Since the 2005–2006 outbreak of extensively drug-resistant TB in KwaZulu-Natal, health experts have been grappling with how to detect and treat the disease.

CAPE TOWN, SOUTH AFRICA—A gaunt man with dark, deep-set eyes nods toward the uniformed security guards at the gate and the nurses who wear double-thick “respirator” masks when they make their rounds. The cheerless ward, surrounded by a 3-meter fence, is “more like a prison than a hospital,” he says. “Many patients are depressed; they don’t want to be here,” the chief nurse tells a visitor as a TV soap opera drones in a nearby room.

That feeling is understandable. The two dozen men and women in the isolated ward are undergoing harsh and possibly futile treatment for the often lethal, contagious, and stigmatized disease that has brought them to Brooklyn Chest Hospital: extensively drug-resistant tuberculosis (XDR TB). The emergence over the past 2 years of the disease—which is even more difficult to treat effectively when patients are coinfected with HIV, as many are—is posing complex medical, ethical, and scientific issues in South Africa, the site of the largest and deadliest XDR TB outbreak to date. Last year, more than 500 cases of XDR TB were diagnosed here, and the total number was probably far higher.

On the medical front, the challenges include treating an infection that resists even last-ditch medications and finding the best ways to prevent hospital transmission of the disease (see sidebar, p. 897). Among the research challenges are identifying new drug targets and rapid diagnostics, as well as investigating the molecular evolution of the TB strains that led to the emergence of this new threat. The main ethical quandary is the extent to which hospitals can or should isolate XDR TB patients against their will or force them to take potentially lifesaving yet toxic drugs—perhaps for years.

**Few warning signs**

In August 2006, researchers made headlines at the annual AIDS meeting in Toronto, Canada, with a report that a new strain of TB, apparently resistant to almost all known drugs, had emerged in South Africa. The cases had been detected in 2005–2006 in the poor, mainly Zulu community of Tugela Ferry in South Africa’s KwaZulu-Natal (KZN) Province; nearly all the victims were also coinfected with HIV. Especially alarming was the fatality rate: 52 of 53 patients had died within a median of 16 days after being tested for TB (Science, 15 September 2006, p. 1554).

XDR TB caught health care workers off guard and sparked fears of a new wave of “killer TB” outbreaks—especially in countries with high rates of HIV infection—that could jeopardize the progress in global TB control. The outbreak provided a “wake-up call,” says Mario Raviglione, director of the World Health Organization’s (WHO’s) Stop TB Department, which had first discussed the emergence of XDR TB of Tugela Ferry and elsewhere at a meeting in May 2006. WHO quickly formed a global XDR TB task force that soon made recommendations for dealing with the threat. These include better TB and HIV/AIDS control and stricter management of drug-resistant TB, as well as better laboratory services and more extensive surveillance.

Although the Tugela Ferry outbreak was startling, XDR TB wasn’t brand-new. Sporadic cases had been reported in the United States, Latvia, Russia, and elsewhere; WHO and the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia, had first defined the strain in a March 2006 article. Nor was the new bug totally unexpected, given the poor record of treating TB in many countries. After multidrug-resistant (MDR) strains of TB surfaced a couple of decades ago, some scientists had warned, it was only a matter of time before new strains, resistant to even more drugs, would emerge.

MDR TB first garnered widespread attention in the 1990s, when researchers and clinicians around the globe began identifying an alarming number of cases that were resistant to at least two of the four standard drugs used to treat TB. Suddenly, the already arduous task of treating TB became even more difficult and expensive. MDR TB can take as long as 2 years to treat, compared with 6 to 8 months for drug-sensitive TB. Costs run 3 to 100 times higher, depending on the country and the drug-resistance pattern. WHO now estimates that of the 8 million cases of active TB diagnosed each year, more than 400,000 are MDR. Cases tend to be concentrated in regions where inadequate health-care services make it harder to ensure that patients can follow the lengthy drug regimen.

