FT Health Combating TB

Friday March 22 2013

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Austerity poses risk to funding for battle ahead

Deep problem: miners attend a mobile TB test centre in Carletonville, South Africa. For story, see Page 3 Getty

Tuberculosis has failed to capture imaginations in the same way as HIV, reports *Andrew Jack*

All it needed was just a short exposure to another student's cough in his overcrowded college dormitory for Endy Fekadu to contract tuberculosis. It took him three years to be diagnosed, plea for access to drugs from abroad and struggle with the side effects, from nausea to depression, before he could be cured.

Today he fights against the political indifference, stigma and poverty that he says are fuelling an epidemic affecting an estimated 200,000 people in Ethiopia alone. His story is mirrored around the world, as health workers try to contain a disease that kills nearly 1.5m people a year and infects 9m, including 600,000 with drug-resistant strains that are particularly difficult to fight and require lengthy treatments.

As donor nations meet in Brussels next month to discuss fresh support for the Global Fund to Fight Aids, TB and Malaria, the world's biggest multilateral funder of health programmes, the fate of such patients will be at stake.

Against the backdrop of austerity and vagaries in international development trends, TB risks being still further relegated.

"The absence of sufficient financial commitments by countries is the top challenge," says Mario Raviglione, head of the TB programme at the World Health Organisation (WHO), which sees a shortfall of $1.6bn a year needed from donors for TB treatment and prevention plus $3.2bn from countries themselves.

TB is the most "neglected" of the three diseases supported by the Global Fund, with disbursements currently capped just above previous levels of 16 per cent of total expenditure until fresh money is pledged.

That is particularly serious because while HIV and malaria have captured the public imagination and triggered funding from diverse sources over the past decade, including an increasing share from governments of the countries most affected, TB has struggled to win support.

Aaron Oxley, head of Results UK, a TB charity, says: "Without the Global Fund there is no international response to the disease. No donor properly champions it."

Financing is more heavily dependent on the Global Fund than for the two other diseases, even though HIV and TB are deeply interconnected, especially in Africa. "Standalone programmes are not where we need to be," says Mark Dybul, the Fund's new executive director. "Everyone with HIV needs to be tested for TB and vice versa. You can't separate projects."

TB affects the most marginalised groups in society. Yet it spreads far more easily around the world than either HIV or malaria, with drug-resistant strains rising fast in western metropolises such as London and Paris as much as in Addis Ababa.

In the past few years, reports of "multi" (MDR) and "extreme" drug resistance have spread from South Africa. In late 2011, researchers even claimed to have identified "totally" resistant strains in India.

Such phenomena are largely man-made, the result of incomplete and partial drug treatments, sometimes using substandard products.

"The thing I really lose sleep about is MDR," says Dr Neil Schluger, chief scientific officer at the World Lung Foundation. "It's completely out of control. We don't have a good handle on how much there is out there, most places lack any means to diagnose it, don't have good protocols or adequate supplies to treat it."

The news is not all bad. After decades of stagnation, new "tools" have also begun to emerge. Janssen's bedaquiline, the first new TB medicine for four decades, won US approval at the end of last year, offering prospects for more effective treatment of MDR strains. A second drug, made by Otsuka, is currently under regulatory scrutiny.

PaMZ, a combination of new and existing drugs, offers the prospect of reducing the duration of treatment for standard, drug-sensitive TB from six to four months – easing the burden of side effects and the difficulties of compliance. Other trials are

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Drug takes tough road to market

Pharmaceuticals The route from pipeline to patient is arduous, reports *Andrew Jack*

When scientists at Janssen began to start hunting for a new medicine to treat tuberculosis in the 1990s they kept it quiet from their bosses.

Their discretion paid off and in the past few weeks they have been able to talk about bedaquiline, the first new drug approved in four decades to treat one of the world's most lethal infections – albeit with continuing concerns about side effects.

Paul Janssen, founder of the eponymous Belgian pharmaceutical company, was long committed to seeking better treatments for TB, from which his sister died. But its marginalisation in the past century into a disease of the poor meant it had little commercial appeal for Johnson & Johnson, which bought Janssen in the 1960s.

