COMBATING TUBERCULOSIS

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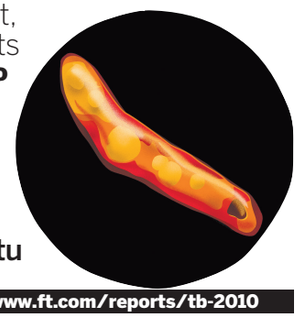

Opinion: a personal view from **Archbishop Desmond Tutu**

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Complacency is one of the greatest risks

Andrew Jack finds scientific progress has been slow with too few targets met for this disease of the marginalised

Not all anniversaries are cause for celebration. Today's annual World TB Day – the 28th to date – is more of a wake than a party, with nearly 2m people killed by tuberculosis in the past year alone and new infections rising to more than 9m.

Since 1882, when Robert Koch, a German doctor, first identified mycobacterium tuberculosis, the bacterium that causes most forms of TB, too few milestones have been met in tackling the disease.

Too many of the crude innovations which have saved lives for a century are still in use, when they should long ago have been superseded. And too few targets to reduce the burden of TB have been met.

In much of the world, diagnostic techniques have barely changed: unreliable microscopic analysis and lengthy laboratory culture of germs.

The only TB vaccine – BCG – dates from the 1920s and has limited value. The most recent drug to be added to the current slow and painful therapy cocktail, which lasts a minimum of six months, was introduced four decades ago.

A community health worker from a Target TB project provides and explains treatment to the father of a patient in the slums of Dehradun in Uttarakhand State, India David Brunetti/Target TB

Yet Mario Raviglione, head of TB at the World Health Organization, is cautiously optimistic. "36m people have been cured since 1995, detection is rising and since 2004 we have been flattening the curve of new cases per capita," he says. "Those are signs of success."

Standardised "directly observed treatment, short course" (Dots) for TB, endorsed and implemented internationally 15 years ago, has saved an estimated 6m lives, according to recent estimates.

Its adoption and expansion has been supported by a significant upsurge in funding from donor governments in the past decade.

From the start of the new millennium, the Bill & Melinda Gates Foundation and other organisations have also helped support work by companies, academics and public-private partnerships in the search for new diagnostic techniques, vaccines and more affordable, practical and effective drugs.

Several promising experimental medicines have begun advanced clinical trials in patients, and helped catalyse unprecedented co-operation with regulators.

The US Food and Drug Administration this month discussed ground-breaking proposals with other US regulators, which should permit innovative treatments to be tested simultaneously rather than – more slowly – one after another.

Swifter and cheaper diagnostic techniques are being introduced even in very poor countries, and a range of intriguing, if uncertain, future approaches – from TB-sniffing rats to cell phones that may be able to help provide remote analysis of coughs – are being studied. "We live in a time of great excitement," says Mark Harrington, head of Treatment Action, an advocacy group.

Just as important, there is increased political awareness and action in some of the countries with the greatest burden of TB, notably China, India and South Africa, as well as Brazil.

But there has been almost a sense of complacency in a field that has been left largely to medical specialists and failed to draw the attention of a wider audience. International objectives aim to detect 70 per cent of new TB cases via microscopic examination, and successfully treat 85 per cent. Many countries are falling short of these targets, which likely underestimate the burden of the disease and the efficacy of treatment.

Patrizia Carlevaro, head of Eli Lilly's International Aid Unit, says: "We have been working with a Fiat when we need a Ferrari."

Given the market is modest and concentrated in developing countries, there are few incentives for drug companies such as hers to research new therapies. It has had difficulties finding partners to take on production of its existing TB drug, despite its offer of technology transfer and no patent costs.

Hers is one of very few businesses with significant philanthropic involvement.

The reality is that TB remains the orphan of the "big three" killer infectious diseases, with less attention or funding than either HIV or malaria.

The UN's sixth Millennium Development Goal is

Continued on Page 3

Inside

On FT.com

Voices against stigma **Craig David** (below), R&B musician and Goodwill Ambassador against TB, says we must address the shame associated with it

Play as a team As with football, fighting the disease requires co-operation and endurance says **Luis Figo,** retired football player and Goodwill Ambassador

The biggest challenge is the health system **Jonathan Wheatley** looks at recently invigorated disease control efforts in Brazil

Combating Tuberculosis

Treatment is too complex and too slow

Drug resistance

Andrew Jack on why resistant strains are more prevalent

From her office in Kibera on the outskirts of Nairobi, one of the biggest slums in Africa, Liesbeth Ohler sees the pain and delays of treating TB all too often – and also the far greater problems of drug resistance.

After a patient with symptoms comes to her Médecins Sans Frontières clinic, it can take eight weeks from an initial positive test of sputum under a microscope before confirmation from a "culture" conducted in the national reference laboratory.

If this shows the infection is resistant to first-line treatments, it can be another two months while sputum samples mixed with different alternative medicines are cultured to see which kills the bacteria.

Only then – assuming the patient is willing and able to return to the clinic or can be tracked down – does up to two years of drug therapy begin. "It's not just the length of the treatment but the pill burden that's a challenge," she says.

The delays and difficulties of the treatment help explain why multiple drug resistant or MDR-TB is increasingly prevalent, accounting for an estimated 440,000 cases in 2008, of which a tiny fraction are treated in line with best practice.

Patients take four or five pills a day, supplemented by a daily injection – into alternate buttocks because it is so painful.

Most feel nauseous initially; some develop neuropathy, with a numbness in their hands and feet; others become irreversibly deaf. Less frequently, they report thyroid problems and depression.

All of this adds to the likelihood patients will skip treatment, diminishing their chance of a cure and increasing the risk of drug resistant strains developing.

In line with efforts to ensure all patients take their medicine properly, they are expected to attend the clinic twice a day, so they can be observed doing so.

"That means they lose their jobs, have no money and suffer socially," she says. "They need counselling. It's a huge workload for everyone in the clinic."

Currently, Kibera has two MDR patients and 200 with drug-sensitive TB. She estimates that 14 per cent of those who begin treatment give up.

