HARVARD MEDICAL SCHOOL
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CASES IN GLOBAL HEALTH DELIVERY

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Multidrug-Resistant Tuberculosis Treatment in Peru

Katiuska Chalco had been working as a nurse with *Socios en Salud* (SES), a community based health organization, for three months when she met Juana Valdez[•] in 1996. The story she heard from Juana was typical of many stories she had heard since joining the organization. Juana's parents came from two small provinces in Peru, and she was one of 11 children (see **Exhibit 1** for more on family members). When she was five, Juana's family sent her to live with her nine sisters in a one-room house under the care of her older brother, Carlos, in Carabayllo, a shantytown north of Lima, Peru. Though Carlos worked hard in the market, selling lemons, chili peppers, and whatever else he could find, his earnings were frequently not enough to support his sisters. The girls would go to Lima on their own to look for work or to ask passersby for money. Eventually a woman who operated a pay parking lot near the area where Juana worked invited Juana to live and work in her house. Juana was overworked and underfed. She returned to live with Carlos when she was 11 years old.

Soon, Carlos developed a fever, cough, and chills. He continued working, but the girls worried about him. When they told their mother he had been sick, she took him to the local health center where he was diagnosed with tuberculosis (TB). No one in the house knew what TB was. Carlos started to sleep on the opposite side of the house. He did not know where he contracted the disease but did remember an older neighbor he visited as a child hiding pill bottles.

Carlos took medication given for free at the nearby health post and felt better. Later he relapsed. He started another treatment regimen. The health center eventually distributed monthly food baskets for less than USD 1, but it was often more than Carlos could afford.

A few years later, Juana's sister Yasmín came down with a cough, fever, and excessive sweating. She began TB treatment in the same health center as Carlos and completed it without any improvement. Health workers were required to treat according to government standards, and Yasmín soon began a second

[•] Patient names have been changed for privacy.

Julie Rosenberg and Joseph Rhatigan prepared this case for the purposes of classroom discussion rather than to illustrate either effective or ineffective health care delivery practice.

regimen. By this time, the word "resistant" had come up in Carlos's care; he was failing to respond to any of the regimens offered.

Around the time Carlos and Yasmín were both considered treatment "failures," Juana returned pregnant to Carabayllo from a two month trip to the jungle with her husband, Pedro. Juana did not tell Pedro about Carlos' sickness until they moved into the family's house because she was afraid of what he might think. Soon Juana's sister Alicia came down with night sweats, cough, and fever, and was diagnosed with TB.

Carlos was told that he needed to buy two medications for TB that were not available from the Ministry of Health: ethionamide and ciprofloxacin. He would sit and stare at the unfilled prescriptions, knowing that he would never be able to afford his cure. Carlos kept working but could not hold the family together. Their mother had gotten sick and had stopped coming to visit. After eight years of illness, Carlos died. Juana was about 18 and her sisters, Alicia and Yasmín, were still sick. Alicia found a religious group that she claimed could save her, abandoning western medical treatment, and Yasmín continued the Ministry of Health's free treatment protocol.

When Juana was 21, her shoulder started to hurt, and she would get a pain running down her arm. She waited for it to go away. Soon she had a cough and fever. She took antibiotics and pain medication, but neither helped. Alicia had died by that time, and a fourth and fifth sister, Silvia and Flor, had recently been diagnosed and begun treatment. Juana was scared to go to the health post in the zone where her brother and sisters had gone. "One more Valdez and there won't be any pills left," the health workers would say each time a new sibling arrived. They blamed the family and treated them terribly. After eight months, Pedro insisted Juana go to the health center. She went far from the house where no one would know her, and she used a new last name so she could not be traced to the "resistant" Valdez cases. She became Juana Valdivia and began the standard first-line regimen, *esquema único* (the unique regimen).

Juana had never taken pills because she was scared to swallow them. It took her an hour five days per week to take them all, and they made her throw up. "I took them, though," she said, "I took them just to take them. I knew that they weren't going to make me better. I also took them so that I wouldn't cough up the microbe because that's what they told me, that I had to take them so that I wouldn't infect my kids."

Juana did not get better, and when she had almost finished the six-month treatment, the health workers realized she did not live in their zone. They sent her to the post near her house where she kept her false last name and began on the new standardized regimen, *esquema dos* (regimen two). She was down to 88 pounds. "It's my turn to die," she said to herself. "I have to keep going for my kids because they need me…. No, I am just going to get them sick by being here; I should just go." She wavered back and forth, feeling the only people she had to turn to were "herself and God."

When Juana thought she was at her worst, her mother-in-law died from cancer. Everyone was counting on her husband, Pedro, to keep the family going. But, Pedro began to get sick. He continued to work throughout the first standardized treatment and was considered cured. A month later, Juana explained, "from living with me, he relapsed." Pedro blamed Juana for his sickness. Remembering her brother staring at the unaffordable prescriptions, Juana knew that she would not be able to afford treatment and went to look for her father. Though she had never known him, he was her last hope. With hints from family members and many days of searching, she tracked him down. He, too, was unable to help.

Juana finished *esquema dos* barely able to walk with no hope. When someone told Juana about SES, a nonprofit organization that was giving patients with drug resistant TB treatment, it was hard for her to get excited. "If you want to, give it to me," she told them. SES health promoters found out about Juana's case and went to visit her shortly after.

Overview of Carabayllo

In 1999 Metropolitan Lima was divided into 30 districts, nine of which were considered part of *El Cono Norte* (the Northern Cone). While the density of Metropolitan Lima was one person per hectare, the density of the Northern Cone, on the outskirts of the city, was 140 people per hectare.[1] The population of the Northern Cone in 1981 was 990,463 inhabitants, and by 1996, estimates indicated a population of 1,792,340 inhabitants.[2] Carabayllo, located 8 kilometers from the city center, was the northernmost and largest district of the Northern Cone. It grew from 52,800 inhabitants in 1981 to 138,880 in 1998.[3] Carabayllo comprised an area of 346.88 square kilometers of which 9.6% was developed, 12.6% was rural and 77.8% was unoccupied.[4]

The presence of *el Sendero Luminoso* (the Shining Path), a violent Maoist guerrilla organization, had forced many citizens living in rural provinces to move to cities such as Lima out of fear and hunger. In the early 1980s developers promised families simple plots with basic services in Carabayllo. They did not follow through with the services, however, and many families were not given legal recognition of land ownership. New families hacked out level plots further and further up the unregulated, rocky hillsides of Carabayllo, saturating the dusty slopes with straw and cardboard dwellings as they claimed their plots (see **Exhibit 2** for photo). Migrants organized themselves in neighborhoods that they named *asentamientos humanos* (human settlements). They held protests, led marches, and blocked roads to draw attention to the lack of basic services, but most demands were unmet by 1999.[3]

