MICROBIOLOGY SOCIETY

Tuberculosis

KEY POINTS

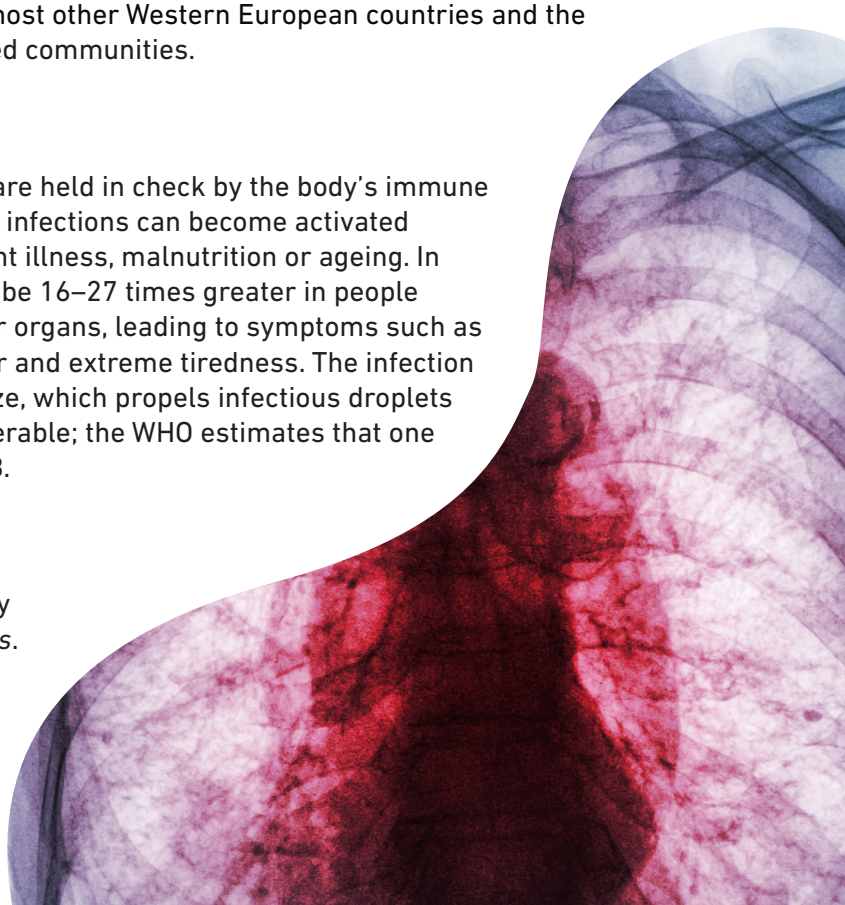
- Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis.*
- Global estimates indicate that in 2017, 10 million people became ill as a result of TB, including 5,102 people in the UK and 320 people in Ireland.
- Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS).
- TB must be prioritised in the global health agenda. The World Health Organization (WHO) members have pledged to achieve a 90% reduction in TB deaths by 2030. However, at the current rate of decline this target will not be achieved.
- Ending tuberculosis is possible with better science, improved health systems, substantial investments, and renewed political will.

SUMMARY

Tuberculosis (TB) is a debilitating multi-organ disease caused by the bacterium *Mycobacterium tuberculosis*. The most important form of the disease is pulmonary TB, an infection of the lungs and respiratory tract. Other types of TB include TB meningitis and miliary TB, which are associated with high mortality in infants and young children. The disease is usually treatable with antibiotics, but it remains the leading cause of death from a single infectious agent and a significant health threat worldwide due to the increasing prevalence of antibiotic resistance, difficulty of diagnosis and the absence of a wholly effective vaccine. In the UK, tuberculosis incidence remains high compared to most other Western European countries and the disease disproportionately affects the most deprived communities.

