FT Health Combating Tuberculosis

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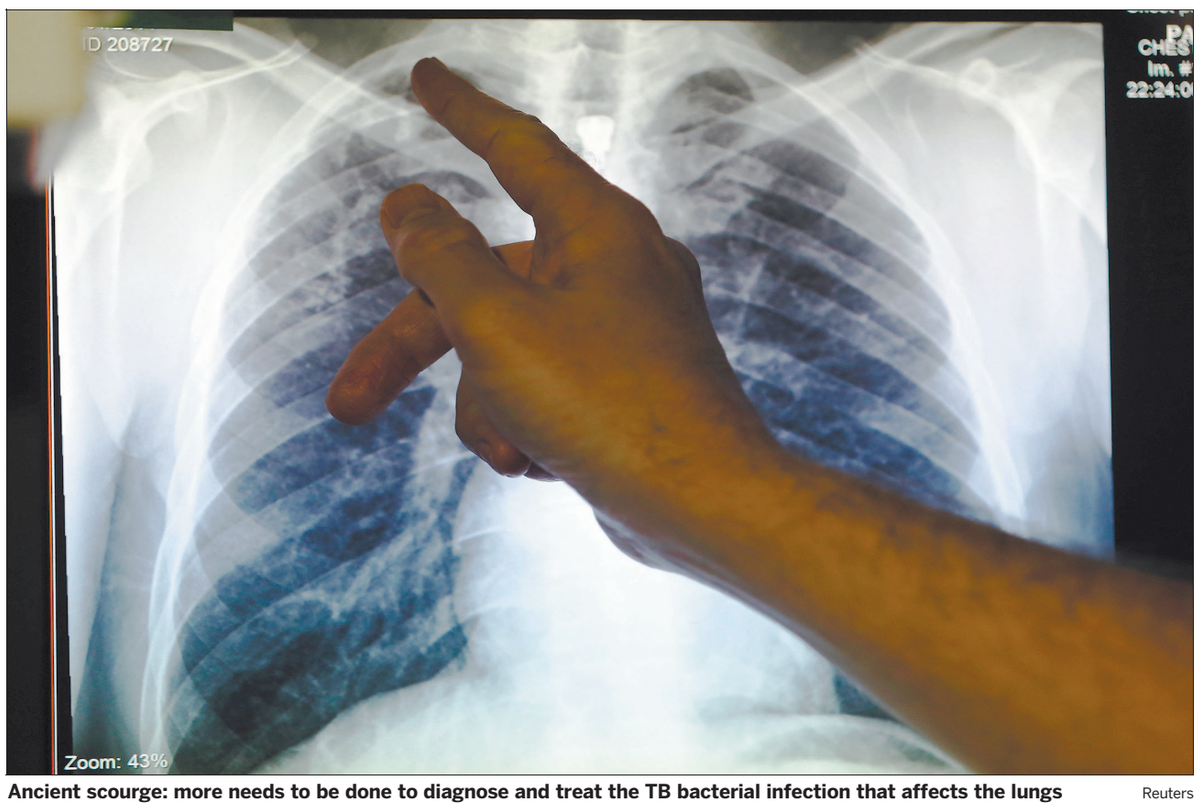
Killer of the poor now threatens the wealthy

TB incidence has been falling for a decade but it still kills 1.3m people a year, says *Andrew Ward*



Ancient scourge: more needs to be done to diagnose and treat the TB bacterial infection that affects the lungs Reuters

Its victims have included George Orwell, Frederic Chopin, Franz Kafka, Emily Brontë and Eleanor Roosevelt.

If tuberculosis were still killing such cultural giants, it would not be hard to attract attention and funding to the campaign for its eradication.

Yet, today, even though it kills 1.3m people a year, TB is the poor relation of global diseases, struggling to match the resources attracted by more high-profile causes such as HIV.

In 2013, research spending on TB by the US National Institutes of Health amounted to $266m, compared with $2.9bn on HIV/Aids, despite the two diseases causing a similar number of deaths.

"TB has killed more people than all other pandemics combined," says Aaron Oxley, executive director of Results UK, an anti-poverty group. "But it has been with us for thousands of years and it is a slow disease. Aids is all about sex and drugs. TB is about coughing and spitting. Which are people more likely to want to get involved in?"

Despite the funding difficulties, significant progress has been made. Incidence of TB has been falling steadily for a decade and the mortality rate is down 45 per cent since 1990 – within reach of the target for a 50 per cent reduction by 2015 set in the UN's Millennium Development Goals.

By some estimates, TB accounts for more than half the estimated 8.7m lives saved by the Global Fund to fight Aids, TB and Malaria since its launch in 2002, despite receiving only 16 per cent of the funding. Such figures are hard to pin down but few would dispute that the TB programme has produced a good return on investment.

"I can't think of another field of public health where so much has been achieved with so little but progress is painfully slow," says Mel Spigelman, director of research and development at TB Alliance, a non-governmental organisation.

While headline numbers are coming down, a closer inspection reveals how much more is still to be done. Of the 8.6m people estimated to contract TB each year, 3m do not receive diagnosis and treatment, according to the World Health Organisation.

Mr Oxley said the likely success in meeting the Millennium Goals on TB was no cause for celebration. "Every day 3,000 people still die from this disease which shows that the goals were very unambitious. We're coming from a long way back."

> 'Tuberculosis has killed more people than all other pandemics combined'

TB – a bacterial infection that usually affects the lungs and spreads through sustained contact between people living or working in proximity – has been a scourge of humanity for millennia. Fragments of the spinal column from Egyptian mummies show clear signs of the disease and possible traces were detected in the skull of a fossilised Homo erectus – early human ancestors – dating back about 500,000 years.

Today, TB has been mostly banished from the rich world aside from pockets of vulnerability among impoverished communities in cities such as London. But it remains one of the greatest public health risks in many low- and middle-income countries, where 95 per cent of fatalities occur. India, China, South Africa, Indonesia and Pakistan top the list in terms of volume of cases.

