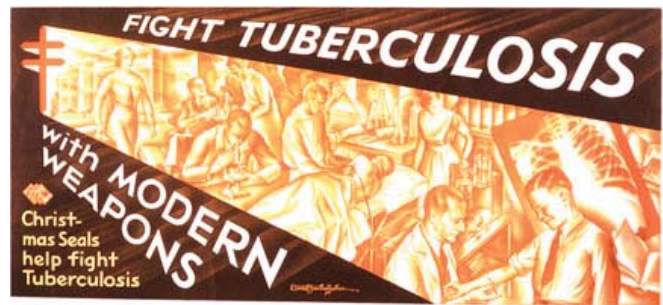


# MDR Tuberculosis: A Case Study for Non-Science Majors Focused on Social Justice

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## Part I—Drug Resistant TB on the Rise

The phone had been ringing all morning. Aisha picked up the receiver and, after a few moments of conversation, put the caller on hold. She turned to her mentor, Dr. Sanjari, who was busy shuffling through a pile of paper and asked “Do you want to take this call?” Barely taking her eyes off the stacks of paper, Dr. Sanjari replied “English or Spanish?”

Ever since the *Morbidity & Mortality Weekly Report (MMWR)* had come out a couple of weeks ago, the Division of TB Control at the New York City Department of Health (NYCDOH) had been bombarded with phone calls from concerned citizens and policy makers. The publication of the report coincided with World TB Day, March 24<sup>th</sup>. Aisha always thought it was interesting that even though only 10% of those exposed to TB became infected, one-third of the world’s population was currently infected with the bacterium that causes tuberculosis. So the World Health Organization (WHO) dedicated a day to TB to raise international awareness of the nine million new infections and the two to three million deaths caused by this disease each year. Since 1982, World TB Day has served to promote advocacy for prevention, screening, and treatment of tuberculosis.

Soon after starting her DOH internship, Aisha realized that New York City, like many urban centers, had experienced a TB outbreak because TB control had become lax. For many years, TB rates were low, so funding for TB public health programs were cut. But in the late 1980s, HIV and increased immigration both contributed to higher rates of TB incidence; HIV+ individuals were susceptible to new infections, while recent immigrants were entering the country with high rates of latent TB infection, which had the potential to develop into disease later in life. Other more consistent factors, such as drug abuse, incarceration, and poverty, continued to fuel the outbreak.

Aisha recognized that poverty could result in inadequate health care and that drug abuse could weaken the immune system and the sharing of unclean needles could spread HIV, but she had been unaware of how incarceration could lead to higher rates of transmission. As an intern, Aisha learned that prisoners in cells share the same air for extended periods of time, and movement within the prison system as well as the cycling that occurred between the prison and general population presented a challenge in terms of monitoring patients’ completion of extended TB treatment. New York City was able to mount an aggressive TB control program to reduce the transmission rate and provide treatment, resulting in a 95% drop in case rate.

But beyond the city, TB rates continued to rise. Though antibiotic treatment and vaccination exist for the disease, Aisha was discouraged to learn that in communities around the world many people did not have access to TB screening and treatment facilities. For those who had access, other challenges surfaced; women

who were concerned about their marriage potential would avoid a TB diagnosis for fear of rejection, others were not interested in knowing their diagnosis if there were no funds for treatment.

Aisha saw the international situation as important, since TB is transmitted through aerosol droplets that are dispersed when someone who has the disease coughs. Those who are in close contact for sustained periods of time are most at risk and these are often the children of those with the disease. As people continued to move from rural areas to urban centers to find work, TB often migrated with them, and these urban centers were populated with people from around the world. Aisha knew from her first days at the internship that “TB has no borders,” and she was not surprised that in 1993 the WHO declared TB a global emergency, emphasizing the importance of solidarity in fighting this epidemic.

As a DOH intern, Aisha was particularly interested in outreach that could increase New Yorkers’ awareness about TB screening and treatment, and minimize the stigma associated with the disease. She was researching international programs and hoped to identify those that dropped the TB case rate but did not further discriminate against those most underserved by society—underrepresented minorities, the poor, sex workers, drug users, and prisoners.

