NEIL WEBB

TRANSMISSION

Control issues

Once tuberculosis takes hold in a population it can be hard to control, but scientists are finding new ways to understand and stop its spread.

BY EWEN CALLAWAY

The USS *Richard E. Byrd* left its Norfolk, Virginia port in January 1965, bound for the Mediterranean. The 4,000-tonne destroyer carried more than 300 sailors — one of whom was infected with *Mycobacterium tuberculosis*, the bacteria that cause tuberculosis (TB). By the time he left the ship more than a year later, coughing violently, almost half the crew had acquired silent infections and seven of his cabin mates and other close contacts had full-blown TB.

"It was just a beautiful case of being able to pin down when transmission happened and when disease happened," says Clifton Barry, head of the Tuberculosis Research Section at the National Institute of Allergy and Infectious Disease in Bethesda, Maryland.

The USS *Byrd* and other locally limited outbreaks offer an opportunity to monitor the spread of the bacterial disease. They provide critical epidemiological data for scientists studying TB transmission in less cramped quarters, and highlight the challenges to combatting a disease that can spread wildly before even being noticed. "We never find the cases before they've infected 10 or 15 other people," Barry says.

Many experts see reducing the spread of *M. tuberculosis* infection as the only way to manage the disease. "Transmission is really the dominant problem we have in TB control," says Chris Dye, an epidemiologist at the World Health Organization (WHO) in Geneva, Switzerland. "We know how to treat patients in clinics and cure them and save their lives and reduce illness, but what we've been far less successful at doing is cutting out transmission."

STEMMING THE TIDE

TB infections come in two general forms: active and latent. People with latent TB, like most of the infected sailors aboard the USS *Byrd*, are not symptomatic and are unlikely to develop the disease (see 'Latency: A sleeping giant', page S14). A long course of antibiotics can rid the body of the low levels of bacteria they carry, but even without treatment, they will probably never pass on their infection to others.

Most TB control efforts target the active form of the disease. Active infections can spread the mycobacterium like wildfire, even before patients develop symptoms such as a cough — and start expelling droplets filled with the infectious bacteria into the air for other people to inhale. Mark Perkins, chief scientific officer at the Foundation for Innovative New Diagnostics, in Geneva, uses the analogy of mopping up "the spill" of highly infectious people with active TB "before you turn off a tap that is barely dribbling".

Poor quality medical care can exacerbate transmission. In countries such as India it is not uncommon for patients with active TB to visit four or more healthcare providers over a period of up to several months before getting a correct diagnosis[1], and unregulated medical practices are rife. "Patients are spending far too long in the community transmitting TB to other people, before they end up in a clinic that can diagnose their TB and put them on the right treatment," says Dye.

In most parts of the world, a diagnosis of active TB is confirmed by observing the tiny bacilli in a sample of sputum put under the microscope (see 'Diagnosis: Waiting for results', page S10). But by the time *M. tuberculosis* reaches high enough numbers to be seen in this way, patients are already infectious. "You've missed the boat on stopping transmission," says Perkins.

Efforts to control TB should focus on lowering the costs of diagnostics (and drugs) for governments, healthcare providers and, ultimately, patients, says Dye. "The TB control community are not by themselves going to remedy the problem of poor health systems, but they're going to have to make a contribution."

BEYOND BORDERS

Among the countries with a high burden of TB in Eastern Europe, Africa and Asia, one stands out as having had particular success at getting to grips with TB transmission. Estonia, a nation of 1.3 million people perched on the Baltic Sea, experienced a surge in TB in the early 1990s, after the collapse of the Soviet Union — and with it the healthcare infrastructure it provided.

With support from nearby Scandinavian countries, the Estonian government implemented a TB control programme, involving medical training, public-health screening and treatment programmes, says Manfred Danilovits, a physician at Tartu University Hospital who heads the programme. As a result, incidence dropped dramatically — from over 50 cases per 100,000 in 2002 to about 25 cases in 2011 (ref. 2). The TB control programme is now experimenting with ways to tackle drug-resistant TB and co-infection with HIV, says Danilovits. For instance, some people living with HIV, many of whom will have acquired the infection through intravenous drug use, who are also infected with TB can get all their medicines — antibiotics, antiretrovirals and, if necessary, methadone — at one clinic instead of three, improving their adherence to a strict treatment programme.

