. Despite this surprising frequency, nocturnal and prolonged coughing episodes were unusual. This paper suggests that attention should perhaps also be given to the nature of a cough and not only its duration.

Shata AM et al. **(1996)**. Sputum induction for the diagnosis of tuberculosis. *Archives of Disease in Childhood*, 74:535-537.

This paper decribes the use of sputum induction following the inhalation of nebulized saline to assist the confirmation of the diagnosis of tuberculosis in children. Induction was attempted in 30 Malawian children aged 3-15 years and was successful in 29. Four sputa were smear-positive and *M. tuberculosis* was cultured from 3, and a further 4 specimens were culture-positive although smear-negative. The authors found the procedure to be safe in children as young as 3 years, but considered gasric aspirate to remain the method of choice particularly in infants. At the time there were no comparisons of gastric aspirate with sputum induction.

Garay JE (1997). Clinical presentation of pulmonary tuberculosis in under 10s and differences in AIDS-related cases: a cohort study of 115 patients. *Tropical Doctor*, 27:139-142.

Site and population studied. Children with tuberculosis seen at a peripheral hospital in Matabeleland South (Zimbabwe) during 1993 and 1994; 25 (22%) of 115 children were HIV-infected, and findings were compared to a matched group of non-HIV-infected children selected from the larger population of children with tuberculosis seen during this period.

Results. When the HIV-infected children were compared to those not infected significantly more presented with fever (40% vs 8%), but more of the non-HIV-infected children presented with cough (98% vs 52%). Similar percentages of both groups had

weight loss of > 10%, failure to thrive, diarrhoea and cavitation on chest radiograph, although more non-HIV-infected children had adenopathy on chest radiograph (64% vs 32%). More non-HIV-infected children had a positive culture of *M. tuberculosis* (56% vs 24%). In the HIV-infected group, 36% had lower lobe infiltrates, but only 8% of the non-infected group. In the larger group of 115 children, 81% presented with cough, which the author then regards as an important indication to suspect tuberculosis, and 50% had a household contact.

Mukadi YD et al. **(1997)**. Impact of HIV infection on the development, clinical presentation, and outcome of tuberculosis among children in Abidjan, Côte d'Ivoire. *AIDS*, 11:1151-1158.

Population evaluated. 161 children aged 0-9 years with newly-diagnosed tuberculosis were enrolled at two outpatient tuberculosis centres and two university hospitals in Abidjan (Côte d'Ivoire). Of the 161 children, 39 (24%) had culture-confirmed pulmonary tuberculosis, 80 (50%) clinically-diagnosed pulmonary tuberculosis and 42 (26%) extrapulmonary tuberculosis. Of these children, 31 (19%) were HIV1-seropositive. The findings in these children were compared with those in a group of 161 children randomly selected from among the healthy siblings of the patients who were referred for tuberculin skin-testing.

Diagnostic criteria. Three groups of children were identified:
(1) *Confirmed pulmonary tuberculosis*. These children had pulmonary tuberculosis diagnosed using specific clinical and radiological criteria (fever and cough of more than 2-weeks duration, and pulmonary infiltrates with or without adenopathy on chest radiograph) confirmed by a positive culture of *M. tuberculosis.*
(2) *Clinical pulmonary tuberculosis*. Those with pulmonary tuberculosis diagnosed according to the above criteria, and whose symptoms and radiological abnormalities did not respond to a 10-14 day course of antibiotics, but did improve after 2 months of antituberculosis treatment.
(3) *Clinical extrapulmonary tuberculosis*. Defined as extrapulmonary or disseminated tuberculosis, the symptoms of which responded clinically (and when applicable radiologically). These cases were not confirmed by culture or histology.

Children completing 6 months of therapy were defined as "improved" if they had a continued absence of symptoms and improved radiological findings, and as "not improved" if they continued to have clinical or radiological abnormalities, even if no positive sputum-smear was documented.

Tuberculin tests were performed by the intradermal injection of 5 TU of PPD (Institut Merieux).

Treatment regimen. Children were treated with the National Tuberculosis Control Programme regimen of 2HRZ 4HR; the doses are not given.

Significant results. 7 (23%) of the HIV-positive children died and 5 (4%) of the HIV-negative children. There were no differences between the HIV-positive and -negative children as regards loss to follow-up, non-compliance or improvement among survivors at the end of 6 months of treatment.

Fourie PB et al. **(1998)**. Procedures for developing a simple scoring method based on unsophisticated criteria for screening children for tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 2:116-123.

This study took place under the auspices of the IUATLD and brought together data from cases of childhood tuberculosis from 10 countries that included a spectrum of developing and developed communities. Data from 794 children were evaluated and bacteriology, histology and chest radiography utilized, either collectively or singly, as definitive reference standards. The more subjective criteria (symptoms, clinical signs and skin-test) were then evaluated against these standards. The relative importance accorded to each criterion was then evaluated by a statistical methodology and a weight assigned to each of the criteria.

In settings with low tuberculosis prevalence, heavy reliance was placed on a history of close contact with a case of tuberculosis and a positive skin-test, in high prevalence countries a more or less equal weighting was assigned to low body weight, prolonged fever, cough, household contact and skin-test positivity. Table 5 from the paper summarizes the frequency with which the criteria were encountered in the cases analysed. Parts of this table are shown below. Later a weighting is assigned to the various criteria (table 9 in the paper). In a way this is another self-fulfilling prophecy in that it still does not answer the question of how many children presented with these criteria and then how many of the children with the criterion actually had tuberculosis according to the "gold standard" criteria. For this a prospective evaluation is needed.

A valuable point made in this paper is that the emphasis was on "providing a screening tool" for use in resource-poor countries where radiographic and bacteriological facilities might not be within reach of the health worker in the periphery. This scoring system would then not be used so much to diagnose tuberculosis in a child as to select those who should be further evaluated at district hospitals. Arising out of this point is the question: where is the decision made to commence antituberculosis treatment in most countries? Is it made in peripheral primary care clinics or is it made on referral to district or secondary hospitals? At least one attempt has been made to evaluate these criteria and the authors considered that the criteria were too liberal and would lead to the "overdiagnosis" of childhood tuberculosis and unnecessary treatment of a large number of children (Suryanarayana & Jagannatha, 2001).

Ten criteria most commonly associated with a diagnosis of probable/confirmed tuberculosis in study of Fourie et al. (1998)

Criterion used	Criterion positive		
	n	**n**	**%**
Total cases	794		
Low body weight	773	696	90
Mantoux	738	471	64
Chest radiograph	756	452	60
Contact history	690	407	59
Weight loss	700	357	51
Gastric aspirate (culture)	293	146	50
Cough	758	333	44
Fever	751	324	43
Listlessness	690	253	37
Histology	246	81	33

Franchi LM et al. (**1998**). Detection of *Mycobacterium tuberculosis* in nasopharyngeal aspirate samples in children. *Lancet*, 352:1681-1682.

Summary. The authors of this paper describe the use of nasopharyngeal aspirate to assist the confirmation of the diagnosis of tuberculosis in children. Children aged 1 month to 16 years from Lima (Peru) were enrolled and specimens for culture collected by both gastric aspiration and nasopharyngeal aspiration on two consecutive days. A comparable yield was obtained for AFB staining and PCR, although gastric aspirate was slightly more sensitive for culture (92% vs 73%). This is a potentially important study as it suggests a relatively simple technology that can be applied in the community to improve the confirmation of the diagnosis of childhood tuberculosis.

Houwert KA et al. (**1998**). Prospective evaluation of World Health Organization criteria to assist diagnosis of tuberculosis in children. *European Respiratory Journal*, 11:1116-1120.

Site and population evaluated. Children presenting to the outpatient department of a tertiary care hospital in a community with high tuberculosis incidence close to Cape Town with recent weight loss or failure to gain weight, cough of more than 2-weeks duration or close household contact with an adult with active pulmonary tuberculosis.

Methodology. Children with one or more of the criteria were investigated by chest radiography, tuberculin-testing and gastric aspirate for culture of *M. tuberculosis*.

Results. One or more of the criteria were present in 206 (33%) of 627 children evaluated. Tuberculosis was confirmed by culture of *M. tuberculosis* in 10 children (5%) and a further 23 children were considered to have probable tuberculosis. After 8 weeks follow-up, 173 children (84%) were considered not to have tuberculosis; 7 (64%) of 11 children who had all three of the criteria evaluated had either confirmed tuberculosis (3 children) or probable tuberculosis (4 children). Perhaps one of the more interesting aspects of this study was that it provided a glimpse of how many children presenting for medical treatment in a developing community have persistent cough (27%), weight loss or failure to gain (77%) and household contact with tuberculosis (24%). As HIV infection was not a significant factor at the time of this study, the advent of HIV/AIDS is likely to lead to many more children presenting with persistent cough and weight loss.

Lobato MN et al. (**1998**). Detection of *Mycobacterium tuberculosis* in gastric aspirates collected from children: hospitalization is not necessary. *Pediatrics*, 102: (http://www.pdiatrics.org/cgi/content/full/102/4/e40).

Summary. In this retrospective study, the yield of gastric aspirates in a paediatric hospital was compared with that from two tuberculosis control programmes in California. Of 100 children who had tuberculosis, 80 had at least one gastric aspirate collected and *M. tuberculosis* was identified on culture from 33 (41%). Among inpatients, 48% had a positive culture compared to 37% among outpatients, but this difference was not statistically significant. This study demonstrates that with planning, the collection of gastric aspirate is possible in community facilities, and the children should be kept nil per mouth until the specimen has been collected.

Qazi SA, Khan S, Kahn MA **(1998)**. Epidemiology of childhood tuberculosis in a hospital setting. *Journal of the Pakistan Medical Association*, 48:164-167.

Study site and population. Study of 200 children "up to 12 years of age" with pulmonary tuberculosis presenting to the Federal Government Services Hospital (Islamabad).

Diagnostic criteria. "Children were diagnosed as having tuberculosis in the light of suggestive clinical features, history of contact, positive Mantoux test, ESR $\geq$ 30 mm and evidence of tuberculosis in chest radiograph for pulmonary tuberculosis". The Mantoux test was considered positive if $\geq$ 10 mm induration in children without a BCG scar and $\geq$ 15 mm among those with a BCG scar.

The most commonly affected age group was 2-5 years that included 52% of the cases studied. A history of contact with a case of tuberculosis was elicited in 129 cases (65%). The most common presenting complaints were fever in 81% and both cough and weight loss or failure to thrive in 70% of cases. Pulmonary tuberculosis was diagnosed in 79% of the children. Culture facilities were not available but the Mantoux test was positive in 83% of cases and had an induration of $\geq$ 20 mm in 59% of cases despite the high incidence of malnutrition. This is one of the few studies to make use of the erythrocyte sedimentation rate to support the diagnosis of tuberculosis in children.

Van Beekhuizen HJ (1998). Tuberculosis score chart in children in Aitape, Papua New Guinea. *Tropical Doctor*, 29:155-160.

Site and population. A tuberculosis score chart developed by Edwards (1987) to assist the diagnosis of childhood tuberculosis was evaluated during 1994 and 1995 among 349 patients in Aitape (Papua New Guinea).

Diagnostic criteria and results. The score chart is set out in the table and the diagnosis of tuberculosis can be made without recourse to a chest radiograph. A score of > 7 indicates probable tuberculosis. After exclusions 301 children were evaluated with the help of the score chart and in 82 children the initial score was > 7. Of the 82 children, 11 initially had a score < 7; admitted for malnutrition, they failed to gain weight over the period of one month and on rescoring had a count of > 7. Nine patients did not improve on antituberculosis treatment and further investigations were done leading to other diagnoses. In one case the child re-presented and had a score of > 7.

Feature	0 points	1 point	3 points
Illness length	<2 weeks	2-4 weeks	>4 weeks
Nutritional status	>80%	60%-80%	<60%
Family TB history	None	Verbal history	Sputum positive
Significant Mantoux			3
Enlarged neck glands			3
Night sweats, FUO*			2
Spinal deformity			4
Malnutrition persisting after a month			3
Joint swelling			3
Abdominal swelling			3
Coma > 48 hours			3

* FUO = fever of unknown origin.

The Mantoux test was regarded as positive if ≥ 15 mm or more in a child who had received BCG and ≥ 5 mm in a child who did not have a BCG scar.