More than 70% of adults in Carabayllo were unemployed. Those who found legal work usually set up stalls in the crowded market, and few made more than USD 5 per day. Gangs, prostitution, and violence were common. Two out of every 10 families did not have adequate housing. In 1999, 47,000 residents received nutritional support from the public *Vaso de Leche* (Glass of Milk) program, and the number of people who needed nutritional assistance was estimated to be even greater.[3] Two out of five families had access to an adequate supply of water, and in many parts water was restricted to one or two hours per day.[3] Two principal roads ran north-south through the Northern Cone, but smaller roads linking the districts were inadequate, and using public transportation often meant switching routes several times even for short distances.[2] Only 20% of the population had access to medical care despite the various government health facilities within walking distance. [5]

Basic Socioeconomic and Demographic Indicators for Peru[1]

INDICATOR		YEAR
UN Human Development Index ranking	73 out of 162	1999
Population (thousands)	26,004	2000
Urban population (%)	73	2000
Drinking water coverage (%)	79	2000
Poverty rate (% living under USD 1.25 per day)	9	1996
Gini index	46	1996
GDP per capita in PPP (constant 2005 international dollar)	5,438	1999

[1] This data was comprised from the following sources: United Nations (UN), United Nations Children's Fund (UNICEF), World Bank, United Nations Educational, Scientific and Cultural Organization (UNESCO).

INDICATOR		YEAR
GDP per capita (constant 2000 USD)	2,021	1999
Literacy (total, female, male)	88, 82, 94	2004

Multidrug-Resistant Tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) was an infectious disease caused by an isolate of *Mycobacterium tuberculosis*, which was resistant to at least isoniazid (INH) and rifampin (RIF), two of the first-line anti-TB drugs (see **Exhibit 3** for more on MDR-TB). MDR-TB could be contracted directly or could develop with inadequate chemotherapy for drug-sensitive TB.

MDR-TB and TB presented with the same signs and symptoms and appeared the same on smear microscopy examinations. Cultures using drug susceptibility testing (DST), which require more time and additional equipment, could diagnose MDR-TB by differentiating it from drug-sensitive TB. While the basic treatment for TB was six months, MDR-TB required a course of chemotherapy lasting at least 18 months with more expensive, potentially toxic medications, often referred to as second-line agents (see **Exhibit 4** for second line agents).[6] MDR-TB treatment could consist of individualized treatment regimens (ITR) tailored to the resistance profile of the infecting strain or of empiric standardized treatment regimens (STR).

TB was the eighth leading cause of death worldwide in 1999, and between 1996 and 1999, 5.1% of all TB cases had MDR-TB.[7] In 2000 there were an estimated 273,000 new cases of MDR-TB worldwide.[8] Among previously treated cases, the prevalence of MDR-TB was six times higher than in new cases.[7]

Drug-Resistant Tuberculosis Treatment and Policy

Soon after the first TB drugs were introduced in the 1940s, scientists discovered that resistance could develop if multi-agent chemotherapy was not used. Scientists searched for the perfect combination of drugs and dosing to prescribe for TB over the next several decades. A 1985 editorial accused those in the field of ignoring MDR-TB, but few paid attention to the warning, focused on finding the best treatment for the most common strain of TB.

In 1993 the World Health Organization (WHO) published the first *Treatment of Tuberculosis: Guidelines for National Programs.* The guidelines outlined different patient categories according to their priority for treatment (highest to lowest) and provided recommended regimens (see **Exhibit 5** for summary of recommended regimens). The lowest priority was Category IV, "chronic tuberculosis patients."

> Management of these patients who have a high likelihood of MDR-TB is highly problematic. Even with optimal therapy, cure may be possible in only half of such cases. Second-line drugs are very expensive, are generally more toxic and are significantly less effective than conventional regimens in drug-susceptible cases. More over, the patients must remain in the hospital for several months. If possible, the drug sensitivity of the bacilli should be established and a re-treatment program should be attempted with second-line and experimental drugs. However, in countries with limited resources, treatment of patients with chronic tuberculosis should be given the lowest priority and should not divert resources from higher priority patients.

Those who spoke directly with WHO representatives at the time said the organization "felt (but didn't state publicly) that [MDR-TB patients] would most likely die anyway."[9] Arata Kochi, WHO TB Division Director, defined MDR-TB as TB bacilli resistant to at least INH and RIF. He wrote, "This type of MDR-TB is very difficult to cure; even in very sophisticated specialized TB institutions, the cure rate is less than 50%. In

many developing countries, this MDR-TB is virtually incurable."[10] Kochi wrote, "Data is quite limited at this time…. An accurate picture of the drug resistance problem in the world is not available because a limited number of countries have a reliable drug resistance surveillance system." Some scientists argued that MDR-TB was less of a problem because in the course of acquiring resistance, the bacteria became less virulent.

By 1994 WHO had produced a Framework for Effective TB Control, outlining policy on how to treat and control TB. The group promoted a strong pan-sensitive TB program as the best solution to resistance[10] and branded the strategy as DOTS, short for Directly Observed Therapy Short-course. The standard WHO-DOTS treatment eliminated the need for intense clinical management of the disease and its implementation became tied to World Bank loans for health sector reform. Within five years, 120 countries had adopted DOTS, including all 22 high-burden countries.

In 1997 results from the first WHO/International Union Against Tuberculosis and Lung Disease (IUATLD) Global Project on Antituberculosis Drug Resistance Surveillance showed that there was resistance in each of the 35 countries that participated (see **Exhibit 6** for select results). WHO revised the treatment guidelines to address the potential for drug resistant cases and released *Guidelines for the Management of Drug-Resistant Tuberculosis*. The guidelines defined the disease and its causes, some basic principles for managing it, information on how to assess cases, available drugs and regimens, and the role of surgery. The guidelines reinforced "the top priority is not the management, but the prevention of MDR-TB."[11] Treatment was something to consider for "more economically prosperous countries" that "might wish to do so."

