

## In Pursuit of Better Weapons to Combat TB

Tuberculosis remains a stubborn foe despite the efforts of the public and private sector's efforts to deploy new antibiotics and diagnostic tools against a disease that thrives on poverty and ignorance

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**LENDING A HELPING HAND:** Lubov Potaskaeva, 85 years old and sick with tuberculosis, relies on an outreach program and the aid of a neighbor to treat her disease.  
Merrill Goozner/© Scientific American

TOMSK, RUSSIA— After a half century of neglect, a search for better drugs and diagnostics to treat tuberculosis (TB) is underway. But progress is slow, and the breakthroughs that will help reduce the global burden of TB remain years away.

The modern diagnostics lab under construction in this Siberian capital is a good example. It will shorten the time it takes to identify a case of multidrug resistant (MDR) tuberculosis from two to three months to two or three weeks by using liquid media instead of solid media to grow individuals' samples of *M. tuberculosis* and test them for resistance to first-line treatments. MDR-TB accounts for a shockingly

high 15 percent of cases here, and its misdiagnosis almost always leads to treatment failure.

When the \$1.5-million lab opens in December (built with funding from international aid groups), it will have at best an incremental impact on public health. Because all patients initially diagnosed with TB here are hospitalized in crowded wards, a lab that can quickly

diagnose which of those patients have MDR-TB should reduce the amount of time the other patients will be exposed to a harder-to-treat form of the disease.

It should also improve the MDR-TB patients' survival chances, because it will get them on the proper drug regimen more quickly. "There will be more MDR-TB because of better diagnosis, but that's good because...they will be better treated with the latest technology," says Albert Adamyan, the region's minister of health.

Eventually, however, the health authorities here would like to install DNA-amplification techniques for identifying resistant TB strains, such as those used in a test recently unveiled by the Geneva-based Foundation for Innovative New Diagnostics (FIND). That could shorten the analysis time to two or three days.

But even that method will not meet the needs of the globe's poorest precincts, which account for the vast majority of the nine million new cases of TB each year, a growing share of which are resistant to some first-line drugs. In sub-Saharan Africa and south Asia, for instance, TB treatment is usually offered in rural health clinics without access to sophisticated labs. "What we really need is point-of-care testing for resistance," says Michael Rich, a physician with the nonprofit Partners in Health who splits his time between Russia and Rwanda.

And that is the number one priority for FIND. "Where we're investing the most is in riskier research to develop a dipstick test that can be used in the lowest technology settings," says Richard O'Brien, a former U.S. Centers for Disease Control and Prevention (CDC) official who now runs product development at FIND. "It would be a rapid assay that you could use with blood or sputum or even urine." But such a test is still far off.

The drug regimens for treating both "susceptible" and resistant forms of TB are also badly in need of an overhaul. The World Health Organization (WHO)-approved DOTS regimen (directly observed therapy, short course) isn't very short. It involves taking four first-line antibiotics—isoniazid, rifampin, pyrazinamide and ethambutol—for two months, and continuation therapy with isoniazid and rifampin for another four months. Rifampin, in particular, is problematic because it induces liver enzymes that break down the protease inhibitors used to combat HIV/AIDS, which co-infects many TB patients.

The MDR-TB regimen, meanwhile, is simply brutal. It can last up to two years, and involves taking drugs like capreomycin, which must be injected every day; cycloserine, which patients have dubbed "psycho-serine" because of its mind-bending side effects; or one or more fluoroquinolones. The last are among the most expensive antibiotics on the market, even when acquired through the multilateral purchasing consortium organized by the WHO and CDC known as the Green Light Committee. They also can cause liver problems and tendon ruptures.

Most of the antibiotics deployed against TB were developed in the 1940s and '50s. Over the next half century, virtually none of the new antibiotics that came on the market were

tested against TB, a disease that has probably always plagued mankind (its devastating spread to the bones has been found in ancient Egyptian mummies), but has largely disappeared from the advanced industrial world where new drugs get developed.

Over the past decade, though, substantial new investment has poured into the field. The U.S. National Institutes of Health, the Bill and Melinda Gates Foundation and a handful of pharmaceutical and start-up biotechnology firms invested \$413 million in tuberculosis research and development in 2006, according to a recent report by the New York City-based Treatment Access Group. Although that is less than half what was called for by the WHO's Global Plan 2006–2015, released at the World Economic Forum in January 2006, it makes "money no longer the limiting factor," says Michael Kimerling, who took over the Gates Foundation's treatment program portfolio in July.

Although the pipeline of new drugs is growing, progress has been slow. One group with several drugs in development is the nonprofit Global Alliance for TB Drug Development (TB Alliance). It is furthest along toward shortening the regimen for treating susceptible TB by using Bayer HealthCare Pharmaceuticals's moxifloxacin, a U.S. Food and Drug Administration–approved fluoroquinolone. The drug is being used off-label against MDR-TB because fluoroquinolones have never been rigorously tested as a potential first-line TB treatment.

The goal is to shorten therapy for so-called susceptible TB from six to four months. Enrollment is already underway in a handful of African countries for a 2,400-patient phase III clinical trial that substitutes moxifloxacin for ethambutol. Another arm of the trial substitutes moxifloxacin for isoniazid.

"It won't improve the cure rate, so statistically, it's a noninferiority trial," says Melvin Spigelman, director of research and development for the TB Alliance. "But it would be a superior treatment."

Spigelman wouldn't divulge the terms of the group's license with Bayer, which retains the right to sell the drug in the developed world. But the TB Alliance, largely funded by the Gates Foundation, insists that any drug licensed from a private firm whose development it supports must be sold to the developing world at nonprofit rates. Gatifloxacin, another fluoroquinolone produced by Lupin, Ltd., an Indian generic drug manufacturer, has also entered phase III clinical testing through a consortium that includes the WHO/Special Program for Research and Training in Tropical Diseases, the European Commission and the Paris-based Institute of Research for Development.

Another drug in the Global Alliance's pipeline is PA-824, an experimental compound in the nitroimidazole class that was licensed from Pathogenesis, a small pharmaceutical firm later acquired by Novartis's Chiron. Though it's only gone through early-stage safety tests, preliminary bactericidal studies show it could be effective against both susceptible and drug-resistant TB.

Ironically, TB has lately become interesting to a number of private firms that have entered the fray with drug candidates of their own—developed without prompting or help from nonprofit charities. The fact that TB is still endemic in parts of rapidly developing countries including China, India and Russia suggests to a start-up company like Sequella, Inc., of Rockville, Md., that there could be a \$400-million annual market for a successful new TB drug.

Sequella's prime candidate, SQ109, is chemically similar to ethambutol but has a different action mechanism and could open up a whole new class of antibiotics for fighting both susceptible and resistant TB. It entered phase I human safety tests last year. Otsuka Pharmaceutical Group and the Johnson & Johnson subsidiary Tibotec also have new anti-TB drugs in early-stage human testing. Another estimated 20 drug candidates are undergoing preclinical study in industry, academic and government labs around the world.

"The pipeline is much better than it was four or five years ago," says Jerome Premmereur, a former sanofi-aventis executive who recently became CEO of the TB Alliance. "But we still need much more."

Given how long it takes to develop new drugs, better technology is unlikely to arrive in time to help the WHO meet its goal of cutting the global incidence of TB in half by 2015. To succeed, countries where TB is endemic must develop better health care systems for delivering existing drugs, and reduce the grinding poverty on which *M. tuberculosis* thrives.