FT HEALTH
Combating Tuberculosis

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On FT.com
Action by Bric and oil-producing countries could make rapid headway against TB and HIV, writes **Jorge Sampaio**

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Basic needs: a patient in a Haiti hospital. Short-term funding to tackle a stigmatised disease concentrated among the poor, the old and the disenfranchised is limited Getty

Fight needs money and leadership

Financial austerity is a broad threat to progress, with cuts in healthcare budgets and international donor support, writes **Andrew Jack**

In a room locked by an electronic key in Bucharest's Marius Nasta Institute, a teenage girl is bracing herself for the daily cocktail of medicines she must take for two years: a minimum of 14 pills, one injection and a liquid.

Andrea is one of the lucky few. She appears to be recovering, after accurate diagnosis of an extremely drug resistant (XDR) form of tuberculosis, and gaining access to one of just two clinics in Romania with supplies of costly "salvage" drugs and strong infection control.

Her personal story mirrors a broader picture of cautious progress in the face of substantial difficulties felt by many TB specialists, as they are reinvigorated by recent advances in drug diagnosis and treatment.

It is offset by the need for much greater effort to tackle obstacles permitting the disease to impose a global burden of 9.4m new infections and 1.7m deaths each year; and a fresh funding squeeze and increasing drug resistance that threaten progress.

"We are in a situation where I am much more optimistic than one or two years ago," says Mario Raviglione, head of the TB programme at the World Health Organization (WHO).

He stresses that 49m lives have been saved over the past 15 years through improved diagnosis and treatment. After decades without significant progress in lengthy and arduous drug treatments, there are now several new compounds backed by pharmaceutical companies in mid and late-stage clinical trials, offering the prospect of boosting efficacy, cutting side-effects and reducing the length of TB therapy.

Alongside scientific breakthroughs, medicines development has been helped by regulatory innovation. The US Food and Drug Administration has offered the prospect of accelerated approval by testing of novel compounds together, instead of the more usual but slower staggered testing.

New research partnerships are emerging, such as the International Scientific Exchange Foundation of China, reinforcing efforts by the US National Institutes of Health to strengthen clinical trial networks.

Still more radical innovation has come from a new diagnostic test, "Xpert", endorsed last year by the WHO. It could revolutionise the speed and accuracy of both drug-sensitive and drug-resistant TB, providing results in a matter of hours, compared with weeks or months at present.

But such innovation brings challenges. The equipment is costly for low-income, high-burden TB countries to buy and operate, requiring regular electricity supply and refrigeration. The consequences of its findings are even more severe, since each confirmed diagnosis brings a responsibility to treat the newly identified patient.

"This piece of kit has huge potential to produce results really quickly, but we need to make sure we have the capacity," cautions Bertie Squire from the Liverpool School of Tropical Medicine.

Theoretically, more reliable results will allow sophisticated diagnostics to pay for themselves in the medium-term, while higher treatment volume

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Combating Tuberculosis

Business retreats from unattractive market

Drug supply

Orders are fragmented and there is pressure to price products as cheaply as possible, notes **Andrew Jack**

When US patients began to suffer "stock-outs" of the antibiotic Amikacin last year, it was a sobering reminder of the fragile supply chain for tuberculosis drugs even in the world's richest economy. It was also far from an isolated incident.

Panpharma, the only EU supplier of Kanamycin, another second-line drug, was unable to supply patients for several months in 2010, after it discovered problems its supplier of "active pharmaceutical ingredients" was having with maintaining sterility.

Existing treatments are frequently of limited effectiveness, long duration, and trigger unpleasant side-effects. They are also often expensive and in short supply, threatening appropriate treatment and risking the development of still more resistant strains.

First-line drugs are relatively cheap and easy to obtain, but studies suggest many are of questionable quality and are often prescribed intermittently and in combinations that are not officially recommended.

Supply and cost concerns are greater for the rarer and more tightly controlled medicines to treat patients with multi-drug resistant (MDR) forms of TB.

"We just can't get producers of quality, and prices are going up as demand goes up," says Michael Kimerling, senior programme officer for TB at the Bill & Melinda Gates Foundation. "It's just a broken market."

In 2007, the World Health Organization established the Green Light Committee (GLC) to order and distribute MDR drugs directly. Yet it provides only about 22,000 treatments a year – or 5 per cent of the estimated number of MDR cases.

Mark Harrington, head of the Treatment Action Group, says: "It's been a massive failure. It's not made second-line drugs more affordable or available. The structure is inadequate for the current phase of scale-up. The GLC should be put out for competitive tender."

Paul Nunn, TB operations coordinator at the WHO, deflects responsibility. "Countries are not putting together treatment programmes they should be," he says. "There is not the demand because of lack of political will."

He says many governments are slow to put in place the systems required for tackling MDR and slow in despatching funds from donors such as the Global Fund to Fight Aids, Tuberculosis and Malaria, which pay for drugs.

Fragmented orders from a small market and strong pressure to provide drugs as cheaply as possible to poor countries, has done little to stir interest among drug manufacturers.

The result is limited competition. A few medicines, such as Bayer's Moxifloxacin, are still under patent in some markets. Other companies are divesting themselves of their unprofitable TB drugs.

Eli Lilly is providing technology transfer to shift production to generic manufacturers for Capreomycin and Cycloserine.

Yet take-up is slow, and without Lilly's subsidised supplies, prices are rising.

Prothionamide and Ethionamide have a single supplier each, and manufacturers for several drugs are dependent on very few producers of active pharmaceutical ingredients periodically subject to quality problems.