Tuberculosis in Peru

TB and MDR-TB Epidemiology in Peru

In 1983 TB was the fifth-leading cause of death in Peru,[12] and some estimated that it was the top killer among 15 to 44 year olds.[13] At best, only 60% of those who received treatment were cured. Of those initiating treatment, up to 47% abandoned treatment prior to completing the six-month regimen.[14] In 1984 and 1985, two large national studies concluded that "many years of poor chemotherapy resulted in a high prevalence of patients with drug-resistant organisms."[15, 16] Through the 1980s Peru was one of 20 countries with the highest TB burdens in the world.

By 1990 the national incidence was 175.9 per 100,000 people, higher than rates seen in the 1960s.[17] In 1991, 42,763 cases were identified, and 48% of all registered cases were in Lima and nearby urban Callao (see **Exhibit 7** for case distribution in 2000). Seventy-eight percent of patients receiving treatment between July and December of 1991 were declared cured; 3.8% of patients failed treatment, 11.3% abandoned treatment, 2.8% transferred sites without confirmation, and 4.1% died. Incidence peaked at 243.2 per 100,000 people in 1992. The prevalence of all forms of active TB among 15 to 44 year olds in Carabayllo was 800 per 100,000 in 1993.[18]

The 1994 *Bulletin of the WHO* published results on a random sample survey of initial drug resistance among TB cases in Latin America. Seventy-eight samples were tested from newly diagnosed, smear positive patients in Peru. In the port city of Callao, 54.4% of cases had some form of resistance. A total of 18.2% of cases in that area were resistant to more than two drugs. The cluster sampling method found that 39.4% in Lima had some form of resistance and none were resistant to more than two drugs (see **Exhibit 8** for select additional results).[19]

Between October 1995 and March 1996, the Pan American Health Organization (PAHO), an affiliate of the WHO, did a proportionate cluster survey. Twenty percent of the sample–-a total of 1958 new and

previously treated patients diagnosed in 814 health establishments in 31 regions and sub-regions–-was tested. Among 1500 new cases tested in Peru, over 15% had some resistance and 2.5% had MDR. Among the previously treated patients, 36% had some resistance and 15.7% had MDR.[20] Peru's drug resistance rates were above the median and weighted mean of all participating countries.

Health System and Epidemiologic Indicators [2]

INDICATOR		YEAR
Average life expectancy at birth (total, female, male)	72, 74, 70	2000
Maternal mortality ratio (per 100,000 live births)	240	2005
Under five mortality rate (per 1,000 live births)	41	2000
Infant mortality rate (per 1,000 live births)	36	2000
Vaccination rates (% of DTP3 coverage)	93	1999
Undernourished (%)	20	1996
Adult (15-49 years) HIV prevalence (per 100,000)	480	2005
HIV antiretroviral therapy coverage (%)	42	2006
Tuberculosis prevalence (per 100,000)	289	1999
DOTS coverage (%)	100	1999
Malaria cases (per 1,000)	8	2006
Government expenditure on health as a % of total government expenditure	12.4	1999
Government expenditure on health per capita (international dollar, USD)	134, 57	2000
Total health expenditure per capita (international dollar, USD)	229, 96	2000
Physician density (per 10,000)	12	1999
Nursing and midwifery density (per 10,000)	7	1999
Number of hospital beds (per 10,000)	9	2004

TB Control in the 1990s

In 1990, Pedro Guillermo Suarez, a young physician managing the local TB program in a health center in Northern Lima, became the director of the National TB Program (NTP). Using the argument that TB "is not only a public health problem, it's a social and political problem," Suarez convinced the government of the importance of a strong NTP.[12]

Suarez selected a dedicated team at the national level and young nurses and physicians to serve as the new departmental-level TB Control Program coordinators. Many local-level health workers were hired on a contract basis to fill the roles of early retirees as well. Their contracts were renewed every three or six months if they performed well, as measured by standard program data on case detection, cure rates, and compliance, as well as reviews from their supervisors.

With ongoing technical guidance from PAHO, the NTP improved Peru's laboratory and diagnostic capacity (see **Exhibit 9** for more on growth of infrastructure) and prepared the first set of National TB

[2] This data was comprised from the following sources: WHO, UNICEF, UN.

Control Program Guidelines that were distributed in 1991. Suarez remembered, "there were some people with different ideas, but we sent a clear message: We are a public health program, and we must implement a national standard."

The NTP leadership made technical and management decisions. The regional teams designed local strategies, carried out regular program evaluations, supervised diagnostics and other local activities, trained community personnel, and ensured distribution of supplies. Directors of the health posts, health centers, or hospitals led the local teams. Health centers were responsible for managing the social aspects of the program, evaluating the program monthly and annually, providing case notification, and being accountable to the community and patients for developing comprehensive action plans.

All TB patients were given the same treatment, *esquema único*, the unique regimen that lasted for six months and was divided into two phases: two months with four recommended drugs, including ethambutol (EMB) and pyrazinamide (PZA), followed by four months with only isoniazid (INH) and rifampin (RIF; see **Exhibit 10** for NTP treatment regimens over time).

Those who failed treatment – defined as those who finished treatment with a positive smear (see **Exhibit 11** for WHO case definitions) – were given *retratamiento* (retreatment regimen), which was not standardized or specific. Each region had a doctor assigned to assess failure cases and determine the course for these patients. The 1992 NTP report acknowledged that resistance could occur through various means, including "inadequate drug regimens, abandonment, inadequate dosing, treatment irregularity, unavailability of the needed quantity of medications, insufficient training of program personnel, self-medication, or drug addiction." The report stated, "treatment failures should not occur because with an efficient control program, it is easier to avoid them than to cure them."[21]

Every person diagnosed with TB had a "case notification card" recorded on a triplicate form and an attendance and medication administration card. Treatment failures and patients who abandoned treatment were recorded in the registry book, but their case notification cards were not included in the regional notification reports or the annual report to the district-level manager. National goals for each program area included 100% cure, diagnosis, and training coverage. Health workers in successful health centers often were promoted to larger centers or district level positions.

The first data were released in 1992. The total number of health establishments offering the NTP TB treatment had increased from 977 in 1991 to 2,774. The number of laboratories able to culture had increased from 13 to 24. Cure rates were almost 80% (see **Exhibits 12** and **13** for a graph showing the number of cases detected and treated and a table showing treatment outcome). Suarez met WHO TB Division Director, Dr. Arata Kochi, and requested a formal, international evaluation from WHO. The evaluation confirmed the positive results and cemented the Peru–WHO relationship. Peru's NTP was touted as a model DOTS program the following year in 1994.