Problems of "salvage therapy" – final treatment for patients who are non-responsive – do not occur everywhere.

In neighbouring Uganda, for example, the government – already facing periodic supply shortages of basic TB and other drugs – has not approved MDR treatments.

Bertie Squire, president of the International Union Against Tuberculosis and Lung Disease, notes that extreme TB drug resistance can be a disease of relative wealth.

Patients with enough money may seek the advice of private doctors and purchase drugs, which may be inappropriate or taken incompletely, fuelling resistance.

As the latest World Health Organization figures show, drug resistance is also widespread in parts of the former Soviet Union, a result of the collapse of the health system and support structures since the 1990s.

For Dr Ohler, there may be options for TB, but they are far from satisfactory.

"Diagnosis has to be much faster, treatment has to become much easier and shorter, with fewer pills. And we need new drugs," she says.

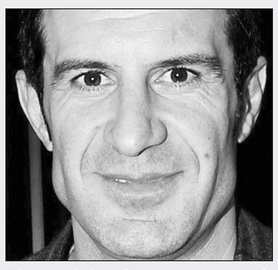
Corporate involvement

When Markus Semer saw one of his employees diagnosed with TB lose his work permit and struggle to get treatment, it brought back memories of his own positive test in Germany as a teenager, which lost him his job and his girlfriend.

In his role as senior vice-president for corporate affairs and strategic planning at the Kempinski group, which has hotels in Europe, the Middle East, Africa and Asia, these experiences helped inspire the launch of the Be Foundation.

Kempinski joined the Stop TB Partnership, a forum with other public and private sector members. It supported an image-raising campaign with the footballer Figo, placing leaflets in its hotel rooms.

Now it is launching Be as a brokerage that will identify and help pay for treatment for its own staff and those of other companies operating where health facilities are weak.



Figo: raising the game on TB

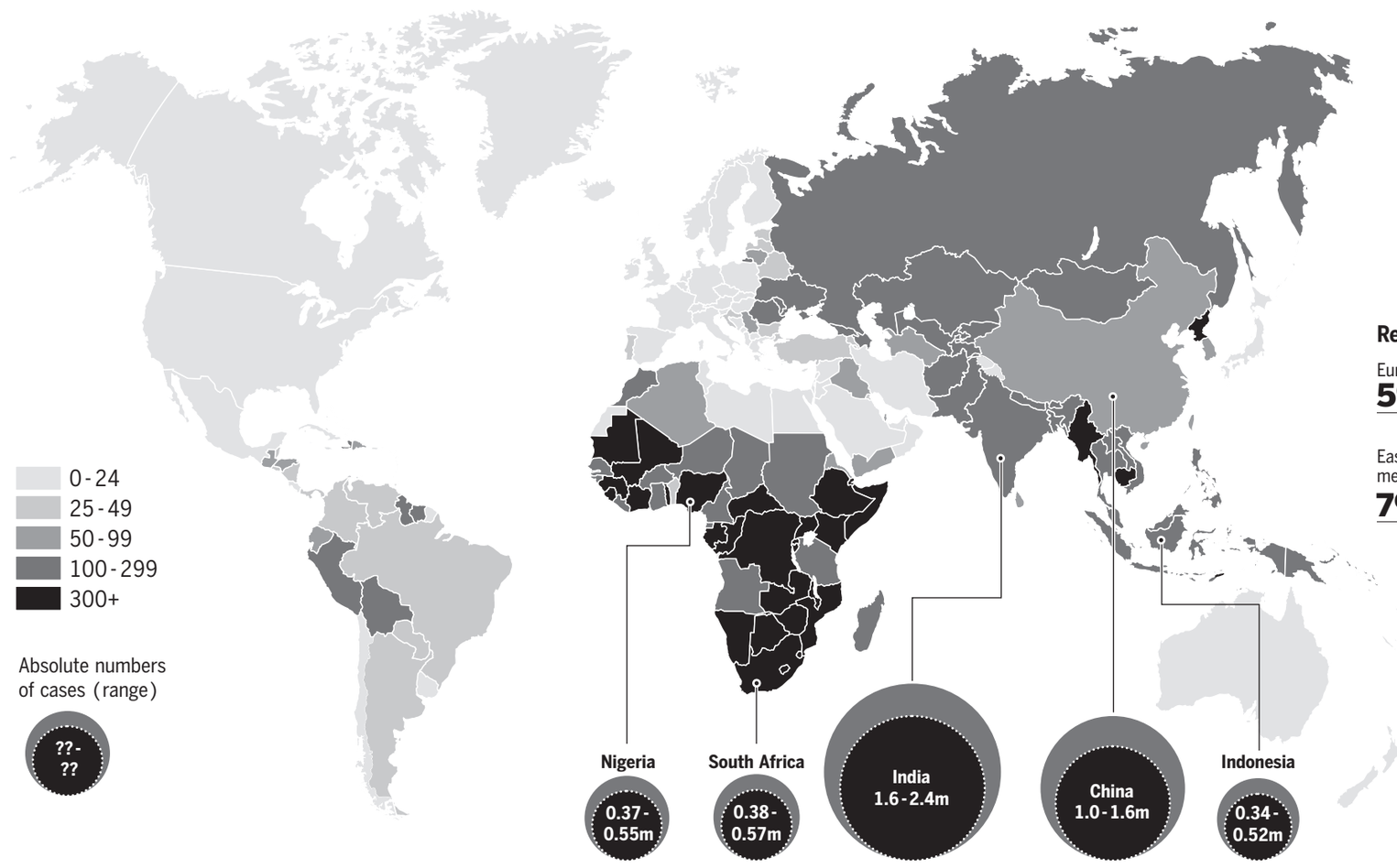
John Tedstrom, head of the Global Business Coalition on Aids, TB and Malaria, which supports corporate involvement, says: "There is a big challenge, because TB patients live close to poverty and are not employed by big multinational corporations."