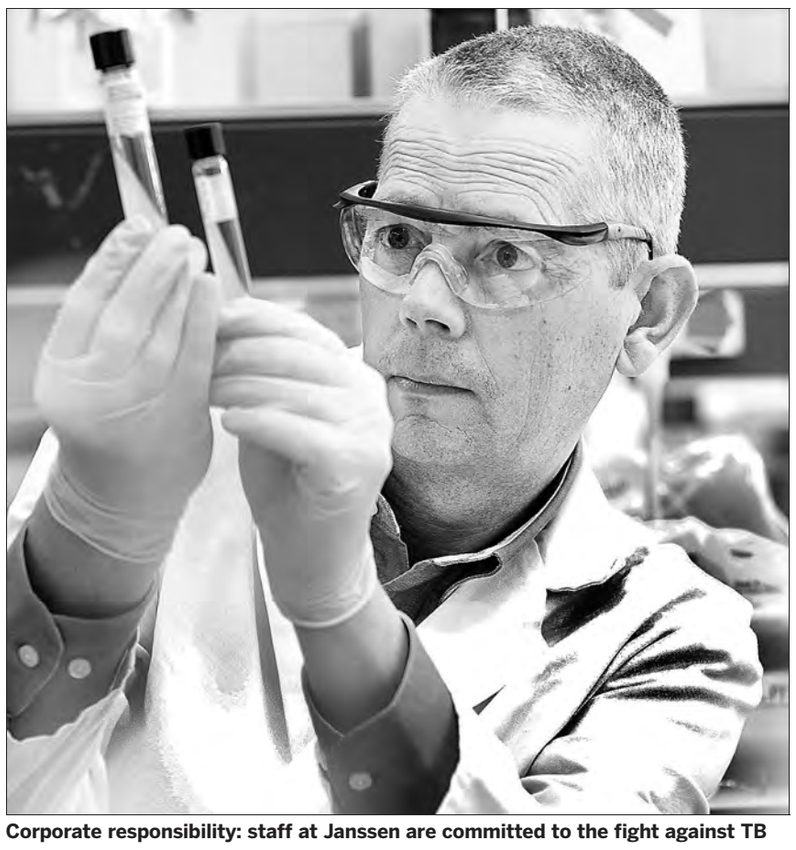
"Research did not start from top down but by one of my managers, who added TB to a panel of tests," says Koen Andries, who led the discovery efforts not long after Mr Janssen's retirement. "There was no upfront agreement. We were a bit prudent in being quiet for some time. If you ask upfront, there is a high risk of many people saying no. We kept it under the table till we had really convincing data."

His team screened large numbers of the company's experimental medicines, including one originally synthesised in-house designed as an anti-inflammatory treatment. While discarded for that purpose, it did show potential for TB. Unusually, it was also highly specific, with no value as an antibiotic for other infections.

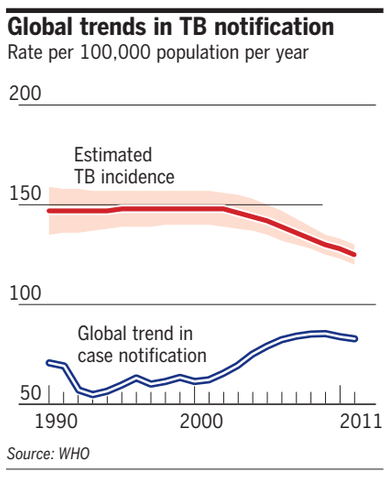
It took many more years to get the drug through laboratory tests before its effect in patients could begin to be assessed. But bedaquiline – now given the brand name Sirturo – was approved by the US Food and Drug Administration on the last day of 2012 for drug-resistant TB on the basis of a small number of results from patients in mid-stage clinical trials.

The story of the drug and the challenges of its development highlight the broader difficulties in improving the range of costly, complex, cumbersome and unpleasant medicines for TB, which bring side effects over a minimum course of six months' treatment.

"It is a historic discovery to find a new target for such an important disease," says Paul Stoffels, worldwide chairman of Janssen. "You can't just leave it there. Somebody had to take it on.



Corporate responsibility: staff at Janssen are committed to the fight against TB



"There's corporate responsibility. A company consists of people, who may decide to pursue something they consider important."

He argues that both tax reductions and a "priority review voucher" – allowing US regulators to accelerate their scrutiny of another drug as a reward for developing the TB medicine – helped offer some incentives. "All together we came to the conclusion that, even if we don't earn a lot of money [from the drug], we won't lose a lot and it will make a huge difference in the world," he says.

Bedaquiline is just the furthest advanced of a series of drugs now moving through the TB development pipeline. Mel Spigelman, head of the TB Alliance, a non-profit drug development partnership, says: "We are entering a brave new world. It's going to be an amazing year with potential for new drugs. There's a lot of stuff going on."

He points to a second new TB drug, under review by European regulators, developed by Otsuka of Japan. He hopes two other big companies – Pfizer and AstraZeneca – with experimental treatments at an earlier stage will soon advance their work alone or in partnership.