As noted by other investigators working in areas with a high incidence of childhood HIV/AIDS and tuberculosis, the advent of HIV has complicated the use of score charts considerably and HIV/AIDS on its own could generate more than the 7 points needed to diagnose tuberculosis in a child.

Neu N et al. **(1999)**. Diagnosis of pediatric tuberculosis in the modern era. *Pediatric Infectious Disease Journal*, 18:122-126.

The primary aim of this study was to evaluate the utility of a commercially available PCR assay to facilitate the detection of *M. tuberculosis* in children with suspected tuberculosis. Although *M. tuberculosis* was cultured from gastric aspirate of 5 of 76 (6.6%) specimens from 27 children, PCR detected *M. tuberculosis* DNA in only 3 of these specimens, and there was a poor correlation between culture and PCR. CT scans were undertaken in 19 children and were diagnostic of hilar adenopathy in 6 children with equivocal chest radiographs, and confirmed the presence of hilar adenopathy in another 8 children. Alternative diagnoses were made in 8 children. In 2 children infiltrates not visible on conventional chest radiography were detected by CT. Although the main interest in this study was the evaluation of a PCR methodology for detecting *M. tuberculosis,* part of the interest in the study is the gap that it demonstrates between the facilities in a developed country and those in a developing country where even tuberculin may not be available.

Mahdi SA et al. **(2000)**. HIV-1 co-infection in children hospitalized with tuberculosis in South Africa. *International Journal of Tuberculosis and Lung Disease*, 4:448-454.

Population evaluated. Children aged 2 months to 12 years presenting to the hospitals associated with the University of Witwatersrand, Johannesburg (South Africa) from August 1996 to January 1997. Of 161 children enrolled, 42% were HIV-infected: 67/137 with pulmonary tuberculosis and 1/24 with extrapulmonary tuberculosis.

Diagnostic criteria
  (1) A positive tuberculin skin-test defined as ≥ 5 mm in an immunocompromised child or ≥ 10 mm in those immunocompetent. RT23 PPD 2TU was used for tuberculin-testing and read in transverse diameter after 48-72 hours.
  (2) An adult contact with active tuberculosis and/or who had received treatment within the previous 6 months.
  (3) A chest radiograph suggestive of tuberculosis. Radiographs were considered suggestive of tuberculosis if there was hilar adenopathy, a miliary pattern or cavitation. For those children with a history of contact with tuberculosis or a significantly reactive tuberculin test, any lung infiltrate was considered indicative of tuberculosis.
  (4) Signs and symptoms of tuberculosis (signs and symptoms not stated).
  (5) Positive auramine fluorochrome stain on gastric washings or sputum.
  (6) Histology suggestive of tuberculosis.

Case definitions
  • Clinical TB: clinical and/or radiological evidence of tuberculosis.

- Probable TB: positive auramine fluorochrome stain on any specimen submitted for microscopy and/or histology suggestive of TB in the presence of other clinical signs and symptoms of TB.
- Culture-confirmed TB: *M. tuberculosis* isolated from any site.

Treatment regimen not stated. Extrapulmonary tuberculosis was defined as tuberculosis at any extrathoracic site and those with EPTB and pulmonary involvement were classified as EPTB.

Significant results. Of the 137 children with HIV results, 42% were HIV-infected. Of the 137 children with pulmonary tuberculosis, 67 (50%) were HIV-infected but only 1 (4%) of those with EPTB. The odds of producing no measurable reaction to tuberculin were 12.11 times higher in HIV-infected than in non-infected children.

De Charnace G, Delacourt C **(2001)**. Diagnostic techniques in paediatric tuberculosis. *Paediatric Respiratory Reviews*, 2:120-1125.

This paper reviews the diagnosis of tuberculosis in childhood.

Tuberculin skin-test. The authors give a definition of the standard preparation for the tuberculin test. This "is the dose that corresponds to 5 tuberculin units, i.e. biologically equivalent to 0.1 mg/0.1 ml of PPD-S or 0.4 mg/0.1 ml of PPD-RT 23". They discuss which cut-points should be used for diagnosing tuberculosis infection and state: "Usually *Mycobacterium tuberculosis* infection is associated with an induration of 10 mm or more. However a cut-point of 5 mm or more may be considered for individuals with false-negative results and those who are at greater risk of developing clinical tuberculosis." They also state that an increase in size of $\geq$10 mm within a period of 2 years is "important".

Chest radiograph. They consider that a chest radiograph is indicated for all children when a diagnosis of possible tuberculosis is being considered. They also discuss the value of computed tomography, but although valuable do not think that the systematic use of CT is justified in cases of suspected tuberculosis. With reference to the finding of hilar nodes on CT with a "normal" chest radiograph, they consider this to indicate "minimal active disease" and that this finding should not alter the treatment regimen.

Flexible bronchoscopy. It is the authors' practice to perform flexible bronchoscopy (FB) in all cases when the chest radiograph is abnormal, however the culture and smear results of bronchial aspirates or bronchiolar lavage do not yield better results than gastric aspiration, and they consider that the value of bronchoscopy lies in selecting patients for corticosteroid therapy or resection of granulation tissue in the presence of airway narrowing.

Microbiological investigations. The authors emphasize the importance of technique in the success of gastric lavage and point out that even with radiometric broth systems, three serial respiratory specimens are necessary for a "firm diagnosis".

Nucleic acid amplification techniques and immunodiagnosis. The authors discuss the sensitivity and specificity of the various available investigations, but conclude that despite

some promising results, contradictory results from different workers indicate the need for further refinement of these investigations.

This paper touches on several points of research interest. Once again the validity of choosing a cut-point of 5 mm in immunosuppressed children requires further study, and the value of nucleic acid amplification and immunodiagnostic tests could be best assessed in multicentre prospective trials under the supervision of a central laboratory.

Ibadin MO, Oviawe O **(2001)**. Trend in childhood tuberculosis in Benin City, Nigeria. *Annals of Tropical Paediatrics*, 21:141-145.

Population evaluated. Children diagnosed and treated for tuberculosis at the paediatric tuberculosis clinic of the University of Benin Teaching Hospital between January 1981 and December 1995. Altogether 1026 children were enrolled. The age range of the children included is not stated, but in a table is given as 0.25–15 years.

Diagnostic criteria. Microbiological identification of AFB from sputum, gastric washings or other body fluids by Ziehl-Neelsen stain.

Clinical criteria
A. Major
      (a) Cough for more than 4 weeks
      (b) Progressive weight loss.

B. Minor
      (a) Adult in close contact with open PTB
      (b) Positive Mantoux test (10TU) … ≥ 10 mm
      (c) ESR (Westergren) ≥ 8 mm/hr
      (d) Abnormal auscultation of the chest on absence of other evidence of disease
      (e) Abnormal chest X-ray consistent with PTB.

The presence of one or both major criteria plus three or more minor manifestations supported the diagnosis of PTB. Culture of *M. tuberculosis* was not undertaken. Definitions of disease features were not stated.

Treatment. "All cases were treated with antituberculosis chemotherapy regimens that included various combinations of streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide …Completion of therapy by 931 (90.7%) cases among whom there were no relapses ... Chemotherapy was continued on average for 12 months and thereafter patients were followed for another 24 months to detect relapses."

Only 17 children were screened for HIV infection, all of whom were negative. The most common presenting complaints were cough, weight loss and evening fever, but the number of children presenting with these complaints is not given.

Kiwanuka J et al. **(2001)**. Diagnosis of pulmonary tuberculosis in children in an HIV-endemic area, Malawi. *Annals of Tropical Paediatrics*, 21:5-14.

Population evaluated. Children with suspected TB selected for further evaluation from among children attending Queen Elizabeth Central Hospital, Blantyre (Malawi). The

children with suspected TB had persistent cough and/or weight loss for > 1 month and no response to antibiotics; 110 children were then further investigated.

Investigations included:
- A Mantoux test with 10 IU of RT23 PPD and an induration of $\geq$ 10 mm was regarded as positive, irrespective of BCG status, and $\geq$ 5 mm in those known to be HIV-infected.
- Microscopy and culture for *M. tuberculosis* of three sputa samples from those old enough to supply a specimen; gastric aspirate and laryngeal swab in the first 60 children evaluated.
- Chest radiography.

Definition of pulmonary tuberculosis
- (a) Confirmed PTB: smear or culture of *M. tuberculosis* from sputum, gastric aspirate or laryngeal swab.
- (b) Probable PTB: a positive Mantoux test and/or a chest radiograph with unilateral hilar/mediastinal adenopathy and focal infiltration/consolidation, cavitation or calcification.

Treatment regimens. $2R_3H_3Z_3/6HE$ for smear-negative PTB; $2R_3H_3Z_3E_3/6HE$ for smear-positive PTB. All the children received antituberculosis treatment and were followed up to completion of treatment.

Outcome. 49 children were finally found to have confirmed (8) or probable (41) PTB; of these 45 were HIV-tested and 26 (53%) were HIV-infected. A final diagnosis could not be established in 43 children (40 HIV-tested and 30 (75%) positive); 61 children could be followed up, 1/26 HIV-positive children with confirmed or probable PTB died, and 4 (15%) had a poor response to treatment, compared to no deaths and a good response among all the HIV-negative children. Among the "unknown" group of 40 children who were followed up and whose HIV status was known, 4 (10%) died and 5 (13%) were considered to have had a poor response.

Comment. This is one of the few studies to include a group of children among whom a final diagnosis could not be made. The majority of these children were HIV-infected. This reflects the real world of clinical practice in those countries most severely affected by the HIV/AIDS epidemic.

Suryanarayana L, Jagannatha PS **(2001)**. Scoring method for diagnosis of tuberculosis in children: an evaluation. *Indian Journal of Tuberculosis*, 48:101-103.

This very ambitious study was undertaken by the National Tuberculosis Institute, Bangalore (India) in 62 randomly-selected villages surrounding Bangalore. The aim of the study was to evaluate the scoring system suggested in the paper by Fourie et al. (1998). A total of 24 069 children were registered for the study; 20 063 were permanent residents in the villages.

The children were examined clinically and a Mantoux test carried out. A group of 6071 was identified for further evaluation including mass miniature chest radiography and sputum evaluation in those older than 5 years. These children had one or more of: an induration on Mantoux test of > 10 mm, undernutrition according to the Quillet Index,

symptoms suggestive of tuberculosis, lymph node enlargement or history of contact with a case of tuberculosis.

Bacteriology detected 17 children, radiological examination 50 children, but by the proposed scoring system 941 children had a score of 5 and a further 73 a score of 6.

The authors list a number of problems with the application of the scoring system including the undue influence of malnutrition, cough and fever as these are often non-specific. They suggest that the scoring system could perhaps serve as a screening tool to identify children for further investigation.

Wong KS et al. **(2001)**. Childhood and adolescent tuberculosis in northern Taiwan: an institutional experience during 1994-1999. *Acta Paediatrica*, 90:943-947.

Population evaluated. Children and adolescents up to 18 years of age admitted to a referral children's hospital in northern Taiwan between 1994 and 1999.

Diagnostic criteria. TB was defined as the presence of chronic symptoms (chronic cough, fever, weight loss or failure to thrive) in association with the radiological appearance (hilar lymphadenopathy, miliary shadows) and the histological appearance of biopsy material resembling the appearance of TB-affected tissue (granulomatous tubercles or caseous necrosis); or the isolation of *M. tuberculosis* from sputum, gastric aspirates, body secretions and/or surgical specimens.

During the study period, 62 patients were identified. The most common presenting symptoms were fever (18, 23%), cough (18, 23%) and swelling and/or pain of the extremities (17, 22%). Pulmonary TB was found in 31% of children aged < 5 years, but in 85% of adolescents (15-18 years). Conversely extrapulmonary TB was found in 69% of children aged < 5 years and only 15% of adolescents aged 15-18 years. Loss of weight was noted in only 2 (3%) patients. *M. tuberculosis* was isolated from sputum (20 patients), gastric aspirates (8 patients), and other tissues or body fluids in a further 19 patients. Details of treatment and outcome are not given.

Zar HJ et al. **(2001)**. Aetiology and outcome of pneumonia in human immunodeficiency virus-infected children hospitalized in South Africa. *Acta Paediatrica*, 90:119-125.

