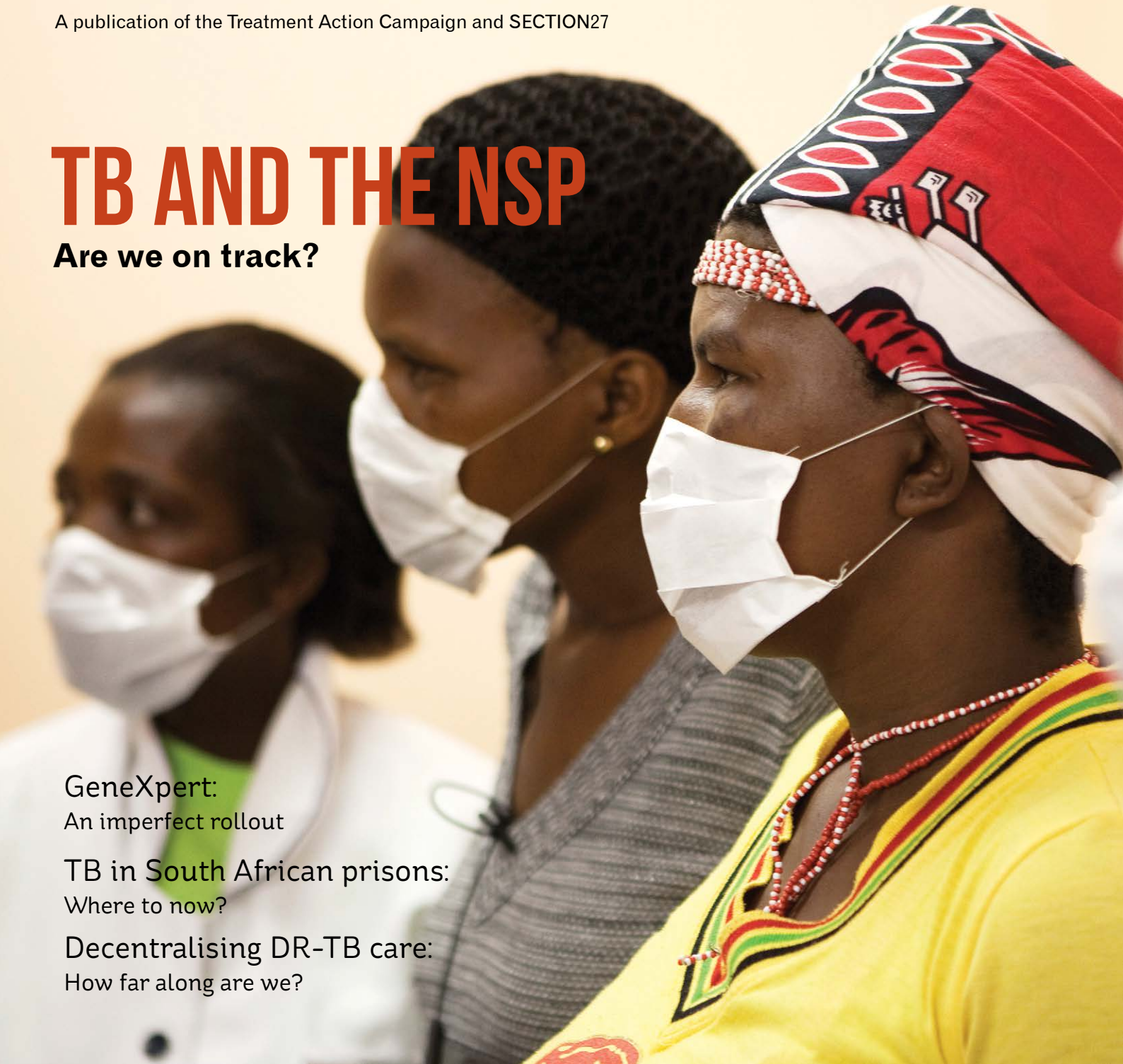
NSP REVIEW

Engaging with South Africa's National Strategic Plan for HIV, STIs and TB | **Edition 7** | **July – August 2013**

A publication of the Treatment Action Campaign and SECTION27



TB AND THE NSP

Are we on track?

GeneXpert:
An imperfect rollout

TB in South African prisons:
Where to now?

Decentralising DR-TB care:
How far along are we?

CONTENTS

NSP Review, July – August 2013

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This is the seventh issue of NSP Review. We aim to provide quality analysis and monitoring of the implementation of the current NSP. It is our hope that this publication will increase awareness of, and critical engagement with, the NSP. We will try to keep it relevant with evidence from new research and feedback from the various district offices of the Treatment Action Campaign as well as organisations with which we work closely. Our vision is a vibrant, evidence-based publication that will help all stakeholders drive a more successful response to HIV, STIs and TB. We encourage you to get in touch with us should you want to contribute to future editions of NSP Review. You can e-mail the editor at nsp@tac.org.za.

NSP Review is now online at www.nspreview.org

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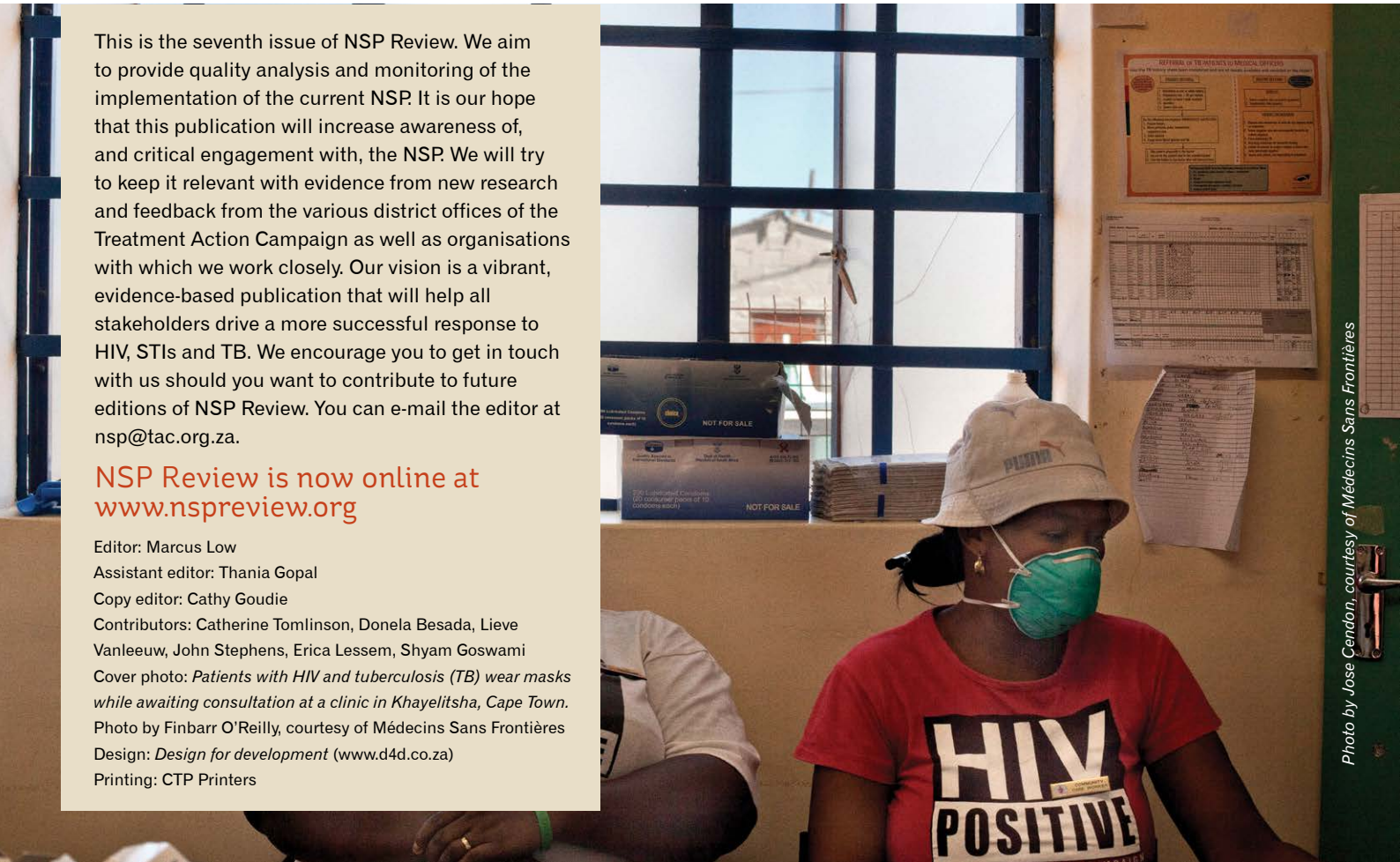


Photo by Jose Cendon, courtesy of Médecins Sans Frontières

EDITORIAL

Photo courtesy of Professor Robin Wood

What will it take to control TB in South African prisons?

In 1903 the New York Times claimed that sending people to jail condemned prisoners both to hard labour and tuberculosis (TB) infection. Approximately 40-60% of all jail deaths at the time were due to TB, and most autopsy findings showed evidence of infection with the TB bacillus, Mycobacterium tuberculosis.

Over a century later, TB is the leading cause of morbidity and mortality in South African prisons. TB in our correctional facilities can be transmitted to the general population via prison workers or inmates released back into the community. Correctional facilities are thought to be responsible for 3-17% of active cases of the disease in the general population.

Tuberculosis is spread by infectious particles breathed out from the lungs of infected people. These bacilli remain airborne long enough to be breathed in by others and gain access to the deeper parts of their lungs. In susceptible people – those whose immune systems are unable to fight off the infection – these particles may cause further cases of active TB.

TB spreads easily in prisons because inmates with active TB are confined together with other inmates who may be susceptible to infection. The risk of transmission for those in jail depends therefore on the prevalence of active TB and the amount of air exchanged between prisoners.

Inmates are specifically identified in the 'National Strategic Plan for HIV, TB and STIs 2012 – 2016' as a key population in the management of TB. The existing TB control programme calls on the Department of Correctional Services (DCS) to identify infectious cases both when prisoners are admitted and during the period of their incarceration. The programme also specifies what therapy is effective for treating inmates with TB.

The treatment of active TB is highly beneficial. It can decrease the prevalence of cases and help to reduce the quantity of contaminated air in prisons. Four factors determine the efficiency of TB transmission and the amount of air shared between inmates: the number of prisoners per cell, the length of the lock-up time, how much external uncontaminated air is used for ventilation, and the separation of potentially infectious cases from the wider prison population.

To control TB in our prisons, the DCS must address both the prevalence of TB and help to reduce the transmission efficiency of the disease. Overcrowding and poor ventilation in our jails are boosting the efficiency of TB transmission to such an extent that even regular screening and well-run control programmes would fail to keep the disease in check.

Improving physical conditions without reducing TB prevalence will not contain the spread of infection in our prisons. But providing effective identification and treatment, implementing South Africa's prison crowding regulations, and providing moderate ventilation could decrease TB transmission by 40% or more. The introduction of prisoner lock-up periods not longer than 14 hours at a time, and the implementation of internationally recommended standards for space and cell ventilation could decrease TB transmission by 80%.

If a strategy of stronger TB control and environmental improvements is introduced in our prisons, the challenge would then be to create measurable targets for each key component. TB treatment is monitored for success and completion rates but as yet there is no measurement available to determine the efficacy of screening. The proportion of the prison population screened using sensitive TB diagnostics such as the GeneXpert testing system would be a useful interim way to assess this.

Cell ventilation is a difficult parameter to measure. However, it is easy to gauge carbon dioxide levels within cells. Doing so could help to quantify the amount of ventilation per cell occupant. Maintaining carbon dioxide levels below 1,500 parts per million would ensure that prisoners who are confined for long periods would have high ventilation standards similar to those recommended for schools and work environments.

TB is out of control in our prison system. Its spread has been aided by environmental conditions that fall far short of international standards – even those developed during the apartheid era. We need a fresh strategic approach incorporating better TB diagnosis and care together with improvement in South Africa's appalling conditions of incarceration. Monitoring this new combined approach will require the DCS to introduce scientifically-determined targets for identifying cases and to provide minimum levels of ventilation.

Professor Robin Wood, Director, Desmond Tutu HIV Centre

TB IN THE NSP: ARE WE MEETING THE TARGETS?

By Catherine Tomlinson

People awaiting TB testing and treatment at Kuyasa Clinic in Khayelitsha, Cape Town. Photo by Jose Cendon, courtesy of Médecins Sans Frontières

"Reduce the number of new TB infections as well as deaths from TB by 50%" – a key target of the NSP 2012–2016

The first year of the five-year National Strategic Plan for HIV, TB and STIs (NSP), launched in December 2011, has come to an end. Now is an important time to reflect on what has been done so far to put the country on track to meet the NSP targets, especially in one of the plan's key focus areas: tuberculosis (TB).

TB in South Africa is closely linked to HIV. More than 70% of people with active TB disease are also HIV-positive. By including TB in the current NSP, South Africa is seeking to improve the coordination and integration of the TB and HIV responses.

