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COMPARATIVE CONTEXTS

THE STANFORD NORTH KOREAN TUBERCULOSIS PROJECT[1]

Sharon Perry

Building professional exchange with North Korea focused on mutual interests in control of tuberculosis (TB) has potential to address a growing health crisis for Northeast Asia, while also opening new perspectives in cooperative health policy to enhance prospects for peace in the region. This chapter describes ongoing efforts of Stanford's DPRK Tuberculosis Project to develop research collaborations with the North Korean Ministry of Public Health (MOPH) centered on building cooperation for prevention and control of drug-resistant TB.

Background

1) Tuberculosis and Health

M. tuberculosis (Mtb), the cause of human TB, infects over one third of the world's population, causing nine million cases and three million deaths each year, primarily in the developing world.[2] Despite these grim statistics, the normal human immune system is substantially equipped to fight a TB infection.[3] Of those exposed to an infectious TB case, only 30% are thought to develop the state of latent infection, during which the host remains healthy, but TB bacilli may survive for decades within clusters of immune cells. However, in 10% of these latently infected persons the latent state is terminated by the development of active disease characterized by a fatal outcome and dissemination of the TB bacillus to ten to twenty other persons. Risk factors associated with progression to the active form of the disease include malnutrition and other conditions that compromise the immune system.

Although antibiotics have greatly improved the treatment of active TB, current therapy requires the combined use of four different antibiotics administered in an uninterrupted matter for at least six months. The use of fewer drugs, interruption of drug therapy, infection with drug-resistant strains, and inadequate nutrition can result in treatment failure. In turn, treatment

failure results in a poor clinical outcome (including death) in the generation of drug-resistant strains and in the dissemination of these strains to other persons. If inadequately treated persons migrate or cross national borders, then the regional spread of these strains can be expected to occur.

2) Tuberculosis and the Emergence of Drug-resistant Strains

The discovery of curative drugs in the middle of the 20th century, including their application to massive global public health campaigns, came at a critical time in the political realignment of the postwar world and the emergence of modern global markets. These developments have fundamentally altered the course of TB epidemics, particularly in the West.

By the late 20th century, however—within the short span of one human generation—two developments began to threaten these gains.[4] The first was the emergence of the AIDS epidemic, a disease that attacks the same immune cells required to control a TB infection. The second was the emergence of new drug-resistant strains of TB.[5] Multi-drug-resistant strains, which have proven 20–50 times more costly to treat with cure rates only marginally better than in the pre-drug era, now account for more than a half million TB cases each year.[6,7] An important epicenter of the global drug resistance epidemic is in states of the former Soviet Union, where as many as one in ten TB patients are multi-drug-resistant.[8] Resistant strains from this epicenter have now been tracked by molecular fingerprinting methods into Western Europe, the Middle East, and even South Africa. This experience shows that drug-resistant strains of TB, generated in one region as a consequence of failed public health programs, can disseminate to spawn outbreaks of drug-resistant disease both regionally and remotely.

For much of the 20th century, TB care in the former Soviet Union advanced in line with the West. Drug-resistant strains may have emerged during the period of economic destabilization that accompanied collapse of the Soviet bloc in the 1980s.[9,10] Thus, both the TB epidemic associated with AIDS in Africa and the emerging epidemic of multi-drug-resistant strains in the former Soviet Union have found their niche in vulnerable states with radically different social and economic development agendas than the developed Western economies.

3) Origins of the North Korean Tuberculosis Epidemic

During the 1960s, North Korea implemented a universal health care program (Article 72 of the Constitution), and the "#3 TB Department" of the MOPH built a multi-tiered residential treatment system for TB. This system, which includes approximately 225 remotely located 60–70 bed tuberculosis "rest homes" in each of the country's counties and municipal districts, established a WHO-sponsored "directly observed therapy" short course (DOTS) program in 2001. The country relies almost entirely on external assistance for essential

TB drugs and diagnostic supplies. Since 2002, more than 90% of this support has come through WHO-sponsored commodities programs. In June 2010 the country was approved for two years of support from the Global Fund against AIDS, Tuberculosis and Malaria. The country is ineligible for health sector development support, such as from the World Bank, IMF, or Asian Development Bank.

Health indicators provided by the MOPH for 1994, the period just before the great famines, depict a TB incidence rate of about 38/100,000 population. These estimates are likely inaccurate; however, in 2002, estimated incidence had risen to 220/100,000.[11] For 2010, North Korea is expected to report nearly 100,000 new TB cases, for a rate of 345/100,000 population,[12] one of the highest in the world outside of sub-Saharan Africa. Chronic food shortages as well as inadequate drug supplies have continued to fan the epidemic.

4) Implications for Northeast Asia

TB departments throughout much of Northeast Asia were isolated from the West during a critical period of advancement in laboratory technologies and outpatient drug management. More than 100,000 cases of drug resistance, over one-fifth of the global incidence, are thought to emerge in China each year. In two Chinese provinces bordering North Korea (Liaoning and Heilongjiang), sentinel laboratory studies have reported that as many as 10% of new TB patients and 35% of previously treated TB patients harbor multi-drug-resistant TB strains.[13] These rates are two to three times higher than corresponding global averages. The DPRK TB epidemic has significant repercussions for the epidemiologically fragile communities of Northeast Asia.

