Tuberculosis

Introduction

Key points

- Each year, almost 400,000 new cases of TB are diagnosed in Europe, and more than 40,000 people die of the disease.
- TB is particularly problematic among the countries of the former Soviet Union, where multidrug-resistant TB is also highly prevalent.
- The proportion of TB cases with HIV infection among all TB cases tested for the virus in the WHO European region is increasing by 20% a year.
- The World Health Organization's Stop TB Strategy is a comprehensive public health approach to controlling the disease.
- There have been significant advances in diagnostic techniques for TB, but there remain logistical and financial obstacles to their widespread adoption.
- TB treatment is complex and takes many months, using a combination, usually of four drugs.

Tuberculosis (TB) is a bacterial disease caused by Mycobacterium tuberculosis, an organism belonging to the M. tuberculosis complex, which also includes other genetically related mycobacteria. M. tuberculosis mycobacteria need to be distinguished from nontuberculous mycobacteria (NTM), which are widely distributed in the environment (soil, water) and can sometimes cause disease but are not transmitted from human to human. Using modern molecular techniques, more than 150 different species of NTM have now been identified. Epidemiological data from some industrialised countries suggest that cases of disease due to NTM are increasing and that NTM disease may even exceed the incidence of TB in countries in which TB incidence is low. The most important NTM is M. avium, which can particularly cause disease in patients with HIV/AIDS; in total, however, more than 40 NTM species have been reported to cause pulmonary disease, mostly in patients with impaired immune systems or an underlying lung disease, such as chronic obstructive pulmonary disease (COPD), bronchiectasis or cystic fibrosis. These organisms are generally less susceptible to antibiotics than M. tuberculosis, and the decision to treat an individual with a long-term combination of antibiotics depends upon the clinical picture and the causative NTM. Cervical lymphadenopathy (swollen lymph nodes in the neck) caused by M. avium complex is the prevailing manifestation in HIV-negative children, and surgical removal of the nodes is the treatment of choice, combined with antibiotics where necessary.
27 countries are classified as ‘high multidrug-resistant-TB burden’ countries, the top 13 of which are states of the former Soviet Union

TB is an important clinical and public health problem worldwide. Although its incidence and prevalence have declined notably in high-income countries over the past century, they have increased in low- and middle-income countries, owing to the emergence of strains resistant to several antimycobacterial drugs and to co-infection with HIV/AIDS.

Epidemiology

Global burden
In 2011, the global incidence of TB was estimated by the World Health Organization (WHO) to be 125 cases of TB per 100 000 people, which is equivalent to 8.7 million newly diagnosed patients (incident cases). Of the 8.7 million new cases, 12–14% (i.e. 1.0–1.2 million people) were HIV positive; these people were mainly African (79% of the total TB/HIV co-infected individuals). The total number of people with TB (prevalent cases) in 2010 was estimated to be 12 million (range 10–13 million), equivalent to 170 cases per 100 000 people globally. The number of prevalent cases has trended downwards since 1990; the same is true for the incidence of new cases, although there was a slight increase in the latter at the beginning of the 21st century.

The total number of patients dying of TB in 2011 was estimated to be 1.4 million (range 1.3–1.6 million), corresponding to a rate of 20 deaths per 100 000 people. The mortality rate of TB patients who were HIV negative was 14 per 100 000 in 2011 (a mortality rate of 15%), equivalent to an estimated 990 000 deaths (range 840 000–1.1 million); an estimated 430 000 HIV-positive people with TB (range 400 000–460 000) died in the same year (a mortality rate of 39%).

Epidemiology in Europe
In 2011, the estimated incidence of TB in the WHO European region was 42 per 100 000 people, with an estimated total of 380 000 incident cases. Overall, the TB notification rate has declined since 2007, from 56.3 per 100 000 inhabitants to 42 per 100 000 in 2011, a decrease of 27%.

The four countries with the highest TB notification rates (which include both incident cases and people who have relapsed) in the WHO European region in 2011 were Kazakhstan, Moldova, Georgia and Kyrgyzstan, with 118, 119, 105 and 103 cases per
100 000 inhabitants, respectively. A TB notification rate of 50–100 per 100 000 inhabitants was reported in seven states, including several former Soviet Union countries; the 11 countries with new/relapsing case-notification rates above 50 per 100 000 account for about 76% of the total number of notifications in Europe. Conversely, 32 western and central European nations notified less than 20 cases per 100 000 inhabitants. Estimated TB incidence is detailed in figure 1.

