Many tuberculosis (TB) experts and health authorities believe that the majority of the world’s drug-resistant TB cases are undiagnosed and untreated. These strains of the airborne disease are resistant to standard antibiotic treatment and present significant challenges in controlling its spread, diagnosing patients quickly and accurately, and using drugs to treat patients effectively. In Russia in recent decades, the rise of drug-resistant TB has been exacerbated by social, political, and economic upheavals. The size of the country presents additional problems in monitoring its occurrence and controlling its spread.

The Institute of Medicine (IOM) Forum on Drug Discovery, Development, and Translation, in conjunction with the Russian Academy of Medical Sciences (RAMS), held a workshop May 26–27, 2010, in Moscow, Russia—the second in a series of international meetings designed to gather information from experts on the threat of drug-resistant TB and ways to combat it. Representatives from the Russian public health community shared their experiences in fighting drug-resistant TB, and participants discussed lessons learned, best practices, and new approaches that can be used worldwide to treat and prevent TB. The workshop was co-hosted by the IOM and RAMS and held at the International Science and Technology Center in Moscow.

**The Nature of the Threat**

Although antibiotics developed in the 1950s are effective against a large percentage of TB cases, resistance to these first-line therapies has developed over the years, resulting in the growing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. MDR TB is resistant to first-line
drugs and must be treated with second-line drugs that are more expensive and more toxic, often require injection, and involve longer treatment regimens (two years or more to treat MDR TB compared with six to nine months to treat drug-susceptible TB).

Gail Cassell, Forum co-chair, Eli Lilly and Co. (retired), emphasized that global estimates of the burden of drug-resistant TB grossly underestimate the magnitude of the MDR and XDR TB problem. She noted that, given the limitations of surveillance systems in many developing countries, statistical models often are used to derive the estimated burden of TB in a community or country. According to Cassell, it is estimated that only 10 percent of new MDR TB cases are treated each year, and fewer than two percent of patients are receiving verifiable, quality-assured second-line anti-TB drugs. She stressed that, among the small population of patients receiving treatment, many are not receiving drugs that actually address their drug resistance profile, and therefore their treatment is ineffective.

### Burden and Spread of Drug-Resistant TB

Workshop presenters described the tremendous global health burden posed by drug-resistant TB. Salmaan Keshavjee, Harvard Medical School, noted that globally over the next 10 years, five million new cases of MDR TB will occur if current incidence rates persist, and if current mortality rates continue, more than one million people will die. He added that many countries are reporting increasing levels of XDR TB, and the number of totally drug-resistant TB cases is completely unknown. He suggested that a major transformation is necessary to have a meaningful impact on this growing epidemic.

According to Mikhail Perelman, Moscow Medical Academy, the breakdown of the Soviet Union exacerbated TB by increasing unemployment, poverty, migration, and social unrest. He added, however, that the situation has been slowly improving over the past decade. Elena Skachkova, Central Research Institute for the Organization and Informatization of Health Care, presented information about developments in the surveillance and tracking of incidence of drug-resistant TB in Russia. She noted that the number of MDR TB cases in Russia has increased over the past decade, although part of this increase is attributable to improved surveillance.

Speakers addressed prevention of transmission of MDR and XDR TB. The workshop presenters’ key messages regarding transmission patterns and infection control included:

- Even many patients previously treated for TB acquire MDR TB through transmission rather than through the evolution of resistance in an ongoing infection.
- Prompt and effective treatment stops transmission, even among patients who remain smear positive.
- Systemic and long-term infection control measures within hospitals, including use of ventilators, bactericidal lamps, and mechanical ventilation, could be useful in reducing nosocomial transmission.

### Needs for Diagnosis and Treatment of Drug-Resistant TB

A number of workshop participants observed that an inability to diagnose drug-resistant TB rapidly and accurately is contributing to the severity of the DR TB epidemic. Workshop presentations summarized new molecular-genetic methods, including gel-based biological microchips, that can reduce diagnostic intervals to as little as one to two days. Jeffrey Drazen, *New England Journal of Medicine*, urged that quantitative research techniques be used to study the new diagnostic methods to determine sensitivity and specificity relative to standard diagnostic techniques.
Dale Nordenberg, Novosano Health and Science, stressed that laboratory information management systems allow use of diagnostic results to maximum advantage and monitoring of treatment results, but global laboratory diagnostic capacity is desperately insufficient. He noted that the effectiveness of these laboratory information management systems would be enhanced if information could be shared in common public health databases even if the information management systems were based in different technology and software platforms.

