Seminar

Tuberculosis

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Among communicable diseases, tuberculosis is the second leading cause of death worldwide, killing nearly 2 million people each year. Most cases are in less-developed countries; over the past decade, tuberculosis incidence has increased in Africa, mainly as a result of the burden of HIV infection, and in the former Soviet Union, owing to socioeconomic change and decline of the health-care system. Definitive diagnosis of tuberculosis remains based on culture for *Mycobacterium tuberculosis*, but rapid diagnosis of infectious tuberculosis by simple sputum smear for acid-fast bacilli remains an important tool, and more rapid molecular techniques hold promise. Treatment with several drugs for 6 months or more can cure more than 95% of patients; direct observation of treatment, a component of the recommended five-element DOTS strategy, is judged to be the standard of care by most authorities, but currently only a third of cases worldwide are treated under this approach. Systematic monitoring of case detection and treatment outcomes is essential to effective service delivery. The proportion of patients diagnosed and treated effectively has increased greatly over the past decade but is still far short of global targets. Efforts to develop more effective tuberculosis vaccines are under way, but even if one is identified, more effective treatment systems are likely to be required for decades. Other modes of tuberculosis control, such as treatment of latent infection, have a potentially important role in some contexts. Until tuberculosis is controlled worldwide, it will continue to be a major killer in less-developed countries and a constant threat in most of the more-developed countries.

Tuberculosis has probably killed 100 million people over the past 100 years,[1] although a cure was available for the second half of the 20th century. This review summarises the current status of tuberculosis epidemiology, pathophysiology, diagnosis, treatment, and control. Although most cases of tuberculosis occur in less-developed countries, this review is relevant to both more-developed and less-developed countries.

Epidemiology

Tuberculosis is the world's second commonest cause of death from infectious disease, after HIV/AIDS. There were an estimated 8–9 million new cases of tuberculosis in 2000, fewer than half of which were reported; 3–4 million cases were sputum-smear positive, the most infectious form of the disease.[2] Most cases (5–6 million) are in people aged 15–49 years. Sub-Saharan Africa has the highest incidence rate (290 per 100 000 population), but the most populous countries of Asia have the largest numbers of cases: India, China, Indonesia, Bangladesh, and Pakistan together account for more than half the global burden. 80% of new cases occur in 22 high-burden countries (figure 1).

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The global tuberculosis caseload appears to be growing slowly. Case numbers have declined more or less steadily in western and central Europe, North and South America, and the Middle East. By contrast, there have been striking increases in countries of the former Soviet Union and in sub-Saharan Africa (figure 2).[3]

Tuberculosis rates have increased in the former Soviet Union because of economic decline and the general failure of tuberculosis control and other health services since 1991.[4] Periodic surveys have shown that more than 10% of new tuberculosis cases in Estonia, Latvia, and some parts of Russia are multi-drug resistant[5]—ie, resistant to at least isoniazid and rifampicin, the two most effective antituberculosis drugs. However, resistance is a byproduct of tuberculosis resurgence in these countries, not the primary cause of it.

HIV infection accounts for much of the recent increase in the global tuberculosis burden.[2] Worldwide, an estimated 11% of new adult tuberculosis cases in 2000 were infected with HIV, with wide variations among regions: 38% in sub-Saharan Africa, 14% in more

Search strategy and selection criteria

We searched PubMed/MEDLINE for articles with tuberculosis as major topic, and epidemiology, pathophysiology, diagnosis, treatment, or control as secondary topics. The Cochrane database was searched for reviews of tuberculosis. We also examined the websites and publications of the WHO, International Union Against Tuberculosis and Lung Disease, British Thoracic Society, American Thoracic Society, and US Centers for Disease Control and Prevention, as well as major current tuberculosis textbooks. Many other papers were found in the reference lists of articles identified through initial searches. The databases and publications were searched between April, 2002, and March, 2003. We did not limit the search to articles published in English, nor specifically to particular dates.

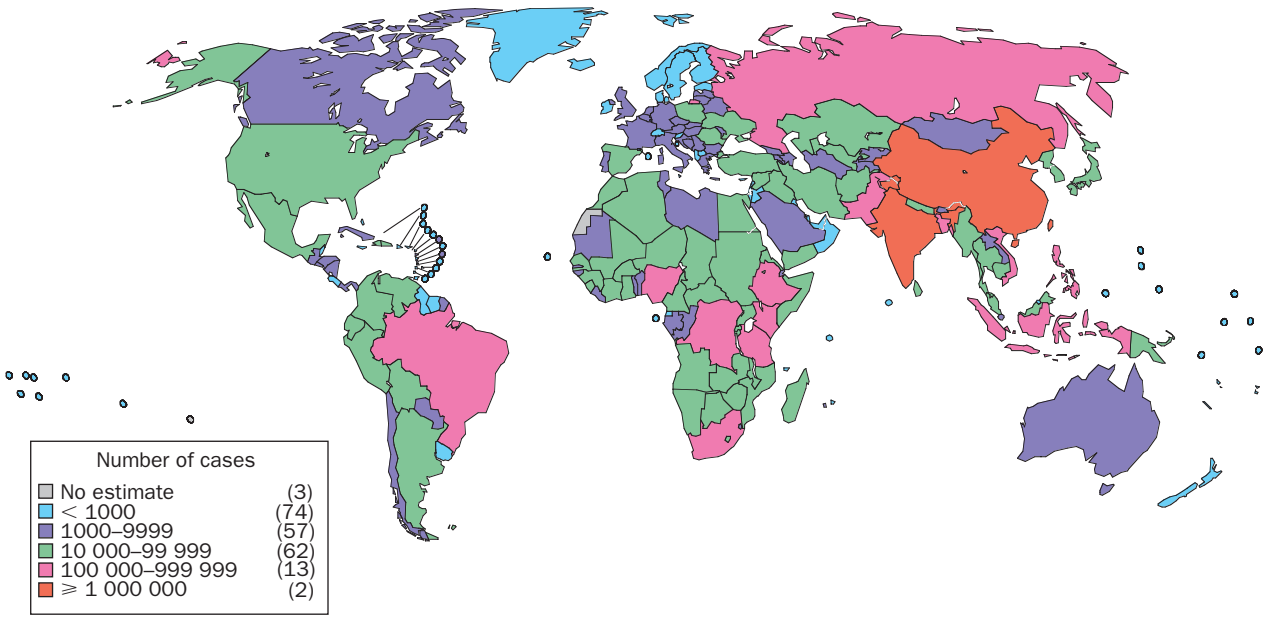

Figure 1: **Estimated number of new tuberculosis cases by country, 2001**

developed countries, and 1% in the Western Pacific Region. Rates of HIV infection among patients with tuberculosis have so far remained below 1% in Bangladesh, China, and Indonesia. The increase in tuberculosis incidence in Africa is strongly associated with the prevalence of HIV infection.[6] Rates of HIV infection among tuberculosis patients are correspondingly high, exceeding 60% in Botswana, South Africa, Zambia, and Zimbabwe. About two million people died of tuberculosis in 2000; about 13% of these people were also infected with HIV.[2]