Inder Singh from the Clinton Health Access Initiative, which is examining how to increase availability and reduce MDR drug prices, says: "A major barrier is fragmentation: different standards, different products, different buyers. Demand is so low for some drugs there is a natural monopoly."

More domestic and international funding could increase demand and stimulate producers, generating more diverse, reliable supplies at lower cost.

One reform under discussion is an "advance market commitment", a pot of money pooled from several countries to provide a larger guaranteed market for MDR drugs.

That could be boosted by the Global Fund and other donors pooling their drug funds directly to provide joint procurement on better terms, whether through the GLC or another mechanism.

Tido von Schoen-Angerer, head of the campaign for essential medicines at Médecins sans Frontières, wants more public data on drug supplies, pricing and stock-outs to hold the system to account. "The GLC is too controlling, and we need more honest reporting," he says.

Mr Nunn says such criticisms are outdated, and reforms under way to boost technical assistance by the WHO will boost the GLC's capacity to respond.

But Mr Harrington calls for greater pressure from within countries and advice from expert groups with local experience to wrest power from Geneva. "If we'd had a GLC for HIV drugs, we'd never have got so many patients on antiretroviral therapy so fast."

Knowledge of the enemy will widen our armoury

New medicines

Recent discoveries about the basic biology of TB should help to improve treatment, writes **Clive Cookson**

The scientific assault on tuberculosis is gathering pace. Over the past year, researchers have been learning more about the fundamental biology of the disease, which should lead to better treatments in the long term, as well as adding to the pharmaceutical armoury that will become available to treat patients in the slightly nearer future.

The immediate need is for antibiotics that clear Mycobacterium tuberculosis from the human body more quickly, conveniently and safely.

Patients whose disease is still sensitive to the standard antibiotics have to take a combination of drugs that have been in use for 40 years under direct supervision of a doctor or nurse to ensure compliance.

People unfortunate enough to have a drug-resistant form of TB must take a cocktail of more toxic compounds for 18 months.

And those who are co-infected with both TB and HIV face extra problems because of undesirable interactions between antibiotics and antiviral drugs.

Eleven treatments are in clinical trials. Six have been developed specifically to fight TB and five are "repurposed" drugs that were originally used for other diseases but show promise against TB. In addition, two dozen other compounds are in earlier stages of pre-clinical testing or research.

The Global Plan to Stop TB 2011-2015 – the programme of the Stop TB Partnership representing the World Health Organization and a host of other international and national bodies from the public and charitable sectors – estimates that $3.7bn will be needed to achieve its drug development objectives over the next five years.

These objectives include regulatory approval of two antibiotics for drug-sensitive TB and one for drug-resistant varieties.

The aim is to cut the standard TB treatment regimen to four months by 2015 and one-to-three months by 2020.

Given that new TB drugs need lengthy clinical trials with large numbers of patients – partly because there are no good "biomarkers" such as blood tests that clinicians can use to assess an individual's progress towards being cured – the cost estimates for the Global Plan seem modest. The commercial pharmaceutical industry expects to spend an average of more than $1bn to bring one drug to market.

The two drugs that have gone furthest in clinical trials for TB, gatifloxacin and moxifloxacin, are both "repurposed" antibiotics – oral fluoroquinolones that are already licensed to treat other bacterial infections. Their existing record will speed up the process of demonstrating in large-scale (phase III) trials in Africa that one or both can substitute for some of the older antibiotics used to treat TB.

Long-standing treatment: the standard antibiotics have been extant for about 40 years AFP/Getty

At the opposite end of the drug development process, early discovery research is making progress too. A recent contribution has come from scientists at the University of California, San Diego, working with colleagues at Leeds University in England.

They published in November what they called the TB-drugome. The project has linked hundreds of licensed drugs to more than 1,000 proteins in Mycobacterium tuberculosis, in an effort to identify more targets for existing medicines.

The complex network of drug-target interactions discovered by the San Diego and Leeds researchers not only showed that one-third of the drugs examined might have the potential for repurposing to treat TB, but also pointed to unexploited bacterial proteins that could serve as novel anti-TB targets.

However, as Lei Xie of UC San Diego points out, this new computational high-throughput process of drug discovery is just a first step: "only experimentation can validate the most promising drug-target combinations, and there will be many failures along the way."

Other discoveries about Mycobacterium tuberculosis have raised the hopes of researchers. Scientists at Brookhaven National Laboratory and Stony Brook University in New York have found a difference in the way cells from humans and Mycobacterium tuberculosis deliver unwanted proteins, marked with a "kiss of death" molecular sequence, to respective cellular recycling units.

The bacterial system for marking proteins and then chopping them up with protease enzymes turns out to be quite different from its human counterpart – giving a possible lead towards drugs that could cripple Mycobacterium tuberculosis without causing side-effects.

Meanwhile, researchers at Birmingham University in England have identified the enzyme IMPDH which is involved in the first stages of the bacterial biosynthesis of DNA.

By screening cell cultures, they found three potential drugs (diphenyl urea compounds) that inhibit the enzyme and kill Mycobacterium tuberculosis cells.

"The compounds we tested have selective activity against Mycobacterium species, meaning that any drugs based on these would be specific and would not affect human cells," says Gurdyal Besra of Birmingham. "We are tapping the potential of a so far unexploited target that could lead to the synthesis of a novel anti-tubercular drug, and our findings so far are extremely encouraging."

Nurses are underused and undervalued

Patient care

Frontline workers have untapped knowledge relevant to everything from clinic design to treatment, says **Sarah Murray**

In the fight against tuberculosis, resources are often focused on developing drugs and diagnostics, while less attention has been given to the people administering those drugs and diagnostic tests.