This study evaluated the etiology and outcome of pneumonia in 250 hospitalized children of whom 151 were HIV-infected. *M. tuberculosis* was identified in 11 (7.4%) HIV-infected children and 8 (8.3%) non-HIV-infected children. This study and a similar study from Johannesburg (Mahdi et al., 2000) suggest that tuberculosis should be considered in the differential diagnosis of children even when they appear to have an acute bacterial infection. In some cases it may well be that the acute bacterial infection serves to bring the child to hospital and that further investigation uncovers the additional presence of tuberculosis.

Blussé van Oud-Alblas HJ et al. **(2002)**. Human immunodeficiency virus infection in children hospitalized with tuberculosis. *Annals of Tropical Paediatrics*, 22:115-123.

Site and population studied. Children admitted to a tuberculosis hospital in the Western Cape Province of South Africa between January 1998 and December 1999.

Diagnostic criteria

A diagnosis of *confirmed tuberculosis* was made in the presence of a culture of *M. tuberculosis* from any source or sputum-smear microscopy or histology showing acid-fast bacilli.

A diagnosis of *probable tuberculosis* was accepted in the presence of two or more of the following:

(1) A Mantoux test with 2 TU of RT23 PPD (Statens Serum Institut, Denmark) giving an induration of ≥ 15 mm in immunocompetent children or ≥ 5 mm in HIV-infected children.

(2) A chest radiograph showing clear hilar or paratracheal adenopathy.

(3) A history of recent close household contact with a sputum microscopy smear-positive case of pulmonary tuberculosis.

(4) In the case of tuberculous meningitis, a CT scan showing hydrocephalus and basal enhancement indicative of a granulomatous meningitis.

Results. Of 261 children admitted to the hospital, HIV serology was evaluated in 150 and was positive in 36 (24%). More HIV-infected children died (17% vs 2%), and while only 10% of non-HIV-infected children had a Mantoux test of < 5 mm induration, 56% of the HIV-infected children had a negative result. As with a number of other studies from the developing world, the incidence of extrapulmonary tuberculosis was similar in those children who were HIV-infected and those who were not infected.

Hesseling AC et al. **(2002)**. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 6:1038-1045.

In this paper the authors review and describe 16 published approaches intended to assist the diagnosis of tuberculosis in childhood. Without discussing their results in detail it can be stated that the authors came to the conclusion that definitions and characteristics used had not been standardized, that almost no studies had validated the approaches suggested, and that only a minority of systems had been adapted for use in malnourished and/or HIV-infected children. Studies using previously-agreed standards are necessary to validate any new approach to the diagnosis of childhood tuberculosis, and such an approach should also be applicable in communities with a high incidence of malnutrition and HIV infection.

Other points made include:

- Response to therapy in non-HIV-infected children is not well defined.
- The cut-off point of 5 mm induration on tuberculin testing of HIV-infected children is of uncertain accuracy for such children and requires validation in communities with a high HIV incidence.
- The value of repeating the tuberculin test after nutritional rehabilitation should be quantified.
- The majority of studies were conducted in hospital-based populations and the validity of the sensitivity and specificity of the criteria used is thus of doubtful value.

Finally the authors conclude that multicentre studies are needed to assess the validity of diagnostic approaches in a variety of epidemiological settings.

Jeena PM et al. **(2002)**. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. *International Journal of Tuberculosis and Lung Disease*, 6:672-678.

Population studied. Children with culture-proven pulmonary tuberculosis admitted to the King Edward VII Hospital, Durban (South Africa). The children were identified by a review of positive cultures of *M. tuberculosis* obtained from the microbiology service of the hospital. The children were classified as HIV-infected, non-HIV-infected and HIV-undetermined.

Results. Medical records were available for 118 (86%) of the 138 children from whom a positive culture was obtained. Of these, 40 (34%) had close contact with an adult with tuberculosis; a Mantoux test gave an induration of $\geq$ 15 mm in 41 (35%), and in 36 children (31%) AFB were identified in the clinical specimen. The chest radiograph suggested a diagnosis of TB in 93 cases (79%).

In 25 of the children, the diagnosis of TB was not initially made; 15 of these children were HIV-infected. Among these children the clinical features and chest radiology findings were not suggestive of TB; cough of less than 10 days in all 25 children and non-specific bilateral lung opacities in 18 (72%).

Outcome. The overall mortality of the group was 14% (n = 16) and was 18% among the HIV-infected children and 11% among those not HIV-infected. Clinical markers such as clubbing (P < 0.02), generalized lymphadenopathy (P < 0.01), malnutrition (P < 0.009) and a high globulin concentration (P < 0.01) were more common among the HIV-infected children.

Palme IB et al. **(2002)**. Impact of human immunodeficiency virus 1 infection on the clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. *Pediatric Infectious Disease Journal*, 21:1053-1061.

Population evaluated. Ethiopian children presenting to the main paediatric hospital in Addis Ababa from December 1995 to January 1997.

Diagnostic criteria applied: adaptation of WHO criteria (WHO, 1983); any two of the following:
(1) Symptom complex of fever > 2 weeks, cough > 2 weeks, night sweats, weight loss.
(2) Household contact with proven TB or with symptoms highly suggestive of TB.
(3) Suggestive chest radiography findings (primary complex, hilar adenopathy, cavitation, miliary pattern, pleural effusion and any opacity or infiltration not explained by other disease).
(4) Identification of mycobacteria by acid-fast staining.
(5) A positive tuberculin skin-test defined as an induration of $\geq$ 10 mm with 2 TU of PPD RT23 (Statens Serum Institut, Denmark).
(6) Pathology findings compatible with TB from cerebrospinal fluid, fine-needle aspiration, biopsy or other surgically-removed lesion.

Definitions
- Pulmonary TB: manifestations restricted to the lungs.
- Extrapulmonary TB: TB affecting organs other than the lungs.

- Disseminated TB: TB affecting more than one organ.

Treatment regimens. A 2-month intensive phase of SHRZ, SHR or SHE was used followed by a 6- or 10-month continuation phase of either HR or HE/HT respectively.

This was a prospective study that enrolled more than 500 children and attempted to follow up the children for at least 6 months after treatment was completed. An excellent documentation of the eventual outcome in all the children was achieved and illustrated again a very high death rate among the HIV-positive children (41% compared to 7% among those not HIV-infected). In common with many paediatric studies, cure is equated to treatment completion.

Sánchez-Albisua I et al. **(2002)**. Twenty years of pulmonary tuberculosis in children: what has changed. *Pediatric Infectious Disease Journal*, 21:49-53.

Population studied. Children aged under 15 years diagnosed with pulmonary tuberculosis from 1978 through 1997, and seen at the Unit for Infectious Diseases of the Children's Hospital, La Paz (Madrid, Spain).

Diagnostic criteria
(1) A tuberculin skin-test giving an induration of $\geq$ 5 mm 48 hours after intradermal injection of 2TU of RT23 tuberculin, and an abnormal chest radiograph. Clinical, epidemiological and laboratory data were also considered.
(2) A culture or smear-positive for *M. tuberculosis.*

Results. During the 20 years, 405 cases of tuberculosis in children aged < 15 years were diagnosed. Between 65% and 67% of cases occurred in children < 5 years age, and the mean age was between 4 and 5 years; 54 children were tested for HIV infection, but only 4 were positive. The most common reason for evaluating the children was a contact investigation (37%-38%). During the period 1978-1987, 25% of cases were culture-positive and 3% in the period 1988-1997. The isolation rate was significantly higher in children < 3 years of age (43% compared to 36% in those older). Only 6 children (2%) had cavitation; pulmonary infiltrates were seen in 62 children (15%).

Treatment. From 1978-1980, patients received INH and RMP for 12 months; between 1981 and 1985 the same drugs were given for 9 months; thereafter all patients received short-course treatment 2HRZ/ 4HR and treatment was extended to 9 months in the presence of extrapulmonary tuberculosis. There is no comment on the response to treatment.

Van Rheenen P (2002). The use of the paediatric tuberculosis score chart in an HIV-endemic area. *Tropical Medicine and International Health*, 7:434-441.

Study site. St Theresa's Mission Hospital in the Copperbelt Province of Zambia.

Study population. All children up to 12 years of age with chronic cough (> 3 weeks) or a body weight < 80% of the NCHS median admitted to the paediatric ward between January and December 1999 were screened for TB and HIV. This selected population was then evaluated by tuberculin skin-testing, chest radiography, Ziehl-Neelsen staining and

microscopy, culture, PCR and HIV-testing. Children were excluded only if an HIV test was refused.

Tuberculin skin-testing was with "0.1 ml of purified protein derivative", but the number of TU is not stated. If HIV-negative without a BCG scar $\geq$ 15 mm induration was accepted as positive, if there was no BCG scar $\geq$ 10 mm and in HIV-positive children any induration $\geq$ 5 mm was regarded as positive.

Details of *chest radiograph* interpretation are not given.

Paediatric score chart (PSC). The details of the PSC are modified from that of Edwards (1987).

	Feature	0 points	1 point	3 points
1	Duration (weeks)	< 2	2-4	> 4
2	Nutritional status	Above 80%	60-80%	<60%
3	TB in family	None	Yes	Sputum+
4	Positive Mantoux			3
5	Enlarged painless neck glands			3
6	Night sweat or prolonged fever			2
7	Angle deformity of spine			4
8	Malnutrition not improved after 1 month			3
9	Firm non-fluid, non-traumatic joint swelling			3
10	Ascites or abdominal masses			3
11	Coma > 48 h or slowly developing neurological signs			3
	Total score			

Results. A total of 147 were enrolled, 75 children with TB (23 HIV-positive, 52 HIV-negative) and 72 children without TB (21 HIV-positive and 51 HIV-negative). The differences in the TB scores between the four groups were not significant. The sensitivity of the score was 88%, however the specificity was only 25% and the positive and negative predictive values were 55% and 67% respectively. Malnutrition and AIDS were the most serious confounding elements and the author concluded that the PSC in its present form could not be used in an HIV-endemic area.

This is an important study as it also included children who were evaluated and considered not to have tuberculosis, thus enabling the calculation of specificity and predictive values.

Weismuller MM et al. **(2002)**. Diagnosis of childhood tuberculosis in Malawi: an audit of hospital practice. *International Journal of Tuberculosis and Lung Disease*, 6:432-438.

Setting and population evaluated. This was a cross-sectional study of all children 14 years of age or younger receiving antituberculosis treatment in Malawi during April to June 2001.The focus of the study was to evaluate the criteria used for the diagnosis of tuberculosis in these children.

Results. There were 150 children identified with a median age of 3 years, of whom 98 had PTB and 52 EPTB. Only four hospitals had access to tuberculin. In 93 children, a chest radiograph was performed and of these 7 were lost or of poor quality and could not be assessed. Of those remaining 4 (5%) were thought to be normal, 9 (10%) were abnormal but not consistent with tuberculosis while 72 (84%) were thought to be compatible with a diagnosis of tuberculosis. The WHO score chart or a modification was used in only 13

(9%) patients and all 13 children scored more than the 7 points needed to support a diagnosis of tuberculosis. The investigators used the chart themselves on all 150 patients and found a score of > 7 in 53 children with pulmonary tuberculosis (54%) and in 38 of the children with extrapulmonary tuberculosis (73%). HIV-testing was done in only a small minority of patients (8%). Tuberculin-testing was carried out in only 12 children (8%).

The authors comment that the scores of many children tended to be low because so few children were tuberculin-tested and because many malnourished children were removed from hospital before nutritional rehabilitation could be assessed. Chest radiography also played a prominent part in the diagnostic process and the "availability of chest X-ray services would appear to be essential for the diagnosis of childhood TB *as well as* adult smear-negative PTB".

Indian Academy of Pediatrics (2004). Consensus statement of IAP Working Group: status report on diagnosis of childhood tuberculosis. *Indian Pediatrics*, 41:146-155

This document is an important contribution to the debate surrounding the need for consistent criteria for the diagnosis of childhood tuberculosis.

Clinical criteria for suspecting tuberculosis include:
- Fever and cough > 3weeks.
- Unexplained loss of weight and appetite; unexplained poor weight gain is regarded as relevant in infants, but not older children.
- "Contact is defined as any child who lives in a household with an adult taking anti-TB therapy or who has taken such a therapy in the past 2 years."
- "Significant superficial lymphadenopathy should be specially looked for …"

Therapeutic trial with anti-TB drugs is not recommended.