26% of notified TB cases in the European Union (EU)/European Economic Area (EEA) were foreign-born; in Israel, Norway and Sweden, this proportion was more than 85% of the total (figure 2). More than two-fifths (41%) of newly notified patients were 25–44 years of age. 16 countries reported a male-to-female ratio of > 2, due to males being more exposed to risk factors for developing TB such as HIV infection, smoking, alcohol abuse and homelessness.

In 2011, 12 751 (56.5%) European patients co-infected with TB and HIV were detected, out of an estimated 22 554 coinfected cases in the WHO European region. The proportion of TB cases with HIV infection among all TB cases tested for the virus in the WHO European Region is increasing by 20% per year (from 2.8% in 2006 to 6.5% in 2011). TB/HIV co-infected patients made up more than 10% of the total TB notifications in Luxembourg (40%), Ireland (20.2%), Ukraine (18.5%), Malta (16.7%) and Estonia (15%) (figure 3).
The estimated TB prevalence in Europe in 2011 was 55.9 cases per 100 000 inhabitants, corresponding to 502 763 patients. There is a strong gradient from East to West, and non-EU/EEA countries showed sharply higher rates than EU/EEA countries (104.4 versus 18.4 cases per 100 000 inhabitants, respectively).

The overall estimated TB mortality rate in Europe in 2011 was 4.9 deaths per 100 000 inhabitants, equivalent to 44 304 deaths in total; it was much higher in non-EU/EEA countries than in EU/EEA countries (10.1 versus 0.9 per 100 000 inhabitants, respectively) (figure 4). Among the EU/EEA member states, only Lithuania and Romania had death rates higher than 5 per 100 000 inhabitants, whereas more than 10 people per 100 000 inhabitants died of TB in Kyrgyzstan, Kazakhstan, Russia, Tajikistan, Moldova and Ukraine.

Drug-resistant tuberculosis
An important epidemiological and public health issue is the global emergence and spread of multidrug-resistant TB (MDR-TB), caused by M. tuberculosis strains resistant to at least isoniazid and rifampicin, the most efficacious anti-TB drugs. In 2006, an even more severe form of drug-resistant TB was described in several settings; this was defined as extensively drug-resistant TB (XDR-TB), caused by MDR-TB strains resistant to any fluoroquinolone and to at least one injectable second-line drug (kanamycin, capreomycin, amikacin).

The WHO estimated that the global prevalence of MDR-TB cases in 2011 was 630 000. 27 countries were classified as ‘high MDR-TB burden’ countries, the top 13 of which were states of the former Soviet Union. Belarus and Kazakhstan reported the highest MDR-TB prevalence among both new and previously treated TB cases. Overall, the highest proportions of MDR-TB among both new (15.1%) and previously treated (44%)
TB patients were detected in Europe out of all WHO regions; however, the burden of MDR-TB among previously treated TB cases was unequally distributed, being greater than 50% in Belarus, Estonia, Kazakhstan, Moldova, Russia, Tajikistan, Ukraine and Uzbekistan. Figure 5 shows the proportion of notified MDR-TB cases. Almost 12% of MDR-TB cases had XDR-TB. Unfortunately, drug-susceptibility testing (DST) to ascertain MDR-TB status is carried out worldwide in less than 4% of new TB cases and 6% of previously treated cases; furthermore, treatment tailored to MDR-TB was started in only 23% of confirmed MDR-TB cases globally in 2011.

Causes/pathogenesis

TB is a mainly airborne infectious disease caused by *M. tuberculosis*. Organisms are spread by droplets in the air from individuals with active TB ('contagious patients') who cough, sneeze, sing or speak. The highest risk of acquiring TB infection is among individuals intensively exposed at a short distance for a prolonged period of time ('close contacts').