These frontline healthcare workers play an essential role in improving infection control and ensuring patient compliance with drug regimes.

While nurses are always essential in efforts to combat diseases, this is particularly true when it comes to TB.

While diagnostic procedures have become simpler and new drugs that shorten the treatment time are becoming available, nurses are the most important link between treatments and the patients receiving them.

"Nurses need time to speak to patients, to do a proper assessment of what the issues are and find out what support someone might need," says Gini Williams, TB project director at the International Council of Nurses.

Frontline healthcare workers provide the first point of contact with a TB patient.

They give advice to help minimise the risk of that patient infecting others, administer the drugs, work with patients to ensure they finish the treatment and help them cope with side-effects of the medicine.

"Nothing could be more important to the patient than the caregivers," says Krista Thompson, vice-president and general manager for global health at BD (Becton, Dickinson and Company), a healthcare equipment company, that has formed a partnership with the Geneva-based International Council of Nurses to provide health services to frontline healthcare workers in several African nations.

"The minimum course of treatment is six months and for a resistant form of TB, patients may need to be on the drugs for a year or more," explains Ms Thompson.

"Frontline healthcare workers are crucial in helping them understand the importance of staying on the drugs the entire time and ensuring they don't develop resistant forms of the disease," she adds.

Nurses help patients deal not only with the physical effects of the disease and the side-effects of the drugs they are taking, but also to cope with the social stigma attached to TB and the potential loss of income for families with members who have the disease.

Patients find it easier to stick to their treatment when their economical, psychological and social needs are also addressed, says Ms Williams.

This reduces the time spent following up patients who do not attend appointments and helps prevent incidences of multiple drug resistant, or MDR-TB.

"The whole of the patient context needs to be taken care of," Ms Williams says. "And nurses tend to come from the community they serve. They usually have a good knowledge of their caseload and they know where their patients are coming from."

At the same time, they work in tough conditions and are at risk of infection themselves.

Often overstretched, they can find it hard to provide sufficient non-medical support for patients or to trace those who do not attend appointments or fail to keep to their drug regimen.

However, many point to another big problem: nurses' voices are not being heard frequently enough, even though they have a wealth of on-the-ground knowledge about what works and does not work in treating TB.

Their experience can be helpful to companies, particularly for devising tools and treatments for countries where medical resources are stretched.

"When we were developing . . . products, they were our best source of information," says Ms Thompson. "We watched them to see how they used our products and made design changes as a result."

Even more important, says Ms Williams, is for nurses to have representation at local, national and global policy debates or during the early stages of the development of diagnostics and treatment technologies.

Nurses tend to come from the community they serve and have a wealth of experience

This was acknowledged in a World Health Organization report* on efforts to strengthen nursing and midwifery services.

"Governments, civil society and professional associations must work together with educational institutions, NGOs and a range of international and bilateral organisations . . . so that the input of nurses and midwives is more actively sought and acknowledged," wrote the report's authors.

Yet Ms Williams says this message has not yet reached many of those working to combat TB.

"At the moment, we have a global strategy that talks about patient-centred care but it's completely rhetorical," she says.

"Nurses are rarely consulted at country level when a Global Fund [to Fight Aids, Tuberculosis and Malaria] application is being put together."

She argues that they should be asked for input on everything from the design and layout of clinics – to allow for confidentiality and reduce the possibility of infection – to training and the development of tests and treatments.

"Nurses feel undervalued," says Ms Williams. "They are a fantastic resource and they're not being consulted."

**Strategic Directions for Strengthening Nursing and Midwifery Services 2011-2015, World Health Organization, 2010*

Fight demands money and leadership

Continued from Page 1

will help reduce drug prices. Yet short-term cash is limited, especially for TB, a stigmatised disease concentrated among the poor, the old and the disenfranchised.

The impact of financial austerity is threatening progress more broadly, through cuts in healthcare budgets and international donor support that is channelled through bodies such as the Global Fund to Fight Aids, Tuberculosis and Malaria.

The crunch is affecting the organisations conducting research into drugs, vaccines and diagnostics, as well as operational groups.

Mr Raviglione is facing cuts to the TB team of 120 employees at the WHO in Geneva, for example.

Mel Spigelman, head of the TB Alliance, a US-based non-profit partnership with industry to develop drugs, feels similar pressure.

"We are working off reserves, and have had to put on the brakes," he says.

We could be getting more aggressive in testing more drugs, faster, but we can't afford to run out of cash."

Part of the solution is money. That includes foreign aid and greater domestic efforts by rich and poor countries alike.

London has repeatedly been awarded the unflattering title of TB capital of Europe and planned decentralisation of UK health service decision-making risks making matters worse.

The emerging countries led by Brazil, Russia, India and China also need to do more.

Jorge Sampaio, the UN Secretary-General Special's Envoy to Stop TB, writes: "TB is having a massive impact on working people in the Brics . . . If all four countries aspire to continue their current pace of growth, it behoves them to make TB a top priority."

Money also needs to be accompanied by fresh political leadership. The African Leaders' Malaria Alliance, which has brought together heads of state in recent months to tackle another infectious disease, is a model being eyed by the TB community.

Some also argue for a broader reorganisation of the existing machinery and greater ambition backed by more advocacy and grass-roots support. That includes holding governments and international organisations to account and questioning official figures on successful TB treatment.

