CHAPTER 6

TUBERCULOSIS
complacency kills
In the era of antibiotics, tuberculosis seemed to be a thing of the past but this ancient scourge has made a comeback in new, more dangerous forms. The World Health Organization’s efforts to fight tuberculosis show how coordinated action can save lives.

Edinburgh, United Kingdom, 1950s. A young British doctor by the name of John Crofton watched as some of the patients died in his tuberculosis (TB) ward in Edinburgh, Scotland, puzzled as to why the drugs they were given did not cure them. “We found that some patients had already been infected primarily by tubercle bacilli that were resistant to one of the drugs,” said Crofton, who later became ‘Sir John’. “Isoniazid had just been discovered, a drug which did not destroy the bacilli, but which interfered with their reproductive mechanisms, and so we decided to add it to the drugs being administered.”

It worked. “To our astonishment we found that we were curing everyone – all the new cases,” Crofton recalled. It worked so well that some doctors questioned his findings. But what was happening had to do with simple probability. The chances of
any one organism – in this case a TB bacillus – mutating to resist three drugs at the same time were lower than for one or two drugs. His work showed that by treating patients with three drugs simultaneously and monitoring their progress, it was possible to achieve a 100% cure rate. This approach became known as ‘the Edinburgh method’ of treatment. It was a breakthrough.

**Medicine miracle was short-lived**

Tuberculosis has been with us for thousands of years. Evidence of TB damage has been found in human remains dating back 6000 years and in the spines of 3000-year-old Egyptian mummies. The ancient Greek physician Hippocrates observed it to be the most widespread disease of his time. The bacillus that causes tuberculosis was first identified in 1882 by Robert Koch (see Box 6.1 A discovery that paved the way).

Fast forward to the 21st century and TB is still a global menace. Roughly one third of the world’s population – a staggering two billion people – are estimated to be infected with TB. These people are not yet sick and cannot infect others, but they are at risk of developing what is known as ‘active TB’.

Back in 1948, the year the WHO came into being, TB was considered one of the major public health challenges. This highly contagious disease is believed to have accounted for more deaths over the millennia than wars and famines combined. And then, in the middle of the 20th century, scientists put an end to the hopelessness surrounding TB when they discovered an antibiotic called streptomycin. It was the first medicine that could cure TB, and it was heralded as a miracle drug that seemed to promise a new TB-free age.

But then TB started fighting back. Like any other living organism, the tubercle bacillus evolves. From generation to generation its DNA
adapts to its environment. Within someone who is infected with TB, each new generation of bacilli produces a few that are resistant or partly resistant to a given antibiotic. In cases where the antibiotic is weak or not administered properly, or where treatment is interrupted, resistant organisms are left alive. These re-populate the space left by the bacteria wiped out by the drugs. At this point infected people are worse off than before and when they cough they are spreading the new drug-resistant bacilli.

To counter the problem of drug resistance, doctors started combining streptomycin with another antibiotic called para-aminosalicylic acid or PAS, giving TB patients the two drugs instead of just one. This worked for a while, but as time went on it worked less. Then the breakthrough came in the 1950s with Sir John Crofton’s triple combination therapy. His approach was a success in Europe. In the Netherlands, for example, the proportion of people, who were sick and infectious (those with active TB) had been falling by 5% every year between 1910 and 1940, as living standards improved. But with the introduction of streptomycin, that annual drop was 13%. And this success was similar across the developed world. However, in China, India and many countries in Africa, the number of active TB cases was barely coming down, despite WHO initiatives (Photo 6.1).

The problem was that WHO-supported TB programmes in Europe relied on specialized staff to diagnose the disease. But when WHO and its partners encouraged India and other developing countries to adopt similar TB programmes, they struggled because of their weak infrastructure, poorly trained staff and cash-strapped institutions.

What was needed was a workable and affordable way to deliver TB diagnostics and treatment to the urban and rural masses in poor countries, countries that in some cases spent no more than a US$ 1 per person per year on health care.

The beginnings of a solution came with a series of trials conducted by the United Kingdom’s Medical Research Council in East Africa, Hong Kong and India in the 1960s and 1970s that proved that new treatment using three drugs: streptomycin, isoniazid and thiacetazone (which replaced PAS) was safe and worked. The great advantage of this new treatment combination was that it took 12 rather than 18 months saving money and making patients more likely to complete their treatment.
When tackling TB, one of the biggest problems health workers face is identifying the people who are sick and infectious early enough to prevent them from spreading the disease. But it is hard to detect TB because people who are sick, do not always go to a doctor or hospital and, when they do, clinics may be ill-equipped and staff do not always identify them. Ideally, clinics should provide rapid testing and put patients on treatment when necessary. But that doesn’t always happen.