Tuberculin-testing. 1 TU PPD with RT 23 Tween 80 (or 5 TU PPD without Tween 80) is recommended and an "induration of 10 mm or more is considered suggestive of natural infection irrespective of prior BCG vaccination".

The routine use of PCR and serological tests for the diagnosis of childhood tuberculosis is not recommended.

Superficial lymphadenopathy is to be considered significant if the nodes are > 1.5 cm in size in the inguinal region or > 1 cm in the axilla or neck.

A number of other definitions and suggestions are provided and the issues touched on should be referred to when attempting to reach international consensus in due course.

Kabra SK, Lodha R, Seth V **(2004)**. Category based treatment of tuberculosis in children. *Indian Pediatrics*, 41:927-937.

Site and population. All children with freshly diagnosed tuberculosis presenting to the paediatric tuberculosis clinic of a tertiary care hospital in northern India.

Diagnostic criteria. The diagnosis of pulmonary tuberculosis was based on clinical presentation (including family history), abnormal chest X-ray with a positive Mantoux test (using 5 TU of PPD-S) or non-clearance of the chest radiograph after a course of antibiotics. Other forms of extrapulmonary tuberculosis were diagnosed following appropriate radiological investigations assisted by biopsy and/or aspiration of the relevant fluids, and culture and histology when available.

Categorization of patients. Depending on these results patients were then assigned to one of the WHO categories for treatment (WHO, 2003):

Category I. "All freshly diagnosed serious cases were included in category I". Patients with joint tuberculosis were also included, the rationale for this being that if inadequately treated, serious long-term sequelae would result.

Category II. Children who received full antituberculosis treatment in the past and were cured and presented again (relapse cases) were included in category II, as were patients inadequately treated in the past, or who interrupted treatment and had subsequently deteriorated. Children who failed to respond, or deteriorated despite compliance with treatment, were also placed in category II.

Category III. Patients with primary pulmonary complex, single lymph node tuberculosis, minimal pleural effusion and isolated skin tuberculosis were included in category III.

Category IV. This included patients who did not improve despite administration of five drugs, as recommended by category II, for at least two months.

Outcome. "Cure" was defined as absence of clinical symptoms with regression of radiological findings of less than two-thirds of the original lesion.

Extension of treatment occurred when the duration of treatment was longer than that initially assigned. Treatment was extended by three months when radiological lesions of pulmonary tuberculosis regressed by less than two-thirds of their original extent. In the case of lymphadenitis, treatment was also extended by three months when nodes increased in size or when fresh nodes developed despite treatment. Patients who did not complete the assigned regimens were considered lost to follow-up.

Results. The mean age of the patients referred to the clinic was 93 months and 459 patients were available for analysis after exclusions; of these 323 (70%) were placed in category I, 12 (3%) in category II, 120 (26%) in category III and 4 (1%) in category IV. Of the 459 patients 365 (83%) completed the assigned treatment, of whom 302 (83%) were cured with the primary regimen to which they were assigned; 63 (17%) patients failed and 54 (15%) were cured by an extension of treatment, while 9 (3%) required a change of regimen.

This is one of the first attempts to apply the WHO treatment categories as developed for adults to children with tuberculosis. If children are to be successfully integrated into the DOTS programmes some similar categorization of childhood tuberculosis will be necessary. None of these children appear to have been evaluated for HIV infection.

Kabra SK, Lodha R, Seth V **(2004)**. Some current concepts on childhood tuberculosis. *Indian Journal of Medical Research*, 120:387-397.

The authors provide a very thorough overview of the various issues related to childhood tuberculosis. They make the relevant point that one of the problems in evaluating the response of children to treatment is the slow resolution of chest radiographic abnormalities. They refer to the preceding article and conclude again that it is possible to manage childhood tuberculosis making use of the same diagnostic and management categories as those used for adults.

Palme IB et al. **(2004)**. Detection of *Mycobacterium tuberculosis* in gastric aspirate and sputum collected from Ethiopian HIV-positive and HIV-negative children in a mixed in- and out-patient setting. *Acta Paediatrica*, 93:311-315.

This is a further addition to a series of publications from Ethiopia and attempts to answer the frequently asked question: how many gastric aspirates are really necessary to give an optimum yield? Overall a positive culture of *M. tuberculosis* was obtained from 183 of 355 (52%) children and a positive smear from 55 of 355 (15%).

In the age group < 5 years, 15% had a positive smear and 55% a positive culture. In this group gastric aspirate only was collected. In the group aged 5-9 years, 11% had a positive smear and 46% a positive culture. Approximately half the children in this group also produced a sputum specimen that was smear-positive in 18% and culture-positive in 47%. In the group 10-14 years, 27% had a positive smear and 52% a positive culture from sputum specimens.

From the 54 HIV-positive children, all of whom were below 10 years of age, only 28% had a positive culture and 9% a positive smear compared to 56% and 17% respectively from among the 301 HIV-negative children. Two gastric aspirates for culture were obtained from 259 children of whom 16 (6%) had a negative first and a positive second culture, and 14 (5%) a positive first and a negative second sample. In this setting therefore one gastric aspirate specimen gave satisfactory results.

Zar HJ et al. **(2005)**. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet*, 365:130-134.

Setting and population. This paper reports on the investigation of 250 children, median age 13 months, with suspected pulmonary tuberculosis investigated in Cape Town (South Africa) by sputum induction and gastric lavage done on three consecutive days.

Results. A positive smear for acid-fast bacilli or culture for *M. tuberculosis* was obtained overall from 62 children (25%), and of these 58 (94%) were positive by culture. Samples from induced sputum and gastric aspirate were positive on culture in 51 children (20%) and 38 (15%) respectively. The first induced sputum specimen was positive in 37 children (15%) and the first gastric lavage in 19 (8%). The yield from the first induced sputum of 37 positive cultures (15%) was equal to that from all three gastric lavages of 38 positive cultures (15%).

Comment. The possibility that one investigation might be sufficient to confirm the diagnosis of childhood tuberculosis as opposed to the traditional three gastric lavages is obviously attractive. One concern, pointed out in an accompanying editorial (Mwinga, 2005) and hinted at by the authors is possible nosocomial cross-infection from the procedure, particularly in the presence of other HIV-infected children, and the need for infection control measures. An exclusion criterion for the study was an oxygen saturation of $< 92\%$ in room air and one wonders how many primary care facilities in high tuberculosis incidence communities would be able to measure arterial oxygen saturation.

See also Zar et al., 2000.

Iriso R et al. **(2005)**. The diagnosis of childhood tuberculosis in an HIV-endemic setting and the use of induced sputum. *International Journal of Tuberculosis and Lung Disease*, 9:716-726.

Setting. This cross-sectional study was undertaken in the holding ward of the Mulago Hospital, Kampala (Uganda). Children were screened for "suspect tuberculosis" according to the WHO guidelines (WHO, 1983) and those with suspect tuberculosis were then further investigated for probable tuberculosis.

Investigations. A standardized questionnaire was administered emphasizing among other factors cough for > 2 weeks, and contact with an adult with "active PTB" within the previous 12 months. Tuberculin skin-testing was with 5 units PPD and a significant induration was taken as an induration of ≥ 10 mm, or ≥ 5 mm in those with possible immunosuppresion. A feature of this study was that a single specimen of induced sputum was used to attempt confirmation of the diagnosis of tuberculosis by culture. A list of definitions of various alternative diagnoses (LIP, bronchiectasis, pulmonary Kaposi sarcoma) is also provided.

Results. Of the 750 children with suspected tuberculosis, 126 (17%) were recruited as probable cases of whom 62 (49%) were HIV-positive; 36 (32%) of 112 children from whom specimens for culture were obtained had a positive culture for *M. tuberculosis*. For possibly the first time, this study provides sensitivity, specificity *and* predictive values for a number of the symptoms, signs and investigations frequently suggested for the diagnosis of childhood tuberculosis. Taking culture positivity as the "gold standard", a sensitivity of 94%, 92%, 81% and 86% was reached for cough > 2 weeks, fever, a history of weight loss, and the WHO scoring system respectively, but the specificity of these criteria was 0%, 3%, 12 % and 22% and the positive predictive values 32%, 31%, 31% and 35% respectively.

Comment. This study contains a wealth of information only hinted at above; as in many other studies wasting, stunting, digital clubbing and insensitivity to Mantoux testing were associated with HIV infection, while other clinical and radiological features were similar in HIV-infected and non-infected children. This study could serve as a model for the studies that are required at a number of sites throughout the world.

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Annex 3
Treatment

Summary of findings from the papers reviewed

The low importance granted to childhood tuberculosis has had a number of consequences in the field of treatment. Therapeutic trials have focused, understandably, on adult tuberculosis where verifiable microbiological endpoints are available to accurately measure success. Very few studies have thus been undertaken in children. Perhaps of more practical importance, contrary to accepted pharmacological principles, children tend to be given the same mg/kg body-weight dosages of antituberculosis agents as adults. This approach can be summarized as "one size fits all". In some instances this might be acceptable but recent experience suggests caution (Schaaf et al., 2005). In addition to the above problem, there are a number of different recommendations for the doses of all the antituberculosis agents used in children (*Table 4*).

Table 4. Doses of antituberculosis agents recommended for the treatment of children

	Daily (mg/kg)					Intermittent (mg/kg)				
	INH	**RMP**	**PZA**	**EMB**	**SM**	**INH**	**RMP**	**PZA**	**EMB**	**SM**
Abernathy et al. (1983)	10-20	10-20	-	-	-	20-40	10-20	-	-	-
Varudkar (1985)	15	10	30	15	-	-	-	-	-	-
Biddulph et al. (1987)[a]	10-20	10-20	25-40	-	20-40	15-30	10-20	-	-	-
Biddulph et al. (1988)	10	10	25	-	20	15	10	-	-	-
Snider et al. (1988)	10-20	10-20	15-30	15-25	20-40	20-40	10-20	50-70	50	25-30
Starke et al. (1989)	10-15	10-20	25-35	20-25	20-25	20-25	10-20	-	-	-
Starke (1990)	10	10-15	30	15	20	20-25	10-15	-	-	-
Acocella (1990)	10	12	30	-	-	-	-	-	-	-
Kumar et al. 1990)	10-15	10-15	20-30	-	-	20-30	10-15	50-60	-	-
Reis et al. (1990)	10-15	10-15	-	-	-	-	-	-	-	-
IUATLD (1991)	5	10-20	30-35	25/15[b]	20	-	-	-	-	-
Crofton et al. (1992)	5	10	35	Do not use	10	-	-	-	-	-
Starke et al. (1992)	10-15	10-20	20-40	15-25	20-40	20-40	10-20	50-70	50	20-40
Al-Dossary et al. (2002)	10-15	10-20	20-40	-	-	20-40	10-20	50-70	-	-
WHO (2003)	5 (4-6)	10 (8-12)	25 (25-30)	15 (15-20)	15 (12-18)	8-12	8-12	30-40	20-35	-
Swaminathan et al. (2005)	6	12	45	-	-	15	12	-	-	-

[a] The lower doses were used whenever possible.

[b] 25 mg/kg for the first 6-8 weeks and 15 mg/kg/day thereafter.

Treatment of children is often unsupervised, and parents or caregivers return to clinics at weekly or monthly intervals for supplies of drugs without any assurance that these drugs will be given. This situation is further complicated by the fact that child-friendly formulations are frequently unavailable. Clinic staff or parents have to crush tablets to make ad hoc suspensions to treat children. A further complication arises when children are placed on antiretroviral treatment as there is very little understanding of the drug-drug interactions that might occur in children, and of the most appropriate dosages of the relevant drugs when given together. What is well established is that HIV-infected children treated for tuberculosis have a significantly poorer response to treatment and a higher mortality. *Table 5* summarizes published data relating to the short-term response to

treatment and mortality among HIV-infected and non-HIV-infected children treated for tuberculosis.