His organisation is studying bedaquiline for "first line" drug-sensitive TB treatment, as well as PaMZ, another combination of new and existing drugs, that could cut the duration of standard treatment from six to four months – the first such reduction in 50 years.

Mr Andries stresses that the path ahead remains difficult. Laboratory testing is protracted because the bacillus grows very slowly. Its complex genetic make up means focusing on a single "target" for a new drug is likely to fail.

Testing in patients is just as difficult. "The availability of qualified laboratories for clinical research is not to the standards of other research fields," he says. "We had to struggle with capacity of people."

Furthermore, ethical rules require new drugs to be added to existing cumbersome cocktails of treatments – four in bedaquiline's case – even when the current regimens have not all been tested rigorously. He argues that researchers desperately need simple "surrogate markers" that would allow them to measure progress more rapidly and effectively.

Two final issues remain for all new TB drug developers, which Janssen is thinking about: pricing and use. The company has committed to discounts and patient access programmes so its medicine can reach the poor, although it must still be combined with existing drugs that limit the ability to offer a cheap treatment package.

Second, it and others need to ensure the drug is used appropriately, rather than used on its own or produced by unauthorised manufacturers with insufficient quality control. Otherwise, the latest treatment for drug-resistant TB risks simply perpetuating the problem.

Simple interventions make a big difference

Ventilation

Charles Batchelor discovers that open windows can help prevent infection

A sticker campaign urging bus passengers to keep the vehicle's windows open is part of the South African authorities' campaign against TB.

Droplets containing the TB bacteria, expelled when a person coughs or sneezes, can remain in the air for hours but are dispersed by good ventilation and killed by sunlight. Sneezing can create tens of thousands of droplets and talking has been calculated to generate 3,000 droplets in five minutes.

"Simple interventions can make a big difference," says Nulda Beyers, director of the Desmond Tutu TB Centre at Stellenbosch University near Cape Town. "We distribute stickers to public transport operators but . . . windows are still closed."

The risks of contracting TB on public transport in South Africa were highlighted in a study of minibus taxi, bus and train travel by JR Andrews and others published in the American Journal of Epidemiology last month. Among daily commuters the annual risk of becoming infected was put at 3.5 to 5 per cent and was highest among minibus taxi users.

It is in hospitals and clinics, where TB sufferers mingle with those who have other conditions, that the threat is particularly acute.

Here opening windows can be more effective than using mechanical ventilation, according to a study of eight hospitals in Lima, Peru, by Rod Escombe of Imperial College, London for the Wellcome Trust.

This found that in isolation rooms, TB wards, outpatient consulting rooms and emergency departments, natural ventilation via open doors and windows was more than double that in mechanically ventilated rooms and 18 times that of rooms with doors and windows shut. Even at the lowest wind speeds, natural ventilation exceeded mechanical ventilation.

Facilities, built more than 50 years ago, with large windows and high ceilings, achieved higher levels of natural ventilation than modern naturally ventilated rooms. "Some of these older facilities had been built for TB patients along the design principles of TB sanatoria when fresh air was part of the treatment for TB in the pre-antibiotic era," the Wellcome Trust said.

The latest thinking on designing well-ventilated housing is being applied to a project to house people in Haiti whose homes were destroyed in the January 2010 earthquake. A total of 147 design teams submitted entries for homes designed to limit the transmission of tuberculosis, the second biggest infectious killer in the country after HIV/Aids.

The competition, staged by Architecture for Health in Vulnerable Environments (Archive), an international non-profit organisation, required the designs to use local materials, construction techniques and practices where possible and to be replicable and inexpensive. The homes are planned for the town of Saint-Marc.

One problem identified by South African researchers was the danger surrounding the collection of sputum – mucus from the respiratory