Efforts to tackle the disease are being complicated by the rise of drug-resistant strains – a consequence of poor management of existing medicines by doctors and poor compliance by patients. Special treatments are available to overcome drug-resistance but they are costlier and longer-lasting with more severe side effects and lower levels of effectiveness.

There was a breakthrough last year when US regulators approved a new treatment for multi-drug resistant TB (MDR-TB) by Johnson & Johnson, the first new TB medicine of any kind for 40 years. Another, from Otsuka of Japan is also on the launch pad. While welcoming the new

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A breakthrough drug is trapped in a Catch-22

Access

Without approval, linezolid is in limbo, writes *Andrew Jack*

It is expensive, inaccessible, poorly tested and potentially toxic with side effects including intense pain. But linezolid offers rare hope in the desperate search for treatments to tackle the worst cases of TB.

The medicine's story – which spans the US, South Korea and South Africa – epitomises the difficulties in offering a cure to a growing number of patients struggling to survive.

In the shadow of Table Mountain and the wealth of nearby Cape Town, dozens of South Africa's poorest people make their way to clinics in Khayelitsha township every day seeking diagnosis and support.

While the country, a hotspot for the disease, has made progress in the past decade, there are still 6,000 patients in Khayelitsha alone, including 200 who are unable to fight highly resistant strains of the microbe with current drugs.

For new weapons to emerge in the battle against resistant TB, attitudes of drug companies, regulators and donors require an overhaul.

Over the past two years, Médecins Sans Frontières, the medical charity that supports treatment in Khayelitsha, has focused on a new possibility among the limited options available: linezolid, commonly known by its brand name Zyvox.

Eric Goemaere, a senior regional adviser for MSF, says: "There is increasing evidence globally, as well as based on our own experience with the drug in Khayelitsha, that it is effective, and often the last treatment option for patients who take it."

But doctors and their patients are caught in a Catch-22 situation. Pfizer, the US pharmaceutical company that owns the drug, has not funded clinical trials to test linezolid for TB; it has not submitted it anywhere for regulatory approvals; and, in the absence of such authorisation, will not even sell it to MSF for use in TB at an affordable price.

Work on the drug dates back to the late 1980s, when Steven Brickner, a chemist at the pharmaceutical company Upjohn of the US, heard presentations on a new experimental class of anti-bacterial medicines called oxazolidinones. It took another decade, a partnership with colleagues working largely in their own time and a takeover of Upjohn by Pfizer before the project came to fruition.

In April 2000, the US Food and Drug Administration approved linezolid to treat patients with infections caused by Gram-positive bacteria, including community-acquired pneumonia and vancomycin-resistant enterococcus infections caused by methicillin-resistant Staphylococcus aureus (MRSA), normally administered over a few weeks.

The authorisation was a breakthrough that remains extremely important, given the escalating scourge of antibiotic resistance: there are rising cases globally of lethal bacteria resistant to all existing drugs, and a scant "pipeline" of potential replacements.

TB treatments are one example of the phenomenon, but also a special case. They are given for longer periods of up to two years,

> For Pfizer, the absence of a clearly lucrative market has militated against investment

in combination with other drugs, and offer scant commercial return, since the disease is concentrated among the poor.

For Pfizer, the absence of a clearly lucrative market, along with the costs and risks of launching complex clinical trials to examine the drug's potential against TB, have militated against investment. More broadly, the company has wound down its antibiotics research division in the past three years.

Filling the gap, an unusual partnership has sprung up over the past decade. South Korea has a high burden of TB, but is rich enough to afford more costly medicines and investment in research.

With financial support from the US National Institutes of Health, it ran a promising trial, whose results were published last year. Pfizer did not fund the trial but did donate linezolid for use in patients.

The study showed 34 of 39 treated patients cleared their infection, despite many significant side-effects. Subsequent small-scale studies by MSF and others showed similar promise.

Linezolid has been included in the World Health Organisation and South African national guidelines for drug-resistant TB treatment and has been approved for TB projects by an expert review panel of the Global Fund to Fight Aids, Tuberculosis and Malaria. Yet because the drug has not been approved by regulators for use in TB, MSF cannot gain access to it at public sector prices.

Instead, it pays R676 ($63) per pill through the private sector, compared with the R288 paid by the South African government to treat MRSA with the same drug.

MSF says Pfizer never responded to its requests for access at the government price in 2011. Pfizer counters it "has to remain mindful of global and local regulatory guidance on the provision of its medicines. As with all innovative medicines, the price of Zyvox is based on the scientific innovation it represents."

Meanwhile, MSF has sought to buy far cheaper generic versions in countries with weaker patent enforcement such as India. The imminent expiry of linezolid's patent could boost its affordability.

But that creates a final paradox: with only generic producers involved, there will be even less incentive for large-scale trials of the drug's effectiveness.

Strong alliances needed to end killer disease

Comment
AARON MOTSOALEDI

It is a challenging time to be the health minister for South Africa, and to chair the Stop TB Partnership. Nearly 9m people fell ill with tuberculosis in 2012 around the world. More than 1m died. We are not reaching the vast majority of people who are at risk.

Rising drug resistance to TB is a global security threat. We cannot fight this problem without new tools. Some of our drugs are more than 40 years old and people continue to be diagnosed using techniques from the last century. Alas, we have a funding gap upwards of $1.35bn every year for research and development.

We need another $2bn a year to help treat TB. Governments, donors and civil society groups must work together.

In South Africa, we know that TB is not just a health issue. It hurts our economy. We are expanding our health services, especially to fight the traditional diseases of poverty, such as TB and HIV/Aids. This World TB Day I salute the progress we have made, while warning of the miles we must still travel to beat this terrible disease.

Let us not underestimate the size of the problem: TB has been with us so long, and has remained so deadly, that the global TB pandemic has killed 1bn people – more than all other diseases combined.

Africa accounts for about 40 per cent of all TB deaths. Those who suffer most are at the margins of society: the malnourished, refugees, and other vulnerable groups. Poverty, financial barriers, and the absence of health services means these people not only suffer from TB, but are being missed by the health systems that could offer them treatment.

One of the biggest barriers is finding those not being reached. Of the 9m people developing TB each year, more than 3m are not diagnosed. We must focus on "hotspots" of high TB transmission and low cure rates.

