[Announcer] This podcast is presented by the Centers for Disease Control and Prevention. CDC – safer, healthier people.

[Peter Drotman] I'm Dr. Peter Drotman, editor in chief of Emerging Infectious Diseases and your host for today. I'm speaking with Dr. Peter Cegielski, team leader for drug resistant TB with the Division of Tuberculosis Elimination at CDC.

Peter is also one of the authors of an important article on the Worldwide Emergence of Extensively Drug-resistant Tuberculosis; it is published in the March 2007 issue of EID .

Within the last few months we've heard a lot about extensively drug-resistant TB – or XDR TB – and there has been a big outbreak in South Africa that has received a lot of media coverage. Peter, what exactly is XDR TB? How does it differ from other forms of drug-resistant TB?

[Peter Cegielski] Thank you, Peter. First, let's clarify the abbreviation. There's been some confusion in the public media. I've heard the disease called "Extreme", "Extra", and other things. But the "X" stands for "Extensively" and the correct name is "Extensively Drug-Resistant TB."

TB drugs were first developed in the 1940s. And since then, about 10 different classes of anti-TB drugs have been developed. Four of them are so-called first-line drugs and the other 6 are called second-line drugs. First-line drugs are the standard drugs used to treat routine, garden variety TB. They're cheap, safe, and highly effective – over 95% of patients with drug-susceptible TB can be cured. When TB is resistant to the 2 main, first-line drugs – isoniazid and rifampin – we call that multidrug-resistant TB or MDR TB. You may remember, in the early 1990s, there were many outbreaks of MDR TB with very high fatality rates – 70, 80, even 90% – especially in HIV-infected patients. In fact, in those outbreaks, death was strongly associated with drug-resistance to the two main, first-line anti-TB drugs. That's how M or multidrug-resistant TB got its name in the first place and also why so much attention focused on MDR TB at that time. With MDR TB, however, you can still treat with the second-line drugs and achieve 70% to 80% cure rates.

Now this is where XDR – or extensively drug-resistant – TB comes into the picture. In the past 15 to 20 years, clinicians have had to use second-line drugs more and more because of the emergence of multidrug-resistant tuberculosis. So, just like with virtually all antimicrobial agents, resistance developed to these same second-line drugs. In the first reports on XDR TB, including the manuscript in Emerging Infectious Diseases, XDR TB was defined as TB that's resistant not only to the 2 main first-line drugs, but also to at least 3 of the 6 main classes of second-line drugs. This kind of TB just cannot be treated effectively, because you have to treat with at least 4 effective drugs, and there just aren't 4 effective drugs left when there's this much resistance. There are no "third-line" drugs, so to speak, that have been proven against TB.

By the way, that definition of XDR TB was revised by a Global Task Force on XDR TB, partly for microbiological reasons, partly for political reasons. So, the new definition of XDR TB is TB that's resistant to the 2 main first-line drugs – isoniazid and rifampin – and, in addition, is resistant to the two most important groups of second-line drugs – fluoroquinolones and injectable agents.

The South African outbreak that's been in the news points to how devastating XDR TB can be and to the importance of taking action quickly.

[Peter Drotman] I see. And how did you first become aware that this wasn't restricted to South Africa and might actually be a global problem?

[Peter Cegielski] I was working with the Green Light Committee, which is an advisory group to the STOP TB Partnership. The Green Light Committee, or GLC, was set up in the year 2000 in response to the global epidemic of drug-resistant TB. The cost of second-line drugs had always been so high that middle- and lower-income countries couldn't afford them. Working with colleagues at Harvard, WHO, and many others, we negotiated a pooled procurement mechanism through which the drug companies gave us massive discounts on the price of second-line drugs, anywhere from 60% to 95% discounts. So countries that needed the drugs applied to the GLC, and then we'd evaluate their program to determine whether they were prepared to treat drug-resistant TB successfully and not make drug resistance even worse. Over the past 6-7 years, we've visited and evaluated over 80 TB control programs all over the world.

When I visited these places I found that physicians were eager to talk about their difficult cases, especially drug-resistant cases. From the very beginning, back in 2000, they would mention 1 or 2 of their patients were "resistant to everything" so to speak. But, in about 2003-2004, all of a sudden, the numbers of patients in these anecdotes jumped into the double digits. We started hearing stories like "We have 17 patients who are resistant to everything." Or, "We have 30 patients who are resistant to everything." That kind of thing. That was worrisome, especially when it was repeated in country after country. So, I checked with the directors of some of the Supranational TB Reference Labs, and they confirmed they were seeing the same thing, each in their own lab.