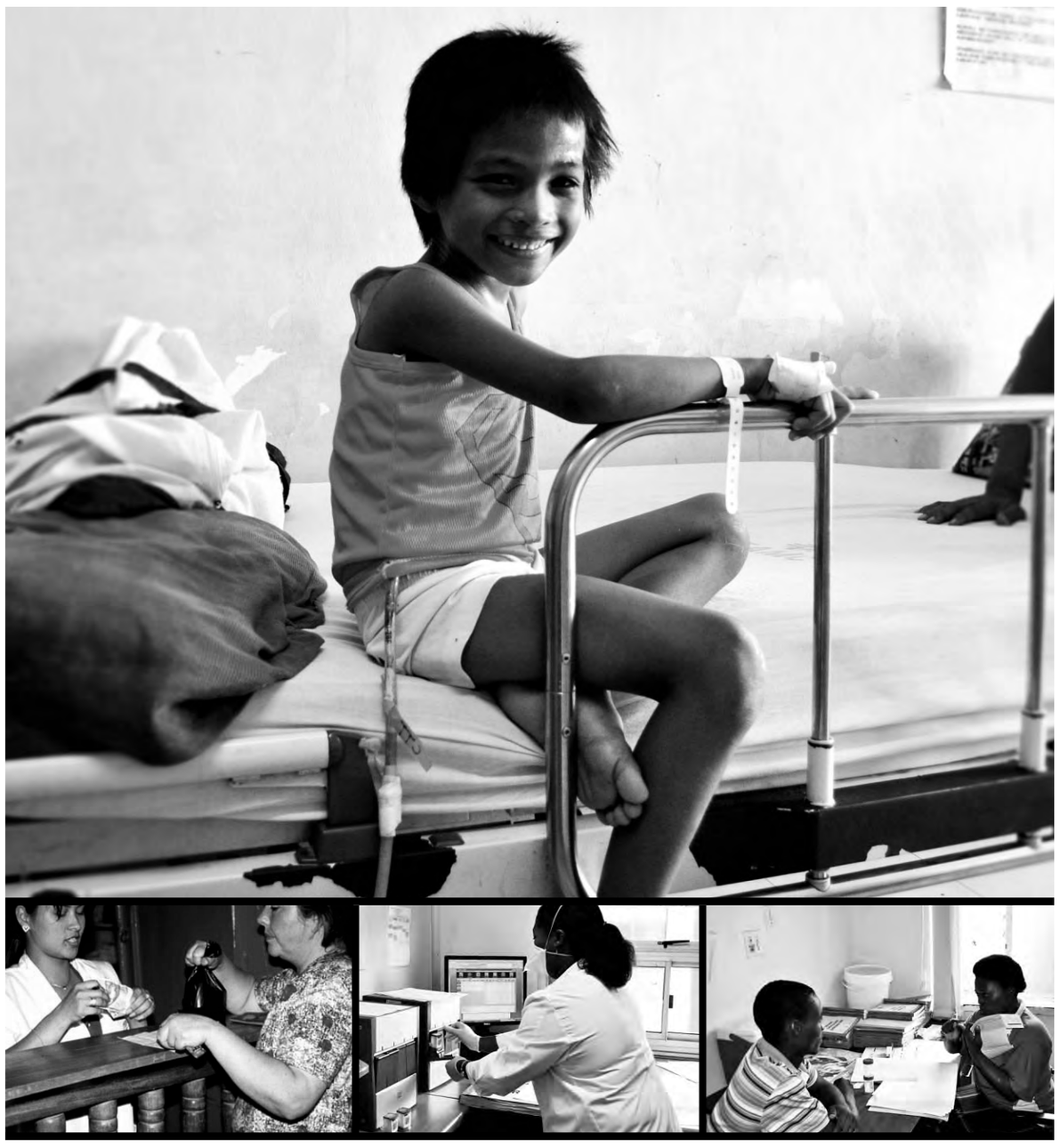
> Among South African commuters, the annual risk of becoming infected was 3.5%-5%

tract – from suspected sufferers.

"Previously you would go to the bathroom or use a bottle," says Prof Beyers. "We worked with engineers to design a sputum booth, with three walls and space between the roof and the walls and put it outside the room where people get TB treatment. They were put in all Cape Town health facilities."

Despite support for natural ventilation, mechanical ventilation, often involving negative pressure rooms that allow air in but not out, is often used. In some climates, open doors and windows may not be an option.

A high-tech version of Cape Town's open-sided booths is a ventilated hood or booth that removes airborne contaminants at or near their source. Fans remove all the airborne particles outdoors, taking care to avoid air-intake vents and people. If air cannot be vented externally it can be passed through filters designed to capture 99.97 per cent of particles of 0.3 microns or larger, a standard known as high-efficiency particulate air.



Haphazard care for young victims has variable results

Paediatric care

The remedies used for children are inadequate, writes *Jessica Twentyman*

About 1m children worldwide are thought to die of tuberculosis each year.

It is hard to be sure of the true number because so many cases go unreported, says Mel Spigelman, president and chief executive of the non-profit Global Alliance for TB Drug Development (TB Alliance).