South Africa has the third highest TB burden in the world. Between 1993 and 2007, the number of cases tripled in South Africa from 305 to 948 per 100,000 people, and the mortality rates quadrupled. The latest national figures for TB mortality from 2010 show that the disease retained its top spot as the leading cause of natural death in the country, accounting for 11.6% of total deaths.

The current NSP seeks to reduce TB deaths. It has set a target of reducing the number of deaths of people who are diagnosed and initiated onto treatment by 50%. The NSP also recognises that many individuals with the disease are slipping through the cracks and are not being properly diagnosed and treated for TB.

To address this problem, the five-year-long NSP aims to screen 30 million people for TB. The plan further aims to increase the percentage of people with active TB who are properly diagnosed and initiated onto treatment to over 85%.

A review of figures from the Department of Health (DoH) shows that the scale-up of screening, diagnosis and treatment aimed at meeting these targets has been sluggish in the first year of the NSP. 2,600,925 people were screened for TB during 2012 – a reduction from 2,718,939 people screened during 2011.

According to the DoH, this decline occurred because using TB screening teams at a household level was not sustainable. The DoH is now absorbing their functions into primary health care ward-based teams. Meanwhile, the total number of patients diagnosed with drug-susceptible TB during 2012 is still being calculated.

The DoH has reported an increase in the number of patients diagnosed with multidrug-resistant TB (MDR-TB), following the rollout of the GeneXpert diagnostic system. But many South Africans with active MDR-TB are never diagnosed. Estimates suggest that up to 50% of all cases in 2011 may not have been diagnosed. As the distribution of GeneXpert machines has gained momentum during 2012, the DoH has registered an increase in MDR-TB diagnoses.

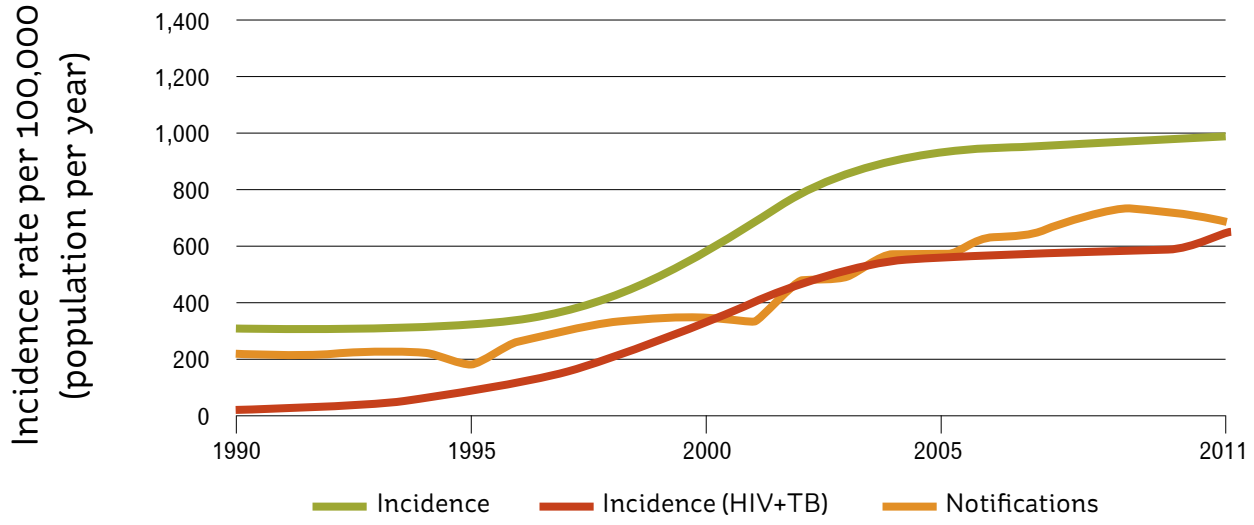
However, while the DoH has diagnosed more people with MDR-TB, it has failed to keep pace by scaling up treatment. The gap between the number of patients diagnosed with MDR-TB versus the numbers enrolled onto treatment widened between 2011 and 2012.

	Patients diagnosed with MDR-TB	Patients enrolled onto treatment for MDR-TB
2011	10,085	5,634
2012	15,419	6,800

These figures show that the DoH's efforts so far to scale-up TB screening, diagnosis and treatment have been slow. Greater momentum is now needed to help South Africa control the TB epidemic and civil society must closely monitor the progress of the DoH.

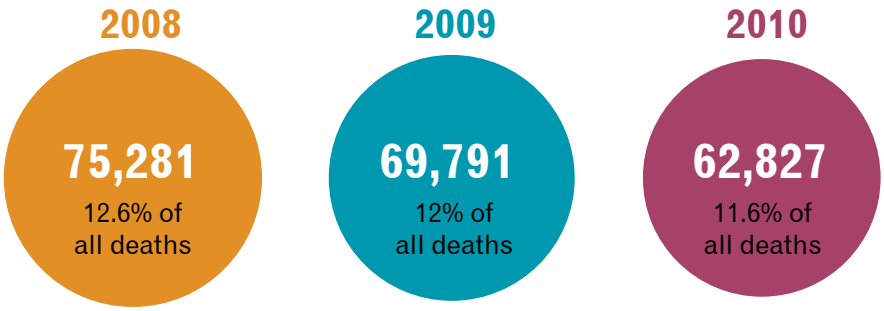
These figures for screening, diagnosis and treatment during 2013 are based on e-mail communication with the DoH on 13 May 2013. The DoH provided these figures but did not respond to requests for clarification and confirmation. The DoH should publicly release official figures for this period.

TB INCIDENCE IN SOUTH AFRICA

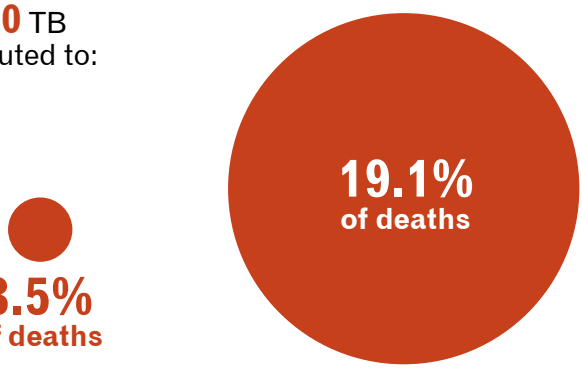


Source: WHO Global TB Control Report 2012

TUBERCULOSIS WAS THE LEADING UNDERLYING NATURAL CAUSE OF DEATH DURING:



In **2010** TB contributed to:



People aged 0 to 14 years
TB was the 5th leading cause of death in this age group

People aged 15 to 49 years
TB was the leading cause of death in this age group

People aged 50 to 64 years
TB was the leading cause of death in this age group

People aged 65 years and older
TB was the 8th leading cause of death in this age group

Source: STATSSA, 'Mortality and Causes of Death in South Africa 2010', published in April 2013

HAVE WE SET THE RIGHT TARGETS?

Professor Robin Wood is the Director of the Desmond Tutu HIV Centre. Wood and his colleagues have published multiple studies examining the risk of TB transmission in South Africa. Through his work, Professor Wood has gained immense insight into the risk of TB infection in settings such as public transport, prisons, townships and the wider context of the city of Cape Town.

When I met Professor Wood to discuss TB transmission in South Africa, I learnt about what he calls his 'gadget' for measuring TB risk. This portable gadget is in fact a continuous carbon dioxide sampling device which measures the amount of carbon dioxide that a person inhales in different environments. Carbon dioxide is a natural indicator of the amount of rebreathed air that a person inhales.

Wood explains that the high risk of TB infection facing South Africans is due to a number of environmental challenges. Professor Wood notes: "[The] risk of contracting TB is determined by the number of people one meets, the environment [one] meets them in, and how many of these people have active TB".

Wood is currently using the gadget to identify which environments pose the highest TB infection risk for children. To do this, he and his colleagues have given the portable devices to children living in Western Cape townships. With GPSs attached, these gadgets measure the fraction of rebreathed air the children inhale as they go about their daily activities. Wood has already found that a child's risk of contracting TB soars in poorly ventilated classrooms.

By the time they turn 18, more than 80% of South African children have been infected at least once with TB. According to Wood, setting stricter building standards to improve ventilation in classrooms could massively reduce new childhood cases of the disease.

Wood and colleagues have identified prisons and public transport as similarly high risk environments for contracting TB.

Having a TB infection is not the same as having active TB disease. But according to Wood, a review of the history of TB in South Africa and elsewhere reveals that curbing transmission is key to curbing cases of active TB and reducing TB mortality.

Wood describes how TB notifications in Europe and America dropped from 1,000 per 100,000 people in 1860 (levels similar to South Africa's at that time) to 100 per 100,000 in 1960. He notes the massive, consistent drop in TB incidence over this 100-year period before the development and availability of effective medicines to treat TB. According to Wood, the massive decline in TB notifications in Europe and America was mainly due to improvements in building standards and ventilation.

Professor Wood argues that the NSP fails to focus properly on reducing TB transmission. He sees this as a major gap in the plan, noting that "transmission is key and we have to stop it".

According to Wood, the failure of the NSP to prioritise reducing transmission is largely due to the fact that the NSP targets originate from a WHO model which uses data from Europe. He explains that "the model makes assumptions that do not fit the South African context". As a result its recommendations are inadequate for curbing the epidemic level of new TB cases in South Africa. "What we need is a South African solution developed from South African data." According to Wood such a solution would place a much greater emphasis on the prevention of TB transmission.

"The NSP Strategic Objective 2 aims to prevent TB infection and disease. This is to be achieved through intensified TB case finding, TB infection control, workplace/occupational health policies on TB and HIV, isoniazid preventive therapy (IPT), immunisation, prevention of multidrug-resistant TB (MDR TB), and reducing TB-related stigma, alcohol consumption and smoking" – From NSP Strategic Objective 2.

UNDERSTANDING TB RISK

The NSP correctly seeks to improve the available evidence regarding the risks of contracting and/or developing active TB. However, there is an existing body of evidence regarding these risks on which we can act now. The infograms below provide a summary of key evidence regarding the risk of contracting and/or developing TB for a number of sub-populations in South Africa.

Photo by Henrik Glette, courtesy of Médecins Sans Frontières

1 TB and HIV

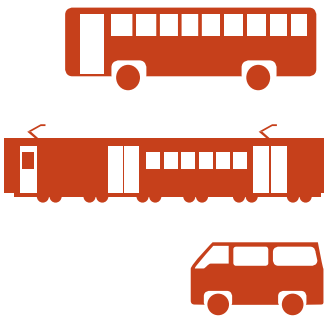
A recent study conducted in Gugulethu in the Western Cape confirmed existing evidence that a person living with HIV who has spent time on ART has a significantly lower chance of developing active TB. The risk of TB incidence for people who are on ART and have CD4 counts below 100 is nine times higher than those who are on ART and have counts above 700. However, even people with HIV who have high CD4 counts continue to have a greater risk of developing active TB than those who are HIV-negative. The study found that TB incidence for patients who are on ART and have CD4 counts above 700, still remains four times higher than HIV-negative members of the same community.

TB incidence of people with HIV on ART at different CD4 counts (measured as cells/μl)		**Overall TB incidence in the local community**	**TB incidence in people who are HIV-negative**
≤ 100	25.49 per 100 PY	1.01 cases per 100 PY	0.62 cases per 100 PY
101 – 200	11.23 per 100 PY		
201 – 300	7.86 per 100 PY		
301 – 400	5.01 per 100 PY		
401 – 500	5.06 per 100 PY		
501 – 700	4.04 per 100 PY		
> 700	2.70 per 100 PY		

* PY = Patient Years

2 TB and public transport

Using crowded public transport which does not have adequate ventilation raises the risk of contracting TB. A 2012 study employed a mathematical model to assess the risk of TB infection on Cape Town public transport by measuring the amount of rebreathed air. The study found that:



Daily bus commuters have a **3.5% risk** of TB infection

Daily train commuters have a **3.7% risk** of TB infection

Daily minibus taxi commuters have a **5% risk** of TB infection

Sources: DoH screening, diagnosis and treatment figures from e-mail communication on 13 May 2013; Gupta A, Wood R, Kaplan R, Bekker L-G, Lawn SD 'Tuberculosis Incidence Rates during 8 Years of Follow-Up of an Antiretroviral Treatment Cohort in South Africa: Comparison with Rates in the Community.' PLoS ONE 7(3): e34156. doi:10.1371/journal.pone.0034156 (2012); Stuckler D, Basu S, McKee M, Lurie M. 'Mining and Risk of Tuberculosis in Sub-Saharan Africa.' American Journal of Public Health Vol 101, No. 3 (2011); Johnstone-Robertson S, Lawn SD, Welte A, Bekker L-G, Wood R. 'Tuberculosis in a South African prison – A Transmission Modelling Analysis.' South African Medical Journal, Vol 101, No 11 (2011); Wood R, Lawn S, Johnstone-Robertson S, Bekker L-G. 'Tuberculosis control has failed in South Africa – time to reappraise strategy.' South African Medical Journal Vol. 101 No. 2 (2011); Andrews JR, Morrow C, Wood R. 'Modeling the Role of Public Transportation in Sustaining Tuberculosis Transmission in South Africa.' American Journal of Epidemiology Vol. 177 No. 6 (2013); National Health Laboratory Services. Pathology Division Surveillance Report (2011); STATSSA. 'Mortality and Causes of Death in South Africa 2010' (2013); WHO Global TB Control Report: South Africa Country Report (2012).

