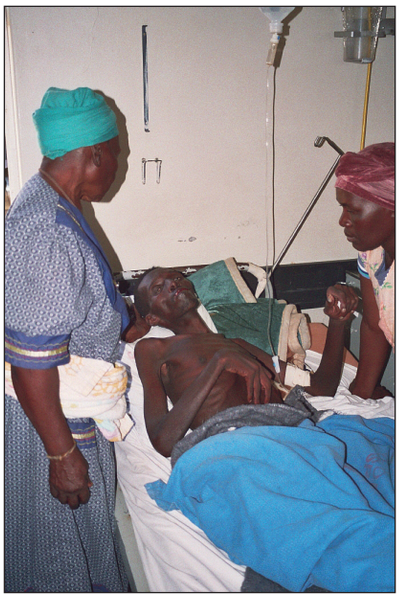
'ONE SHOT' TO KILL MDR TB – OR RISK PATIENT DEATH



A Tugela Ferry XDR TB patient in extremis, *with his family in support.*
Picture: Chris Bateman

HIV is fuelling and disguising the full extent of South Africa's TB pandemic that includes 6 000 multidrug-resistant patients (10% of whom are extremely drug resistant), creating a 'critical need' for a decentralised community-based approach while inexpensive point-of-care diagnostics are developed.

This was the consensus among Médecins sans Frontières (MSF) doctors during a technical briefing of journalists in advance of the annual International Union of Tuberculosis and Lung Disease Conference held in Cape Town last month – the first time this country has ever hosted the event.

The MSF doctors, some of whom were part of the groundbreaking ART rollout in Khayelitsha, said South Africa was an obvious choice for the conference because of the intertwined HIV/TB epidemics and the growing emergence of XDR TB.

The conference presented a 'golden opportunity' to raise awareness of the difficulties imposed by the intertwined epidemics, the bottlenecks faced by a public health response due to the poor availability of drug and diagnostic tools and to explore urgently needed innovative approaches.

Professor Willem Sturm, Dean of the Nelson Mandela School of Medicine (University of KwaZulu-Natal) and head of the university's microbiology laboratory, told *Izindaba* that by June this year XDR had spread to 68 hospitals (two-thirds of the province's health care facilities). By June this year they had identified 3 000 MDR patients and 308 XDR patients (most of the latter will be dead by the time you read this). The remainder of known drug-resistant patients are spread across every single other province in widely varying concentrations.

XDR was first detected by an alert Dr Tony Moll, Chief Medical Officer at Tugela Ferry's Church of Scotland Hospital (COSH), who sent in sputum samples from perplexingly non-responsive ART patients in 1995.

Sturm described XDR as 'almost impossible to treat unless you have susceptibility testing', adding that the only reason his province was better informed than many others was that when he first became KZN's Head of Microbiology in 1993, he ordered susceptibility tests for all TB-positive cultures.

Learning from Tugela Ferry

Two years of research at Tugela Ferry on the effect of administrative, environmental and personal infection control measures on the epidemic trajectory of XDR TB, using a mathematical model, predicts 1 300 new cases in the immediate area by the end of 2012 – if no new interventions are introduced. The index cases in 2005 numbered 53.

A heavyweight scientific team from Yale and KwaZulu-Natal universities predict that more than half of the 1 300 cases will be nosocomially transmitted, adding that a combination of mask use, reduced hospitalisation time and a shift to outpatient therapy could prevent nearly a third of infections.

Supplementing this approach with improved ventilation, rapid drug resistance testing, HIV treatment and TB isolation facilities could avert 48% of XDR TB cases by the end of 2012, they conclude in a recent paper published in *The Lancet* (2007; 370: 1500-1507).

They warn that involuntary detention could result in an unexpected rise in incidence due to restricted isolation capacity at COSH (5-bed isolation units are recommended for the infective phase only). Similar to other rural district hospitals across the country, COSH has 30 - 40-bed open TB wards.

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The crucially important findings are being studied and debated by clinicians across the country.

Sturm said drug resistance was difficult to identify in time to prevent further spread. Only concurrent isolation and treatment could mitigate a problem that he described as 'overwhelming'.

Dr Gilles van Cutsem, MSF co-ordinator in Khayelitsha near Cape Town, said the lay media coverage of the TB pandemic had focused on the dramatic but relatively small number of MDR defaulters, virtually ignoring the largest pool of undiagnosed MDR cases walking around, not to mention those diagnosed and awaiting treatment, and those on treatment but still infectious.

'You have virtually one bullet to kill MDR and if you fail, you have virtually no second chance. Once you have MDR you have to shoot with virtually every drug you can,' he emphasised.

