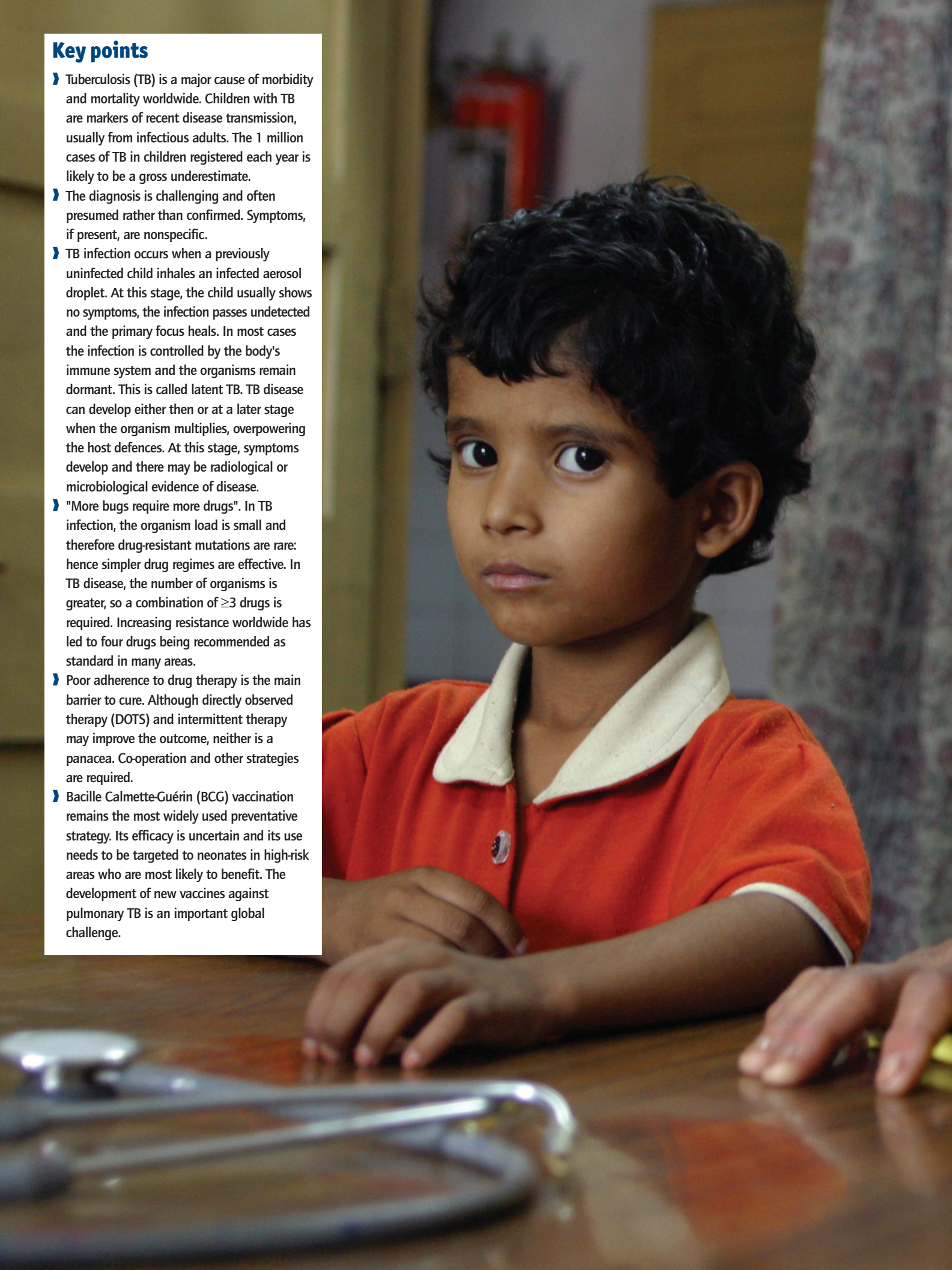
Key points

- Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. Children with TB are markers of recent disease transmission, usually from infectious adults. The 1 million cases of TB in children registered each year is likely to be a gross underestimate.
- The diagnosis is challenging and often presumed rather than confirmed. Symptoms, if present, are nonspecific.
- TB infection occurs when a previously uninfected child inhales an infected aerosol droplet. At this stage, the child usually shows no symptoms, the infection passes undetected and the primary focus heals. In most cases the infection is controlled by the body's immune system and the organisms remain dormant. This is called latent TB. TB disease can develop either then or at a later stage when the organism multiplies, overpowering the host defences. At this stage, symptoms develop and there may be radiological or microbiological evidence of disease.
- "More bugs require more drugs". In TB infection, the organism load is small and therefore drug-resistant mutations are rare: hence simpler drug regimes are effective. In TB disease, the number of organisms is greater, so a combination of ≥3 drugs is required. Increasing resistance worldwide has led to four drugs being recommended as standard in many areas.
- Poor adherence to drug therapy is the main barrier to cure. Although directly observed therapy (DOTS) and intermittent therapy may improve the outcome, neither is a panacea. Co-operation and other strategies are required.
- Bacille Calmette-Guérin (BCG) vaccination remains the most widely used preventative strategy. Its efficacy is uncertain and its use needs to be targeted to neonates in high-risk areas who are most likely to benefit. The development of new vaccines against pulmonary TB is an important global challenge.



Tuberculosis in children

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Educational aims

- To describe the epidemiology and natural history of TB in children, focusing on pulmonary TB.
- To explore the challenges of diagnosis and provide an up-to-date overview of the methods available.
- To outline the management and prevention of pulmonary TB in children.

Summary

Despite advances in diagnosis, treatment and prevention, tuberculosis (TB) remains a major cause of mortality and morbidity worldwide. Diagnosis and treatment in children present a challenge, particularly in the face of growing drug resistance and coexistent disease such as HIV. New diagnostic methods have not yet been fully validated for use in children. No new drugs have become available in the past 30 years and many of the commercially available preparations are unsuitable for children. In 2006, a number of major documents and strategies were launched aimed at improving the care of children with TB, a previously neglected area.

TB is among the world's major diseases. It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis*, the bacterium causing TB. Each year ~9 million people, including 1 million children aged <15 years, become infected and >2 million die [1]. Although TB is mainly pulmonary, disseminated disease is more common in children, with the very young being at an increased risk. Miliary TB and TB meningitis are associated with high mortality and morbidity, and should be considered especially if there is a history of contact with an adult with infectious TB.

Children with TB are markers of recent disease transmission, usually from an infectious adult. They provide a reservoir of disease for the future but are rarely infectious themselves, so their treatment, particularly in endemic areas, is often not a priority.