[Peter Drotman] Hmm…so the beginnings of your global survey began with your travels and your networking. And how did you end up managing to set up a broad network of research partners as quickly as you did and get so many labs around the world to share their key data with you?

[Peter Cegielski] The lab directors were also concerned, of course, because they are the ones who are handling this in their labs. So were the folks at WHO in charge of surveillance for drug-resistant TB. Up to that point in time, they had focused mainly on first-line drugs, but when I asked if they would be willing to collaborate on a rapid survey to get a better handle on the global extent of such highly drug-resistant TB, it was such a compelling issue that they were keen to work together. Led by CDC and endorsed by WHO, the survey had a lot of credibility.

We were fortunate to be supported by this established network of Supranational TB Reference Labs. These labs had a track record of 8 years (at that point in time) of working together and sharing sensitive data in a secure and confidential way and CDC's lab is one of these labs. So the lab network was a critical part of our ability to get the data.

[Peter Drotman] Now your article focuses on the number of XDR TB cases over a 5-year period. Do you think the data identified most of those cases that are out there in these countries? Was there any indication that the numbers are actually increasing?

[Peter Cegielski] Let's consider the data we analyzed. In our report, we had to separate the data from South Korea from the other reference labs. While South Korea routinely tests cultures for the whole panel of second-line drugs, they provided us data for 2004 only. So the results from South Korea may be more representative of that population, but are limited to a single year.

The other 13 labs provided data that included culture results for patients in their own country, so there may well be a referral bias. But in addition, these 13 other labs test cultures from many countries all over the world that participate in the Global TB Drug Resistance Surveillance Project. The results they sent us combined both. That's why we emphasized the number of cases as a percentage of the number tested, not as a percentage of the population. That's also why we emphasized the geographic distribution – in other words, the idea was to get a sense of how widespread XDR TB is. The only trend over time was in the industrialized countries, where both the number and the percentage of XDR TB cases increased.

[Peter Drotman] Now you mentioned that South Korea routinely tests for resistance to the full panel of second-line drugs. Does that mean that other countries' national labs do not do that?

[Peter Cegielski] Good question! And, yes, that's right. Not every lab tests every isolate for all of the second-line drugs. That was one of the challenges in analyzing results from over 17,000 isolates.

[Peter Drotman] So how did you manage that situation?

[Peter Cegielski] Well, we had to take that into consideration and keep clear in our ***own*** minds what the ***denominator*** was, not only for resistance to *each* ***individual*** *drug*, but ***also*** for resistance to ***specific combinations*** of drugs.

[Peter Drotman] Did you face any other controversial or challenging issues in analyzing these data sets?

[Peter Cegielski] *As a matter of fact, we did. One* had to do with making sure the data did not include *multiple specimens* from a *single* person, in other words, one patient:one set of results. We didn't want to be in a situation where one individual TB case might be counted several times in the data from a certain lab or a certain country. By the end of the survey, *we were confident* these results reflected the number XDR TB ***patients***, not the number of ***cultures*** with XDR TB.

The ***other*** challenge had to do with *cross-resistance* between drugs. As an infectious diseases specialist, I'm used to thinking in terms of ***classes*** of anti-microbial agents. But I hadn't

encountered that concept applied broadly to anti-TB drugs. In our analysis, we introduced the idea of *six main classes* of second-line TB drugs, and we had to consider whether resistance to ***one*** drug in a class meant resistance to ***all*** of the drugs in the same class. For *some* drugs, that's true. But for *other* drugs, it's not.

[Peter Drotman] You identified a very serious emerging infectious diseases problem. Do you foresee a solution?

[Peter Cegielski] Certainly not in the short term. We need stronger labs in countries that are most infected by drug-resistant TB. And we need new drugs. But those are years in the future.

[Peter Drotman] Well, Peter, we appreciate your first hand knowledge and your perspective on this serious emerging challenge. Thank you very much.

Our discussion with Dr Cegielski was prompted by the report from a multinational team on the emergence of XDR TB. This article and others on emerging bacterial and viral diseases are available online from www.cdc.gov/eid

Comments on this interview may be sent to eideditor@cdc.gov. That’s eideditor, all one word, at cdc.gov

For Emerging Infectious Diseases, I’m Dr. Peter Drotman.

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