But his group and others have seen growing interest. The World Economic Forum helped organise the Indian Business Alliance, for instance, a coalition of companies supporting workplace testing and non-discrimination in one of the countries with the highest prevalence.

Andrew Jack

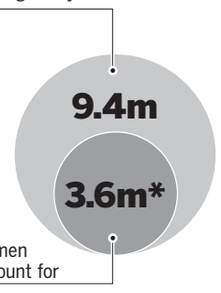
The global burden of TB, 2008

Estimated new cases per 100,000 of population

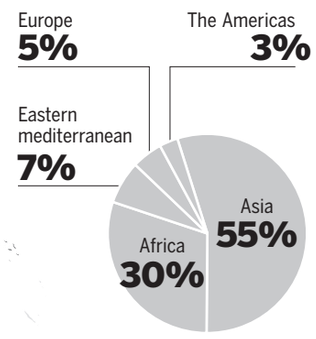


Source: WHO

Estimated incident cases globally



Regional breakdown



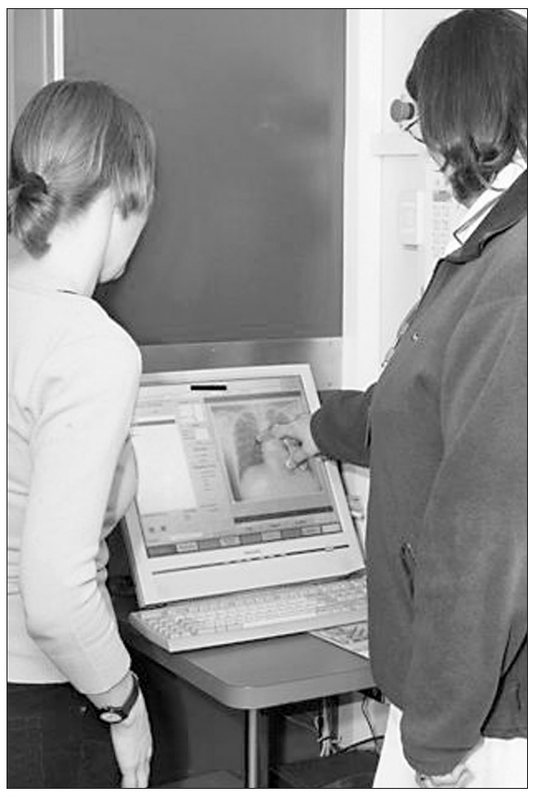
India & China 35% of TB cases worldwide

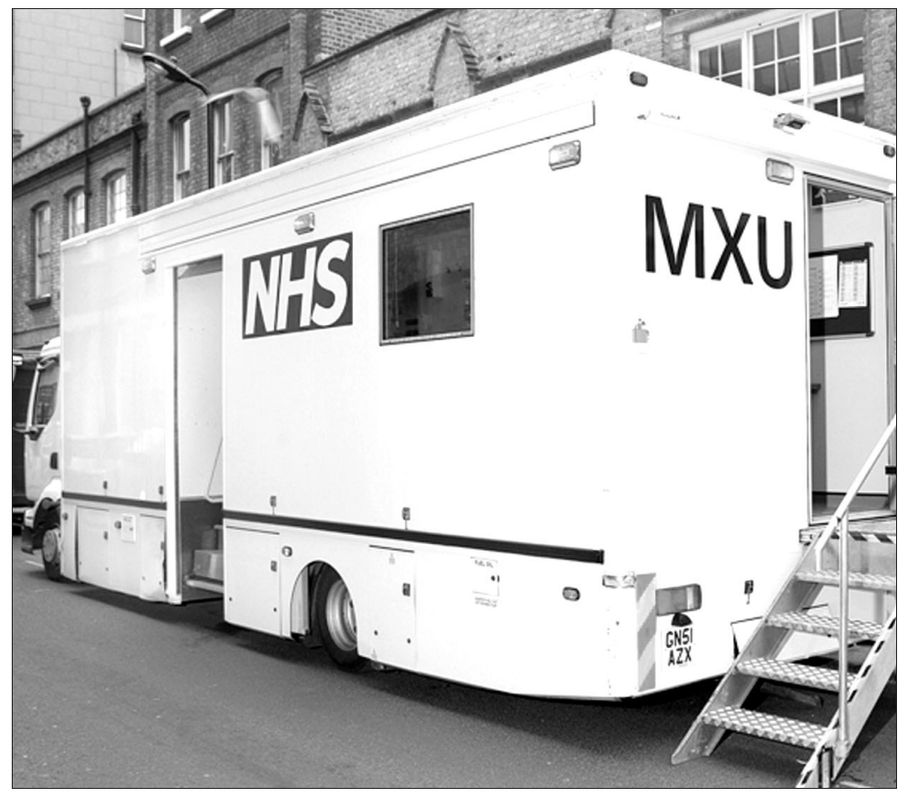
* Provisional analyses

Mobile X-rays can reach farther

UK Case Study

Andrew Jack visits a unit in London that targets drug addicts and the homeless, who are among the most affected





The mobile X-ray Unit – the only one in the country – visits nearly 200 sites around London each year

Outside a shelter for the homeless in Deptford, a short train ride from the centre of London, men and women of all ages climb the metal steps at the rear of an oversized white van. Urged on by posters and staff, and rewarded with a free chocolate bar, they enter a small lead-lined room inside and receive a swift X-ray.

They are using the MXU (Medical X-ray Unit), part of the Find & Treat programme that is helping tackle tuberculosis across the city.

Despite the wealth of the British capital, its size, social composition and certain inequalities have turned it into the city with the highest rate of infection in western Europe.

Across the UK, TB cases have risen steadily for two decades to more than 9,100 last year, while the country's ability successfully to treat the disease is below international targets.

Within an hour of opening, the nurse in charge has scrutinised the images of 30 pairs of lungs, and already identified one gaunt Caribbean man as having tell-tale wispy white lines and circular cavities on his X-ray.

Another member of staff sitting on a couch squeezed into the van explains the diagnosis to him, and refers him to a nearby clinic.