The Stanford DPRK Tuberculosis Project

Stanford's DPRK Tuberculosis Project began in 2007 as a unique undertaking of Asian policy specialists from Stanford's Freeman Spogli Institute (FSI) and medical faculty from the School of Medicine (SOM). In January 2008, with sponsorship from the Center for International Security and Cooperation (CISAC, Lewis) and the Walter H. Shorenstein Asia-Pacific Research Center (APARC, Shin), Stanford School of Medicine organized the Bay Area TB Consortium (BATC) to host five MOPH health officials for a week-long visit to Stanford for joint discussions with Bay Area TB experts and officials of the U.S. CDC and the WHO. Out of these discussions emerged Stanford's DPRK Tuberculosis Project which seeks to develop professional engagement opportunities with North Korea focused on mutual interests in tuberculosis control.

With funds raised through the Global Health & Security Initiative of the Nuclear Threat Initiative, the Project purchased a WHO-recommended inventory of TB laboratory equipment and supplies and formed a partnership with the U.S. NGO, Christian Friends of Korea (CFK) to assist with in-country

logistics, export licensing, and physical infrastructure requirements. Since the spring of 2009, joint Stanford-CFK teams have completed six trips to Pyongyang and made a combined contribution of over $500,000 to remodel and equip a 13-room, 2500+ square foot space at the #3 TB Hospital for reference-level quality assurance, TB culture and drug susceptibility testing services. Over 30 different MOPH personnel worked in tandem with U.S. work teams in all phases, and 14 North Korean physicians and technicians have participated in orientation workshops and training self-assessments organized by Stanford-BATC expert laboratory teams.

The project also developed important networks with officials in Washington, Beijing, New Delhi and Pyongyang to raise awareness of the North Korean TB epidemic. These efforts were instrumental in triggering resumption of negotiations for a Global Fund award to North Korea and in convening U.S. government and world health officials for a face-to-face meeting regarding long-term funding needs of the DPRK TB control program.

On October 18, 2010, DPRK's first national TB reference laboratory was formally opened in a ceremony attended by representatives of the Stanford BATC, CFK, the Ministry of Public Health, the WHO, and the new Global Fund agent for DPRK, UNICEF. The new laboratory was reviewed and commended by WHO Director General Dr. Margaret Chan during her first visit to North Korea in April 2010. The project has been covered by several publications, including articles in *Science*, *The Lancet*, and *The British Medical Journal.*

Opportunities

We have established a new and viable partnership with the DPRK Ministry of Public Health to work on mutual interests in TB control. The collaboration with CFK has also vetted several contingencies necessary for launching an initiative of this type in North Korea. These include the integration of humanitarian and scientific expertise, as well as coordination with export compliance authorities and world health officials. Within DPRK, the project has high credibility for its momentum, follow-through and multiple capabilities. The process of implementing this project has created a highly successful model of cooperative effort with potential to expand professional engagement opportunities with North Korea focused on mutual health security interests.

To prepare for its role in national TB control, the new reference laboratory must undergo international inspections and participate in field trials designed to assure the reliability and quality of laboratory results. Ultimately, the plan is to develop capacity to test several thousand specimens per year by culture, with drug susceptibility testing (DST) on selected cultures. The laboratory is also expected to develop capacity to provide surveillance for the national TB control program, to determine prevalence of drug resistance in North Korea,

and to guide treatment in patients suspected of having drug resistance. We believe these goals are feasible over the next two to three years, particularly if MOPH is able to continue its professional collaborations with projects such as ours and develop affiliations with international reference laboratories. The high education level in DPRK, and the competencies observed by the BATC training team also suggest that MOPH possesses human resources to make a successful "generation leap" in TB laboratory technology. Toward this end, the project has defined the following near-term objectives:

1. Support establishment of external technical assistance and quality assurance affiliations for the new laboratory.
2. Develop academic exchange opportunities, enabling DPRK Ministry of Public Health officials to study at Stanford and for MOPH to receive Stanford researchers in DPRK.

Tuberculosis Engagement as a Model for Educational Exchange

Educational exchange focused on common interests in controlling drug-resistant TB offers several potential advantages. First, as illustrated by the Soviet MDR experience, drug resistance is exacerbated by isolation and economic destabilization, and these epidemics leave costly legacies behind. Second, prevention of MDR-TB requires coordinated international approaches, including technological infrastructure for resource-limited settings. Third, tuberculosis programs are supported by an established international medical and academic fraternity that is remarkably coherent in its professional standards and practices. Through the World STOP TB partnership, the U.S. CDC, and the International Union against Tuberculosis and Lung Disease, this professional community was one of the first to exploit modern communication networks to build training, consultancy, and quality assessment resources. Linking North Korean public health officials to this vital pedagogic community could help spur broader assimilation with the international health community.

Notes

[1] The paper from which this chapter is drawn has been previously published in two formats. See Sharon Perry, Heidi Linton, and Gary Schoolnik, "Tuberculosis in North Korea," *Science* 331 (21 January 2011): 263; and Sharon Perry, Louise Gresham, Heidi Linton, and Gary Schoolnik, "Engaging North Korea on Mutual Interests in Tuberculosis Control," *KEI Academic Paper Series* 6, no. 2 (February 2011): 1–12.

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