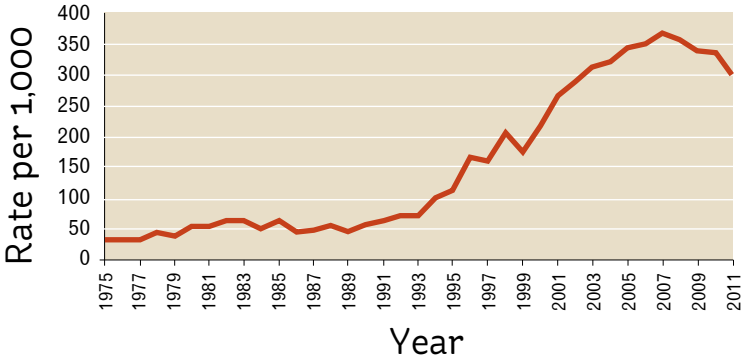
3 TB and mining

TB incidence is estimated to be five to six times higher among miners than in the general population.

The high rate of silicosis amongst gold miners means they have a particularly high risk of developing active TB. In gold-producing countries there is, on average, a 32.4% higher incidence of TB than in countries that do not mine the precious metal.

Source: National Health Laboratory Service, 'Pathology Division Surveillance Report', 2011

Active Pulmonary TB rates in black miners at autopsy (1975 – 2011)



4 TB and prisons

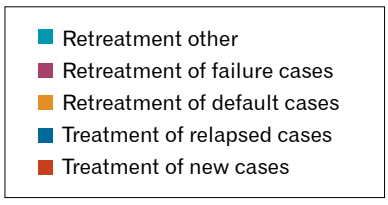
A 2011 study used mathematical modelling to assess the risk of TB transmission in South African prisons. The study found that due to overcrowding, poor ventilation and failure to provide adequate outdoor time, the risk of TB infection is as high as **90%** per annum. (This is the risk of contracting TB, not the risk of developing active TB.)

Risk of contracting TB in SA prisons

5 Lifetime risk of contracting TB in a high-prevalence South African city

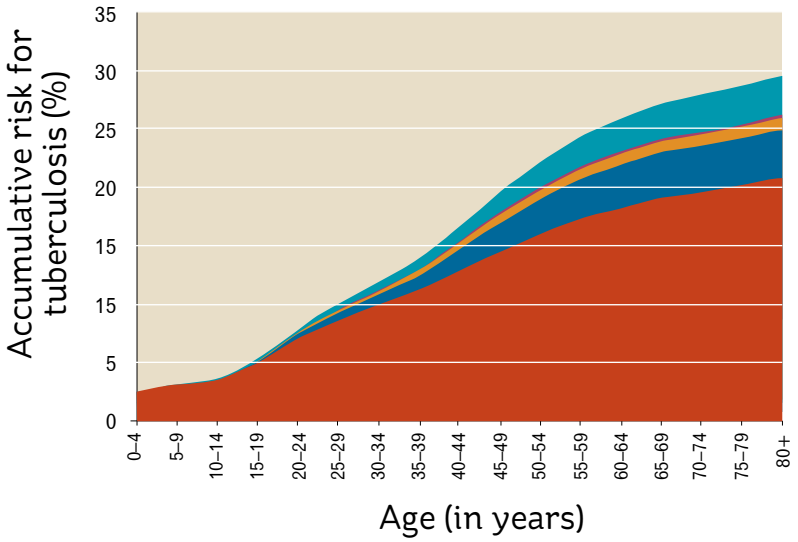
For an HIV-negative person living in Cape Town, the lifetime risk of developing smear-positive pulmonary TB is approximately 10%.

The graph to the right shows the accumulated life-time risk of being notified with new or relapsed TB calculated for HIV-negative individuals. Values are based on cumulative 2009 age-specific TB notification rates for Cape Town.



Source: Wood R et al. 2011

Lifetime risk of contracting TB



XDR-TB survivor and Médecins Sans Frontières peer counsellor Xoliswa Hermanus inspects the Khayelitsha family home of Jonas Cikizwa. Jonas is infected with XDR-TB, HIV and diabetes. Photo by Jose Cendon, courtesy of Médecins Sans Frontières

DECENTRALISING DR-TB CARE: HOW FAR ALONG ARE WE?

By Donela Besada

In August 2011, the Department of Health announced a new policy for the decentralised management of drug-resistant tuberculosis. If this plan is put into action as intended, it could be a major step forward in South Africa's fight against the disease. But almost two years on, implementation remains patchy.

WHAT IS THE POLICY OF DECENTRALISING TREATMENT?

'Multi-Drug Resistant Tuberculosis: A Policy Framework on Decentralised and Deinstitutionalised Management for South Africa' is a Department of Health (DoH) document that begins by recognising the high burden of TB in South Africa. Our nation now has the third highest prevalence of TB in the world, and while our exact burden of MDR-TB is unknown, one estimate – which may even be conservative – suggests that there are 13,000 new cases in the country each year. The prevalence of extensively-drug resistant TB (XDR-TB) is also on the rise.

The policy document discusses the weaknesses of the TB treatment programme that lead to the development of the policy changes. These include delays in the initiation of treatment after diagnosis, limited beds for hospitalisation, poor infection control in health settings, and poor treatment adherence. Poor adherence, the document indicates, is also the result of the many side-effects experienced by patients during their lengthy treatment, and the refusal of patients to be hospitalised because of competing personal responsibilities.

Before the development of this decentralisation policy, all drug-resistant TB (DR-TB) patients had to be hospitalised for a period of at least six months. The new policy stipulates that "all MDR-TB smear-negative, TB culture-positive patients need to be started on [out-patient] treatment. Other MDR-TB patients without extensive disease, [who are] stable [and] smear-positive should be admitted until two negative smear microscopy results are received. Only very sick MDR-TB [patients] with extensive disease and XDR-TB patients will be admitted until they have two consecutive TB culture[-] negative results." (An analysis of sputum is used to diagnose TB, and patients who are smear-negative are less infectious that those who are smear-positive.)

Long hospital waiting lists have often led to delays in treatment initiation of up to four months. Fewer than 55% of MDR-TB patients diagnosed in 2009 started treatment the same year, and this percentage rose to 71% in 2010.

New evidence suggests that a large proportion of DR-TB infection is caused by direct transmission, rather than from patients who default on treatment and develop resistance. Patients who begin treatment and remain adherent rapidly become non-infectious. By contrast, undiagnosed and untreated TB accounts for the highest percentage of transmission.

Treatment outcomes under South Africa's previous TB policy were alarmingly poor. The Department of Health (DoH) conducted a review of their 2007 cohort of MDR-TB patients. The data revealed a treatment success rate of just 42% and a treatment default rate of 9.6%. 20.4 % of the MDR-TB patients died.

The DoH's new policy framework therefore aims to make treatment more accessible and socially acceptable. It seeks both to improve individual patient outcomes and to reduce overall transmission.

According to the policy document, each province will still maintain one centralised TB treatment unit. These units will be responsible for initiating and monitoring all XDR-TB patients, including children, and MDR-TB patients with complications.

Decentralised DR-TB units, which could be as large as an entire hospital or as small as just one ward within a hospital, will be responsible for initiating and monitoring MDR-TB patients and could also be used to manage XDR-TB patients.

Satellite units will assume responsibility for providing medication and monitoring once patients have started their treatment at the centralised or decentralised units. Such units will be transitional and located in hospitals, community health centres or other health facilities. Eventually, many will be equipped to function as decentralised units themselves.

Once patients become asymptomatic and are able to tolerate treatment, they can be discharged to continue it at their nearest primary health care (PHC) facility or at home.

The policy allows for the creation of mobile teams, based at the satellite units of PHC facilities. These teams will be responsible for providing patients with home-based treatment and ensuring good infection control.

HOW DOES THE POLICY LINK WITH THE NSP?

The current NSP, which was released shortly after the decentralisation policy, provides the foundation for South Africa's response to the HIV, STI, and TB epidemics. While the NSP does not specifically refer to the decentralisation policy, it draws on a similar organisational framework.

Ms ZD presented to the obstetric clinic at Rahima Moosa Mother and Child Hospital in the third trimester of her pregnancy with coughing and night sweats. It had taken her two weeks to reach the hospital because she lived far away and had another young child to care for. She was diagnosed with multidrug-resistant TB (MDR-TB) and referred to Helen Joseph Hospital, which houses a decentralised TB unit.

Because Ms ZD was unable to secure transport money for her journey to the Helen Joseph Hospital to begin treatment, her local clinic arranged transportation for her. Two weeks later, further testing revealed that Ms ZD had smear-positive MDR-TB. According to the new treatment guidelines, this meant that she would have to be hospitalised.

The only support system available to Ms ZD was a neighbour who had offered to care for her five-year-old daughter if Ms ZD were admitted to the centralised TB facility, Sizwe Hospital. Newborns are separated from their mothers shortly after delivery at Sizwe, and it was unclear where the baby could go because the neighbour was unable to care for the new child as well.

Those in charge of the care of Ms ZD felt that both the mother and baby would do best if they remained together. Her treatment was therefore continued at the Rahima Moosa Hospital. Her newborn is also receiving specialised care and monitoring at the same health facility.

Decentralised TB care allowed Ms ZD rapid access to appropriate treatment and also enabled her and her infant to remain together, while still receiving the specialised care they need.

Filling the gap in treatment provision to achieve the NSP goals for reducing TB illness and death will only be possible through decentralisation.

One of the broad goals of the NSP is a 50% reduction in the number of new TB infections and related deaths.

The NSP goals will be achieved through interventions grouped according to clear strategic objectives. The third strategic objective of the NSP focuses on health and wellness and aims to reduce death and disability by means of universal access to care. This care ensures that patients remain within the health system and that the services they receive adapt to their needs.

Specific TB interventions include annual screening, tracing close contacts of TB patients, providing access to affordable and good quality drugs – particularly new DR-TB drugs – and ensuring the earliest possible enrolment of patients into care. There is a recognition that referral systems between levels of care will need to be strengthened and the integration of HIV and TB services will need to be improved.

The NSP recognises that further decentralisation of care is possible through community models for household contact. The primary health care re-engineering plan allows for this, and the services offered by the mobile units described in the decentralisation policy document can be integrated within the broader PHC plan.

The NSP talks specifically about the need to prevent DR-TB. This goal can be achieved through increased diagnosis and better treatment of drug-susceptible TB, such as DS-TB, to ensure that further resistance does not develop.

Improved MDR-TB care will also help to prevent the spread of resistant strains. Specific commitments in the NSP include reducing the time between the diagnosis of MDR-TB and treatment to only five working days, ensuring that 100% of patients are treated according to the guidelines, and that there is a 60% cure success rate.

SLOW PROGRESS

In 2007, Médecins Sans Frontières (MSF), in collaboration with the City of Cape Town and the provincial government of the Western Cape launched a pilot project in Khayelitsha to provide decentralised care for patients with DR-TB.

Case detection of DR-TB has doubled over the past five years, and the average number of days between diagnosis and treatment initiation has fallen from 71 days in 2007 to 33 days in 2010. The number of cases treated successfully has almost tripled.

In 2010, 72% of patients were able to start treatment at their local clinic, 15% began treatment at the community-based sub-acute facility in Khayelitsha, and only 14% were admitted to the centralised DR-TB hospital. This approach avoided too much reliance on over-burdened hospitals.

While Khayelitsha has shown notable achievements with its programme of decentralisation, at other sites, such as at the Helen Joseph Hospital in the Johannesburg metro area, overall progress has been slow and variable.

Provincial operational plans, for example, for the decentralisation of MDR-TB have yet to be drafted. Many proposed units for decentralised treatment have not yet been assessed, and the training of health workers has been limited.

Activists can use their presence on Provincial and District AIDS Councils to question the lack of operational plans for decentralised TB care.

FIVE KEYS IN THE FIGHT AGAINST DR-TB

1. Improved diagnosis

The rollout of GeneXpert, a new instrument capable of diagnosing drug-resistant TB in under two hours, has allowed for the rapid diagnosis and referral of patients with drug resistance. With over 190 machines in South Africa, and plans to purchase an additional 134, the country stands to make sizeable progress in DR-TB management. However the success of this new diagnostic technique rests on the constant availability of testing cartridges.

2. Decentralisation of DR-TB care to the primary health care level

South Africa's decentralisation policy still requires admission to a decentralised unit for at least eight weeks at the start of DR-TB treatment. Full decentralisation requires a commitment to invest in sufficient training and infrastructure support to permit the transfer of DR-TB care to the primary health care level.