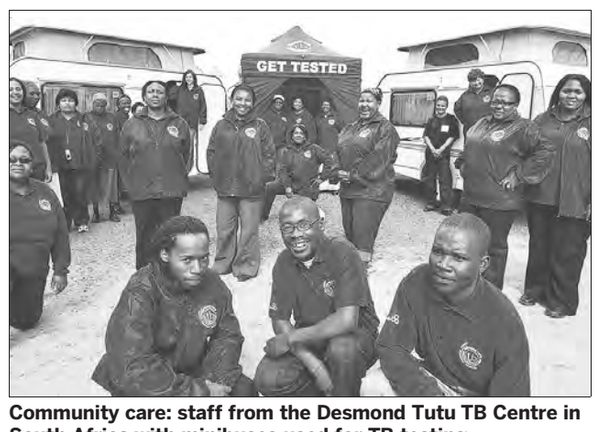
One fact, however, is unavoidable, he says: the treatment currently used for children suffering from TB is woefully inadequate.

Dr Spigelman adds: "It's mind-boggling, absurd. When you look at what's available, you'd never ever want this treatment for your own child."

There are no TB drugs specifically formulated for children. If treating TB among the poorest of the poor has been commercially unattractive for many drug companies, argues Dr Spigelman, treating the children of the poor is an even less profitable prospect.

With this in mind, the TB Alliance was awarded a grant of $16.7m in December 2012 by Unitaid, a global health initiative that aims to tackle market inefficiencies that stop drugs reaching patients in developing countries.

The purpose of this funding is to accelerate the availability of properly formulated paediatric TB regimens.



Community care: staff from the Desmond Tutu TB Centre in South Africa with minibuses used for TB testing

"Forcing children and families to 'make do' with the current treatment is untenable, especially when so many children suffer from tuberculosis," says Anneke Hesseling, director of the paediatric TB research group at the Desmond Tutu TB Centre at Stellenbosch University in South Africa. "This grant gives the paediatric research community hope for the future."

Others, including Otsuka, are also working on paediatric formulations. Until new treatments emerge, however, the options for medics will continue to be unappealing and often ineffective. They mostly involve taking the standard adult dose and reducing it according to the weight of the child. "You take an adult pill, you try and break it up to reduce the dose and then crush it up into apple sauce or what other foodstuff you have around, just to get the child to take it, because they may be too young to swallow a pill or, in all probability, several pills," Dr Spigelman adds.

It is haphazard, with variable results. Of the standard drugs used to treat TB, some are eliminated faster by children than by adults. Others have unwanted side-effects. In children, there may be an increased risk of ocular toxicity, leading to blindness, linked to the use of ethambutol, a common ingredient of TB medications.

Attempts to develop drugs for the treatment of children have run up against a series of barriers, according to a 2010 research paper by Soumya Swaminathan and Banu Rekha of the Tuberculosis Research Centre in Chennai, India. These include "the difficulty of confirming active TB, concerns about paediatric-specific adverse effects, uncertainties about the appropriate time to involve children in drug development, the optimal trial designs for drug development and complex regulatory requirements."

The alliance will have to jump these hurdles.

In three years, says Dr Spigelman, it hopes to have fixed-dose combinations specifically developed for children available in dispersible form, so that they can be dissolved in liquid for children too young to swallow tablets, preferably in palatable forms.

But he admits: "It's a huge amount of work to do, on a hugely accelerated schedule."

The Unitaid funding will be used in different ways. First, there must be studies to understand better the scale of the problem.

"This is important to entice drug manufacturers and other private-sector parties to get involved – and the way to do that is to help them better understand the marketplace," says Dr Spigelman.

Second, the TB Alliance will work with drug companies to formulate the right dosages for children. Those conversations are under way, he says, for example, with companies that already produce TB drugs, those active in paediatrics and with those active in countries with the highest TB burdens. Some of the Unitaid money, he adds, will be put on the table as incentives for drug companies to get involved in drug development for paediatric formulations.

Finally, the TB Alliance will work with the various regulatory authorities to get new paediatric formulations approved for distribution in different areas of the world and with the governments, buyers and distribution partners required to get those drugs to the children who need them.

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Mobility of mine workers stokes continental problem

Africa Fight against HIV and TB is hampered by the large numbers of migrants from rural communities, writes *Andrew England*

The South African mining industry has for more than 100 years been dependent on a labour system that is, in many ways, unique in the country.

Hundreds of thousands of workers come from remote rural areas of South Africa and beyond – particularly from Mozambique, Lesotho and Swaziland – meaning diverse groups of men have been brought together to work deep beneath the surface.

This migrant labour system has meant workers spend months away from home living near gold, diamond and platinum mines. And it is one of several factors contributing to the industry's notorious record of HIV and tuberculosis rates.