In South Africa we have identified three particularly vulnerable communities: the prison population; mine workers; and people living in peri-mining communities. During the 2013 World TB Day South Africa released guidelines on infection control for prisons and deployed the first GeneXpert machine in a prison to ensure rapid diagnosis and treatment of drug sensitive and drug resistant TB, In addition, routine screening of inmates on admission and release for TB and testing for HIV is currently being rolled out to all prisons. Contact tracing for newly incarcerated inmates – screening of their families has also commenced.

More than 30 per cent of TB infections in southern Africa can be attributed to mining (*see article overleaf*). Prevalence can be as high as 4,000-7,000 cases per 100,000 people – 20 times the global average and 10 times that of the region.

Factors ranging from exposure to silica dust and poor living conditions, put miners at high risk. They are also often on the move, taking TB to those close to the mines and to miners' home communities. This constant movement is the most significant challenge we face to ensure miners access healthcare and complete their treatment.

Mining generates 60 per cent of southern Africa's foreign exchange reserves and 10 per cent of regional GDP. One only has to look at the medical costs, revenue and productivity losses, and lost wages to see the immense drag on economic growth.

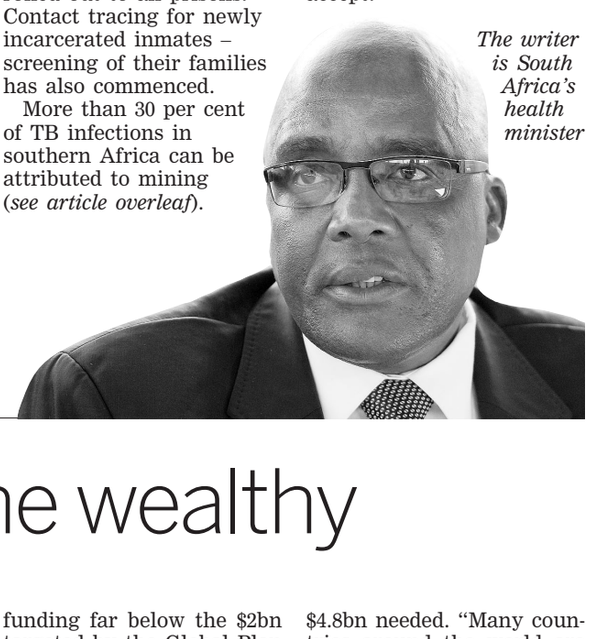
While mining companies have programmes to detect and treat miners for TB and HIV, this is available only to mine workers and not the communities in which these miners live. Additionally, there is no system to ensure continuity of care for miners when they go home for vacation or when their contracts end.

With support from the World Bank and others including The Global Fund and the Stop TB Partnership, South Africa this week hosts a ministerial level meeting with companies and worker representatives to consider ways of securing for migrant miners the best possible care whether they are on the mines in South Africa or when they return to their homes in neighbouring countries. We hope to agree on a true public health response to both TB and HIV as these diseases do not respect borders!

> Drug resistant TB gobbles up more than a third of South Africa's treatment budget

We must come together to help other vulnerable groups. Undetected TB has led to an explosion in difficult, and sometimes impossible to treat drug-resistant cases worldwide.

By finding the missing 3m and giving them quality care we can halt the rise of drug-resistant TB. Although this accounts for only 3 per cent of the cases we treat, it gobbles up more than a third of South Africa's treatment budget. Poor countries with high rates of drug-resistant TB cannot tackle it alone. The human and economic costs of not doing enough to combat TB is simply too grave to accept.



The writer is South Africa's health minister

Stubborn new strains threaten to reverse years of progress

Resistance What started as a problem of people not taking their medicines correctly has spiralled out of control, reports *Andrew Ward*

With global incidence of tuberculosis steadily declining at a rate of about 2 per cent a year, it would be easy to conclude the world had got a grip on one of its oldest and most deadly public health threats.

Yet, this progress masks the rise of new drug-resistant strains of the disease that experts warn could unravel much of the work done to tackle TB in recent decades.

In some countries, up to 20 per cent of new cases are resistant to at least two of the four drugs contained in the standard combination treatment for TB – the definition of multi-drug resistant tuberculosis (MDR-TB).

Drug resistance is a particular problem in TB because many patients do not stick to the full six-month treatment – allowing some hardy bacteria to survive and gradually evolve into new strains.

Neil Schluger, chief scientific officer of the World Lung Foundation says: "It is an enormous problem and it is running out of control."

An additional barrage of medicines is available for those cases where the standard treatment fails. But these "second-line" drugs work in fewer than 50 per cent of cases and involve long and costly programmes with unpleasant side effects. This means many people do not complete the treatment – threatening to create a vicious circle of deepening drug resistance.

At the end of 2012, the World Health Organisation had detected cases in 92 countries of TB that is resistant to both the first and second line medicines.

This form of the illness is called extensively drug-resistant tuberculosis, or XDR-TB, and the WHO calls it "virtually untreatable". All this explains why there has been so much excitement over the approval last year of bedaquiline, a new, more effective MDR-TB treatment from Johnson & Johnson that should bolster the battle against drug resistance.