In 1995 the Peruvian NTP updated the NTP Guidelines "to improve the efficacy of treatment and prevent the occurrence of resistance." *Esquema único* became known as *esquema uno* (regimen one) and addendums were added to adjust dosing for those under 15 years old or under 50 kg. The medications used for this initial treatment remained the same. *Esquema dos* (regimen two) was indicated for patients previously treated, relapses, or patients who had abandoned treatment and returned.[22] The regimen for the first month included streptomycin in addition to the four first-line drugs in *esquema uno*, followed by two months with the four first-line drugs, then five months of twice-weekly treatment with INH, RIF, and ethambutol, for a total of eight months. *Esquema tres* (regimen three) was indicated for new smear-negative extrapulmonary cases and for infants. Those who failed both *esquema uno* and *dos* or who relapsed after completing both were considered for *retratamiento*, which remained without a structured regimen.

After the launch of the updated guidelines, the cure rate went up to 92.1%, and the rate of patients abandoning treatment went down to about 3%. The cure rate for those taking *esquema dos* was 68.8% among those who had previously abandoned treatment and 82.6% among those who had relapsed. Between 4.5% and 6% of patients on *esquema dos* died, and up to 4.1% completed treatment without a cure (see **Exhibit 14** for outcome of patients starting *esquema dos*).

Socios en Salud

In 1983 Paul Farmer and Ophelia Dahl helped establish a community-based health project in Cange, Haiti, called *Zanmi Lasante* ("Partners in Health" in Haitain Kreyol). In 1987 with funding from Boston philanthropists Tom White and Todd McCormack, they established the nonprofit Partners In Health (PIH) in Boston with Farmer's medical school and anthropology doctorate program colleague, Jim Kim. PIH supported the efforts in Haiti to "provide a preferential option for the poor in health care" and alleviate suffering. Money from Farmer's McArthur Fellowship in 1993 funded a new research and advocacy branch of the organization.

PIH advisory board member Father Jack Roussin moved to Carabayllo in the early 1990s, and PIH began supporting him in setting up a small pharmacy in his parish. Months later, the pharmacy was blown up by *el Sendero Luminoso* who saw it as "crumbs for the poor," something that would calm the revolutionary fervor.

When Kim received a Kellogg Leadership Fellowship in 1994, he listened to Roussin's advice to establish a community-based health organization in Peru similar to that in Haiti. Roussin's friend introduced Kim to Dr. Jaime Bayona, a local, bilingual primary care physician with training in public health. Bayona was hired to direct the project that they named *Socios en Salud* (SES; Partners In Health). With help from Farmer and Dahl as well as several local youth from Roussin's church, the new team began conducting a community health census in the area, going door to door to ask about health concerns. While Farmer focused on TB and MDR-TB treatment in Haiti, "The one thing we don't need to do here is TB," he said.[23] Compared to Haiti, most of Peru's problems seemed less grave (see **Exhibit 15** for comparison of the two countries).

The parish loaned SES the back portion of another lot -- a two-story building with three offices, several exam rooms, and unpredictable supplies of electricity, water, and telephone service. With preliminary census results and the encouragement of local nuns, SES decided to focus on improving children's health in the *asentamientos humanos*.

Revealing an Epidemic

The following year, Roussin was hospitalized in Boston for TB. Doctors started him on a standard treatment regimen, but he failed to respond. The Massachusetts State Laboratory Institute (MSLI) began DST on his sputum samples. He died within two weeks from MDR-TB resistant to all first-line drugs.[18]

Farmer and Kim suspected there must be other cases.[18] Bayona asked in health clinics if there were patients with resistant strains, but he received little cooperation. He found out about one patient who did not get better on treatment and went to speak to her in her home. Despite failing treatment, she had been compliant with her medication. Bayona sent her story to Kim and Farmer, continuing his search.

The SES youth looked for more cases, conducting door-to-door inquiries for "chronic" TB cases as part of the ongoing health census. Valia, an SES employee, later explained:

> When asked whether there were other cases of drug resistant tuberculosis, the referring health technician didn't know how to respond. "Drug-resistant tuberculosis" was frankly not a term that people were using in the nursing TB treatment community. However, when presented a different way – are there patients who didn't get better even though they took their pills? — the answer was, yes! many, many…"[24]

Farmer flew to Peru to examine 10 suspected cases of MDR-TB that Bayona and the youth had identified. After hearing their stories—not stories of treatment abandonment as he often heard in Haiti—and examining their records, Farmer, Kim, and Bayona met. Kim explained:

> That first conversation was about what we should do. The *jovenes* [youth] kept saying "if these people have drug resistant strains, we're scared." And they said to Paul, "Aren't you scared?" And Paul said, "Yeah, I'm scared, but what are we going to do? They're right here; they're in our communities; and they're infecting their families. The only way you can stop this is by treating the people who are sick. What do you guys think?" And they said, "Yeah, that's what we should do — we should treat the sick people." That's when the whole thing started.

Farmer and Kim brought sputum samples back to Boston in their suitcases for testing at MSLI. Kim remembered:

> The Mass State Lab folks didn't really know we were doing this — they didn't know what the whole project was, and Paul got the first call — he was a resident at the time — and they were shocked — this patient had five-drug resistance—where was this patient? Was this patient on respiratory precautions?

Creating the Possibility for Treatment

Bayona approached MINSA about helping obtain second-line medications for 10 patients in May of 1996. MINSA turned Bayona away. One official at the Ministry of Health said, "The way to stop MDR-TB is to prevent it. This is a poor country and there are low success rates for treating MDR-TB everywhere."[12] Farmer, Kim, and Bayona lobbied for the provision of second-line medications through the course of several meetings they arranged with MINSA and Suarez. Suarez was opposed to treating MDR-TB patients through the NTP, citing the high costs of treatment and the low success rates. As Kim recalled:

> My memory from the debate is Paul saying, "Look, this is a social justice issue." He was invoking the liberation theology…. Pedro's response was basically to say, "We're concerned about social justice issues too." But, at the time, some article Michael Iseman [a leading TB expert] had written about a case of MDR-TB that cost USD 250,000 had come out. So Pedro threw that number back at us: "I can treat 2500 patients for USD 250,000. I'm short of money to treat regular TB patients, so how do I choose? Twenty five hundred patients versus one patient." He really put it out there.

The PIH and SES leaders decided to start treating just 10 patients and to secure the needed medications themselves. Farmer approached Tom White about funding, and Bayona kept working to get permission from MINSA. As Kim explained, "Jaime was absolutely committed to these patients—to make sure these patients would get on treatment, and he was navigating incredibly tricky political waters."