Pathophysiology

Tuberculosis is spread by airborne droplet nuclei, which are particles of 1–5 μm in diameter that contain *Mycobacterium tuberculosis*. Because of their small size, the particles can remain airborne for minutes to hours after expectoration by people with pulmonary or laryngeal tuberculosis during coughing, sneezing, singing, or talking.[7–9] The infectious droplet nuclei are inhaled and lodge in the alveoli in the distal airways. *M tuberculosis* is then taken up by alveolar macrophages, initiating a cascade of events that results in either successful containment of the infection or progression to active disease (primary progressive tuberculosis). Although the risk of development of active disease varies according to time since infection, age, and host immunity, the estimated lifetime risk of disease for a newly infected young child is 10%, with roughly half of that risk occurring in the first 2 years after infection.[10,11]

After being ingested by alveolar macrophages, *M tuberculosis* replicates slowly but continuously and spreads via the lymphatic system to the hilar lymph nodes. In most infected individuals, cell-mediated immunity develops 2–8 weeks after infection. Activated T lymphocytes and macrophages form granulomas that limit further replication and spread of the organism.[12] *M tuberculosis* is in the centre of the characteristically necrotic (caseating or cheese-like) granulomas, but it is usually not viable. Unless there is a subsequent defect in cell-mediated immunity, the infection generally remains contained and active disease may never occur.

The development of cell-mediated immunity against *M tuberculosis* is associated with the development of a positive result in the tuberculin skin test. At the cellular level, an effective host immune response occurs as follows. Alveolar macrophages infected with *M tuberculosis* interact with T lymphocytes via several important cytokines. The infected macrophage releases interleukins 12 and 18, which stimulate T lymphocytes (predominantly CD4-

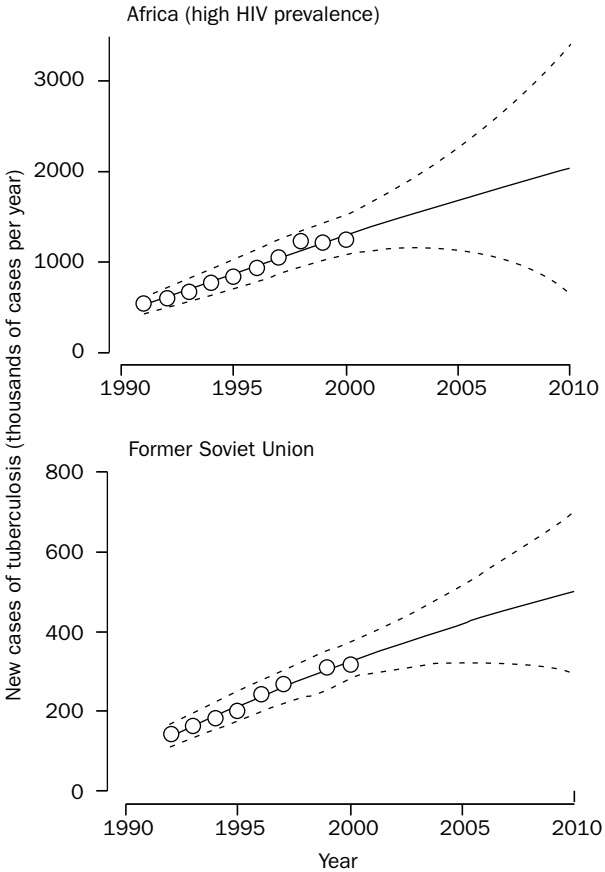

Figure 2: **Trends and projections in numbers of tuberculosis cases to 2010 for countries of eastern and southern Africa with high HIV prevalence, and in the former Soviet Union**
Broken lines indicate 95% CI. Adapted with permission from WHO global tuberculosis report 2003, based on trends in notification rates.[3]

positive T lymphocytes) to release interferon γ.[13,14] This cytokine, in turn, stimulates the phagocytosis of *M tuberculosis* in the macrophage.

Interferon γ does not directly stimulate the killing of *M tuberculosis* by the macrophage, at least partly because the organism inhibits the cytokine's transcriptional responses.[15] Interferon γ is, however, crucial for the control of *M tuberculosis* infection,[16] and it also stimulates the macrophage to release tumour necrosis factor α, which is important in granuloma formation and control of the extent of infection.[17,18] The T-lymphocyte response is antigen specific and is influenced by the major histocompatibility complex.[12,19] Although several *M tuberculosis* antigens have been identified, none confer protective immunity and they are thus unsuitable for a vaccine.

When the host immune response cannot contain the replication of *M tuberculosis* associated with initial infection, active disease occurs. This development is most common in children under 5 years old and adults with advanced immunosuppression (eg, AIDS). This primary progressive disease can manifest in almost any organ system, but it occurs most frequently in the parenchyma of the mid and lower lung, in the hilar lymph nodes, or as generalised lesions resulting from haematogenous dissemination.[1]

Although an effective host immune response can initially contain *M tuberculosis* infection, several factors can trigger subsequent development of active disease from reactivation of remote infection. HIV is the greatest single risk factor for progression to active disease in adults. Other medical conditions that can also compromise the immune system and predispose to development of active disease include poorly controlled diabetes mellitus, renal failure, underlying malignant disease, chemotherapy, extensive corticosteroid therapy, malnutrition, and deficiency of vitamin D or A.[20–22] Defects in the production of interferon γ[13,23] or tumour necrosis factor α,[24,25] as well as in the interferon-γ receptor[26] and interleukin-12 receptor β1, have also been described.[27]

Genetic predisposition

Several studies have suggested that some patients have a genetic predisposition to tuberculosis. This idea has arisen from studies among monozygotic and dizygotic twins[28] and in an assessment of tuberculosis risk according to ancestral history.[29] Population-based studies have found an association between tuberculosis and some HLA alleles, as well as polymorphisms in the genes for natural resistance-associated macrophage protein (NRAMP1), the vitamin D receptor, and interleukin 1.[30–35] Although the functional importance of most of these polymorphisms is unclear, *NRAMP1* polymorphisms could influence tuberculosis susceptibility by regulation of interleukin 10.[36] Associations between genetic polymorphisms and tuberculosis susceptibility differ according to ethnic origin,[37] but the extent to which genetic polymorphisms contribute to the global tuberculosis burden is unclear because of the great difficulty of separating lifelong environmental influences from genetic predisposition.

Clinical manifestations

The most common clinical manifestation of tuberculosis is pulmonary disease. Extrapulmonary tuberculosis accounts for about 20% of disease in HIV-seronegative people but is more common in HIV-seropositive individuals.[38] Among people not infected with HIV, extrapulmonary disease, particularly lymphatic tuberculosis, is particularly common in women and young children.[39,40]

Pleural tuberculosis occurs as a result of either primary progressive *M tuberculosis* infection or reactivation of latent infection. A chest radiograph generally reveals a unilateral pleural effusion. Unlike other clinical manifestations of tuberculosis, pleural disease probably represents an increased, rather than diminished, immune response. In fact, primary serofibrinous pleural effusion resolves without treatment in up to 90% of cases; however, if untreated, nearly two-thirds of patients will subsequently have relapses with tuberculosis at other organ sites.[41]

The most serious clinical manifestation of tuberculosis is involvement of the central nervous system. Such involvement can include inflammation of the meninges, as well as space-occupying lesions (tuberculomas) of the brain. The clinical manifestations are due to the presence of *M tuberculosis* as well as the inflammatory host immune response. Children under 5 years of age and HIV-infected individuals are at increased risk of tuberculous meningitis,[42,43] which can present clinically as chronic meningitis, with headache, fever, and changed mental status. Neurological manifestations can include cranial-nerve palsies and motor, sensory, and cerebellar defects, according to the location of the tuberculomas; seizures can also occur. Meningitis is fatal in almost all cases without chemotherapy, and prompt identification and treatment are essential to prevent serious neurological sequelae.

