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Totally drug-resistant TB emerges in India

Discovery of a deadly form of TB highlights crisis of 'mismanagement'.

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Physicians in India have identified a form of incurable tuberculosis there, raising further concerns over increasing drug resistance to the disease[1]. Although reports call this latest form a “new entity”, researchers suggest that it is instead another development in a long-standing problem.

The discovery makes India the third country in which a completely drug-resistant form of the disease has emerged, following cases documented in Italy in 2007[2] and Iran in 2009[3].

Atul Loke/Panos

An untreatable form of tuberculosis has been found in India.

However, data on the disease, dubbed totally drug-resistant tuberculosis (TDR-TB), are sparse, and official accounts may not provide an adequate indication of its prevalence. Giovanni Migliori, director of the World Health Organization (WHO) Collaborating Centre for Tuberculosis and Lung Diseases in Tradate, Italy, suggests that TDR-TB is a deadlier iteration of the highly resistant forms of TB that have been increasingly reported over the past decade. “Totally resistant TB is not new at all,” he says.

Since the 1960s, two drugs — isoniazid and rifampicin — have been the standard TB treatment. Although episodes of resistance cropped up periodically, during the 1990s the incidence of multiple drug resistance grew significantly, leading researchers in 2006 to refer to it as extensively drug-resistant tuberculosis (XDR-TB). Surveillance data from the WHO indicate that XDR-TB is present in at least in 58 countries, with an estimated 25,000 cases occurring each year.

Epidemiologist Carole Mitnick of Harvard Medical School in Boston, Massachusetts, agrees that TDR-TB is not new, and points to the history of XDR-TB. “When XDR-TB was first named, it was a phenomenon that had existed but hadn’t gotten much attention before. TB in general doesn’t receive a lot of attention,” she says.

Inadequate care

Part of the increase in drug resistance is related to complications that arise in treating patients who are also infected with HIV — 13% of TB cases, according to the WHO. However, the greatest part of the problem results from the management of the disease.

Although the WHO describes TB as a “disease of poverty”, drug-resistant varieties might best be understood as resulting from poor treatment. According to a 2011 WHO report, fewer than 5% of newly diagnosed or previously treated patients are tested for drug resistance. And it is estimated that just 16% of patients with drug-resistant TB are receiving appropriate treatment.

“The cases are a story of mismanagement,” says Migliori. “Resistance is man-made, caused by exposure to the wrong treatment, the wrong regimen, the wrong treatment duration.”

In the management of TB, many factors affect whether the disease is cured or becomes resistant to treatment. Drug misuse or mismanagement can result if a patient does not follow a full course of treatment, or if the correct drugs are not available or patients with undiagnosed resistant TB receive inappropriate therapies.

Part of the problem also relates to TB testing. The WHO recommends sputum smear microscopy, a test developed more than one hundred years ago, as the standard diagnosis. Although inexpensive, this method is prone to false negatives, does not provide information on drug susceptibility, and test results can take several weeks — a large window of time for a patient to potentially receive the wrong drugs or transmit the infection. However in 2010, the WHO approved a new rapid and fully automated test, known as Xpert, which assesses resistance to the first-line drug rifampicin. As of July 2011, 26 countries are using Xpert and 145 are eligible to

purchase kits at a reduced price.

Drug dearth

The fact that no new first-line TB drugs have been developed for half a century has probably contributed to the emergence of strains that are unresponsive to treatment, says Mitnick. “If you keep using the same drugs for that long, resistance is inevitable.”

Tuberculosis trails behind only HIV as the world’s leading cause of death from infectious disease. But in spite of its impact on human health and economic growth, it has not ranked among the pharmaceutical industry's priorities.

“The pharmaceutical industry had scant interest in TB for decades,” says Richard Chaisson, director of the Center for TB Research at the Johns Hopkins School of Public Health in Baltimore, Maryland. “The industry pretty much concluded it wasn’t an attractive market, there was not enough potential profit.”

But with a growing number of public–private partnerships in research, Chaisson says, industry interest is “an order of magnitude greater than it was a decade ago”.

As of 2011, there were 11 new or repurposed TB drugs in clinical trials that have the potential to either shorten treatment duration or improve therapy for resistant TB. Late-stage studies include a phase III trial by Bayer in partnership with the Global Alliance for TB Drug Development (TB Alliance) to assess whether its antibiotic moxifloxacin can help to reduce the duration of standard therapy from 6 months to 4. Tibotec, also in partnership with the TB Alliance, is in phase II trials for a product that may be useful in treating drug-resistant forms.

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References

1. Udwadia, Z. F., Amala, R. A., Ajbani, K. K. & Rodrigues, C. *Clin. Infect. Dis.* http://dx.doi.org/10.1093/cid/cir889 (2011).
2. Migliori, G. B., De Iaco, G., Besozzi, G., Centis, R. & Cirillo, D. M. *Eurosurveillance* **12**, 3194 (2007).
3. Velayati, A. A. *et al*. *Chest* **136**, 136–420 (2009).