In 1996 Bayona went to the Northern Cone's hospital pulmonologist, Felix Alcantara, to inform him of the potential to treat MDR patients. Alcantara, who had recently begun his work there, was pleased: "The people before me were using the regimens designed by the ministry, the national program, but they were bad. They had to use them, though, because there were not other medications. It was really a problem."

Bayona arranged a meeting with Suarez, Alcantara, and a few others from the district hospital. In 1996 the first contract between SES, the Peruvian NTP, and PIH allowed for treatment of 10 MDR-TB patients.[24] All patients had to live in Carabayllo, survive until DST results were found, and be referred by a collaborating MINSA physician after failing at least one course of DOTS and a retreatment regimen. SES would provide the DST, second-line drugs, and additional support for patients who would be treated

within the NTP infrastructure. Tom White had agreed to provide the funding. As Dahl said, "The most important thing for us in being able to treat that first cohort of patients was the fact that we had the money to do it. There was no one else….Tom was the one that allowed us to do this…Tom was the only one donating this kind of money for TB."

Farmer and Kim obtained the needed medications from the Brigham and Women's Hospital's pharmacy where they worked and brought them down to Lima in suitcases.

Beginning MDR-TB Treatment

The first patient enrolled in August 1996. Before enrollment, each patient had to get first- and second-line DST results from MSLI, baseline blood work, audiometric and psychiatric evaluations, chest x-rays, all his or her local health center charts together, and several consultations with Felix Alcantara who would prescribe and then review each test. The patient had to consent to treatment as well. SES health promoters accompanied patients through the treatment prerequisites. Most patients were quite ill from up to 15 years of failed treatments. It took a median of eight months from MDR-TB diagnosis to SES treatment.

Often the hurdles were beyond SES's control. Sonya Shin, a Harvard Medical School student volunteer who lived in the SES clinic for the first 18 months of the project, recalled, "One of the hardest parts—and maybe it still is—is getting patients on treatment—especially when they're sick and just having these [treatment] delays…. Sometimes it can be very frustrating to see patients die before they start treatment, or sometimes patients die just after starting due to delay." One set of suitcases of second-line drugs from Boston to Lima got stuck in customs where officials levied a tremendous tax and held the shipment for weeks.[24] The NTP eventually took care of the regulatory paperwork that was needed to allow entry into the country.

Alcantara and Shin accompanied Farmer when he reviewed the DST results and designed treatment regimens for the first patients. Jennifer Furin, another Harvard Medical School student volunteer, also worked on the team. Alcantara had to recommend each patient for the alternative SES treatment and sign the prescriptions Farmer recommended so that SES could dispense the drugs. When Farmer was in the United States or Haiti, he adjusted each patient's regimen through e-mail. As Alcantara explained:

> It was a really good team at the beginning. It was a good team because it wasn't only me: Dr. Paul, Dr. Jim, Sonya Shin, Jennifer Furin. I remember well: Paul, Jim, they came continuously in this time — every month or month and a half — they came, and we evaluated the cases together and talked about them. Sonya and Jennifer, in the first years, they were here working consistently with me. They didn't just come and go — they worked here with me.

The physicians tried to keep patients on the highest doses of the medications that the patients could tolerate, and they treated side effects whenever possible. As Kim recounted, "Our fears of side effects were far less... than our fear that they would fail therapy."

Every month SES promoters distributed the patients' morning doses to the health posts or clinics closest to their homes. Four health promoters, the youth who had been hired through the church and chosen to work on TB rather than children's health, were responsible for visiting the patients every afternoon and evening seven days per week and supervising the doses that took place when the health centers closed. If patients were unable to walk, the health promoters delivered their morning doses as well. A nursing student, Lourdes Alvarez, was responsible for the daily clinical care with Shin.

Each morning at 8 a.m. the complete team of health promoters, the available doctors, and Alvarez met for rounds. They discussed each enrolled patient's status, how to handle any emergencies that had come up, treatment protocols, and their personal challenges, and they shared ideas on how to support patients at risk.

The morning rounds helped them determine who needed an immediate consultation with Alcantara. All patients saw him and Farmer at least once per month. The team e-mailed detailed notes on each case, questions, and concerns daily through a dial-up connection to Farmer, copying Alcantara, Bayona, Shin, Furin, and Kim.

SES continued looking for MDR-TB cases through contacts, referrals, and door-to-door case finding. Through persistence and many meetings, Bayona got permission for SES to treat more patients in two adjacent districts of the Northern Cone that the district hospital served. Additional nursing students were hired, first as promoters, and then as supervisors to the promoters. The new hires learned their roles by accompanying the original health promoters in the field. One nurse explained, "Field training. Everything was field training. Also we didn't know a lot of what we know now. We went on learning about stuff as we went with time. Together with patients we've gone on discovering."

A secretary began transcribing the morning rounds for the team, and additional staff was hired to help with the phones, sputum sample collection, and drug management (see **Exhibit 16** for table showing SES growth).

Treatment Administration

While at first health promoters and nurses were able to visit each patient every day, as the patient load grew, they were stretched for time and did not see each patient daily. SES recruited community health promoters, volunteers who lived near patients' homes who agreed to directly observe and administer patients' treatment. SES provided community health promoters small food baskets at the end of each month in appreciation of their efforts. Community health promoters reported to project health promoters who reported to the nurses. Nearby health centers recommended the (mostly) women community health promoters, many of whom had been involved with the center previously or were known for community activism, for the positions. Most community health promoters oversaw just one patient. They identified and reported symptomatic family contacts, adverse events from medication, complications, and stressors that threatened patients' adherence as the project health promoters did. One project promoter reported:

> The DOT community health workers…inform us immediately if there has been a problem…that the dose was lost, or that the patient did not want to take the medicine, or that this patient would like to abandon the program…they are there to listen to what the patient says about their family problems, their economic problems, problems in their studies or their work.[24]

All the health promoters learned to "insist with unfaltering patience" when administering the patient's medications. SES and the community promoters made accommodations to allow patients to continue with work and family obligations by administering DOT in patients' workplaces or in nearby restaurants for privacy when possible.[24] The SES team eventually eliminated Sunday doses from the treatment regimen. Sundays became the day patients could make up any missed doses from the week or rest. Health promoters experimented with crushing the larger pills and offering patients milk or juice along with other creative remedies that could help patients take up to 30 pills per day.[12]

One patient explained, "Sometimes I wanted to stop because I felt worse off than before I started taking the pills. I lost my appetite."[12] The side effects--including headaches, nausea, and gastrointestinal upset from the second-line drugs (see **Exhibit 17** for more on incidence of adverse events) along with the pain from the injections and the disease itself—could be excruciating.[25]

Through consistent home visits, the nurses and promoters were able to provide referrals for help in psychosocial issues such as substance abuse and domestic violence. An SES nurse stated:

> When one goes to a house, from the moment you see the house you can see under what conditions the person is living. There are simple things like whether there the roof is made of tin or whether the home is made of clay bricks with plastic sheets on top to cover the house from the rain. You also might notice that it is one small room where so many people live, and in those small moments one can tell the story of the conditions of the life of the patients.