Tuberculosis can affect any bone or joint, but the spine (ie, Pott's disease) is the most common bony structure involved. In the spine, the most common location is the thoracic section. Vertebral-body involvement can be followed by disease of an adjacent intervertebral disc.[1]

Genitourinary tuberculosis (including involvement of the renal and male and female genital tracts) is uncommon and is difficult to distinguish from other infections of the genitourinary tract. In men, manifestations include those of prostatitis or prostate enlargement, epididymitis, and orchitis, but disease can also present as a painless scrotal mass. Urine analysis may show red or white blood cells, or both, with a negative urine culture for bacteria (sterile pyuria). In women, genitourinary tuberculosis is an important cause of infertility in areas with high tuberculosis incidence.[44]

Disseminated tuberculosis is defined as involvement of many organs simultaneously and can occur as a result of primary progressive disease or reactivation of latent infection. The clinical manifestation of pulmonary involvement is a miliary (millet seed) pattern rather than an infiltrate in most cases, but not all patients with disseminated disease have pulmonary involvement. Mortality is high despite chemotherapy and may be related to delays in diagnosis and other commonly present underlying medical conditions.[39]

Diagnosis

Active disease

Criteria for the diagnosis of active tuberculosis vary according to the setting. Patients with persistent cough (eg, lasting longer than 2 weeks) should be assessed for tuberculosis.[45,46] Other common symptoms include fever, night sweats, weight loss, shortness of breath, haemoptysis, and chest pain.[47] Among children, important diagnostic clues are a history of previous exposure to an individual with tuberculosis or evidence of tuberculosis infection (eg, a positive tuberculin skin test). To improve the diagnostic yield in children, diagnostic algorithms and point scoring systems are often used, particularly in less-developed countries.[48]

Tests for the diagnosis of tuberculosis vary in sensitivity, specificity, speed, and cost. Even if additional tests are done, however, culture is required for definite diagnosis and is essential for drug-susceptibility testing. The sputum smear is an inexpensive test that can be carried out rapidly; fluorochrome, Ziehl-Neelsen, and Kinyoun staining methods can be used. The International Union Against Tuberculosis and Lung Disease (IUATLD) and WHO recommend the Ziehl-Neelsen method under most circumstances.[46,49] Although the smear is positive in only 50–80% of individuals with culture-confirmed pulmonary tuberculosis, cases with organisms on the smear are more infectious than smear-negative cases and have higher case-fatality rates.[50,51] Nonetheless, smear-negative disease accounts for 15–20% of *M tuberculosis* transmission.[51,52] In countries with a high prevalence of tuberculosis, a positive direct smear is due to *M tuberculosis* in more than 95% of patients suspected of having tuberculosis;[53] routine cultures are generally neither practicable nor necessary for disease control. Non-tuberculous mycobacteria, particularly in HIV-infected patients, tend to be present in much lower concentrations and are therefore rarely seen on a direct sputum smear. Concentrated smears (ie, those made from samples that have been decontaminated, liquefied, and centrifuged) may be more sensitive and are routinely used in laboratories that also routinely culture all specimens, because decontaminated and concentrated specimens are needed for culturing.[49,54] In less-developed countries, a diagnostic algorithm for sputum-smear-negative patients is commonly used, based on response to antibiotics and results of chest radiography.

Although the organism can take 6 weeks or longer to grow on solid culture media (eg, the egg-based Lowenstein-Jensen medium or the agar-based Middlebrook 7H10 or 7H11), growth generally occurs within 7–21 days with liquid culture media.[55] Ideally, when cultures are done, both solid and liquid culture media should be used, because the former allow examination of colony morphology and the identification of mixed cultures, and the latter enable more rapid diagnosis.

Radiographic findings suggesting tuberculosis include upper-lobe infiltrates, cavitary infiltrates, and hilar or paratracheal adenopathy. In many patients with primary progressive disease and those with HIV infection, radiographic findings are more subtle and can include lower-lobe infiltrates or a miliary pattern. HIV-infected patients, particularly those late in the course of HIV infection, generally experience greater weight loss and fever but are less likely to have cavitary disease and positive smears for acid-fast bacilli[56] than those not infected with HIV, and in one study, 8% of HIV-infected patients with pulmonary tuberculosis had normal chest radiographs.[57]

About 15–20% of adults with tuberculosis (on the basis of clinical, radiographic, and histopathological findings, as well as response to antituberculosis treatment)[47] have negative sputum cultures. Among children, the proportion of culture-negative cases is much higher. False-positive cultures can also occur; in a review of 12 studies that assessed more than 100 patients and used DNA fingerprinting, the median false-positive rate was 2·9% (range 0–33%).[58] False-positive results can be due to laboratory cross-contamination, contamination of clinical devices, or clerical errors, and are more common with liquid culture media.[59] Where resources permit, there should be close scrutiny of cases with no positive smear, only one positive culture, and several negative cultures; selective use of DNA fingerprinting should be considered to rule out a false-positive culture.

Where resources for diagnosis and treatment of drug-resistant tuberculosis allow, drug-susceptibility testing should ideally be done on all initial *M tuberculosis* isolates.[47] Susceptibility testing should also be considered when cultures remain positive after 3 months of treatment, or become positive after being previously negative. Agar-based methods have been standard, although broth-based media are faster.[60] Rapid detection of rifampicin resistance is particularly important, and new methods to detect this and other types of resistance are coming into clinical practice.[61–64] Direct susceptibility testing on agar plates is a highly accurate technique for patients with heavily smear-positive tuberculosis. This technique requires technical expertise, but it can provide first-line and second-line susceptibility results in 10–14 days.[65]

Nucleic-acid amplification assays can be used directly on clinical specimens; they are most reliable in smear-positive respiratory samples from patients with previously untreated tuberculosis. In such samples, the sensitivity and specificity can be as high as 95% and 98%, respectively. The sensitivity is 48–53% in smear-negative respiratory samples, but the specificity is roughly 95%.[47,66] In areas of high tuberculosis prevalence, there is no need to confirm a heavily positive sputum smear, which will in most cases reflect *M tuberculosis*. However, where concentrated smears are used and either the prevalence of HIV is high or the prevalence of tuberculosis is low, amplification techniques can be useful in distinguishing positive smears due to *M tuberculosis* from positive smears with other mycobacteria.

Widespread implementation of nucleic-acid amplification assays has been limited by high cost and potential for poor performance under field conditions. Amplification tests do not replace the sputum smear (which provides a gauge of infectiousness) or culture (which is necessary for drug-susceptibility testing). The assays can still give positive results after effective treatment (because of detection of residual genetic material), so they may not be as useful in people with previous disease or in monitoring response to therapy.

