

Fast action urged to halt deadly TB

Technology holds the key to many of the challenges presented by a particularly virulent form of tuberculosis that broke out in South Africa last year. Countries across the region are making progress in keeping the threat at bay, but not fast enough.

Two new rapid diagnostic tests for multidrug-resistant tuberculosis (MDR-TB) are to be piloted in South Africa, dramatically cutting diagnosis time from two or more months to just two days. It will be the first time new technology is used to tackle the crisis of drug-resistant tuberculosis in Africa.

A pilot study to evaluate the tests in 40 000 tuberculosis patients started on 1 April in five South African provinces and is expected to last for 12 months.

"This is an important breakthrough, as it cuts the time for a definite diagnosis of MDR-TB," said Dr Karin Weyer, tuberculosis research director at the South African Medical Research Council.

Treating patients earlier will save lives, reduce the time spent on inappropriate and ineffective treatment, and reduce the spread of MDR-TB within crowded hospitals and clinics. Perhaps most importantly, it will be possible to diagnose patients with extensively drug-resistant tuberculosis (XDR-TB) at a much earlier stage.

In recent years, doctors had seen isolated cases that were highly resistant to drugs. But in March 2006, the World Health Organization (WHO) and the United States Centers for Disease Control and Prevention first reported XDR-TB as a serious emerging threat to public health and TB control.

XDR is defined as tuberculosis that is resistant to the two most important antitubercular drugs, rifampicin and isoniazid, as well as to any fluoroquinolone and at least one of three second-line injectable drugs: kanamycin, amikacin and capreomycin.

Rapid diagnosis of drug-resistant tuberculosis is crucial for patients infected with HIV. The HIV-positive patients infected with XDR-TB in last year's epidemic in Tugela Ferry, KwaZulu-Natal, survived a median of just 16 days from the time of sputum (matter coughed up from the lungs) collection.

Since September 2006, about 183 people, most of whom were HIV positive, have died from XDR-TB in

South Africa. XDR-TB could exacerbate the HIV/AIDS epidemic in South Africa, where about five million out of a population of 45 million people are HIV positive and as many as 1000 people die of AIDS-related complications every day.

Although the 2007 WHO report, *Global tuberculosis control: surveillance, planning, financing*, announced the good news that tuberculosis prevalence and death rates have been falling globally, the case load continues to grow in WHO's African, Eastern Mediterranean and South-East Asian Regions (www.who.int/tb/xdr/globaltaskforce_update_feb07). And while HIV testing for tuberculosis patients is increasing fast in the African Region, little effort has been made to screen HIV-infected people for tuberculosis even though this is a good method for case finding.

The Foundation for Innovative New Diagnostics (FIND), a non-profit organization based in Geneva, is behind the new rapid tests. Weyer said an interim analysis would be carried out six months into the 12-months pilot study. If the results are positive, Weyer said she hoped the Department of

Health would roll-out the tests to the remaining provinces.

Improved diagnosis was one of the priorities identified by the WHO Global XDR-TB Task Force last October. Following this, eight countries in southern Africa drew up a regional strategy to manage and prevent XDR-TB. Since then, each has delivered individual action plans to WHO and, in February, WHO released a 20-page report, *The Global Task Force on XDR-TB Update*, on XDR-TB in southern Africa.

Dr Mario Raviglione, director of WHO's Stop TB Department, said there has been some progress in the region. "Things are moving, but it is far too slow for the seriousness of the epidemic," he told the *Bulletin*. Weyer agreed: "I don't see any sense of urgency from the health authorities in tackling the problem in the serious way that the situation deserves."

Another priority identified by the task force was for countries to conduct rapid surveys to find out the true extent of XDR-TB.

Rapid surveys to determine the prevalence of resistance to second-line



Woman and child infected with multidrug-resistant tuberculosis receiving treatment at the Brooklyn Chest Hospital in Cape Town, South Africa. Cape Town has one of the highest incidences of tuberculosis in the world.

