



NEWS

# Trench Warfare In a Battle With TB

As tuberculosis took off in Russia in the 1990s, one antibiotic after another failed; the state of Tomsk responded with an epidemic-fighting strategy pioneered by the Boston nonprofit Partners in Health. Deaths have declined, but resistance to drugs remains high

**TOMSK, RUSSIA**—Six mornings a week, nurse Galina Kruchinina circles this Siberian city with a black medicine bag. She's hunting for people infected with tuberculosis—some of them rough customers—who don't show up at the clinic. She and a driver track them down and give them antibiotics. The search this morning leads down a rutted lane near the banks of the Tom River. They're looking for Oleg, 35, who will get three kinds of pills plus an injection, if they find him.

The car pulls up under some tall birch trees. Kruchinina disappears into a wooden building and brings down a sleepy-looking man. It's Oleg, who recently got out of prison, bringing *Mycobacterium tuberculosis* with him. Like many convicts, he has tattoos, including two stark blue ovals inked onto his eyelids that watch you when he blinks. Oleg takes his medicine in the car, accepting

juice and food as part of the treatment from "Mother," as he calls Kruchinina.

If his infection isn't treated continuously for 6 months with a four-drug blitz, it could flourish and kill Oleg. A bigger worry for public health is that intermittent or weak therapy could spawn drug-resistant bacteria.



**Outreach.** The Sputnik (companion) program deploys nurse Galina Kruchinina to find and treat TB patients.

Multidrug-resistant TB (MDR TB), as it's called, is on the rise here and across most of the globe, but luckily Oleg doesn't have it. If he keeps taking his antibiotics twice a day for several more months, he should be okay—which is why Kruchinina and her colleagues seek him out.

Kruchinina and her driver go next into a warren of rickety houses after Ivan, an alcoholic 21-year-old, and his older brother Ruslan, both infected. They've gone away for potatoes, someone says. The medical team doubts this; they track the men to a nearby house. Next they look for Liliana, who's been known

**Tough bug.** *Mycobacterium tuberculosis* (red) likes nothing better than to be ingested by a macrophage, its usual home.

to hide under the furniture; then Alexei, a brawny man in his 30s who lives with his mother. All the patients are difficult at first, says Kruchinina, "but they adapt." At 2 p.m., she gives her seat to another nurse, who completes the day's cycle.

This seek-and-treat program is called "Sputnik" ("companion" in Russian) by its creator, Partners In Health (PIH), a nonprofit linked to Harvard University's Brigham and Women's Hospital in Boston, Massachusetts. Sputnik workers are like family for the 28 people they follow. They reflect the PIH credo that no matter how poor or difficult the patient, the medic's duty is to deliver treatment.

PIH has joined with leaders of the Tomsk oblast, or state, and the Tomsk prison to deploy this aggressive strategy in a place where TB was raging out of control a decade ago. Sputnik is one component of Tomsk's effort, which in recent years has won millions of dollars in international aid. The result, says Harvard-based PIH physician Salmaan Keshavjee, is a program that would be "avant-garde, even in the United States."

PIH doesn't aim to hospitalize patients, as the Russian national TB system often does. Putting people in institutions tends to increase transmission of bacteria, PIH doctors argue. PIH focuses on home treatment or day clinics, with care by nurses or community workers rather than doctors, a method PIH pioneered in Haiti and Peru.

In 1999, PIH founders Paul Farmer and Jim Yong Kim began pushing for changes in international guidelines that once set aside MDR TB patients as untreatable. Farmer and Kim argued that the World Health Organization (WHO) should alter its policy to treat such patients, on both moral and economic grounds (*Science*, 10 August 2001, p. 1049). "If you don't treat MDR TB, it doesn't go away," says PIH doctor Michael Rich: "It only gets bigger and bigger." And the cost of treating each case of TB escalates.

PIH has put its ideas on the line here, making Tomsk a training center for dealing with TB in "resource-limited" jurisdictions. With 5 years of significant outside aid, the results are encouraging, but the statistics are still worrisome. The TB death rate is down; the cure rate is up; but the percentage of new infections that are drug-resistant is higher than in 2002, officially having risen to about 16%. And a new specter looms: extensively drug resistant, or XDR, TB.

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## Where TB lives

*M. tuberculosis* is a tough organism, protected by a waxy lipid coat and an ability to hunker down and fend off immune and chemical attacks. It can travel in droplets expelled from the lungs—studies indicate it may live for several hours this way—and readily infects a new host. Lung infections are the most common, although other tissues can get infected. Poor nutrition increases risk, and some people can't handle the anti-TB drugs or may have an inherited vulnerability to TB. Coinfection with HIV makes TB more deadly, but Tomsk officials say they see relatively little of that.

TB is concentrated in a vast reservoir of the poor, particularly in prisons and hospitals. But everyone is in danger, says Edward Nardell, a PIH doctor, Tomsk consultant, and chief TB control officer for the state of Massachusetts. "The big risk factor is breathing."