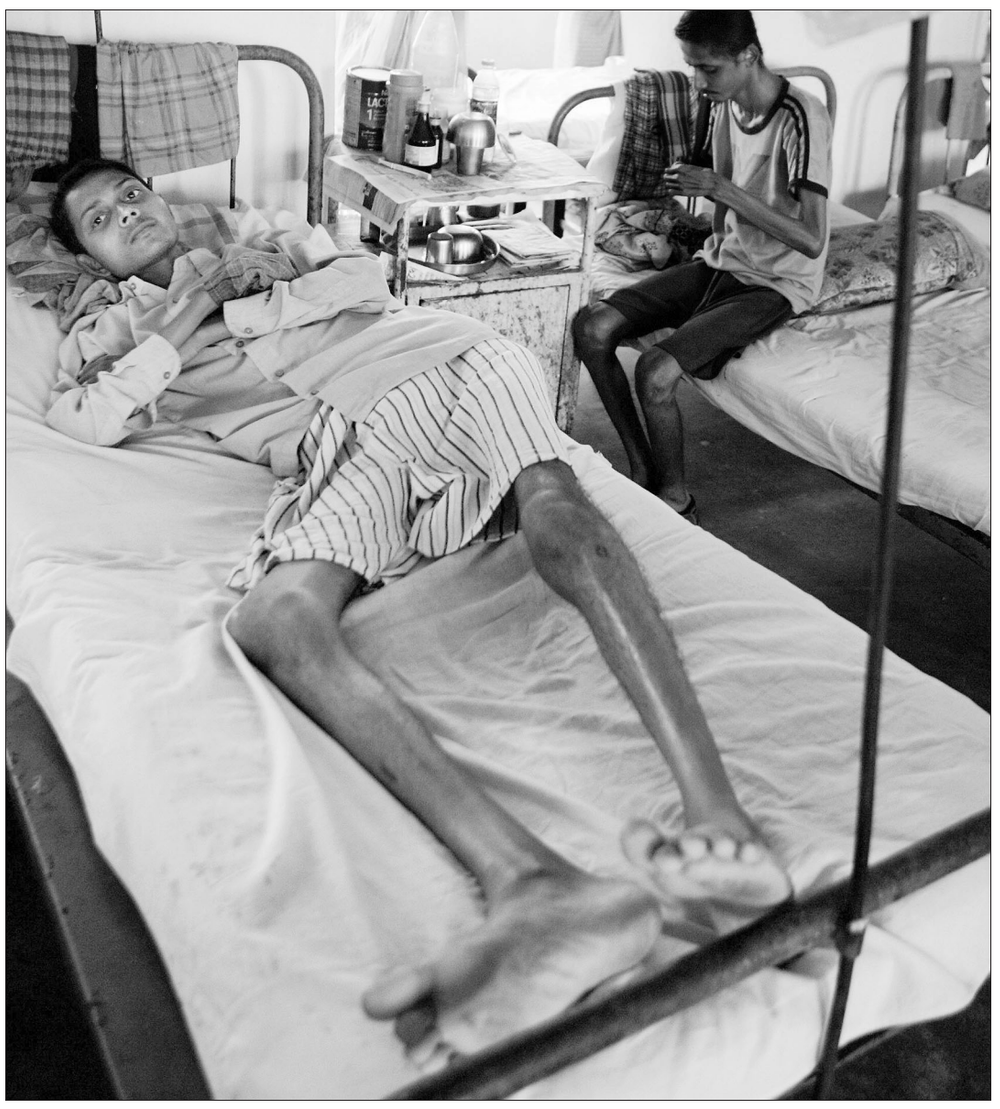
However, access to the medicine – the first new TB drug of any kind for four decades – is being tightly controlled so as to prevent its misuse fuelling the very problem it is intended to address.

The US healthcare group is working to come up with a new combination treatment that will maximise the effectiveness of its new drug and slow the build-up of resistance. "We have to be very careful how we use the drug," says Wim Parys, J&J's head of research and development for global public health. "If you give it alone, bacteria will be able to adapt. That has been the story of antibiotics."

While health experts welcome progress towards better treatments, they say the most urgent challenge is to increase detection. Almost 84,000 patients with MDR-TB were reported globally in 2012, up from 62,000 the year before, but the World Health Organisation estimates the real number at about 450,000, causing 170,000 deaths. More than half the cases are believed to have occurred in India, China and Russia.

According to the Stop TB Partnership, a WHO-backed body that aims to co-ordinate global efforts to tackle the disease, about 1m people will need treatment for MDR-TB between 2011 and 2015 if its spread is to be slowed.

> Only a third of Europeans with drug-resistant TB finished their treatment



Under pressure: a tuberculosis hospital in Kolkata, India
Getty Images

Last year, however, the WHO warned the world was "far off-track" in diagnosing and treating MDR-TB. "This now constitutes a public health crisis that is not being adequately recognised and addressed," it said. "Gaps are growing rapidly in many countries, with patients reported to be on long waiting lists for treatment."

The rise of drug resistance is forecast greatly to increase the financial burden of fighting TB because treatments are costlier and complications more frequent. Whereas the standard treatment takes six months to complete, patients with MDR-TB require medication for two years or more and the drugs are more toxic.

By 2015, the WHO estimates 20 per cent of the $8bn needed by low and middle-income countries to combat TB will be absorbed by treatment of MDR-TB, even though the condition accounts for only 3.6 per cent of all TB cases worldwide.

And despite the rising expenditure, outcomes are often poor. Only 48 per cent of people who enrolled on treatment for MDR-TB in 2009 were reported to have been cured by last year, according to the WHO. Some of the highest concentrations of MDR-TB are in eastern Europe, which accounts for 15 of the 27 countries with the heaviest burden. These include Ukraine, Moldova, Belarus and Armenia and EU members Estonia, Latvia, Lithuania and Bulgaria.

So far there has been no large-scale spread of MDR-TB to western Europe but public health officials are watching warily. In the UK, 1.6 per cent of the 8,751 TB cases reported in 2012 were multi-drug resistant. Nearly 90 per cent of these were among people born outside the UK, according to a report by Public Health England.

Across Europe, only one in three people diagnosed with MDR-TB finished their treatment successfully, according to the European Centre for Disease Prevention and Control.

Says Marc Sprenger, ECDC director: "If we are not able to diagnose and treat patients with multidrug-resistant tuberculosis early and successfully, this not only puts patients' lives at risk but also paves the way for XDR-TB."

He was talking about Europe but the same applies, on a greater scale, across the developing world. "MDR-TB is completely out of control and a growing threat to public health," says Mr Schluger. "The world needs to take this problem seriously."

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treatments, activists say they will not change the landscape on their own.

"Even if you have new drugs you need the public health infrastructure to diagnose patients, deliver the drugs and ensure adherence to the treatment," says Neil Schluger, chief scientific officer of the World Lung Foundation. "That is still lacking in many parts of the world."