Severe forms of TB are thought to be uncommon in children. However, in parts of Africa, TB rivals acute pneumonia as a major cause of respiratory deaths in children [2]. The true extent of childhood TB morbidity and mortality is rarely appreciated as the available data seriously underestimates the true disease burden because of the difficulties confirming the diagnosis and the low levels of notification in many areas of the world [3].

The Stop TB Strategy and the Global Plan to Stop TB launched by the World Health Organization (WHO) as part of the Millennium Development Goals in 2006 aim, by 2015, to reduce TB prevalence and deaths to half of the 1990 levels. An explicit focus of the Stop TB Strategy is to address the chronic neglect of childhood TB.

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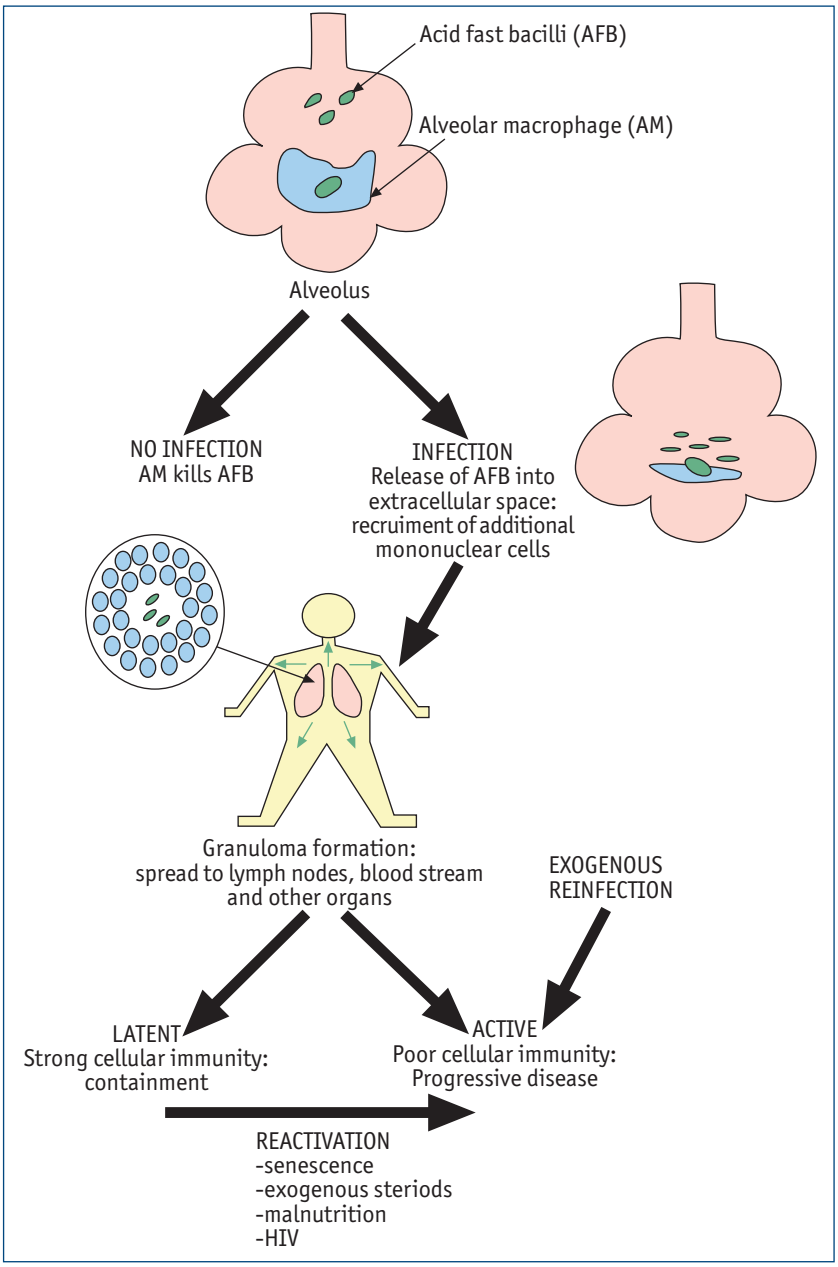


Figure 1
The dynamic relationship between M. tuberculosis *and the human host. Reproduced from [4], with permission from the publisher.*

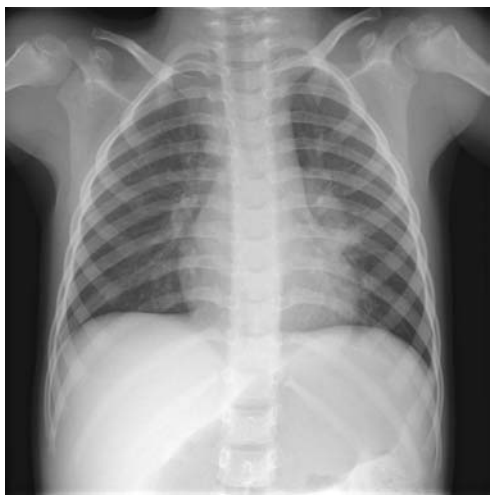


Figure 2
Hilar adenopathy on chest radiography. Hilar adenopathy is frequently the only radiological sign of TB. The primary focus is usually so small that it is not observed on chest radiography.

Natural history in children

An understanding of the natural history of TB in children is central to the clinical presentation, diagnosis, and treatment (figure 1).

Infection with *M. tuberculosis* usually results from inhalation of infected droplets into the lungs spread by someone with pulmonary TB coughing. Nonpulmonary forms are generally not infectious. The source of infection for most children is an infectious adult in their close environment, usually within the same household [5].

Primary infection occurs when a previously uninfected child inhales an infected aerosol droplet. As few as 1–5 tubercle bacilli are sufficient to cause infection. About 30% of exposed people become infected. If the droplet reaches a terminal airway, a localised pneumonic process, the primary pulmonary (Ghon) focus, can develop. Over the next 4–6 weeks, the organisms divide within the Ghon focus and *M. tuberculosis* bacilli drain *via* the lymphatic system to regional lymph nodes in the mediastinum and beyond. The primary "Ghon complex" is the combination of the primary focus with or without some overlying pleural reaction and the affected regional lymph nodes.

This process leads to activation of the cell-mediated immune system (CMI) which stops the organism multiplying. The tuberculin skin test (TST) is a marker of the activation of CMI and may become positive ~3–8 weeks after infection (conversion). At this stage, the child usually shows no symptoms, the infection passes undetected and the primary focus heals. This phase is called TB infection. Hilar adenopathy is the most common marker of recent primary infection in children (figure 2). Occult haematogenous dissemination frequently occurs during this early phase before CMI is fully active and can cause later extrapulmonary infection.