Find & Treat, which runs the MXU, targets the "hard-to-reach" who are among the most affected by TB: the homeless, alcoholics and drug addicts.

"This is a disease of poverty," says Alistair Story, who runs the project. "It's difficult to spot the symptoms because they are so common in those groups anyway – coughing, night sweats and weight loss."

He is particularly concerned about the large numbers of people who use crack cocaine. The extreme heat of the smoke rapidly damages the lungs, affecting the body's first line of defence against infection.

Addicts rarely go to doctors, partly because – unlike with heroin – there is no substitute drug. Windows are usually closed in crack houses, reducing the ventilation that would help limit infection. "It's the perfect environment for transmission," he says.

The MXU – the only one in the country – was created on a small and uncertain budget in 2002. It was purpose-built on the chassis of an old car transporter, using equipment borrowed from the Dutch. Twice a year, it visits the Deptford site, and nearly 200 others around London.

Beyond providing a diagnostic service, Mr Story's team keeps an eye on patients, who often live rough, trying to ensure they adhere to a rigorous drug therapy programme that lasts a minimum of six months.

Failure to complete the course can lead to the development of drug resistant TB at a wider level, as well as complications and even death for the individuals.

Find & Treat staff note patients' pseudonyms, telephone numbers, the hostels they use and any contact with social services or other organisations, to try to keep track of them.

> 'It's difficult to spot the symptoms because they are so common in those groups anyway – coughing, night sweats and weight loss'

With funding from the charity TB Alert, they offer other incentives to help maintain contact and compliance: a mobile phone top-up, a travel card, clothing.

In one case, Mr Story purchased a cheap laptop with a webcam to allow a remote volunteer to verify that one patient was taking his tablets every day.

Another tactic has been to employ peer counsellors such as Josie, who spent 20 years living on the street drinking before she was taken to a hospital, de-toxed, had part of her lung removed and endured a year of treatment for a drug-resistant form of TB.

"A lot of people think TB is a death sentence and don't really care," she says. "I try to offer a friendly word, and at least tell them to think about the risk of transmission to others."

This work to target those most in need could also be useful for other groups particularly badly affected by TB in the UK, including those with antecedents in India, a country with one of the world's highest prevalence rates.

Ignorance and stigma mean even those with funds and a family are often not diagnosed or adequately treated.

Indeed, the UK is still only reporting successful completion of treatment in 82 per cent of cases identified, below the World Health Organization objective of 85 per cent. That has prompted the UK Coalition to Stop TB to demand more rigorous and carefully monitored national standards, and detailed action plans for each primary care trust.

But for now, Mr Story has more short-term concerns. Despite the work of Find & Trust, which the Health Protection Agency recently judged clinically and cost effective, he says there is no indication the Department of Health will provide funding after this year, and he has had no luck persuading local primary care trusts to provide support. "The NHS is so fragmented, and there is no sensible mechanism for funding."

Fresh offensive combines several components

Drugs

Researchers are investigating the disease mechanism and genetics, says **Clive Cookson**

One of many medical triumphs made possible by the great wave of antibiotic discovery in the mid-20th century was the defeat of tuberculosis in the industrialised world. TB cases were already falling, thanks to BCG vaccination and public health improvements, and the introduction of streptomycin and follow-up antibiotics consigned "consumption" to history.

But in the developing world TB was never defeated. Several factors have enabled Mycobacterium tuberculosis to make a terrible comeback there. They include the growth of huge slums where the bacterium can spread easily, the HIV/Aids pandemic which leaves patients' immune system unable to resist TB, and increasing antibiotic resistance.

Even drug-sensitive TB is quite hard to eradicate from an infected patient. The treatment recommended by the World Health Organization requires a combination of four antibiotics to be taken for at least six months, under the observation of a health worker to monitor compliance. If the patient does not complete the course, some antibiotic-resistance bacteria may remain in the body.

The WHO estimates that about 5 per cent of the 8m new cases that occur worldwide every year are multidrug-resistant. Alternative antibiotics can usually be found to treat these MDR-TB cases, as they are known, though at great cost.

Even worse is what is called extensively drug-resistant TB or XDR-TB, which is virtually untreatable. While this is still uncommon, it is believed to be spreading and has been reported from about 50 countries. No one really knows how prevalent it is, because few countries have the lab facilities to monitor it accurately.

However a new scientific assault on TB is under way, with funding from government development agencies, research organisations, companies and charities – above all the Bill and Melinda Gates Foundation, which has invested $750m in the fight against TB.

The campaign has several components, including research into the basic biology of TB, better diagnostic tests, new vaccines and more effective drugs.

The global market for TB drugs was worth $300m in 2007, according to Datamonitor, with an annual growth rate of just 2.2 per cent. India accounted for 39 per cent of the total.

The relatively small size of the market, particularly in developed countries where companies can charge high prices, means that the pharmaceutical industry has little incentive to pour resources into R&D. But companies are collaborating with the charitable and public sector, through organisations such as the Global Alliance for TB Drug Development.

The aim is to produce a treatment regimen – still likely to consist of drugs in combination – that will take far less time than the current six months to rid the patient of TB bacteria.

The ideal is a daily pill that could cure the disease within two weeks, though that is likely to take decades to achieve.

The alliance has three drugs in clinical trials and more than a dozen at earlier stages of development. Furthest advanced is moxifloxacin, a fluoroquinolone antibiotic developed by Bayer of Germany, which has been on the market for more than 10 years to treat a range of skin and respiratory infections.

A large clinical trial in South Africa and Zambia will determine if it can shorten the existing six-month course by substituting for older antibiotics.

While moxifloxacin is an existing drug redeployed to fight TB, several new antibiotics developed specifically to inhibit the bacteria are in earlier clinical trials. They include PA-824 from Chiron and TMC-207 from Tibotec/Johnson & Johnson.

At the same time academic researchers are solving some of the biological mysteries of the disease, which should lead the way to better drugs. One of the biggest mysteries is why 90 per cent of people infected with the bacterium never develop the disease. A weakened immune system, for example through HIV/Aids, greatly increases the risk of active TB but that is far from the whole story.