TB AS A HEALTH PROBLEM

In the majority of infected individuals, the bacteria are held in check by the body's immune system, leading to asymptomatic (latent) TB. Latent infections can become activated by depressed immunity, for example with concurrent illness, malnutrition or ageing. In particular, the risk of developing TB is estimated to be 16–27 times greater in people living with HIV. Active TB affects the lungs and other organs, leading to symptoms such as persistent cough, breathlessness, weight loss, fever and extreme tiredness. The infection spreads when people with active TB cough or sneeze, which propels infectious droplets into the air. Young children are also especially vulnerable; the WHO estimates that one million children worldwide currently suffer from TB.



ZOONOTIC TUBERCULOSIS

Zoonotic TB is a form of TB in people, predominantly caused by the bacterial species *Mycobacterium bovis*. The organism is host-adapted to cattle and can be passed between animals, from animals to humans and between humans. Inhalation of aerosolised bacteria is the most common route of infection

but the disease can also be transmitted by consuming unpasteurised milk or undercooked meat from infected animals.

In 2016, there were an estimated 147,000 new human cases of zoonotic TB globally, and 12,500 deaths due to the disease. In the UK, the current risk of zoonotic TB is very low, accounting for less than 1% of all human TB cases. Mycobacterium bovis is naturally resistant to pyrazinamide, one of the four essential medications used in the standard first-line anti-TB treatment regimen. This may lead to poorer treatment outcomes and the development of further resistance to other anti-TB drugs.

In England, the 25-year Bovine TB strategy aims to achieve Officially Bovine Tuberculosis Free (OTF) status by 2038.

THE GLOBAL TB EPIDEMIC

According to the World Health Organization (WHO), in 2017:

- **10 million** people were estimated to have fallen ill as a result of TB. However, an estimated **3 million** people living with TB were undiagnosed due to poor access to appropriate medical care, in association with social deprivation.
- **Two thirds** of TB cases were seen in Africa and Asia, where the disease has a significant economic impact.
- **1.6 million** people died as a result of TB, including **300,000** HIV positive people who are particularly vulnerable to the disease.

TB IN THE UK AND IRELAND

In 2017, there were nine new TB cases per 100,000 people in the UK. For the first time, this was below the WHO's definition of a low-incidence country (under 10 cases per 100,000 people). Ireland has been a low-incidence country since 2010 and in 2017 the TB incidence rate was estimated to be seven in 100,000.

Despite progress towards TB eradication, some communities are still disproportionately impacted by the disease, with higher incidence rates in some urban areas. The risk of developing TB is also heavily influenced by socio-economic factors. In 2017, TB incidence rates were reported to be seven times higher in the 10% of the population living in the most deprived areas of the UK, compared to the 10% living in the least deprived areas. Furthermore, in 2017, 13% of those suffering from TB were also affected by alcohol or drug misuse, imprisonment or homelessness.

Efforts directed towards tackling TB in the UK are driven by the All-Party Parliamentary Group (APPG) on Global Tuberculosis, co-chaired by Rt Hon Nick Herbert CBE MP and Virendra Sharma MP. The APPG endorses the United Nations High-Level Meeting Political Declaration on the fight to end TB; a commitment to drastically accelerate the global response to TB with the aim of successfully treating 40 million people by 2022.

In 2015, Public Health England and NHS England jointly launched the 'Collaborative Tuberculosis Strategy for England 2015-2020'. The strategy aims to achieve a year-on-year decrease in TB incidence, a reduction in health inequalities, and ultimately the elimination of TB as a public health problem in England.

DIAGNOSING TB

Traditional methods of diagnosis include examining patient sputum for the presence of *M. tuberculosis* and culturing the bacterium from patient derived samples. Sputum microscopy is poorly sensitive, whilst bacterial cultures can take up to 12 weeks to grow, and therefore both tests incur potentially long delays between diagnosis and treatment.