A recent study on the cost of DR-TB care in South Africa found that while the disease made up 2.2% of the overall TB burden in the country, it consumed 32% of the total TB budget. 45% of DR-TB costs were for treatment and 25% for hospitalisation. Laboratory testing and treatment account for 71% of MDR-TB costs, while 92% of XDR-TB costs are for hospitalisation and treatment. The study concluded that a decentralised XDR-TB treatment programme could potentially reduce per patient costs by 26% and lower the total amount spent on DR-TB by 7%.

3. Improved treatment regimens for DR-TB and access to quality assured affordable drugs

The current treatment regimen, lasting between 18 and 24 months, is extremely long and is also expensive. The high pill burden and side-effects are immense challenges to patient adherence. The Medicines Control Council needs to ensure the rapid registration of new drugs and the DoH must negotiate affordable prices.

4. Access to a broader range of treatment options

Certain drugs, including capreomycin and PAS, are required for the treatment of XDR-TB patients or MDR-TB patients who experience side-effects or other difficulties, and are available only at specialised DR-TB sites. As a result, patients must be hospitalised to obtain the drugs. But not all hospital patients may be eligible for admission under the current guidelines. Decentralised sites need access to those drugs if South Africa is to avoid the unnecessary hospitalisation of patients.

5. Information systems

The current policy stipulates that PHC facilities, mobile teams and satellite units must send their data to the decentralised unit for collation. The information is then forwarded to the centralised site and the provincial TB directorate. Data should be captured on an electronic register of drug-resistant TB, known as the EDR-WEB.

It is unclear to what extent the new TB register is being used. Health care providers still point to the lack of centralised electronic medical records as a major barrier to monitoring patients across different levels of care and to ensuring continuity of treatment for highly mobile migrants.

Donela Besada was previously an Advocacy Officer for Médecins Sans Frontières. She is currently working as a consultant.

Sources: South African Department of Health. 'Multiple Drug Resistant Tuberculosis. A Policy Framework for the Decentralised and Deinstitutionalized Management for South Africa' (August 2011) Available at http://www.doh.gov.za/docs/policy/2011/policy_TB.pdf ; World Health Organization, WHO-IUTALD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Anti-Tuberculosis Drug Resistance in the World (Report No. 4) [cited 2008 Apr 30] http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf ; Cox HS, McDermid C, Azevedo V, Muller O, Coetzee D, Simpson J, et al. 'Epidemic Levels of Drug Resistant Tuberculosis (MDR and XDR-TB) in a High HIV Prevalence Setting in Khayelitsha, South Africa.' PLoS One2010; 5(11): e13901 ; Nardell E, Dharmadhikari A. 'Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource-limited settings.' Int J Tuberc Lung Dis 2010; 14(10): 1233- 1243 ; South African Department of Health. 'Multiple Drug Resistant Tuberculosis: A Policy Framework for the Decentralised and Deinstitutionalized Management for South Africa.' (August 2011) http://www.doh.gov.za/docs/policy/2011/policy_TB.pdf ; Médecins Sans Frontières, 'Scaling Up Diagnosis and Treatment of Drug-Resistant Tuberculosis in Khayelitsha, South Africa.' (March 2011) http://www.msfaccess.org/our-work/tuberculosis/article/889 ; http://www.thoughtleader.co.za/msf/2013/04/18/tb-the-good-bad-and-long-overdue/ ; Pooran, A, et al. 'What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?' PloS one 8.1 (2013): e54587.; The Per-patient cost of XDR-TB is four times greater than MDR-TB and 103 times greater than drug-sensitive TB

Photo by Jose Cendon, courtesy of Médecins Sans Frontières

The GeneXpert tuberculosis (TB) test promises to revolutionise TB detection in South Africa. But will the rollout and implementation of this new system be good enough to fulfil its potential?

GeneXpert: AN IMPERFECT ROLLOUT

By Lieve Vanleeuw

"If a minister can do it, it can't be that hard," said Health Minister Aaron Motsoaledi in March 2011 as he launched the rollout of the GeneXpert MTB/RIF® test for tuberculosis (TB). The diagnostic system is set to become the first-line test for diagnosing active TB throughout South Africa. GeneXpert is to replace microscopy, a 130-year-old method in which lab technicians study sputum samples under microscopes to identify TB bacilli.

The new system is completely automated. It is less labour intensive, gives a result in two hours, and is less prone to contamination and human error. But most importantly, GeneXpert is more sensitive than microscopy. It identifies TB and drug resistance at the same time and can be used in settings where resources are scarce.

Exactly two years after the launch, 203 instruments have been put in place. 1,180,669 tests have been carried out across all nine provinces. Case detection for individuals suspected of having active TB infection has increased to an average of 14% and detection of drug resistance stands at an average of 7%. A further 65 machines await implementation. Once South Africa has full GeneXpert coverage, this should allow a national capacity of 11,428 tests per day.

Dr Dimakatso Moloi, Chief Director for TB in the Gauteng Health Department says that the new system "is helping a lot, particularly for drug-resistant TB [DR-TB]. There was an increase in diagnosis of resistant cases unlike in the past when we had to wait six to eight weeks [for results]. The [DR-TB] rate was also as high as 6% [whereas] cases diagnosed through [sputum] culture … were never above 2%."

While the GeneXpert machine itself is relatively easy to operate, as demonstrated by the Minister in 2011, implementing and integrating the machines into the health system is proving to be less simple.

Machines have been placed in provinces according to their TB prevalence. The Eastern Cape currently has the highest capacity, followed by KwaZulu-Natal and Gauteng (see Figure 1). Yet if we compare monthly test results, KwaZulu-Natal significantly outperforms the Eastern Cape (see Figure 2). Similarly, Mpumalanga has more capacity than the Free State and North West provinces, but both provinces significantly outperform Mpumalanga. Gauteng has 38% more capacity than the Western Cape, yet only performs 10% more tests.

Cartridge shortages

According to the National Health Laboratory Service (NHLS), variations in the testing volumes across the provinces are due to several factors. Global shortages in the supply of GeneXpert cartridges during July, October and November 2012 not only delayed the rollout but also interrupted testing across the country.

"We've had a GeneXpert [machine]… in Chris Hani Baragwanath Hospital for many months now," says Bonginkosi Mthembu from the Treatment Action Campaign (TAC) in Ekurhuleni, "but the machine has been gathering dust … because apparently there are no cartridges…".

Despite an assurance from Cepheid, the cartridge supplier, that the NHLS has first priority, further shortages occurred in February and again in March 2013.

"Due to global shortage in the supply of Xpert MTB/RIF® cartridges in … February and March, all sites installed from January to March 2013 only resumed testing in April 2013. Priority was given to … [supplying cartridges to] existing testing sites … whilst the issue was being addressed with the supplier," according to the NHLS. The NHLS has also noted that the shortage has been resolved and should cause no more interruptions.

However, with still more instruments to be placed in South Africa, and more countries implementing the GeneXpert system, the lack of cartridges remains a real concern.

Figure 1. Provincial GeneXpert capacity based on number of GX4, 16, 48 and 80 instruments per province (30 April 2013)

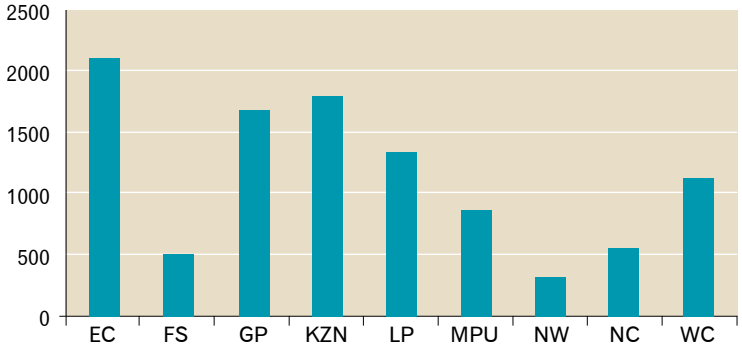
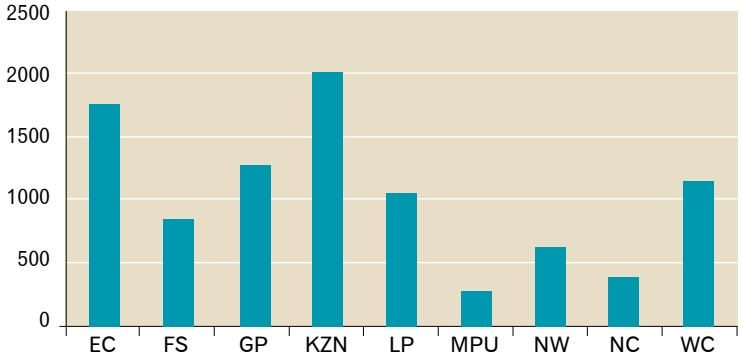


Figure 2. GeneXpert MTB results by province (01-31 March 2013)



Training delays

While the rollout of the GeneXpert machines has been rapid, the same cannot be said for the training of health workers in the GeneXpert testing algorithm This training has been particularly slow and facilities cannot deploy the automated system before staff have been trained how to use it.

The Western Cape uses a different testing algorithm from the rest of the country and does not depend on the National Department of Health (DoH) to conduct training for health workers. This partly explains why the Western Cape is performing better than the other provinces.

Lusikisiki in the Eastern Cape, for example, has two GeneXpert machines: one at the St Elizabeth Laboratory and one at Holy Cross Hospital. The instrument at St Elizabeth was not functional at the time of writing this article.

"This was due to the fact that the hospital does not have money to train nurses … to read and interpret the GeneXpert results for clients," according to Zukile Madikizela from the TAC. "When I last checked … Lusikisiki TB clients were [being] turned [away] by Holy Cross ... [as the facility was becoming overcrowded]."

In its February 2013 reports on the progress of GeneXpert implementation, the NHLS also reported that the DoH training of health workers in the clinical algorithm had been delayed.

Algorithm difficulties

The diagnostic algorithm (see Figure 3) is seen as too complicated and this has led to provinces using different versions.

In South Africa, GeneXpert is used to screen all patients suspected of having active TB and, in time, it will replace microscopy as a first-line diagnosis. However, GeneXpert cannot distinguish between live and dead bacilli and therefore cannot be used to monitor the progress of TB treatment.

Follow-up still requires microscopy or sputum culture testing, but reports indicate that laboratories are also using GeneXpert to monitor treatment.

More research is desperately needed to improve diagnosis of TB in children and in HIV-positive people.

In addition, due to the phased rollout of the automated system, two treatment algorithms are currently in use: the old one for microscopy and the new one for GeneXpert. Testing and clinical algorithms also vary across provinces. This disparity leads to confusion in all aspects of the testing cycle and puts an extra burden on the patient. South Africa urgently needs a simplified clinical algorithm and a massive scale-up in training for both laboratory and clinical staff.

GeneXpert for HIV-positive people and for children

The GeneXpert test has shown a sensitivity of 90.4% and a specificity of 98.4%.* It has been endorsed by the WHO for use on adult sputums. Yet the instrument performs less well when it is used to test HIV-positive people and children.

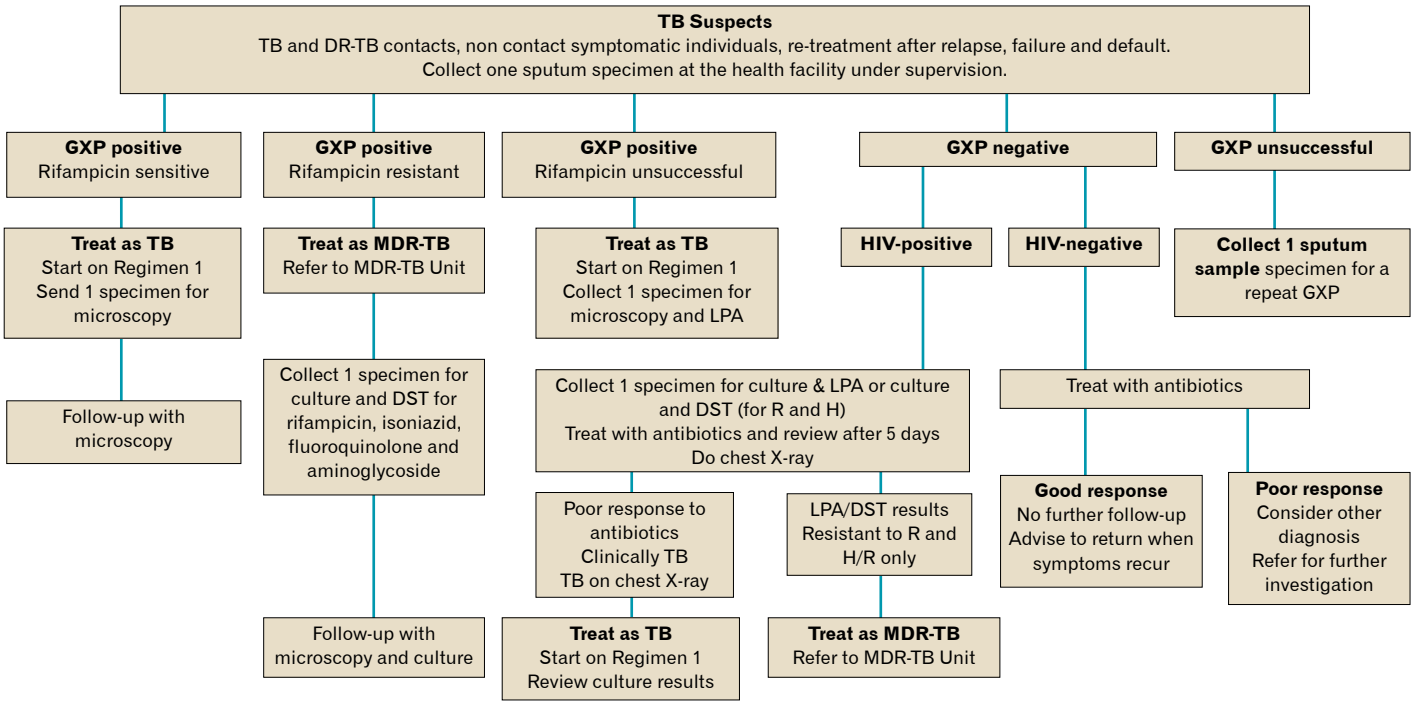
TB in children is rarely confirmed because the sputum samples contain very few bacilli, and because of the difficulty of obtaining high-quality specimens. A recent study in Vietnam reported that GeneXpert detected TB in 50% of the children tested. Compared to smear microscopy, which only detected 37.9% of the cases, this is a great improvement. But it still poses a problem in that only 1 out of every 2 cases will be identified.