What happens next in those with TB infection depends on the adequacy of cell-mediated immunity. In most cases (60–90%), host factors prevail. T-cells, monocytes and macrophages are recruited to form a defensive barrier. The bacilli sequestered in quiescent foci in the body slow their replication [6]. This is called latent TB. The child remains well, is not infectious and the only indicator may be conversion of the TST. The absence of symptoms usually indicates good organism containment.

In the remaining cases, the organism multiplies, overpowering host defences, and TB disease develops. In half of these cases, progression occurs early during the first 5 years after exposure. In the other half, there is a long interval, often several decades, between the onset of infection and the occurrence of disease. This occurs when the body's immune system is weakened by disease (*e.g.* by HIV), medical treatments (*e.g.* chemotherapy or anti-tumour necrosis factor-α drugs) or by old age. At this point, the TB bacilli become reactivated. In this post-primary disease there is greater tissue destruction, liquefaction of lung tissue and the development of cavities. Persistent, unremitting symptoms develop. Since communication of the areas of necrosis with the airways is common, the person coughs up large numbers of TB organisms in sputum and is highly infectious.

Risks of disease progression

The risks of disease progression vary greatly depending on certain circumstances [7].

Age is the most important factor determining progression to disease after primary infection in immunocompetent children. Infants are at the highest risk, with a 30–40% risk of pulmonary disease and a 10–20% risk of disseminated disease. Primary infection before 2 years of age may progress directly to active disease within 12 months without significant prior symptoms. Primary infection between 2–10 years of age rarely progresses to serious disease. Such progression is associated with significant clinical symptoms. Symptoms may enable a clinical diagnosis before serious disease progression occurs. Infection after 10 years of age frequently progresses to adult-type disease [8].

The other major risk factor is immune deficiency. In many parts of the world, particularly Sub-Saharan Africa, the main cause of immunodeficiency is HIV infection. Children with HIV infection and/or other forms of immune compromise seem to experience a similar high risk to very young children.

Because of the frequency and rapidity of progress of disease in those at high risk (very young or immunosuppressed children), exposure to infection and/or evidence of infection with *M. tuberculosis* warrants treatment. In children at lower risk of progression to TB disease, latent TB carries the risk of later reactivation, which is also eliminated by treatment.

TB in children

Although childhood TB is often reported as a single disease, a spectrum of pathology is commonly encountered. Disease containment within the Ghon focus may be the rule but disease progression resulting from either poor or excessive containment in the young or immunosuppressed can lead to a wide variety of clinical presentations (figure 3).

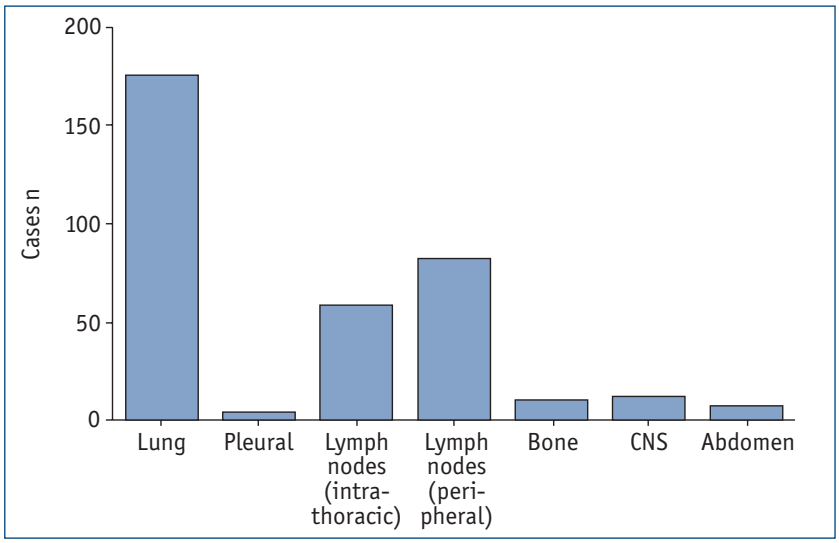


Figure 3
Sites of disease in a 1998 survey. Reproduced from [9], with permission from the publisher.

Diagnosis

The diagnosis of TB in children relies on thorough assessment and appropriate investigation. Most cases are of pulmonary TB.

Fast and accurate diagnosis is a key element in TB control. The major difficulty in diagnosing TB in children is that the gold standard – confirmation of infection by demonstration of *M. tuberculosis* on direct microscopy of sputum or culture – is commonly not achieved and is often not attempted.

Most children with active pulmonary TB have paucibacillary disease and are rarely infectious. Compared with adults, they rarely have cavitatory disease (<6%), they often have little or no cough, and when cough is present it is generally not forceful enough to expel aerosolised bacteria efficiently. Caseation and cavitating pulmonary disease, characteristic of post-primary TB, rarely occur in children before puberty. Children with a poor cell-mediated response may present in this way and are infectious.

Sputum-smear microscopy, which may be the only test available in many endemic areas, is positive in <10–15% of children with probable TB. It may be more valuable in older children with adult-type disease. Culture is little better. Yields of positive cultures for *M. tuberculosis* of 30–40% in children with uncomplicated hilar

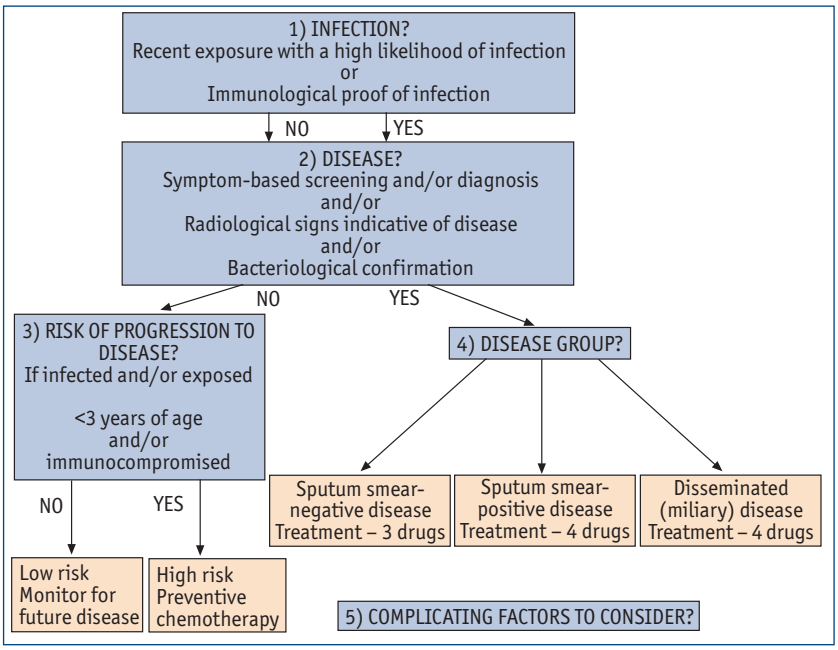


Figure 4
Flow diagram to guide the diagnosis and management of children with suspected pulmonary TB. Reproduced from [7], with permission from the publisher.

