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EMERGING Infections

Drug-Resistant Tuberculosis

Are rates declining or increasing?

It's been decades since the advent of antibiotics and new vaccines, and the apparent victories over diseases such as polio and smallpox, gave us false hope that the total eradication of pathogens was within reach. But these victories were a little premature, and between 1973 and 2003, more than 36 new diseases were identified.[1] In addition to the emergence of these new diseases, which include AIDS and Ebola hemorrhagic fever, old scourges have reemerged, often with heightened virulence or resistance to known drugs. Such is the case with tuberculosis. Although this disease never really went away, it's now become more threatening and dangerous in its drug-resistant form.

"Drug-resistant tuberculosis is a human-made phenomenon, and it arises when either the treatment regimen for tuberculosis is improperly administered or compliance is poor," said Mel Spigelman, MD, president and chief executive officer of the TB Alliance. "A course of treatment, especially for drug-resistant tuberculosis, is long, complicated, and onerous," he continued. "When patients skip doses or take some—but not all—of the medications, resistance may emerge."

According to a recent report from the World Health Organization (WHO), cases of multidrug-resistant tuberculosis are at record levels in some parts of the world, with nearly 50% of cases in India and China. In 2008 there were an estimated 440,000 new cases of multidrug-resistant tuberculosis, accounting for 3.6% of all tuberculosis cases. That same year, an estimated 150,000 deaths were attributable to multidrug-resistant tuberculosis; even in patients who were HIV negative, the fatality rate was roughly 26%.[2]

The recently released data are both alarming and encouraging. In one region of northwestern Russia, 24% to 28% of patients newly diagnosed with tuberculosis were found to have multidrug-resistant disease—the highest rate ever reported to the WHO.[2] At the same time, however, multidrug-resistant tuberculosis appears to be declining in two other areas of Russia—Orel and Tomsk—after having peaked in 2004 and 2006, respectively.[2] Declining rates were also reported in other nations, including Estonia, Lithuania, Latvia, and the United States.

Reporting of multidrug-resistant tuberculosis is too inconsistent and limited to draw any definitive conclusions about the status of the disease. In many countries, sample sizes and study designs have insufficient power to detect small changes and trends. Therefore, the WHO notes that the country-level data reported at this time make it impossible "to conclude whether the [multidrug-resistant tuberculosis] epidemic worldwide is growing or shrinking."[2]

THE PROBLEM OF DRUG RESISTANCE

Mycobacterium tuberculosis has been present in the human population since antiquity. Spinal

A nurse administers a shot to tuberculosis patient Asha Devi, 19, at the state tuberculosis hospital in Gauhati, India. The WHO reports that nearly half of all people with drug-resistant tuberculosis are in China and India, with both countries reporting about 100,000 new cases each year. Photo by Anupam Nath / Associated Press.

column fragments of Egyptian mummies thousands of years old show pathological evidence of tuberculosis, and the disease was also documented by the ancient Greeks and Romans.[3]

Although tuberculosis is both preventable and curable, the emergence of multidrug-resistant forms has greatly interfered with global efforts to slow its transmission and provide effective treatment. As the National Institute of Allergy and Infectious Diseases has written, it's "rapidly becoming a global public health emergency."[4]

Multidrug-resistant tuberculosis has been defined as *M. tuberculosis* that's resistant to one or both of the first-line drugs used to treat it, isoniazid and rifampin. Extensively drug-resistant tuberculosis is resistant to both first-line agents, to any fluoroquinolone, and to at least one of these second-line injectable drugs: capreomycin (Capastat Sulfate), kanamycin (Kantrex), or amikacin (Amikin).[4]

"Extensively drug-resistant tuberculosis was first reported several years ago and defined around 2005," said Matteo Zignol, MD, MPH, a medical officer in the WHO's Stop TB Department. "To date, 58 countries have confirmed at least one case."

California has reported the largest number of multidrug-resistant cases in the country since 2002.

But Zignol emphasized that many cases of extensively drug-resistant tuberculosis haven't been diagnosed because there's a paucity of adequate laboratory and testing facilities in a large number of regions. "The number of actual cases is probably much higher than has been reported," he said.

