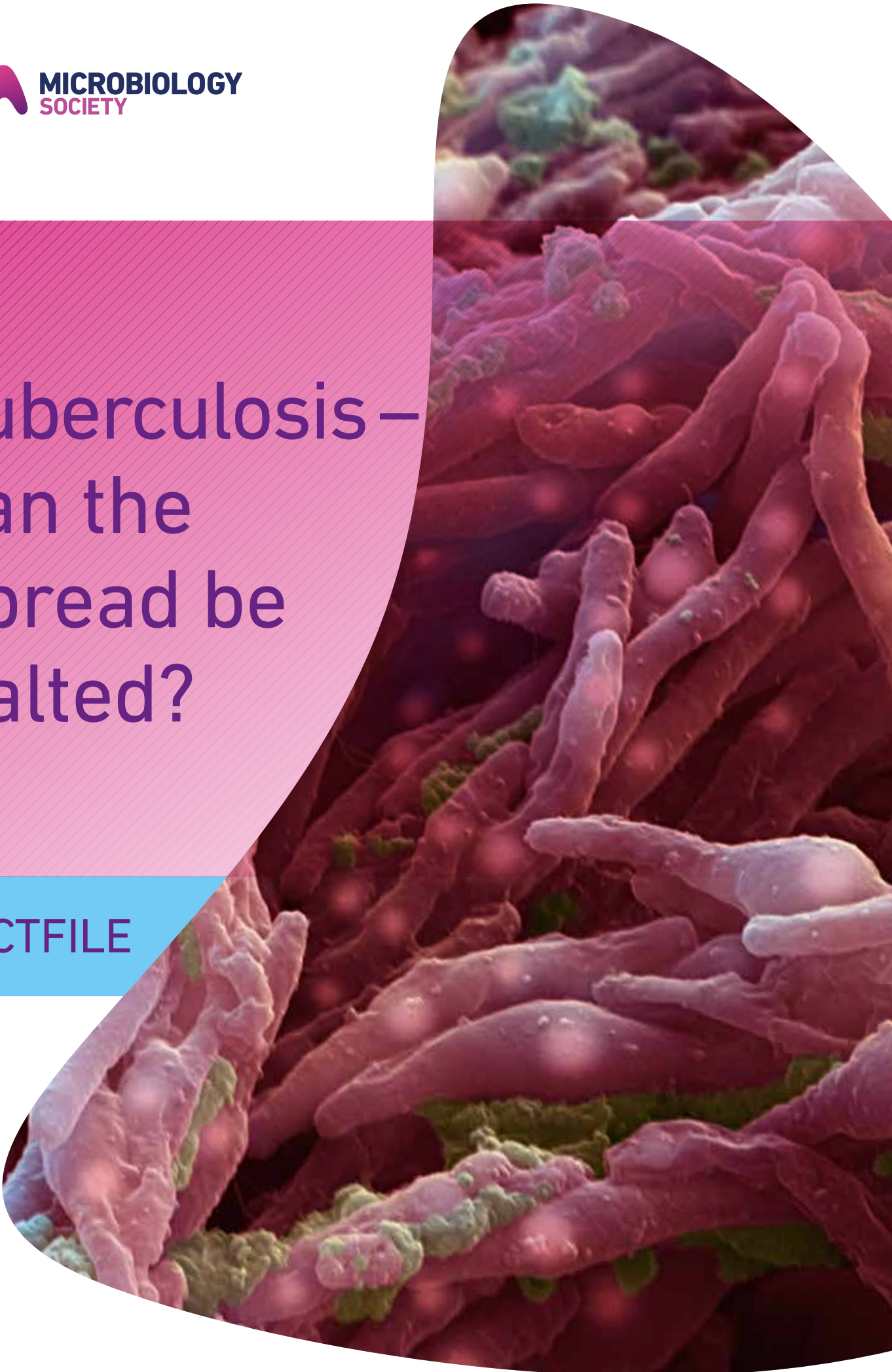


# Tuberculosis – can the spread be halted?

FACTFILE



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# Tuberculosis –

can the  
spread be  
halted?



A 19th-century TB ward. This is the Haskoy Hospital for Women in Constantinople (present-day Istanbul, Turkey).