People spread TB through coughing and sneezing. The person next to you could have it and you would not know. Those who live or work close to someone who is ill with TB and coughing for days are most at risk. As Dr Mario Raviglione, Director of the Stop TB Department at WHO, puts it: “Infectious people are not walking around with the word ‘tuberculosis’ written on their foreheads.” In other words, if they have active disease – which means they are sick and infectious – they are not always easy to identify because the symptoms can be mistaken for those of another disease.

In Europe in the 1950s brochures and posters were distributed to make the public more aware of TB, and mobile X-ray units and specialized drop-in clinics were provided to meet any demand for TB testing. As the number of cases dropped, these units were scaled back. But in India – as in many other developing countries – it was different: a handful of specialized clinics were overwhelmed by a sea of active TB cases. For example, in 1946 India had only 6000 sanatorium beds and an estimated two and a half million active cases, according to the Indian Tuberculosis Control Programme (Photo 6.2).

**Groundbreaking studies in India**

One advantage India did have was a public health system. While far from optimal, this system, which included general hospitals for anyone who could walk or be carried in, became the basis of India’s revised TB screening programme. A study conducted in the Indian city of Bangalore by WHO and the British Medical Research Council in the 1950s revealed that most active TB cases could be identified simply by taking a closer look at patients coming into these hospitals and clinics who showed typical TB symptoms. All that was required to diagnose TB in them was the relatively low-tech method of sputum microscopy, which
dispensed with the need for expensive X-ray machines and specialized staff. The problem with this approach, however, was that it did nothing to prevent cases occurring in the first place.

After Crofton’s Edinburgh method and the Bangalore study in which TB cases were identified by hospital staff, a third advance came in 1956, when a study conducted in the Indian city of Madras showed that TB patients could be treated as successfully at home as in sanatoria. This was the first of a series of studies conducted by the Madras Tuberculosis Chemotherapy Centre that had been established by the Indian Council of Medical Research, the Madras state government, WHO and the United Kingdom’s Medical Research Council.

The 1956 Madras study had a tremendous impact worldwide, and not only in developing countries; developed countries too began closing their sanatoria. The feeling was that if out-patient treatment for TB could work in Madras where living conditions at the time were appalling, it could work anywhere. Indeed according to Dr Wallace Fox, of the United Kingdom’s Medical Research Council, one of the key researchers in the Madras studies, the city was chosen because “everything was unfavourable” for TB treatment.

The 1956 Madras study not only showed that hospital beds were no longer necessary to cure the disease, it also highlighted the importance of Fox’s concept of “entirely supervised administration of medicines” – an echo of Crofton’s Edinburgh method.

On the basis of the studies in Bangalore and Madras, WHO’s expert committee on tuberculosis revised its treatment guidelines in 1964 – that is, its recommendations to countries on how to treat TB – and for the next 10 years many countries started to rely on general health services rather than specialized TB clinics. But in the two-steps-forward-one-step-back manner of many public health advances, the results were disappointing.

While many countries were happy to dismantle expensive specialized TB services, they were less willing to invest extra money in TB diagnosis and treatment provided by general health services. And there were other problems with the outpatient approach to TB care. Doctors’ interest in patients with TB often started with diagnosis and ended with prescription of drugs. Once the patients were out the door, they were left to their own devices. This would have been unhelpful with any disease, but it was problematic with TB because patients need to complete treatment without interruption to be cured and to prevent the spread of drug-resistant forms of TB (Photo 6.3).
New approach is needed

A system was needed to make sure that TB patients completed their full course of treatment and that doctors had some way of knowing whether their efforts to detect and treat TB were working in the long term. In the late 1970s, a system emerged, when, with the support of the International Union against Tuberculosis and Lung Disease (IUATLD), Dr Karel Styblo worked with United Republic of Tanzania’s health ministry to develop a structured programme to support TB services in the general health system. Styblo, who was born in 1921 in Czechoslovakia, had an intimate knowledge of the disease, having grown up surrounded by what was termed ‘galloping consumption’, and having contracted TB as an inmate of a Nazi concentration camp during the Second World War. These experiences led him to become a doctor, eventually working under Crofton in Edinburgh.