In addition to advances in clinical laboratory tests, research methods of DNA fingerprinting can be useful to identify laboratory cross-contamination and elucidate the epidemiology of tuberculosis.[67]

Latent infection

The intradermal administration of tuberculin has been used as a diagnostic test for tuberculosis infection since the early 1900s;[68] the more consistent form of tuberculin, standardised purified protein derivative (PPD-S), has been used to assess latent *M tuberculosis* infection since 1939.[69,70] Although the tuberculin skin test is the best available way to diagnose latent *M tuberculosis* infection, it has limitations, including low sensitivity in immuno-compromised patients, cross-reactivity with bacille Calmette-Guerin (BCG) vaccine and environmental mycobacteria (resulting in decreased specificity), and a requirement that patients must return 48–72 h after the test is done to have the result read.[71] The criteria for a positive test vary according to the population group being tested; they are influenced by the likelihood of being infected with *M tuberculosis* and the risk of developing active disease if infected.[20]

A whole-blood interferon-γ release assay (IGRA), like the tuberculin skin test, assesses cell-mediated immunity to tuberculin.[72] The correlation between the IGRA and the tuberculin skin test has been low.[73,74] IGRA responses are diminished in HIV-infected individuals, resulting in

Treatment category	Patients	Tuberculosis treatment*	
		Initial phase (daily or three times per week)	Continuation phase (daily or three times per week)
I	New cases of smear-positive pulmonary tuberculosis or severe extrapulmonary tuberculosis or severe smear-negative pulmonary tuberculosis or severe concomitant HIV disease	2 months $H_3R_3Z_3E_3$ or 2 months $H_3R_3Z_3S_3$ 2 months HRZE or 2 months HRZS	4 months H_3R_3 4 months HR 6 months HE†
II‡	Previously treated smear-positive pulmonary tuberculosis; relapse; treatment failure; treatment after default	2 months $H_3R_3Z_3E_3S_3$/1 month $H_3R_3Z_3E_3$ 2 months HRZES/1 month HRZE	5 months $H_3R_3E_3$ 5 months HRE
III§	New cases of smear-negative pulmonary tuberculosis or with less severe forms of extrapulmonary tuberculosis	2 months $H_3R_3Z_3E_3$ 2 months HRZE	4 months H_3R_3 4 months HR 6 months HE†

*Subscript after letters refers to the number of doses per week; daily has no subscript. H=isoniazid; R=rifampicin; Z=pyrazinamide; S=streptomycin, E=ethambutol. †A continuation phase of 6 months of HE has a higher failure and relapse rate than a continuation phase of 4 months of HR but can be used for mobile patients and those with limited access to health services; the HE regimen can also be used concomitantly with antiretroviral treatment of HIV-infected patients. ‡CDC/ATS and BTS recommend treatment for such patients based on susceptibility testing, with regimens tailored to the susceptibility profile. WHO recommends susceptibility testing whenever possible for patients with treatment failure. §WHO indicates that ethambutol need not be given in the initial phase of category III treatment if patients have non-cavitary, smear-negative pulmonary tuberculosis, or if patients are known to have a drug-susceptible organism, or for young children with primary tuberculosis.

Table 1: **WHO-recommended treatment regimens**

low sensitivity in this important population,[75] but they may aid in detecting latent infection among certain populations who are at increased risk (eg, recent migrants from countries with high incidence of tuberculosis).[72] Although the IGRA is less sensitive and specific than the tuberculin skin test,[74] responses are less affected by previous BCG vaccination.[76] An enzyme-linked immunospot (ELISPOT) assay has recently been developed that is relatively sensitive and specific in detecting latent *M tuberculosis* infection.[77]

Treatment

The goals of treatment are to ensure cure without relapse, to prevent death, to stop transmission, and to prevent the emergence of drug resistance. *M tuberculosis* can remain dormant for long periods. The number of tubercle bacilli varies widely with the type of lesion, and the larger the bacterial population, the higher the probability that naturally resistant mutants are present even before treatment is started.[78] Long-term treatment with a combination of drugs is required.[79] Treatment of active tuberculosis with a single drug should never be attempted, and a single drug should never be added to a failing regimen.[1,80]

Almost all recommended treatment regimens have two phases,[81,82] on the basis of extensive evidence from controlled clinical trials. There is an initial intensive phase designed to kill actively growing and semidormant bacilli. This action shortens the duration of infectiousness with rapid smear and culture conversion after 2–3 months of treatment, in most cases (80–90%).[83] At least two bactericidal drugs, isoniazid and rifampicin, are necessary in the initial phase. Pyrazinamide given in the initial intensive phase allows the duration of treatment to be reduced from 9 to 6 months, but it offers no benefit if given past the second month to patients with drug-susceptible tuberculosis.[84] The addition of ethambutol benefits the regimen when initial drug resistance may be present or the burden of organisms is high.

Several studies have shown that reliable prediction of which patients will take all prescribed medication by themselves is not possible;[85] only direct observation can ensure that all drugs are taken. Directly observed treatment, in which a trained observer personally observes each dose of medication being swallowed by the patient, can ensure high rates of treatment completion, reduce development of acquired drug resistance, and prevent relapse.[86–88] Non-adherence to tuberculosis treatment is known to have been common ever since the advent of chemotherapy in the 1950s.[85] Thus, most tuberculosis treatment trials since that time have been carried out with direct observation.[89] Randomised controlled trials have not shown a benefit from treatment observation; however, these trials have had a common shortcoming of less than optimum implementation of treatment observation, with rates of treatment success significantly below those of worldwide programmes of DOTS.[90] Direct observation by trained individuals is the standard of practice in most countries[3] and is a component of the five-point DOTS strategy recommended by WHO and IUATLD.[45,46,81] Family members should not be relied on to ensure treatment completion.[91,92] However, direct observation is only one feature of comprehensive tuberculosis care; sensitive, patient-centred treatment that includes direct observation is crucial for cure of patients and success of the programme.

The initial phase of regimens including rifampicin should always be directly observed to ensure adherence and prevent emergence of resistance to rifampicin. The continuation phase eliminates most residual bacilli and reduces numbers of failures and relapses. At the start of the continuation phase there are low numbers of bacilli and less chance that drug-resistant mutants will be selected, and therefore fewer drugs are needed.[83,89]

Standard treatment regimens

WHO-recommended treatment regimens are shown in table 1. For each patient, the recommended regimen depends on the treatment category, which is based on severity of disease and history of previous treatment. For some forms of disease, such as tuberculous meningitis, disseminated tuberculosis, and spinal tuberculosis with neurological involvement, a 7–10-month continuation phase with isoniazid and rifampicin is often recommended.[45]

There are slight differences in the recommendations of the US Centers for Disease Control and Prevention and the American Thoracic Society (CDC/ATS), and the UK Joint Tuberculosis Committee of the British Thoracic Society (BTS) and WHO and IUATLD.[45,46,81,82] WHO, IUATLD, and the BTS do not recommend twice-weekly dosing, although this is one recommendation in the USA. The 8-month regimen (2 months of HRZE/6 months of HE) is not recommended in the USA or the UK. The UK and US guidelines recommend use of the same 6-month rifampicin-based regimens for both smear-positive and smear-negative pulmonary tuberculosis.