Lung Health Image Library/Gary Hampton

drugs in patients considered to be at high risk have been done in Lesotho and Botswana. Similar surveys are planned in Malawi, Mozambique, Namibia and Swaziland in the next few months.

Madagascar, Mozambique and the United Republic of Tanzania are doing nationwide surveys of resistance to antitubercular drugs, while Angola, Lesotho, Malawi, Namibia, South Africa and Zimbabwe plan to start such surveys later this year, or in early 2008.

Weyer said: "The department of health was supposed to start this last year in South Africa but it has not happened, which is very disappointing." The country's department of health has confirmed 269 cases of XDR-TB in South Africa to date, but Weyer believes the true figure is much higher.

"A previous survey showed 6000 cases of MDR-TB a year. If we estimate that up to 10% of these may be XDR-TB, then a conservative estimate is 600 cases." In the United States of America, 5% of MDR-TB cases are XDR; in Latvia, 19% of MDR-TB cases are XDR.

"For doctors on the ground the area most needing improvement is laboratory capacity, and perhaps sur-

prisingly, IT [information technology]," said Dr Mark Sonderup, specialist physician at Groote Schuur hospital in Cape Town. "Patients are mobile, so they move around between hospitals and between primary and secondary care. Tests are often duplicated or are lost in the system. We really need a central database of TB patients."

In the rest of southern Africa laboratory facilities tend to be even worse than those in South Africa. Researchers visiting Lesotho recently found the country's laboratory service was unable to diagnose drug-resistant forms of tuberculosis. FIND has sent technicians to help upgrade Lesotho's laboratory facilities, and these should be up and running in a few months. The Open Society Institute, founded by George Soros, donated US\$ 3 million

to help health-care workers in Lesotho treat people infected with drug-resistant tuberculosis and HIV/AIDS more effectively. The funds will also go towards developing the first global treatment guidelines for this deadly combination of diseases.

South Africa has made progress in infection control. Every province has identified one facility to treat patients

with drug-resistant tuberculosis, and these facilities are being upgraded and infection control procedures implemented. The South African Medical Research Council is running infection control training throughout the country.

An investigation by a team of epidemiologists, including WHO officials, into what happened at Tugela Ferry, started in March. Within a few months, it should be clear to what extent the epidemic arose out of poor infection control.

Could the epidemic in Tugela Ferry happen again? Weyer thinks so: "We are concerned that such outbreaks are happening all the time and are not detected. Deaths can be obscured by HIV and are not attributed to XDR-TB."

At the time of the Tugela Ferry epidemic, South African doctors had a limited drug armoury, as two of the nine antitubercular drugs were not available. However, the South African authorities have moved fast to ensure that capreomycin and *para*-aminosalicylic acid are now available.

But Raviglione cautioned: "Even if all the drugs are available, the important thing is to make sure these are delivered correctly, with patients counselled and supervised properly. In many areas basic TB control is lacking and if we don't have the basics in place, then the result is drug resistance." ■

Jacqui Wise, *Cape Town*

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Dr Mario Raviglione, director of WHO's Stop TB Department.

Russian oblast is model in fight against TB

The chaos following the collapse of the Soviet Union in 1991 triggered a tuberculosis (TB) epidemic across the Russian Federation. A decade and a half later, the Russian "oblast" or region of Orel is reporting progress in fighting killer strains of *Mycobacterium tuberculosis* that are resistant to common TB drugs.

By the end of the 1990s, the tuberculosis epidemic had reached alarming proportions across the Russian Federation. Orel oblast, in the south-western part of the country, was no exception. "The TB situation in the region was very bad, especially from 1999 to 2000," said Dr Boris Kazyenny, chief doctor at Orel Oblast Tuberculosis Dispensary in the regional capital of Orel.

Kazyenny recalled how the supply chains of essential medicines for tuberculosis broke down and, with that, the quality of treatment.

"We didn't have enough essential drugs so we had to prescribe an incomplete course of chemotherapy and many patients did not adhere to the treatment regimen," Kazyenny told the *Bulletin*. "That's why after the beginning of the 1990s, many of our patients did not make a full recovery and continued to transmit bacteria."