Styblo also worked hard to find out why some European countries were more successful in fighting TB than others, working closely with Czechoslovakia and the Netherlands. Meanwhile, a major turning point at the time was the discovery of rifampicin, a TB drug developed in the 1960s and introduced into use in the early 1970s. Wallace Fox from the Tuberculosis Research Unit of the United Kingdom’s Medical Research Council, found that by combining rifampicin with other drugs, patients would recover after six to eight months of uninterrupted treatment – a major improvement over 12 to 18 months. It was this breakthrough that heralded a new approach to TB. Styblo tested the new treatment approach in the field in the late 1970s, initially in the United Republic of Tanzania. This work proved that short-course chemotherapy could be used in the poorest settings.

“He was a quiet man”, Crofton recalled, “but wonderfully persistent and a tremendous worker”. Styblo also had what Crofton termed “a particular genius for persuading governments that TB was a major economic problem”. To convince them, WHO commissioned studies to find out whether TB programmes based on the new approach in Malawi, Mozambique and the United Republic of Tanzania and elsewhere were better value for money than previous TB efforts. The findings were clear: the new approach was cost effective compared with earlier TB programmes and also other health programmes.
The Tanzanian TB programme, launched in 1978, was based on case-finding among patients who showed symptoms, the same approach that had worked in Bangalore. It also relied on district-based government hospitals and clinics to provide treatment. Styblo’s approach used hospitalization or ambulatory supervision (when patients stay at home and visit the doctor for treatment) during the first two months, to make sure the patient took every dose. He created registers and treatment cards that doctors and nurses could use to see that patients continued their treatment and also – a crucial element that was new – to record the details of the patients who were cured. By recording the success rate of TB programmes, public health authorities could show health workers where TB services were working well and where they could be improved. First recommended by the WHO expert committee in the 70s, it was this crucial addition of what came to be known as ‘monitoring and evaluation’ that distinguished these new TB programmes from their predecessors and paved the way for today’s approach.

In 1991, WHO, working with Styblo, adopted the model as the basis for the DOTS approach that it recommends to government, an all-encompassing public health approach with five key elements: government commitment to a sustained national programme; diagnosis using microscopy to look for bacilli in the sputum; standard supervised treatment and support for patients; a regular drug supply system; and monitoring and evaluation.

The DOTS acronym originally stood for ‘Directly Observed Treatment – Short Course’ referring to the central role in the strategy of direct observation of patients to make sure they took their medicine until they were cured. This approach formed the basis for WHO standard recommended treatment and has been taken up by virtually all national TB programmes. Under today’s TB programmes, patients are able to live at home and take their medicine at home or as close as possible to home with the help of a health worker or a friend or relative, who has been trained.

It took more than 30 years after the ‘miracle TB drugs’ first appeared to develop an approach to diagnosis and treatment that worked on a large scale in low- and middle-income countries. During that time, the number of TB cases in wealthy, developed countries fell back dramatically, leading to a false sense of security and a perception that TB was a disease of the past all over the world. This complacency led to a decline in spending on TB. In the USA,
for example, funding for TB research and treatment dropped from US$ 40 million a year in the late 1960s to only US$ 283 000 in 1980, while in 1989 the US Department of Health and Human Services was so confident TB was finally on the run that it predicted TB would be more or less eradicated from the country by 2010.

The USA was not alone. “There was neglect on the part of WHO, for sure,” says WHO’s Raviglione. “It got to the point in 1989 when the Director-General (Dr Hiroshi Nakajima) decided to do something about TB. At that time, WHO had only one epidemiologist and one secretary working on it.” The Organization’s monthly peer-review journal the Bulletin had ceased to produce special issues on the disease, while after 1978 the International Tuberculosis Conference, which had been held every two years, was scaled back to being held once every four years.

**A sinister comeback**

Tuberculosis had gone out of fashion, or so it seemed. But the shadow of the disease was still lurking, as it continued to tighten its grip silently and steadily across the world. This was so in Africa, where an increase in TB was linked to the growing HIV epidemic. People with HIV, a virus that weakens the body’s ability to fight disease, can catch TB more easily than people who are not HIV positive. That is partly why the incidence of TB in Africa has tripled or quadrupled since the early 1980s, while in some countries as many as 70–80% of TB patients are also HIV positive.