What was interesting to Aisha was that in her “History of Medicine” course she had read about affluent and prominent individuals who had suffered from tuberculosis. Keats, the Bronte sisters, Kafka, and Chopin were all revered for their work and contributions to society, and the disease was portrayed as an affliction of passion or a curse of the talented. How ironic, she thought, that with improved healthcare, living conditions, and nutrition, those with access to these resources no longer suffered, relegating the disease to the margins of society where health was no longer seen as a human right.

Her internship last year on the “Access to Essential Medicines Campaign” at Médecins Sans Frontières (MSF) had given her hope. There, she learned about Partners in Health, a program founded by physicians Paul Farmer and Jim Yong Kim. They developed the program to provide second-line antibiotics to individuals infected with multi-drug resistant TB (MDR TB). Though these antibiotics proved more toxic, less effective, and more costly, under directly observed treatment (DOTS) the program was successful in saving the lives of entire communities. Their work convinced the WHO to revise their guidelines in 1999, which until that time recommended no treatment for individuals with MDR TB. In an effort to expand DOTS-Plus (DOTS plus second-line antibiotics), the WHO established the Greenlight Committee in 2000. This committee works with programs and pharmaceutical companies to secure the necessary drugs at 99% less than the open market price.

But now the MMWR was making Aisha anxious. The report had been picked up by the media, and the inflammatory information about the rise in drug resistant TB and the distribution of these cases in the population could be presented in a way that would reverse all the positive outcomes of the last year. Aisha hoped the “cycle of neglect” that left marginalized populations infected with TB would not be revisited and she scanned the report to look for positive indicators. On the one hand, the report presented good news. The U.S. TB case rate was at an all time low in 2005. But the decline in case rate was leveling off, and those who continued to be infected were those with inadequate health care due to financial, linguistic, cultural, or legal barriers. This is what had Aisha most concerned. The TB rate in foreign born individuals was 8.7 times higher than U.S. born. Equally upsetting was that Black Americans had a 7.3 times higher TB rate than white non-Hispanic Americans. The statistics on drug resistance were just as dire. Drug resistance was becoming more extensive and more frequent. In 2004, the number of MDR TB cases increased by 13.3%, the largest one-year increase since 1993, the peak of the period of the TB outbreak in New York. Furthermore, the countries of origin for these foreign born cases were identical to those with the highest rates of immigration.

Aisha stood up and went to speak to Dr. Sanjari, who had returned to her office. Enough mulling things over. They needed to develop a plan to counteract any potential damage that might stem from the recent news. She knocked on Dr. Sanjari's door and broached the subject: "What do you make of the news coverage of the report?" Dr. Sanjari looked up and said, "Well, we certainly have our work cut out for us."

Aisha agreed and reminded her of the case in California, "Remember that high school student, Debi French, who was infected with TB by a Vietnamese peer? She ended up losing a lung, suing the department of health, but in the end, became a poster-child for extremely drug resistant TB, and never placed blame on the immigrant student. Instead she raised awareness for the need for better diagnostics and screening protocols. Her illness demonstrated that anyone can contract TB. The healthy, the young, no one is immune."

Dr. Sanjari suggested that they focus on the portions of the report that would most affect New York City. What puzzled Aisha and Dr. Sanjari was the new nomenclature "XDR TB." The Centers for Disease Control and Prevention (CDC) wanted to distinguish XDR TB from MDR TB. The latter is resistant to first-line antibiotics, while XDR TB is resistant to all first-line and three of the six second-line antibiotics. Dr. Sanjari turned to Aisha and said, "As you know, this kind of bacteria, 'XDR TB,' has caused one to two cases of TB in New York City every year since the last major outbreak in the early 1990s." She turned the page and noticed that in the same MMWR there was another report titled "Emergence of a *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004." Dr. Sanjari wrinkled her brow and read the grim statistics of the report, "The case rate of XDR TB increased from 5% to 7% between 2000 and 2004." She sighed, "In just four years this thing has spread around the world, and some of these strains are no longer responding to any antibiotics we have available. I hope those six new antibiotics specific for TB hit the market soon. If not, we could have a serious problem on our hands here in the city."