## History

Tuberculosis (TB) is primarily a disease of the lungs caused by the bacterium *Mycobacterium tuberculosis* and is an ancient disease. Traces of the disease have been found in the remains of Egyptian mummies and the bones of an Iron Age man who died in Dorset around 300BC. It seems that TB has been with us since the beginning, but really began to thrive when humans formed settlements and started living in the overcrowded, close-contact situations in which *M. tuberculosis* thrives.

TB was rife from 1600 to 1800, particularly in overcrowded cities like London. During the 17th and 18th centuries, at the height of the epidemic, up to 30% of deaths in Europe were caused by TB. During the 19th and 20th centuries, deaths due to TB started to decrease as living standards improved, thanks to better diet, water quality and housing conditions. People became healthier and so their immune systems were better at fighting infection. The only treatment for the disease at this time was the transfer of patients to sanatoria where it was hoped that the combination of good food, plenty of rest and fresh air would result in a cure. This was often ineffective and many patients never recovered. As a last resort, surgery to remove the infected lung tissue was often carried out; this was also most often ineffective.

In the late 1940s, the incidence of the disease fell further due to the availability of treatment with effective antibiotics and prevention through the

introduction of vaccination programmes, such as vaccination with the live vaccine BCG, which was launched in Britain in 1954. The first antibiotic successfully developed to treat TB was streptomycin. It was initially given to a critically ill TB patient on 20 November 1944 who went on to make a rapid recovery. After this treatment success, a succession of anti-TB drugs started to emerge. The effect of this was a decrease in TB in developed countries which could afford the drugs, but it was not reflected in developing countries where the disease continued to thrive.

## TB returns

In 1993, the World Health Organization (WHO) declared TB a global emergency. TB causes more deaths than any other infectious disease. This means that 203 million people will die from TB each year, which is approximately 1 death every 10 seconds. The WHO reported that TB is spreading at a rate of one person per second. Although 95% of cases are in the developing world, it is also re-emerging in cities in the developed world. The WHO predicts that between 2000 and 2020 nearly 1 billion people will be newly infected with TB, 200 million people will get sick and 35 million people will die from the disease.

Despite many people believing TB has been eradicated in the UK it never went away. In fact, the UK experienced a two-decade-long rise in cases from the mid-1980s. It is only in the last three years that the UK has begun to match the global trend for falling rates of TB. In

2014, there were 6,520 TB cases in the UK, 39% of these cases were in London.

There are three main reasons why there has been resurgence in the disease:

1. TB never went away in the first place. Increased population movements due to global air travel and immigration have helped to spread the disease from countries with high TB burden (e.g. sub-Saharan Africa and Asia) to those countries with low TB burden (eg. Western Europe).
2. There has been an increase in the number of people susceptible to TB (see section on 'TB and HIV', p. 9).
3. There has been an increase in the number of cases of multidrug-resistant, extensively drug-resistant and totally drug-resistant TB cases (see section on 'Emergence of drug-resistant TB', p. 8).

### What causes TB?

Most mycobacteria are non-pathogenic and are found in habitats such as soil or water, for example *Mycobacterium smegmatis*. Some are opportunistic pathogens of humans, for example *Mycobacterium avium* is a problem in AIDS patients and *Mycobacterium marinum* which naturally infects fish and frogs, can cause ulcerative skin lesions in humans. A few species are obligate



Coloured X-ray of the chest of a male patient with pulmonary TB. The affected areas of the lungs are red.

pathogens of humans and animals such as *Mycobacterium leprae* which causes leprosy. *Mycobacterium ulcerans* is a bacterium which causes an ulcerative skin disease, known as Buruli ulcer which is endemic in Africa.

*Mycobacterium tuberculosis*, along with *M. bovis*, *M. africanum* and *M. microti*, all cause the disease tuberculosis and are members of the tuberculosis complex. Although closely related, these bacteria have different host ranges (see table below).

*M. bovis* can infect humans, probably through drinking untreated milk, and used to cause many infections in humans prior to the introduction of pasteurisation but rarely causes TB in humans these days.