Following infection, one of two clinical outcomes is possible: 1) early development of active disease (so-called ‘primary TB’), which occurs particularly in small children and immunocompromised patients; and 2) latent TB infection (LTBI), which occurs in the majority of infected individuals. The
lifetime risk of developing clinical TB after infection is 5–10% in the immunocompetent. The cumulative risk of developing TB is correlated with the age at primary infection: it is estimated that children who are infected after close contact with a contagious case have a 30–50% risk of developing TB. Furthermore, several medical, social and environmental conditions impairing the immune system can increase the risk of active TB: HIV/AIDS, diabetes mellitus, chronic renal failure, silicosis, exposure to immunosuppressive drugs, tobacco smoking and malignancy. Preventive drug treatment of infected individuals at higher risk of reactivation can significantly decrease the probability of them developing active TB.

Poor clinical and public health management of individuals with latent or active disease can favour the emergence and spread of MDR-TB. This is, in essence, a man-made phenomenon caused by inadequate treatment, including human errors related to any phase of the drug-delivery process involving regimen choice (for instance, the addition of a single drug to a failing regimen, prescription of low quality-assured drugs) and duration, drug dose, treatment adherence, infection control and other determinants (such as poverty and difficult access to the healthcare system). Inadequate drug treatment may promote the selection of pre-existing resistant strains or the emergence of new resistant strains.

**Clinical manifestations and consequences**

While any organ of the human body can be affected by TB, in HIV-negative individuals pulmonary disease is the most frequent clinical manifestation (70–80% of cases). Extrapulmonary involvement (for instance, meningitis or lymphadenitis) occurs in 20–30% of patients, sometimes accompanied by pulmonary disease; in settings with high HIV prevalence, this proportion can be higher.
Pulmonary and/or extrapulmonary TB can occur many years after exposure to an individual with infectious TB, provoked by temporary or permanent immunological impairment; only on rare occasions do symptoms develop after primary infection.

The most frequent symptoms of active disease are fever, anorexia or reduced appetite, weight loss, night sweats and persistent cough (i.e. lasting more than 21 days), usually productive of purulent and/or blood-stained sputum. Occasionally, patients complain of localised thoracic pain due to pleural inflammation; in extensive and long-lasting pulmonary disease, patients may complain of breathlessness (dyspnoea) and of coughing up blood (haemoptysis).

The first, and to date, only licensed vaccine against TB was introduced in 1921 in order to reduce the incidence of pulmonary disease: it consisted of an attenuated strain of *Mycobacterium bovis* (*M. bovis* bacille Calmette-Guérin (BCG)). Experimental studies in different geographical areas showed it to be highly efficacious in the prevention of meningitis and disseminated disease (so-called ‘miliary TB’) in children, whereas it provides unpredictable immunity against pulmonary disease. Currently, it is prescribed to neonates in endemic countries where there is a risk of being infected shortly after birth (see chapter 26, figure 4). In Europe, several countries (for instance, Austria, Denmark, Germany and Spain) have discontinued their mass universal vaccination programmes. However, several non-EU/EEA countries such as Belarus and Uzbekistan recommend three BCG vaccinations, with the last dose given during adolescence. Some European countries continue to suggest BCG vaccination for individuals at particular risk of being infected (such as healthcare workers).

Due to the narrow target of the BCG vaccine, the WHO advises that the best preventive approach is to focus on interrupting transmission, by case-finding and antibiotic treatment of infectious cases.

The WHO public health approaches, the DOTS (Directly Observed Treatment, Short course) strategy and Stop TB strategy, launched in 1996 and 2006, respectively, aimed to reduce the global burden of TB and have changed the global epidemiological situation. Over the past decade, they have contributed to the achievement of the United Nations Millennium Development Goals, related to the reduction of 1990 TB prevalence and mortality by 50%, by 2015.
The Stop TB strategy, a revised and updated public health approach, added new components in the fight against TB, to take account of the new epidemiological features of the disease, particularly TB/HIV co-infection and the rise of MDR-TB (table 1).

The fight against TB/HIV co-infection relies on HIV diagnosis and anti-HIV therapy and on the application of the ‘3 Is’: intensified case finding, infection control, and isoniazid preventive therapy for latent infection.