Gini Williams at the International Council of Nurses, says: "Nurses are working in impossible conditions, frequently unable to offer adequate treatment support, trying to address drug stock-outs, working in unsafe conditions, having to turn people with [multi drug resistant-TB] away." "In the meantime, country-level reports show all is dandy bar a few hiccups."

> 'We need to be more independent of the WHO, working more with civil society'

Lucica Ditiu, the new head of the Stop TB Partnership, says: "We have not always been transparent and open enough. We need to be more independent of the WHO, working more with civil society and the affected communities."

Businesses could play a greater part, especially in poorer countries with weak health systems. "We need to extend what's already happening," says Dr Herbert Schilthuis, medical adviser to Heineken, the brewing group, who sits on the Stop TB Partnership board. "As donors and governments pull back, there is pressure for companies to do more."

There is a need for closer collaboration with the private sector in other ways. Non-state funded healthcare remains dominant in countries such as India, making it imperative that the most appropriate drugs and diagnostics are used in line with best practice.

Many inaccurate tests and poorly made drugs given inappropriately are creating "therapeutic anarchy", adding costs and triggering greater resistance.

Experts are belatedly discussing ways to pool resources, providing larger and more certain markets to encourage high quality manufacturers into TB.

Donors such as the Global Fund and the US President's Emergency Plan for Aids Relief may need to be more aggressive in pushing recipient countries to co-operate, including over the frequent links between TB and HIV.

Greater TB screening of those diagnosed with HIV – which receives far more money – and prescription of the drug isoniazid as a prophylactic, for instance, could help sharply reduce tuberculosis.

"The world's worst bacterium is teaming up with the world's worst virus," says Paul Jensen, research director of Action to Control TB Internationally, an advocacy group.

Back in Bucharest, Andrea's health remains in the balance. So does that of people in Romania and across the EU, which has admitted the country to membership, allowing its citizens to migrate more freely.

Europe, where the bacterium that causes the disease was first identified 120 years ago, is yet to do enough to tackle it.

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Molecular test offers hope for detecting drug resistance

Diagnostics

The WHO has endorsed 'Xpert' but the machines are expensive, says **Charis Gresser**

For more than 100 years, the world has been relying on the same basic technology to detect tuberculosis: a smear test from sputum that is peered at through a microscope.

But a few months ago, the World Health Organization (WHO) endorsed an automated molecular test (Xpert MTB/RIF) that many hope will revolutionise the detection of this killer disease, especially for strains of multi-drug resistant TB (MDR-TB) and TB in those living with HIV.

The most important advantage of this test over the usual smear is its greater reliability in identifying TB cases, otherwise known as the sensitivity rate.

In studies, the WHO says the sensitivity of the "Xpert" test was 91 per cent, compared with 59.5 for the standard smear test.

The test's sensitivity to TB that is resistant to an important antibiotic – Rifampicin – was 95.1 per cent. Ordinary smears cannot detect antibiotic resistance. It can also help to diagnose cases of TB that coexist with HIV, which may be missed in smear tests.

The gold standard for detecting TB remains the culture of the mycobacterium that causes the disease, but this has drawbacks: it takes many weeks to grow the culture and it requires expensive infrastructure, with laboratories and technicians, which are scarce in poorer countries.

Xpert, on the other hand, can be used in more basic labs because it is simpler and safer to use and results are available in a couple of hours.

This is particularly important for MDR-TB, a disease that is of extreme concern to public health officials because it is so hard to treat.

Gilles Van Cutsem, medical co-ordinator for the charity Médecins sans Frontières for South Africa and Lesotho, says: "If you don't test for MDR-TB, you don't find it. It's the hidden epidemic. But where you test, you find it in very high numbers . . . Survival improves when you test, because you can start early treatment and you can treat in local clinics. Also, just as important, early diagnosis cuts transmission. It's the key to decreasing the epidemic."

Typically, this dangerous form of TB is diagnosed from culture only after treatment with first line antibiotics fails.

As Karin Weyer, co-ordinator at the WHO's Stop TB Department, explains: "To diagnose MDR-TB, you have to rely on

Gilles Van Cutsem: 'If you don't test for MDR-TB, you don't find it. It's the hidden epidemic'

expensive tests that are only available at reference labs nationally. Today, less than 10 per cent of MDR-TB patients are tested . . . The sooner you can start treating patients with MDR-TB, the more lives you will save. [It] is spreading fast in vulnerable populations, such as those with HIV co-infection, who die prematurely, often before the diagnosis of MDR-TB is made." The WHO believes the new test could lead to a three-fold increase in the diagnosis of patients with MDR-TB and a doubling for HIV-associated TB in areas where there are high rates of HIV.

More than 20 countries have received the new test, according to the Foundation for Innovative New Diagnostics (Find), one of Xpert's developers. Its advocacy officer, Lakshmi Sundaram says uptake will partly depend on how "flexible and proactive" large donors are.

For all the excitement, Xpert is not the perfect diagnostic test – one that can be cheaply and reliably performed anywhere (like the urine dipstick test for diabetes or pregnancy).

The test machines require a regular power supply. They need to be calibrated each year and require some training. Also they do not come cheap.

Even after big discounts – more than 60 per cent – for low and middle-income countries, the device will cost roughly $17,000. This is much more than the $1,500 cost of a microscope, though much less than that of equipping a lab for culture according to the WHO.

The costs per test will range from $10.72 to $16.86 depending on volumes, roughly comparable – at the low end – to the cost of repeating a smear test several times, as is often done.

The WHO has recommended that Xpert be used as the initial test where patients are suspected to have MDR-TB or HIV-associated TB.

In other cases, microscopy will remain the mainstay.