*M. tuberculosis* is an aerobe, consequently the bacteria grow successfully in tissues with high oxygen concentrations such as the lungs. However, TB can affect any organ of the body and additionally, the infection can spread in the blood from the lungs to all organs in the body such as the kidneys, spine and brain. *M. tuberculosis* has a complex thick waxy cell wall due to its high lipid content; this acts as a barrier to many antibiotics and is resistant to lysosomal enzymes, helping the bacteria to survive inside macrophages in the body. This waxy layer also protects

Organism	Host
<i>M. tuberculosis</i>	Humans
<i>M. africanum</i>	Humans (tropical Africa)
<i>M. microti</i>	Voles and rodents
<i>M. bovis</i>	Wide range of mammals, especially cattle and badgers

the bacilli from drying out so they may survive for many months in the air and dust.

### How is TB spread?

TB is spread from person to person through the air. When a person with active TB coughs, talks or sneezes, mucus and saliva loaded with the infectious organism are propelled into the air. The moisture quickly evaporates from these particles to leave droplet nuclei (dried microscopic pellets) that may remain airborne for hours or days and can spread over long distances. Droplet nuclei are between 1 and 5 µm in size and contain one to three infectious organisms. Infection occurs if the inhaled organisms reaches the alveoli of the lungs. A single sneeze will release millions of mycobacteria into the air; one person with active TB can

go on to infect 10–15 people throughout the year.

Once in the alveoli, the organisms are engulfed by white blood cells called macrophages. Macro meaning big and phage meaning eat, these cells are highly capable of eating and killing most invaders, however *M. tuberculosis* has evolved several means by which to evade the macrophages' killing mechanisms. The host's cell-mediated immune response, of which the macrophage is integral, is activated and can limit further multiplication and spread of *M. tuberculosis* in the majority of cases. However, in around 10% of cases some bacilli may remain viable but dormant within the body for many years after the initial infection causing a latent infection where the individual has no disease symptoms, but the disease can reactivate at any time, often due

to ill health, ageing or HIV status. As one third of the world's population is infected with a latent infection, this a huge reservoir of infection.

### The immune response to TB

In the lung the bacteria are engulfed by macrophages. However, they are relatively resistant to destruction while inside these cells and can evade death by numerous mechanisms, many of which hinge upon the molecules within their thick and waxy cell wall. A macrophage takes up invading pathogens by phagocytosing or enclosing them in a membrane-bound vesicle, which then becomes filled with acid and enzymes after fusing with a lysozyme. However, *M. tuberculosis* can inhibit this fusion and survive and replicate within the macrophage. *M. tuberculosis* can then also actively cause the macrophage to die, releasing bacterial cells that can infect further macrophages, setting up a cycle of infection and multiplication.

### Mechanism

Initial infection stimulates a cell-mediated response which, if successful, seals the bacilli inside nodules (or tubercles) and prevents them from spreading. A tubercle is a granuloma (a tightly clustered organised collection of chronic inflammatory cells) consisting of a central core containing mainly macrophages infected with *M. tuberculosis*. An outer wall made of white blood cells called lymphocytes surrounds the core. Within each granuloma or tubercle there is a battle between the host and the bacteria. In some cases the bacteria are killed and the lesions may become calcified (where the lung tissue is replaced by

## Latent TB Infection

### People with latent infection:

- Have no symptoms
- Don't feel unwell
- Can't spread it to others
- Usually have a positive skin test reaction (see section on vaccination)
- Can develop TB disease in later life if they don't receive preventative therapy

## Active TB

### People with the disease have the following symptoms that get more severe over time:

- Bad cough for longer than 2 weeks
- Pain in the chest
- Greenish or bloody sputum
- Weakness or fatigue
- Weight loss (the gradual wasting of the body gave the disease the name consumption)
- No appetite
- Chills
- Fever
- Night sweats

calcium deposits). Calcified lesions show up clearly on chest X-rays. In other cases the tissue of the tubercle breaks down and becomes soft and crumbly like cheese. This is known as a caseous necrotic lesion. Surviving mycobacteria can multiply rapidly under

these optimum conditions where there is oxygen and plenty of nutrients. As well as destroying the lung tissue, this allows bacteria to spread to other parts of the lung. The patient will be infectious because mycobacteria will be coughed up and transmitted to others.