Understanding transmission is critical to stemming the rise of TB in Western countries as well. London earned a reputation as the 'TB capital of Europe' after cases rose by nearly 50% between 1999 and 2009, from 2,309 to 3,450 (ref. 3). More than half of TB cases in regions such as the United Kingdom are in immigrants from high-burden countries, says Iacopo Baussano, an epidemiologist at WHO's International Agency for Research on Cancer in Lyon, France, who has studied the effectiveness of TB screening among new immigrants.

In a 2012 survey[4] of 29 high-income countries, Baussano and colleagues found that 25 of them screen immigrants for active TB infections — typically with a skin test or chest X-ray, or by checking for symptoms such as a cough. Only a third of those countries screen people seeking entry before arrival; nearly all of them screen migrants soon after they arrive. Just 16 of the countries screened any immigrants for latent TB infection.

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Undocumented immigrants and refugees are at the greatest risk of TB infection, Baussano says, because they often emigrate from countries with a high incidence of TB and live in high-density housing that fosters transmission.

Existing TB screening programmes do a good job of identifying cases in new immigrants, with infection rates typically matching those of the immigrants' country of origin. But it has proven more difficult to prevent new TB cases in people who have recently migrated to cities such as London. His work suggests that marginalized immigrant populations should be screened more closely for TB in the years after they arrive.

TB risk tends to decrease the longer individuals live in a country, presumably after people gain access to health care and more stable housing. And Baussano says that there is no evidence to suggest that the TB circulating among some groups of immigrants ever spreads into the general community.

Unfortunately, in the European Union, there is a political impediment to coordinated TB screening. Procedures vary widely between countries and even between cities, and many cases slip through the region's open borders. "It's not easy to integrate the systems," says Baussano.

MARIANNE LOORENTS/OHTULEHT

TB patients await treatments in Estonia.

TAKING THE STRAIN

One major challenge to understanding the transmission of different forms of TB, such as those that are resistant to drugs or spread more quickly, is identifying them, says Ruth McNerney, a molecular microbiologist at the London School of Hygiene and Tropical Medicine. Related TB strains can differ very little at the genetic level, and most laboratory tests cannot tell them apart. McNerney's team is turning to sequencing the entire genome (made up of approximately 4 million building blocks) of clinical isolates of TB, to track their spread more closely.

McNerney and colleague Taane Clarke are building a reference library of TB varieties so that researchers can easily trace a strain they have identified back to those circulating elsewhere in the world. Even with the cost of genome sequencing falling and states such as the United Kingdom integrating the technology into routine health care, genome sequencing is unlikely to influence care in poor, high-burden countries any time soon, McNerney concedes. But she believes that data gained from sequencing will be used to develop simpler, cheaper tests to discern different strains of TB and help inform treatment.

TACKLING RESISTANCE

Sequencing is also helping researchers to analyse outbreaks of drug-resistant TB, McNerney says. Her team recently looked at strains of drug-resistant TB from people in Uganda who had been hospitalized twice with the disease, comparing the *M. tuberculosis* genomes of the two infections. In some patients, the strains differed very little, suggesting that drug resistance had resulted from poor compliance with antibiotics. But in other patients they differed markedly, says McNerney, and the second infection often matched the genome of a strain circulating in the same clinic. "There seems to be problem of multidrug resistance being shared amongst re-treatment cases," she says.

Whole-genome sequencing can also help reveal the underlying social causes of a TB outbreak. A team led by Jennifer Gardy, a molecular epidemiologist at the British Columbia Centre for Disease Control in Vancouver, investigated an outbreak in Vancouver that resulted in 41 cases of active TB between 2006 and 2008. Genome sequencing revealed that the epidemic was really two outbreaks, caused by distinct strains of TB that had emerged at the same time[5]. Gardy's findings suggested that the rise of crack-cocaine use in the city sparked the outbreaks, with crack houses becoming centres of TB transmission.

Her team also found that a handful of 'super-spreaders' were responsible for transmitting most of the TB cases. Biological factors, such as the levels of TB bacilli in a person's sputum or cough, or a suppressed immune system that allows rampant bacterial replication, may explain this phenomenon, she says. But Gardy's work indicates that social contact is often the most important element of an outbreak. "TB fundamentally is a social disease," she says. "Social factors are what makes an outbreak, versus one sick person who doesn't transmit to anybody else." ■

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