Aisha then noticed something of particular importance to urban centers that serve as ports of entry for immigration, "The percentage of MDR cases that were XDR were 4%, 19%, and 15% in the U.S., Latvia, and South Korea, respectively." Because she had studied the New York City TB epidemic in the early 1990s, she was aware that the TB strain, W/ Beijing, had migrated from the Russian prison system to New Jersey and New York. DNA fingerprinting had revealed the similarities in the strain's drug resistance genes. But she did not understand the inclusion of South Korea in this study, so Dr. Sanjari explained, "South Korea is one of the few countries that performs a drug susceptibility test on all its culture-positive TB patients at its National Reference Library."

Dr. Sanjari anticipated that inquiries about the report would become more frequent, so to prep Aisha for phone duty she asked Aisha to join her in a debriefing meeting to review the protocols for answering some of the most pressing and challenging questions. She stressed the importance of answering these questions from a biological and social perspective.

*Read the following articles, view the videos, and try to answer the questions that callers might pose to Aisha.*

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## Questions

1. Who is at risk for contracting and developing TB, and why?
2. How do antibiotics stop or slow bacterial growth? What do they target?
3. What are the scientific factors that influence the development of drug resistant TB?
4. What is XDR TB and what social factors contributed to the increase in cases?
5. Why has the NYCDOH chosen to employ DOTS to minimize the development of drug resistance? What are the major components of the DOTS program and how do they address the scientific and social factors which influence the development of drug resistance?
6. Why are people on the margins of society more susceptible to developing drug resistant infections?
7. What do these percentages and rates mean; how many cases are there per year?
8. Are there new treatments on the horizon for XDR TB? Why are pharmaceutical companies reluctant to develop drugs to combat this kind of TB? How are public health organizations shaping the future of drug development?
9. Can I vaccinate my child for TB?
10. If my child is vaccinated, is he/she protected from MDR TB?



## Part II—The Challenge of Public Health in an Age of Immigration

Over the next few months, the call load at the Division of TB Control died down. Aisha continued to work on public outreach programs and to consider ways that the Directly Observed Treatment Short (DOTS) course programs could be expanded. One thing that Aisha really liked about DOTS was the inclusion of community workers and the fact that the drugs were taken to the patient, lessening the burden on the patient. Patients trusted those who were familiar with their needs, culture, language, and challenges, and thus were more likely to comply with the daily dose of antibiotics over a six- to 12-month period. Aisha came across programs that went a step further to provide patients with food, shelter, and money in exchange for the antibiotic treatment. Still, there were challenges.

There was something else troubling Aisha as her internship was coming to a close. The Senate Immigration Bill had jumped over many hurdles and many believed the President would approve it, allowing close to two million illegal immigrants to apply for citizenship in the next two years. Aisha was surprised to see the newspapers neglect the impact such a bill would have on the public health infrastructure and especially TB screening for latent TB infection (LTBI). The most recent drug susceptibility reports indicated that more than half the foreign born disease cases were in persons from Mexico, the Philippines, Vietnam, India, and China, with the largest contribution from Mexico. More disconcerting was that 50% of all foreign born MDR TB patients were from Mexico, that California accounted for 30% of the total MDR TB cases in the U.S., and that immigrants with LTBI converted to active disease within the first few years of entry. “If only we could screen and treat these latent infections before disease developed,” Aisha thought to herself.

By federal law, anyone 15 years or older applying for citizenship in the U.S. must undergo TB screening via x-ray and, if positive, undergo an additional test to clarify the disease status. Test results determine whether the person can enter or needs to follow a course of treatment before entry. Individuals who test positive for latent infection via x-ray are allowed to enter and are not required to be treated. Individuals who test positive for disease via x-ray but negative via sputum are not infectious and allowed to enter without treatment. Individuals who test positive for active disease via x-ray and sputum test are required to undergo treatment before entering the U.S. and the cost of treatment is the responsibility of the patient.