Joel Spicer, senior strategist at the Stop TB Partnership, says of the 1.4m people dying globally of TB each year, 40 per cent of the deaths are in Africa. Three quarters of deaths are centred in 10 countries, six in southern Africa.

"The epicentre of the epicentre is in the mining sector," he says. The rates of HIV infection across southern Africa are among the world's highest, and TB is one of the diseases commonly associated with those infected with the virus that causes Aids.

In mining, the problems are exacerbated by the concentration of large numbers of men around mines, who, living away from their families, take on partners from local communities, experts say. Silicosis, a lung disease, exacerbates the situation as miners are exposed to silica dust.

Rates of TB in the mining industry are estimated to be between 3,000-7,000 per 100,000 population, which contrasts sharply with a national rate in South Africa of about 1,000 per 100,000 or a global rate of 125 per 100,000 population, says Mr Spicer.

"The mining industry has a problem with TB and we really need to face up to it and get on and deal with it," says Brian Brink, chief medical officer at Anglo American, which employs about 71,000 people in South Africa.

Most large miners have recognised the problem and have HIV and TB programmes that test for the diseases and provide free treatment.

Anglo American, for example, says about 12,000 of its South African workforce are HIV positive, with just over 5,000 having antiretroviral treatment. New cases of TB at the mining company last year were 958 per 100,000 population, he says, putting it below the national average and illustrating that progress is being made.

At AngloGold Ashanti, South Africa's biggest gold producer, there has been a 60 per cent drop in the rate of new cases of occupational TB and a 40 per cent fall in new cases of HIV in the past seven years, says James Steele, the company's medical officer.

Yet, it is still estimated that 20-30 per cent of AngloGold's 30,000-strong workforce is infected with HIV. "HIV and TB still remain one of our biggest health concerns but, I think, both as a company and as a country we are winning the battle," says Dr Steele.

A critical problem facing companies and health authorities is ensuring those suffering from HIV or TB remain on the correct treatment programmes when they travel between their workplaces and their homes.

Occupational hazard: miners face a particular risk of developing TB Reuters

Many mine workers come from poor rural areas with inadequate health facilities and, because TB is highly infectious, the problems can be multiplied as the disease spreads among miners' home communities. If those infected fail to follow through with their treatment course, this can fuel drug resistance, another complication.

"The problem in southern Africa is the mobility of mine workers coming and going from a rural area or an adjacent country, moving backwards and forwards, kind of halfway through the treatment, lost continuity of care and then inadequately treated TB, and then it becomes resistant to the drugs," says Dr Brink.

To tackle those issues, southern African governments signed a declaration last August pledging to strengthen co-ordination and mechanisms in the battle against HIV and TB as they committed to the ambitious goal of "moving towards a vision of zero new infections".

Experts say the declaration was a significant step in the right direction, with co-operation between companies and governments a key to ensuring progress is made in the work place and vulnerable communities.

For years South Africa was criticised for not properly addressing the HIV/Aids pandemic, particularly under the presidency of Thabo Mbeki, who flirted with the ideas of dissident scientists who disputed a link between HIV and Aids. But the government's attitude has changed markedly in recent years.

"When you have the right leadership in place things move and there is very strong leadership in Swaziland, Lesotho and, particularly, South Africa," says Mr Spicer. "South Africa is leading globally, and is doing things we would like to see replicated in other parts of the world."

But, the key, he says, is turning the political momentum into action, and ensuring the lessons learnt in South Africa are heeded in other mineral-rich African states, which are garnering increasing investor attention.

"Mining is going to expand in Africa . . . so it's not only mopping up the problem now but it's also getting it right next time," says Mr Spicer.

Austerity poses risk to funding

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examining improved efficacy by raising the dose of rifampicin, a backbone of existing therapy.

With help from Unitaid, another global health funder, the TB Alliance, a non-profit group, is beginning to test drug combinations and doses specifically for the estimated 1m children infected. Until now they have relied on poorly understood and poorly diluted versions of adult treatments.

Trials of a vaccine have been disappointing but GeneXpertMTB/RIF, a rapid molecular TB diagnostic, has been distributed in some 80 developing countries over the past three years, offering the prospect of identifying the disease more swiftly. Innovative programmes such as TB Reach have identified new ways to find and respond to infection.

A surge in funding and attention is having an effect. Statistics from the WHO suggest the prevalence of TB began to decline a decade ago.

Yet the figures are estimates, with countries only reporting identification and treatment of about two-thirds of projections of total cases.

More vigorous efforts are still required to delegate from physicians to community health workers. "The doctor is the general on the hill but nurses are much closer to the frontline where the action is and could play a much more important role, in counselling, patient support and early identification of side effects," says Evan Lee, head of the Lilly MDR-TB Partnership.