In 2007, 772 cases of extensively drug-resistant tuberculosis were reported to the WHO from 28 countries, and that number rose to 963 cases from 33 countries in 2008.[2] The low level of reporting has made it difficult to estimate what proportion of multidrug-resistant tuberculosis cases involve extensively resistant strains. For example, of the 27 nations today with a high burden of multidrug-resistant tuberculosis, only Estonia and Latvia routinely test multidrug-resistant cases for susceptibility to second-line drugs. And of those 27 countries, 11 haven't yet reported a case of extensively drug-resistant disease, which the WHO states is more likely a result of a "lack of laboratory capacity than actual absence" of extensively drug-resistant strains.[2]

TUBERCULOSIS AT HOME

Tuberculosis was once the leading cause of death in the United States, but in the 1970s and early 1980s it was believed to no longer represent a threat. Then, after decades of declining rates, the country experienced a tuberculosis epidemic from 1985 to 1992 that caught public health officials off guard.[5] Coinciding with the advent of the AIDS epidemic, scattered cases of multidrug-resistant tuberculosis were reported in New York City in the early 1980s. Within a decade, outbreaks of multidrug-resistant tuberculosis were identified in other states, and epidemics were also reported in other parts of the world.

Declining rates. In contrast to rates of tuberculosis in some countries, overall rates in the United States have dropped. The Centers for Disease Control and Prevention reported an 11.4% decrease in tuberculosis cases in 2009 (from 4.2 per 100,000 population in 2008 to 3.8 in 2009), the largest single-year decrease ever recorded.[6]

"In the United States, multidrug-resistant tuberculosis has markedly decreased, and most cases are in people who were infected outside the country," said William Burman, MD, medical director of the Infectious Diseases Clinic at Denver Public Health. "There's very little transmission in the United States, thanks to a renewed focus on controlling tuberculosis."

But Burman is cautiously optimistic about the recent progress in controlling the disease. "The flipside is that what happens in the world happens in the United States," he said. "We're not an island, so we need to be concerned about what's happening around the world because it will directly affect us."

Increasing resistance in some places. California has reported the largest number of multidrug-resistant cases in the country since 2002, and as of 2006 a study showed that 4.2% of cases were extensively drug-resistant and 18% were considered "pre–extensively drug resistant," meaning they were "multidrug resistant (resistant to isoniazid and rifampin) and resistant to either a fluoroquinolone or an injectable agent, but not both."[7] The authors of that report also note that the proportion of such cases steadily increased from 7% in 1993 to 32% in 2005.

And there's an even scarier trend, according to Burman. Multidrug-resistant and extensively drug-resistant tuberculosis have evolved into their own distinct strains that can be transmitted between people. "It's no longer a disease that occurs because of inadequate treatment, lapses in treatment, or the improper use of drugs," he said. "We're now seeing drug-resistant disease in patients who've never been treated."

Zignol agreed. "We definitely need to shorten the treatment regimen and to come up with therapies that are more affordable," he said.

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FUTURE DIRECTIONS

The WHO has established a target for 2015—that 80% of multidrug- and extensively multidrug-resistant tuberculosis cases worldwide will be diagnosed and treated.[2] To reach that goal, more investment and funding are needed for the development of better therapies and infrastructures in many of the hardest-hit countries.

"It would be ideal to attack the problem of drug resistance from both ends," said Spigelman. "A shorter and simpler treatment for drug-sensitive tuberculosis would help tighten the spout of new drug-resistant cases, and better and shorter treatment regimens consisting of drugs with novel mechanisms of action would be able to treat existing cases of drug-resistant tuberculosis much more effectively than the treatments available today."

Better treatments are also needed for extensively drug-resistant tuberculosis. "We now have a success rate of 50%, and we would like to improve on that," he said. "There are several drugs in the pipeline now that should be available in three or four years."

Accurate, rapid diagnosis of drug-resistant tuberculosis is also needed to ensure that appropriate therapy can begin without delay. However, there's a severe insufficiency of laboratory capacity in the regions most in need of them, Zignol pointed out. "In Africa there are only two laboratories on the entire continent that have the ability to diagnose extensively drug-resistant tuberculosis," he said. "They're in Nigeria and South Africa."

As of 2008, 22 of the 27 countries hardest hit by multidrug-resistant tuberculosis reportedly had an officially recognized national reference laboratory, but only 17 countries reported that there were facilities within their borders that could perform drug-sensitivity testing of second-line drugs, and four other countries had some degree of access to laboratories outside their borders.[2]

To help rectify this situation, the WHO, the Global Laboratory Initiative, and other partners are pursuing the EXPAND-TB (Expanding Access to New Diagnostics for TB) Project, which will invest $87 million in 27 countries, 15 of which have a high burden of multidrug-resistant tuberculosis, over a five-year period. The goal is to increase laboratory services and introduce new technology for the rapid and accurate diagnosis of drug-resistant tuberculosis. ▼

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