Another nurse stated, "Sometimes we [the nurses] would joke about having to be a psychologist, a nutritionist, a social worker, a little of everything to be able to understand the person in all of his realms, be able to see him fully."

A patient spoke about the importance of the nurses and promoters in her treatment:

> I stopped taking care of myself. I didn't bathe, comb my hair, or brush my teeth. I looked like a crazy person. I would just stare, not at anything specific but into space or at people. I was ready to give up. Socios helped me and inspired me to live on through these times. My promoters and nurses would remind me that my son needed me and that I had to stay around for him. While everyone on the streets looked at me disgusted, my promoter stuck by me. She told me that I smelled and forced me to start taking care of myself without speaking harshly or making me feel bad. My promoter was kinder than my parents and really pushed me to get through.

Health promoters and SES staff visited health centers to ensure the NTP technicians responsible for delivering morning DOT were fulfilling their jobs and to exchange patient information. Each nurse was assigned to a specific region of the Northern Cone.

The nurses and health promoters supported one another. "I remember it was really hard at first. I never had thought that people could suffer so much, and the solutions to their problems, to alleviate their sadness, were not easy to find," Katiuska Chalco recounted. Her colleague added:

> There was no time to get sad, and among ourselves, among the nurses, we helped each other. When someone died, we all suffered. When someone was sick, we all suffered. We had to help one another. When someone completed treatment, we all yelled and cheered. When patients died, we went to the funerals. If it was a birthday, we all celebrated together.

The nurses reported to Alcantara when in doubt and collected updates on each patient for the monthly consultation. Everyone involved had 24-hour support; there were always a project health promoter and a nurse on call. The on-call project health promoter, all the nurses, and Alcantara had cellular phones from SES that worked as radios. They communicated with one another quickly if patients were unstable. Alcantara had left MINSA three months after starting, but he continued working as a consulting physician for SES and was there whenever he was needed.

Socioeconomic Support

SES provided treatment for MDR-TB and adverse events free of charge. SES also prepared monthly food baskets for about 90% of patients when the project started. Some got fuel for cooking. SES delivered prepared food or made accommodations at a *cocina popular* for patients living alone. The group prioritized patient needs by clinical state and risk. They created a short form to collect basic data about each patient, including personal information, family information, living situation, access to basic services, and income.

Means of socioeconomic support included everything from bus fare for clinic visits to beds that would allow sick parents to sleep separately from their children. SES encouraged patients to apply for hospital discounts to cover specialist consultations, surgical costs, and laboratory and imaging fees. Discounts ranged from 30% to 50% of the total fees, and SES covered some or all of the remaining costs. SES often helped homeless patients find a room to rent and subsidized housing costs when necessary.

Local Reaction

During the first years, health centers and others referred 731 patients for MDR-TB evaluation. Six hundred fifty six of the referrals lived outside the zone in which SES was permitted to treat.[26] As Shin wrote, "nurses from local health centers would wait for hours on the days that SES's patients were seen by [Alcantara] to thrust a chart onto the table for review. Siblings and children of SES patients would approach the health promoters, describe how they too, were in treatment for TB and were not getting better. Parents would knock on the SES office doors at night, seeking a moment to plead with the SES staff for treatment for their dying child."[24] Furin commented, "Telling a patient that we can't treat them even though we know how to treat them is devastating, absolutely heartbreaking," she said. "It means telling them they are going to die." SES was the only group offering what was known as "alternative treatment."

Not all the MINSA health centers were proponents of SES. Eda Palacios, an SES nurse, explained:

> The health centers didn't accept the community health worker.[…] They didn't believe that the community health promoters could administer a dose or supervise the treatment or understand the adverse events of the patients—how a community health promoter could be part of the [treatment] team. They eventually accepted, but they didn't want to.… Little by little…they saw that the patients responded and that they became more compliant with the treatment.

Some initial mistrust caused in part by clofazimine turning patients' skin bronze or darker, a very unfavorable trait in Peruvian culture, and by the duration and intensity of the treatment, did not last long. Seeing the results from the patients' cultures helped convince skeptics of the treatment's validity. In 1998, 57 patients in addition to the first 10 had enrolled in what then became referred to as "individualized treatment."

Results

Two Harvard epidemiology doctorate students had been working with PIH/SES to document the treatment and its outcome. They went through paper charts, the nursing notes, physician evaluations, drug regimens, and all other data. Alcantara noted, "We wrote everything down. This is one of the virtues. We wrote everything we did down very clearly."

In 1998, Kim presented data that suggested an 85% cure rate; 85% of the first 57 patients had smears and cultures that had remained negative over a year into treatment. He explained, "I remember the very first day we presented our data on treatment outcomes. TB experts were there, and they were just shocked to see the treatment outcomes." There was no other project providing MDR-TB treatment under the same conditions as SES, and even in the US treatment success was lower than in SES patients.

Some questioned the SES data. As Kim explained, "When we showed our data at first, people would say, 'Why are you only reporting cure rates among patients who have been on therapy for at least four months.' We said, 'Because a lot of the patients were so sick, they die in the first month, and we don't think of it as a treatment failure—it was a system failure.'"

The first patients were mostly young, single people living in large households who had been sick for many years before beginning individualized treatment. For the 75 patients enrolled before February 1, 1999, there were 58 unique treatment regimens comprised of five to nine different medications used for an average of 23 months.[35] Some patients were resistant to up to 12 drugs (see **Exhibit 18** for more on characteristics of first 75 patients). About 10% of patients were former healthcare workers.[27] Sixty-six patients completed at least four months of therapy, and 55 (83%) of them were cured. SES collected sputum samples for smear microscopy and culture at base line and monthly thereafter at the Sergio E. Bernales Hospital in Northern Lima. Conversion was evident in smears and cultures in a median of just over one

month (38 days for smears with a range of 14-264 and 35 days for cultures with a range of 23–181 days) among the first 66 patients.[26] There were "18 poor clinical outcomes" during therapy and follow up (see **Exhibit 19** for causes of death).