The recommended drug doses differ also; WHO recommends doses that are generally lower than those recommended by other authorities and which are supported by clinical trials, although the lower doses appear to have been safe and effective in large-scale treatment. Tables 2 and 3 give recommendations on dosing and monitoring,

Drug	Route	Mode of action	Daily dose			Twice-weekly dose			Thrice-weekly dose		
			Children	Adults	Maximum	Children	Adults	Maximum	Children	Adults	Maximum
Isoniazid	Oral or IM*	Bactericidal	5–10 mg/kg†	5 mg/kg	300 mg	15 mg/kg	15 mg/kg (range 13–17)	900 mg	10 mg/kg	10 mg/kg (range 8–12)	900 mg
Rifampicin	Oral or IV	Bactericidal	10–20 mg/kg‡	600 mg (range 8–12 mg/kg)	600 mg	10–20 mg/kg‡	600 mg (range 8–12 mg/kg)	600 mg	10–20 mg/kg‡	600 mg (range 8–12 mg/kg)	600 mg
Pyrazinamide§	Oral	Bactericidal	20–30 mg/kg	1·5 g (<50 kg) 2·0 g (51–74 kg) 2·5 g (⩾75 kg)	..	50 mg/kg (range 40–60 mg/kg)	2·5 g (<50 kg) 3·0g (51–74 kg) 3·5g (⩾75 kg)	..	35 mg/kg (range 30–40 mg/kg)	2·0g (<50 kg) 2·5 g (51–74 kg) 3·0 g (⩾7 5 kg)	..
Ethambutol¶	Oral	Bacteriostatic	15–25 mg/kg	15–25 mg/kg	2·5 g	30–50 mg/kg	45 mg/kg	..	30–50 mg/kg	30 mg/kg	..
Streptomycin	IM, IV	Bactericidal	15–30 mg/kg	15 mg/kg	1000 mg	15 mg/kg	15 mg/kg	1000 mg	15 mg/kg	15 mg/kg	1000 mg
Thioacetazone	Oral	Bacteriostatic	2 mg/kg	150 mg	..	NR	NR	NR	NR	NR	NR

Adapted with permission from the New York City Department of Health. Tuberculosis treatment, 3rd edn. City Health Information: 1999, 18 number 2 (available at http://www.nyc.gov/html/doh/pdf/chi/chi18-2.pdf). IM=intramuscular; IV=intravenous; NR=not recommended. *Intravenous and suppository forms are available in some countries. †WHO, IUATLD, and BTS recommend 5 mg/kg in children; CDC/ATS and the American Academy of Pediatrics recommend 10 mg/kg. ‡WHO, IUATLD, and BTS recommend 10 mg/kg in children; CDC/ATS and the American Academy of Pediatrics recommend 10–20 mg/kg. §WHO and CDC/ATS recommend dosing of pyrazinamide in adults on a weight basis, but dosing based on weight categories as recommended by BTS and by tuberculosis programmes is more useful in practice. Recommendations of dosing for this drug vary widely. Adults weighing <45 kg can have paediatric doses. The doses given here are based on the New York City Tuberculosis Control Program. ¶WHO, IUATLD, and BTS recommend 15 mg/kg ethambutol for daily administration in adults and children and 30 mg/kg for thrice-weekly dosing.

Table 2: **Doses, route of administration, and mode of action of primary drugs used in the treatment of tuberculosis**

along with information on common and major adverse events for the standard drugs. Detailed information on adverse effects and their management is available from several excellent resources.[45,93–96]

Extrapulmonary tuberculosis

In most cases of extrapulmonary tuberculosis there are many fewer organisms present.[97] In general, regimens used for pulmonary tuberculosis are effective in the treatment of extrapulmonary tuberculosis.[98–102] WHO recommends classification of the disease into severe and non-severe forms. Severe forms include meningeal and central-nervous-system tuberculosis, spinal tuberculosis, abdominal tuberculosis, bilateral pleural effusion, pericardial effusion, and bone and joint tuberculosis involving more than one site. WHO recommends category I regimens for severe forms and category III regimens for non-severe forms.[45] All major organisations agree that some forms of disease, such as meningitis, may benefit from a longer treatment course.[45,81,82] Steroids should be used for patients with large pleural effusions, pericardial disease, and meningitis, particularly with neurological impairment, since these drugs are likely to decrease morbidity and mortality in such cases.[103–110]

Treatment in pregnant and breastfeeding women

Isoniazid, rifampicin, pyrazinamide, and ethambutol are not teratogenic,[111] and WHO recommends their use in women who are pregnant.[45] In the USA, pyrazinamide is not recommended for use during pregnancy except when alternative drugs are not available or are less effective.[81] Active tuberculosis in pregnancy must be treated, because

Drug	Major adverse reactions	Recommended regular monitoring	Comments
Isoniazid	Increases in hepatic enzymes; hepatitis; peripheral neuropathy; CNS effects; increased phenytoin concentrations; interaction with disulfiram	Hepatic function tests (if baseline abnormal)	Aluminum-containing antacids reduce absorption. Pyridoxine (vitamin B6) can decrease peripheral neuritis and CNS effects, and should be used in alcoholic, pregnant, and malnourished patients.
Rifampicin	Hepatitis, fever, thrombocytopenia, flu-like syndrome. Lowers concentrations of many drugs, including methadone, warfarin, oral contraceptives, oral hypoglycaemic agents, theophylline, dapsone, ketoconazole, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors.	Hepatic function tests (if baseline abnormal)	Orange discolouration of secretions, urine, tears, and contact lenses. Patients on methadone need a higher dose (average 50%) to avoid opioid withdrawal. Interaction with many drugs leads to low concentrations of one or both. May make glucose control more difficult in diabetes. Women should be advised to use barrier contraceptives during treatment. Contraindicated for patients taking most protease inhibitors and non-nucleoside reverse transcriptase inhibitors.
Pyrazinamide	Gastrointestinal upset; hepatotoxicity; hyperuricaemia; arthralgias; gout, rarely; rash	Hepatic function tests (if baseline abnormal	May complicate management of diabetes mellitus. Hyperuricaemia can be used as indicator of compliance. Treat raised uric acid only if symptomatic.
Ethambutol	Diminished red-green colour discrimination; decreased visual acuity; rash	Check colour vision and visual acuity monthly	Optic neuritis may be unilateral; check each eye separately. If possible avoid in children too young to undergo vision testing.
Streptomycin	Auditory and renal toxicity; hypokalaemia; hypomagnesaemia	Audiometry, renal function, and electrolytes	Ultrasound and warm compresses on injection site may reduce pain and induration.
Thioacetazone	Rash and hypersensitivity reactions such as erythema multiforme and Stevens-Johnson syndrome; gastrointestinal upset, hepatitis	Close observation for skin reactions	Do not use in HIV-infected patients. If rash develops, do not rechallenge.

Not all toxicities are listed here. Full prescribing information should be checked in the package insert or pharmacology texts.