Aisha reviewed the Senate bill carefully. The bill had two provisions that were of interest to her: (1) illegal immigrants who had been in the U.S. between two and five years were required to leave the country and reenter; (2) those who had been in the U.S. longer than five years would stay and apply for citizenship from within the U.S. In both cases, these individuals would be subjected to TB screening. For those required to reenter, anyone diagnosed with active infectious disease would need to undergo treatment before reentry. If they were unable to secure the essential antibiotics in their country of origin, they would be blocked from reentry. For those immigrants applying for citizenship from within the U.S., a diagnosis of active infectious TB disease would require administration of antibiotic treatment and it was unclear who would cover this cost. The cost could be substantial and compliance sketchy. Should anyone be diagnosed with MDR TB disease, the length of treatment could extend to 24 months, and the individual could be asked to stay home until they were no longer infectious. This could be especially problematic for the 1.5 million farm workers who would apply for citizenship under the guest worker provision. Their citizenship would be sponsored by their employers, who would expect them to be working every day.

“How could the media neglect this from the long laundry list of other requirements, which includes learning to speak English, undergoing a criminal background check, paying back taxes, and fines?” Aisha thought to herself. She did a quick literature search and came across an appalling editorial that proposed deportation of all illegal immigrants and no access to healthcare or treatment as the country was unable to support and

care for its own. Stunned, Aisha forwarded the editorial to Dr. Sanjari and they spent the afternoon arguing the pros and cons of treating those who might test positive for the disease during the application process for citizenship under the provisions of the bill.

*Read the following material and develop both a pro and con argument for instituting a public health infrastructure that can meet the demands of the newly proposed bill. In preparing your statements, reflect on the challenges that Aisha alludes to in the first paragraph.*

### **Resources**

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### Part III—Preventing the Development of MDR TB

After her conversation with Dr. Sanjari, Aisha began to think about the children of the immigrants. So often the specific needs of children are overlooked, and with TB it was no different. There were many public health specialists and physicians advocating for a more effective vaccine and more appropriate diagnostics for children, who often are unable to cough up a sufficient amount of sputum. Some of Aisha's friends had been vaccinated as children in other countries since the vaccine can reduce symptoms, but in the U.S., TB vaccination is not promoted.

Aisha reflected on the fact that an effective vaccine had not yet been developed. Despite the number of studies that demonstrated variable effectiveness of the current Bacillus Calmette-Guerin (BCG) vaccine, the vaccine had been used around the world in childhood vaccination programs. The vaccine appeared to reduce the symptoms of TB disease and, thus, its spread. Because rates of TB infection in the U.S. are relatively low and because vaccination can result in inaccurate readings of the Mantoux PPD skin test during TB screening, most U.S. born are not vaccinated. Work on a new vaccine was underway, but it would be some time before it would be available.

New diagnostics had also been approved and implemented in the last few years in Europe. The QuantiFERON-TB-Gold (QFT) detection system is more sensitive and specific than the Mantoux skin test. But since the test was only just approved by the FDA in 2005, it is not yet in wide use in the U.S. Just the other day, Aisha had attended a meeting where researchers were discussing the difference in positive diagnoses of infection using these two tests. If the same isolates were tested, QFT-Gold detected a lower number of positives as compared to the Mantoux test, suggesting that each test might target a different stage of infection. Aisha had asked if QFT-Gold might be detecting recent infection and not latent infection, and she was pleased to learn that research was underway to determine if this was the case. Since the QFT-Gold uses blood samples to detect the presence of IFN-gamma, an immune protein, it might not be an effective means to conduct mass screening as it would involve needles and more equipment for analysis.