A similar problem affects people who are HIV-positive. HIV infection is associated with more smear-negative and paucibacillary TB disease, and the Xpert MTB/RIF® test is less sensitive with smear-negative samples.

According to a Cochrane review published in February 2013, GeneXpert sensitivity for smear-negative TB is 68%, a figure significantly higher than the sensitivity of microscopy. But the problem is that in a population which is more susceptible to TB due to suppressed immunity, the best available tool for TB diagnosis is far from ideal.

* A sensitivity of 90.4% means that out of every 100 people who have active TB the test will correctly detect about 90. A specificity of 98.4% means that out of every 100 people who do not have active TB the test will in about 98 cases correctly diagnose no TB.

Figure 3. Algorithm for TB diagnosis



HOW YOU CAN USE AIDS COUNCILS TO STOP TB

By getting involved, you can ensure that AIDS Councils improve the quality of tuberculosis services in your district

STEP 1: GET INVOLVED

One of the key ideas in the NSP is the provision of structures that channel communication up from districts to provinces, and from provinces to the national level. Most people can get involved in District AIDS Councils. Ask your clinic or mayor's office when the next local District AIDS Council meeting will be held and whether you or your organisation can attend.

If there is no District AIDS Council in your district, write to your mayor asking him or her why there isn't one and insist that one must be formed. You can write as an individual, but remember that doing so as part of an organisation or as a group of interested citizens is likely to be more effective.

STEP 2: GET INFORMED

You have a right to know what services are provided in your district and what health plans are in place. Investigate this by asking what services local clinics offer, by reading publications such as the NSP Review, or by researching on the internet.

You can then take up specific issues at District AIDS Council meetings. For example, you can ask the chairperson whether there is a provincial operational plan to decentralise TB care in your province. If there isn't, you can request that representatives from your District AIDS Council raise the matter when the provincial AIDS council next meets.

STEP 3: REPORT PROBLEMS AND SUGGEST SOLUTIONS

It is vital for activists to take proactive roles in organisational structures such as District AIDS Councils. You must do all you can to educate yourself about the nature of health care problems in your community. Also use all the tools at your disposal to help find solutions. Most importantly, you can't simply wait for things to get better.

Volunteer, for example, to write a letter to the head of the Provincial AIDS Council to advocate for the development of a provincial operational plan for decentralised TB care in your province.

Or, if you discover problems such as TB tests taking too long to process in your district you can try to find out what has been going wrong. If you learn, for example, that the GeneXpert testing machines have no cartridges, you can report that to the District AIDS Council. You can ask that the shortage be investigated and that the provincial authorities be notified.

Photo by Chelsea Maclachlan, courtesy of the Treatment Action Campaign Archive

TB IN SOUTH AFRICAN PRISONS: WHERE TO NOW?

By John Stephens

South Africa stands at a crossroads in the fight against tuberculosis. An important victory in the Constitutional Court has affirmed the direction that we should take, but we need sustained political will and activism to ensure that we do not squander this momentum.

The Dudley Lee case

Dudley Lee spent over four years in Pollsmoor Prison outside Cape Town as an awaiting trial detainee. Eventually he was acquitted and released, but not before being infected with tuberculosis.

Lee asked the Constitutional Court of South Africa to decide whether the Department of Correctional Services (DCS) could be held liable for causing his TB infection. In December 2012, seven long years after he started legal proceedings against the DCS, the Constitutional Court ruled in Lee's favour.

The Treatment Action Campaign (TAC), Wits Justice Project, and the Centre for Applied Legal Studies, represented by SECTION27, participated in the case as amici curiae (friends of the court). In doing so they helped Lee to achieve one of the major legal victories for human rights and public health in recent history.

The legal issues raised in the case included complex theories of legal causation and their interaction with constitutional rights and health policy. The judgment is broad and likely to have wide-ranging legal implications.

While the lower courts have yet to interpret the ruling, any fair reading of it suggests that it would now be easier for a claimant to prove that the DCS caused his or her TB infection. The DCS is thus at risk of potential lawsuits from a large number of current or former detainees.

This Constitutional Court ruling has at least three interconnected consequences.

First, individual prisoners now have a way to vindicate and protect their rights.

Second, the state has been held accountable and therefore cannot violate rights and disregard its duties with impunity. It must do what it is supposed to do or pay compensation.

Third, because the state is accountable, it has an incentive to carry out its duties better, which hopefully means that it will. This could have enormous benefits for the health of prisoners, their families and the wider communities to which many of them return after their incarceration.

Photo courtesy of GroundUp groundup.org.za

Awaiting trial detainees waiting to be tested for tuberculosis at Pollsmoor Prison in Cape Town. Photo courtesy of Gallo Images, The Times, and Shelley Christians

A window of opportunity

In South Africa the Lee case energised TB activism to a degree that has not been seen in many years. This was most evident in the direct involvement of organisations like TAC and SECTION27 in the Constitutional Court case. It was also visible in demonstrations held to raise awareness of Lee's case and about the growing crisis of TB in prisons.

Meanwhile, an expanding body of scientific evidence suggests that to tip the scales in our favour in our battle against TB we should focus on reducing transmission rates in prisons.

In light of recent legal, social and scientific developments, the case for tackling TB in prisons is stronger than ever. Whether or not we do so could affect the health of millions for years to come.

Are prisons TB factories?

If you consider the high TB transmission rates in South Africa's prisons and the vast number of people who have been through these institutions, it is staggering to realise how many individuals the DCS may have exposed to TB infection over the years. A study of Polllsmoor Prison, where Dudley Lee contracted TB, showed that conditions in the facility created an approximately 90% risk of TB transmission per annum.

Today, over 150,000 people crowd South Africa's prisons. A third of these inmates are awaiting trial and presumed innocent. Yet most of them will, presumably, contract TB within a year.

As you read this, Pollsmoor Prison is – in the words of the Constitutional Court judgment – "notoriously overcrowded" and provides "ideal conditions for transmission of TB."

The failure to control TB in prisons is worrying for a number of reasons:

- First, TB diagnosis, treatment and prevention should be easy in prison. After all, the prison population is – or should be – known and captive. The question we face is: if we cannot manage TB in a confined population, how can we expect to control it outside prisons?
- Second, detainees in South Africa are endowed with constitutional rights that should work against TB transmission. These include rights of access to

health care services, rights to bodily integrity, and a right to detention in conditions that are consistent with human dignity. This latter right includes the provision of adequate accommodation, nutrition, and medical treatment.

- Third, the DCS has already established the foundations of a rigorous, effective programme for the prevention and treatment of TB in prisons. This programme is outlined in the Correctional Services Act No 111 of 1998 as well as in regulations and 'Standing Orders' made in terms of the Act. Yet, as the Court found, the DCS has failed to implement these laws.

- Finally, new evidence is emerging to suggest that tackling the TB problem in prisons is crucial to beating the disease in the general population. Professor Robin Wood, Director of the Desmond Tutu HIV Centre at the University of Cape Town, is a key figure behind the development of this theory. In a recent study, Professor Wood and his colleagues compared the experiences of New York City and Cape Town during the early 1900s. At this time, the size of the TB epidemic in each city was approximately the same.

  While New York has managed to control its TB problem, Cape Town has not: in 2010, for example, 27 people died of TB in New York while 3,000 died in Cape Town. Wood suggests that one of the major reasons for this difference is that New York prioritised the control of TB in its largest prison, Rikers Island. The experience of Dudley Lee in Pollsmoor – Cape Town's largest prison – clearly illustrates that a similar prioritisation is needed.

What difference will activism make?

The success of the 2002 TAC case that forced the South African state to provide treatment for prevention of mother-to-child transmission (PMTCT) of HIV is a subject that has been written about extensively. In analysing the impact of this case, commentators have largely agreed that the social movement that led to the case was largely responsible for bringing about this landmark judgement.

Supporters of this movement have transformed the judgment into real change: pregnant women now have access to treatment, and organisational support is provided for campaigns and education.

In short, social activism turned the court's judgement into a history-making, life-saving force. The first generation of children to benefit from this ruling are testimony to the extraordinary power of combining legal action and social activism.

But ten years after the PMTCT case, TB remains the number one cause of death in people with HIV. TB is an entirely preventable infection and, for the most part, is curable.

Prevention is relatively simple and the basic principles remain the same: better ventilation and sanitation, and early detection – a simple set of common-sense precautions. These well-known methods should have eliminated the disease decades ago.

Controlling TB presents many challenges but these are not insurmountable. Unfortunately, there has been a stagnation in political and legal thinking about TB. Today, the disease which continues to have a huge impact on so many lives still receives nothing like the attention it should.

2012 witnessed a flurry of activism thanks to Dudley Lee's story and the growing realisation that we must target prisons if we are to defeat TB, even if this means that we need to address the complex relationship that South Africa has with crime.

The Constitutional Court has spoken on the issue of TB control in prisons and has handed activists a remarkable tool. How then should we use this?

The way forward

TAC, SECTION27, the Wits Justice Project, and the Centre for Applied Legal Studies have made the development and implementation of a comprehensive TB prevention, diagnosis, treatment, care and support programme a priority for 2013 and beyond.

The DCS must develop the specifics of this programme. It must be costed and budgeted for, and accompanied by a detailed implementation plan specifying milestones and indicators.

The DCS has a wealth of models and support available, from sources such as the World Health Organization and the Centres for Disease Control and Prevention to organisations like TAC, SECTION27, and their partners.

Moreover – and this is something that the DCS appears to have overlooked – the foundation for such a plan is already in place. The body of law comprising the Correctional Services Act and the associated regulations and orders are detailed and thorough. The DCS therefore does not need to create a policy from scratch. It must focus on implementation instead.

TAC members and other activists gathered outside the Constitutional Court in Johannesburg, where Dudley Lee's case was being heard, to protest against the poor living conditions inside South Africa's prisons. Photo by Legogang Mokwela, courtesy of Treatment Action Campaign Archives

In an encouraging development, the DCS and the Department of Health (DoH) jointly announced the "Guidelines for the Management of Tuberculosis, Human Immunodeficiency Virus and Sexually-Transmitted Infections in Correctional Centres, 2013" (the Guidelines) on World TB Day, 24 March 2013.

The publication of these guidelines may indicate that the DCS is stepping up to its duties. The DoH's close involvement in creating these guidelines suggests that much-needed collaboration between these departments may also be taking place.

The coalition of organisations working on these issues has made a submission on the guidelines. To assist the DCS in developing the plan, a round-table meeting was held on 28 May 2013. Medical and legal experts, activists, representatives of the DCS and DoH and other interested parties came together to shape the contours of the plan and agree on how to implement it. A short report of that meeting is published on page 28 of this magazine. A more detailed report is available at www.section27.org.za

We have won a major legal victory in the Dudley Lee case, but the real work begins now. The judgment is only a tool—it does nothing unless we use it. However, properly used, it could change the course of the TB epidemic as we know it.

John Stephens is a researcher with SECTION27.

Sources: Johnstone-Robertson et al, 'Tuberculosis in a South African Prison – A Transmission Modelling Analysis' 101 SAMJ (2011) ; Minister of Health v Treatment Action Campaign (TAC) (2002) 5 SA 721 (CC)

KNOW TB: GET LITERATE!