According to Dr Van Cutsem, cost is an important constraint. "The price . . . needs to be reduced for scale-up to be possible. It is the main barrier at the moment. The situation where there's only one manufacturer for a diagnostic test that has the potential for an enormous public health impact . . . is not optimal and the emergence of generic competition is highly desirable," he says.

Developments such as cheaper power supplies and remote calibration would improve the situation. There is also research into whether the devices could be used to run other tests, such the viral load in HIV cases.

At the Global Fund to fight Aids, Tuberculosis and Malaria, Mohamed Abdel Aziz, senior TB adviser, sums up the importance of this new technology: "This is a big step forward, but it is not the end of a long route to discover a diagnostic tool that is available everywhere...This test will not replace microscopy."

Surgery can help in some difficult cases

Treatment

Russia has always been wedded to an approach that can be useful against resistant strains, writes **Andrew Jack**

Long considered expensive, complicated, dangerous and largely superfluous, surgery is making a comeback as a way to treat tuberculosis. This is despite limited data, relatively scant scrutiny and weak guidelines on practice.

There are anecdotal cases of TB surgery designed to drain abscesses in the lungs in the 19th century. By the start of the 20th century, the practice was becoming much more widespread as a way to close infected cavities.

Then, in most parts of the world, the advent of powerful antibiotic drugs, accompanied by rising optimism that TB could be conquered with the use of medicines, led to a sharp decline in the use of surgery.

An exception was the Soviet Union, where surgery retained a significant role under important surgeons including Mikhail Perelman, an authority in "phthisio-pulmonology" who is still active at 86. Russia has continued to carry out surgery on more than 10,000 patients a year.

"In striving to improve the outcome of tuberculosis treatment, especially among seriously advanced forms of the disease, it is important to explore the possibility of surgery, where there are the appropriate indications, and to operate on patients at the time," Prof Perelman wrote in a recent paper.

After the collapse of Communism, Russia initially resisted the introduction of "directly observed treatment, short-course" (Dots), the highly effective standardised combination drug-based approach pioneered in the late 1980s and endorsed as the standard of care by the World Health Organization from the mid-1990s.

Dots clashed with what some observers have described as a culture of "personality-based medicine" in Russia, driven by individuals and their bespoke approaches

Surgery, combined with long follow-up care in sanatoria, reflected a traditional approach with firm supervision of patients to ensure compliance and limit risk of infecting others.

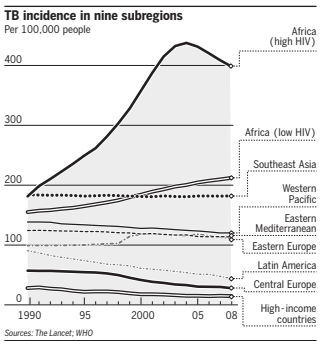
To critics, it also meant high costs, keeping older style TB medical institutions in business and diverting scarce resources from more efficient drug-based treatments.

It also had a human cost, with post-surgical mortality of up to 8 per cent.

Surgery maintained a role in other countries too, including the US, Japan, Korea and Peru, where it has been used essentially to treat rising numbers of cases of multiple drug resistant (MDR) and extremely drug resistant (XDR) tuberculosis.

Resistance has also become the most typical indication for surgery in Russia, where MDR and XDR are at extremely high levels, against a backdrop of a very large number of overall cases. This is partly explained by disruption at the time of the collapse of the Soviet Union, which was associated with a rise in poverty, migration and stress.

A homeless patient in a Siberian clinic: TB soared when the Soviet Union collapsed AFP/Getty



Sources: The Lancet; WHO

Resistance has intensified in Russia because of a frequent lack of drugs – "stock-outs" – and poor treatment compliance during the 1990s.

MDR is particularly acute among the large prison population, long seen as a breeding ground for infection.

Economic dislocation also contributed to a resurgence in TB surgery elsewhere in the former soviet bloc, mirroring the rise in MDR.

Elmira Ibraim, head of the National TB Programme in Romania says: "Surgery was marginalised for a while. Now, it's coming back as an adjuvant for MDR, if the status of the patient is good enough, and the lesions are limited. It's turning back to history."

Tido von Schoen-Angerer at Médecins sans Frontières says: "The challenge is to have facilities with adequate hygiene. At the moment, we are supporting surgery in Armenia after MSF renovated the operating theatre."

An internal literature review conducted by the charity, drawing on reported experiences with surgery in South Korea, Japan, the US, Peru, South Africa, Taiwan and Turkey, concluded that surgery combined with continued drug treatment could prove an effective approach for MDR TB.

Elsewhere, a team led by Tarek Mohsen at the Kasr El Aini Hospital in Cairo concluded in a paper in 2007: "Surgery should be considered as an adjunct to medical therapy when eradicating multi-drug resistant tuberculosis in affected patients. Anatomic lung resections can be performed with acceptable morbidity and mortality."

They argued that, as surgery combined with drug treatment offered a cure in up to 93 per cent of patients – compared with much lower rates for extremely costly and less efficacious MDR treatment – the benefits exceeded the risks.

There are concerns, however, that statistics on the extent of the practice are scant, systematic studies are difficult to conduct, definitions vary widely, and there is little consistency on issues such as precisely when to conduct surgery. More guidance and research seem overdue.

Meanwhile, a solution that was long championed by Russians, and partly triggered by a distinctly Russian problem of drug resistance, may yet find a broader market in the post-Cold War TB world.

'The future looks really dark'

Romania

Global Fund money runs out next year, notes **Andrew Jack**

Marioara Micu, the TB manager for Ages district, holds a morning meeting with local officials, visits a sanatorium until mid-afternoon, and then stops off in the regional capital's hospital to clock in for night duty.