This month an international scientific collaboration, led by Lalita Ramakrishnan at the University of Washington, announced the discovery of a gene involved in susceptibility and resistance to TB – LTA4h.

This gene controls the balance between pro-inflammatory and anti-inflammatory responses to infection. People whose LTA4h genes are out of balance are more likely to become ill. The finding suggests that TB patients may fare better if a drug that rebalances the immune system is added to their antibiotic regimen.

In the same issue of the journal, Cell, where the work of Ms Ramakrishnan and colleagues appeared, an Indian group headed by Kanury Rao at the International Centre for Genetic Engineering and Biotechnology in Delhi published a comprehensive study of the "molecular machinery" in human macrophages – the cells primarily targeted by TB – which influences the course of infection.

This too could offer leads. "Rather than targeting the pathogen itself, our studies highlight an alternative strategy wherein the host factors required to support pathogen survival can be used as targets for TB therapy," says Mr Rao.

Mycobacterium tuberculosis

Drive is on to replace venerable 90-year-old vaccine

Inoculations

Clive Cookson says 'recombinant' drugs aim to produce a stronger immune response than BCG

A vaccine of limited efficacy, introduced 90 years ago, is medicine's only current preventive weapon against tuberculosis.

In the face of the global TB pandemic, an international drive is under way to develop vaccines that will work better than the venerable BCG (named Bacillus Calmette-Guérin after the French scientists who developed it at the Institut Pasteur).

BCG is an old-fashioned vaccine, based on a weakened strain of live bacteria. (It uses *Mycobacterium bovis*, the species responsible for TB in cattle, rather than the usual human pathogen *Mycobacterium tuberculosis*.) While BCG can prevent some childhood forms of TB, it has little or no effect on adult pulmonary disease, the form mainly responsible for the current pandemic.

The "recombinant" vaccines that are in development are genetically engineered to produce a stronger immune response than BCG.

Two international non-profit organisations are leading the programme: Aeras Global TB Vaccine Foundation, based in the US, and the Tuberculosis Vaccine Initiative (TBVI) in Europe. Both are funded mainly by charities (such as the Bill and Melinda Gates Foundation) and by governments, and both work with universities and industry worldwide.

Joris Vandeputte, TBVI senior vice-president, says the main reason why no TB vaccine better than BCG has been developed is lack of funding and attention given to the issue, rather than any fundamental scientific difficulty.

"For 50 years the world fell asleep," says Mr Vandeputte. "TB disappeared from the medical agenda during the second half of the 20th century, and only since the beginning of this millennium has it reappeared.

"On both sides of the Atlantic scientists are confident that by the end of this decade we will have come up with better vaccines," he adds. But current funding of vaccine R&D, about $90m a year, needs to quadruple to $360m a year or $3.6bn for the decade.

Lew Barker, senior medical adviser to Aeras, says no one should underestimate the fundamental difficulty of the task. "We have to be optimistic because we know that BCG provides some protection against TB," he says.

"But TB is a very complicated disease, and the more we look at it the more we realise how complicated it is," Dr Barker adds. "Overcoming the scientific hurdle to making an effective vaccine may be as difficult as it is for HIV or malaria."

TBVI's projects are generally at an earlier stage than those of Aeras. It has 37 candidate vaccines in research, eight of which it hopes to put through clinical trials.

'TB disappeared from the medical agenda during the second half of the 20th century'

Joris Vandeputte, senior vice-president, Tuberculosis Vaccine Initiative

About half of these are "priming vaccines" that could replace BCG, and half are "boosting vaccines" that would enhance its effects. TBVI is also developing "biomarkers" that will enable doctors to monitor the effectiveness of vaccination and the progress of TB in patients.

Aeras – named from the Modern Greek word for "air" – talks in similar terms to TBVI about its "prime-boost" strategy.

Initial inoculation, with BCG or a genetically enhanced form of it, would be followed by a booster shot of a different vaccine.

Researchers believe prime-boost would not only strengthen protection but also extend it over a longer period.

Four of Aeras's six vaccine candidates are in early trials in Africa, and the last two are expected to begin human testing this year.

The most advanced candidate is MVA85A, based on a genetically modified vaccinia virus, which Aeras is developing with Oxford University and Emergent Biosolutions, a vaccine biotechnology company.

Following closely behind is Ad35, an adenovirus modified to express several immune-stimulating proteins on the TB bacillus. This is produced by Crucell, another vaccine biotech company.

Clinical trials of both MVA85A and Ad35 are under way on children in South Africa.

Aeras is working with larger vaccine companies too, including GlaxoSmithKline and Sanofi-Aventis. Last year, it opened its own TB vaccine manufacturing plant near its headquarters in Rockville, Maryland.

"When we started out we had trouble finding a [facility] willing to take on making an experimental TB vaccine," says Dr Barker.

"We recognised that this could be a bottleneck, because we wanted to be able to do early process development and to evaluate scale-up."

The plant can produce "aerosol" formulations of vaccine, for delivery directly to the lungs, which may be more effective than a traditional BCG injection.

With sufficient resources – a Phase III trial leading to commercial licensing would cost $160m – Aeras says the first new TB vaccine could be ready for use by 2016.

Untreated HIV exacts a high price

TB and Aids

Margaret O'Connor on efforts to integrate treatment in South Africa

National treatment guidelines that take effect in South Africa on April 1 will make antiretrovirals (ARVs) available to almost 500,000 people, including HIV-positive infants, some pregnant HIV-positive women, and all TB/HIV co-infected patients.

Some 70 per cent of people treated for TB in South Africa are also HIV-positive. The introduction of earlier-stage HIV treatment should help prevent those with latent TB from developing the full-blown disease.

The push by Dr Aaron Motsoaledito, South Africa's minister of health, to integrate TB and HIV treatment breaks with a century-old tradition of isolating TB treatment in standalone public healthcare facilities.