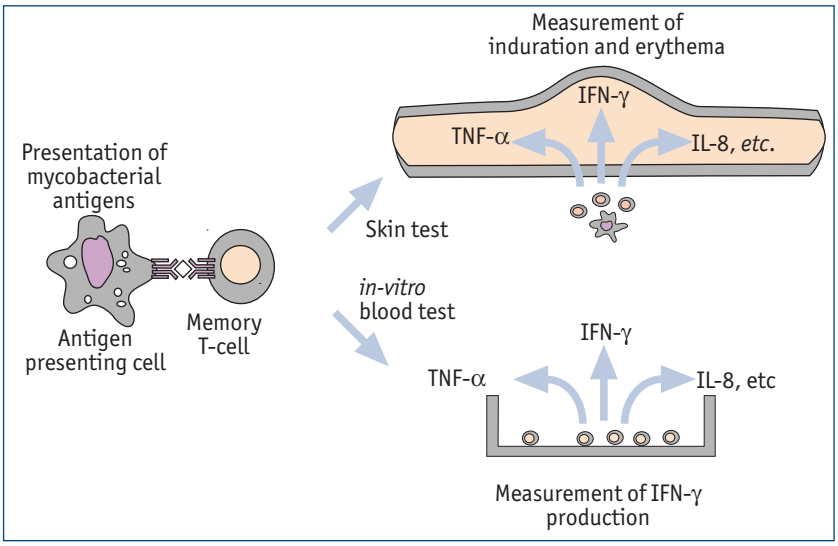
adenopathy are typical. Obtaining adequate samples in children is often difficult.

The importance of contact screening

Because TB in young children generally develops from recent disease transmission, contact tracing is of great importance in the detection of children with a high likelihood of developing infection.

In low-prevalence settings, such as the US or the UK, 5–10 close contacts are often identified per adult with newly diagnosed smear-positive TB. Of these, ~30% develop latent TB and 1–4% TB disease. In endemic areas, 50% of household contacts are found to have latent TB and 10–20% TB disease. In this setting, ~6% of all contacts could be expected to have TB disease [10].

Figure 5
The TST and interferon-γ tests. Reproduced from [11], with permission from the publisher.



Contact screening aims to detect not just those with TB disease, but also those with latent disease or evidence of recent exposure. In practice, distinguishing low-risk children with primary TB infection from those with active early disease is often difficult. Offering preventative treatment at this stage may reduce the progression to TB disease by up to 90% [7]. In nonendemic areas, treatment of all of these groups is important. However, in many endemic areas there are insufficient resources to follow WHO advice on active tracing and screening of children aged <5 years with a household contact. Preventative treatment is reserved for those at the highest risk.

Investigations

Investigation of children suspected of having TB is difficult. MARAIS *et al*. [7] have developed a diagnostic algorithm, based on a number of key questions, to guide individual patient management (figure 4). In many cases the diagnosis reached is one of probable, rather than proven, TB.

Since *M. tuberculosis* is an intracellular pathogen, an assessment of whether a patient's T-cells have been sensitised by antigens specific to *M. tuberculosis* provides an alternative diagnostic approach. Confirming *M. tuberculosis* infection makes it more likely that the presenting illness is TB, since such infection in young children is likely to be recent. However, without other information, such as the presence of symptoms or chest radiographic changes, these tests do not distinguish between TB infection and disease.

There are now two tests that can be used to help decide whether a child has been infected with *M. tuberculosis* – the TST and the interferon (IFN)-γ test (figure 5) [11].

Tuberculin skin test

The TST (Mantoux or Heaf Test) has been used for >50 years to support the diagnosis of TB. It measures the induction of cutaneous induration as a result of delayed hypersensitivity reactions after the intradermal injection of purified protein derivative (PPD), a complex mixture of mycobacterial antigens prepared from heat-killed cultures of *M. tuberculosis*.

The TST should be standardised for each country using either 5 tuberculin units (TU) of tuberculin PPD-S or 2 TU of tuberculin PPD-

RT23, as these give similar reactions in TB-infected children.

Despite the TST's longevity, its use and the interpretation of results remain controversial. The test has a number of major drawbacks, including poor specificity and negative reaction occurring in 10–25% of tuberculosis patients, reducing specificity to <50% in patients with advanced disease. In areas such as HIV, where TB diagnosis is difficult, this is particularly problematic. An important limitation is that the patient must return to the clinic 46–72 hours after injection to have the test read. Correct interpretation is a skill that requires training in both performing and reading the test.

The size of the reaction needs to be interpreted in light of the child's risk of being infected and the risk of progression to disease. Other factors, including the use of BCG vaccine and the frequency of TB in the area need to be considered. Most guidelines agree that:

- In a high-risk child (HIV-positive, malnourished) a reaction of ≥5mm is positive.
- In all other children, an induration ≥10mm should be considered positive, whether or not they have had BCG.

It is important to remember that cut-offs are arbitrary, that they should be interpreted in a clinical context and that a negative test does not exclude TB (table1).

Interferon-γ tests

Among the most important recent developments in TB diagnosis has been the development of *in vitro* T-cell-based assays (figure 6). A number of tests are commercially available, including the QuantiFERON TB Gold and T-SPOT tests [11, 13–15]. These whole-blood assays measure IFN-γ production by previously sensitised lymphocytes in response to the *M. tuberculosis*-specific protein antigens ESAT6 and CFP-10. Only one visit is required and the test offers a number of potential advantages over the TST.

Some studies have shown that, compared with TST, these tests have higher specificity, correlate better with exposure to *M. tuberculosis* and have less cross-reactivity with the BCG vaccine and environmental mycobacteria. However, other studies have shown poor concordance with TST. There is no good evidence for the use of these tests in young children at present. Recent guidelines do not recommend the routine use of these tests and highlight the need for future research comparing TST and IFN-γ tests in young children [12].