Resistance can arise when patients fail to complete their therapy, thereby giving the TB bacteria
an opportunity to mutate to evade the drugs. That’s why a cornerstone of TB therapy has long been directly observed treatment—short course (DOTS), which focuses on supervised adherence to a fixed combination of anti-TB drugs. However, DOTS does not require drug-resistance testing, meaning that many undiagnosed MDR TB patients have been treated by an ineffective DOTS drug regimen that may have allowed those MDR TB strains to develop even further drug resistance. To help address that problem, WHO in March 2006 began recommending what’s called the “DOTS-Plus” protocol—which calls for using second-line TB drugs for people with confirmed or presumed MDR TB—for some high-incidence countries.

“The major challenge is to see that TB patients stay on the treatment regimen,” says Karin Weyer, head of the TB program at South Africa’s Medical Research Council (MRC). Lindiwe Mvusi, who heads the South African Health Department’s TB Program Directorate, estimates that at least 20% of the country’s MDR TB patients are defaulting, making it more likely that some may eventually end up with XDR TB. Because XDR TB is resistant to most of the second-line drugs that are used to treat MDR TB (including fluoroquinolone-category medications as well as either amikacin, capreomycin, or kanamycin), clinicians have few options, other than trying older drugs or new combinations of drugs.

Paul van Helden, co-director of the Centre of Excellence in Biomedical TB Research at Stellenbosch University, questions whether the DOTS drug protocols are always the best approach in high-incidence TB countries such as South Africa. He believes more investigations are needed to determine the best mixture of drugs to treat MDR and XDR TB in different regions.

At this point, no one knows exactly how many cases of XDR TB there are globally, because most go undiagnosed and are not reported. WHO recently estimated that XDR TB may infect about 27,000 people a year in at least 41 countries. But this is just an educated guess, based on a percentage of the MDR TB cases diagnosed each year. Later this month, a new WHO report will give a more detailed picture of the spread of drug-resistant TB.

Flash point at Tugela Ferry

In retrospect, it’s not surprising that the 2005–2006 outbreak occurred in KZN Province, which includes areas of extreme poverty. Although for centuries tuberculosis has been called The White Plague, in South Africa it is predominantly a disease of black Africans, a byproduct of poverty, poor health care, and—perhaps most perniciously—a high HIV infection rate. About 5.5 million South Africans are HIV-infected, about 11% of the population, with the highest infection rate in KZN. The combination of drug-resistant TB and HIV is especially dangerous because the weakened immune systems of HIV-infected persons make them more vulnerable to TB and also more difficult to treat.

The Tugela Ferry outbreak was detected when doctors at Church of Scotland (COS) Hospital began investigating the unexpectedly high mortality rate among TB-HIV-coinfected patients. Drug-sensitivity tests revealed that not only was MDR TB rampant, but even more severe XDR TB outbreaks or an anomaly resulting from an unusual convergence of risk factors? Gerald Friedland of Yale University School of Medicine—whose research group reported the outbreak at the 2006 AIDS conference as part of its collaboration with physician Anthony Moll’s COS hospital staff and other institutions—worries that interlinked HIV and XDR TB epidemics could “create a firestorm” in many South African communities. He argues that the current South African statistics are unreliable and the extent of the problem underestimated because “there has been a marked underreporting of XDR TB.”

But other TB experts, including Weyer and Mvusi, regard Tugela Ferry as atypical, in large part because its mortality rate has not been matched anywhere else in South Africa. Mvusi says there were 183 confirmed deaths from XDR TB in South Africa last year, but 342 XDR TB patients were still under treatment—giving hope that some cases can be managed. Although the Eastern Cape and KZN provinces had the most XDR TB cases, the strain has been found in all nine South

Isolation. The new XDR TB ward at Brooklyn Chest Hospital in Cape Town is guarded around the clock and surrounded by a high chain-link fence. A patient who tested positive for XDR TB awaited treatment at a rural hospital in Tugela Ferry in 2006 (right).
Research Project Mimics TB Transmission

PRETORIA, SOUTH AFRICA—A half-century ago, Richard L. Riley of Johns Hopkins University in Baltimore, Maryland, and others set up an innovative experiment at a Baltimore Veterans Administration Hospital: venting air exhaled by tuberculosis (TB) patients in a six-bed ward into an “exposure chamber” housing 150 guinea pigs. The challenge was to prove that TB can be transmitted by tiny airborne droplets and that individual patients vary greatly in how infectious they are to others.