Africa does not face the new TB epidemics alone. Countries of the former Soviet Union also saw a surge in TB after the end of communism in the 1990s, driven by disintegrating health-care systems, falling living standards and the rapid switch to a market economy. China and India too faced major TB epidemics. In China, migrant workers who left their homes in rural areas to work in the cities were the group most affected. This migration started in 1992. Lodged in unhygienic and cramped living conditions, they were more exposed to TB. At the same time their health care was tied to their place of birth and so when they became ill, they could not get treatment. These two factors became an important driving force behind China’s TB epidemic, estimated by WHO to be running at 1.3 million new cases per year (Photo 6.4).
Affluent countries also saw a surge in TB. In the USA from 1985 to 1992 the average number of TB cases leapt by 20% from 22,201 to 26,673. In New York City alone, TB cases tripled. In contrast to developing countries, the trend in the USA was driven by drug abuse, homelessness and poverty. Moreover, many cases were among recent immigrants from developing countries, which goes to show that TB has no borders and must be tackled globally.

Tuberculosis was coming back – in new drug-resistant forms. In the USA, for example, Raviglione recalls the first time he realized that drug-resistant TB was a serious problem in New York while he was working at the Cabrini Medical Center between 1984 and 1990. “The question of multidrug-resistant TB came up at a morning report,” he says, referring to 30 or so junior doctors who met every day to discuss admissions from the night before (see Box 6.2 Drug-resistant tuberculosis). “This was in 1987,” Raviglione says. “Someone with TB had come in, and one of the doctors said, ‘Oh yeah, he is homeless so we have to give him three drugs’. I asked why, given that standard practice at that time was to prescribe two drugs, so the doctor said it was because he was likely to have resistance.”

The problem, according to the doctor, was that homeless people stayed in hospital for a few weeks only, started the prescribed course of drugs, started to feel better and then disappeared. Then, some time later, they showed up at another hospital and the whole cycle would start again. Raviglione and a young doctor from Mexico, Ariel Pablos-Mendez, decided to look into the issue. “We went back through the records starting in 1981,” says Raviglione. “And what we discovered was that more than half the cases of resistant TB were among homeless people.” Feeling that the situation should be brought to the attention of the medical community, they wrote a study and submitted it to the Annals of Internal Medicine, a leading medical journal in the USA.
Months later the journal rejected the piece because of its “incomplete” statistical analysis. Raviglione and his colleagues were dumbfounded. So much time had slipped away, when something could have been done about the problem of drug-resistant TB. A few months later, the editor of another journal, the *New York State Journal of Medicine*, called Raviglione, expressing interest in the piece. He published it 12 months later in 1990. Raviglione’s bleak summary of the episode: “We lost a couple of years.”

It wasn’t until a year later that the media finally gave the problem the attention it deserved. In 1991, news of an outbreak of drug-resistant TB in New York prisons that had killed several inmates, both in the city and upstate, was splashed on the front page of the *New York Times*, which reported that officials were calling it “the most alarming medical development in the state prisons since AIDS was discovered a decade ago”.

Indeed, from 1978 to 1992 the number of patients with tuberculosis in New York City had nearly tripled, while the proportion of these patients with drug-resistant forms of TB had more than doubled. This was the grim finding of one study, but it also gave hope. It found that efforts to make sure patients completed their treatment without interruption and to improve detection of TB in hospitals, shelters for the homeless and prisons between 1992 and 1994, had reduced the number of TB cases by 21%.

What had been happening in New York was mirrored elsewhere. In 1993, based on findings that showed a substantial increase in the number of cases worldwide, WHO declared TB to be a “global emergency” and proposed DOTS as the best and most cost-effective approach to combating TB and worked hard to persuade countries to adopt it, as this old enemy re-emerged in many countries across the world. WHO was raising the alarm. “Complacency towards tuberculosis in the last three decades led control programmes to be run down in many countries,” said the *World health report1998*. “The result has been a powerful resurgence of the disease.”

For WHO, DOTS was the next key step to tackling the TB emergency. It was around the time that TB made its comeback that WHO, in 1991, started implementing its WHO strategy for global TB control based on the Styblo model. Also, in 1991 the World Health Assembly adopted its first ambitious international targets: to detect at least 70% of active TB cases and to cure 85% of patients by the year 2000. But huge challenges lay ahead, not least the lack of funding and the need to roll out DOTS on a massive scale in countries that were most affected by TB.
China and India gear up

China had made great progress in fighting TB in the 1960s and 1970s, when Chairman Mao Zedong’s government sent an army of barefoot doctors into the villages to provide basic health care, while health workers in hospitals were also trained to treat TB. During the late 1980s, standards of health care started to improve and, with the opening of the economy, hospitals and dispensaries started charging fees for their services. Many people who needed it could not afford to be diagnosed and treated for TB. That began to change in the early 1990s, when China became one of the first countries to adopt the WHO-recommended TB control approach, with the help of WHO, the World Bank and others, and to offer these services free of charge for infectious patients (Photo 6.5).