Like dozens of her colleagues in the Romanian government's National TB Programme, including its director, she remains a full-time clinician, seeing patients and trying to make ends meet on her modest salary.

Yet she also volunteers in a second job, helping manage prevention, diagnosis and treatment of one of the country's most serious infectious diseases.

"Sometimes, the TB managers look tired and burnt out, but we don't criticise them," says Silvia Asandi, head of Romanian Angel Appeal Foundation, a non-governmental organisation involved in tackling the disease. "We understand. They donate their time."

Lack of money is one frequently cited difficulty of dealing with tuberculosis in Romania.

Accelerated by the 2008 crisis, the result has been: a squeeze on doctors' and nurses' salaries as living costs have risen; restrictions on drugs and diagnostics; and scant funding for training or programmes of incentives for patients to take their medicine.

Many doctors have sought ways to supplement their income in the private sector, or emigrated, further weakening medical infrastructure in a country that already has one of the lowest ratios of doctors to citizens in the European Union.

Others have faced important infection risks while treating TB patients.

"Money is very important, but more important are the people," says Elmira Ibraim, head of the national TB programme. In her office in the Marius Nasta Institute of Pneumology in Bucharest, in between patient consultations, she points to figures showing impressive overall progress.

The disease rose steadily in Romania from the mid 1980s, accelerating after the revolution in 1989 to reach a peak of 31,000 new cases in 2003, reflecting increased migration, unemployment and social problems at a time of transition.

It has since steadily declined, reaching a little over 19,000 last year.

But that still remains the highest absolute number of cases anywhere in the EU, and the largest in the broader European region after Russia and Ukraine.

The overall trend conceals important nuances.

Dr Ibraim shows a map indicating a close correlation between TB and social problems, with the greatest concentrations on the more rural, impoverished eastern and southern borders.

Furthermore, she estimates that more than 700 patients a year are contracting multiple drug resistant MDR-TB, which is far more costly and complex to treat, requiring drugs over two years. A 10th of these have extremely resistant (XDR) strains, which is still more difficult to tackle.

Samples from fewer than half of patients who do not respond to first line drugs are tested for resistance, suggesting that many cases are not being counted.

'I just don't feel the decision-makers understand or are taking any action'

The money from international donors through the Global Fund to Fight Aids, Tuberculosis and Malaria will run out next year, with the last cohort of MDR patients it is supporting set to be recruited by June. There is scant sign of alternative sources of funds.

"TB is a huge public health issue, but I just don't feel the decision-makers understand or are taking any action," says Dana Farcasanu, head of the Centre for Health Policies and Services in Bucharest.

"We are talking about free movement of [contagious] people. This is a security issue, but I just don't see any concern at EU level."

She also criticises decentralisation introduced into the health system in 2007, which may have theoretical advantages but has further fragmented treatment and undermined community nurses and Roma mediators who were reaching the most affected groups.

Drug procurement has also suffered, with inexperienced local staff handling smaller quantities of TB drugs causing "stock outs" that risk causing further drug resistance in patients.

The government has promised to recentralise purchases, but is yet to act.

At Dr Ibraim's institute, and another in the north of the country, MDR patients have access to good care. At other units, including the Valea Iasului sanatorium with more than 100 beds for first-line treatment, the conditions appear good.

Yet at a time of resource constraints, there will be a growing debate over whether the money used on such specialist centres should instead be reallocated to a "community-based" model, with those with TB discharged rapidly and treated as outpatients.

"The future is really dark," says Ms Asandi.

"The Global Fund was a real success, but we don't see any other source of funding. We have days when we are really depressed. We have a problem, we have the solution, but someone needs to give us the money."

Combating Tuberculosis

New vaccines A financial booster

Scientists are rapidly coming up with new vaccine candidates to supplement and then replace BCG, which has for 90 years been the only way of preventing tuberculosis.

Several dozen vaccines are at various stages of development, but large amounts of money will be needed to bring the best ones through clinical trials to the market.

The Tuberculosis Vaccine Initiative, an independent non-profit organisation, proposes a new funding mechanism for the purpose, given that conventional mechanisms (the pharmaceuticals industry and venture capitalists) are not available on the scale required.

TBVI calculates that a "financing gap" of €560m ($784m) must be filled to bring the first, most advanced vaccine(s) to market in about 2020 – the earliest realistic date, since extensive clinical trials will be required to prove safety and efficacy.

The proposal is that European governments or state agencies should provide guarantees that enable financial institutions to lend money to support the development of the vaccine portfolio through specific stages.

This loan will be repaid through royalties after the successful vaccines are commercialised by the pharmaceuticals industry.

The new funding model will help governments to stimulate research and innovation – and to alleviate the dreadful global burden of the disease – without having to pay all the costs up front at a time when most countries are under severe pressure to cut public spending.

Research grants from the European Union and its member states have yielded 39 vaccine candidates that fall into the portfolio of TBVI.

The Aeras Global TB Vaccine Foundation is another non-profit body, based in the US, which has half a dozen candidates in more advanced stages of clinical development.

Joris Vandeputte, TBVI senior vice-president, says that analysis over the past year in conjunction with Aeras shows that the market for new vaccines will be greater than previously projected.

"Industry is starting to knock at our door, asking about collaboration," he says.

"We can foresee a revenue payback on the basis of royalties."

The market will be mainly in wealthier developing countries that face substantial numbers of TB cases, where BCG vaccination remains routine.

Many countries in the industrialised west no longer vaccinate children routinely with BCG.