But Riley’s classic experiments did not test the effectiveness of interventions such as air filters and bacteria-killing ultraviolet lights that aim to reduce airborne TB transmission. They also took place before the emergence of drug-resistant TB strains and the AIDS epidemic, two key factors that influence airborne spread of TB and patient susceptibility in Africa’s crowded hospital wards.

This spring, South African and U.S. researchers will use a hospital setup similar to Riley’s to investigate those and other variables in TB transmission at the new Airborne Infection Research (AIR) Facility in the coal-mining city of Witbank. In helping to plan the studies, TB researcher Edward Nardell of Harvard School of Public Health in Boston consulted with his mentor Riley before his death in 2001 along with scientists at South Africa’s Medical Research Council (MRC) and the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia.

Research at the new facility will focus on patients who are coinfected with HIV and drug-resistant TB, Nardell says. The goal is to “tease out the importance of infectious source strength, microbial resistance to environmental interventions, and the critical importance of microbial genotype and host factors” in airborne transmission, says Nardell.

Lindiwe Mvusi, the chief TB official in South Africa’s health department, hopes the AIR experiments will yield more data on the best ways to block airborne transmission of TB. During the deadly extensively drug-resistant (XDR) TB outbreak in Tugela Ferry in 2005–2006 (see main text), hospital transmission was a major factor. Eight hospital staff members later died from drug-resistant TB (half of them from XDR TB, the other half from multidrug-resistant TB) before ventilation was improved and other control steps were taken.

Although the experimental setup is complex, Nardell says Riley’s model is the only one developed so far that accurately mimics airborne TB transmission in hospital wards. Other efforts to simulate hospital conditions by exposing lab animals to artificially aerosolized TB bacteria have failed to simulate the natural infection process.

The AIR experiments will expose as many as 360 guinea pigs at a time to air vented directly from a six-bed TB unit. Preliminary experiments last year validated the model, Nardell says, showing the same sorts of infections found in humans. Karin Weyer, who heads MRC’s TB program, agrees that AIR is “an ideal model for studying environmental infection control.”

—R.K.

Meanwhile, other groups are searching for faster and cheaper ways to detect XDR TB, as well as new drugs to treat it. Testing for resistance to second-line drugs can take up to 2 months using the standard techniques, by which time patients may have been treated with the wrong drugs.

In South Africa and elsewhere, clinical trials of new, molecular-based tests for drug resistance are already under way by MRC, in cooperation with the Foundation for Innovative New Diagnostics in Geneva, Switzerland. If WHO validates the results, approval seems likely for a German firm’s test that can quickly detect drug-resistant TB (half of them from XDR TB, the other half from multidrug-resistant TB) before ventilation was improved and other control steps were taken.

No cases were diagnosed until the end of last year. Many of those were being treated for an indefinite period.”

Involuntary isolation or confinement of XDR TB patients is controversial, allowed in some nations only if the disease is found to pose an immediate threat to public health. WHO recommends separating XDR TB patients from others, especially in regions with high HIV prevalence, and South Africa’s health department has adopted that policy.

But even high fences and guards at some specialized TB hospitals in South Africa haven’t kept all patients inside. In December 2007, 20 XDR TB patients and 28 MDR TB patients in another ward cut a hole in the fence and fled a TB hospital in Port Elizabeth. A month later, eight of those patients had not returned, despite court orders.

Mvusi says overcrowding at some hospitals and clinics, especially in high-incidence areas such as KZN, has made it difficult to separate XDR TB patients. King George V Hospital had a waiting list of 120 drug-resistant TB patients at the end of last year. Many of those were being treated as outpatients.

Master says the caseload is challenging the health care system. If patients with M(X)DR TB survive their entire 2-year treatment regimens and still test positive for drug-resistant TB, Master asks, “What do you do then? You can’t put everyone in the hospital for an indefinite period.”

—ROBERT KOENIG