A big push is under way to improve detection with the introduction of testing equipment that can shorten the time to diagnosis from weeks to a few hours – and with increased accuracy. Many diagnoses still take place using the same slide and microscope technique pioneered by Robert Koch, the German microbiologist who won the 1905 Nobel Prize for Medicine for his work on the disease.

But this is beginning to change as 1.4m state-of-the-art testing kits are distributed to 21 countries under a $26m scheme backed by the WHO, the Stop TB Partnership and Unitaid, a Geneva-based funding body.

A sample of a patient's sputum is deposited in a cartridge which clicks into a device that looks similar to an espresso machine.

Philippe Duneton, executive director of Unitaid, says the technology, called GeneXpert, has already helped increase detection in India and South Africa. Uptake has been encouraged by a cut in the previously prohibitive cost of cartridges from $18 to $10 each.

Work is also continuing on potential vaccines, despite the failure last year of the first large clinical trial of a new TB vaccine for nearly a century. The £30m programme led by Oxford university tested the MVA85A vaccine on 2,800 South African children but failed to show a positive impact on immune response.

Ann Ginsberg is chief medical officer of Aeras, a US non-profit organisation focused on developing a vaccine for TB. She says there are about 12 further potential vaccines being tested but the cost, length and complexity of full-scale trials remain obstacles.

Other areas of research include links with HIV, diabetes and smoking, all of which increase the risk of developing TB.

Overall, global spending on TB-focused research and development fell by $30m to $627m in 2012, according to the latest report by the Treatment Action Group, which monitors investment in HIV and TB programmes. This leaves annual R&D funding far below the $2bn targeted by the Global Plan to Stop TB.

Private sector companies cut spending by 22 per cent to leave them accounting for just 18 per cent of the total – a sign of most drug-makers' reluctance to invest in a disease concentrated among poor people in poor countries.

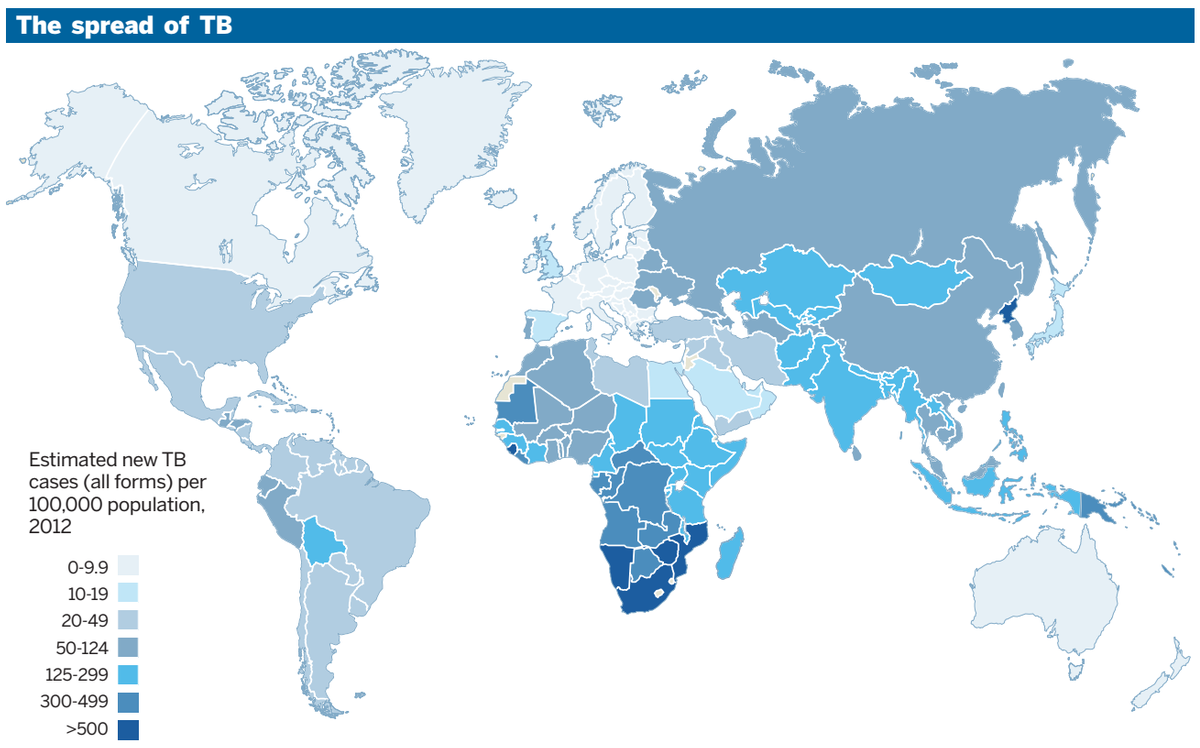
Public funding accounted for 61 per cent and philanthropic organisations, such as the Bill and Melinda Gates Foundation, provided 20 per cent.

Money for treatment and diagnostic programmes is also tight, with the WHO last year reporting a $1.6bn annual shortfall in the $4.8bn needed. "Many countries around the world are not contributing their fair share," says Mr Spigelman.

As well as rich nations, he says developing Bric countries must also help out given their growing wealth and big TB problems. "India and China are putting in more resources but they tend to focus on domestic initiatives rather than taking part in international efforts."

Mr Schluger says: "The biggest challenge is for people to realise how much TB is out there. The rate is going down 2 per cent a year but that is too slow for eradication to happen for decades to come."

The spread of TB



Source: WHO

Al Story boards the Find & Treat van, a mobile service that looks for and treats people suffering an active infection Reuters

Resurgence of an illness that respects no borders

Europe Public health services look at ways to fight an infection widely considered to have been purged from the developed world, says *Rose Jacobs*

Cruising the streets of London, a white van emblazoned with the National Health Service's logo is seeking out a specific subsection of the capital's population: the people most vulnerable to tuberculosis.

The infection is often thought to have been purged from the developed world. But London is western Europe's TB capital. Some boroughs have incidence rates comparable with those of Nigeria, Mali, Brazil, and Iraq.