The pitfalls of this strategy were highlighted in 2006, when news that 52 of 53 HIV-positive patients with extreme drug resistant or XDR-TB had died while being treated at a Church of Scotland Hospital TB ward in Tugela Ferry. This tragedy fuelled fears in high-prevalence communities of only emerging from a TB hospital in a coffin and drove people with suspected cases underground.

Halting the cycle of fear and denial requires sustained public education campaigns by healthcare counsellors and treatment activists.

Stigma surrounding HIV-Aids, and to a lesser extent TB, continues to prevent affected people going to clinics for testing and treatment. However, the government's determination to dispel the myths and misinformation about the infectious diseases that are commonplace in most poor communities has impressed activists.

"Dr Motsoaledi is leading the pace of engagement now," says Mark Heywood, a director of the Treatment Action Campaign. The TAC is supporting the government's drive to enrol 1.8m people in ARV programs by 2013. More than 5.5m South Africans are believed to be living with HIV-Aids and runaway rates of infection have had a grave effect on immunity to TB.

The South African Ministry of Health and the US President's Emergency Plan for Aids Relief (Pepfar) will share financial responsibility for the drug roll-out. Existing Pepfar commitments are due to expire at the end of US President Barack Obama's first-term in 2014.

Dr Brian Brink, a private sector representative on the ethics committee of the board of The Global Fund to Fight Aids, TB, and Malaria and medical consultant for Anglo American, the mining group says: "We're paying the price of untreated HIV with current TB incidence rates. How we respond will determine when we turn the corner in conquering co-infection.

"Donor fatigue is apparent among the NGOs involved in HIV. They're moving into prevention because long-term funding for treatment is too expensive."

Civil society and business are urging government to control drug costs by pursuing generic options and forecasting drugs needs, so that pharmaceutical companies can operate in a more predictable environment.

'Donor fatigue is apparent among the NGOs involved in HIV. They're moving into prevention'

Building management capacity across the public health care system will require massive investments in training, development, and further education. The national government says it will commit the resources. Ring-fencing budget items should ensure the money is properly allocated.

A doctor does her rounds in a South Africa treatment centre Getty

Pockets of innovation in community health care delivery provide beacons of hope.

The Western Cape Department of Health has joined with Médecins Sans Frontières to pioneer a system for streamlining HIV and TB testing, diagnosis, and treatment at 10 community clinics in Khayelitsha, a township near Cape Town.

KwaZulu Natal, the province with the highest HIV-Aids infection rate, has pioneered integrated care at the Caprisa eThekwini TB-HIV clinic in Durban and the Church of Scotland Hospital in Tugela Ferry.

These programmes are predicated on the belief that home-care with strict professional monitoring of drug treatment and contagion control procedures for families cohabitating with patients undergoing treatment has the highest chance for long-term success.

The shift in attitudes with patients taking more ownership for their drug treatment is derived from the community-care model developed for treating HIV-Aids.

The main difference in implementation is that TB patients must still take their medication in the presence of a health care worker. Directly Observed Treatment (Dot) is a cornerstone of World Health Organization guidelines.

Treatment for XDR-TB is a painful daily injection that a patient must endure for four to six months. There is widespread agreement that this should be administered in a clinical setting.

A workshop the US National Institutes of Health (NIH) held in Pretoria several weeks ago raised expectations in the clinical community that the institutes will invest in a range of TB prevention and treatment programmes that could rival their record in helping to develop 20 Aids drugs in 25 years.

Professor Gavin Churchyard, the director of the Aurum Institute, a Johannesburg-based health research organisation, says: "The NIH will devote millions, if not billions, of dollars to radically transforming the TB landscape."

Read more about by Margaret O'Connor TB control in South Africa at **www.ft.com/tb-2010**

Tests are of limited use without labs and skills

Diagnostics

Detection techniques are improving in developing countries, says **Sarah Murray**

Unlike the modern methods used to detect many diseases, diagnosing tuberculosis makes use of slow, unreliable techniques more than a century old.

In recent years, faster, more effective diagnostics technology has been developed. However, the challenge is to ensure it can be used in developing countries where healthcare infrastructure is weak or non-existent but where most of the world's TB patients live.

"Like TB vaccines and drugs, current TB diagnostic technologies are sorely outdated and severely flawed," says Mel Spigelman, head of the TB Alliance, a non-profit drug-development partnership.

Traditional diagnosis involves microscope analysis of sputum coughed up by a patient. It relies on the naked eye, so a large amount of micro-bacteria is required – at least 10,000 micro-bacteria per micro-litre of sputum – before the presence of the disease can be detected.

Not only is the method unreliable; patients may also be quite ill and have had the disease long enough to pass it on before they can be diagnosed. Moreover, the spread of HIV-Aids has complicated matters.

"Most HIV-positive patients with TB might still end up with only a few micro-bacteria in their sputum because they're don't have a good system that can sequester the micro-bacteria," says Giorgio Roscigno, chief executive of the Foundation for Innovative New Diagnostics (Find). "So co-infection with HIV has made the disease much more complicated to diagnose."

Part of the reason for the slow progress on diagnostics is that in developed countries, TB is seen as an old disease.

"A couple of generations ago, TB was a major cause of death in Europe," says Shuma Panse, a senior manager at the Global Business Coalition on HIV/Aids, TB and Malaria (GBC). "But public health measures were implemented so TB decreased in the US and Europe, and the perception in the west is that it's no longer a problem."

The creation of Geneva-based Find in 2003 has proved a catalyst for advances. It has no manufacturing capabilities, but works with companies on the development of TB diagnostics.

Another big step forward has been the development of techniques based on molecular diagnostics. Because the technology detects the DNA of the micro-bacteria, only a very few bacilli need to be present in the sputum to enable diagnosis.

'Co-infection with HIV has made the disease much more complicated to diagnose'

This technique has also speeded up the process of detection. Line probe assay, a technology approved by the World Health Organization two years ago, can detect multi-drug resistant tuberculosis (MDR-TB) in two days, for example.