The workshop presentations and discussions highlighted a number of challenges and open questions for consideration in efforts to improve the treatment of drug-resistant TB, including:

- Aggressive drug therapy can increase the range of options for MDR TB patients.
- HIV infection is a major driving force behind the TB epidemic in adult populations.
- Adherence is the key to treatment success for both TB and HIV.
- The combination of aggressive drug treatment and surgery, which is widely used in Russia, can improve the outcomes of patients with MDR TB.
- An important component of an effective public health treatment program is the promotion of scientific research into new technologies and methods of diagnosing and treating patients and the rapid incorporation of scientific innovations into the program.

Unique Challenges for Addressing Drug-Resistant TB in Vulnerable Populations

Speakers at the workshop addressed TB and drug-resistant TB among three particularly vulnerable populations: children, people with drug and alcohol dependencies, and the incarcerated. Their key messages included the following:

- Pediatric TB is generally underreported since children can be difficult to diagnose and are often overlooked or slighted in TB statistics.
- Treatment of children calls for quality-assured pediatric formulations with standard regimens.
- Interventions in the lives of TB patients who suffer from alcohol or drug dependence can greatly reduce treatment default rates and the spread of drug-resistant strains.
- Despite an increase in HIV infection rates, the number of active TB patients in Russian prisons has fallen by more than half over the past decade, in part because of more effective diagnostic and treatment programs.

Access to Needed Drugs for Drug-Resistant TB

Cassell and other workshop participants highlighted the need for new TB drugs to treat the variety of emerging drug-resistant strains, as well as cases that are considered to be untreatable with
existing drugs. Margaret Hamburg, Commissioner of the U.S. Food and Drug Administration, presented at the workshop about the importance of new therapies. She emphasized that regulatory science—the knowledge and tools needed to assess a product’s safety, efficacy, quality, and performance—serves as the critical link between biomedical research and safe and effective new medicines and therapies, including combination therapies, stem cell therapies, and pediatric TB therapies.

Keshavjee described the situation with respect to access and supply of second-line drugs for MDR TB as being characterized by an inadequate number of manufacturers of these drugs, a limited supply of quality-assured drugs, and insufficient forecasting of need that contributes to opaque markets for drug manufacturing. Second-line drugs also have seen serious delivery delays. Paul Zintl, Partners In Health, described a paradigm shift that is taking place with respect to the second-line drug supply chain—from reliance on the existing Green Light Committee (GLC) drug qualification mechanism to countries’ assuming responsibility for the supply of quality drugs for their populations. He noted that, because of the magnitude of scale-up plans, risks of poor program implementation and supply of poor-quality drugs remain. Zintl expressed the hope that the GLC and World Health Organization will create the necessary mechanisms to monitor these risks and encourage countries themselves to ensure proper program implementation and quality drugs.

Need for Social Medicine Perspective and Collaborative Approaches

Several workshop presenters emphasized the need for a social medicine perspective and collaborative approaches to address the problem of drug-resistant tuberculosis. Paul Farmer, Partners In Health, suggested that a social medicine perspective is useful in understanding the causes of the development of drug-resistant strains of tuberculosis and is essential in considering new diagnostics, new therapeutics, or programs to prevent and respond to drug-resistant TB, particularly in Russia, where social vulnerability is a leading cofactor for TB.

Hamburg noted that success in the development of new TB diagnostics and drugs will depend on outreach and collaboration. She added that regulators must be active participants in research and development through partnerships with academia, industry, and government agencies, and she emphasized the importance of the sharing of clinical trial data across regulatory authorities to answer important questions of safety and efficacy. She noted that, on the morning of the workshop, she met with Russian regulatory authorities (Roszdravnadzor) to sign a Statement of Intent on Collaboration between the U.S. Food and Drug Administration and the Federal Service on Surveillance in Health Care and Social Development of the Russian Federation (agreed to on May 27, 2010).