Médecins Sans Frontières, the health charity, is calling for strengthened financing, price transparency and a growing stockpile of quality-assured drugs, notably for MDR treatment, where gaps between supply and demand are large. Others stress the scope for greater preventive methods through everything from smoking controls and improved ventilation to more prophylactic use of drugs for those at risk.

TB is rising up the political agenda. China and India are starting to take the disease much more seriously, reflected in the Delhi communiqué of health ministers from leading emerging countries in January.

Their counterparts across southern Africa pledged fresh co-operation last autumn. A particular focus has been mining, which often sent employees with TB back home where they were poorly treated and infected others.

Debate is focused on agreeing more ambitious targets to reduce TB deaths to "near zero" over the coming decade. "We need a change in tone," says Lucica Ditiu, head of the Stop TB Partnership, which represents leading public and private organisations. "We need to shake things up."

Yet progress will not be easy. The UK's Department for International Development, which has long been a generous donor to groups fighting TB and other infectious diseases, is undergoing a "value for money" review. This has frozen support to the non-profit partnerships working on new TB drugs, vaccines and diagnostics.

The fear is the demand for short-term results will come at the expense of support for the better drugs, vaccines and diagnostics, which will inevitably be required but which are the uncertain fruits of costly work over many years.

Without new tools and fresh energy, TB will continue to take a heavy toll.

India faces drug resistant strain

Epidemic fears Health experts are critical of government's response, says *Amy Kazmin*

Mithapur is a bustling working-class neighbourhood of New Delhi, home to cooks, clerks and other service workers. Here Karishma Chowdhury, a 30-year-old mother of two, comes to a small clinic each week for free government drugs to treat the tuberculosis that forced her to give up her job as a cook for a middle-class family.

Four months into her six-month course of treatment supervised by Operation Asha – a partner of India's national TB control programme – Mrs Chowdhury feels better and hopes to resume work soon. But she knows she must take her medicine for another two months. "It's a course, and the course has to be completed, otherwise the disease will come back – and next time, it will be worse," she says.

Unfortunately, many of India's estimated 2m TB patients stop taking medicines once their health improves, which why India is confronting the problem of drug resistant tuberculosis – including some virulent new strains doctors say do not respond to known drugs. "The world is on the brink of a multi-drug resistant TB epidemic, and India will be the epicentre," says Shelly Batra, Operation Asha's founder.

The World Health Organisation says about 99,000 Indians have multi-drug resistant TB, one of the largest burdens in the world, although India's laboratory capacity to diagnose the virulent strains is far short of requirements. Most Indians with drug resistant TB have had the disease previously, but about a third are first-time patients. Many doctors believe the problem is worsening. "I've seen the resistance pattern relentlessly amplify before my eyes," says Zarir Udwadia, a Mumbai-based TB expert at Hinduja Hospital.

Dr Udwadia galvanised India's health establishment last year, when he reported to the medical journal Clinical Infectious Diseases he had identified four patients infected with what he called "totally drug-resistant TB" that did not respond to any first or second line drugs.

The article said each of the four patients had received "erratic, unsupervised second line drugs, added individually and often incorrect doses from multiple private practitioners".

Completing the course: health worker Amit Saxena, left, watches Karishma Chowdhury take her medicine Simon de Trey-White

'I've seen the resistance pattern relentlessly amplify before my eyes'

India's fight against TB had been considered a rare bright spot in a bleak public health scenario. Since 2006, the revamped national TB control programme has worked with charities and community groups to establish a national network for detection and treatment, screening about 7m suspected cases and treating some 1.5m TB patients with free first-line drugs every year.

Since the 1990s, new TB cases in India have fallen by 1.5 to 2 per cent a year, and TB deaths have halved to about 300,000 a year, according to the WHO. But some public health experts are sceptical of government claims it detects 70 per cent of TB cases and cures 88 per cent of those found.

"What people say and what is the truth are two entirely different things," says Dr Batra. "In our country, the numbers are fudged."

Treatment centres, theoretically covering the entire country, are few and far between, which means patients travel long distances to reach them and often stop going once they feel better. In remote areas drug supplies are unreliable.

An independent consultant in one northern state estimates treatment default rate from the government's programme at around 36 per cent.

"What we see on paper . . . everything looks very good, but the ground reality is not like that," says Sarman Singh, head of clinical microbiology at the All India Institute of Medical Sciences, India's top public hospital. "Patients have to have counselling, which is usually lacking. Once they are asymptomatic [if a patient is a carrier for a disease or infection but experiences no symptoms], they usually don't treat."