More recently, a number of DNA-based tests have been developed, which expedite the diagnostic process and enable identification of

antibiotic-resistant strains. The WHO currently recommends the rapid Xpert MTB/RIF test, which can detect *M. tuberculosis* DNA in sputum and determine resistance to the first-line antibiotic rifampicin within two hours. In the UK, the recent availability of whole genome sequencing techniques for *M.tuberculosis* has enabled rapid identification of antibiotic susceptibility, facilitating appropriate antibiotic selection.

In poorly-resourced communities across the globe, access to diagnostics tests can be limited and antibiotic susceptibility is often not assessed. This leads to misdiagnoses, treatment delays and inappropriate antibiotic use, culminating in prolonged patient suffering and driving the development of antibiotic resistance.

Policy recommendation
Policies that facilitate greater access to modern diagnostics in resource-poor settings would support rapid case identification and help break the transmission of infection.

EXISTING MEDICAL SOLUTIONS FOR TB

Antibiotics

First-line treatment protocols involve taking a combination of four antibiotics during a two-month initial phase, followed by a combination of two antibiotics during a four-month continuation phase and are reported to be successful in 85% of cases. Inappropriate or insufficient antibiotic use has contributed to the development of antibiotic resistance, which was estimated to affect 558,000 people worldwide in 2017. Second-line antibiotics, reserved for treating resistant cases, must be given over extended periods (up to 24 months) and are less efficacious. A newly-developed nine-month treatment regimen for patients with resistant TB is currently being tested in a UK study (STREAM Stage 1), co-funded by the Medical Research Council. The aim of this investigation is to show that this shorter treatment is at least as effective as the lengthier treatments recommended by the WHO.

Policy recommendation
Policy support for additional basic and applied research is urgently required to deliver affordable medications, with shorter treatment durations and fewer side effects.

Vaccines

The only vaccine currently available for prevention of TB is the Bacillus Calmette-Guérin (BCG) vaccine. The vaccine is effective at preventing the disease in young children, but has variable efficacy against TB lung disease in adults.

Efforts to develop a new, more efficacious vaccine have so far been unsuccessful, although there were promising results in a clinical trial for the M72/AS01 vaccine, developed by GlaxoSmithKline. This vaccine was shown to reduce the development of clinical disease in adults with latent infection. Larger trials are now needed to refine the vaccine's dosing schedule and potentially target specific groups of patients who are most likely to benefit.

Policy recommendation
As vaccine development is expensive and long term, policies that support national and international collaborative teams, across academia, government and the pharmaceutical industry, are critical to support and enhance the full continuum of R&D.

MORE NEEDS TO BE DONE

WHO'S END TB STRATEGY

The goal of the WHO's End TB Strategy is to end the global TB epidemic by 2030. Endorsed by WHO Member States at the World Health Assembly in 2014, it outlines a unified response to ending suffering from TB. The Strategy fulfils the targets of Goal 3 ('ensure healthy lives and promote well-being for all at all ages') of the United Nations Sustainable Development Goals (SDGs) for 2030. It calls for: (1) a 90% reduction in TB deaths; (2) an 80% reduction in TB incidence; and (3) no TB-affected households facing catastrophic costs due to TB by 2030.

The UK was at the forefront of negotiating the SDG and the End TB Strategy targets and will be at the forefront of delivering them. The current global TB incidence rate is falling by 2% per year and this needs to increase to 10% by 2025 in order to reach the 2030 target. Much can be done now to accelerate progress to end TB:

- A global and multi-sectoral accountability framework to ensure a sustained response against the disease.
- Further investment into research and development for improved diagnostic techniques, treatments and vaccines.
- Cross-country collaboration in research and development strategies, including improved flexibility on intellectual property rights.
- National notification and vital registration systems to directly count TB incidence and mortality in all countries.
- Improved access to universal healthcare within the context of the SDGs

Performant TB programmes are crucial to achieve the SDG and End TB Strategy targets set for 2030. In addition to addressing the challenges facing ending TB, well integrated programmes will also strengthen health systems to respond to diseases beyond TB, help move towards universal health coverage, widen social protection and address economic inequalities.

FURTHER READING

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