Aisha was concerned about the latent TB infections that might be MDR but which would not be detected by these two diagnostics. Both the Mantoux skin test and the QFT-Gold detect a generic immune response to tuberculin proteins, but don't provide unique genetic or molecular information about the *M. tuberculosis*. Drug susceptibility tests require a sputum sample and are performed only on those with active disease and not latent infection. The testing involves culturing the bacteria and subjecting it to genetic analysis, or alternatively the bacteria could be grown in the presence of antibiotics that would reveal the drug resistance profile. The lengthy process could take months. A few companies were joining forces with the Foundation for Innovative Diagnostics (FIND) to develop tests that could shorten the testing time and use technologies appropriate for the developing world. "So what happens if we treat latent tuberculosis infection with antibiotics that don't work on that person's strain of *M. tuberculosis*?" Aisha thought to herself. "There must be some way to test the latent infections for drug resistance." She decided to go to the library to see what she could find.

While conducting a literature search, Aisha came across a book titled *Ending Neglect: The Elimination of Tuberculosis in the United States* published by the Institute of Medicine in 2000. In the appendix, there was a proposal to prevent TB in newly arrived immigrants from countries with a high rate of TB. The proposal referred to studies that administered isoniazid for nine months to individuals who tested positive for latent tuberculosis infection (LTBI) and reported a 75% completion rate. This was part of a shift in policy, as many public health professionals were debating the pros and cons of prophylactic treatment of LTBI.

Aisha thought about TB screening and treatment protocols as they applied to immigrants applying for citizenship. Skin tests were not used in this setting; an x-ray and subsequent sputum test were analyzed in those over the age of 15, since children have difficulty producing a sufficient sputum sample. Immigrant parents who were not infectious, but tested positive for LTBI, would not receive treatment and gain entry. But the children of these individuals could later become infected with TB, should the parent's latent infection develop into active disease. "Wouldn't it be great if the Senate bill incorporated treatment for LTBI," she thought. "Then the children of these immigrants would not be at risk for developing infection. But I suppose the screening alone will place a heavy burden on the states most affected by this bill."

With a little more hunting, Aisha discovered more recent studies that were conducted on adolescent Latinos in the California high school system. These students were screened for TB using the Mantoux skin test. Anyone who tested positive for LTBI was treated for three months with rifampin and isoniazid to prevent development of TB. These students were targeted because they came from high risk countries, and childhood LTBI is more likely to progress to TB than in adults. In general, LTBI can develop into TB later in life when the immune system might be compromised by old age, smoking, or secondary infections such as HIV. Some of the studies involved coaching and DOTS-like methods of antibiotic delivery.

Though Aisha was relieved to see that something was being done to help the children, she couldn't help but wonder if these children might suffer any negative consequences from these approaches. She also kept coming back to the risks involved in prophylactic treatment. "Could prophylactic treatment of LTBI in this recent immigrant population promote the development of XDR TB?" she wondered.

*Skim the articles that Aisha collected and answer the questions below.*

## Resources

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## Questions

1. How does the Mantoux PPD skin test work? Can you hypothesize as to why vaccination might compromise this screening test?
2. Specifically, how does QuantiFERON-TB Gold differ from the Mantoux PPD test in terms of test sample, time, cost, and information?
3. When a person is diagnosed with LTBI, why don't they feel or look ill? What is happening in the body of the infected individual?
4. Explain how old age, smoking, and HIV infection influence the progression of TB infection.
5. Compare the prophylactic approaches described in the *Ending Neglect* book to those targeting adolescent immigrants. Which do you think might be more successful and why? Compare the risks involved with each approach.
6. Can you hypothesize as to why the studies referenced in the Institute of Medicine text reported that only 75% of the patients in the study completed treatment?
7. Can you suggest methods or approaches that could result in better compliance with the drug regimen in adolescents?
8. Extend Aisha's thinking and answer her question “Could prophylactic treatment of LTBI in the immigrant population promote the development of XDR TB?”
9. Do you think there are any issues of social justice or human rights that need to be addressed before a study on children is approved? Who oversees the ethics of such studies? Should minorities in the U.S. be targeted in public health campaigns?

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