Tuberculosis specialists have long known that erratic drug supplies and failure to make sure patients complete treatment lead to drug resistance.

But amid falling living standards, mass migration and a crumbling health

system after the 1991 collapse of the Soviet Union that resulted in drugs shortages, doctors in the Russian Federation had little choice but to administer ineffective and incomplete treatment.

In November 1999, the region introduced the World Health Organization (WHO)-recommended DOTS strategy and, in November 2002, it started implementing the DOTS Plus strategy to deal with drug-resistant tuberculosis.

"We introduced international diagnostic and treatment standards for the management of tuberculosis patients," Kazyenny said. "Thanks to all these measures, we managed to stabilize the tuberculosis epidemiological situation in Orel oblast. By 2006, incidence had decreased by 26.5%, mortality by 48.3% and prevalence by 44.5%."

DOTS originally stood for Directly Observed Treatment, Short course. Now

the acronym refers to the five-element treatment strategy encompassing: political commitment; case detection through quality-assured bacteriology; standardized treatment with supervision and patient support; an effective drug supply and management system; and systems to monitor treatment progress and evaluate programme performance.

Initially, Orel oblast received drugs for its DOTS and DOTS Plus programmes from WHO. Now the oblast pays for the medicines, which are free to all patients, Kazyenny said.

The Russian Federation as a whole has also made some progress in fighting the killer disease. Prevalence fell slightly from 160 cases per 100 000 people in 2004 to 150 in 2005.

But the legacy of the dark days of the epidemic is still palpable, not least in the country's high incidence of drug-resistant tuberculosis, estimated at 10% of total new cases in 2004, according to the 2007 WHO report, *Global tuberculosis control: surveillance, planning, financing*.

Multidrug-resistant tuberculosis (MDR-TB) is a specific form that occurs when the bacteria are resistant to the two first-line antitubercular drugs, isoniazid and rifampicin. Last year, WHO defined an even more resistant – and frightening – form: extensively drug-resistant tuberculosis or XDR-TB, which is resistant to isoniazid and rifampicin, as well as to any fluoroquinolone and at least one of three second-line injectable drugs: kanamycin, amikacin and capreomycin.

Resistant forms are more difficult to treat. While a normal course of treatment lasts up to about six months, treatment of drug-resistant forms can take as long as two years, while second-line medicines are more expensive, not always available and can produce severe adverse reactions.

Today, Orel oblast is achieving better results in fighting tuberculosis than many other parts of the country. Last year, 81% of newly detected sputum (matter coughed up from the lungs)



“People react differently, but all of them are afraid of the disease.”

Larissa, a tuberculosis patient.

Elena Zolotova

Tuberculosis is spread when droplets, from the respiratory tract of a person who is infected with the bacteria, enter the air and are inhaled by another person. Larissa (right), a tuberculosis patient at Orel Oblast Tuberculosis Dispensary, wears a mask to prevent spread of the disease.

smear-positive patients successfully completed treatment, just short of the Stop TB Strategy goal and Millennium Development Goal 6 to cure 85% of new sputum smear-positive patients. However, this is high compared with the Russian national average of 59% DOTS treatment success in 2004.

Detection has improved too. According to Kazyenny, 55% of new cases are detected by smear microscopy at general health system facilities across the Orel oblast. In contrast, the national average was 30% in 2004, according to the 2007 WHO report.

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Dr Boris Kazyenny, chief doctor at Orel Oblast Tuberculosis Dispensary.

Kazyenny said that 7–8% of newly detected patients have MDR-TB, compared with an estimated 10% nationally. In 2003, there were 130 such patients in the region, but by 2006 that number nearly halved to 73. Recently, the number of resistant cases increased slightly, due to improved diagnostics. Last year, the oblast had just one patient with XDR-TB, who died.