Table 1 ***Recommended preventative treatment for children with no evidence of TB disease***

1–15 years	*No previous BCG* *Mantoux ≥6mm* *Previous BCG* *Mantoux ≥15mm*	*6 months isoniazid* *or* *3 months isoniazid and rifampicin#* *Standard preventative treatment*
4 weeks–2 years	*Isoniazid started pending Mantoux result* *No previous BCG* *Mantoux ≥6mm* *Mantoux <6mm* *Previous BCG* *Mantoux ≥15mm* *Mantoux <15mm*	 *Standard preventative treatment* *Isoniazid continued until repeat testing after 6 weeks. If Mantoux remains <6mm treatment stopped and given BCG* *If repeat test ≥6mm* *Standard preventative treatment* *Standard preventative treatment* *Repeat Mantoux after 6 weeks, if still <15mm no further action* *If repeat Mantoux ≥15mm or increased by >5mm then standard preventative treatment*
Neonates < 4 weeks	*Isoniazid started and continued until Mantoux at 3 months* *Mantoux <6mm* *Mantoux ≥6mm*	 *Stop isoniazid and give BCG* *Standard preventative treatment*
HIV-positive children, any age	*Mantoux testing may be unreliable*	*6 months isoniazid* *Increased rates of stopping treatment due to side-effects when combination therapies were used in this group*

#: American guidelines suggest 4 months of rifampicin and isonaizid or 9 months of isoniazid. Table modified from [12].

Is there evidence of TB disease?

Children who have TB may develop symptoms, have abnormal signs on examination or on chest radiography and, in a minority, there may be bacteriological confirmation of disease.

Clinical presentations

In endemic areas, the clinical diagnosis of TB represents a major challenge. Symptoms traditionally associated with TB, such as cough, breathlessness, weight loss, fatigue, fever and night sweats, are all common in the community and frequently reported in children without TB [16]. In one recent study from South Africa, 50% of children with newly diagnosed TB were asymptomatic. However, the natural history of TB in children is that progressive disease is associated with the development of symptoms. A persistent,

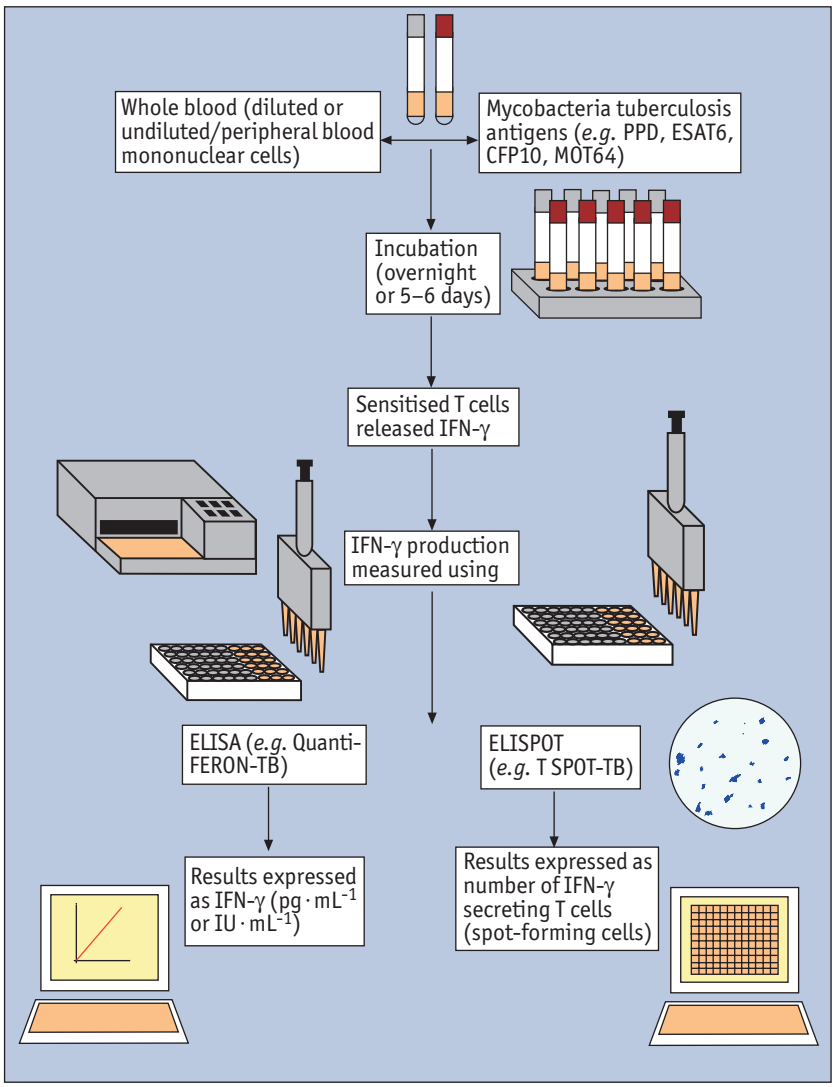


Figure 6

Flow diagram outlining sample processing in the QuantiFERON Test and the ELISPOT test.

nonremitting cough and fatigue of recent onset have been shown to be sensitive and specific features in children with TB [17]. The combined presence of three well-defined symptoms at presentation (persistent, nonremitting cough of >2 weeks duration; objective weight loss (documented failure to thrive) during the preceding 3 months; and reported fatigue) has been shown to provide good diagnostic accuracy in HIV-uninfected children ≥3 years of age, with clinical follow-up providing additional value. This approach performed less well in children <3 years or children who were HIV-infected [18].

In nonendemic areas, where TB is often very uncommon, remembering to think of TB in children as a possible diagnosis is often the major issue.

Although there are no specific, characteristic features of pulmonary TB on clinical examination, some features, such as gibbus of recent onset, are highly suggestive of extrapulmonary infection.

Radiology

The radiological findings in TB are varied and neither specific nor diagnostic of TB except in miliary TB. In some studies, up to 20% of cases of TB were missed on chest radiography [10].

Hilar adenopathy on chest radiography is the commonest disease manifestation in children with TB and is usually regarded as the hallmark of recent primary TB. From the natural history, active TB would be marked by the onset of persistent symptoms, whereas the absence of symptoms would indicate containment of the organism and would be in keeping with recent primary disease. However, by convention, asymptomatic hilar adenopathy in a child is currently treated as active TB disease.

Studies have shown poor adreement between those reporting chest radiography in detecting hilar adenopathy. Lateral views and computed tomography (CT) have been used to try to improve the accuracy of diagnosis. Lateral views have not been shown to improve the results [19]. CT is very sensitive, probably overdiagnoses hilar adenopathy and is not currently recommended in the diagnosis of TB in asymptomatic, immunocompetent children exposed to TB [7].

Bacteriology

It is good practice to try to confirm the diagnosis of TB using whatever specimens and laboratory facilities are available. Direct microscopy and, if possible, culture of any specimens is important.

Bacteriological confirmation is difficult in children, as there are fewer organisms and obtaining clinical samples can often be difficult. Sputum is smear-positive in ≤10–15% of those with probable TB.

