Totally drug-resistant tuberculosis reported in Mumbai

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Late last December, in a letter to the medical journal *Clinical Infectious Diseases*, doctors at the PD Hinduja National Hospital and Research Center in India's largest city, Mumbai, reported that they had confirmed four cases of Totally Drug Resistant Tuberculosis (TDR-TB) at their facility.

Dr. Zarir Udwadia and his team have been grappling with drug-resistant cases of tuberculosis in their clinic for some time. In 2010 they published research showing that incorrectly written prescriptions by doctors working in the private sector health system were a large factor in creating drug-resistance to first- and second-line tuberculosis drugs in the country.

Antibiotics to control tuberculosis have been available for more than half a century. But TB bacteria have shown a resilient capability to evolve drug resistant varieties. Successful treatment of active TB requires several months of medication with more than one type of antibiotic. If treatment is interrupted before all bacteria have been eliminated there is a danger that highly resistant bacteria may infect others and continue to evolve.

The poverty of society as a pump for new and more deadly strains of tuberculosis is an international phenomenon. In the late 1990s a television documentary, *The Coming Plague*, exposed how the collapse of the USSR at the beginning of the 1990s led to a collapse of the public health system. Multi-drug resistant strains of tuberculosis (MDR-TB) found in Europe at the time were thought to originate in areas of the former Soviet Union.

Twenty percent of current infections worldwide involve Multi-Drug-Resistant Tuberculosis (MDR-TB), which is resistant to the commonly used first-line antibiotics. Two percent involve Extensively-Drug-Resistant Tuberculosis (XDR-TB), which is resistant to second-line antibiotics as well.

Together, India and China accounted for forty percent of the nine million cases of tuberculosis worldwide reported in 2010. With the World Bank warning of another major economic downturn, perhaps greater than that of 2008, the cost of containing the tuberculosis scourge will become even more prohibitive.

India has the highest burden of TB of any country in the world, accounting for nearly two million cases in 2010, one-fifth of the world's total. According to the UN World Health Organization (WHO), while the incidence rate in India is very high, the estimated incidence rate in sub-Saharan Africa is nearly twice that of the Southeast Asia Region, with over 350 cases per 100,000 population.

The deadly strain of tuberculosis in Mumbai was cultured and found resistant to all first-line and second-line drugs. But Indian authorities and WHO responded to the national and international media coverage of the report by questioning the doctors' findings and their use of the label TDR-TB.

The *Hindu* reported this week that even after 12 cases of TDR-TB were detected at the hospital, a team of doctors sent by the central government insisted the strain should only be called extensively drug resistant, or XDR-TB, though three patients at the hospital had died of the disease. XDR-TB was first reported in isolated cases in Europe in 2006. TDR-TB was first used in published reports to label 15 cases in Iran in 2009.

WHO responded to a worldwide media furor over the report of the cases in India with a January, 2012 media response objecting to the use of the term TDR-TB. They said the term "'totally drug resistant' tuberculosis is not yet recognized by the WHO. For now these cases are defined as extensively drug resistant tuberculosis (XDR-TB), according to WHO definitions."

For India and for most less-developed countries, tuberculosis is a daily concern. The TB bacillus is estimated to be present in one third of the world population, spread through breathing infected air. In India, over a thousand people every day die of the disease due to inequality, poverty and poor health care and resistance to medications.

Tuberculosis (TB) is a contagious disease that spreads through the air. People infected with TB bacilli will not necessarily become sick with the disease. The immune system "walls off" the TB bacilli which, protected by a thick waxy coat, can lie dormant for years.

Five to ten percent of people who are infected with TB bacilli (but who are not infected with HIV) become sick or infectious at some time during their life. People with HIV and TB infection are much more likely to develop TB.

The burden on individuals, families and communities worldwide from this disease is appalling. *India Times* told the story of Supriya Davare, 20 years old, who they believe is one of the patients diagnosed with the highly resistant strain of the disease. She died in early January, but only after suffering for an extended period.

Her mother, Anita, told the newspaper that her daughter had gone from 42kg to 18 kg as she was unsuccessfully treated for TB in four different hospitals over the long months of her illness. Two others who died were reported to be auto-rickshaw drivers in Mumbai.

Despite the official Indian response to the December report,

including a decision by doctors not to isolate the identified patients, other reports indicate the problem may exist elsewhere in the country as well. A research group in Bangalore's St. John's Research Institute selected 100 TB patients randomly and found six had TDR-TB, 30 had MDR-TB and 13 had XDR-TB. Dr. John Kenneth, Head, Infectious Diseases at the Institute told the Indian press that the data was pending publication.