Thanks to strict supervision of patients, social programmes for patients, and information campaigns for general practitioners and the public, Orel oblast has become a model of Russian tuberculosis control success. Recently, experts

from the World Bank and the Global Fund to Fight AIDS, Tuberculosis and Malaria visited Orel to see what could be achieved in other parts of the country.

Treatment may involve taking multiple medicines several times a day for months. If patients are not closely supervised, many stop taking their medicine when they start to feel better.

But in Orel oblast, only 3% of tuberculosis patients fail to complete a full course of treatment. Kazyenny said that this “is less than in any other [Russian] region” because Orel has a strict system of monitoring patients.

“If a patient breaks off treatment, we contact his district TB doctor three days later and ask a local TB doctor to visit him. If the patient is unable to return to the dispensary, outpatient treatment is arranged,” said Kazyenny’s deputy, Dr Elena Kiryanova.

“If the local TB doctor doesn’t call back, we send our own representative. As a last resort, we report it to the local police who can visit the patient. Sometimes the appearance of a police officer is enough to make the patient resume treatment,” said Kiryanova, deputy chief doctor for methodological and organizational work.

“We also have the right to apply to a court which can order obligatory treatment of patients who refuse to be treated, on the grounds they are dangerous to society,” she said, adding: “But the more effective method is social support for tuberculosis patients.”

Many tuberculosis patients are men with alcohol problems and a history of imprisonment, unemployment and homelessness. These and others receiving outpatient treatment also receive free food and hygiene parcels, and free train or bus tickets to come to the dispensary.

In collaboration with WHO, Orel oblast also plans to introduce incentives this year for medical workers to provide timely, proper and effective detection and treatment of TB patients.

One of the greatest hurdles to detecting cases is not so much the failure of general practitioners but patients' lack of awareness. Tuberculosis is heavily stigmatized in Russian society.

Larissa, a patient in her thirties, feared social exclusion after being diagnosed with tuberculosis when she was hospitalized with pneumonia. "I wasn't afraid of the treatment, but how would my family, my colleagues and other people react? That was the problem," she told the *Bulletin*.

Alexander, 20, another patient at the dispensary, underwent tuberculosis screening when he applied for a new job and was surprised when people were sympathetic. "Relatives, friends, no one showed hostility towards me when they heard I had tuberculosis."

Larissa confessed that although she was on the road to recovery, she was afraid of going home: "People react differently, but all of them are afraid of the disease". ■

Elena Zolotova, *Orel*

New tools for an old disease

A range of promising new tools to prevent, detect and cure tuberculosis (TB), which kills some 1.6 million people globally every year, could soon be within reach. But more funding to feed the research and development (R&D) pipeline is needed if the reinvigorated fight against TB is to succeed.

An array of new – and a few recombined – compounds and methods hold the potential to revolutionize the way TB is prevented, diagnosed and cured.

Thanks to generous funding from donors, particularly the Bill & Melinda Gates Foundation, three public–private partnerships are among a number of groups working to develop a new generation of diagnostics, medicines and vaccines for TB.

Scientists are researching vaccines that have the potential to be more effective than Bacille Calmette–Guérin (BCG), which was introduced in 1921 and is still the only TB vaccine. Diagnostic tools are being tested that may detect TB in patients more quickly than those used today and that may be used in places where medical staff have little or no laboratory training. And candidate drugs that reduce months-long treatment regimens may soon be available.

"The new and exciting thing is that for the first time in decades we have a fairly robust clinical drug portfolio being tested," said Dr Melvin Spigelman, director of research and development for one of those public–private partnerships, the Global Alliance for TB Drug Development, known as the "TB Alliance". "But there is a tremendously high attrition rate in developing drugs. You never can count on any one drug or a handful of drugs to be successful. We need to set up a pipeline to continually feed the process."

Arguments for shorter drug treatment regimens abound. Currently, a

full course of treatment means taking multiple medicines daily for about six months under the supervision of a health-care worker. Many patients break off treatment once they start feeling better. But failure to complete the full course has encouraged the development of bacteria that are resistant to common drugs, prompting the need for new drugs.