Culture is the only way to differentiate *M. tuberculosis* from other mycobacteria and is particularly important if drug-resistance is suspected. Unfortunately, culture is positive in <40% of children with probable TB.

Culture using solid media takes 4–6 weeks. Treatment is usually started based on a presumptive diagnosis of TB without waiting for the culture result. Rapid liquid-based cultures (*e.g.* BACTEC) are available and can give results in 1–3 weeks. However, these are expensive and require specialist equipment and training, making them unavailable in many centres, particularly in the developing world.

Appropriate samples for bacteriology include sputum, gastric aspirates and biopsied nodes or fine-needle aspirates.

Sputum expectoration

Older children or adolescents suspected of having pulmonary TB may be able to produce sputum spontaneously. This is more likely to be positive than other samples [12]. Three specimens are recommended: one on the spot, an early morning specimen and a second on the spot at follow-up.

Gastric washings

Gastric aspiration using a nasogastric feeding tube can be performed on young children who are unable or unwilling to produce sputum. Samples are collected on each of three consecutive mornings. This usually requires admission to hospital to obtain samples following an overnight fast of 8–10 hours. It is important that the correct technique is used and that the timing and processing of the sample are standardised. Even under optimal circumstances <50% of samples will be positive in those with TB [20]. The main disadvantage is that gastric aspirates are uncomfortable, involve fasting and require repeated attendance or admission to hospital. Some studies have shown comparable results in the community, with suitable support, avoiding the need for admission [21].

Nasopharyngeal aspirates can be used as an alternative. The procedure can be done at any time of the day, does not require admission and is inexpensive. One study comparing the two methods showed a yield of 30% in nasopharyngeal aspirate compared with 38% in gastric aspirates in the same unit [7].

Induced sputum

Recent studies have found that sputum induction is safe and well tolerated in children. It can be carried out as an outpatient even in very young children. Several studies have shown it to be superior to gastric lavage, with twice as many positive cases from one specimen of sputum than a single gastric aspirate [22]. One specimen of induced sputum was equivalent to three gastric aspirates. Careful environmental and infection control measures are required because of the potential to induce an infectious aerosol. Bronchospasm was the only significant adverse effect and can be prevented by nebulising with salbutamol prior to the procedure. Recent guidelines, such as those produced by the UK's National Institute of Health and Clinical Excellence (NICE), now recommend induced sputum rather than gastric aspirates if the facilities are available.

One recent study from Peru described a test whereby a capsule is swallowed and the string attached to the capsule is taped to the cheek. The capsule is then withdrawn over a 5-second period and sent for culture along with the string. The yield was higher than induced sputum and was less risky to health workers. Further assessment of the technique is required in children before it can be recommended [23].

Bronchoalveolar lavage

Bronchoscopy may be useful in selected cases to look for airway compression or endobronchial TB, which may be present in up to 60% of children with TB disease. However in terms of bacteriology, specimens obtained by bronchoalveolar lavage have an even lower yield than gastric aspirates [20].

HIV testing

In areas with a high prevalence of HIV infection, where TB and HIV are likely to co-exist, HIV testing and counselling are indicated for all TB patients as part of their routine management. In other areas, those at high risk of HIV exposure should be counselled and tested.

Other techniques

Although new diagnostic methods, PCR-based detection systems and DNA fingerprinting, are available and in development, they have not yet been extensively validated in children. The expense and the facilities required are likely to preclude their use in many areas with endemic TB.

The need for new diagnostic tests for TB has been repeatedly highlighted. It has been estimated that a rapid diagnostic test, which required no laboratory infrastructure and had 97% sensitivity, ≥85% sensitivity and a result unaffected by HIV status could save ~400,000 lives annually.

Treatment

Prior to the introduction of effective drugs, mortality from untreated TB approached 50%. In most cases TB is now completely curable if the correct drugs are taken for the correct period of time. There are barriers to effective treatment, however, as multiple drugs are required over a prolonged period. This is of major concern as worldwide drug resistance rates are increasing and no new first-line drugs have become available in the past 30 years.

Treatment is recommended for three main categories of children:

- Children at high risk of progression to TB dis-ease who have been exposed to smear-positive TB but have no evidence of TB infection or disease. Young children (<3 years), neonates and HIV-positive children are included in this high-risk group. This is sometimes referred to as chemoprophylaxis.
- Children exposed to smear-positive disease where there is evidence of infection but not of disease, *i.e.* latent infection.

  These two categories are given preventative treatment.
- Children with clinical or radiological evidence of TB disease, who are given curative treatment.

When considering either preventative or curative therapy, a number of differences between TB in adults and children are important in determining treatment.

1. TB in children is usually paucibacillary, as cavitating disase is rare in those under 13 years

M. tuberculosis replicates slowly and can remain dormant for prolonged periods. The organisms are only killed during replication, which occurs in organisms that are metabolically active. Bactericidal drugs (isoniazid and rifampicin) are important at the beginning of treatment to ensure a rapid reduction in organism load, preventing disease progression, and thus reducing the risks of transmission and the development of resistance. Sterilising drugs (rifampicin and pyrazinamide) are important in ensuring effective eradication of dormant and intermittently dividing organisms, thereby preventing relapse. A combination of agents is therefore required.

The number of infecting organisms is important in determining how many drugs are required for effective cure. Resistance occurs because of mutations in the organisms. These occur randomly but at a fairly low rate. If there are fewer organisms, resistant mutations are less likely.

In general, a good guiding principle for antimicrobial treatment is "more bugs require more drugs".

In TB infection, the organism load is small and therefore drug-resistant mutations are very rare – hence 1–2 drugs are usually effective.

In TB disease, the number of organisms is greater so a combination of ≥3 drugs is needed to achieve cure [24]. Increasing rates of drug resistance (there is now ~6% resistance to isoniazid in the UK, for example, and rates are much higher in other areas of the world) mean that four drugs are now recommended as standard therapy.

2. Children are more likely to develop extrapulmonary disease, including TB meningitis and miliary disease, than adults

Drug regimens should therefore include drugs which cross the blood-brain barrier and offer good penetration to other tissues.

3. Children may require higher relative doses of treatment

Young children eliminate isoniazid faster than older children, and children as a group eliminate it faster than adults. Some guidelines [25] therefore recommend a higher dose (10–15 mg per kg) rather than the 5 mg per kg isoniazid suggested in UK and WHO guidelines [26].

4. Children tolerate TB drugs better than adults

Most children tolerate TB medications well. A transient rise in liver transaminases is common, but significant liver toxicity is rare [21, 24]. Children who have severe disease, are malnourished or are taking other treatment such as anticonvulsants are more likely to develop significant hepatotoxicity. Ethambutol was previously avoided in young children due to concerns about ocular toxicity but studies have shown this side-effect to be very rare in children.