Tuberculosis had been curable with antibiotics for over 50 years and WHO reported some progress, especially in China, in reducing the number of cases annually in 2011. However, the implications of the XDR-TB discovery are dire. In an article in the same medical journal where Dr. Udwadia's correspondence was published, nearly five years ago another research team from the US called for action on the matter. Principal investigator Dr. Carol Dukes Hamilton of Duke University Medical Center described the problem as complex and urgent even then.

"The emergence of what has been termed extensively drug-resistant TB (XDR-TB) threatens to return TB treatment to the preantibiotic era, when 50 percent of patients with TB died of the disease," the Duke study warned. "The revised definition of XDR-TB is disease caused by bacteria that are resistant to at least isoniazid and rifampin—both first-line TB drugs, resistance to which defines multidrug-resistant TB (MDR-TB)—plus resistance to any fluoroquinolones and resistance to at least 1 second-line injectable drug (amikacin, capreomycin, or kanamycin.) …

"Why should North American and European physicians, scientists, citizens, and policymakers be concerned about increasing rates of drug-resistant TB overseas? Increasing rates of drug-resistant TB directly reflect a breakdown in the adequacy of TB control programs. The breakdown may occur at a local, regional, or national level; an example of the latter can be found in the outbreak of MDR-TB after the collapse of the former Soviet Union. Thus, we should be very concerned that our investments in TB control worldwide—which have paid off, with steady decreases in TB case rates in many countries—may evaporate."

In January, a WHO press release questioned the validity of the in vitro tests. They said: "Thus, a strain of TB with in vitro DST results showing resistance could in fact, in the patient, be susceptible to these drugs."

They also point to new drugs that are being developed as important factors in their decision to write the press release. At the same time, the WHO press release states that just one quarter of people with multi-drug-resistant TB (MDR-TB) in 2010 "were treated in accordance with recommended international guidelines."

Again, in the very same press release the UN agency admits that XDR-TB is, more often than not, lethal. They say: "Data (unpublished) collected by WHO show that just over a half of MDR-TB patients in recent cohorts completed their treatment successfully, and among patients with XDR-TB, death is more common than successful treatment; default and treatment failure rates are also high."

To prevent the emergence of drug-resistant strains, WHO recommends that TB treatments be conducted following a strategy known as a Directly Observed Treatment Short-Course (DOTS). The essence of DOTS is regular supervision by a health-care worker for the duration of the treatment, together with a guaranteed supply of drugs until the treatment is completed.

Dr. Udwadia notes that the country's Revised National Tuberculosis Control Program (RNTCP) does not cover MDR-TB patients, pushing suffering patients into the private health system. The chest physician and his colleagues urged that the treatment of MDR-TB be limited to government sanctioned DOTS-plus programs to counteract the private health delivery system's failures. The inadequate national health system leads the majority of Indian tuberculosis patients to private doctors for treatment.

The team in India has written extensively on tuberculosis and problems in the country's health system. In a 2010 article entitled "Tuberculosis Management by Private Practitioners in Mumbai, India: Has Anything Changed in Two Decades?" they also made startling revelations.

They found the resounding answer to their question was no, with results similar to those discovered in a similar survey 20 years ago. Most alarmingly, the study found that of doctors from the private sector practicing in Dharavi, who were surveyed at a continuing education conference at the hospital, only 5 of the 106 respondents could write an appropriate prescription for treatment of multi-drug-resistant TB.

The tuberculosis crisis is one consequence of criminal inequality in society. Mumbai, population about twenty million and India's financial capital, is the richest city in India. Yet more than half of the city's population are poor and live in crowded and wretched housing in areas such as Dharavi.

According to *Forbes* magazine, Mumbai is also home to Mukesh Ambani, the fourth richest man in the world. His net worth is $29 billion. He runs Reliance Industries, the oil, retail and biotechnology conglomerate that is the largest private sector enterprise in India. He recently built a 37,000 square meter home worth $1 billion in the city.

WHO reports in their 2011 report, *Global Tuberculosis Control*, that 86 percent of funding for tuberculosis control is considered "domestic funding" because it comes from countries battling the disease domestically. This money goes to address the UN agency's modest goal of halving the 1990 levels of prevalence and death rates by 2015. The domestic shortfall for 2011 is $1 billion.