STANDARD REGIMENS FOR DS-TB, MDR-TB AND XDR-TB

New cases of TB

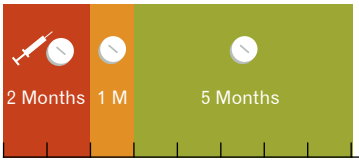
Patients who have never been treated for TB in the past or have taken treatment for less than 4 weeks in the past

Intensive Phase: 1 pill (FDC) daily containing: isoniazid, rifampicin, pyrazinamide, ethambutol

Continuation Phase: 1 pill (FDC) daily containing: isoniazid, rifampicin

Retreatment cases of TB

Patients who have been treated for 4 weeks or more in the past



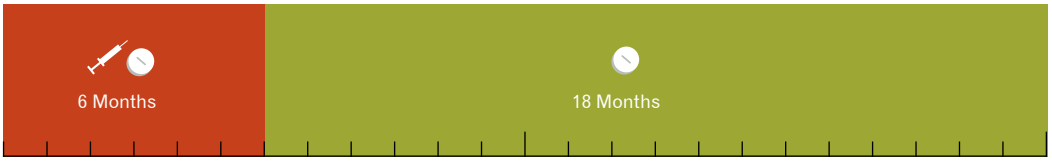
Intensive Phase: A daily injection of streptomycin + 1 pill (FDC) daily containing: isoniazid, rifampicin, pyrazinamide, ethambutol

Intensive Phase: 1 pill (FDC) daily containing: isoniazid, rifampicin, pyrazinamide, ethambutol

Continuation Phase: 1 pill (FDC) daily containing: isoniazid, rifampicin, ethambutol

Multi-Drug Resistant TB

MDR-TB patients have a strain of TB that is resistant to one or more anti-TB drugs i.e. rifampicin and/or isoniazid

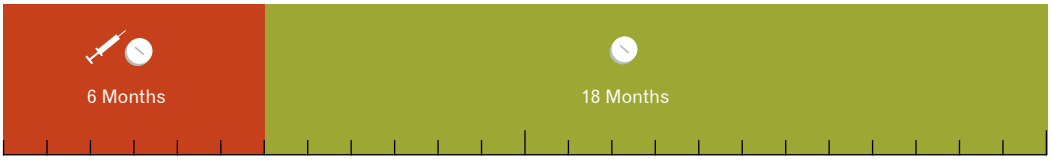


Intensive Phase: An injection of kanamycin at least 6 times a week + oral intake at least six times a week of: moxifloxacin, ethionamide, terizidone, pyrazinamide

Continuation Phase: Oral intake at least six times a week of: moxifloxacin, ethionamide, terizidone, pyrazinamide

Extensively Drug Resistant TB

XDR-TB patients have a strain of TB that is not only resistant to first-line drugs but also resistant to two key classes of second-line anti-TB drugs



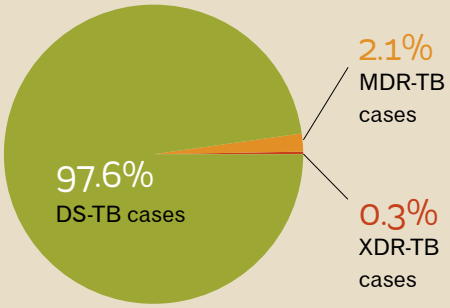
Intensive Phase: A daily injection of capreomycin + daily oral intake of: moxifloxacin, ethionamide, terizidone, pyrazinamide, PAS, clofazimine

Continuation Phase: Daily oral intake of: moxifloxacin, ethionamide, terizidone, pyrazinamide, PAS, clofazimine

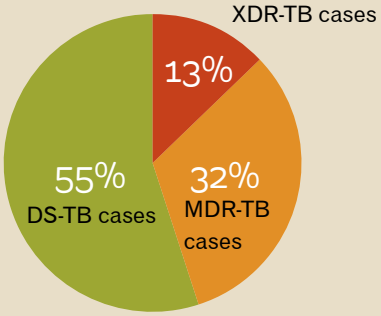
Note: With MDR and XDR-TB, standard regimens can be switched to individualised regimens that are individually designed. Changes are based on a patient's previous history of treatment and DST (Drug Susceptibility Test) results.

References: National Tuberculosis Management Guidelines 2009; Management of Drug-resistant Tuberculosis. Policy Guidelines, August 2011

TOTAL NUMBER OF TB CASES



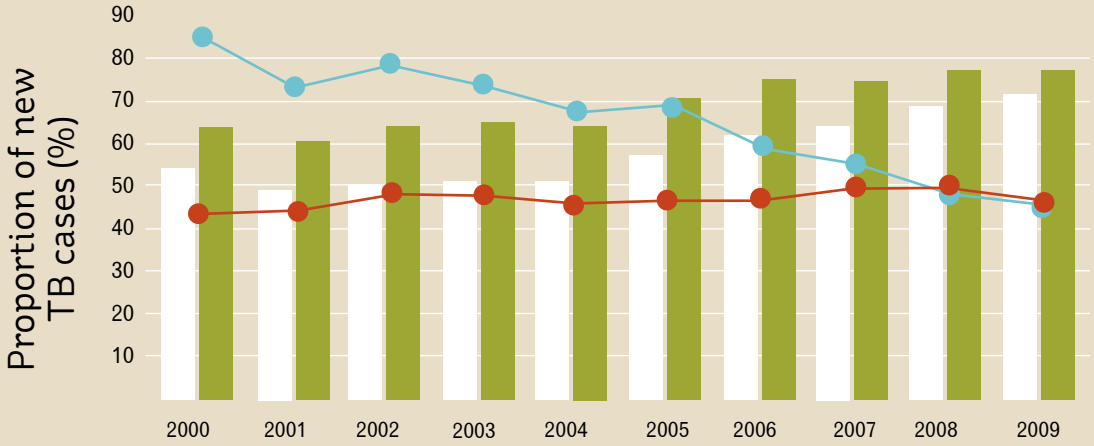
TOTAL COST OF TB TREATMENT



XDR-TB cases form a small proportion of the total case burden, but consume a disproportionate and substantial amount of South Africa's total annual TB budget.

Source: Pooran A, Pieterson E, Davids M, Theron G, Dheda K (2013) What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa? PLoS ONE 8(1): e54587. doi:10.1371/journal.pone.0054587

TREATMENT OUTCOMES OF NEW TB CASES 2000–2009

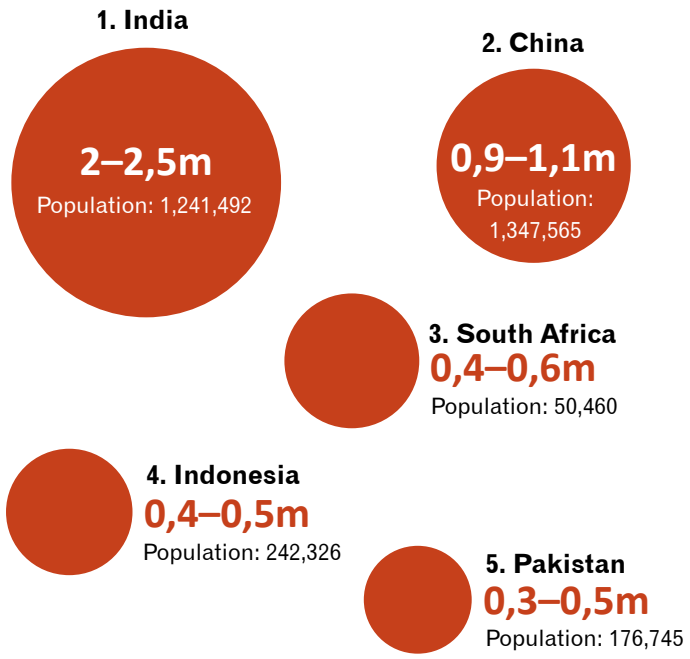


The TB cure rate has improved from 54% in 2000 to 71% in 2009. The treatment success rate of new infectious TB cases in 2009 was 77%. This is below the global target of 85%.

Source: National Strategic Plan on HIV, STIs and TB 2012-2016, Available at www.sanac.org.za

GLOBAL TB BURDEN

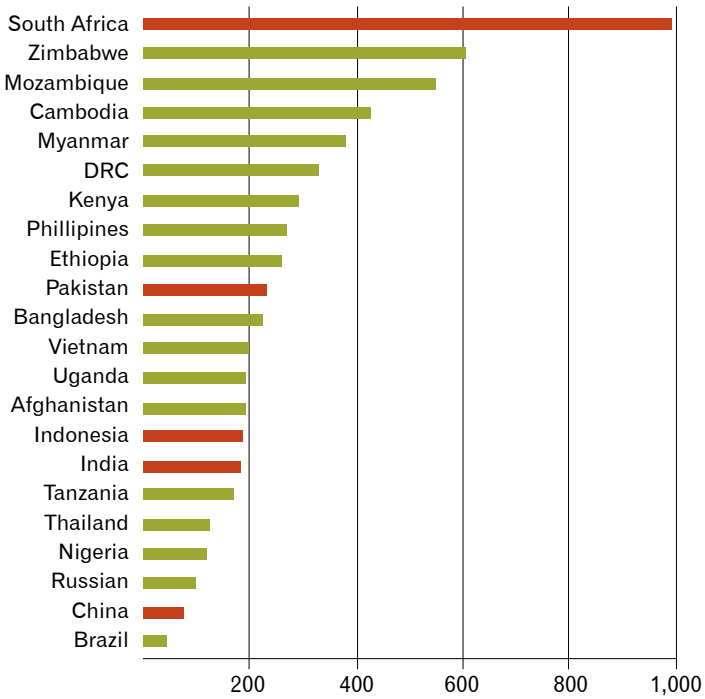
The five countries in the world with the largest number of new TB cases in 2011



Source: WHO Global Tuberculosis Report 2012

ESTIMATED BURDEN OF DISEASE CAUSED BY TB

Incidence rates per 100,000 population



South Africa has the third highest estimated total burden of TB in the world after China and India. While total TB burden numbers give us a picture of where most cases of TB are located in the world, the incidence rate per 100,000 population gives us an idea of the concentration or density of TB in our population. TB is a highly infectious disease and every active TB case can infect up to 20 people in its surroundings per year. The incidence rate therefore helps to tell us how serious the threat of TB in our population actually is.

Data measuring the TB incidence rate per 100,000 population show that South Africa has the highest burden of disease globally, and at a level that is far above China's and India's. According to this measure, China drops to 21st place and India to 16th place globally, while Zimbabwe and Mozambique rise to the 2nd and 3rd places respectively. A large amount of cross-border labour migration occurs between Zimbabwe, Mozambique and South Africa and this makes the concentration of TB in these neighbouring countries worrying.

RIFAPENTINE

TRIALLED IN SA BUT NOT AVAILABLE IN SA

A new tuberculosis treatment regimen has been shown to be safe and effective in a clinical trial conducted in southern Africa. However, the high cost and a lack of clear support from producers mean that access to the drug in the South African public sector is unlikely for years to come.

The RIFAQUIN trial

Tuberculosis (TB) treatment consists of a combination of four medicines taken daily for two months, followed by two medicines taken daily for another four months – a total of six months of treatment. Researchers are exploring ways in which the duration of treatment and the number of pills that patients must take can be reduced.

The results of the RIFAQUIN trial were reported recently at the 2013 Conference on Retroviruses and Opportunistic Infections held in Atlanta in the USA.

In this trial researchers compared the current standard treatment against two experimental alternatives: one regimen that also lasted six months (but with fewer pills), and one that only lasted four months.

The researchers reported that the six-month experimental regimen was non-inferior to (i.e. it was at least as good as) the current standard treatment. 5% of the 163 patients who received the standard treatment had unfavourable outcomes compared to 4% of the 187 patients on the six-month experimental treatment. Those on the four-month treatment did much worse: 17% of patients had unfavourable outcomes. (These included treatment failure, relapse, and death.)

In other words, patients who took moxifloxacin and rifapentine only once a week for the last four months did as well as patients who took isoniazid and rifampicin every single day for the last four months. This means the experimental regimen is as effective as the current standard treatment, but with a much lower pill burden.

Taking treatment just once a week is likely to be more convenient for patients and may require fewer visits to the clinic, depending on how the treatment is be rolled out. Similarly, where treatment has to be directly observed by a health worker, it will require much less time to monitor treatment once a week instead of every day.

No rifapentine in South Africa

The RIFAQUIN trial was conducted from 2008 to 2012 in southern Africa and included sites in Cape Town and Johannesburg. Yet, despite the encouraging findings, it seems unlikely that the new regimen will be available here any time soon.

In order to implement the new regimen with its lower pill burden in the South African public health sector we will need access to both affordable moxifloxacin and rifapentine. In the South African private sector a supply of ten 400mg moxifloxacin pills costs over R250 per month. By comparison, a 4-in-1 fixed-dose combination of the current standard regimen costs R38.

The prospects for rifapentine are even worse. Even though the drug was registered with the Food and Drug Administration in the USA in 1998, it has not yet been registered with South Africa's Medicines Control Council and can therefore not be sold in South Africa. According to the French pharmaceutical company Sanofi, "plans are underway to register rifapentine in South Africa".