Shortening treatment would result in better patient adherence, reduced transmission of TB and less drug resistance, leading to fewer deaths. It could also save costs for patients and health services.

The not-for-profit TB Alliance has two drugs in clinical trials. Spigelman told the *Bulletin* that the aim is to produce a drug that reduces treatment duration from the current six-to-nine months down to four and, eventually, to two months. The long-term goal of the TB Alliance is to provide a drug that can cure TB in two weeks or less.

Among the TB Alliance's most advanced candidates is moxifloxacin, which it is developing with Bayer HealthCare AG of Germany. The drug has been used for other respiratory tract conditions since 1999 and is now being tested for use against TB.

Dr Martin Springsklee, vice president of global clinical development for therapy area anti-infectives at Bayer, said that if phase III trials, due to start this year, are successful, moxifloxacin could be available as early as 2010 and could become the first new antituber-

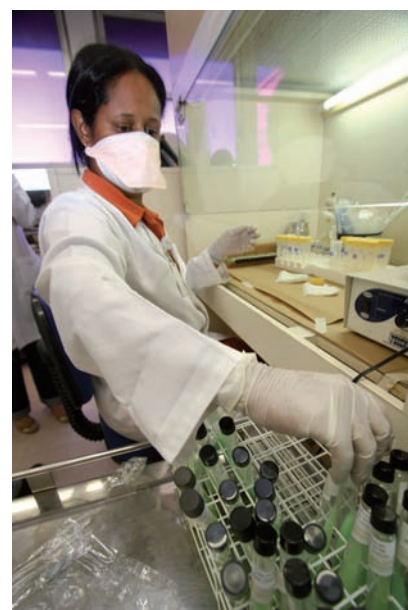
cular treatment in almost four decades.

Springsklee said there was "no significant commercial value" in the project for Bayer, but that the company had a moral obligation to make any resulting TB drug available to developing countries at affordable prices.

Separately, the TB Alliance has developed an antibacterial agent, called nitroimidazole PA-824, with Chiron Corporation of the USA. The compound is now in phase I clinical development.

The TB Alliance has received around US\$ 200 million from donors to fund its projects, including the Gates Foundation as well as the governments of Ireland, the Netherlands, the United Kingdom and the United States of America (USA).

New diagnostics are also desperately needed to speed up the detection of TB. The main method, sputum-smear microscopy, was developed in



Scientist in a laboratory at the Universidade Federal do Rio de Janeiro, Brazil, sorts TB culture samples.

TB Alliance

the 1880s. But this method can take four to six weeks to grow bacteria cultures capable of producing a test result and it is generally not performed on the spot. Results are not always accurate – particularly when the patient is co-infected with HIV – and skilled laboratory staff are not always available in the countries that are worst affected by the disease. These problems cause treatment delays and leave patients infectious.

Another public–private partnership, the Geneva-based Foundation for Innovative New Diagnostics (FIND), was set up in 2003 with an initial US\$ 30-million grant from the Bill & Melinda Gates Foundation. It already has four products for TB that have completed development and are now in the final phases of large-scale demonstration projects.

One is the *Mycobacterium* Growth Indicator Tube (MGIT) that FIND is developing with US-based Becton, Dickinson and Company. The MGIT–TB culture system permits the rapid growth and detection of TB bacteria, reducing average detection time from three-to-four weeks with solid egg or agar-based culture to 10–14 days.

With Tauns Co. Ltd of Japan, FIND is developing Capilia TB, a strip test that confirms the presence of TB bacteria in cultures in 15 minutes. Both MGIT–TB and Capilia TB could be available at concessionary prices for the public sector of developing countries as early as 2008.

The other two tests in the FIND portfolio that have completed development are for drug resistance in smear-positive patients. One is the *FAST-Plaque-Response* test, which FIND developed with Biotec Laboratories of the United Kingdom; and the other is the GenoType MTBDR test, the result of a partnership with Hain Lifescience GmbH of Germany.