## Diagnosis

Diagnosis of tuberculosis relies on X-rays of the chest, clinical examination of the patient and microscopic and microbiological examination of sputum. The most widely used method to detect TB in most disease-endemic countries

## Cell-mediated immunity

This type of immunity involves lymphocytes called T cells and macrophages, rather than antibodies formed by another lymphocyte, the B cell. After the *M. tuberculosis* has been engulfed by the macrophages, mycobacterial antigens (proteins) are digested into small peptide fragments. These fragments are inserted into the membrane of the macrophage, which then acts as an antigen-presenting cell (APC) presenting these antigens to T cells and other lymphocyte sub-types.

T cells (T lymphocytes) are a type of white blood cell which are made in the bone marrow and mature in the thymus gland. They are an essential component of the response against the mycobacteria. Each T cell has a membrane receptor that recognises a specific mycobacterial antigenic peptide fragment when it is located on the surface of the APC (macrophage).

T cells can be divided into:

**CD4+ T cells.** These are helper cells which have a molecule called CD4 on their surfaces. CD4+ T cells bind to the antigen presented by the antigen-presenting cells. The CD4+ T cells then secrete cytokines, molecules which cause the macrophages and other



Coloured scanning electron micrograph of a macrophage (purple) engulfing TB bacteria (pink).

immune cells to become activated. Activated macrophages are able to more readily kill bacteria. They also release chemokines (cytokines which attract other immune cells) that attract other cells to the area resulting in inflammation of the tissues and the formation of granulomas. CD4+ T cells can also activate B cells which produce antibodies.

**CD8+ T cells.** These are killer (cytotoxic) cells which have been reported to specifically destroy mycobacteria-infected cells. They secrete

molecules that destroy the cell to which they have bound and can also secrete cytokines and chemokines.

The way in which particular mycobacteria antigens have been processed and displayed on the macrophage surface determines whether CD4+ or CD8+ T cells are activated, but both of these cell types are present in an infection. A combination of both types of T cell appears to be important in protective immunity against TB.



Sputum samples on glass slides to be stained and examined for the *Mycobacterium tuberculosis*.

is the 125-year-old sputum smear microscopy test, which has a number of drawbacks including low sensitivity and the inability to determine drug-susceptibility. Diagnosis can also be made by a positive tuberculin skin test, but this also has its limitations. Tuberculin, a partially purified protein extract obtained from *M. tuberculosis*, is injected into the dermis of the forearm. If there is a strong reaction characterised by a hardening and reddening of the area around the site of the injection, which is larger than 10mm, it means that there is hypersensitivity to the tuberculin protein. This could be due to a previous TB infection (latent or active disease) or it could be a false positive due to previous exposure to other mycobacteria or it could be due to having received the BCG vaccination. A newly developed type of test called the IGRA or interferon-gamma (IFN-gamma) release assay has the ability to differentiate between TB infection and BCG vaccination and is often used where there are complications with diagnosis. These tests are based upon the presence of T cells secreting the cytokine IFN-gamma in response to antigens specific to *M. tuberculosis*, which are not present in BCG-vaccinated individuals.

Conventional diagnosis of drug-resistant TB relies on mycobacterial culture and drug susceptibility testing (DST), a slow and cumbersome

process. During this time patients may be inappropriately treated and drug-resistant strains may continue to spread.

The Xpert MTB/RIF assay is a new rapid diagnostic test which identifies both the presences of TB bacteria and resistance to rifampicin in a few hours. This can enable early and appropriate treatment initiation, as well as accelerating the implementation of MDR-TB control measures, and ultimately reducing TB incidence.

## Prevention and control

### Drug therapy

Current treatment involves three to four different kinds of antibiotics given in

combination over 6–9 months. Multiple antibiotics are necessary to prevent the emergence of drug resistance in the bacteria. A combination of isoniazid and rifampicin for six months with pyrazinamide and ethambutol for the first two months is usually used, as this provides the highest antibacterial activity as well as having the capacity to inhibit the development of resistance. It results in a 90% cure rate. Patients stop being infectious to others after two weeks. After one month patients should feel well and start to regain weight.