Table 5. Outcome of treatment of children (%) with and without HIV infection

Author	HIV+ No	Cure	Death
Espinal (1996)	+26	71	16
	-178	97	0
Jeena et al. (1996)	+ 40	-	15
	- 40	-	0
Mukadi et al. (1997)	+31	68	23
	- 129	81	4
Mahdi et al. (2000)	+68	-	13
	-93	-	1
Kiwanuka et al. (2001)	+ 26	58	4
	- 19	79	0
Blussé van Oudblas et al. (2002)	+ 36	-	17
	-114	-	2
Jeena et al. (2002)	+ 57	-	18
	- 44	-	11
Palme et al. (2002)	+58	58 (32/55)	41
	- 459	89 (335/337)	7

Because of the diversity of disease in childhood, many studies of the treatment of childhood tuberculosis enrol children with a wide spectrum of disease. The natural history of these manifestations can vary considerably, making it difficult to judge the success of treatment among subgroups of children. It is thus essential that in evaluating the success of the treatment of childhood tuberculosis, the spectrum of disease being treated is accurately defined.

With regard to the treatment of drug-resistant tuberculosis in children, there is even less information about the pharmacokinetics in children of the second-line agents that must be used than there is about the standard drugs. The doses recommended for children are once again based upon inadequate data.

Priority areas for this research include reviewing existing published studies and undertaking pharmacokinetic studies of the first- and second-line agents used in children.

Review existing published studies of the treatment of tuberculosis with emphasis on the methods used to stratify cases and evaluate the response to treatment, the outcome of treatment and the pharmacokinetics of antituberculosis agents in childhood.

Pharmacokinetic studies of the first- and second-line agents used in children. These studies should also include evaluation of drug-drug interactions and cover all the paediatric age groups (children aged < 2 years, 2-6 years and 7-14 years) and include children with HIV/AIDS. There is now a considerable literature documenting poor absorption of antituberculosis agents in adults with tuberculosis and HIV infection (Berning et al., 1992; Peloquin et al., 1996; Sahai et al., 1997), although not all studies have demonstrated poorer drug absorption in HIV-infected tuberculosis patients (Chuodri et al., 1997; Taylor & Smith, 1998). Few data are available describing the absorption of antituberculosis agents in children with tuberculosis and HIV infection, and this is obviously an important area for study.

Long-term follow up of children after treatment. The recurrence of tuberculosis, whether due to relapse or reinfection, is reported in a significant number of children, particularly in the presence of HIV infection. Very few studies of childhood tuberculosis record treatment success or failure, or relapse rates in children followed up for a substantial length of time. As with criteria for diagnosis, the evaluation of treatment success or cure in children is seldom based on well-defined consistent criteria. If a positive culture has been obtained, then culture negativity can obviously contribute to the assessment of treatment success, but most often the child's well-being is evaluated making use of weight and the opinion of a caretaker with regard to activity or appetite. Some authors have attempted to classify radiological response, but this is complicated by the fact that some features, such as mediastinal adenopathy, may take several years to respond to treatment. The assessment of different treatment regimens in children require the development and evaluation of previously agreed crtiteria for treatment success.

Summary of each paper reviewed

Smith MH (1982). What about short course and intermittent chemotherapy for tuberculosis in children? *Pediatric Infectious Disease*, 1:298-303.

This review of the treatment of tuberculosis in childhood featured in the first volume of *Pediatric Infectious Disease* later to become the *Pediatric Infectious Disease Journal*. In this review, a number of points are touched on that are still relevant today, more than 20 years later. These include:

- The treatment regimens used in childhood have been crudely adapted from those used for cavitary tuberculosis in adults, one of the reasons for this being that children rarely produce sputum to enable those precise quantitative studies that established the validity of the various regimens used in adults.

- "The paucity of pharmacokinetic data and well-controlled clinical studies in children leads, in the United States, to "orphan" clauses for all but the two oldest drugs, STM (streptomycin) and INH. Thus physicians treating tuberculosis must either use suboptimal regimens or risk serious criticism." This is still true to a greater or lesser extent for most of the major drugs and certainly the second-line agents and the attitude of "one size fits all" is still prevalent in tuberculosis-control circles.

- Reference is made to the evaluation of 5-, 4- and 3-month regimens, but with the addendum that the relapse rates of 10%-15% were unacceptably high. In adult pulmonary tuberculosis patients with sputum smear-negative, but culture-positive, pulmonary tuberculosis, 4-month regimens had 5-year relapse rates of 2% among 293 patients with initial drug-sensitive cultures and 4% among 325 patients with initially negative sputum cultures. Among 709 patients with all their cultures negative initially, the combined relapse rate for a 3-month regimen was 7% (Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council, 1989). During an earlier study by the same group, 1019 Chinese patients with radiologically active, but sputum smear-negative pulmonary tuberculosis were studied and treated with 2-month, 3-month or 12-month

regimens. Of the 161 patients whose initial cultures were all negative, 7% of those treated for 3 months relapsed during a 5-year follow-up (Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council, 1984). Similar results were reported by American researchers for 4-month regimens of INH and RMP (Dutt et al., 1989). It is not unlikely that similar results might be obtained in children with negative cultures and smears and nothing more on chest radiography than hilar adenopathy and minimal parenchymal involvement. Such regimens would however require considerable numbers of children to be enrolled to achieve statistically significant results.

Abernathy RS et al. **(1983)**. Short-course chemotherapy for tuberculosis in children. *Pediatrics*, 72:801-806.

This is one of the first evaluations of short-course chemotherapy in children, although the short course for most of the children was 9 months rather than the now accepted 6-month course.

Population treated. Children aged 15 years or less were eligible for the study unless it was thought likely that they were infected by drug-resistant organisms. Between May 1977 and March 1982, 50 children, median age 3 years, 47 (94%) of whom had pulmonary involvement were enrolled in the study. Of the 47 children with pulmonary disease, only 15 were symptomatic: 5 had cavitary disease; 3 hilar adenopathy only; 5 hilar adenopathy and pulmonary infiltrate; and 2 a pleural effusion. Of the 32 asymptomatic children, 21 had hilar adenopthy only and 11 had pulmonary infiltrates in addition to adenopathy. A culture of *M. tuberculosis* was obtained from 6 children (12%).

Regimens. INH 10-20 mg/kg, RMP 10-20 mg/kg daily for the first 30 days and then twice weekly in doses of INH 20-40 mg/kg and RMP 10-20 mg/kg for a further 8 months. Later children with only hilar adenopathy were treated for 6 months.

Results. Results were judged by the resolution of symptoms, the development of negative sputum cultures, disappearance of extrapulmonary findings and clearing of chest radiograph abnormalities. Symptoms responded rapidly, sputum cultures became negative within 2 months, and pulmonary infiltrates cleared by the end of 9 months in the majority of patients. Hilar adenopathy resolved much more slowly and in 12 children did not resolve for 2-3 years.

Varudkar BL (1985). Short course chemotherapy for tuberculosis in children. *Indian Journal of Pediatrics*, 52:593-597.

Population studied, regimens and results. Three short-course regimens were evaluated over a period of five years. No details are given regarding the allocation of patients and whether the allocation was randomized or not, nor how many were culture-positive. Patients with more serious forms of disease were not included. The regimens evaluated were:
- 2RHE/4HE: 100 patients
- 2HZE/4HE: 50 patients
- 6HRE: 50 patients

The response, given as a percentage, to these regimens was noted as excellent in 90%, 90% and 86% respectively. Less than 10% of patients were not compliant compared to a figure of more than 50% previously. No statistical evaluation is given and there is probably no difference between the three regimens in the patients evaluated.

Jacobs RF, Abernathy RS **(1985)**. The treatment of tuberculosis in children. *Pediatric Infectious Disease*, 4:513-517.

This review highlights the role of RMP in enabling the shortening of treatment to 9 months. The advantages in cost-saving, enhanced compliance, less supervision time and the opportunity for direct supervision of each dose are emphasized. Mention is again made of the Hong Kong studies and the Arkansas studies of 4-month regimens in adults with pulmonary tuberculosis who were culture-negative, but "radiologically positive" and after regimens of 3 months in Hong Kong experienced relapse rates of only 7% (Hong Kong Chest Service, 1984). The potential for using such abbreviated regimens for prophylaxis in children is discussed but, given that much childhood tuberculosis is culture-negative with limited lung parenchymal involvement, such shorter regimens could also be considered for many other children.

Seth V (1986). Antituberculous therapy in children. *Indian Journal of Pediatrics*, 53:179-98.

This paper reviews the treatment of tuberculosis in children. Perhaps the most interesting aspect is the discussion of an incomplete trial of 2- and 3-drug regimens given for 6-12 months. *Radiological improvement* is taken as an objective criterion of success and the response was graded:

      I.   complete clearance
      II.   moderate to significant clearance
      III. mild clearance
      IV. no clearance or deterioration.

These criteria remain subjective to a certain extent, but represent an attempt to introduce some consistency into an important area of evaluation, if multicentre drug trials in paediatric tuberculosis are to be carried out. It is also important that a relationship was noted between radiological response and compliance with treatment. The author states an obviously important principle: "The efficacy of a new drug can only be measured if the patient takes the recommended drug for the required duration".

Biddulph J, Mokela D, Sharma S **(1987)**. Compliance of children with tuberculosis treated by short-course intensive chemotherapy. *Papua New Guinea Medical Journal*, 30:159-187.

Population studied and aims. This paper describes the implementation of short-course chemotherapy in children with tuberculosis managed from Port Moresby General Hospital in Papua New Guinea. The main thrust of the paper is the improved compliance that resulted from the introduction of short-course chemotherapy. With a 6-month regimen, compliance was 75% as compared to 25% with the previous 18-month regimen.

Regimen. The 6-month regimen consisted of an A component (intensive–phase) … 2 months of daily INH, RMP, PZA and SM followed by a B component

(continuation/sterilizing phase) consisting of 4 months INH and RMP; this is then the conventional 2RHZ/4RH. When it was considered likely that there would be poor compliance with the B portion of the regimen, the A component was extended to 3 months and followed by 3 months of INH alone.

Results. Of the 328 children placed on the A regimen, 28 completed 3 months, 4 died while on the A regimen, and 25 (8%) of the 324 survivors absconded. On completion of the A regimen or intensive phase, 299 children were placed on the B regimen and 115 were 100% compliant, 11 transferred out, 2 died, and 38 defaulted treatment. The final failure rate on the B regimen was 16%. Compliance for all aspects of the approach was 75%.

This regimen and the compliance figures should be seen in the light of the very difficult circumstances prevailing in a poorly developed area such as Papua New Guinea, where any gain in compliance is to be welcomed. Several later publications (see below) gave more details of the treatment of tuberculosis in children in Papua New Guinea. In the discussion the authors emphasize the importance of an efficient organizational framework for the management of tuberculosis treatment and the importance of gaining the trust and cooperation of the patients.

Biddulph J, Kokoha V, Sharma SS **(1988)**. Short course chemotherapy in childhood tuberculosis. *Journal of Tropical Pediatrics*, 34:20-23.

Population studied. Children registered with tuberculosis admitted to the paediatric wards of Port Moresby General Hospital, Papua New Guinea. Between November 1984 and June 1986, 437 children (286 with pulmonary tuberculosis and 151 with extrapulmonary tuberculosis) were registered and entered prospectively in the study. This study is a continuation of the study described above in Biddulph et al. (1987).

Results. 269 children (62%) completed both the A and B components of the regimen (see above), and a further 32 (7%) completed the alternative regimen of 3 months of the A regimen and 3 months of INH, 2 children died and 101 (23%) defaulted during either the A or B regimens. Only 2 children were known to have relapsed but, as acknowledged by the authors, the follow-up of the patients was very poor. The authors considered, however, that most children who relapsed would have returned to the Port Moresby General Hospital as the only facility available to them.

One can view the low relapse rate reported in this study from two points of view: firstly it may reflect the relatively benign nature of much childhood tuberculosis that is such that even a truncated course of treatment may be sufficient to control the progression of hilar adenopathy and limited parenchymal infiltration; alternatively a more cynical view might be that a number of children may have died without the authors becoming aware of this.

Snider DE et al. **(1988)**. Tuberculosis in children. *Pediatric Infectious Disease Journal*, 7:271-278.

This review paper was written immediately prior to the first realization of the implications of HIV/AIDS, and it discusses all aspects of tuberculosis in childhood in an era of declining case rates. With regard to treatment, the principles underlying modern treatment are set out and each drug is discussed together with details of pharmacokinetics, when

available. The relatively high doses recommended for INH and RMP should be noted. This was accompanied by the note that "there is mounting evidence that INH doses of 10-20 mg/kg/day are not necessary, and the Committee of Treatment, International Union Against Tuberculosis and Lung Disease, has recently recommended a dose of only 5 mg/kg/day for children". There was only one death and all but 15 children completed treatment satisfactorily.