Table 3: **Major adverse reactions and recommended regular monitoring of primary drugs used in the treatment of tuberculosis**

Drug	Route	Mode of action	Daily dose	Major adverse reactions*	Recommended regular monitoring	Comments
Capreomycin	IV, IM	Bactericidal	Children 15–30 mg/kg Adults 15 mg/kg Maximum 1000 mg	Auditory, vestibular, renal toxicity; eosinophilia; hypokalaemia; hypomagnesaemia	Audiometry, renal function, electrolytes	Ultrasound and warm compresses on injection site may reduce pain and induration.
Ciprofloxacin	Oral or IV	Bacteriostatic	Adults 750–1500 mg	Abdominal cramps; gastrointestinal upset; restlessness; insomnia; headache; interactions with warfarin and theophylline	..	Antacids containing aluminum, magnesium, or calcium, and sucralfate reduce absorption and should not be given within 2 h of dose. Caffeine effects may be increased. Not approved for use in children yet.
Cycloserine†	Oral	Bacteriostatic	Children 15–20 mg/kg Adults 500–1000 mg Divided doses	Psychosis; seizures; headache; depression; suicide; other CNS effects; rash; increased phenytoin concentrations	Assessment of mental status	Increase gradually, checking serum concentrations. Pyridoxine (vitamin B6), 50 mg with each 250 mg, may reduce CNS effects.
Ethionamide Protionamide†	Oral	Bacteriostatic	Children 15–20 mg/kg Adults 500–1000 mg Divided doses	Gastrointestinal upset; bloating; hepatotoxicity; hypothyroidism (especially with aminosalicylic acid); metallic taste	Hepatic function tests (if baseline abnormal); thyroid function	Antacids/antiemetics and lying flat for 20 min after doses may help tolerance. Start with 250 mg daily and increase as tolerated.
Kanamycin Amikacin	IM, IV	Bactericidal	Children 15–30 mg/kg Adults 15 mg/kg Maximum 1000 mg	Auditory and renal toxicity; rare vestibular toxicity; hypokalaemia; hypomagnesaemia	Audiometry, renal function, electrolytes	Ultrasound and warm compresses on injection site may reduce pain and induration.
Levofloxacin	Oral or IV	Bacteriostatic, possibly bactericidal	Adults 500–1000 mg	Similar to ciprofloxacin but many fewer side-effects and drug interactions	..	Similar to ciprofloxacin. More active than ciprofloxacin and ofloxacin.
Moxifloxacin	Oral or IV	Bactericidal	Adults 400 mg	Similar to ciprofloxacin but fewer drug interactions	..	Similar to ciprofloxacin. Data on long-term use are limited at present. Avoid in patients with prolonged QT interval, and those receiving class Ia or III antiarrhythmic agents.[112]
Ofloxacin	Oral or IV	Bacteriostatic	Adults 600–800 mg	Probably similar to ciprofloxacin; possibly fewer drug interactions	..	Similar to ciprofloxacin.
Aminosalicylic acid	Oral	Bacteriostatic	Children 150 mg/kg Adults 4 g every 12 h Maximum 12 g	Gastrointestinal upset; hypersensitivity; hepatotoxicity; hypothyroidism; low digoxin, high phenytoin concentrations; concentrations decreased by diphenhydramine	Thyroid function	Begin gradually and increase dose as tolerated. May cause haemolytic anaemia in patients with deficiency of glucose-6-phosphate dehydrogenase.
Rifabutin	Oral	Bactericidal	Children 10–20 mg/kg Adults 5 mg/kg Maximum 300 mg	Rash; hepatitis; fever; neutropenia; thrombocytopenia; low concentrations of many drugs;‡ uveitis with high doses	Complete blood-cell count with platelets; hepatic function tests (if baseline abnormal)	Orange discolouration of secretions, urine, tears and contact lenses. Can be used in daily, twice-weekly, or thrice-weekly dosing. See text for dosing in HIV infection.§ Methadone dose generally does not need to be increased. Patients should be advised to use barrier contraceptives during treatment.

Adapted with permission from the New York City Department of Health. Tuberculosis treatment, 3rd edn. City Health Information: 1999, 18 number 2 (available at http://www.nyc.gov/html/doh/pdf/chi/chi18-2.pdf). *Not all toxicities are listed here. Full prescribing information should be checked in the package insert or pharmacology texts.†WHO-recommended daily maximum doses are 750 mg for cycloserine, ethionamide, and protionamide. ‡Including protease inhibitors, non-nucleoside reverse transcriptase inhibitors, dapsone, ketoconazole, and oral contraceptives. §Contraindicated with saquinavir or delavirdine. See drug reference manuals for details on individual drugs.

Table 4: **Reserve drugs used in the treatment of tuberculosis: doses, major adverse reactions, and recommended regular monitoring**

untreated disease will harm the mother and the unborn child more than standard drugs would. However, some reserve drugs may be more toxic (table 4); the risks and benefits of these drugs must be assessed for each woman separately, and in some instances treatment with reserve drugs should be deferred.

Most antituberculosis drugs can be used during breastfeeding.[113] No data are available for ethionamide. Although data are lacking on amikacin and capreomycin, they are likely to be safe given their structural similarity to streptomycin and kanamycin (which are considered safe). Concentrations of antituberculosis

Drug	Safety in pregnancy*	CNS penetration†	Dose in renal insufficiency‡	Dose in hepatic insufficiency
Isoniazid	Has been used safely§	Good (20–100%)	No change	No change but use with caution
Rifampicin	Has been used safely (isolated reports of malformations)	Fair; inflamed meninges (10–20%)	No change	No change but use with caution
Rifabutin	Use with caution (limited data on safety)	Good (30–70%)	No change	No change but use with caution
Pyrazinamide	Recommended by WHO, not by US FDA (limited data on safety)	Good (75–100%)	Increase interval (use with caution)	No change but use with caution
Ethambutol	Has been used safely	Inflamed meninges only (4–64%)	Decrease dose/increase interval	No change
Aminoglycosides (streptomycin, kanamycin, amikacin)	Avoid¶ (associated with hearing impairment in fetus)	Poor||	Decrease dose/increase interval**	No change
Capreomycin	Avoid (limited data on safety)	Poor	Decrease dose/increase interval**	No change
Ciprofloxacin, levofloxacin, ofloxacin	Do not use (teratogenic in animals)	Fair (5–10%); inflamed meninges 50–90%	Decrease dose/increase interval	No change
Ethionamide, protionamide	Do not use (premature labour, congenital malformations)	Good (100%)	No change	No change, but use with caution
Cycloserine	Use with caution (limited data on safety)	Good (50–100%)	Decrease dose/increase interval	No change
Aminosalicylic acid	Has been used safely	Inflamed meninges only	Probably no change (limited data)	No change
Thioacetazone	Has been used safely	Unknown	Avoid	Avoid

*As with all medications given during pregnancy, antituberculosis medications should be used with extreme caution. The risk of tuberculosis to the fetus far outweighs the risk of most medications. Data are limited on the safety of antituberculosis medications during pregnancy. This table presents a consensus of published data and recommendations. †Steroid treatment seems to improve outcome in tuberculous meningitis, particularly in patients with altered mental status. ‡If possible, monitor serum drug concentrations of patients with renal insufficiency. §Supplement with pyridoxine (vitamin B6). ¶If an injectable medication must be used during pregnancy, streptomycin is preferred. ||Has been used intrathecally; efficacy not documented. **Avoid aminoglycosides and capreomycin in patients with reversible renal damage, if possible.