A problem with treatment arises when patients stop taking the drugs as soon as they feel better, because of inconvenience, unpleasant side effects of the drugs or to save money. This is mainly seen in patients in poorer countries or those of low socio-economic status in developed nations. Badly supervised, incomplete or wrong treatment programmes may lead to recurrence of illness in the individual and the emergence of drug-resistant strains of *M. tuberculosis*. Examination



Selection of second line drugs that are used to treat TB, including Amikin, Avelox and ciprofloxacin. Second line drugs are used when the bacteria have become resistant to, or the patient is unable to take, the first line drugs.

of the bacteria isolated from relapsed cases shows that 52% are resistant to one or more drugs. To combat the rise in resistant strains a Directly Observed Treatment, Short Course (DOTS) programme has been implemented in many countries. DOTS uses a nurse to make sure that each patient takes their complete course of drugs by watching them swallow every tablet. However, DOTS is often not possible in countries with the highest rates of TB, and without such support, treatment adherence can be difficult and the disease can spread.

#### Emergence of drug-resistant TB

Today, cases of TB are declining on a global scale, in part due to the enormous efforts made towards preventing the spread of HIV. Yet the rate of decline remains slow and TB remains one of the leading infectious disease killers around the world. Furthermore, the emergence of drug-resistant strains of TB now threatens a return to a time when we were unable to control TB.

In 2014, an estimated 480,000 people worldwide developed multidrug-resistant tuberculosis (MDR-TB). MDR-TB is defined as resistance to isoniazid and rifampicin. The reasons why MDR-TB continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission. In some countries, it is becoming increasingly difficult to treat MDR-TB. Treatments are limited and expensive, recommended medicines are not always available, and patients experience many adverse effects from the drugs. In some cases even more severe drug-resistant TB may develop. Extensively drug-resistant tuberculosis (XDR-TB), is a form of multidrug-resistant TB with additional resistance to more anti-TB

drugs. It therefore responds to even fewer available medicines. It has been reported in 105 countries worldwide.

MDR-TB responds poorly to standard short-course chemotherapy, so second line drugs are required. Treatment is long (often lasting for 2 years), as the drugs are less active than first line drugs and the drugs are more toxic to patients. It is also extremely expensive due to the price of second line drugs and the extended period for which they have to be taken. It can be 100 times dearer to treat MDR-TB than drug-susceptible strains, which often makes it too expensive for developing countries with MDR-TB to treat the disease successfully. XDR-TB is very difficult but not impossible to treat. Successful outcomes depend greatly on the extent of the drug resistance, the severity of the disease, whether the

patient's immune system is weakened, and adherence to the long treatment.

#### Vaccination

The control of infectious disease through vaccination has been one of the most successful accomplishments of public health in the 20th century, enabling the eradication of smallpox and virtual eradication of polio from the world. Today, vaccination remains our most effective and cost-effective tool for infectious disease control and must be considered as an integral part of any global effort to control disease.

In 1921, Albert Calmette and Camille Guérin of the Pasteur Institute in Paris developed the BCG vaccine from a live attenuated strain of *M. bovis* which is used today, with around 388 million doses being administered worldwide each year. It took 13 years of



Four-week-old baby boy receiving a BCG vaccination.



subculturing *M. bovis* to produce a vaccine for tuberculosis. However, the efficacy of BCG vaccine varies from 80% to none at all in India and Africa.

In the UK, BCG does not protect about 25% of the people who receive it. Protection in the rest is thought to last for more than 10–15 years. A second vaccination with BCG, a so-called booster, has been shown to confer no further protection. Genetic differences in populations and variations in exposure to environmental mycobacteria are thought to have something to do with the efficacy of the BCG in different countries. Environmental mycobacteria prefer the habitats in tropical countries; this correlates with those countries where the efficacy of BCG is lower. Exposure to environmental mycobacteria results in a weaker immune response to the BCG vaccine (partial immunity) and does not produce enough of an immune response to protect against TB.

Vaccination with BCG is widely used because it is cheap, offers some degree of protection against TB meningitis in infants and also prevents leprosy. However, a more effective vaccine for TB is needed as BCG does not protect against pulmonary TB in adults.