Maria Rubina, a young patient at the main TB hospital in Tomsk, illustrates the point. She was diagnosed with TB when she was a student 3 years ago, at age 20. Since then, she has been living full-time in the Tomsk TB hospital, a big pink sanatorium built in 1937 across the river from town. No one knows for sure where she got the infection, but in retrospect, it seems she may have contracted it from a neighbor who died in her apartment complex (not in Tomsk). A postmortem showed that he had MDR TB.

Aivar Strelis, the top surgeon and a renowned TB expert at the hospital, has concluded that Rubina has XDR TB. This means that even the "second-line" products commonly used against MDR TB—the bulky injectables and less potent drugs with nastier side effects—cannot be given to her. A large part of her left lung has been removed. The infection is dormant, meaning that it has lapsed into the latent state of most TB infections, when bacteria are not ejected in sputum. WHO estimates there are a staggering 2 billion people in the world infected with this dormant type of TB. WHO also estimates there are 450,000 new cases of MDR TB each year.

Cases like Rubina's are the legacy of what Sergey Mishustin, the chief TB officer of Tomsk oblast, describes as a "collapse" of the health system after the end of the Soviet Union in the 1990s. He was formerly head TB physician in the Tomsk prison, part of the federal justice system. He recalls that there just wasn't enough money to buy medicines. Ventilation wasn't adequate in prisons or hospitals, and there was little effort to segregate MDR TB prisoners from so-called drug-susceptible cases. A short stay in prison could become a death sentence.

"I was in horror," Mishustin says, to find that medics in one clinic were feeding TB patients whatever antibiotics they had at hand. Because there was no systematic testing for resistance, they were amplifying resistant



organisms in patients already infected with them by wiping out only the competing bacteria. It's called an "epidemiological pump," an effective way to incubate lethal bacteria. In his own clinic, Mishustin says, he wouldn't allow antibiotics to be given this way. When people learned that he left thousands of dollars' worth of drugs on the shelf and threw them out on their expiration date, Mishustin says, investigators accused him of misconduct. But he says he was excused when TB experts came to his defense.

By 2000, the incidence of TB had increased among Russians to more than 107 cases per 100,000 people, according to WHO. For com-

| TB burden in selected countries, 2006 |            |            |
|---------------------------------------|------------|------------|
|                                       | Incidence* | Mortality* |
| Russian Federation                    | 107        | 17         |
| China                                 | 99         | 15         |
| India                                 | 168        | 28         |
| South Africa                          | 940        | 218        |
| United States                         | 4.6        | 0.2        |

\*Rate per 100,000 population.

| TB burden in Tomsk oblast             |       |       |
|---------------------------------------|-------|-------|
|                                       | 2002  | 2007  |
| Incidence*                            | 114.2 | 102.7 |
| Mortality*                            | 18.6  | 12.2  |
| Primary MDR TB, prison <sup>†</sup>   | 12.2% | 18.7% |
| Primary MDR TB, civilian <sup>†</sup> | 13.2% | 14.1% |

\*Rate per 100,000 population. <sup>†</sup>Percent positive among those tested for resistance.

parison, the U.S. rate is below 5 per 100,000 (see table). Since 2000, Tomsk has brought TB incidence to a "stable" state (102.7 per 100,000), Mishustin says.

A British medical group, MERLIN (Medical Emergency Relief International), was the first, in 1994, to bring outside help to Tomsk. The



**Last resort.** Patients in the main tuberculosis hospital may have drug-resistant infections that require surgical removal of part of the lung, explains Aivars Strelis.

group distributed microscopes around this Poland-sized oblast, parts of it unreachable by car, so that medics could examine sputum samples and quickly determine who was shedding infectious bacteria. Billionaire George Soros provided more support in the mid-1990s, then turned the operation over to PIH. Tomsk got a World Bank loan and, with PIH advice, won the first anti-TB grant (for about \$11 million) from the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Through the Global Fund, Eli Lilly and Co. in Indianapolis, Indiana, agreed to provide capreomycin and cycloserine at cost.

Prison and city clinicians say that the joint TB control system they've created here is unique. TB prison doctor Alexander Pushkarev took some Western visitors around to show off the improvements in June. Prisoners are now segregated into 14 wards and separated by medical status. MDR TB cases have a dorm and exercise area. All patients are registered in a 7000-record database, and by law, when they leave prison, medical details are shared with the Tomsk city operation overseen by chief doctor Vera Golubchikova. Her staff keeps tabs on each case and tries to get all of them cured—by Sputnik's team if need be. Both the prison hospital (1000 inmates) and the oblast TB hospital (370 beds, 1000 patients



**Isolation.** In Tomsk's 1000-inmate TB prison hospital, those with multidrug-resistant infections are kept in a separate ward.

reaction tests that monitor variable TB organism genes, signaling within 24 hours whether the strain is resistant to

per year) have new ventilation systems and—a recent addition—airtight cabinets to hold sputum samples while they're waiting to be tested. Basic improvements have made a difference. The prison hospital, which reported 60 TB deaths in one recent year, according to Pushkarev, has had none so far in 2008.