Dr Roscigno says that a new molecular test – soon to be submitted to the WHO for approval – will bring the time required to detect MDR-TB and TB in HIV-positive patients down to 90 minutes.

Molecular diagnostics have been used for years in Europe. However, the challenge has been to apply them in parts of the world that lack sophisticated laboratories and skilled staff.

"We're working with partners to carry out laboratory training," says Ms Thompson. "Because that kind of capacity really needs to be developed in resource-constrained countries"

Ms Panse agrees. "A test doesn't mean anything if you don't have a good lab system," she says. "So investing in strengthening labs in developing countries is crucial."

At the same time, Find is working on tests that could be more portable and easy to use in remote areas.

"First-generation molecular technology requires a good laboratory and the second-generation technology can be performed near a microscopy centre," says Dr Roscigno.

"But the real dream is to develop a rapid test so community healthcare workers themselves can detect and screen large numbers of people in the villages."

The technology he has in mind would work much like a pregnancy test and therefore would not require sophisticated infrastructure.

While the test remains two to three years away, Dr Roscigno says the reason it is only now being developed is due to the lack of spending on research and development over the past 20 years – a state of affairs that is finally changing.

As progress accelerates, Dr Spigelman is optimistic. "The future of TB diagnostics is more promising than ever," he says.

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Complacency is one of the most significant risks

Continued from Page 1

to "combat HIV/Aids, malaria and other diseases", with the objective of halving TB prevalence and deaths by 2015 only mentioned in the detail.

The US has its bespoke President's Emergency Plan for Aids Relief and the President's Malaria Initiative, but TB is subsumed into more general projects.

The Global Fund to fight Aids, TB and Malaria – which channels multilateral donor support – estimates it has "supported" the treatment of 6m TB patients since 2002. Yet its total cumulative disbursements to tackle the disease were $1.5bn, compared with $5.7bn for HIV and $2.8bn for malaria.

One reason is that TB does not have the same "star appeal" as other diseases to generate attention, advocacy and support.

In the past, well known figures, from the Brontë sisters and Balzac to George Orwell and Eleanor Roosevelt died from the disease.

Today, where HIV and even malaria affects rich westerners and children and mothers in developing countries, TB kills the most marginalised groups – the poor, drug addicts, prisoners and the homeless.

Bertie Squires, president of the International Union against TB and Lung Disease, says much more must be done to target those in most need, who often cannot afford transport and time away from work, even if diagnosis and treatment is offered free of charge.

"You have to work against every system to get to the poor," he says.

Another challenge is that the science itself is difficult, not least because of the time required to culture TB

"More than a sea change, we need a storm," says Tony Fauci, director of the US National Institute of Allergy and Infectious Diseases, as he calls for new blood in the field.

But there are problems that could be tackled more rapidly, even at a time of stretched resources.

One is the need for tighter integration of health services, rather than the "vertical" approach that targets particular diseases such as HIV, with which patients are often co-infected before dying of TB.

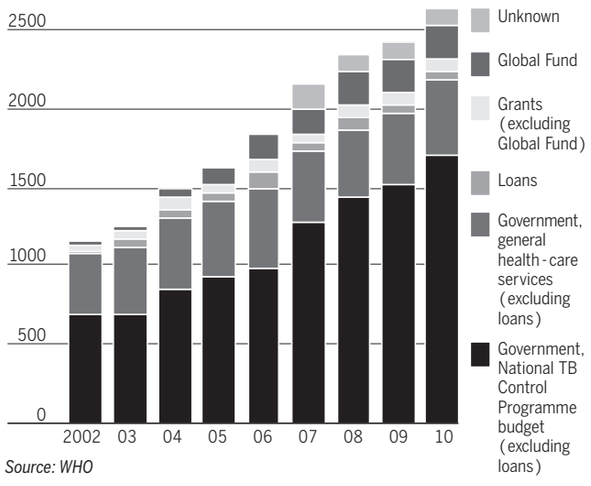
Another is more prevention. That includes wider prescription of the drug cotrimoxazole to protect HIV patients being treated for TB from other infections.

Infection control needs to be much better, to limit transmission to other patients and health workers. And undiagnosed patients should be sought more actively. "We need to move from passive to active case finding," says Peter Gondrie, head of the Netherlands-based KNCV Tuberculosis Foundation.

Finally, national and international agencies need to be overhauled to reinforce efforts to intensify treatment and advocacy, so they can encourage affordable production of high quality drugs and are held accountable for meeting targets. Failure to do more could have serious results.

Funding for TB control

By source of funding, high-burden countries ($m)



Source: WHO

A recent report from the World Health Organization estimates that there were 440,000 cases of multi-drug resistant TB in 2008. Resistant strains require lengthy, painful and sometimes ineffective therapy. Extensively drug resistant TB has now been reported in 58 countries, including many in the developed world.

Most cases result from treatments being wrongly prescribed by doctors or poorly followed by patients, notably those with HIV. But such strains may also be transmitted directly. That could turn TB back into a much bigger concern for rich as well as poor.

Combating Tuberculosis

Private sector has a crucial role to play

Guest Column
Jorge Sampaio

Jorge Sampaio, the UN Secretary-General's special envoy to stop TB, is the former president of Portugal

In December during a visit to Kenya, I met a group of young people who gave me a renewed sense of purpose in my role as the UN secretary-general's special envoy to stop TB.

They were girls and boys aged 12 to 14, who had come to the Mathare Depot field in Nairobi to play a football tournament on World Aids Day. These youngsters had also come, under the auspices of Kenya's health ministry and the Mathare Youth Sports Association, to learn more about tuberculosis.

In their bright young faces, I saw Kenya's future. Being able to contribute to their understanding of TB and how to prevent its spread was important to me, knowing as I do that every one of them is at risk. Kenya, like many other African countries, is experiencing a grave epidemic. At least one out of every 400 Kenyans face the prospect of catching tuberculosis this year.