### **TB and HIV**

TB and HIV form a deadly synergistic combination. When people are infected with both TB and HIV, TB is much more likely to become active because in AIDS patients the immune system is weakened. HIV replicates in CD4+ T cells. The CD 4+ T cell is damaged as the virus attaches and enters it and is no longer able to function. This weakens the body's defence mechanism to *M.*

*tuberculosis*. TB is the leading cause of illness in HIV-positive individuals. As more TB cases become active it means larger numbers of people carry and spread TB to healthy populations. Additionally, TB also appears to speed up HIV's replication rate.

### **Latest research**

New advances in basic sciences, such as molecular biology, immunology and pathogen genomics are altering the way we design and make our vaccines. In 1998, scientists at The Sanger Centre and the Pasteur Institute sequenced the genome of *M. tuberculosis*. Researchers are now using this information to design novel vaccines and drugs and to identify parts of the organism most suitable for targeting with drugs and vaccines.

Various vaccine strategies are being investigated and these include:

### **Heterologous prime boost vaccines –**

The BCG vaccine is used as the priming vaccine and the boosting vaccine candidate is either protein-based, DNA-based or viral vector-based. Each vaccine, the prime and the boost, uses the same antigen from the pathogen that the immune system will target and remember. The vaccines are given separately. The advantage of this method is that we can keep using the current BCG vaccine, which does protect against TB meningitis in infants, and then give our booster vaccine to protect children from developing lung TB as adults.

**Modified BCG vaccines –** The BCG vaccine is genetically modified to over-express one or more of its proteins. The hypothesis is that the immune system will then make a stronger response

to the over-expressed protein. BCG expressing a lytic protein called listeriolysin from another bacterial species is currently being tested in clinical trials (2016).

### **Attenuated *M. tuberculosis* vaccines –**

These vaccines work on the hypothesis that a TB vaccine derived from the human *M. tuberculosis* bacterium would offer better protection than the BCG vaccine which is based on *M. bovis*. Several live attenuated mutants of *M. tuberculosis* have been tested in animal models but none have given significantly more protection than BCG to date. As it is possible for individuals to become infected with multiple strains of *M. tuberculosis*, it is unlikely that this strategy will work.

**DNA vaccines –** A DNA plasmid is designed to encode for one or more protein antigens from *M. tuberculosis*.

The DNA vaccine can then be used alone or in a heterologous prime-boost combination with another vaccine. This strategy showed much promise in the mouse model. However, in humans the immune response to DNA vaccines has been very poor and there is no DNA vaccine for TB in clinical trials.

### **Protein and adjuvant vaccines –**

These vaccines are based on purified mycobacterial proteins which are administered in combination with an adjuvant. Administering a protein alone only gives a weak immune response but good immune responses are seen when proteins are given with complex molecules that we call adjuvants. Protein+adjuvant vaccines can be used alone or in heterologous prime-boost with other vaccines and there are

several currently being tested in clinical trials.

**Viral vector vaccines** – These TB vaccines use a viral vector to express an antigen. Viral vectors can generate strong cellular and humoral immune responses without the need for an adjuvant, are readily manufactured and can be used to target specific immune cells. The majority of the viral vector vaccines currently being tested are based upon the *M. tuberculosis* protein antigen 85 (Ag85) which has been shown to promote a large CD4+ and CD8+ T cell immune response.

### The future

The future of vaccine development most likely lies in developing more diversity, both in antigen specificity and the immune response and much vaccine research is now focused on developing more non-conventional vaccine strategies, e.g. stimulating mucosal immunity and non-CD4+ or CD8+ T cell responses.

### Drug development

Although effective if taken correctly, the current regime of 2–4 drugs for 6 months is too long and complicated to be implemented in many high TB burden countries. In addition, there are TB strains emerging that are resistant to all current TB drugs, and are as such untreatable. In short we need new drugs with a novel mode of action that are active against drug-sensitive and drug-resistant strains of TB, and we need drugs that will shorten therapy time from 6 months. In addition we need the drugs to be low-cost, suitable for oral administration and compatible with anti-retroviral therapy for people with TB-HIV co-infection.