New vaccines will fall into two types.

Booster vaccines are likely to come first. They will be given to children to strengthen the rather poor immune protection given by BCG.

Later, we can look forward to new priming vaccines that will take the place of BCG.

Clive Cookson

BCG vaccination is no longer routine in the west

Rural healers can help with treatment

India

The country has made big strides in improving diagnosis and treatment, writes **Amy Kazmin**

The Sunderbans are one of India's most inaccessible areas – low-lying islands and mud flats that are part of the vast Ganges delta in the Bay of Bengal.

Accessible only by boat, the region has a population of about 4m people, poorly educated and living at the mercy of the tides.

In this swampy wilderness, the government has often struggled to deliver basic services such as primary healthcare, leaving the inhabitants to rely on their own means, including traditional healers, or erratic, poorly-regulated use of modern medicines.

But here, in waterways normally plied by fishermen and locals, volunteers from the Southern Health Improvement Samity – a local charity known as SHIS – are now travelling tirelessly, spreading information about tuberculosis, its symptoms, diagnosis and proper treatment.

Using colourfully painted boats, traditional folk musicians, and community meetings, the outreach workers urge those who have had a persistent cough to be screened for the disease.

Sputum tests can be carried out immediately – there are kits on the boats and patients who test positive are put under treatment, supervised by trained volunteers.

Sidhajoti Parija, the TB control programme manager for SHIS, say results have been encouraging, with rising rates of TB detection, and successful treatment.

But it is not easy, given the physical challenges. "In these areas, there are no roads, the islands are muddy, and there is no communication," he says.

"These boats have been running 24/7, 365 days. But people have got more aware and the results are improving day by day."

India has the biggest caseload of TB in the world, and long struggled to make progress in controlling the disease.

It registered 2m new cases in 2009, the highest of any country in the world, and about 280,000 deaths, according to The Lancet, the medical journal. Estimated TB incidence – of 168 per 100,000 – has remained steady over the past two decades.

But experts say the country has made big strides in building diagnosis and treatment infrastructure, increasing the number of cases it has identified and treated, while reducing fatality rates, though new cases have yet to show a substantial decline.

Partnerships with various NGOs – which are taking the lead in education and outreach in many of the most remote areas where diagnosis rates had been lowest – have been crucial.

"India has made tremendous efforts in the past few years," says Mohamed Abdel Aziz, a senior TB adviser for the Global Fund to Fight Aids, TB and Malaria.

"It was a huge effort by the national [TB control] programme to reach each and every corner in India. But controlling TB is an effort of everybody – not only of the government. The government cannot do everything."

Currently, about a dozen charitable groups have banded together as TB Consortium, an NGO that reaches out to suspected tuberculosis patients in some of the most remote, neglected districts, including tribal areas, where armed Maoist rebels are battling the state.

The workers focus on educating villagers about getting a proper diagnosis for any persistent cough.

They also sometimes serve as couriers, carrying sputum samples from suspected cases to laboratories that may be up to 20km from the village – a distance that can be a big barrier to those seeking diagnosis and treatment.

> 'If we don't rope in unqualified practitioners, we will have very low case detection'

"We are primarily taking the message to the community that if you have anybody who has the symptoms – a cough for two weeks – you must get to the diagnosis centre," says Subodh Kumar, a TB programme manager with World Vision, the charity, which is playing a big role in co-ordinating the NGO efforts.

"If the distance is very far, we help them in carrying the sputum. Once they are diagnosed positive, we immediately link them to the treatment."

In some areas, NGOS work with rural healers, who are trained to supervise the Dots – Directly Observed Treatment, Short-course – approach to therapy, and are offered a financial incentive for every patient who successfully completes it.

"We have a lot of unqualified practitioners in the remote areas and they are often the first point of contact for the patients," says Mr Kumar.

"If we don't rope them in, we will have very low case detection. We also don't want them to misuse the anti-TB drugs."

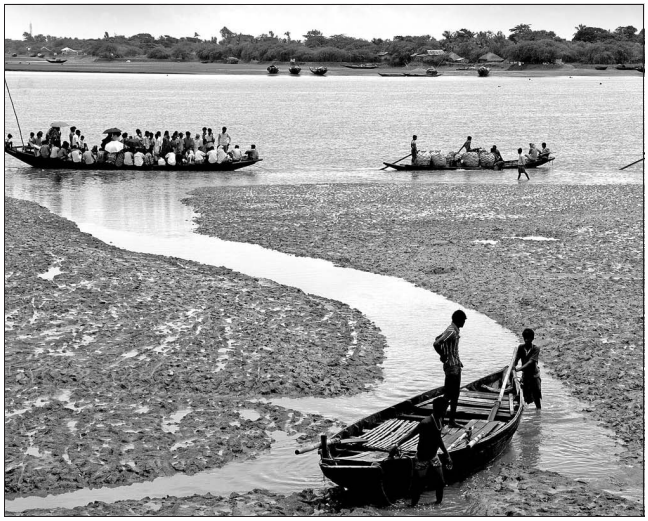
Of greater concern to public health experts than the unqualified healers – who are proving quite co-operative with the national programme – are the private, qualified medical doctors, who often refuse to follow the national treatment protocol.

Instead, many prescribe a combination of drugs, that experts warn could lead to the proliferation of multi-drug resistant TB.

"The so-called highly qualified doctors are using more and more second-line drugs – this is the most dangerous issue," says TB expert Rajdeep Srivastava, a World Vision adviser.

The Global Fund's Dr Aziz says: "We need to be sure the private sector is playing the correct game, and not doing harm rather than correcting the TB situation.