Private doctors or traditional healers, who treat many TB cases, are another concern as they barely supervise their patients and often do not prescribe the correct drugs.

A survey of 106 health practitioners in a Mumbai slum with rampant TB found only six knew the correct prescribing practice for routine TB, and only three knew how to correctly treat drug-resistant strains. "Because TB drugs have been available off the shelf, and in the private sector, a lot of use, or misuse has taken place," says VS Chauhan, director of India's International Centre for Genetic Engineering and Biotechnology.

New Delhi recently declared all TB cases, including those found by private doctors, must be reported to the government, though experts say incentives will be needed to ensure all doctors and healers comply.

India is also increasing its capacity to diagnose drug-resistant TB, which experts say must be done quickly to ensure suspected cases are treated properly. It has also pledged to increase funding to treat drug-resistant TB, which takes two years and requires costly patented drugs.

"The good thing is the government is willing to look at the problem," says Dr Chauhan. "But it would be silly to say 'we will fix everything in two to three years'."

Trial setback fails to damp enthusiasm

Vaccines

Researchers remain in an upbeat mood, reports *Clive Cookson*

The Third Global Forum on TB Vaccines will open in Cape Town next week with several hundred researchers and clinicians determined to remain upbeat, despite the setback their field received last month.

The first large clinical trial for 90 years of a new vaccine against tuberculosis, MVA85A, failed to show efficacy when the Lancet published results.

The trial was intended to show MVA85A, developed at Oxford university in a £30m programme over 10 years, would boost the immune response of 2,800 South African babies inoculated with BCG. The Bacille Calmette – Guérin vaccine, introduced in 1921 and based on the bacterium that causes bovine tuberculosis, does not produce a good enough response to stop the TB pandemic.

"The MVA85A vaccine induced modest immune responses against TB in the infants but these . . . were insufficient to protect against the disease," says Helen McShane, who led the Oxford programme.

But Professor McShane insists there is still mileage in MVA85A and says a dozen other vaccine candidates working by different mechanisms are in clinical development globally. "We need new drugs too, but the only way we're going to tackle this epidemic in the long term is through an effective vaccine," she says.

The team is not giving up on MVA85A. Samples from the infants in the trial will be analysed for clues about how the immune system reacts to vaccination and infection with the Mycobacterium tuberculosis, the TB germ. Researchers will look to improve the immune response with higher or multiple doses, combining MVA85A with other vaccine, or delivering it into the lungs.

Optimistic: Helen McShane

Meanwhile a trial of MVA85A in 1,400 HIV-positive adults, at particular risk of developing TB, is going ahead in South Africa and Senegal with results due in 2015, says Prof McShane. The dozen vaccine candidates at earlier stages of clinical development, and a couple of dozen more in pre-clinical research, span a range of approaches. As with MVA85A, some are based on viruses genetically modified to stimulate the immune system against TB. Some, including BCG, are based on mycobacteria such as the one that causes TB. Some are proteins. For example GlaxoSmithKline, the UK-based pharmaceutical group, has developed a vaccine, M72/AS01E, based on a combination of proteins and adjuvant (a booster chemical). Crucell of the Netherlands uses Ad35, a harmless adenovirus with antigens from Mycobacterium tuberculosis, to stimulate production of protective antibodies.

Two non-profit international bodies organise funding and logistical support for TB vaccine development: the Tuberculosis Vaccine Initiative in Europe and Aeras, based in the US. According to Ann Ginsberg, head of science at Aeras, it is too early to talk about which approach is likely to be most promising.

Dr Ginsberg is confident the MVA85A setback will not undermine funding for vaccine research, which will need hundreds of millions of dollars over the next few years: "Our funders, organisations like the Gates Foundation, [US] National Institutes of Health and the [UK] Department for International Development, are realistic about what it takes to develop a TB vaccine."

But other TB experts say the challenge of developing an effective vaccine is so great that available money should be focused more on diagnostics and drug development. They express their reservations in an article due to appear in a forthcoming issue of The Lancet Infectious Diseases.

"Without a clear scientific basis for protective immunity against the disease and a biological marker for this, which we don't have, it is difficult to know how to make an effective vaccine," says one of the group, Richard Anthony of the Royal Tropical Institute, Amsterdam. One fundamental problem, he says, is past tuberculosis infection does not offer protection and patients recently treated for TB can become reinfected.

At next week's Cape Town congress, however, most delegates will see the scientific challenge as a reason for making more rather than less effort. "I see the meeting as a rallying of the troops," says Dr Ginsberg. "Now is the time to push forward, not pull back."