For Kenya, as for other developing and emerging economies in Africa, Asia and Latin America, TB represents both a humanitarian crisis and a limiting factor to economic stability and growth. It mainly affects young adults who should be contributingto shaping their countries' futures.

It does not respect borders or social class. But while it is prevalent among the poor and disadvantaged, it also affects individuals who are literate, have considerable education and earn good incomes.

We have evidence that not addressing the disease is more expensive than treating people. A 2009 World Bank research report showed that countries heavily burdened by TB could recoup 9 to 15 times their investments in TB control. For example, India – which has a heavy burden of the disease but is striving to address it – can realise a return of $125 for every dollar invested in control.

Half the people who become ill with TB in Kenya are also infected with HIV. Because HIV weakens their immune systems, people infected with both are particularly vulnerable to becoming ill and dying from TB, even if they are receiving antiretroviral and other treatments for HIV.

The two diseases are so closely linked that the dual epidemic has come to be called HIV/TB or TB/HIV.

Many countries are making good progress on helping people with HIV lead productive lives. Some 4m people living with HIV are now receiving antiretroviral drugs. But too much of this investment is being squandered because of inattention to TB.

An HIV/TB patient queues for drugs at a clinic in Nairobi Reuters

All people living with HIV should be screened regularly for TB. Those who are sick with the disease need effective treatment, and those without it should receive preventive therapy. These treatments are quite affordable. A six-month course of treatment costs about $20; and preventive drug therapy costs $2.

> Governments and their partners must recognise that health is an investment

The world faces another threat that represents a serious obstacle to development: multidrug drug-resistant TB. This week, the World Health Organization issued a report which shows that, in 2008, some 440,000 people were ill with multidrug-resistant TB (MDR-TB).

This form of TB is caused by bacteria that are resistant to the most effective drugs. To treat it, doctors must turn to far costlier drugs that have toxic side-effects and can cure the condition only after about two years of treatment. It costs 20 times as much to treat MDR-TB.

We know the best way to prevent the spread of drug resistance – to ensure those who catch TB receive prompt diagnosis and effective treatment.

Governments and their international partners must recognise that health is an investment.

The only successful exit strategy in the struggle against the TB, HIV and TB/HIV pandemics is to include them as part of broader development and poverty reduction strategies, and to strengthen health systems to respond more effectively to the needs of the most vulnerable populations.

The private sector has a key role in making this happen. Businesses with a commercial presence in affected countries have a responsibility to protect their workers against the disease and to help those who become sick to be diagnosed and treated.

They should also support community outreach programmes and contribute to improvements that will enhance control, such as building or upgrading laboratories for diagnosis.

But every corporation, even those without direct commercial interest in affected countries, can make a real difference.

Corporate responsibility projects can educate people, create greater awareness in their corporate communities, and advocate greater investment in research.

This is a time of economic uncertainty, but few would disagree that hopes for the future are tied to the growth of more viable economies and expanded markets in the developing world.

Providing TB care to all who need it is a vital step in this investment. We need new commitments, and we need to turn those commitments into action.

Disease control remains an uphill struggle

Profile
China

But the prerequisites for an effective treatment and prevention strategy do exist. **Geoff Dyer** reports

China provides a demonstration of just how hard it is to tackle tuberculosis in the developing world. The country has many of the prerequisites for constructing an effective strategy for treatment and prevention. It has a relatively well-organised health system and a long history of aggressive action against infectious disease.

It first began to implement Dots – Directly Observed Treatment Short course, the internationally recommended strategy for controlling TB – in 1991 and has won international praise for what is the largest such programme in the world.

Yet despite all these efforts, it still faces an uphill struggle to control the disease.

China has about 4.5m cases of TB according to the World Health Organization, putting it second only to India in the global rankings. There are around 1.3m new cases every year and the disease caused 160,000 deaths in 2008.

Even more worrying is that it now has one of the highest incidence rates of multi-drug resistant TB, with 112,000 new cases recorded in 2007, according to the WHO, again second only to India.

There are a number of reasons for the persistence of TB in China and the spread of MDR-TB. One important factor is the waves of migration to the cities. There are few exact figures, but the government reckons as many as 150m people have moved to take jobs in cities, especially in factories and construction sites.

In theory, if migrants have a job in the formal labour market, they should get access to healthcare in the city they work in. However, in reality, migrant workers can easily fall through the cracks in the TB control system, in part because some work for only short periods in a job.

One important factor in the rise of drug-resistant TB is migration to cities such as Shanghai AFP

Moreover, the fact that migrants move around and often live in relatively cramped conditions makes them more vulnerable to infectious diseases such as TB.

As in other countries, the incidence of TB is also connected to the rising prevalence of HIV-Aids, which makes patients more vulnerable to other infections.

Cost can be a factor. The treatment for TB is free for many patients but there can be lots of additional costs that can end up causing low-income patients to abandon treatment. These include having to pay for some diagnostic tests or for drugs for TB side-effects not covered by the health system or just the cost of travelling to the hospital for regular check-ups, given that many TB patients live in rural areas.

If patients do not compete the six-month treatment course, this can increase drug resistance and make them more vulnerable to MDR-TB, which costs much more to treat.

The Health Ministry is working on a plan to make treatment for drug-resistant TB available through the health system and has launched a pilot project in Qinghai province in the north-west.

Yet while the challenges of dealing with drug-resistant TB are immense for developing countries, China is also part of pioneering steps to deal with the disease.

Last year, the Institute of Microbiology at the Chinese Academy of Sciences (IMCAS) signed an agreement with the Global Alliance for TB Drug Development to try to develop treatments based on traditional Chinese medicine. With the pharmaceutical industry showing little interest in TB because of the small market in developed countries, experts are hoping this type of partnership can help give impetus into research.

Having identified 24 natural product extracts that might have some anti-TB activity, the partnership will do more research to see if any of these could form the basis of new therapies.

The hope is that treatment based on natural products might be less susceptible to resistance. Meanwhile, researchers at another institute in Beijing have announced promising early results from animal studies which use a leprosy drug called clofazimine to treat TB.