

## Tuberculosis: A long story with an open ending

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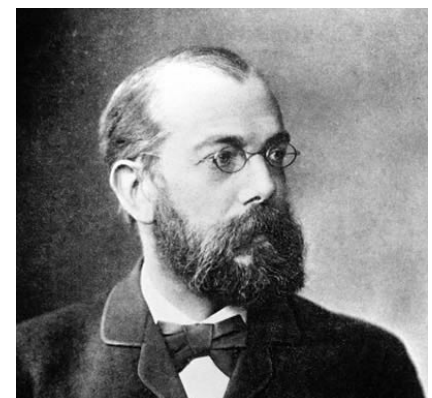
**Most epidemics come and go again. It might take weeks, months or even years, but the time can be marked – no comfort to the afflicted, of course – in a fraction of a lifetime. For epidemics of tuberculosis (TB), however, another scale must be adopted: centuries can go by before the disease loses its hold on the population. The Great White Plague, the TB epidemic that hit Europe in the 17th century, lasted for more than two centuries and was responsible for up to 25% of deaths at times. The disease – also called “consumption” because of the wasting away of its victims - is believed to have caused more than 1 billion deaths between 1700 and 1900. Yet with improved living conditions and the discovery of effective antibiotics, TB had almost disappeared from industrialized nations by the mid-20th century, and global elimination was in sight. Key word: “was”. In 1993, the WHO declared TB a global emergency. What happened?**



Before the development of antibiotics in the 1940s, tuberculosis (TB) was a major cause of death worldwide. Far from conquered, TB – now in drug-resistant forms – is threatening a new epidemic. © National Library of Medicine (NLM)

On March 24, 1882 Robert Koch presented his discovery of *Mycobacterium tuberculosis* (*M.tb*), the bacterium that causes TB, to the Physiological Society of Berlin. In a written version of his lecture “The etiology of tuberculosis” published less than 3 weeks later Koch wrote, “If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera and the like. One in seven of all human beings dies from tuberculosis. If one only considers the productive middle-age groups, tuberculosis carries away one-third, and often more.”

The threat of TB in the 21<sup>st</sup> century isn’t as apparent - at least to those of us living in developed countries – but it’s still there. The World Health Organization (WHO) estimates that 2 billion people - approximately one-third of the world’s population – are infected with *M.tb*, nearly 14 million are living with active disease, and 1.7 million died from it each year. While the global rate of active infection “per capita” is falling slowly, absolute numbers are increasing as the population grows. “Global eradication” has been replaced by “Re-emerging”.

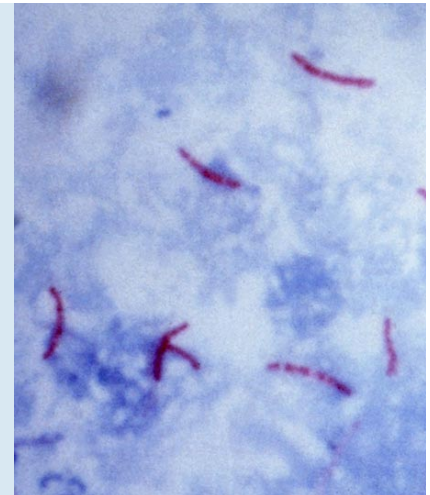


Robert Koch (1843-1910) also searched for a cure for TB; his “tuberculin” failed miserably as a treatment but became useful in diagnosis of disease.

### **Mycobacterium tuberculosis – the bug**

- first described by Robert Koch in 1882; he received the Nobel Prize for it in 1905
- obligate aerobic, non-motile rod-shaped bacterium measuring 2–4 micrometer in length
- acid-fast Gram-positive: no outer cell membrane but impervious to Gram staining because of its high lipid (mycolic acid) content; identified by acid-fast staining
- divides slowly (every 15–20 hours); in culture colonies visible after 4–6 weeks
- spread when an individual with active disease expels bacteria into the air (coughing, sneezing, spitting)
- taken up by alveolar macrophages in the lungs of mammals; if untreated, can move to other parts of the body including lymph nodes, brain and bone

(for more information see the fact sheet on tuberculosis)



Diagnosis of TB is largely dependent on staining of sputum with the Ziehl-Neelsen acid-fast staining method originally introduced by Paul Ehrlich in 1882. © Public Health Images Library

### **The turning point**

With the introduction of new antibiotics – streptomycin, para-aminosalicylic acid, isoniazid – between 1944 and 1954, TB became a curable disease and the incidence dropped dramatically. However in the mid-1980s, the number of TB cases started increasing again in some industrialized countries, and a closer look at the developing world revealed that the disease was running rampant in many areas. TB is striking sub-Saharan Africa and South Asia with a particular vengeance; where poverty results in poor nutrition, crowded living conditions and a lack of adequate healthcare, up to 40% of active TB may remain undiagnosed, and it is often difficult for patients to obtain and complete the prolonged antibiotic therapy necessary to eliminate infection with *M.tb*.

### **A curable disease**

More than 95% of patients infected with fully drug-sensitive *M.tb* are cured after completing a full course of treatment. The standard therapy for TB currently comprises four antibiotics (usually isoniazid, rifampicin, pyrazinamide, and ethambutol) administered for 6 to 9 months. By combining multiple antibiotics, resistance can be prevented. The long duration of therapy may be necessary because *M.tb* replicates very slowly in the lung of patients with active TB.