Medical Research Council Tuberculosis and Chest Diseases Unit (1989). Management and outcome of chemotherapy for childhood tuberculosis. *Archives of Disease in Childhood*, 64:1004-1012.

Population evaluated and results. This retrospective study describes the management and outcome of childhood tuberculosis in England and Wales during 1983. It thus reviews medical practice rather than making recommendations on the basis of results. Of the 393 children included in the survey, 313 (80%) had respiratory disease and nearly all the remainder had extrathoracic lymph node disease. The disease was confirmed in 58 (19%) of those with respiratory disease only. A pulmonary lesion was noted in the lung fields in 122 (44%) of those with a radiograph available. All but 15 children (4%) completed treatment satisfactorily.

Treatment was most commonly with INH and RMP with added EMB in 96 children, and the mean duration of therapy was 9 months. For all the drugs used, a very wide range of doses was prescribed: for INH, for example, doses varied from 2-5 mg/kg in 15% of cases to 15-21 mg/kg in 3% of cases. Two (1%) children only, of 278 treated for respiratory tuberculosis, were reported to have relapsed. The authors comment on the fact that only 5% of the children appear to have been given PZA.

Starke JR, Taylor-Watts KT **(1989)**. Tuberculosis in the pediatric population of Houston, Texas. *Pediatrics*, 84:28-35.

Population studied. This paper describes the features and management of tuberculosis in 110 children managed at the children's tuberculosis clinic, Houston, Texas from September 1984 to December 1987.

Treatment regimens. At the start of the study children with thoracic disease received 18 months of INH and RMP. In early 1986 those with thoracic disease received 9 months of INH and RMP, which later that same year was further reduced to 6 months of INH and RMP with PZA added for the first two months of treatment. Directly observed therapy was not practised from the start of treatment, but in patients who were not compliant, twice-weekly supervised treatment was given by nurses or outreach workers. Treatment was successfully completed in all 103 patients who remained in the area. Only two relapses occurred in children who had drug-resistant disease.

Starke JR (1990). Multidrug therapy for tuberculosis in children. *Pediatric Infectious Disease Journal*, 9:785-793.

This is a very comprehensive review of the treatment of childhood tuberculosis and of the hypotheses, principles and clinical trials that support our understanding of the various drugs and their actions. What is noteworthy is the slightly more conservative approach to the dosages of the drugs in children that can be seen emerging here.

Acocella G (1990). The use of fixed dose combinations in antituberculous chemotherapy. Rationale for their application in daily, intermittent and pediatric regimens. *Bulletin of the International Union against Tuberculosis and Lung Disease*, 65:77-83.

This paper discusses, for the first time, the possible use of fixed-dose combinations (FDC) in children. It also represents one of the first occasions when the needs of children were "officially" recognized. The author, realizing the need for children's formulations, suggests that tablets be constituted to provide for 1-tablet increments for each 5 kg body weight, as opposed to 10 kg in adults. The doses of drugs suggested in this calculation were INH 10 mg/kg, RMP 12 mg/kg and PZA 30 mg/kg. Interestingly the dosage of INH differs from the 5 mg/kg recommended for adults, and a dose of 6 mg/kg has been used in the subsequent manufacture of some paediatric FDC formulations. At the top extremes of some of the weight categories, this leads to a dose of < 5 mg/kg. These suggestions were, of course, made without the backing of any pharmacokinetic data from children.

Kumar L et al. **(1990)**. A randomized trial of fully intermittent vs daily followed by intermittent short course chemotherapy for childhood tuberculosis. *Pediatric Infectious Disease Journal*, 9:803-806.

Population studied. Newly-diagnosed children aged 1-15 years with pulmonary, lymph node or disseminated tuberculosis from Chandigarh (India) were studied.

Treatment regimens. Two fully-supervised 6-month regimens were studied in 76 children:
    2HRZ/4HR
    $2H_2R_2Z_2/4H_2R_2$
The dose of INH for daily use was 10-15 mg/kg, for RMP 10-15 mg/kg and for PZA 20-30 mg/kg; for intermittent use the doses were INH 20-30 mg/kg, RMP 10-15 mg/kg and for PZA 50-60 mg/kg.

Patients on intermittent therapy took their doses in the clinic and those on daily therapy took a week's supply home at a time.

Results. 27 children had tuberculous lymphadenopathy; 15 received regimen A and 12 regimen B. 18 children (10 and 8 in groups A and B respectively) were considered to have had a good response and 8 (5 in group A and 3 in group B) a moderate response. Similarly, of the 43 children with pulmonary tuberculosis (20 in group A and 23 in group B), there were 4 and 6 "drop-outs" in groups A and B respectively, 1 death in each group, and 13 and 16 children were considered to have had a marked response to treatment. Of 6 children with disseminated tuberculosis, 2 received the A regimen and 4 the B regimen, and all were considered to have had marked improvement. The two deaths that were reported appeared not to be related to tuberculosis.

These results were encouraging although the numbers of patients were not large when compared to adult studies, and the loss of patients to follow-up always creates a sense of unease about the final conclusions.

Reis FJ et al. **(1990)**. Six-month isoniazid-rifampin treatment for pulmonary tuberculosis in children. *American Review of Respiratory Diseases*, 142:996-999.

Population studied. Children < 15 years of age, from Minas Gerais (Brazil) diagnosed as having pulmonary tuberculosis between July 1979 and December 1988. The diagnosis was based on chest radiographs showing parenchymal infiltration or mediastinal lymph nodes plus at least two further criteria: suggestive symptoms and signs, direct contact with a tuberculous adult, a positive tuberculin test or acid-fast bacilli in sputum or gastric washings. Of 152 children diagnosed in the period of the study, 117 were being treated for the first time.

Mediastinal nodes were present in 80% of children, parenchymal infiltration in 44%, calcification in 13% and a pleural effusion in 4%. No patients had cavitation or collapse or miliary lesions.

Regimen. The treatment was INH 10-15 mg/kg and RMP 10-15 mg/kg/day and the majority of the children were treated as outpatients. Treatment does not appear to have been supervised, but "the use of medications was checked at each visit".

Results. At 6 months there was radiological improvement in all patients, and in 22% the chest radiographs were completely normal. Calcifications were present in 32% and mediastinal nodes persisted in 36%. The authors state that the mean follow-up period was 21.4 months and that no recurrence of tuberculosis had occurred, but do not state how many children were successfully followed up.

This study is encouraging with regard to the majority of cases of childhood tuberculosis that are managed by health services, but the description of the radiology changes suggests that few of the children had really serious forms of tuberculosis.

International Union against Tuberculosis and Lung Disease Scientific Committee (1991). Tuberculosis in children. *Bulletin of the International Union against Tuberculosis and Lung Disease*, 66:61-67.

This statement by the Scientific Committee of the IUATLD addressed a number of issues related to tuberculosis in children, and also made recommendations regarding the doses of antituberculosis agents to be used in children. These included:
- Isoniazid, 5 mg/kg/day
- Streptomycin, 20 mg/kg/day
- Rifampicin, 10-20 mg/kg/day
- Pyrazinamide, 30-35 mg/kg/day
- Ethambutol, 25 mg/kg/day for the first 6-8 weeks and thereafter 15 mg/kg/day.

Starke JR, Jacobs RF, Jereb J **(1992)**. Resurgence of tuberculosis in children. *Journal of Pediatrics*, 120:839-855.

This review paper takes the paediatric tuberculosis literature into the era of HIV/AIDS and all its complications. There are several carefully-worded definitions of what should be considered to be tuberculosis infection in children and what should be considered disease. These are given in the section dealing with diagnosis. The suggested dosages of INH, RMP and PZA are given again in the table and the upper limits are fairly generous in contrast to those of WHO and some other official bodies. This may well be appropriate taking into account what is known of the pharmacokinetics of the drugs, especially in young children.

Ramachandran P, Kripasankar AS, Duraipandian M **(1998)**. Short course chemotherapy for pulmonary tuberculosis in children. *Indian Journal of Tuberculosis*, 45:83-87.

This study reports on the treatment of 137 children with respiratory tuberculosis "stratified" to receive one of two regimens: (a) 9HR; or (b) $2H_3R_3Z_3/4H_2R_2$. The dosages of the drugs were RMP 12 mg/kg, INH 6 mg/kg and PZA 45 mg/kg, this last dosage being somewhat higher than usual.

The diagnosis was confirmed by culture of *M. tuberculosis* in 32% of the children; on chest radiograph 56 (41%) children were classified as most probably having tuberculosis and the remainder as probable tuberculosis.

The results were similar in both groups of patients. It is of interest that, as with other paediatric studies, despite a satisfactory clinical outcome, residual lesions were still present on completion of treatment in 60 (44%) of the children. These continued to improve and at the end of follow-up (24 months after starting treatment), only 20 children had minimal residual lesions. Three patients died while on therapy and all had been culture-positive. Two of these children were among the 10 children who had cavitary lesions upon admission to the study; their organisms were fully sensitive, but the remaining child that died harboured organisms that were resistant to SHR.

This appears to be a well-conducted study that once again illustrates the complexity of studying treatment regimens in paediatric tuberculosis.

Wilkinson D, Davies GR **(1998)**. Pediatric tuberculosis in rural South Africa. *Journal of Tropical Pediatrics*, 44:266-269.

Patient population. This is a retrospective description of certain clinical features and epidemiology of childhood tuberculosis and an analysis of its community management in the Hlabisa district of KwaZulu/Natal, a province of South Africa. Between 1991 and 1995, 679 children < 16-years of age were diagnosed with tuberculosis. These children constituted 19% of the case-load in the district (this then confirming the often-quoted assumption that children in high-incidence communities may make up 20% of the tuberculosis case-load).

Regimen. Daily INH, RMP and PZA "in standard doses" while (and if) hospitalized, followed by the same drugs twice-weekly "in higher dose". If the patient is discharged from hospital, the drugs are given either by clinic staff or by community supervisors, often store managers.

Outcome. The majority of children (75%) were managed in the community, and of these 46% (215/464) were managed by volunteer lay people. Most children (513, 85%) completed treatment successfully. HIV-infected children were more likely to die than those not infected (20% vs 3%). More children managed in the community failed to complete treatment (13% vs 4%), but among those managed in the community non-health workers were just as efficient as health workers at case-holding.

Although local factors and personalities probably played a role in the successful implementation of community treatment in this area, this report holds out some hope for

the successful management of childhood tuberculosis in economically deprived areas affected by the HIV epidemic.

McMaster P, Isaacs D **(2000)**. Critical review of evidence for short course therapy for tuberculous adenitis in children. *Pediatric Infectious Disease Journal*, 19:401-404.

This is a comprehensive review of the various regimens that have been evaluated for the management of tuberculous adenitis. Of a total of 22 studies, the authors selected 7 in which the outcome for children could be identified. In all the studies in which regimens of less than one year were applied, 1526 patients were reported on with a relapse rate of 2.2%. The authors found that there were no studies for two of the WHO-recommended regimens (2-months INH, RMP and PZA followed by 4-months daily INH and RMP or 2-months INH, RMP and PZA daily followed by INH and RMP 3 times weekly for 4 months). They suggest in conclusion that "well-designed studies of the treatment of childhood lymph-node TB in areas of high prevalence would be helpful", and that "although short-course therapy may be appropriate, good studies would ensure that the WHO-recommended regimens are based on the best evidence".

In certain respects, there is more to this debate than just the management of cervical adenopathy. A review of many studies of childhood tuberculosis shows that a considerable proportion of the disease being treated is intrathoracic lymphadenopathy. It might also be possible to manage these cases with less than 6 months of treatment.

Al-Dossary FS et al. **(2002)**. Treatment of childhood tuberculosis with a six month directly observed regimen of only two weeks daily therapy. *Pediatric Infectious Disease Journal*, 21:91-97.

Population studied. Children 1 month to 18 years of age seen at the Children's Tuberculosis Clinic at the Ben Taub General Hospital, Houston (Texas) with pulmonary, lymph node or pleural tuberculosis were enrolled in this prospective observational study of short-course chemotherapy. From February 1994 through May 2000, 185 children were eligible for enrolment and after exclusions, 175 patients could be evaluated.