In order to combat the MDR/XDR-TB epidemic, a WHO-convened Task Force developed a specific global MDR-TB and XDR-TB Response Plan in 2007–2008, and in 2009 a governmental conference launched the Beijing Call for Action. Recommendations were developed for the control of XDR-TB, including the following:

- Prevent XDR-TB through basic strengthening of TB and HIV control.
- Improve the management of individuals suspected to be affected by XDR-TB through accelerated access to laboratory facilities with rapid DST for rifampicin and isoniazid resistance.
- Strengthen the management of XDR-TB through adequate use of second-line drugs and patient-centred approaches to ensure support and supervision.
- Better protection of healthcare workers against infection.
- Implement XDR-TB surveillance activities through the network of supra-national and national reference laboratories.
- Initiate advocacy, communication and social mobilisation activities to inform and raise awareness about TB and XDR-TB.

However difficult it is to reach, the ultimate goal of international and national public health activities is the elimination of TB, decreasing the incidence of new infectious cases (i.e. those with a positive result on direct microscopic examination of the sputum) to less than 1 per 1 million population by 2050.
1. **Pursue high-quality DOTS expansion and enhancement**
   - Secure political commitment, with adequate and sustained financing
   - Ensure early case detection and diagnosis through quality-assured bacteriology
   - Provide standardised treatment with supervision, and patient support
   - Ensure effective drug supply and management
   - Monitor and evaluate performance and impact

2. **Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations**
   - Scale up collaborative TB/HIV activities
   - Scale up prevention and management of MDR-TB
   - Address the needs of TB contacts, and of poor and vulnerable populations, including women, children, prisoners, refugees, migrants and ethnic minorities

3. **Contribute to health system-strengthening based on primary healthcare**
   - Help improve health policies, human resource-development financing, supplies, service delivery and information
   - Strengthen infection control in health services, other congregate settings and households
   - Upgrade laboratory networks, and implement the PAL
   - Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health

4. **Engage all care providers**
   - Involve all public, voluntary, corporate and private providers through PPM approaches
   - Promote use of the ISTC

5. **Empower people with TB, and communities through partnership**
   - Pursue advocacy, communication and social mobilisation
   - Foster community participation in TB care
   - Promote use of the Patients’ Charter for TB Care

6. **Enable and promote research**
   - Conduct programme-based operational research and introduce new tools into practice
   - Advocate for and participate in research to develop new diagnostics, drugs and vaccines

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**Table 1** – The World Health Organization-recommended strategy for tuberculosis (TB) control (the Stop TB strategy). DOTS: Directly Observed Treatment, Short course; MDR-TB: multidrug-resistant TB; PAL: Practical Approach to Lung Health; PPM: public–private mix; ISTC: International Standards for TB Care. Reproduced and modified from World Health Organization, Global Tuberculosis Control 2011, with permission from the publisher.
Accurate bacteriological diagnosis prior to starting anti-TB drugs is the best clinical and public health approach to TB: this is based on microscopic examination, solid or liquid culture and rapid or conventional DST. The latter is required to optimise the antibiotic combination, taking into account the resistance pattern of the isolated mycobacteria.

The turnaround time for direct microscopy of a sputum smear is 1 day; however, its diagnostic sensitivity is affected by the concentration of mycobacteria in the sample. This can be improved by centrifugation and by collection of at least two sputum specimens on different days (particularly early in the morning).

Due to the suboptimal sensitivity and specificity of microscopic examination, definite diagnosis requires trying to grow mycobacteria in culture. The mean time for detection of *Mycobacterium* complex is 3 weeks. New diagnostic methods such as nucleic acid amplification tests can reduce the time to presumptive bacteriological diagnosis, thereby increasing the pre-culture probability. Recently, similar techniques have been used for the rapid detection of resistance to MDR-defining drugs. The GeneXpert (Cepheid), for example, a new molecular technique, based on a nucleic acid amplification test, can detect whether TB and resistance to rifampicin (considered a reliable marker of MDR-TB) are present in less than 2 hours. It was recently endorsed by WHO because of its higher sensitivity (it detects from ~70% to > 90% of cases) and specificity (> 90% of uninfected patients will have a negative test); however, at present, cost limits the availability of this innovative technique in low-income countries.

Chest radiography and computed tomography are useful tools to complement bacteriological examinations in the diagnosis of TB. Radiography is commonly used to screen individuals with a significantly higher risk of TB than that of the general population [such as prisoners or contacts of infectious cases] and individuals with symptoms suggestive of TB.