The disease does not respect national borders. It destroys people's lives and racks up huge medical costs. And so the white van project, set up in 2005 by a medical professional called Al Story and staffed by a small team of nurses, social workers and former TB patients, has its work cut out: find people who might be suffering an active infection (a third of the world population is infected but it lies dormant in 90 per cent of that group); persuade them to start a course of medication; and make sure they see it through the minimum six-month period.

Two independent evaluations have found the Find & Treat service to be not only highly cost-effective, but potentially cost-saving – and no wonder, given that treating TB can run from £5,000 for "straightforward" cases to £250,000 in the case of multi-drug-resistant strains.

Vehicles like Mr Story's van were used in the UK after the second world war, but were phased out in the late 1970s and early 1980s as TB prevalence fell. Today's model, however, operates in a more targeted way than its predecessors, which aimed for broad screening of the population and whose usefulness was dwindling by the time they were scrapped. When Mr Story was testing the idea in 2002, he borrowed a Dutch unit and focused on high-risk communities: "We found three active cases in a day and a half of screening. We decided we should reintroduce this."

The van has cutting-edge diagnostic technology that is particularly useful for testing people with HIV – a common pairing with TB. Other risk factors include homelessness, addiction and immigration. And yet 80 per cent of cases in the UK are either people born in the country or who have lived in Britain for more than two years.

"Most of the TB among the immigrant community is latent activation," says Aaron Oxley, executive director of Results UK, an anti-poverty group. Poor diet, exhaustion or crowded housing weaken the immune system, allowing TB to break free from the body's walling-off mechanisms. It is no coincidence that immigrants often face these conditions. People from the former Soviet Union present a particular problem, says Fanny Voitzwinkler at Global Health Advocates in Brussels. They are much more likely than anyone else in the world to become infected with multi-drug-resistant strains of the disease. Eastern European approaches to treatment, such as insisting on in-hospital rather than ambulatory care, have meant patients often avoid seeking help, thereby infecting others with the more dangerous MDR strains.

"It's the MDR bug that's spreading," Ms Voitzwinkler says, adding that some European countries, such as Romania, have lower MDR treatment success rates than, say, the Democratic Republic of Congo. She fears the situation could worsen as the Global Fund to Fight Aids, Tuberculosis and Malaria changes its funding model to focus more on the world's lowest-income countries.

> 'Some parts of London have TB rates comparable to those of Mali or Iraq'

In Germany, the law can force hospital treatment on patients. Timo Ulrichs, a doctor leading the TB section of the Koch-Metschnikow-Forum, a health partnership with Russia, sees this as one of many tools for fighting the disease in the developed world.

Others include technology, such as public health information that can be translated into multiple languages using a smartphone, and reintegration of TB into the medical education system, where it has been neglected.

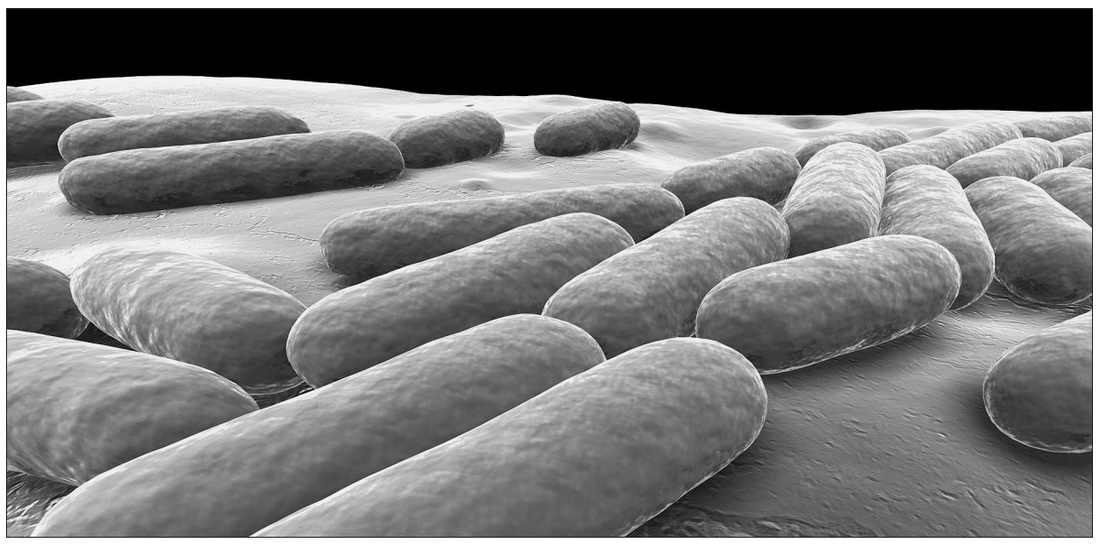
This measure might have helped Amy McConville. The 27-year-old policy assistant at a UK charity visited her GP in Ealing, London, in 2005 when she was an aspiring law student with a persistent cough. Nine months of visits failed to identify the problem, despite the borough having high rates of TB. She says: "I don't fit the profile of the illness, and I hadn't travelled anywhere with high rates of TB."

By the time she started the daunting treatment, she had lost three stone, her hair was falling out and her left lung had collapsed.

Struck by both the harrowing side effects of the drugs – including joint pain, nausea and, in extreme cases, blindness – and the loneliness of being a TB patient in a "low-burden" country, Ms McConville helped found the TB Action Group, the UK's only support and advocacy group for TB. Its work includes running telephone help lines, political advocacy and awareness-raising. "When you look at the people in our network, many of whom are not representative of the disease, you can see what happens when people don't think about TB."

Genetics offers route to cure

Science Molecular and genomic research points to new treatments, writes *Clive Cookson*



Breakthroughs: one project is working on an antibiotic to attack the TB bacteria

Around the world, laboratories are working to make up for time lost during the late 20th century, when tuberculosis was ignored or seen as a health problem that had gone away.

Although some of the fruits of this research are already in trials – with 10 drugs in late clinical development and a dozen vaccines in the pipeline – much is still at the earlier stages of scientific investigation.

This month, for example, École Polytechnique Fédérale de Lausanne in Switzerland has set up a charitable foundation to develop what its scientists say is an extremely powerful antibiotic discovered through a European research programme. PBTZ169, as it is known, attacks the TB bacterium *Mycobacterium tuberculosis* through its strong point, the cell wall that shields it from antibiotics and the patient's immune system.