5. Available drug preparations are not always suitable for children

The commercially available forms (tablets and combination drugs) of many drugs are designed for adults. Many children with TB, and in particular TB infection, are relatively well and treatment is long, so if the drugs are difficult to administer or the drugs are not well tolerated, parents or patients may stop treatment.

Liquid forms or crushable tablets are preferable for children. Some of the liquid formulations have a short shelf-life and communication with the dispensing pharmacist regarding the length of treatment is important to ensure uninterrupted treatment. The combination medications recommended for adults often use dose ratios and doses which make them unsuitable for many children.

Preventative treatment

Chemoprophylaxis refers to preventative treatment given to children who have been exposed to a case of TB without proof of infection, whereas treatment of latent infection implies that infection (documented by a positive TST) has been documented.

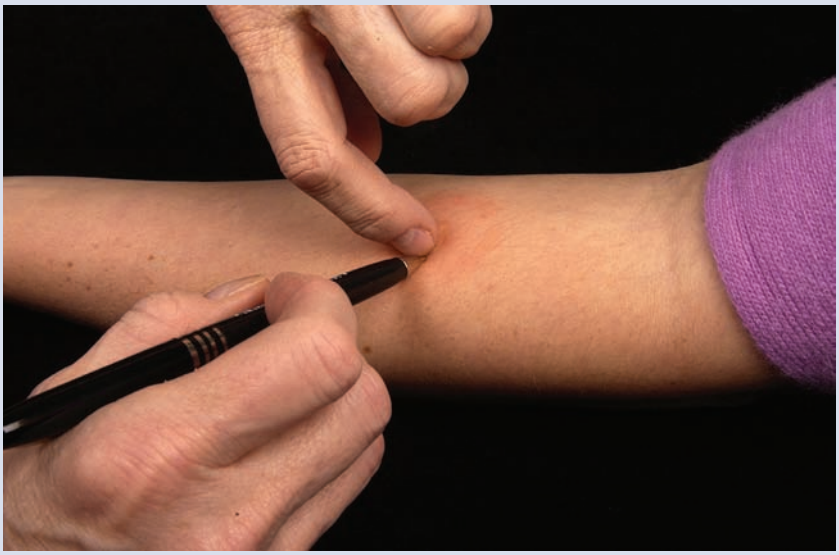
In many areas where TB is endemic, there are insufficient resources to follow the WHO guidance on active screening and treatment of young children with a smear-positive household contact. In these areas, preventative treatment is reserved for those at the highest risk.

Isoniazid for 6–9 months is the best-studied chemoprophylatic agent. This has been shown to reduce the risk of TB by two-thirds and by as much as 90% if there is good adherence to treatment.

The main treatment problem is poor adherence. There are few paediatric studies, but one shows that although adherence to curative treatment in the group was good (82.6%), only 44.2% of those prescribed preventative treatment adhered to it [27]. There is some evidence that shorter courses of treatment (3 months of isoniazid and rifampicin) are as effective and have higher rates of adherence (69.9%, compared with only 27.6% in the group given 6 months of isoniazid alone). Adherence might also be improved by using supervised preventative treatment therapy.

Other preventative strategies: BCG vaccination

BCG vaccination is the most widely used preventative strategy and has been in use since the 1920s. BCG is a live-attenuated vaccine derived from *M. bovis*. Studies have shown highly variable protection against TB. Most observers agree that it offers significant protection against the most severe forms of disseminated disease, such as miliary TB or TB meningitis, in very young children but less protection against adult-type pulmonary TB. Data from UK studies suggest that efficacy wanes from 80% initially to 59% 10–15 years after vaccination. A recent study has also shown that BCG was associated with a significant reduction (24%) in the risk of infection in those immunised children exposed to TB compared with children with no previous BCG. This reduction in risk appeared to be greatest in children who had scarring following their BCG [28].



A physician measures the result of a TST. Image ©Greg Knobloch.

In countries with a high prevalence of TB, BCG is recommended by the WHO for neonates as soon as possible after birth. In low-prevalence countries, the variable protection offered by BCG and the changing epidemiology of TB has led many to concentrate on targeting BCG to those children most likely to benefit [29]. Other countries, including the USA, do not recommend BCG use because of its uncertain efficacy and the need to maintain the use of the TST for screening.

The immune response to BCG vaccination may be reduced in HIV-infected individuals and the conversion to a positive TST after BCG is less frequent. Although there have been several reports of disseminated BCG disease in HIV-infected individuals, BCG vaccination appears to be safe in the vast majority of cases. The WHO recommends that in countries with a high TB prevalence, the benefits of vaccination outweigh the risks.

The development of new vaccines against pulmonary TB is an important global challenge. Humans are the only reservoir of *M. tuberculosis,* so a more effective vaccine could potentially eradicate the disease.

Curative treatment

When treating TB disease, the bacterial load is greater and the organisms may be distributed

Table 2 Recommended drugs and dosages for children

	Daily		Intermittent 3 times per week	
	mg per kg body weight	Maximum mg	mg per kg body weight	Maximum mg
Isoniazid	5–15	300	20–30	900
Rifampicin	10–20	600	10–20	600
Pyrazinamide	20–40	2–3g	50–70	2–3g
Ethambutol	15–25	2–5g	40–50	2–5g

Data taken from [1, 7, 12, 25].

differently to the well-contained, small number present in TB infection. In disseminated disease, it is important to include drugs which penetrate the central nervous system.

Drug regimens, therefore, involve 3–4 drugs depending on the risk of resistance. The recent UK NICE Guideline, the WHO National TB Programme and the International Standards for Care [1, 10, 12] all recommend four drugs as routine in children. The American guidelines [25] recommend three drugs as standard unless there is an increased risk of resistance or adult-type disease.

Treatment is divided into two phases. The intensive phase lasts for the first 2 months and aims to rapidly reduce the organism load, improve symptoms and prevent the development of resistance. During this phase, four drugs are generally recommended (pyrazinamide, ethambutol, rifampicin and isoniazid; table 2). During the next 4 months (the continuation phase), two drugs (isoniazid and rifampicin) are sufficient to eradicate the disease. Several trials show excellent outcomes with this regimen: 95% of patients are completely cured, 99% show significant improvement and clinically important adverse reactions occur in <2% of children.

However, a recent systematic review shows successful completion of therapy in just under 75% of cases in Europe, with some countries reporting success rates as low as 56% [30]. These figures fall well below the WHO target of 85% required to improve control of TB.