The patients themselves believed strongly in the treatment. Farmer reported, "Sometimes these patients were loath to stop any of the drugs, even when we recommended it; they were so pleased to be smear-negative each month. When we said, 'you can stop your capreomycin now,' some would reply, 'Frankly, I don't want to. I'd rather continue it.'"[18] Many patients were scared to stop treatment without a job and needed employment to replace SES's support. SES provided capital toward one patient's newsstand and another's candy cart, but employment assistance was the exception rather than the norm.

Financing and Supply

Tom White funded the first cohort of patients. The cost for the first 75 patients ranged from USD 504 to USD 32,383 per patient with a mean cost of USD 15,681. As Kim explained, "I remember Tom kept saying, 'When is it going to stop? How far should we go?' And Paul and I kept coming back, and all we had to do was tell Tom about the patients—that they had nothing, show pictures--and Tom would get upset and say, 'Keep going.'"

Farmer and Kim had accumulated a bill of USD 92,000 at the Brigham and Women's Hospital by "sweet talking" various people. When it finally reached the attention of the hospital president, they brought the bill to White to get themselves out of trouble. "And Tom paid it," Kim said.

In early 1998 Farmer asked the Open Society Institute for a donation. The Institute turned him down on the grounds that it was supporting another TB program in Russia that was following WHO recommendations. Farmer responded with an impassioned letter. He was invited to a meeting with George Soros and Alex Goldfarb, who ran the Soros-funded Russian TB project. After a week of passionate arguments, Farmer ultimately won Goldfarb and Soros over.[9]

PIH hired the first procurement manager in Boston to help put the suitcases together, and SES hired a young computer information systems student who had been helping with the community diagnosis, Flor Pachao, to track the medication supply and distribution as well as patients' monthly sputum sample collection. The medication going to Peru "wasn't just from Boston. We got capreomycin from New Mexico at one point; we got capreomycin from the New York TB authority. We were literally calling over the US for where they had stocks," Kim explained.

Pachao did most of her tracking by hand, on paper, for the first years. She would project what was needed every quarter for the next three months and inform Bayona who would make the request to the PIH office in Boston. Each time medication was given out, Pachao would dispense a receipt with the date of distribution, name of patient, quantity of medication, and project health promoter's name. The promoters would return the receipt with the patient's signature. Pachao read pharmacology manuals and knew the medications better than many of the doctors after a short time.

Global MDR-TB Movement

In 1997 after a patient MINSA had not approved for SES's alternative treatment died, Bayona told Farmer, "If you want to change this, forget the national program. You have to go to higher authorities."[23] Through a colleague, Farmer was invited to give a speech about TB at the annual North American IUATLD Conference in February of 1997. Many WHO and other TB specialists were there. Farmer's speech was entitled "Myths and Mystifications about MDR-TB."[23] In the speech he cited WHO's policy. The US CDC

Division of TB Elimination Director referred to the talk as "provocative," and Bayona heard a rumor that someone had called Suarez and told him, "Farmer says you're killing patients."[23]

Local Impact from Global Movement

WHO had begun working with the NTP in Peru to create a standardized regimen for resistant disease that would be given to all patients who failed the first regimens. In early 1997, the NTP added *esquema dos reforzado (*reinforced regimen two*)*, which extended the time patients took streptomycin by an additional three months. *Esquema dos reforzado* was used only for *esquema uno* failures, while *esquema dos* was indicated for relapses and patients who had abandoned treatment and returned. *Esquema dos reforzado* eventually reached failure rates of 70%.[28]

After October of 1997, another revision was made. *Retratamiento estandardizado* (standardized retreatment regimen) was added. It included kanamycin for the initial three months, complemented by ciprofloxacin, ethionamide, pyrazinamide, and ethambutol for 18 months. The *retratamiento estandardizado* was indicated for patients who had failed *esquema uno* and *esquema dos reforzado*. *Esquema uno* cost MINSA about USD 50 per patient. *Retratamiento estandardizado* cost over USD 1000 per patient (see **Exhibit 20** for MINSA expenditures).

Suarez established an independent evaluation committee, *Comité de Evaluación de Retratamiento National* (National Retreatment Evaluation Committee; CERN), to review cases and approve each patient before he or she began r*etratamiento estandardizado*. CERN received hundreds of requests. The meeting frequency increased from monthly to every two weeks until intermediate groups called CERs were formed in each district.

On World Health Day, 1998, Pedro Suarez gave a talk, speaking to the progress of the program in achieving the goals of the WHO. He reviewed the growth of the program and direction for the future:

> …what today we call directly observed therapy, this… is the most cost-effective strategy for controlling TB …it allows high percentages of cure with low percentages of abandonment, avoiding the multidrug-resistance, lowering the incidence rate of TB considerably.

Sharing Ideas: DOTS-Plus for MDR-TB

Harvard Medical School and SES/PIH helped convene a meeting in April 1998 to discuss the potential for treating patients suffering from MDR-TB in resource poor settings after determining the results from their first cohort of patients. Howard Hiatt, a member of the PIH Board of Directors, was the former professor of Arata Kochi. Kochi had never forgotten the time that Hiatt had invited him to his home, so when Hiatt invited him to participate, he felt indebted. He attended the meeting with several other WHO TB officers. The meeting, co-sponsored by the WHO's Global TB Programme and the American Academy of Arts and Sciences (AAAS), brought together 50 TB experts—including key pharmaceutical agencies, multilateral aid organizations, and foundation representatives—to re-examine policies for controlling tuberculosis.[29] There was heated debate about whether MDR-TB merited money from the limited budgets of leaders making decisions for large nations infected with TB. PIH/SES representatives argued that taking on MDR-TB might lead to an expansion of resources for the problem and long term change.[23]

The PIH/SES team left the meeting satisfied because for the first time participants agreed that "in some settings, DOTS alone is clearly insufficient." They agreed on a resolution that "all patients with active tuberculosis, regardless of drug susceptibility patterns, have a right to treatment." Kochi's colleague wanted to call the individualized treatment based on DST results that SES was using DOTS-Plus given the consensus that the treatment was best suited for places with strong DOTS programs. Participants were

supportive of the idea and decided that a new WHO working group would be formed to initiate and oversee DOTS-Plus pilot projects.