"Our molecule makes the bacterium burst open," says Stewart Cole, director of the Swiss study.

Animal tests show PBTZ169 is very effective when combined with two existing TB drugs, pyrazinamide and bedaquiline. "This could be the winning strategy," says Dr Cole. "These molecules attack different targets in the bacterium. By combining them, we drastically reduce the risk it will mutate into more resistant forms."

Early versions of PBTZ169 were not absorbed fast enough into the body, so the team enlisted new technologies such as structural biology to redesign the molecule. "Tuberculosis is often wrongly considered a disease of the past, but to fight it, we need 21st-century technologies," Dr Cole adds.

The rising power and collapsing cost of genome sequencing are likely to provide important leads to improved TB diagnostics and drugs.

In September, the journal Nature Genetics published papers by four independent research teams on the full DNA sequences of 600 strains of *M. tuberculosis* from around the world. By comparing the genomes, scientists gain insights into the emergence of drug resistance and possible targets for drug development.

For example, China's BGI (formerly Beijing Genomics Institute) discovered 121 genes and mutations strongly associated with drug resistance, which indicated a more complex genetic basis for resistance than previously suspected. "We expect our breakthrough can shed new insights for exploring the mechanisms of drug resistance and lay a solid foundation for protection against TB," says Dongfang Li, BGI project manager.

Another recent study, published in Lancet Respiratory Medicine, demonstrated the diagnostic potential of DNA sequencing in cases where TB recurs after treatment. Until now, it has been hard for doctors to establish whether a patient has suffered a relapse of the original infection or picked up a new infection with a different strain. Genome sequencing gives the answer, which is important for managing the disease.

"What surprised us in this study is the frequency with which patients were infected with two separate strains of *M. tuberculosis*," says co-author Stephen Gillespie, professor of medicine at St Andrews University. "As well as being important for TB clinical trials, this has implications for the evolution of multiple drug-resistant tuberculosis."

Genomics has also shed light on the evolution of TB. Researchers at the Swiss Tropical and Public Health Institute in Basel sequenced the full DNA complement of 259 *M. tuberculosis* strains from around the world and found the bacteria must have moved out of Africa with the first modern humans more than 70,000 years ago and spread round the globe with them.

> The rising power and falling cost of genome sequencing are likely to provide important new leads in TB diagnostics

"The evolutionary paths of humans and TB bacteria show striking similarities," says Sebastien Gagneux, the study leader. A study of skeletons from a 7,000-year-old site in Hungary by scientists at the University of Szeged found traces of TB proteins and genes in the bones. In parallel with all the genomic analysis, an international project is mapping the molecular circuitry of *M. tuberculosis* – the regulatory networks that adapt to changing conditions in the human body.

"We have generated the first large-scale experimental map of thousands of molecular interactions in the bacterium that enable it to cause disease," says James Galagan of Boston University, lead author of the project's report. The study showed, for instance, how TB bacteria cope with a low oxygen environment inside host cells and how they consume human cholesterol.

"Based on this map, we have developed the first computer models that will enable us to study more easily this challenging infectious organism and develop drugs, therapeutics and diagnostics," Dr Galagan adds.

Molecular and genomic research of this sort will take decades to translate into widely available TB treatments, but it should ensure the pipeline of drugs does not run dry again.

Filling the gap where big pharma fears to tread

Investment

Incentives needed where profits scarce, says *Andrew Ward*

For an industry so often on the back foot over ethical issues, the approval last year of the first tuberculosis drug in 40 years was a chance to trumpet Big Pharma's positive role in tackling global health problems.

However, while Johnson & Johnson's launch of its bedaquiline treatment has been widely celebrated as a breakthrough, it remains an exception to the generally gloomy outlook for private sector investment in TB research and development.

More typical was the decision by AstraZeneca in January to shut a laboratory in India where it was conducting early-stage research into TB as well as malaria and neglected tropical diseases.

The UK-based company said it would continue working on an experimental TB drug undergoing Phase II trials in South Africa and pledged to share information. But its decision underscored the difficulty of persuading drugmakers to invest in the field.

Mene Pangalos, head of innovative medicines and early development at AstraZeneca, says the company thinks it can make a bigger impact in other areas.

"We have limited R&D budgets," he says. "You can spread yourself so thin you end up not doing anything well."

Critics point out that AstraZeneca's priorities – cancer and cardiovascular, respiratory and autoimmune diseases – are all most common in the developed world, and cite the closure of its Indian R&D centre as proof that a new model is needed for developing drugs where there is no commercial market.

"Drug companies want to make drugs for chronic diseases that people in western countries are going to take for the rest of their lives," says Neil Schluger, chief scientific officer of the World Lung Foundation.

"Companies will need incentivising by governments and non-governmental organisations if they are going to invest," he adds.

TB is particularly unattractive as a commercial proposition because, unlike HIV, which affects significant numbers in rich countries, it is heavily concentrated among the indigent in poorer countries.

So why did J&J press ahead when others have retreated? In part, it stemmed from the commitment of Paul Janssen, founder of Janssen Pharmaceutica, now part of J&J, whose sister died of TB. But it required the backing of the US parent group to keep going. There were some economic incentives, including a scheme offered by US regulators under which J&J can put another, potentially more lucrative new drug through an accelerated review process as a reward for developing a TB treatment.

Limited budgets: Mene Pangalos

Wim Parys, head of R&D for global public health at J&J, says the group is not expecting to make money from bedaquiline.

"We have been extremely fortunate that we have people right to the top level of the company who have supported this product, not for any commercial reason but because it was the right thing to do," he says.

"We just had to convince them that it was a significant drug that would change health outcomes."

Bedaquiline, known by its brand name Sirturo, was approved by the US Food and Drug Administration last year as a treatment for multi-drug resistant tuberculosis (MDR-TB) after trials showed it cured 57.6 per cent of patients after 120 weeks, compared with a 31.8 per cent success rate for existing treatments.

Mr Parys says the discovery stemmed from Janssen scientists including TB in tests to screen new compounds for potential impact on a range of conditions.