Immunological tests, such as the tuberculin skin test and the recently introduced interferon-gamma release assays, are helpful for the diagnosis of latent TB but cannot replace bacteriological diagnosis of active TB.

The aims of anti-TB therapy are to cure the patient and to avoid the transmission of mycobacteria to other people. Treatment is characterised by an intensive phase (2 months) and a continuation phase (4 months). For new cases, the intensive phase usually includes four drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) and is designed to eliminate actively growing, as well as semi-dormant, mycobacteria. The continuation phase, based on the combination of isoniazid and rifampicin, kills residual mycobacteria.

MDR- and XDR-TB require the use of second-line drugs, which are more expensive, toxic and difficult to manage. Treatment is prescribed for at least 20 months [with an intensive phase of at least 8 months] and should rely on at least four effective drugs.
**Prognosis**

TB prognosis can be affected by numerous factors: coexistent HIV/AIDS, age, chronic comorbidity (for instance, diabetes mellitus, silicosis or cancer), exposure to immunocompromising drugs, smoking, drug and/or alcohol abuse, malnutrition and MDR/XDR-TB status. More scientific evidence is needed in order to understand the role of social determinants on the outcome of disease.

The majority of untreated patients with pulmonary disease die within 1.5 years of developing the first symptoms. The 10-year case fatality rate for untreated HIV-negative sputum smear-positive patients is 53–86% (with an average of 70%); in sputum smear-negative individuals, the rate is 20%. The average duration of the disease from the first symptoms to cure or death, is about 3 years. Unfortunately, failure and death rates are high in MDR- and XDR-TB – the treatment success rate is often less than 50%.

**Research needs**

The main recent development in TB is represented by the introduction of diagnostic rapid molecular methods (such as GeneXpert), as previously mentioned. Through international support, the vast majority of countries with intermediate and high TB incidence and MDR-TB prevalence (including those of the former Soviet Union) are implementing these new techniques at a central, regional and local level. The main challenge at present is to ensure that countries are able to set up and maintain the equipment, manage the large number of newly diagnosed MDR-TB cases, and ensure quality treatment and clinical management, adequate infection control and prevention of further drug resistance.

Global and European control (and, eventually, elimination) of TB will only become possible when significant advances in prevention and treatment are also achieved through better vaccines and drugs. A strong public health approach aimed at correctly applying the WHO-recommended strategy of TB control (the Stop TB strategy) is also necessary, in order to ensure the effectiveness of new therapeutic drugs is not lost, as has already occurred for first- and second-line anti-TB drugs in many countries.
Future developments

Among the three weapons used in the fight against TB (vaccines, diagnostics and drugs), the most spectacular improvement recently has been in the diagnostic field. Rapid molecular tests are available to identify, within a timeframe of less than 2 hours to 1 day, whether a biological sample includes \textit{M. tuberculosis}, and whether the strain is resistant to MDR- or XDR-TB defining drugs.

The challenge now is represented by the development of model programmes in former Soviet Union countries, where innovative diagnostic and treatment algorithms (involving new drugs) are being scientifically validated and integrated within a strong public health policy. To pursue elimination, innovative treatment regimens involving new drugs will need to be validated to treat LTBI and TB, and model programmes demonstrating feasibility, efficacy, and cost-effectiveness need to be implemented. This is a preliminary step to the strengthening of the elimination strategy to which Europe has been committed since 1990 but which it has never embarked upon. Pre-registration trials are evaluating the therapeutic impact of new, short-length regimens, as well as the safety, tolerability and efficacy of new drugs for the treatment of MDR-TB.

New vaccines, when available, will increase the chances of complete elimination of TB in Europe. Currently, only a few vaccines are under advanced clinical evaluation. Of particular interest are the listeriolsin-expressing BCG construct, and vaccines that utilise a viral delivery system.

Further advances should allow identification of surrogate markers to better validate the efficacy of therapeutic and preventive products. The present development pipelines for new TB diagnostics, drugs and vaccines are outlined in the WHO Global Tuberculosis Report 2012.

Further reading

**Epidemiology**

Drug-resistant tuberculosis


Diagnosis


Clinical management


Public health management

Nontuberculous mycobacterial diseases