Scratching the surface of ignorance on MDR tuberculosis

In *The Lancet* today, Abigail Wright and colleagues provide the most up-to-date assessment of global multidrug-resistant (MDR) tuberculosis. By contrast with the more than 9 million people with drug-sensitive tuberculosis who can each be cured with US$14 worth of drugs, the 0·5 million patients (as of 2006) with MDR tuberculosis will need to take thousands of dollars’ worth of antibiotics over 12–18 months and will still have an increased risk of death. Rising trends of MDR tuberculosis in some administrative regions of the former Soviet Union suggest an epidemic of an increasingly untreatable airborne disease. The few data for extensively drug-resistant (XDR) tuberculosis, a disease for which treatment options are severely limited, show high rates in the former Soviet Union. Because of inadequate surveillance methods and systems, there are no data on totally drug-resistant tuberculosis. Fortunately, we know how to prevent the emergence of drug resistance: consistent use of good, basic tuberculosis control. The bad news is that this measure is not being done in many affected countries.

These global estimates are based on data for more than 90000 patients from surveys in 2002–07 in 83 countries and territories, and on earlier data, since 1994, for more than 250000 patients. The collection of these data represents a Herculean effort by WHO, the International Union Against Tuberculosis and Lung Disease, and their partners. However, data are still limited: the 250000 patients included in drug-resistance surveillance were drawn from more than 100 million estimated cases, many countries are not yet included, and few countries have trend estimates. Current estimates of the burden of MDR tuberculosis are particularly limited in the countries likely to have the highest rates and numbers of patients with the disease. For instance, no nationally representative data are available from Russia, China, and India.

A combination of sparse sampling, antiquated methods for drug-susceptibility testing, and general neglect of tuberculosis by the global community means that we are still scratching the surface of ignorance on drug-resistant tuberculosis. We know little about the drivers of drug resistance at the population level. Additionally, although the assumption is that the main determinant of multidrug resistance at this level is the inappropriate use of drugs in the past, we do not know by how much future resistance will be determined by transmission of these resistant strains. Little is known about patients with MDR tuberculosis who seek care in the private sector. There is a wide range of biological questions linked with the scaling-up of the diagnosis and treatment of MDR tuberculosis. Although resistance-conferring mutations are known for most strains of *Mycobacterium tuberculosis* with resistance to rifampicin (*rpoB* gene) and isoniazid (KatG and *inhA*), many resistance mutations for streptomycin and several second-line drugs are still unknown, which is a crucial gap in the ability to exploit the power of molecular techniques for the diagnosis and tracking of drug resistance.

Experimental and theoretical population genetics in bacteria offers hope to transform the epidemiology of drug resistance from a descriptive to a predictive science. For example, the propagation of isoniazid-resistant tuberculosis depends on the mutations involved. Furthermore, we need to know the effect of various measures for tuberculosis control, such as basic directly observed treatment, short-course (DOTS), MDR-tuberculosis diagnosis and treatment, and infection control of MDR tuberculosis.

An important step forward for drug-resistance surveillance, as noted by Wright and colleagues, might be the use of simpler survey methods to obtain baseline and trend information from countries with limited infrastructure. Molecular techniques are already available for the identification of most rifampicin-resistant and isoniazid-resistant strains. Efforts should continue to
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expand the database of drug-resistance mutations to make molecular surveillance more useful.7 Such transformational efforts will need concerted global cooperation, including sharing of knowledge, technology, and strains.

Surveillance is a crucial intermediate step to allocate resources and design treatment regimens. But all of thispopulation-based surveillance is a temporary measure until we know the drug-susceptibility profile of every patient on treatment, as happens in the developed world. Fortunately, WHO’s recent endorsement of line-probe assays for isoniazid and rifampicin, which can determine drug susceptibility of acid-fast-bacilli smear-positive samples within hours, represents great progress.11 Rapid drug-susceptibility testing needs to be scaled up so that patients with susceptible tuberculosis can get DOTS, those with single drug resistance can get concierge DOTS to prevent multidrug resistance, and those with MDR disease can get the life-saving treatment they need.

Surveillance data have no value if they do not precipitate action; enough is now known to start urgent action to prevent and control MDR tuberculosis. Exercising basic tuberculosis control more effectively to prevent MDR disease is the highest priority.11 In some settings where the rate of transmission is low, this strategy can be sufficient.11 However, multidrug resistance is already an established problem in many places and additional measures to address these cases are needed in some regions and have been implemented and shown to be effective in others.10–15

Ultimately, the solution for MDR tuberculosis involves new instruments and innovative health-care systems to deliver them. This drug-resistant epidemic is being tackled with antiquated and inadequate diagnostics, drugs, and vaccines. Fortunately, progress is being made: rapid diagnostic tests are in late stages of development, three drug candidates with new mechanisms of action have recently shown positive results in trials, and six vaccines will be in human trials by the end of this year.

Maintaining this momentum will need additional resources and a commitment to innovation from traditional donors, and from countries with emerging economies that are working to address their own domestic tuberculosis problems. Worldwide, there are early signs of action. A group of countries, which together have nearly 45% of the world’s tuberculosis and high rates of drug resistance, are leading new control efforts. In March, Brazil hosted the Stop TB Partners’ Forum in Rio de Janeiro, and China convened a meeting of countries most affected by MDR tuberculosis. India has set an objective for universal access to MDR tuberculosis treatment and South Africa is home to crucial clinical research trials of vaccines, drugs, and diagnostics. These commitments could herald a new framework in global health in which endemic countries with emerging economies stimulate a global response.

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