China trained thousands of health workers to deliver specialized detection, diagnosis and treatment services. It set up a better drug supply system and started to keep records of progress made while treating patients for TB. Half of China’s provinces benefited from this project. The results have been proclaimed a major public health success. As the Washington-based Center for Global Development put it: “China has averted hundreds of thousands of deaths and paved the way for future wins in the battle against TB.” Ten years into the project, a national TB survey in 2000 suggested that the number of people with active TB had dropped by one third in those provinces. Since then, the programme has been rolled out across most of this vast country.

In April 2009, Chen Zhu, China’s minister of health, declared the TB programme a major public health success. He said that between 2001 and 2008, 6.42 million pulmonary tuberculosis cases had been detected and treated in his country.

Chen said that China was providing the DOTS approach, as recommended by WHO, across the whole country. By the end of 2008, the TB programme had detected 78% of people diagnosed with active TB and had cured 93% of those treated. “China has achieved, as scheduled, the phase targets of TB control that its government promised to the international community,” Chen said.

Meanwhile, in the world’s second biggest country by population after China, India, another massive DOTS programme got under way in 1997 with support from WHO, donors and other partners. At the time, India’s National TB Programme was not achieving enough.
As other developing countries began to adopt DOTS, challenges remained. Not all governments were committed to providing DOTS and the funding needed to step up their TB efforts. Another problem was ensuring an adequate supply of medicines. Poor countries could often only afford irregular supplies of medicines of unproven quality, which undermined the whole basis of the WHO-recommended DOTS approach.

In March 1998, a WHO committee of TB experts met in London to discuss these challenges. Its conclusion was bleak. Since the beginning of the decade, the percentage of infectious cases that had been detected, treated and reported under DOTS had increased from almost nothing to 23%. But this was far from WHO’s goal of detecting 70% of TB cases and curing 85% of cases by the year 2000. Many countries had adopted DOTS, but few had really made it work. The TB experts called for a sea change, urging political leaders to join forces to fight TB together and solve the problems with drug supply.

To give new impetus to TB control efforts, WHO launched the Stop TB Initiative in 1998. “It was a low-profile launch, compared to other priorities of the time,” Raviglione recalls. Stop TB’s goal was to make countries more aware of the growing TB problem and promote the DOTS strategy as the best approach to fighting it.

In 2000, health ministers from across the globe gathered in Amsterdam, some faced rampant TB epidemics at home others were there to donate funds. Rich and poor countries joined forces pledging to act together against TB. In 2001, the initiative expanded and, always hosted by WHO, became the Stop TB Partnership that brought together many other organizations engaged in the fight against TB and they launched the first Global Plan to Stop TB, 2001–2005. Great importance was placed on encouraging research for new drugs, diagnostics and vaccines as well as on TB care and control. Instead of seeing TB as a problem of individual countries it was seen as a disease that knew no borders and thus costs were calculated to find out how much money was needed to tackle the TB epidemic on a global scale. By 2005, nearly all the goals of that first plan had been achieved. A further plan for 2006–2015 was developed. To date, the Partnership has been commended in two external evaluations.

In order to address the bottleneck in TB drug supplies, the Partnership established the Global Drug Facility in 2001. This provides countries with high-quality drugs free of charge or helps countries in procuring drugs at low cost, and supports national programmes to manage TB drug supplies and
ensure that these drugs are properly administered. The Partnership also helps countries apply for donors funding to purchase these drugs.

Between 2001 and 2009 the Global Drug Facility organized the delivery of 13.9 million treatments to 110 countries. Managers of DOTS programmes in poor countries no longer need worry about where they will get their next TB drugs, allowing them to concentrate on improving patient care.

A major concern for some DOTS programmes, however, was that some patients were not recovering from the prescribed ‘cocktail’ of medicines, raising fears that drug-resistance was to blame. Many DOTS programmes developed after previous years of poor drug supply and as a result drug resistance had already started to emerge. DOTS aims to minimize the emergence of drug resistance by supporting improved adherence. But where drug resistance is already a problem, DOTS alone is insufficient to contain it. Many programmes were unable to test for drug-resistant TB and often lacked the reserve drugs needed to treat this type of TB. In some places, the numbers were fortunately small; in other places, 10% or more of patients were not being cured due to multidrug-resistant TB (Photo 6.6).