Regimen. Two weeks of daily INH, RMP and PZA were followed by 6 weeks of twice-weekly INH, RMP and PZA and then 16 weeks of twice-weekly INH and RMP. All therapy was given directly observed from the local health department.

Results. Of the 175 children that could be evaluated, 159 with pulmonary or thoracic node disease, 4 with pleural disease and 12 with cervical lymph node disease completed therapy in 6 months. The 33 patients who received extended treatment did so because of physician choice (3), inadequate response (17), significant adverse drug reactions (2) and poor adherence (16). Only 37% of patients had complete resolution of disease, although all continued to improve after the completion of treatment. Only one relapse was documented and this occurred four years after treatment completion in a child who later acknowledged cryptic non-compliance.

This study documents the considerable problems attached to the management of tuberculosis even in a developed society with the application of considerable resources. The persistence of radiological and physical signs, such as persistently enlarged cervical nodes, again emphasizes the difficulty of documenting the success of therapy in children

in the absence of microbiological markers. The clinician is frequently left with non-specific parameters such as weight gain and the presence or absence of abnormal sounds on chest auscultation.

Swaminathan S et al. **(2005)**. Short-course chemotherapy for paediatric tuberculosis: 5-year report. *International Journal of Tuberculosis and Lung Disease*, 9:693-696.

Patient population and methodology. This was a prospective randomized controlled trial of short-course chemotherapy conducted in a group of 137 children with pulmonary involvement (56% < 5 years of age) by the Institute of Child Health, Egmore, Chennai (India). Culture-confirmation was obtained in 47 children (34%); parenchymal lung lesions were present in 68% of children, but only 2 had cavitation.

Regimens
I. 9RH (collection of drugs once weekly with dose observed on day of drug collection).
II. $2R_3H_3Z_3 / 4H_2R_2$ (all doses directly observed).

Drug dosages
- INH: 6 mg/kg daily (max 150 mg); 15 mg/kg intermittent (max 300 mg).
- RMP: 12 mg/kg (max 300 mg) for daily and intermittent dosages.
- PZA: 45 mg/kg (max 1g).

Outcome. By the end of 2 years, 71% of chest radiographs were normal; at 6 years, 8% of children had residual changes (excluding calcification found in 7 patients). Residual fibrosis was present in 7 patients, atelectasis in 2, persistent adenopathy in 1 and bronchiectasis in 1. Only one child experienced a relapse with fully drug-sensitive organisms. These are very good results, but it should be kept in mind that the lesions in these children reflect the relatively mild nature of much childhood tuberculosis; only 10 children (7%) were noted to have cavitation on chest radiography.

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Annex 4
Incidence and management of BCG-related disease

Summary of findings from the papers reviewed

BCG is a most successfully administered vaccine and is given to almost 90% of children throughout the world. Although there is considerable doubt as to its effect on the occurrence of adult forms of tuberculosis, it is thought to assist in the prevention of disseminated forms of tuberculosis in young children. While vaccine development probably does not fall within the ambit of this proposal, the occurrence and management of the complications of BCG vaccination, in particular as they affect HIV-infected children, are certainly of importance to national programmes. In the past, disseminated BCG disease was relatively unusual and nearly always associated with severe forms of immunosuppression (Lotte et al., 1988). There was therefore understandable concern regarding the possible susceptibility of the newborn HIV-infected infant to disseminated BCG disease (Von Reyn et al., 1987; Reichman, 1989). Prospective evaluation of immunization practices has tended to suggest that HIV infection is not associated with an increased incidence of BCG disease (Ryder et al., 1993), but case reports have indicated that some degree of caution is needed (Talbot et al., 1997; Hesseling et al., 2003). During a study in Zambia, the occurrence of bacteraemia due to mycobacteria was studied in HIV-infected adults and children (Waddel et al., 2001). Among 387 children (median age 15 months) hospitalized with symptomatic HIV disease, only 1 (0.26%) child had a blood culture positive for *M. bovis* BCG. Although the authors claimed that this illustrated that bacteraemia due to BCG was a rare event, this translates into an incidence of 258/100 000, a not inconsiderable incidence for a potentially lethal complication of vaccination. More recently the development of resistance in *M. bovis* BCG Danish strain has also been described in a child with disseminated disease, together with inherent resistance to isoniazid (Hesseling et al., 2004).

Current WHO policy recommends that BCG vaccine should be given to children as soon after birth as possible, and that it should also be used in asymptomatic HIV-infected infants, but not in those who are symptomatic. This in effect means that all newborns should receive the vaccine. Prospective surveillance of the occurrence of BCG disease is urgently needed to inform both national and international policies with regard to the use of BCG in populations with a high prevalence of HIV infection. There is also a need for a systematic evaluation of the most appropriate treatment for BCG-related disease.

Summary of each paper reviewed

Von Reyn CF, Clements CJ, Mann JM (**1987**). Human immunodeficiency virus infection and routine childhood immunization. *Lancet*, 2:669-672.

In this review the authors considered the evidence available at the time to support decisions about the use of routine immunizations in childhood in the era of HIV infection. With regard to BCG they concluded that the rate of dissemination in HIV-infected patients could not be determined, but that case reports that they cite "… raise the possibility of an increased risk of this otherwise unusual complication of BCG immunization".

Ryder RW et al. **(1993)**. Safety and immunogenicity of bacillus Calmette-Guérin, diphtheria-tetanus-pertussis and oral polio vaccines in newborn children in Zaire infected with human immunodeficiency virus type 1. *Journal of Pediatrics*, 122:697-702.

This prospective cohort study enrolled 474 children born to 466 HIV-seropositive women in Zaire. BCG was administered at an age of 2 days. The incidence of regional lymphadenopathy and ulceration at the site of vaccination was similar in HIV-infected and non-infected children, and in control children. No case of disseminated BCG was diagnosed, but the authors acknowledge that their study enrolled an insufficient number of children with HIV infection and they were also unable to systematically examine all children who died before their first birthday.

Talbot EA et al. **(1997)**. Disseminated Bacille Calmette-Guérin disease after vaccination: case report. *Clinical Infectious Diseases*, 24:1139-1146.

This case report describes the occurrence of disseminated BCG disease in an HIV-infected infant who had been vaccinated with BCG at the age of 10 days. The authors also reviewed the recent literature and identified 28 cases of disseminated BCG disease that had been reported since 1980. Of the 28 cases, 24 (86%) occurred in association with HIV infection, and the response to treatment was poor with a mortality of 71%. The authors speculate that the relative scarcity of cases reported from developing countries may be due to inadequate facilities to identify *M. bovis* BCG as a pathogen. Most prospective studies undertaken to date are relatively small and patient follow-up inadequate to predict the risk of disseminated BCG disease in HIV-infected children with accuracy.

The authors provide a useful *Working definition of disseminated BCG disease* (see table 2 in the article). In abbreviated form this definition includes:
    11. BCG cultured and identified.
    12. Evidence of dissemination either by blood or bone-marrow culture, or evidence of disease located beyond the region of vaccination.
    13. A compatible systemic syndrome complex.

Hoft DF et al. **(1999)**. Clinical reactogenicity of intradermal Bacille Calmette-Guérin vaccination. *Clinical Infectious Diseases*, 28:785-790.

In this study healthy volunteers were vaccinated with intradermal BCG and observed for clinical reactogenicity. Of the 48 volunteers, all but one developed an ulcerative lesion that drained for nearly a month. Viable mycobacteria could be cultured from these lesions. Aside from the other findings of this study, this finding has significant implications for communities with a high prevalence of HIV infection. The implication is that newly BCG-vaccinated infants could potentially serve as a source of infection with *M. bovis* BCG for their close contacts, especially parents and health workers, and clinical complications have been reported following the accidental contact spread of BCG vaccine organisms.

Hesseling AC et al. **(2003)**. Danish Bacille Calmette-Guérin vaccine-induced disease in human immunodeficiency virus-infected children. *Clinical Infectious Diseases*, 37:1226-1233.

During this study the authors analysed isolates of *M. tuberculosis* complex obtained from 49 HIV-infected children, and identified *M. bovis* BCG from 5 children. In two instances the children suffered from BCG pulmonary disease. The authors acknowledge that their data did not allow them to estimate the true risk of disease, and they suggest that prospective community-wide surveillance of a population of at least 10 000 vacinees annually would be necessary to establish such a risk.

Hesseling AC et al. **(2004)**. Resistant *Mycobacterium bovis* Bacillus Calmette-Guérin disease in human immunodeficiency virus-infected children. *Pediatric Infectious Disease Journal*, 23:476-479.

In this case report, the authors describe the presence of inherent isoniazid resistance in an isolate of *M. bovis* BCG Danish strain and the further acquisition of rifampicin resistance following the use of an inadequate regimen in the face of unappreciated isoniazid resistance. The need to develop appropriate regimens for the management of BCG-related disease in countries with a high prevalence of HIV infection is emphasized.

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Annex 5

Proposed research to improve the management of childhood tuberculosis as part of national tuberculosis programme activities

Summary of research suggestions from the papers reviewed

Epidemiology

- Determine the precise burden of childhood tuberculosis under different epidemiological situations.
- Check whether national or regional notifications reflect the burden of childhood tuberculosis.
- Carry out annual risk-of-infection studies in different countries and communities.
- Utilize existing national and regional programme data to determine the burden of childhood tuberculosis.
- Determine the risk of infection and disease in HIV-infected children and in children in contact with HIV-infected adults.
- Establish where the infection of children of different ages occurs under different epidemiological settings.

Diagnosis

- Evaluate the value of nasopharyngeal aspirate in the diagnosis of childhood tuberculosis.
- Study the value of polymerase chain reaction (PCR) in the diagnosis of childhood tuberculosis.
- Prospectively evaluate score charts as a diagnostic methodology for childhood tuberculosis.
- Evaluate the various cut-points suggested for Mantoux testing of children under different epidemiological circumstances.
- While carrying out the above diagnostic studies, evaluate newer technologies for the diagnosis of childhood tuberculosis.
- Determine the diagnostic yield if children who are contacts of sputum smear-negative cases of pulmonary tuberculosis are also evaluated.
- Develop and evaluate serological tests for the diagnosis of childhood tuberculosis.
- Evaluate the enzyme-linked T-cell-based (ELISPOT) assay to aid diagnosis.
- Determine the sensitivity, specificity and predictive value of the various criteria suggested for the diagnosis of tuberculosis in children.
- Undertake clinical and autopsy studies of children with acute and chronic pneumonia to determine the incidence of tuberculosis.

Treatment

- Develop and evaluate family-centred services for treatment and for prophylaxis.
- Evaluate the feasibility of mothers or other caregivers acting as DOTS providers and supervisors.

- Determine treatment outcome in childhood tuberculosis, particularly in relation to compliance, the drugs used and the doses of the drugs, and whether recurrences are due to reinfection or relapse.
- Establish whether certain forms of childhood tuberculosis could be treated for a shorter period and whether HIV-infected children require a longer period of treatment.
- Evaluate the pharmacokinetics of antituberculosis drugs in children and the efficacy of shorter courses of combinations of drugs for prophylaxis.
- Establish a network of field sites for the conduct of the above studies, in particular the evaluation of new diagnostic methodologies and treatment regimens.
- Establish a data bank to collect and collate epidemiological and other data related to childhood tuberculosis.

Summary of each paper reviewed

Uke BT, Seth V (**1991**). National tuberculosis programme in India: lacunae in relation to childhood tuberculosis. *Indian Pediatrics*, 28:239-241.

This paper reviews the development of the Indian National Tuberculosis Programme up to the point of publication. Problems related to childhood tuberculosis are pointed out. The annual incidence of infection is given as 0.8% at age < 5 years, 1.1% at 5-9-years, 1.3% at 10-14 years and 1.6% for all ages. They plead for urgent attention to the following:
- "Uniform diagnostic criteria for common forms of childhood tuberculosis.
- Dosage and regimens as for short-course antituberculosis treatment.
- Children of sputum-positive patients must be considered as high risk for the disease and need at least a tuberculin test and an X-ray test.
- Pharmacokinetic studies in children should be done at referral centres so that proper dosages can be recommended."