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Sturm warnings went unheeded

Sturm has criticised the health department for not paying attention to his red flag waving about its treatment response in 1995. He provided evidence to back his contention by tracking the evolution of drug resistance in KwaZulu-Natal, the worst affected province, between 1994 and 2002. By analysing samples of a highly transmissible strain called F15/LAM4/KZN he discovered that some patients were already resistant to treatment in 1995 – when the World Health Organization (WHO) advised South Africa to implement a four-drug combination for treating first-time TB patients (isoniazid, rifampicin, pyrazinamide and ethambutol).

This meant that some patients were inadvertently getting a drug cocktail with only one or two effective ingredients, and so rapidly developed resistance to these drugs too. 'I said to the health department then that it was a recipe for disaster but no one listened and MDR strains spread,' he said.

Sturm claims that 6 years later, the same mistake was made when South Africa introduced WHO-approved guidelines stipulating which medicines to use for treating MDR TB – and the absence of susceptibility testing for second-line drugs this time led to the emergence of XDR TB. Patients got either ethambutol or cycloserine, in combination with pyrazinamide, ethionamide, kanamycin and ciprofloxacin or ofloxacin. Unknown to the health department, there was already resistance to both ethionamide and ethambutol, dating back to 1997. Sturm and his scientific team traced kanamycin resistance back to 1999 and fluoroquinolone back to 2000. The researchers also found resistance to streptomycin as far back as 1994.

National health department TB Chief Dr Lindiwe Mvusi said routine susceptibility testing would be 'impractical' but confirmed that her department's most recent drug resistance survey was done in 2001. She said an urgent new study was due to begin at the end of this year.

While Sturm sympathised with the difficulties of routine susceptibility testing, he said this did not mean that one could ignore continued surveillance 'in order to keep the finger on the pulse'.

The WHO estimates that 9 million people develop active TB globally every year, with 1.7 million deaths annually, while 80% of TB patients in sub-Saharan Africa are living with HIV.

AIDS hides TB infections

The increasing prevalence of drug-resistant TB in South Africa (as surveillance steps up) is complicated by HIV hugely increasing both the risk of developing active and extrapulmonary forms of TB, and rendering TB more difficult to diagnose due to a higher incidence of sputum-negative infection.

Less than half of HIV-positive people tested show up as TB smear-positive because of their immune-compromised systems.

Dr Tony Moll, principal medical officer at the Church of Scotland district hospital at Tugela Ferry helps a patient with her ARV drug compliance.

The limited diagnostic tools and lack of laboratory capacity in South Africa (and many other African settings) aggravates the lack of timely detection of TB and MDR TB. Literally thousands of cases go undiagnosed and therefore untreated, fuelling the disease burden. When detected, centralised responses are often too overwhelmed to absorb the need, something that managers in the worst affected provinces in South Africa (KwaZulu-Natal and the Western Cape) have freely admitted. Funds are being poured into MDR-appropriate infrastructure but little exists on the ground in terms of decentralised community-based TB care.

MSF TB specialist Dr Cheryl

McDermid said TB treatment was complicated by drug interactions and the side-effects of existing regimens. Inexpensive, sensitive, specific and rapid point-of-care diagnostic tests were 'still a long way away'.

'We've been using the same drugs for 40 years,' she emphasised, adding that this was in spite of TB having become the leading cause of death in low- and middle-income countries, with South Africa carrying the world's highest incidence. She said the weak sterilising properties of ordinary TB drugs remained one of the biggest drawbacks that scientists faced. Current chemotherapy did not achieve a bacteriological cure.

McDermid said what was most needed was the shortening of first-time treatment and for it to be effective against MDR – and that the regimen does not interact with ARV drugs. The tragedy was that TB and MDR TB were 'preventable and curable, yet it still kills one person every 15 seconds'.

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Dr Mvusi released figures showing a 0.5% increase in registered TB patient deaths from 2005 to last year (25 871 up to 29 787 mortalities) and portraying stark contrasts in the ability of different provinces to track patients.

KwaZulu-Natal fared worst with 16.6% of registered patients known to have defaulted (probably higher as 9.1% were lost to follow-up) while 11.1% of Mpumalanga's patients defaulted (10% here fell off the radar). The number of registered TB patients for the two provinces stand at 103 642 and 14 496 respectively.

The country's last recorded overall cure rate (1995) stands at 57.7%, well short of the WHO's target of 85%. This represents a 7.1% rise on 2004 cure rates. New TB cases rose by 8% between 2004 and 2005 (312 436 up to 337 309 new cases).

The country is bracing itself for the latest morbidity and mortality figures.

Chris Bateman