Table 5: **Use of antituberculosis drugs during pregnancy, tuberculous meningitis, and renal and hepatic failure**

drugs in breastmilk are too low to prevent or treat tuberculosis in infants. If tuberculosis is suspected in the child, he or she should be treated.

Treatment in patients with liver disease

Drug-induced hepatitis can be fatal.[93,94] WHO recommends that pyrazinamide should not be used in patients with known chronic liver disease. In decompensated liver disease, a regimen without rifampicin can be used.[45] Streptomycin, ethambutol, and a reserve drug such as a fluoroquinolone can be used if treatment is necessary in patients with fulminant liver disease.[81]

Treatment of patients with renal failure

Normal doses of isoniazid, rifampicin, and pyrazinamide can be given in renal failure, since these drugs are eliminated almost entirely by biliary excretion or are metabolised into non-toxic compounds.[114] In severe renal failure, patients receiving isoniazid should also receive pyridoxine to prevent peripheral neuropathy. Ethambutol can accumulate and cause optic neuropathy.[112] Recommendations on the use of the other drugs in patients with renal failure are given in table 5. Individuals on haemodialysis should receive primary drug treatment by direct observation after dialysis; several of the drugs are eliminated during dialysis.[115,116]

Treatment of HIV-infected patients

Recommended treatment regimens are similar for HIV-infected and HIV-negative tuberculosis patients. However, thioacetazone should never be used, because it is associated with an increased risk of severe and in some cases fatal skin reactions in HIV-infected individuals.[117,118] In addition, response to treatment and survival are better in HIV-infected patients treated with short-course treatment including rifampicin than with other regimens that do not include rifampicin.[118,119] Therefore, all attempts should be made to use directly observed rifamycin-based regimens.

The clinical, radiographic, and microbiological responses to short-course treatment are similar irrespective of HIV status, although death during antituberculosis treatment is much more common in HIV-infected individuals.[120–122] There is evidence that direct observation of treatment is even more important for HIV-infected patients, and it is considered the standard of care.[121,123] Several studies have found that, although relapse rates are low, they are higher than in HIV-negative individuals,[124–126] whereas other studies have found similar relapse rates in HIV-infected and HIV-negative individuals.[127,128] Others have identified reinfection rather than relapse as a common cause of recurrence of tuberculosis in HIV-infected patients in areas with high incidence of tuberculosis.[129] Clinical suspicion of recurrence of disease, due to relapse or reinfection, should be high in HIV-infected patients who have completed treatment.

Several antiretroviral drugs (ie, most protease inhibitors and non-nucleoside reverse transcriptase inhibitors except efavirenz) should not be used with rifampicin.[130] Rifabutin has similar activity against *M tuberculosis*,[131–133] has less effect on the pharmacokinetics of some antiretroviral drugs, and is recommended in the USA as an equivalent alternative agent for HIV-infected patients receiving certain antiretroviral drugs.[134–136] There are concerns that patients with less than 100 CD4-positive cells per μL who are treated with highly intermittent regimens may have a higher risk of relapsing with acquired rifampicin resistance. Therefore, twice-weekly therapy with any rifamycin-based regimen is not recommended for HIV-infected individuals with less than 100 CD4-positive cells per μL.[137]

Rifapentine is a rifamycin derivative with a long half-life and its activity against *M tuberculosis* is similar to that of rifampicin. It is not recommended in HIV-infected patients because of increased risk of acquired rifampicin resistance.[138] It has not been studied in patients with extrapulmonary tuberculosis. Rifapentine is recommended in the USA in the continuation-phase treatment of HIV-negative patients with non-cavitary

pulmonary disease.[81] Most but not all strains resistant to rifampicin are resistant to rifabutin and rifapentine.

Paradoxical worsening of tuberculosis (defined as increased fever, worsening of pulmonary infiltrates, or new clinical manifestations of disease) can occur in patients on effective treatment. Although described in both HIV-seronegative and HIV-seropositive patients, it may be more common in the latter.[139–141] The underlying pathophysiology of paradoxical worsening is not well understood, but it probably involves increased recognition of mycobacterial antigens resulting from improved immune function.[142] Other possible causes of the signs and symptoms should be excluded; these include drug failure, drug resistance, non-adherence, and other diseases such as lymphoma. Paradoxical worsening can occur after initiation of tuberculosis treatment or can be associated with the initiation of antiretroviral therapy in HIV-infected patients with tuberculosis.[139,143]

Management of drug-resistant cases

The treatment of patients whose organisms are resistant to standard drugs or who do not tolerate them is difficult. Reserve drugs are generally less effective and more toxic than standard therapy; they must be given daily, and some need to be taken several times a day.[45,80]

When devising a regimen for suspected or confirmed drug-resistant disease, several important principles must be followed. The initial regimen should include at least three drugs to which the bacilli are likely to be fully susceptible. Drugs should not be kept in reserve; the regimen most likely to be effective should be prescribed. Second-line drugs should be given daily under direct observation. Bacteriological results (smear and, if possible, culture) should be monitored.[45,80]

If susceptibility test results are available, a regimen can be chosen, based on the drugs to which the strain of *M tuberculosis* is susceptible. Most authorities recommend three or four oral drugs plus one injectable drug (such as capreomycin, amikacin, or kanamycin) to which the isolate is susceptible for 3–6 months, and then at least three effective oral drugs for 15–18 months, for a total of 12–18 months after culture conversion to negative.[45,80]

All efforts should be pursued to obtain an accurate susceptibility profile in patients for whom a standard regimen with first-line drugs fails, particularly if the treatment was given under direct observation. If drug-susceptibility testing is not available, standard retreatment regimens can be used. Decisions must take into account the regimens the patient has received before, and whether the previous regimens were fully administered under direct observation and for how long. Longer use of injectable drugs is associated with improved outcomes,[144] but long-term administration is commonly complicated by ototoxicity, nephrotoxicity, and local adverse reactions (eg, pain, induration, abscess formation). Details on the doses and major common adverse effects for the reserve drugs are given in table 4.