FIND is also working with molecular and other technologies that are in earlier stages of development. “Our highest priority is to create simple and accurate tests that could revolutionize care by allowing TB detection at primary health-care centres,” said Dr Mark Perkins, FIND’s chief scientific officer.

Perkins cited a modelling study, commissioned by the Gates Foundation, that found that a test with only 85% sensitivity, if sufficiently simple to use, could get many patients on treat-

ment at an earlier stage of their illness, saving an estimated 400 000 lives a year.

“Even at the microscopy level new testing could have a big impact,” Perkins said. “Currently, microscopy misses more than half of all TB patients. The availability of a simple molecular test to pick up microscopy-negative patients could translate into many more patients detected early, saving resources, interrupting transmission, and saving lives.”

TB vaccine development has also found new funding and energy.

Aeras Global TB Vaccine Foundation, another public–private partnership, is leading efforts to produce new vaccines for TB. Dr Jerry Sadoff, president and chief executive officer, said that this year six vaccine candidates have entered or are about to enter phase I clinical trials, while phase II trials could begin in 2008. Candidates that show high efficacy will move into phase III trials in 2010, with eventual licensing in 2014 of any that are proved suitable.

Of the six, one – a recombinant of BCG – is being tested by Dr Marcus Horwitz of the University of California, Los Angeles (UCLA) in the USA. BCG can prevent severe forms of TB in children, but is ineffective in protecting adults in countries where TB is common.

USA-based Aeras is backing clinical trials of two proteins used as antigens. One was developed jointly with GlaxoSmithKline Biologicals and is in phase I clinical trials. The other was developed by Dr Peter Andersen, vice president of Vaccine Research and Development at Statens Serum Institut in Denmark.

The three other Aeras candidates are viral-like vectors. One vector is being tested by a team from the University of Oxford in the United Kingdom, in healthy volunteers who are HIV positive. Aeras is involved in researching the two other vectors, one jointly with Crucell a biotechnology company based in the Netherlands, and the other independently.

“I am confident we will make a vaccine out of [one of] these six candidates that will be better than BCG and have a major impact on TB,” Sadoff said.

For TB control advocates, such as Dr Lee Reichman, this cannot happen fast enough.

“We need a new vaccine very badly because the one we have now is effective only in children. The other major problem is treatment, although effective, is prolonged and most people don’t take their medicines properly,” said Reichman, a senior adviser to the Stop TB Partnership and professor of medicine, preventive medicine and community health at New Jersey Medical School in the USA.

Robert Koch’s discovery of the *Mycobacterium tuberculosis* bacillus in 1882, which earned him a Nobel prize, spurred the development of the BCG vaccine four decades later. The era of TB drug development started with the introduction of streptomycin in 1944 and ended with the introduction of rifampicin in 1963. No new anti-TB drug has been widely introduced since.

Interest in TB research waned during the 1970s and until the end of the 1990s, as TB was brought under control in industrialized countries. As a result, governments reduced R&D funding for the disease and pharmaceuticals companies deemed developing-country markets too small to justify substantial investment in TB products.

Then in the 1990s, TB epidemics swept the globe, including several countries of the former Soviet Union and New York City, and have been spurred by HIV/AIDS in sub-Saharan Africa. Since then, efforts by the Stop TB Partnership, the World Health Organization, donors and many others have returned the fight against TB to the world stage.

But more remains to be done. Dr Dermot Maher, senior research adviser in WHO’s Stop TB Department, said that basic research was underfunded and that because of this, too few compounds were entering the R&D pipeline. Maher said funding for TB research is roughly one-tenth of that for HIV/AIDS.

“The Gates Foundation has transformed the situation for funding in research and development for new diagnostics, vaccines and drugs for TB, but basic research needs a boost in funding,” Maher told the *Bulletin*. “Without the stimulation of basic research, there won’t be sufficient priming at the start of the development pipeline to feed intense research and development for TB. We need to do more.” ■

Paul Garwood, *Geneva*