Starting in 1999, WHO and its partners tested a new TB management strategy called DOTS-Plus in pilot projects. This was built on the basic DOTS foundation and aimed to make expensive ‘reserve’ second-line TB drugs more accessible to those who needed them. Access to these powerful medicines was provided by the Green Light Committee of WHO made up of experts from institutions such as CDC, Harvard University and the nongovernmental organization, Médecins Sans Frontières (Doctors Without Borders). As a result of the initiative and negotiations with the drug producers, some countries saved up to 94% of money they would have spent on multidrug-resistant TB drugs while ensuring that treatment was sound and the drugs they received were of good quality.

Following the establishment of the WHO Global TB Monitoring and Surveillance Project in the mid-1990s, the number of TB cases detected has shot up from 11% to 62%, while the level of successful treatment has climbed from 77% to 86% in 2007. This was achieved against a major increase in cases detected. It has also put the world within reach of achieving the Millennium Development Goal 6 to fight major infectious diseases, including TB, by 2015 (see Box 6.3 Fact file: tuberculosis).
Russians face new TB epidemic

Resistant forms of TB have also emerged in the Russian Federation. According to Grigory Volchenkov, chief doctor at Vladimir Region Tuberculosis Dispensary, it is a problem that goes back well before the collapse of the Soviet Union in 1991. “The growth of drug resistance is first of all a result of irregular taking of drugs and TB drugs of poor quality,” he says, adding that even in earlier decades medical staff did not always ensure that patients were completing their full course of treatment: “Between 1970 and 1999 we did not have adequate protocols of treatment.” A study by a group of Russian scientists published in 2000 in Russian tuberculosis journal Problemy Tuberkuleza traced evidence of drug-resistance back to 1979 and found a steady increase in the problem up to 1998.

By the end of the 1990s, the tuberculosis epidemic had reached alarming proportions across the Russian Federation, amid a failing economy, falling living standards and a crumbling health system, the supply chain for TB medicines broke down, greatly affecting treatment success. Orel province, in the south-western part of the country, was no exception. “The TB situation in the region was very bad, especially from 1999 to 2000,” says Dr Boris Kazyenny, chief doctor at Orel Province Tuberculosis Dispensary in the regional capital (Photo 6.7).

Kazyenny recalls how the supply chains of essential medicines for tuberculosis broke down and, with that, the quality of treatment. “We didn’t have enough essential drugs so we had to prescribe an incomplete course of chemotherapy and many patients did not adhere to the treatment regimen,” he says.

---

**Box 6.3. Fact file: tuberculosis**

**What is tuberculosis?** Infectious disease caused by the tubercle bacillus. It can kill up to two-thirds of infected people over a period of five years if left untreated.

**What does TB stand for?** Tuberculosis.

**Origin:** Found in human remains dating back 6000 years, but is probably older.

**Bacteria family:** Mycobacteriaceae.

**Main form:** 75% affect the lungs (pulmonary), but practically all organs can be affected.

**Transmission:** Coughing, through airborne droplets containing tuberculosis bacilli.

**Symptoms include:** Cough, coughing up blood, fever, night sweats and weight loss.

**Diagnostic tests include:** Microscopy, culture, new molecular methods, chest X-ray, etc.

**What is tuberculin?** A mixture of proteins found in the tuberculosis bacterium, used to test whether a person has a latent infection (see Box 6.5 Latent or active?)

**Treatment:** Combination of four drugs taken under direct supervision. Standard treatment duration is six months. Resistant strains take up to two years of treatment to cure and require a cocktail of different ‘reserve’ or second-line drugs.

**Vaccine:** Bacillus Calmette-Guérin vaccine, better known as BCG.
“That’s why after the beginning of the 1990s many of our patients did not make a full recovery and continued to transmit bacteria.” Since introducing the WHO-recommended DOTS strategy in 2001, the TB epidemic has stabilized in Orel and control efforts have made progress across the country (see Box 6.4 Evolution of a global strategy to ‘Stop TB’).

Just like in China, India and the USA, poor living conditions were a driving factor behind the TB epidemic in the former Soviet Union. Victor Punga, a researcher at the Central Research Tuberculosis Institute in Moscow, notes that TB rates took off during industrialization of the 1930s. Punga says: “We always had a lot of TB, before the (1917) revolution. At that time, they tried to explain the high level of the disease as a legacy of capitalism. But it wasn’t so. The situation was determined by social problems. Even if we have high-tech treatment, when people have no food and no place to live, the level of TB increases.... When industrialization began, people lived in very bad conditions and were underfed. This is the best soil for TB to grow.”