Control

To control tuberculosis, WHO and IUATLD recommend the DOTS strategy,[145] which has five elements: political commitment, diagnosis primarily by sputum-smear microscopy among patients attending health facilities, short-course treatment with effective case management (ie, direct observation), regular drug supply, and systematic monitoring to assess outcomes of every patient started on treatment. Standard short-course regimens can cure more than 95% of cases of new, drug-susceptible tuberculosis. DOTS should be used as the basis for more complex tuberculosis-control strategies where rates of drug resistance or HIV infection are high. The international targets for tuberculosis control by 2005 are to detect 70% of new pulmonary smear-positive cases annually, and to treat 85% of detected cases successfully.[146]

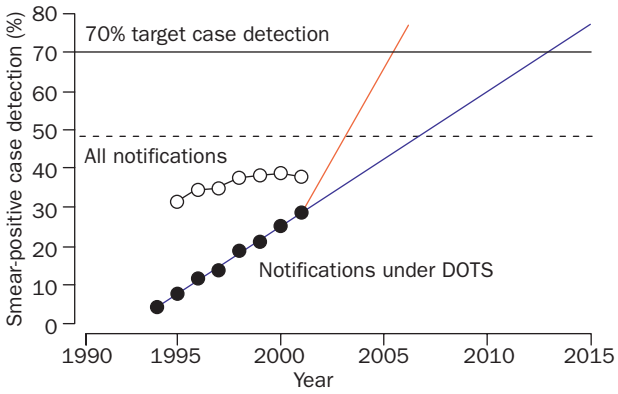

Figure 3: **Observed and projected rate of detection of smear-positive cases compared with the 70% global target**
The lower set of points is derived from case notifications submitted to WHO by DOTS programmes divided by the estimated incidence rate for these countries. Linear projection of the trend observed from 1995 to 2001 (blue line) indicates that, if the trend is maintained, 70% case detection will be reached in 2012. To reach 70% case detection by 2005, case finding must be significantly accelerated (red line). The upper set of points represent all smear-positive cases notified to WHO from all sources, including DOTS and non-DOTS programmes. Observations on the implementation of DOTS suggest that case-detection rates may reach a maximum of less than 50%, indicated by the broken line, unless case detection improves. Adapted with permission from Dye et al.[147]

Many of the 155 national DOTS programmes in existence by the end of 2001 have shown that they can achieve high cure rates: average treatment success was 82%, not far below the 85% target,[3] with lower rates in Africa (72%) and some countries of the former Soviet Union (eg, 68% in the Russian Federation). However, only 32% of all estimated new smear-positive cases were treated under DOTS programmes in 2001.[3] The increase in case notifications under DOTS has been steady since 1995 (figure 3); if the current rate of progress in DOTS expansion is maintained, the target of 70% case detection will not be reached until after 2010. However, there is a risk that progress will be slower: if DOTS programmes fail to reach beyond traditional public-health systems, they may never be able to detect more than the 50% of cases currently notified to WHO (figure 3).[147]

Both mathematical modelling and practical experience suggest that, if case-detection and cure rates can be increased to 70% and 85%, respectively, tuberculosis incidence will decline at 5–10% per year in areas of high incidence and in the absence of HIV.[148,149] At a 7% annual decline, incidence would be halved in 10 years. In Peru, where DOTS was introduced in 1990, high rates of case detection and cure have decreased the incidence of pulmonary tuberculosis by at least 6% per year (figure 4).[150]

With effective treatment, tuberculosis mortality typically falls faster than case numbers. Thus, incidence in the Netherlands decreased at an average of 7% per year between 1950 and 1995, but the death rate fell more than 12% annually.[149] Indirect assessments of the effect of DOTS suggest that hundreds of thousands of lives have been saved in China and India.[151,152]

Where the prevalence of HIV infection is high, as in eastern and southern Africa, tuberculosis treatment alone will not be able to reverse the rise in incidence of

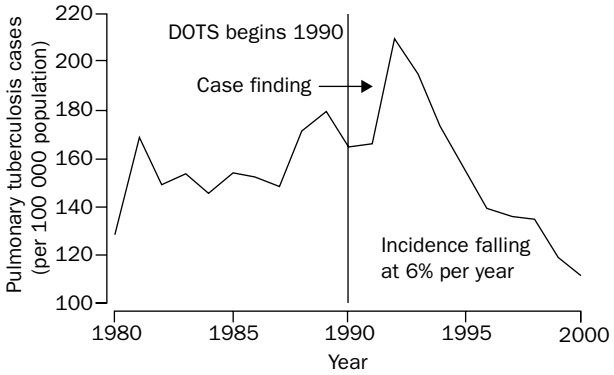

Figure 4: **Notified pulmonary tuberculosis cases per 100 000 population, Peru, 1980–2000**
The DOTS strategy was introduced in 1990, and the incidence of pulmonary tuberculosis has been falling at an average of 6% per year since 1996. Adapted with permission from Suárez et al.[150]

tuberculosis. At present, the most effective way to address HIV-associated tuberculosis is via a sound DOTS programme coupled with comprehensive, effective HIV prevention and care.[153,154]

BCG vaccination

Randomised and case-control trials have shown consistently high protective efficacy (mostly above 70%) of BCG against serious forms of disease in children (meningitis and miliary tuberculosis), but variable efficacy against pulmonary tuberculosis in adults.[155] Thus, in high-prevalence areas, vaccination is recommended for children at birth or at first contact with health services, except for children with symptomatic HIV infection.[156] Even with high coverage, BCG has not had any substantial effect on transmission or incidence, because its main action is to prevent serious (but non-infectious) disease in children.[157] Adverse events from BCG vaccination can occur, including local subcutaneous abscess and ulcers, suppurative lymphadenitis, and, more rarely, disseminated disease.[158]

Despite continuing efforts to develop more effective tuberculosis vaccines, none have been identified to date. Even if one were to be developed, it might not prevent progression to active disease among the more than 2 billion people already infected with *M tuberculosis*. Therefore, even if a new vaccine were to be implemented worldwide, more effective treatment systems would be required for decades.

Treatment of latent tuberculosis infection

Treatment of latent infection has generally consisted of daily administration of isoniazid for 6–12 months. Such treatment is 60–90% effective in reducing the risk of progression from tuberculosis infection to disease.[159] HIV-infected, tuberculin-positive individuals can benefit greatly from treatment of latent tuberculosis infection, if practical aspects of programme administration can be addressed. Contacts of active cases (especially children), recent converters to tuberculin skin test positivity, and selected individuals at high risk of disease can also benefit.[20] Recent trials have shown that drug combinations, particularly rifampicin and pyrazinamide for 2–3 months, can be as effective as 12 months of isoniazid but are not as safe.[160–162]

Long-term isoniazid treatment, although safe and reasonably cheap, cannot easily be administered to the large number of infected people who are at low risk of developing tuberculous disease. In the coming years, treatment of latent tuberculosis infection will be used more frequently to prevent tuberculosis among HIV-infected individuals even though, in areas of high transmission, protection may not extend for more than 2–3 years beyond the end of treatment, and there is at most a short prolongation of life.[163–165]

Conclusion

The current state of tuberculosis diagnosis, treatment, and control reveals striking contrasts. On the one hand, new diagnostic methods have been developed, and widespread application of control strategies has increased the number of patients effectively diagnosed and treated annually from 696 000 in 1995 to 2·4 million in 2001 (all forms of tuberculosis treated under DOTS), with more than 10 million patients treated in the past 10 years. Effective tuberculosis control is both inexpensive and cost-effective.[166] On the other hand, the mainstays of diagnosis remain the sputum smear and culture, both 100 years old. No new first-line drugs have been discovered for several decades, and two-thirds of patients who develop tuberculosis are not effectively diagnosed, treated, or monitored. The influence of HIV infection on the tuberculosis burden in eastern and southern Africa will be difficult to reverse without more effective HIV prevention and more widely available antiretroviral therapy in the less-developed countries. Further progress will require continued rigorous and dedicated application of current technology and will be greatly facilitated by the discovery and widespread application of new diagnostic techniques, drugs, and prevention strategies, such as an effective vaccine.

Conflict of interest statement
None declared.

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