The price of rifapentine in the USA has varied recently between R450 and R660 per month. The drug was patented in the USA in 1970. The patent on rifapentine has expired and there is no barrier to another manufacturer producing a generic version of the medicine.

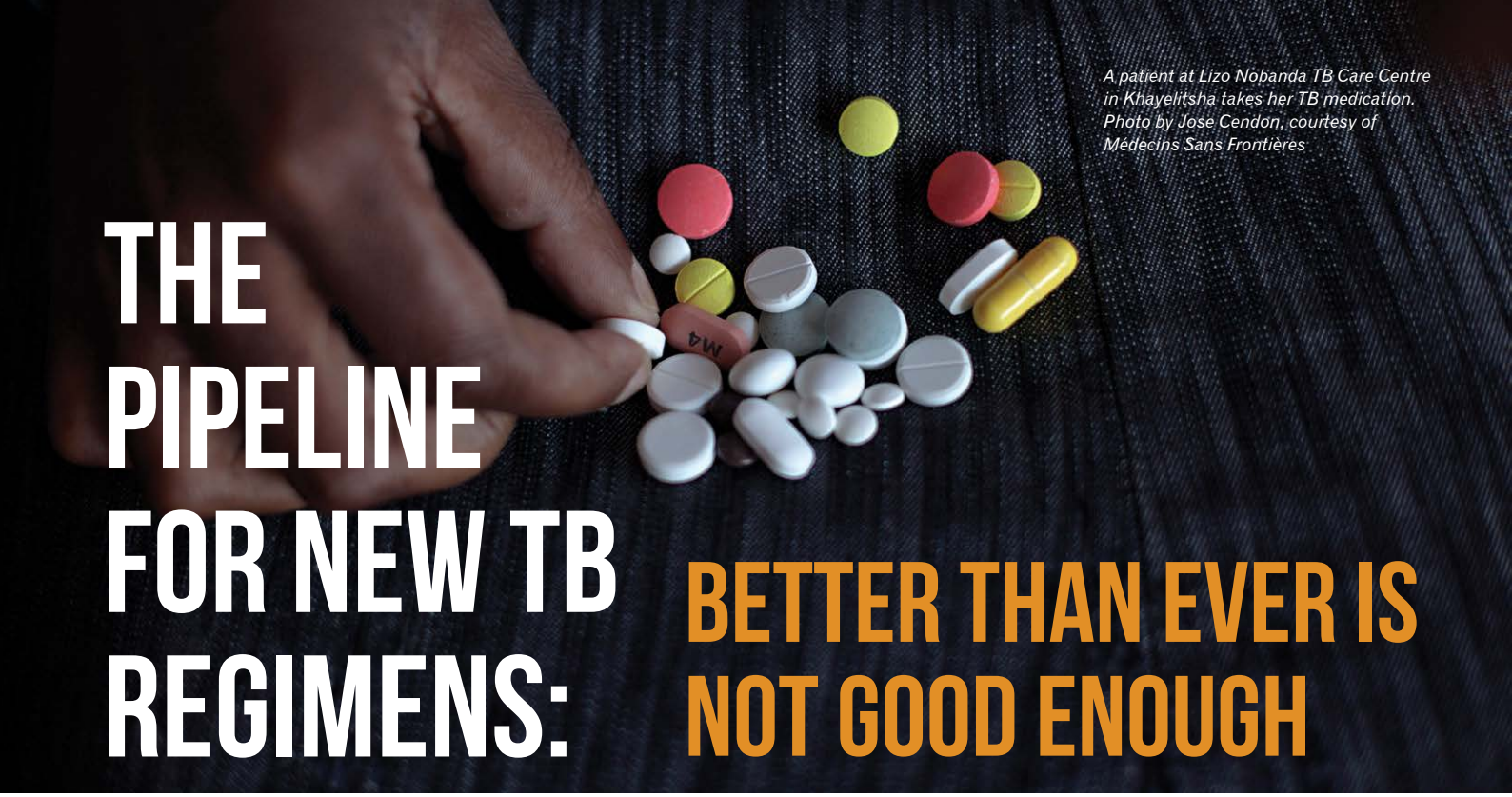
This is a simplified and updated version of an article by Nathan Geffen first published in the journal HTB South. HTB South is published by HIV i-Base and can be found at http://i-base.info/htb-south/.

The trial was conducted in South Africa, and it's therefore unacceptable that Sanofi has waited so long before trying to register rifapentine with the Medicines Control Council. Registration must be accelerated and rifapentine made available at a reduced price that would allow the state to buy it for use in the public sector TB programme.

Regimen	Unfavourable outcomes (Per-protocol analysis)	Unfavourable outcomes (Modified intention-to-treat analysis)
Control regimen (standard World Health Organization treatment regimen): Two months of daily ethambutol, isoniazid, rifampicin and pyrazinamide followed by four months of daily isoniazid and rifampicin.	**5%** 8 in 163 participants	**14%** 27 in 188 participants
Six-month experimental regimen: Two months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by four months of once-weekly moxifloxacin (500mg) and rifapentine (1200mg)	**4%** 7 in 187 participants	**14%** 30 in 213 participants
Four-month experimental regimen: Two months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by two months of twice-weekly moxifloxacin (500mg) and rifapentine (900mg).	**17%** 28 in 163 participants	**26%** 50 in 192 participants

Per-protocol analysis: This analysis looks only at those study participants who completed the study as prescribed. It excludes people who dropped out of the trial or who stopped taking treatment.

Modified intention-to-treat (ITT) analysis: Normal ITT analysis includes all the study participants who were assigned to a treatment arm – even if they dropped out of the trial or had poor treatment compliance. Modified ITT analysis allows for some specified study participants to be excluded from the analysis.



A patient at Lizo Nobanda TB Care Centre in Khayelitsha takes her TB medication. Photo by Jose Cendon, courtesy of Médecins Sans Frontières

THE PIPELINE FOR NEW TB REGIMENS: BETTER THAN EVER IS NOT GOOD ENOUGH

By Erica Lessem

In December 2012, tuberculosis (TB) treatment reached a major milestone with the first approval in over forty years of a new medication from a novel class of TB drugs. The US Food and Drug Administration (FDA) approval of bedaquiline reflects a newly revitalised global effort to develop fresh, more effective treatments for TB after decades of stagnation.

Existing treatment for drug-susceptible TB (DS-TB) is effective, but it takes six months or more and has a high pill burden. The medication causes side-effects that often make patients feel worse than the disease itself does.

The treatment of drug-resistant TB (DR-TB) is even longer. It lasts 9 to 24 months, is very expensive, and involves painful daily injections. The regimen is even harder to tolerate, with side-effects that include hearing loss, heart toxicity, and psychosis.

Most DR-TB drugs have not been validated in clinical trials, and cure rates for the disease are much worse than for DS-TB. People latently infected with TB – particularly DR-TB – also need better, shorter-duration therapies to prevent the onset of active TB disease.

The road to adequate treatment for people with TB remains a long one. Currently the clinical development pipeline contains just six TB drugs (see the table below). This progress is inadequate given the urgency of improving treatment. Bedaquiline, though approved, has not yet begun to reach the thousands who need it. Other drugs lag even farther behind in the development cycle.

New TB drugs in development

Drug	Sponsor	Development Phase
Delamanid	Otsuka	Phase III
Bedaquiline	Janssen	Phase IIb (FDA-approved)
AZD5847	AstraZeneca	Phase IIa
PA-824	TB Alliance	Phase IIb
SQ109	Sequella/Infectex	Phase II/III
Sutezolid	Pfizer	Phase IIa

Clinical trials involving humans are conducted in four phases. Medicines are usually considered for registration and marketing only after two successful Phase III trials

FOUR KEYS TO BETTER TB REGIMENS

1. **Governments and donors need to increase funding for TB research at least threefold.**

   Investment in TB drug studies stands at just a third of what is needed. In 2011 alone, there was a shortfall of nearly $500 million. In the USA, automatic and discretionary cuts to the National Institutes of Health (the leading funder of TB research and development) and the Centers for Disease Control and Prevention are harming already underfunded research programmes.

   A recent review also calls on countries with high TB burdens to take a greater share in funding TB research. It recommends that the size of each country's share should be based on its gross domestic product, TB disease burden, and the size of its treatment programme.

2. **Sponsors must commit to developing their drugs and to making them accessible to other research groups and affordable once licensed.**

   On the research side, this means investing in the development of drug compounds using human and financial resources. It also implies working with other research consortia at an early stage to study drugs in combination. This approach would optimise the use of such drugs and make clinical research more efficient.

   On the delivery side, companies must price TB drugs affordably, and manufacturers must work to maintain steady supply. The sponsors of promising candidate drugs must also make their compounds available for urgent cases through responsible pre-approval access programmes.

3. **More research is needed in key vulnerable populations.**

   At present, TB is a disease of the vulnerable and the marginalised. Consequently, there is little economic incentive to develop new drugs. Research into important TB-affected communities is scarce or is done too late.

   Sponsors and researchers must commit to studying TB drugs as thoroughly as possible, and as quickly as safety allows, in vulnerable populations. These include children, women, people with HIV, people with Hepatitis B and C, people who use alcohol, and people who inject drugs or use opioid substitution therapy.

   Comprehensive drug-drug interaction studies and modelling need to be done with antiretrovirals, with methadone and buprenorphine, and with TB drugs. This is vital because many such medications interact or have overlapping side-effects, such as heart and liver toxicity. Regulatory authorities can also play an important role by appropriately encouraging, and providing incentives for, research in these populations.

4. **Regulatory authorities must build their capacity and expertise to appropriately regulate clinical trials, early access, accelerated approval, postmarketing studies, and drug safety for new TB drugs and regimens.**

   Regulatory agencies – particularly those in high TB burden countries – must increase their ability to rapidly review submissions. This is as important in drug registration as it is in clinical research, where study design and approvals for drug importation can be unnecessarily lengthy and cumbersome. Research and development of new TB drugs is ultimately meaningless if new treatment options are not approved and available to those who need them.

THE ROAD AHEAD

To reach the goal of no TB deaths and no new infections, we must provide people with treatment for TB infection and active TB disease that is effective against their particular strain. Rapid, universal testing for drug susceptibility is therefore vital.

To humanely treat TB, we need shorter, more tolerable regimens. For DR-TB in particular, treatment must also be all-oral, less toxic, and more effective. We need better access to existing and new treatment options, and the auxiliary care and psychosocial support necessary to make TB care patient-centred.

Budget cuts, the spread of DR-TB, and many scientific challenges all threaten progress. But if donors, sponsors, researchers, and regulators commit the necessary resources and will, the potential to improve TB treatment and ultimately to eradicate the disease will be huge.

Erica Lessem is Assistant Director of the TB/HIV Project at the Treatment Action Group. This article has been modified from the 2013 Pipeline Report's TB treatment chapter. To read more, please visit www.PipelineReport.org.

Sources: Jiménez-Levi, E '2012 Report on tuberculosis research funding trends, 2005–2011', New York: Treatment Action Group and Stop TB Partnership (2012). Available from: http://www.treatmentactiongroup.org/tbrd2012 (Accessed 29 April 2013); Walwyn, D 'Determining quantitative targets for public funding of tuberculosis research and development', Health Research Policy and Systems. (2013 Mar;11:10). Available from: http://www.health-policy-systems.com/content/11/1/10. (Accessed 29 April 2013)

TB VACCINES

The search for an effective TB vaccine has so far failed to produce a silver bullet against the disease and recent trial results have been disappointing. However, a number of vaccine trials are underway and the South African TB Vaccine Initiative is playing an important part in this work.

By Shyam Goswami

LITTLE PROGRESS IN 90 YEARS

The only tuberculosis (TB) vaccine in use is the Bacillus Calmette-Guérin (BCG) vaccine. It was developed in 1921 in France using a strain of bovine TB. The World Health Organization recommends giving the BCG vaccine to infants in countries with high TB rates. The vaccine is effective in preventing severe TB disease in children (especially TB meningitis – the inflammation of the lining of the brain), but unfortunately it provides little or no protection to adults.

TB vaccine research has been slow and little has been produced since the development of the BCG vaccine more than 90 years ago. However, in the last decade research activity has intensified and a number of new vaccines are now being investigated. The South African TB Vaccine Initiative is playing an important part in these efforts.

Recent findings, however, have been disappointing. A clinical trial conducted by SATVI on a vaccine called MVA85A showed no efficacy in infants, after having produced promising results in four different animal models.

This trial tested the efficacy of MVA85A in infants who had already received the BCG vaccine. According to Principal Investigator Dr. Michele Tameris of SATVI, infants were chosen because they are a 'captive audience' and this means it is easier to monitor them. MVA85A is presently being tested in HIV-positive adults in Senegal.