Many studies examining nonadherence to therapy in chronic disease, show that 40–50% of patients have significant problems in correctly taking their treatment. Stopping and starting antituberculous therapy allows cycles of killing of organisms followed by regrowth, favouring the growth of drug-resistant, mutant organisms. Such is the concern regarding poor adherence to therapy and its impact on both the patient and the wider public that, almost uniquely, recent guidelines suggest that responsibility for ensuring completion of therapy lies with the provider of treatment rather than the patient [1, 10, 12, 25].

Strategies to improve adherence and completion of therapy include intermittent therapy and DOTS. Although there is some evidence of improved outcomes, neither is a panacea and co-operation is still required. Free prescriptions, combination therapy where possible and the use of patient-held treatment cards can also aid successful completion of treatment.

Daily *versus* intermittent therapy

Intermittent (3 times per week) therapy using higher doses of drugs is as effective as daily therapy, and is recommended for patients undergoing supervised therapy in both the UK and WHO guidelines. Twice-weekly regimens are no longer recommended. Although intermittent therapy is easier to supervise, it may involve large numbers of tablets or volumes of unpleasant liquids, which may be harder for children to tolerate, adversely affecting adherence and completion of therapy.

Directly observed therapy

There is varying evidence to support the use of DOTS. A recent Cochrane systematic review showed no difference in outcomes between patients allocated to DOTS and those self-administering treatment. Other studies, however, have shown benefit. It is likely that the difference between studies depends on factors other than supervising the taking of medication. Patient-centred DOTS programmes that offer support (financial incentives, help with housing, *etc.*) and increased contact with health professionals have been shown to be more effective. These are often referred to as enhanced DOTS.

The WHO and US guidelines recommend DOTS in all children with TB disease. The UK guidelines do not recommend a universal DOTS approach but suggest a risk assessment at the start of treatment and the use of DOTS if risk factors such as adverse social circumstances (homelessness, mental illness or substance abuse in the family), a previous history of poor adherence to therapy or nonattendance at clinic are identified.

Monitoring

The aims of monitoring during therapy are: to assure adherence to therapy, to monitor for side-effects and to ensure that the disease is coming under control, reflected in symptom resolution and weight gain. A child who is not responding to anti-TB treatment needs a careful assessment

to identify problems with adherence, complications of TB or drug-resistance.

The use of follow-up chest radiography is controversial. The WHO guidance suggests follow-up radiography is not routinely required [1]. Others suggest radiography at the start of treatment, 1–2 months into treatment and at the end of treatment is sufficient unless there are concerns that the disease is not improving. Two-thirds of children will have persistently abnormal, but improved, chest radiography at the end of treatment. This is not an indication to continue treatment providing the child is well, but follow-up should continue until the radiography is either normal or stable.

Pyridoxine

Pyridoxine to counteract the peripheral neuropathy that can occur with isoniazid is not required in most children. It is indicated in some groups including HIV-positive children, malnourished, breast-fed or premature infants and pregnant or breast-feeding adolescent girls.

The use of corticosteroids

Steroids are used in conjunction with anti-TB therapy for the management of some complicated forms of TB, *e.g.* TB meningitis, complications of airway obstruction by TB lymph glands and pericardial TB. In TB meningitis, steroids have been shown to reduce mortality and long-term sequelae. Dose regimens vary, but 2 mg per kg prednisolone for 4 weeks with subsequent tapering over 1–2 weeks is suggested.

Coexistent HIV infection

It is estimated that >500,000 children become infected with HIV each year, most commonly (90%) through perinatal transmission, 95% of cases are in developing countries. TB is the most common opportunistic infection in HIV-infected people worldwide. This has also led to an increase in TB in many countries, with the incidence of TB among patients with AIDS being 500 times that in the general population. Latent infection has a much higher risk in these patients, with progression to TB disease in 7–8% of HIV-infected patients per year, compared with a lifetime risk of 10% in the general population.

The diagnosis of TB can be difficult in HIV-infected patients as the TST is less likely to be positive and any radiological changes caused by TB are difficult to distinguish from other lung disease found in HIV. In nearly two-thirds of HIV patients, TB is not confirmed and it may be necessary to treat on suspicion of disease with a trial of treatment.

TB in this group of children tends to be more severe and progress more rapidly. There may also be an increased risk of pulmonary cavitation and extrapulmonary disease. There is some evidence that the response to standard short-course treatment may achieve lower cure- and higher death-rates. The treatment also tends to be less well tolerated. Detailed discussion of management of TB in this group of patients and co-treatment with anti-retroviral therapy is beyond the scope of this article.

A TB clinic pharmacy ©Lung Health Image Library/Pierre Virot

Conclusion

TB in children is formally recognised as a neglected area.

Patterns of disease in the world are changing. Increasing drug resistance and the emergence of highly resistant organisms (XDR-TB) in some countries, particularly in eastern Europe, threaten TB control efforts. Central European countries, several of which border countries with high TB prevalence, should not be complacent. These factors and increasing movement between countries within Europe emphasise the need for enhanced surveillance to prevent re-emergence of TB.

The management of TB in particular groups, including those with coexistent HIV or drug resistance are beyond the scope of this review and would be interesting topics for future articles.

Strategies exist to address some of the challenges. Unfortunately, the hopes engendered by new diagnostic and therapeutic methods are tempered by the reality that most of the world's children with TB are excluded from them by poverty and poor medical infrastructure.

Educational questions

1. Which of the following statements is not true with respect to *Mycobacterium tuberculosis*?
   a) One-third of the world's population is estimated to be infected.
   b) Children with TB are markers of recent disease transmission from an infectious adult.
   c) Of children who become infected with TB, only 5–10% develop TB disease.
   d) Hilar adenopathy is the most common disease manifestation in children with recent primary infection.
2. Which of the following statements about diagnosis is/are true?
   a) Bronchoalveolar lavage specimens obtained at bronchoscopy are more likely to be positive than gastric aspirates.
   b) Chest radiographic changes are diagnostic in TB disease.
   c) Interferon-γ tests are less affected by previous BCG than TST.
   d) A negative TST does not exclude TB.
3. Are the following statements about TB prevention true or false?
   a) Children in close contact with a sputum-positive case should be offered immediate BCG.
   b) BCG is no more than 50% effective in preventing pulmonary tuberculosis.
   c) BCG is recommended for all school-aged children.
   d) Children with TB are infectious and should be isolated and kept off school when diagnosed.
4. Which of the following statements about treatment are true?
   a) Twice-weekly supervised treatment regimens are recommended as being as effective as standard daily regimens.
   b) Children may require higher doses of medication per body weight than adults.
   c) The risk of ocular toxicity is very low in children given ethambutol.
   d) There is clear evidence that DOTS has been shown to be more effective than self-administered treatment.

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Suggested answers

1. c
2. c and d
3. All the statements are false
4. b and c