This programme is not very different from that now being promoted to advance the integration of childhood tuberculosis into national tuberculosis programmes.

Eamranond P, Jaramillo E (**2001**). Tuberculosis in children: reassessing the need for improved diagnosis in global control strategies. *International Journal of Tuberculosis and Lung Disease*, 5:594-603.

The emphasis in this paper is placed on improving the diagnosis of childhood tuberculosis. By improving the accuracy of diagnosis, the impact of tuberculosis on child health will be better quantified and recognized. The point is also made that, irrespective of the role of childhood tuberculosis in tuberculosis control, there is a moral imperative to effectively manage, prevent and control childhood tuberculosis. Some of the points made include:
- The global strategy for tuberculosis control would benefit by incorporating childhood tuberculosis.
- The precise burden of childhood tuberculosis is not actually known.
- Issues related to compliance and outcome among children have not been well studied.
- Alternative methods of diagnosis such as PCR, nasopharyngeal aspirate and even computerized tomography have not been systematically studied with regard to the

- contribution they might make to our understanding of the pathogenesis and epidemiology of childhood tuberculosis.
- Tuberculin skin-testing, although extensively studied, encounters problems related to false-positive and -negative results.
- The traditional symptoms and signs are of a non-specific nature.
- Although usually considered non-infectious, there is evidence that children may well make a significant contribution to the spread of infection and this needs to be quantified.

They conclude with regard to childhood tuberculosis and its diagnosis and control: "The challenge we face is how to develop the research agenda that will enable us to achieve this goal".

Harries AD et al. **(2002)**. Childhood tuberculosis in Malawi: nationwide case-finding and treatment outcomes. *International Journal of Tuberculosis and Lung Disease*, 6:424-431.

This paper describes a countrywide assessment of the diagnosis and outcome of childhood tuberculosis in Malawi during 1998. Data were collected from tuberculosis registers, treatment cards and health-centre registers regarding childhood tuberculosis.

During 1998, 22 982 cases were registered in Malawi of which 2739 (12%) were children, defined as persons $\leq$ 14 years. Children represented 1.3% of all notifications for smear-positive tuberculosis, but 21.3% of smear-negative tuberculosis and 15.9% of extrapulmonary tuberculosis. Only 45% of children completed treatment and there were high rates of death (17%) and default (13%). Treatment outcome was unknown in 21% of children.

Several important points emerge from this paper:
- In Malawi the diagnosis of childhood tuberculosis is "generally made in a hospital setting".
- The diagnosis of pulmonary tuberculosis in children is usually made on the basis of a constellation of symptoms, signs, growth faltering, poor response to antibiotics, chest radiography showing pulmonary infiltrates and mediastinal adenopathy, and a history of close contact with smear-positive pulmonary tuberculosis.
- Tuberculin solution is not routinely available.

The authors then identify research and operational questions arising from their study:
- Do notifications really reflect the burden of childhood tuberculosis?
- Score charts are often proposed, but seldom evaluated. In HIV-endemic areas they are less sensitive and less specific.
- A sensitive and specific serological test is needed for smear-negative tuberculosis.
- Treatment outcomes should be evaluated. Are the poor outcomes in children caused by poor compliance or are other factors such as inadequate drug dosages for children involved?

Starke JR (2003). Pediatric tuberculosis: time for a new approach. *Tuberculosis*, 83:208-212.

In this paper a plea is made for "a more systematic approach to pediatric tuberculosis …". Again the inconsistencies that result from the use of a variable constellation of clinical

signs, symptoms and special investigations are highlighted as one of the major reasons for the uncertainties that surround the place of children in tuberculosis control programmes and the burden of childhood tuberculosis in the world. An additional important point made is that, even if controlling adult tuberculosis is the most rapid way to control childhood tuberculosis, control of adult tuberculosis is not going to be achieved in the near future and the situation may well get worse before it improves; in the meantime children will continue to suffer from an unnecessarily heavy burden of tuberculosis that will be inadequately managed.

Five steps are listed that could lead to a rapid and sustained improvement in the situation:
- continuation of BCG vaccination;
- the creation or development of family-centred services to assist in preventing disease in recently-exposed and -infected children;
- treating the childhood household contacts of adult cases;
- using DOTS for all children with disease and when possible for those with infection as well;
- improved availability and quality of diagnostic tests.

Chauhan LS, Arora VK **(2004)**. Management of pediatric tuberculosis under the revised National Tuberculosis Control Program (RNTCP). *Indian Pediatrics*, 41:901-905.

This paper represents a joint statement by the Indian Central TB Division Directorate General of Health Services, Ministry of Health and Family Welfare, and experts from the Indian Academy of Pediatrics. The paper sets out plans for the incorporation of children into the national tuberculosis control programme. The reasons for the lack of priority accorded childhood tuberculosis include:
- diagnostic difficulties
- the fact that the disease is rarely infectious
- limited resources
- misplaced faith in BCG
- lack of data on treatment.

The history of the national tuberculosis control programme and its 1992 revision is briefly recorded, before turning to childhood tuberculosis. It is stated that good data on the burden of all forms of tuberculosis among children are lacking. In 2002 only 1.7% of smear-positive pulmonary tuberculosis cases placed on treatment in India were children and only 3% of the total case-load recorded by the RNTCP were children; tuberculosis cases in children were being diagnosed in many health facilities, but not recorded. Cure and completion rates for children, according to the national programme, were above 90% but other data indicated that figures for paediatric cases not treated under the national programme were 80% and 70% respectively, with default rates of 27%-33%. Against this background a workshop was held in 2003 to assist in the integration of childhood tuberculosis into the national programme. Significant points from these recommendations include the following.

Diagnosis. Suspect cases of tuberculosis are those with fever and/or cough for more than 3 weeks, with or without weight loss or no gain; and a history of contact with a suspect or diagnosed case of active tuberculosis within the past 2 years.

Diagnosis would be based on a combination of clinical presentation, sputum examination wherever possible, chest radiograph, Mantoux test and a history of contact. An important rider is added that the diagnosis of tuberculosis in children should be made by a medical officer. Scoring systems are not recommended.

Treatment. "DOTS is the recommended strategy … Children should receive the same treatment as adults and the same categories should be used as recommended for adults."

Chemoprophylaxis. "Asymptomatic children under 6 years of age, exposed to an adult with infectious (smear-positive) tuberculosis from the same household, will be given 6 months of isoniazid (5 mg/kg daily) chemoprophylaxis."

Monitoring and evaluation. Children should be followed up as part of the national programme and clinical or symptomatic improvement assessed at the end of the intensive phase and at the end of treatment. Improvement should be judged by the absence of fever or cough, the decrease in lymph node size and weight gain, and smear-negative pulmonary tuberculosis cases by radiological improvement.

Operational research issues
- A multicentric evaluation of a paediatric tuberculosis scoring system;
- the feasibility of mothers acting as DOTS providers;
- the diagnostic yield if children are also evaluated who are contacts of smear-negative adult patients.

This is a very comprehensive document that touches on many of the issues that will have to be addressed on a global scale. Points of interest include the use of 1 TU PPD RT23 for Mantoux testing and the integration of the treatment of children into the same categories as adults. The requirement that tuberculosis in a child should be diagnosed by a medical officer also introduces a degree of control into the system, although this may not be feasible in other parts of the world.

Wells CD, Nelson LJ (**2004**). New international efforts in childhood tuberculosis: proceedings from the 2002 Workshop on Childhood Tuberculosis, Montreal, Canada, 6-7 October 2002. *International Journal of Tuberculosis and Lung Disease*, 8:630-634.

The goals of this workshop were to highlight gaps in knowledge concerning childhood tuberculosis and to establish a coalition of interested bodies to foster working partnerships and identify critical areas of research and programmatic needs and strategies to increase the international focus on childhood tuberculosis. It was stated that childhood tuberculosis "can comprise a sizeable proportion of the overall burden of TB in some countries" and that approximately 15% of the tuberculosis burden in high-burden countries could be ascribed to childhood tuberculosis. It was acknowledged that more accurate estimates of the burden of childhood tuberculosis were needed.

- The potential value of existing data was emphasized and that there was much descriptive clinical and programmatic data collected by national tuberculosis programmes that could be analysed.

- The re-institution of annual risk of infection (ARI) surveys was proposed and the exploration of techniques to make these more efficient.

- The importance of a standard clinical case definition was emphasized for both research and programme activities. Such definitions should be prospectively evaluated in different clinical and epidemiological settings.

- Published outcomes of the treatment of childhood tuberculosis were scarce and what was known of compliance suggested high default rates.

- New diagnostic tools were needed and among others the evaluation of the enzyme-linked T-cell-based (ELISPOT) assay should be evaluated.

- A network of field sites for testing new and improved assays and studying other aspects of childhood tuberculosis under different settings should be established.

- A consortium of interested parties should establish a databank for surveillance data, ARI surveys, household studies, pilot studies and clinical trials to serve as a resource for research purposes.

Nelson LJ, Wells CD **(2004)**. Global epidemiology of childhood tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:636-647.

This paper describes current knowledge of the epidemiology of childhood tuberculosis and at the same time highlights the following areas requiring research.

Challenges as regards childhood tuberculosis include:
- the difficulty of establishing a definitive diagnosis;
- the increased incidence of extrapulmonary disease in young children;
- lack of a standard case definition.

Reference is again made to the desirability of ARI surveys as an objective method of assessing the tuberculosis situation in a country, and the fact that some countries already collect data that if analysed might provide valuable insights into childhood tuberculosis. Operational studies of contact-tracing are suggested to elucidate how much disease occurs in contacts of smear-positive cases. The optimal length of chemoprophylaxis for children and the value of contact-tracing for dually-infected parents or household contacts requires exploration.

Finally it is pointed out that accurate data are needed to make informed decisions and that nearly every aspect of childhood tuberculosis lacks accurate data reported in a uniform manner.

Graham SM et al. **(2004)**. Childhood tuberculosis: clinical research needs. *International Journal of Tuberculosis and Lung Disease*, 8:648-657.

In this review the authors identified improved capability to confirm the diagnosis of childhood tuberculosis as the most critical research need for the better management of childhood tuberculosis.

In this well-structured review, research needs and suggestions were classified under the following headings.

Risk of infection and disease
- Determine the ARI in different countries and communities.
- Determine the degree of increased risk of TB infection and disease in children with HIV infection and/or malnutrition.
- Determine where transmission occurs in the various age groups and in different settings of TB prevalence and socioeconomic circumstances.
- Determine what individual factors protect a child in close contact with an infectious case from becoming infected and developing disease.
- Determine the risk of infection and prevalence of MDR tuberculosis in children in high-prevalence MDR settings, as well as the optimal management of MDR disease and infection in children.

Diagnosis and clinical presentation
- "A large multicentre collaborative study of children with suspected TB in high TB prevalence regions using various means for diagnostic confirmation …".
- Within such studies, evaluate new diagnostic techniques and management guidelines and evaluate systematically symptoms and signs used in various scoring systems, and management and diagnostic algorithms.
- From the data generated by the above studies construct case definitions for childhood tuberculosis.
- Undertake clinical and autopsy studies of children with acute and chronic pneumonia.
- Determine the availability and use of tuberculin in different parts of the world.
- Evaluate the various cut-off points suggested for tuberculin skin-testing in different clinical and epidemiological situations.
- Improve the diagnostic value of chest radiographs.

Treatment
- Identify reasons for poor compliance and treatment outcome particularly in malnourished and HIV-infected children.
- Review and undertake pharmacokinetic studies of antituberculosis agents in children.
- Determine whether children with limited and uncomplicated forms of tuberculosis (hilar adenopathy with limited parenchymal involvement) could be treated for a shorter period of time.
- Evaluate whether children with HIV infection and certain forms of disseminated tuberculosis or extrapulmonary tuberculosis need longer periods of treatment.
- Determine the rates and causes of recurrence of tuberculosis in children and whether such recurrences are due to relapse or re-infection.

Management of childhood contacts of infectious adults
- Determine the efficacy of chemoprophylaxis in different settings of tuberculosis and HIV prevalence.
- Study the potential role of chemoprophylaxis in children of different ages.
- Evaluate efficacy of shorter-course combination chemoprophylaxis.

This paper provides a comprehensive list of possible research activities that might benefit childhood tuberculosis.

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