"The only way to discover new drugs for TB is if it is part of that initial screening process," he says.

In addition to J&J, Japan-based Otsuka also won provisional European approval in November for its delamanid treatment for MDR-TB, ending a drought in innovation. Yet, few are following these companies' example.

Mining bosses have 'chance to be the heroes' in combating TB

Industry

Some groups have achieved results, but much work remains, writes *Rose Jacobs*

Seven years ago, the picture of tuberculosis infection among workers at Anglo American's coal mines was relatively grim: the incidence rate stood at about 900 people per 100,000 – above the rate for South Africa as a whole at the time, despite the country-wide rate having tripled in the previous decade.

The numbers were not entirely surprising. Miners in southern Africa are often migrant workers, living far from their hometowns and villages, staying in often crowded, poorly ventilated shared housing that can serve as a hotbed for TB.

Prostitution drives up HIV infection rates, and HIV exacerbates TB; about two-thirds of people with active TB in South Africa are also HIV-positive, according to World Health Organisation estimates.

Moreover, the dust in many mines irritates the lungs, leaving workers particularly prone to infection.

What is surprising, then, is what has happened in the years since: even as TB incidence rose across South Africa, it fell by two-thirds at Anglo American's coal operations, to 330 per 100,000 in 2013. What changed?

"Everything," says Brian Brink, the company's chief medical officer. "Somehow, we got everything right."

Part of the change was down to company-wide policies, such as a pledge to offer all contractors access to the high-quality medical care enjoyed by company employees. Anglo American also shifted away from the bunkhouses of old in favour of family-style housing. And it has managed down lung disease in the workforce, reporting zero cases of silicosis in 2012 and 2013.

The one division, however, shows where the company as a whole needs to go: the coal mines are leading in areas such as healthcare information systems and using new technologies to keep track of sick workers and their treatment regimes. "All that says to me is that it can be done," says Dr Brink.

Unfortunately, Anglo American's story is not necessarily representative of the industry as a whole. Its numbers are helped, for example, by the fact that the company no longer mines gold in southern Africa; gold tends to be found in silica rock, whose dust particles are particularly jagged and thereby hard on the lungs.

"You couldn't invent a better environment to generate TB among workers," says Aaron Oxley, executive director Results UK, an anti-poverty group. "Being a South African gold miner is one of the biggest risk factors for developing TB – or, unfortunately, being married to one."

Indeed, despite what big mining companies have done to combat TB among their staff (small and medium-sized groups often have a poorer record), miners often unwittingly infect their families back home.

Employees who stick to their treatment regime while at the mine, supported by health workers, managers and peers, may drop it on visits home because of stigma or practicality. Often, they are returning to poor, rural communities lacking strong healthcare facilities.

"We think of TB as a snake. The head is in South Africa [at the mines] and the body is in the other countries in the region,"

> 'Being a South African gold miner is one of the biggest risk factors for developing TB'

says Lucica Ditiu, executive secretary of the Stop TB partnership. Countries particularly affected are Lesotho, Mozambique and Swaziland.

Dr Ditiu hopes that a declaration by southern African heads of state, signed in 2012, committed to ending the TB epidemic in the mining sector might be a significant step forward in fighting the body of the snake.

Benedict Xaba, minister of health for Swaziland at the time, who was instrumental in getting the declaration signed, agrees that a regional approach is essential, not only to co-ordinate treatment but to create educational campaigns that fight stigma.

"In our countries, people don't want to believe they are suffering from TB," he says. "They consult traditional healers. They don't want to be diagnosed." Stop-and-start courses of treatment can also lead to multi-drug-resistance, multiplying the cost and suffering by many factors.

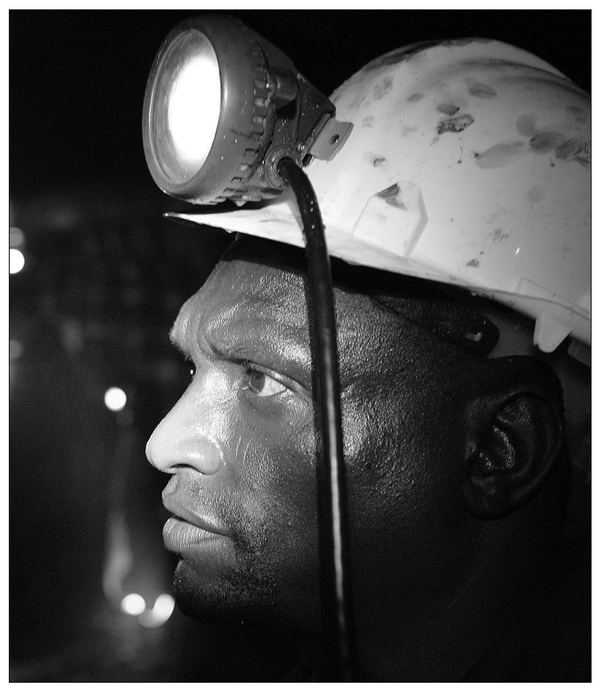
A strong association of ex-miners doing outreach work in communities is helping, says Mr Xaba. But, just as everything needs to go right at Anglo American's coal mines, everyone needs to lend a hand more broadly – from governments to charities to funding organisations.

"I'm optimistic that we're moving in the right direction. Now we need to put our foot on the pedal and accelerate," he says.

A high-level Southern African Development Community summit in Johannesburg this week, hosted by Kgalema Motlanthe, South Africa's deputy president, and looking at the regional response so far, could do just that.

The event will "provide analytic evidence of the economic costs and benefits of investment on TB in the mines while engaging key stakeholders to commit resources to address gains in the current response", according to its organisers.

Results UK's Mr Oxley believes this is the time for mining groups to act. He acknowledges some have made huge efforts to combat the disease. But there is still a way to go for the industry as a whole, from ensuring better housing to investing more in silicon dust technology to ensuring contract workers get the same care as employees. "They have a chance to be the heroes here," he says. "But if they don't come to the table with something meaningful, they'll start to look like villains."



Migration: workers can spread TB on visits home Reuters