Dr Willem Hanekom, Director of SATVI, believes there could still be hope for MVA85A. Speaking about the infant trial, he says, "This trial was one dose, in one age group, in one setting, and at one time frame. If we [were to] do it in China we don't know if [the results] would be different." BCG has proven to be more effective in certain populations. It was found to have little efficacy in trials in India, but was 60% to 80% effective in British trials."If we give a double dose, it's unknown if it will work," Hanekom notes.

HIGH RISK RESEARCH

Given setbacks like those in the MVA85A infant trial some might be doubtful about the prospect of an effective vaccine. But, it could be argued that the benefits of an effective vaccine would be so great that trials are worthwhile even if the chances of success appear slim.

"Until we know more about [the origin and development of] TB, any vaccine trial is a high-risk undertaking. But in my view, we have no choice," says Hanekom. "If you look at the epidemic in South Africa, 500,000 develop TB each year. Worldwide, 1.4 million die [of TB each year]. Until we have a cure, we need high-risk research."

Clinical trials involving human participants, like those testing MVA85A, are very expensive and time consuming. It can take years before you know whether a vaccine works or not. For this reason, SATVI has taken a two-pronged approach to vaccine research. One focus is on conducting clinical trials of new vaccines and the other is on researching biomarkers.

Biomarkers are measurements of specific blood levels, cells or other physical processes that can indicate the progression of a disease. Finding biomarkers that accurately indicate whether a vaccine is working or not could potentially cut down on the length of trials. It could also help to eliminate vaccines that are ineffective more quickly.

Currently we do not know what to look for in patients who have received a TB vaccine to know if the vaccine is working. "Right now, we're in the dark," says Dr. Hennie Geldenhuys, Clinical Researcher and Medical Officer at SATVI. "We need to know what gives protection. Now, it's a bit of a lottery."

In the early phases of testing a vaccine, researchers look for an immune response, which is evidence that the vaccine can cause the kind of immunity that is thought to be important for protection against TB. We know that a type of immune cell called CD4 T-cells are critical in protection from TB, and after administering a test vaccine, researchers look to see if the vaccine is stimulating these cells. This technique however is not specific enough. What researchers lack is a more specific indicator (biomarker) showing whether the vaccine is working as intended. Such a biomarker would most likely be something that could be detected in a blood test.

TB biomarkers can be divided into two groups: those that are linked to a person's risk of infection and those that are indicators of protection against TB. Enrolling people who have a higher genetic risk of developing TB would reduce the size of trials by thousands of participants. This would in turn lower the cost of the studies. Identifying biomarkers that are linked to protection would drastically decrease the time it takes to determine if a vaccine works.

OTHER VACCINE OPTIONS

MVA85A is only one of a number of TB vaccines being tested. SATVI is also involved in testing a vaccine called M72. This is currently entering Phase IIB trials. In phase IIB, a vaccine is studied for its efficacy. M72 will be tested in 7,000 young adults who are HIV-negative. Trials of the same vaccine are also being conducted among infants in Ghana.

The vaccines we listed above were all proposed as boosters to the BCG vaccine (i.e. they were given to people who had already received the BCG vaccination). One limitation of BCG is that it is not safe for people with HIV. For this reason, MVA85A will also be tested in infants who have not received the BCG vaccine.

Photo by Shyam Goswami

Research is now mostly focused on finding a vaccine to boost the effectiveness of BCG. "We either need to boost BCG or find a new or replacement [vaccine] that protects everyone forever," says Principal Investigator Dr. Tameris of SATVI. Until that vaccine arrives, people will continue to struggle with TB.

Given our current knowledge of TB, it is very difficult to know whether a vaccine will prove effective in blocking the disease. Vaccines that contain only one or two antigens – substances capable of inducing an antibody response from the immune system – are less promising, because researchers do not know if the body will 'take' the vaccine. "We do not know what little bits will work," says Dr Hanekom.

For this reason, a live vaccine could be more promising because all the parts of the bacteria are present. Phase I trials of MTBVAC – a whole-organism vaccine developed by the Spanish pharmaceutical company Biofabri – are beginning very soon.

Safety can be of greater concern with live vaccines, such as MTBVAC and BCG. There was a disaster in Lübeck, Germany in 1929, when 72 infants died of TB because of an improperly prepared BCG vaccine. Today, vaccines are heavily regulated.

Shyam Goswami is a freelance journalist. He formerly worked as an engineer for Médecins Sans Frontières.

TB ROUND TABLE

Stakeholders met to discuss strategies to prevent and treat tuberculosis (TB) – the leading cause of death in South Africa's correctional centres – at the University of the Witwatersrand on 28 May 2013. The TAC, the Wits Justice Project, the Centre for Applied Legal Studies, and SECTION27 hosted the round-table meeting.

The round table focused on strengthening the Guidelines for the Management of Tuberculosis, Human Immunodeficiency Virus and Sexually Transmitted Infections in Correctional Centres, 2013. These Guidelines were jointly announced by the Department of Correctional Services (DCS) and the Department of Health (DoH) on World TB Day in March 2013.

Participants included representatives of the DCS and DoH, legal experts, medical experts, representatives of the Judicial Inspectorate for Correctional Centres, and a range of organisations involved in providing services in correctional centres as well as in health and human rights more broadly.

- John Stephens of SECTION27 gave a presentation on the legal framework relevant to health, infection control and human rights in correctional centres.
- Two former inmates, Dudley Lee and Ludwick Mabiyane, shared their experiences of contracting TB while in custody.
- Maria Mabena of the DCS and Patricia Ntsele of the DoH presented the Guidelines. Jameelah Omar of the Centre for Applied Legal Studies presented a joint submission on the Guidelines authored by the hosting organisations.
- Professor Robin Wood discussed the conditions of imprisonment that contribute to high TB transmission rates, including overcrowding, long lock-up times, and a lack of ventilation.
- Paul Silver, an architect specialising in prison design, gave a presentation on the need for improved ventilation in South Africa's prisons and models for improving ventilation and infection control generally.
- Dr. Andrew Black of the Wits Reproductive Health and HIV Institute gave a presentation on the treatment aspects of the Guidelines.

Presentations from the round table are available on the TAC website (http://www.tac.org.za/news/high-level-round table-tb-management-south-africa's-correctional-centres-held-wits). The hosting organisations will produce an outcome document to capture the discussions at the event. The document will be sent to stakeholders, including Government departments, and made public in the near future.

John Stephens noted with concern that the Guidelines seemed to have been developed without considering the existing laws about these issues. At worst, he said, the Guidelines contradicted them.

Professor Wood and Mr Silver expressed concerns that the Guidelines do not adequately address the need for improved prevention methods in correctional centres and agreed that attempts to curb transmission rates will not be successful unless issues like ventilation and overcrowding are addressed directly.

Dr Black noted that, for the most part, the Guidelines have simply stacked together previously existing DoH treatment guidelines. At least one of these DoH guidelines had already been updated by the DoH but the update was not reflected in the Guidelines.

KEY RECOMMENDATIONS FROM THE ROUND TABLE

- Partnership with the Minister of Police to manage TB in police holding cells and to avoid the interruption of treatment when people are arrested;
- Partnership with the Department of Public Works to improve ventilation and infection control in correctional facilities;
- Implement systems to ensure more accurate reporting of TB cases in prisons and open sharing of data on TB in prisons;
- Improve diagnosis and treatment for detainees and staff; and
- Integration of anti-retroviral treatment and TB treatment.

HOW TO FIX AIRFLOW IN PRISONS

TB is an airborne disease with an increased potential for transmission in poorly ventilated and overcrowded spaces. An infectious individual is far more likely to transmit TB in such environments. Unfortunately, conditions in South African jails have meant that prisons are particularly undesirable settings for the control of the disease.

How safe a prison environment is for prisoners and staff depends on the conditioning and control of the air coming in and going out, and how this flow is managed.

The principles are simple: purge the air from the space occupied by a TB patient and discharge all of it so that no part is recirculated. Also make sure that the number of air changes in an hour are such that the level of CO2 in the air inside is no higher than the level of CO2 in the air outside. Spaces must be configured to function in all expected local weather conditions.

Experience has shown that unless a mechanical system maintains the number of air changes, it is almost impossible to keep a constant, measured flow of air and ensure a sufficient purging of the space. Natural ventilation alone is too unreliable and does not ensure the required number of air changes.

Natural ventilation depends on air movements. These stop once the interior and exterior temperatures equalise, unless there is a constant, natural minimum wind speed outside – and this is highly improbable.

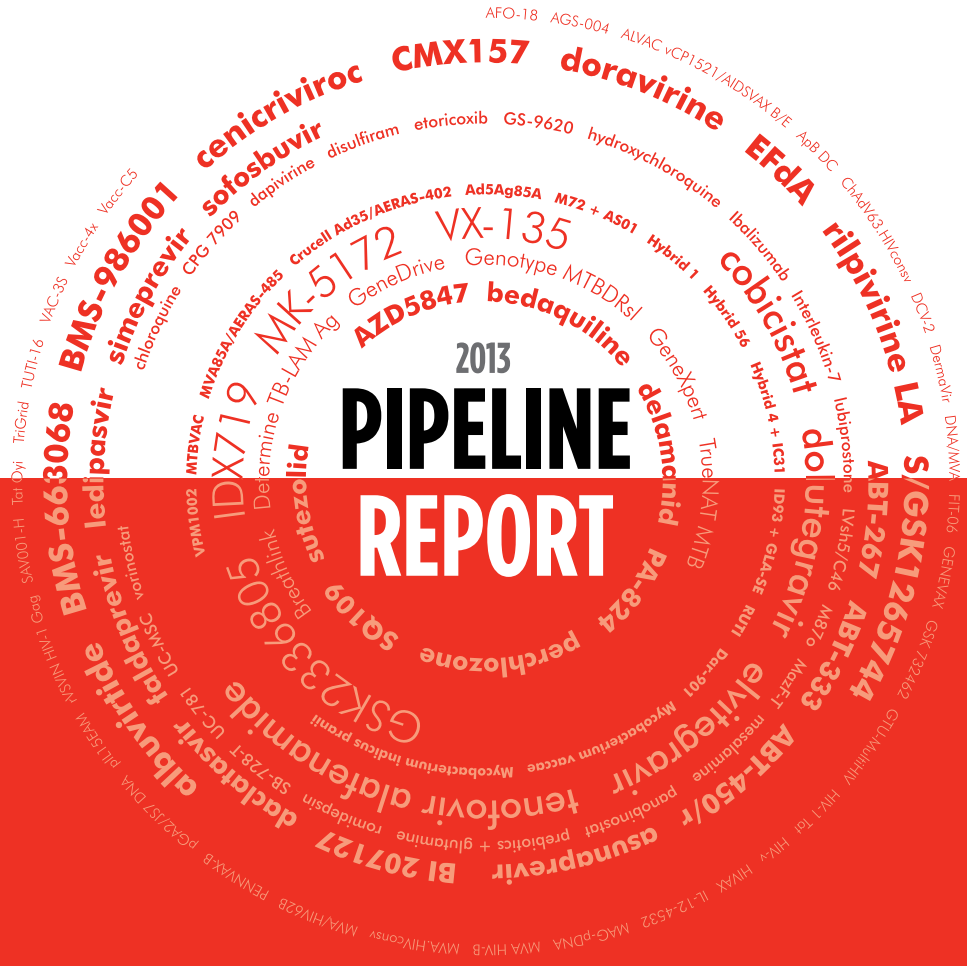
Just installing fans are not good enough since it does little to prevent cross contamination.

HOW PRISONS SHOULD BE DESIGNED

1. The air entering the patient's room should be fresh and contain no part that has been recirculated
2. An anteroom adjacent to the patient's room should act as both an airlock and a positively pressured chamber. In other words, the air in the anteroom should be maintained at a constantly higher level of pressure than the air in the patient's room
3. Air is then drawn from this airlock into the patient room's room which is negatively pressurised (i.e. the air pressure in the patient's room). This imbalance in air pressure prevents any air containing live bacteria from migrating back into the building and into other adjacent rooms
4. The air from the patient's room is discharged into a duct and exposed to an appropriate frequency of ultraviolet light for a brief prescribed period. This exposure kills nearly 90% of the TB bacteria in the air. The purged air then needs to be discharged from the building as far away as possible from the fresh air that is brought into the air system so that cross contamination is avoided.

This configuration has been used successfully for many years and has achieved the kind of infection control which other strategies have consistently failed to achieve.

Based on notes shared by the architect Paul Silver FAIA NCARB



THE 2013 PIPELINE REPORT
NOW AVAILABLE

The Pipeline Report is an annual joint publication produced by HIV i-Base (UK) and the Treatment Action Group (TAG) (USA). The Report surveys experimental agents and technologies which are being developed for the treatment and prevention of HIV, Hepatitis C (HCV), and tuberculosis. Topics covered in this year's publication include: new HIV drugs for adults and children, and updates on a "dream regimen" for HIV/AIDS which is simpler, less toxic, and more effective; TB diagnostics, drugs, and vaccines; HCV drugs and the growing global demand for access; HIV vaccines and other prevention technologies; immune-based therapies; and research toward an HIV cure.

The 2013 Pipeline Report can be accessed online at:

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