### Making existing tools work

Even in well-funded Tomsk, resource limits are visible. The TB hospital's forbidding "department four" is not much more than a shelter for tough MDR TB cases, a way station on the final descent. In the larger "department three" building next door, MDR TB patients, including contagious ones, live four to a room.

The grim dorms and complex 2-year treatment regimens for MDR patients wouldn't be needed if doctors had a single pill they could give, say, once a day for a couple of weeks and knock out the mycobacterium. No such dream medicine is on the horizon. But several new prospects are in clinical development—for the first time in 4 decades—thanks to work by nonprofits such as the Global Alliance for TB Drug Development and a few companies (see sidebar). Perhaps one will be available in Tomsk in 5 to 10 years.

This is encouraging, but what excites Tomsk TB doctors is the near-term plan for rapid diagnostics. Tomsk oblast has bought a building for a dedicated diagnostic lab, says health department chief Albert Adamyan; by the end of the year, he hopes it will be using liquid media in drug-susceptibility testing.

Drug-susceptibility testing with solid culture media can take several months, and even that isn't done routinely across Russia. The liquid media should enable Tomsk clinics to get results in 3 weeks, officials say. Shorter diagnosis times make it possible to use medicine more efficiently, reduce MDR TB transmission, and attack the worst infections earlier—a critical factor in this battle, says PIH expert Rich.

"What we really need," Rich adds, "is a good, cheap, point-of-service test." Wealthier countries have access to polymerase chain

the first-line drugs isoniazid and rifampin. It's still expensive for Tomsk. But a new, gene-based test that costs \$8 is being promised by WHO and the Foundation for Innovative New Diagnostics in Geneva, Switzerland.

For now, PIH leaders put most of their time and energy into teaching medical workers in places with a heavy TB burden how to use the cheapest susceptibility testing methods and how to deploy antibiotics already in the cabinet. Medics from 10 nations, for example, were in Tomsk in June for training by PIH and

local physicians. Keshavjee chairs an international group called the Green Light Committee that works with drug companies to distribute high-quality TB medicines at cost to programs that meet its standards.

What Tomsk has done, says Neel Gandhi, the AIDS researcher at Albert Einstein College of Medicine in New York City who reported a famous outbreak of XDR TB in KwaZulu-Natal, South Africa, in 2006, "will create a center of excellence and a model" for others. "What works in Tomsk may not work" everywhere, partly because HIV is a bigger factor in Africa, he says; climate, government, and cultures differ. But Gandhi adds, "It would be wonderful to create a center of excellence in South Africa" like the one in Tomsk.

With creative drug cocktails and carefully staged protocols, it's been possible to extend the use of decades-old drugs that are losing much of their punch. But it requires vigilance and huge persistence—the kind provided by Sputnik's workers. That could prove a tall order elsewhere.

—ELIOT MARSHALL

## Anti-TB Drugs: And Then There Were None

Two crucial antituberculosis drugs are valued today precisely because they didn't seem valuable a short time ago. Capreomycin and cycloserine were nobody's first choice when Eli Lilly and Co. in Indianapolis, Indiana, developed them as antibiotics in the 1950s, says Lilly Vice President Gail Cassell. Capreomycin must be injected; cycloserine causes psychosis in 1% or more of those who take it. Patients must be watched closely for central nervous system effects. But because the drugs were little used, bacteria were not widely exposed to them and didn't develop much resistance. Now they are among the best "second-line" treatments for people with multidrug-resistant TB (MDR TB).

In 2001, however, Lilly decided to get out of antibiotics after a "very painful" review of its "limited resources," says Cassell. (Antibiotics are not big moneymakers.) In recent years, nonprofit groups have been working with Lilly and other companies to extend the life of the few effective drugs on a dwindling list. Lilly, for example, makes capreomycin and cycloserine available at cost to programs vetted by the so-called Green Light Committee of the Global Fund to Fight AIDS, Tuberculosis, and Malaria. The company is transferring manufacturing expertise to nonprofits as well. Other companies—such as Bayer, GlaxoSmithKline, Johnson & Johnson, and Novartis—are looking for ways to subsidize antibiotics for developing nations, which need them desperately.

Melvin Spigelman, clinical chief of the Global Alliance for TB Drug Development in New York City, recently drew up a list of the most promising TB drugs on the horizon; it's alarmingly short (see table). Some prospects, such as moxifloxacin, are simply refurbished versions of existing medicines. Even so, when pressed to say when one might be ready for wide use, experts speak of 3 to 4 years at best, not months.

—E.M.

### Near-term TB drug prospects

| Drug type                 | Testing stage |
|---------------------------|---------------|
| Gatifloxacin              | Phase III     |
| Moxifloxacin              | Phase III     |
| Diarylquinoline (TMC207)  | Phase II      |
| Nitroimidazole (OPC67683) | Phase IIA     |
| Nitroimidazole (PA824)    | Phase IIA     |
| Pyrrrole (LL3858)         | Phase I       |
| Diamine (SQ109)           | Phase I       |