Many companies, governments, charities and non-profit organisations started investing in developing TB drugs over 20 years ago, and these investments are starting to bear fruit. In 2013, Bedaquiline became the first new US FDA approved drug to treat TB in 40 years. However, it is only approved for use in MDR-TB cases where no other

treatment options are available due to a significant mortality risk when taking the drug. Delamanid has also received approval in some countries (but not the US) for MDR-TB where no other treatment options are available. Many more drugs are in the development pipeline or in early stage clinical trials, but it will be many years before we know if any of these will make it to the clinic.

There have been several clinical trials to shorten treatment but so far none have been successful. For example, one clinical trial to try to reduce therapy from 6 months to 4 months (called REMoxTB) which substituted moxifloxacin for either isoniazid or ethambutol in the first-line treatment for drug-sensitive TB, were more bactericidal in the earlier stages of treatment and converted patients to negative culture sooner than the standard of care. However, patients in the experimental arms were more likely to relapse in the year following therapy.

## Key points

- TB is caused by the bacterium *Mycobacterium tuberculosis*.
- It is primarily a disease of the lungs.
- TB is spread from person to person through the air.
- People with latent TB infection have no symptoms and are not infectious.
- People with TB disease have symptoms and may be infectious.
- Treatment of TB disease involves a combination of 3–4 antibiotics given over a 6–9 month period.
- Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the two most powerful anti-TB drugs.
- Extensively drug-resistant TB (XDR-TB) is a type of multidrug-resistant tuberculosis (MDR TB) that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (e.g. amikacin, kanamycin, or capreomycin).



A conceptual illustration of TB.



Specimen of lung tissue showing lesions caused by TB.

There are several other treatment-shortening trials in progress and we eagerly await the results. Even if we can shorten treatment to 4 months, compliance rates will rise and cost of treatment will drop, making treatment more accessible to all.

### The future – can the spread of this killer disease be halted?

The WHO End TB strategy, adopted by the World Health Assembly in May 2014, is a blueprint for countries to end the TB epidemic by driving down TB deaths

## Terms explained

**Cell-mediated immunity** – A type of immune response brought about by T cells.

**Epidemic** – An outbreak of a disease affecting a large number of individuals at the same time.

**Lymphocyte** – A type of white blood cell made continuously in the bone marrow. If they continue to mature in the bone marrow they become B cells. If they mature in the thymus they become T cells.

**Macrophage** – A large white blood cell important in phagocytosis and activating B and T cells. They extend long pseudopodia that attach to the surface of a microbe and then engulf it or phagocytose it.

**Obligate pathogen** – An organism that is known to cause disease in humans and other animals.

**Opportunistic pathogen** – A microbe that normally doesn't cause disease but can do so when the immune system is suppressed.

**Phagocytosis** – A non-specific defence mechanism. Micro-organisms that invade the body are engulfed by certain types of white blood cells which can then release lysosomal enzymes, destroying most invading pathogens.

**Neutrophil** – A white blood cell which is important in phagocytosis. After the neutrophil has engulfed and destroyed the microbe it self destructs.

and incidence. It outlines global impact targets to reduce TB deaths by 90% and to cut new cases by 80% between 2015 and 2030.

While rates of TB are expected to continue to drop, the WHO sets out five priority actions to accelerate progress against TB. These are to:

- reach the three million people who currently miss out on TB treatment every year, through improving health systems and raising awareness;
- address MDR-TB as a public health crisis, improving the capacity of countries with high rates of MDR-TB to diagnose and treat the disease;
- ensure TB-HIV co-infection is a priority – increase coverage of ART for HIV-positive patients towards 100% and expand TB preventive treatment among people living with HIV;
- increase funding to ensure the resources are available globally to control TB;
- ensure new tools and strategies for better diagnosis, treatment and prevention of TB can be implemented rapidly in countries around the world.

## Sources of further information

[www.textbookofbacteriology.net/tuberculosis.html](http://www.textbookofbacteriology.net/tuberculosis.html)

[www.netdoctor.co.uk/diseases/facts/tuberculosis.htm](http://www.netdoctor.co.uk/diseases/facts/tuberculosis.htm)

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**Front cover and right** Coloured scanning electron micrograph of *Mycobacterium tuberculosis* bacteria.