(see Garton et al. below)

The return of TB can also be linked to the emergence of the human immunodeficiency virus (HIV). The time frame fits (HIV started emerging in the early 1980s), and we know that TB becomes active when the immune system is weak; while TB becomes active in 5-10% of healthy individuals within their lifetime, approximately the same risk faces HIV-positive individuals each year. It's estimated that one-third

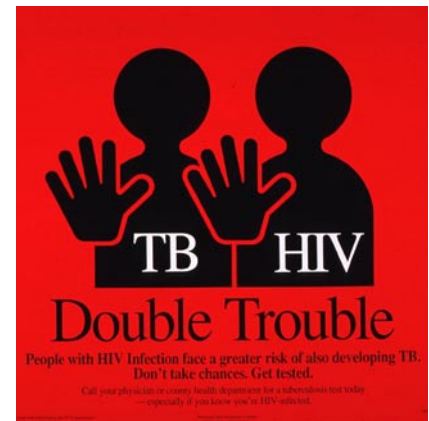
of the 40 million people infected with HIV worldwide are also infected with *M. tb*, and the major “hot spots” of HIV/AIDS and TB largely overlap: sub-Saharan Africa, South Asia and the former Soviet Union.

Both the emergence of HIV and the relentless poverty in many developing countries enable the spread of TB and complicate its treatment. But what really gets health experts agitated is the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), which threaten to transform TB into an untreatable, highly fatal disease, particularly in countries already struggling to fight the it.

### It's not the same TB anymore

MDR-TB starting emerging on the scene in the 1990s, the spawn of incomplete/inadequate treatment and poor adherence to therapy. It's a painful price to pay: treatment of MDR-TB can take up to 2 years and costs 3-100 times more than standard TB therapy. But the outlook for patients – at least those who complete their therapy - is good.

The same cannot be said for all drug-resistant strains. In 2005 doctors in Tugela Ferry, South Africa noticed that a number of patients – most HIV-positive – were not responding to anti-TB drugs. Out of the 53 patients, 52 died. The median period from TB testing to death was only 16 days. The culprit was a strain of XDR-TB. While fatality rates reaching those reported in South Africa are not the norm, treatment of XDR-TB is successful in only 30-50% of HIV-negative patients (and a much lower frequency HIV-positive individuals) after 18-24 months of treatment with four to six second-line anti-TB drugs. The situation may get worse: strains of TB resistant to all available antibiotics could be the next hurdle.



Without the right treatment, ~90% of HIV-infected individuals die within months of contracting TB. TB kills up to half of all AIDS patients worldwide. © National Library of Medicine (NLM)



Patients with MDR-TB and XDR-TB may need to take as many as 20 pills per day. The second-line drugs used to treat resistant TB strains are much more expensive and cause more serious side effects than standard TB therapy. © fotolia.de

### Agents of a new pandemic?

**MDR-TB:** resistant to at least rifampicin and isoniazid from among the first-line drugs; WHO estimated more >500,000 new cases diagnosed in 2007 (57% in China, India and the Russian Federation), with more than 50% resistant from the start

**XDR-TB:** MDR-TB (rifampicin/isoniazid-resistant)+resistance to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin); found worldwide (now in 55 countries), prevalence estimated at 6.6% of MDR-TB cases

## Our future with a killer

During the Great White Plague – before effective antibiotics existed - TB proved deadly for 80% of its victims. What does the emergence of MDR-TB and XDR-TB mean for us? A pandemic of drug-resistant TB is a realistic threat, and the treatment of resistant strains is stressing a system already partially strained beyond its limits. New weapons in the fight against TB are desperately needed, and there are concerted international efforts pushing research.

**Old tools:** Rapid, inexpensive and sensitive diagnostic tests need to be made available worldwide. Sputum smear microscopy – the most widely used method to diagnose active TB - is fast and inexpensive but has limited sensitivity; it can identify the most infectious cases, but TB in many patients (particularly those with HIV co-infection) slips through undetected. Currently available inexpensive rapid TB blood tests also have sensitivity problems. Diagnosis of drug resistance is plagued by long culture times for slow-growing *M.tb*; final diagnosis may take 6-16 weeks. New tools are long overdue.

**Old drugs:** The last drug effective against infection with *M.tb* was introduced in 1966. Several new drugs are in clinical development/clinical trials, but none are expected to become available for at least 5 years. Pharmaceuticals that provide a cure over a shorter time period might increase the adherence to therapy – and decrease development of new resistance. Knowledge about the interaction of antiretroviral (HIV) drugs and anti-TB drugs is also of crucial importance.

**Old vaccine:** Bacille Calmette-Guérin (BCG) is not effective in preventing adult pulmonary TB. Several new vaccines are being developed, and some are being tested in clinical trials.

Using a mathematical model, researchers (see Abu-Raddad L.J. *et al.* below) have predicted that –if used in combination - the vaccines, drugs and diagnostics currently under development will have a substantial impact on the battle against TB. However, high-tech research won't be enough to beat the disease. Poverty and HIV are powerful forces influencing the spread of TB, and until progress in these areas is made, it seems unlikely that TB can be effectively controlled.



## References and further reading

### General information

World Health Organization <http://www.who.int/tb/en/>

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