While it is too early to talk about winning the war against TB, after more than a decade of rising rates of TB, the numbers are stabilizing. Still, daunting challenges remain, notably with regard to the ever-changing microbe itself and its potential to spread fast in a world without borders, in an age of frequent jet travel and mass population movement.

**Multidrug-resistant TB**

The World Health Organization estimates that there were 440 000 new multidrug-resistant TB cases in 2008. Meanwhile, cases of extensively drug-resistant TB – which was first identified by WHO and CDC in March 2006 – are also on the rise. Extensively drug-resistant TB cannot be treated with first or most of the reserve second-line drugs, and has so far been found in

---

**Box 6.4. Evolution of a global strategy to ‘Stop TB’**

In 2006, WHO launched the Stop TB Strategy. It underpins the Stop TB Partnership’s Global Plan to Stop TB, 2006–2015 that sets global targets for TB control for 2015, including those for Millennium Development Goal 6. The six components of the Stop TB Strategy are:

- Pursue high-quality DOTS expansion and enhancement;
- Address TB/HIV, MDR–TB, and the needs of poor and vulnerable populations;
- Contribute to health system strengthening based on primary health care;
- Engage all care providers;
- Empower people with TB and communities through partnership; and
- Enable and promote research.
nearly 60 countries. Extensively drug-resistant TB can sometimes be successfully treated, when the necessary drugs are available, but it is a death sentence for most people who become sick with it. In August 2006, 52 out of 53 people infected with extensively drug-resistant TB died during an outbreak in Kwa-Zulu Natal, South Africa. Most of the dead were also HIV positive.

One of the places where the threat of multidrug-resistant TB and extensively drug-resistant TB is most apparent is the former Soviet Union. For example, official figures show that in 2008 nearly 1 in 4 of new TB cases in some parts of the north-western part of the Russian Federation were multidrug-resistant TB. In other newly independent states, such as Azerbaijan, the Republic of Moldova and Ukraine up to 1 of every 5 TB cases has multidrug-resistant TB, posing a serious threat to TB control. WHO is working with partners in those countries and internationally to control multidrug-resistant TB.

Tuberculosis rates in the Russian Federation are generally falling now and there are some successes in fighting drug-resistant forms of TB – not least in the province of Vladimir, home to over one and a half million people.

Since 2002, WHO has worked with the Provincial TB Dispensary in Vladimir, the country’s Central TB Research Institute, CDC and USAID (the USA’s government development agency) to implement an intensified programme for infection control aimed at preventing transmission of multidrug-resistant TB between TB patients, as well as reducing the risk of health-care personnel becoming infected. This helped to cut the number of cases among health workers of the Provincial TB Dispensary from 1080 per 100 000 personnel (1993–2002) to 160 (2005–2007) per 100 000 personnel. The Vladimir Provincial TB Dispensary also runs an Excellence Training Centre for health workers from across the country.

But, as we have seen in the past, such successes can always be overshadowed. In one of the last interviews before he died in 2009, Sir John Crofton said he considered the emergence of extensively drug-resistant TB a matter of grave concern and that it posed a similar challenge to the one he faced in Scotland 60 years earlier. He was nevertheless hopeful that several new drug candidates could still have an impact on it, but feared a period of time when many patients’ lives will be lost because of drug resistance.
For WHO’s Raviglione, while the emergence of highly drug-resistant strains is a serious concern, it is important not to lose sight of the TB problem as a whole. “All TB cases have to be treated properly or we will get more multidrug resistant cases,” Raviglione says, underlining the fact that to treat TB properly it is imperative that health ministers around the world realize the enormity of the problem. “They need to put more money into this and where they cannot, they need to apply for grants from the Global Fund (to fight AIDS, Tuberculosis and Malaria) or other international sources of aid.”

Raviglione wants to see more laboratories upgraded with new diagnostics technology. “We also need drugs of proper quality and trained physicians. Countries should not be afraid to call for outside experts to come in and teach them how to deal with this problem,” he says.

There are signs of political resolve at a global level, for example in 2009, at a meeting on drug-resistant TB organized by WHO in Beijing, China, in cooperation with the Chinese health ministry and the Bill & Melinda Gates Foundation. The meeting was attended by health ministers from the 27 countries carrying the greatest burden of drug-resistant TB, including four – China, India, the Russian Federation and South Africa – that account for an estimated 60% of multidrug-resistant TB cases worldwide.

---

Box 6.5. Latent or active?