"A multitude of regimens and dosages not consistent with any standard, or international recommendations is the best way to create multi-drug resistant TB."



The government still struggles to deliver healthcare to people in inaccessible areas, such as the Sunderbans Dreamstime

Eradication becomes harder as cases dwindle

Case Study US

Now the disease is rarer, fewer doctors can diagnose it, says **Alan Rappeport**

The battle against tuberculosis in the US is one that is fought at the margins. The number of cases and deaths has fallen sharply in recent years.

Latest figures from The US Centers for Disease Control and Prevention (CDC) on the prevalence of the disease reveal a mere 11,545 cases in 2009, down by 10 per cent from the prior year and 57 per cent from 1992, when TB was resurgent.

Meanwhile, its most recent fatality figures – from 2007 – showed 554 deaths. With a fatality rate of just 0.2 per cent, those who die from TB in the US either realised they were infected too late or were not treated properly.

"The US is one of the few countries in the world where such remarkable progress in fighting TB continues to be made," says Kenneth Castro, director of the CDC's Tuberculosis Elimination programme. "Last year was the lowest incidence rate in the history of surveillance in the US."

According to Dr Castro, that progress is expected to continue. However, the fight to eradicate TB actually gets harder. As it becomes rarer, fewer doctors are trained to diagnose it and have good knowledge of the drawn-out treatment process.

"Many healthcare providers are working in areas where they don't see people with TB with enough frequency to remain proficient," says Dr Castro, explaining that doctors are more likely to suspect cancer if a patient comes in with symptoms, which include a cough, fever, sweats and fatigue.

In the US, the disease is concentrated in California, Texas, Florida and New Jersey. It continues to be most common among Asians, Hispanics and African-Americans. Poor people who have little access to healthcare are the most vulnerable.

Foreign-born residents account for the majority of cases, stoking the debate on the importance of immigration screening.

CDC efforts against TB remain aggressive. The agency has four regional centres and actively seeks out high-risk people for testing and treatment.

Relapses and latent cases that go undetected remain significant challenges.

Although prevalence in the US is dwindling, the field of research is rich.

Paul Edelstein, a professor of pathology and laboratory medicine at the University of Pennsylvania, co-authored a forthcoming study that shows how the duration of therapy could be cut in half from a year.

The study, to be published in the journal Cell, pinpoints why the effectiveness of treatment diminishes over time, explaining that microscopic pumps in the bacteria that cause TB are can flush out antibiotics. If these pumps can be inhibited, it would reduce treatment times.

"It has a lot of promise for shortening the course of therapy," Prof Edelstein says, noting that in some African countries only 40 per cent of people with TB finish the arduous treatment course, which can require six drugs. In the US, about 90 per cent complete the treatment.

The CDC says prevention is still the best remedy for eliminating TB and that testing people who are in prison, have HIV, or are homeless is crucial to further reducing the infected population.

CDC headquarters in Atlanta

Case study UK: an exercise in persuasion

A short tube ride west of the centre of London is the South Acton estate.

Over the past four years, crumbling tower blocks have given way to open spaces and new buildings. Ealing, the local borough council has redeveloped the area, replacing grim 1950s concrete with two and three storey housing.

In an area with a reputation for drug and alcohol abuse, tuberculosis went hand in hand with deprivation.

It is hoped that regeneration will change this, helping attack the social roots of the disease.

The estate has been a particular focus of Acton's TB outreach worker Mohamed Ahmed, as he combats another problem: the cultural taboo attached to the disease.

Tucked away in the Acton Health Centre, on the edge of the estate, he works with the staff of community centres and the doctors of nearby hospitals.

He communicates the threat of TB to ethnic communities and identifies discharged patients most in need of attention.

TB has been a growing problem in the UK for 20 years, predominantly in London. Of the 9,000 cases in 2009, almost 3,500 were in the capital. "It's a London-wide problem" says Onn Min Kon, consultant respiratory physician at St Mary's Hospital, Paddington. "The city is now looking to co-ordinate, but as things stand it's not there yet."

Nearly three-quarters of cases in the UK are in recent migrants; people who have come from endemic areas in the past two to five years. This is reflected in Ealing, explains Mr Ahmed: "The majority are from the Indian subcontinent, then from sub-Saharan Africa. Since European Union enlargement, we have had a lot of patients from eastern Europe as well."

The TB bacterium infects the weakened and can remain dormant in the lungs for years. A healthy patient can fight it off but it can become active in those with a rundown immune system.

For migrants escaping hunger, poverty or conflict, it is something of a mystery why it only activates when they arrive in Britain.

"Perhaps it is diet or vitamin D deficiency. There is a factor that makes their TB active, but it is not fully understood," says Dr Kon.

Mr Ahmed's work is in part an exercise in persuasion. Some communities see TB as incurable and patients are ostracised. He works hard persuading people to seek treatment and not conceal their disease.

Over the past six years, he has seen improvement: "At first, people were reluctant to talk, to come forward and seek help. Now they take the leaflets and ask questions."

Encouraging people to ask for the treatment is only the first step, as it is important that it is completed. If it is not, this can lead to drug resistance, a serious problem for both the patient's and public's health. Resistant strains are more difficult and costly to treat.

In the UK, 82 per cent of patients complete their treatment. The international standard is 85 per cent.

In Acton, Mr Ahmed can boast completion rates above this global target. "Directly observed treatment" – watching patients take their medication – is one technique he uses. He also believes that changing people's perceptions counters entrenched fears, prejudice and denial.

Jack Serle