The TB bacillus lodges itself in tiny air sacs in the lungs, known as alveoli. And as soon as it takes up residence, the immune system of a healthy person – the mechanism by which the body fights infections – sends macrophages, which are a type of white blood cell, to attack the TB bacteria that are protected by a tough waxy shell.

The macrophages gobble up the bacteria but then start to clump together, attracting other white blood cells that attach themselves to the clumps. Within a few weeks of infection, the clumps form small hard “tubercles” in which lung cells begin to die, breaking down into a cheese-like substance. For many people, the TB bacteria remain trapped inside the tubercles and this is as far as the disease goes. This state – when the infected person shows no symptoms and is not infectious – is known as latent or dormant TB. More than 90% of people in this state do not develop active disease or any symptoms, which means they do not develop ‘active TB’. An estimated two billion people – about one third of the world’s population – are latentely infected today.

But if the immune system of someone with latent TB is weakened, for example by HIV infection, the bacteria break out of the tubercles, attracting more macrophages and creating more tubercles. Left unchecked, tubercles continue to grow, destroying lung tissue and replacing it with more of the cheese-like substance, which eventually liquefies and is carried up the airways, leaving behind cavities and scar tissue. The build-up of mucus that results from the liquefaction of dead cell tissue causes persistent coughing, one of the main early warning symptoms of TB.

At first, TB can be mistaken for a bad cold or bronchitis. The patient experiences extreme fatigue and a cough that just won’t go away. But as the TB bacteria keep killing cells and destroying lung tissue, blood vessels are affected, and blood appears in the sputum or matter from the lungs that is coughed up. And as the tubercles make holes in the lungs, breathing becomes more difficult. The patient loses weight, and often becomes pale and lethargic. It is this characteristic weight loss that inspired the term ‘consumption’, and the pallor that inspired one of the many nicknames for the disease: the ‘white plague’. In the famous poem, Ode to a nightingale, poet John Keats, who died of tuberculosis in 1821, wrote of a condition “…where youth grows pale, and spectre-thin, and dies”, alluding to TB’s relentless deterioration of the body.
Participants pledged US$ 15 billion to finance the TB response particularly to drug-resistant strains and set a deadline of 2015 to do so. They also called for increased investment in research and development of new TB diagnostics, drugs and vaccines, and called upon WHO and the Stop TB Partnership to provide technical support to help them implement plans to respond to drug-resistance. The Organization believes that only 3% of the half million multi-drug-resistant TB cases estimated to occur each year worldwide are receiving adequate treatment from public services. Although it is unclear how many more are receiving care from the private sector, it is still a small number. That means that there are people with multidrug-resistant TB who may not be aware they have it and who can spread potentially untreatable pathogens to people around them (see Box 6.5 Latent or active?).

You don’t have to be rich

Despite the enormity of the challenge, Raviglione is optimistic about the future: “I know that when people have the will, they get things done… And I’ve seen that with my own eyes.” Raviglione cites Estonia and Latvia, which were once part of the former Soviet Union and where 9% of TB cases were already multidrug-resistant 10 years ago. “They decided to request external aid. They got technical help. They created hospitals where they could isolate cases. They got the drugs, and they got the laboratories.”

Swaziland is another country that has asked for external funding and technical support. As in other parts of sub-Saharan Africa, TB is closely associated with the HIV/AIDS epidemic there – an association that invites a combined response. In fact, Swaziland has the highest per capita rates in the world for both TB and HIV/AIDS. This fact was brought home to Raviglione in
2008 when he travelled to Swaziland, a country sandwiched between Mozambique and South Africa. There he helped the health ministry convene a meeting with nongovernmental and faith-based organizations working on the frontline of the AIDS epidemic to persuade them to put TB on their agenda. As a result Swaziland received a grant from the Global Fund To Fight AIDS, Tuberculosis and Malaria to tackle the double scourge. “We helped to create a national partnership between government and local and international nongovernmental organizations, so that access and delivery of services can be much more effective,” Raviglione says.

Another case in point is Lesotho, a small country surrounded by South Africa that also sought external funding to tackle its TB epidemic in 2006, an epidemic that Raviglione described as “disastrous”. “So the decision was made by the Minister of Health to invest in labs to do diagnostic tests”, he says, “and within a year I was there to inaugurate the lab in the capital city (Maseru), which was able to use the most advanced liquid culture media equipment that produces a result within a week rather than three months. Now they have introduced a new molecular method that can diagnose multidrug-resistant TB in a day – a method that is not even widely used in the rich world yet. So where there is a political will, there is a way” (Photo 6.8).