Kim and Farmer tried to keep their momentum alive by publishing an article in the *British Medical Journal*, "Community-based approaches to the control of multidrug resistant tuberculosis: introducing 'DOTS-plus.'" The article recapped the parts of the meeting they agreed with and stated the reasons that DOTS alone was not sufficient:

> *(a)* those already ill with the disease would not be cured with short course chemotherapy based on isoniazid and rifampicin; *(b)* nosocomial transmission is likely when untreated patients continue to seek care in clinics and hospitals; and *(c)* patients with primary resistance to isoniazid and rifampicin who receive standard, short course chemotherapy are likely to develop resistance to pyrazinamide and ethambutol as well. Since empirical retreatment regimens are often based on the same four drugs plus a short course of streptomycin, patients initially resistant to two drugs may become resistant to as many as five. This "amplifier effect" of short course chemotherapy has contributed to a large outbreak of multidrug resistant tuberculosis in urban Peru.

Kim and Farmer wrote: "it was noted 'you can pay now or you can pay later.' The costs will only rise with delay." The AAAS meeting was followed by many others. Kim and Farmer were opposed to the standardized treatment program being implemented in Peru, arguing that it was poorly designed and likely to be ineffective.

Global Access to Second-line Drugs

In 1999 the Working Group on DOTS-Plus for MDR-TB was established at WHO with two subgroups: drug procurement and a scientific panel for developing treatment guidelines. The Subgroup on Drug Procurement identified the cost of second-line drugs as a major impediment to DOTS-plus pilot projects. Kim was confident they could make the prices drop. By the mid 1990s, all but one class of second-line MDR-TB drugs were off patent, but prices had not shifted. A group from Harvard Medical School, PIH, and the Communicable Diseases Cluster of the WHO submitted an application to include seven second-line anti-tuberculosis drugs on the WHO's Model List of Essential Drugs to be used "in settings with established DOTS programs and in WHO-approved DOTS-Plus treatment regimens." The applicants hoped that including the drugs on the list would increase demand and increase market competition, lowering prices. Others feared that lowering prices would increase irrational use and lead to the development of "super-resistant" strains of MDR-TB. They believed that prohibitive pricing had helped prevent widespread MDR-TB.

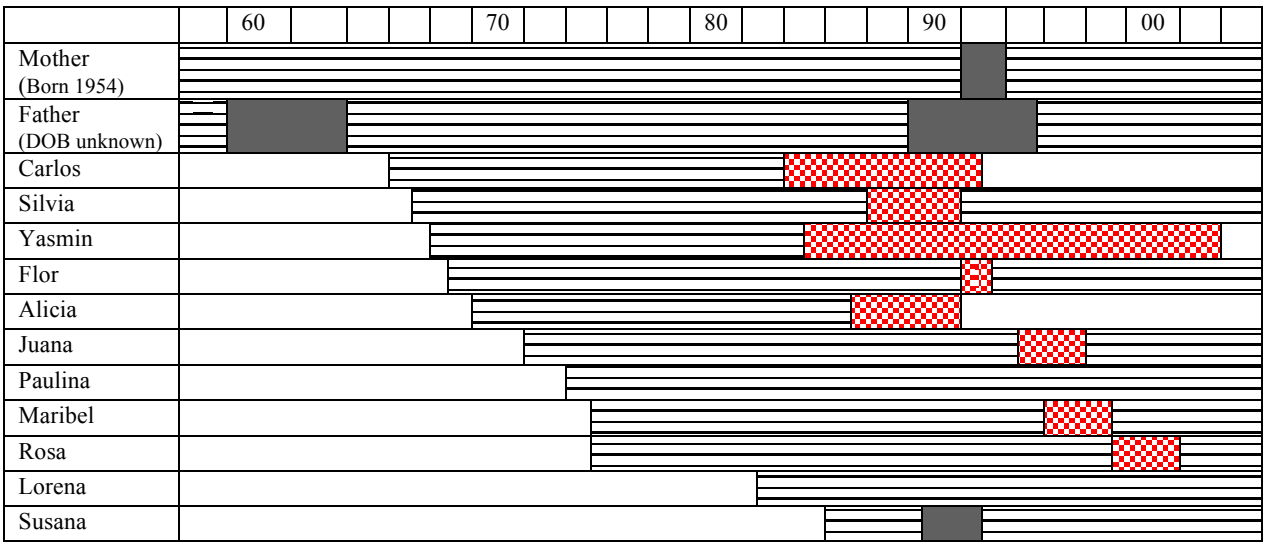
The group was successful in getting second-line TB drugs added to the WHO Model List of Essential Drugs in the "complementary medicines" section (see **Exhibit 21** for prices over time).

Expanding Treatment

In 1999 SES got permission to treat all MDR-TB patients in metropolitan Lima. By this time, five nursing students from the community had been integrated into the SES team and had assumed leadership of the project as the central coordinators for patient care. Each nurse was responsible for 25 to 30 patients; promoters were each responsible for 10 patients; volunteers supervised the daily treatment of three to four patients. SES hired two more secretaries, two assistants to the drug dispensary supervisor, and several drivers to transport food donations, medication, and personnel around the Northern Cone. When the whole team could no longer fit into the original lunch and meeting room, lunch was organized in shifts. A new patient therapy group helped reduce some of the time SES staff spent with individual patients.

By 1999, 85% of 80 patients who had completed treatment – including Juana and her husband – had remained smear and culture negative.[30] As funding began to run low for both SES and White, and with the eyes of the international TB community watching, the SES team had to figure out how it would sustain and expand the program in order to prove the feasibility of treating MDR-TB worldwide.

Exhibit 1 *Valdivia/Valdez Family History of Tuberculosis*



Living and healthy Living with TB Living with suspected case of TB

Source: Created by case writer.

Exhibit 2 *Asentamiento Humano in Carabayllo-Lima, Peru*

Source: Julie Rosenberg, 2009.

Exhibit 3 *Multidrug-Resistant Tuberculosis*

Multidrug-Resistant Tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) was an infectious disease caused by an isolate of *Mycobacterium tuberculosis*, which was resistant to at least isoniazid (INH) and rifampin (RIF), two of the first-line anti-TB drugs. MDR-TB could be contracted directly or could develop with inadequate chemotherapy for drug-sensitive TB. Inadequate therapy (insufficiently potent regimens or interrupted administration) selected for the survival of naturally-occurring drug resistant mutants. These mutants, present in the usual population of tubercle bacilli, occur at a frequency of roughly one in a million, and they can become the dominant strain in a patient.[31] Only 10% of people carrying any form of TB bacteria develop active disease over the course of their lifetime. Those with inactive disease are not contagious, but active disease is contagious. Bacteria are spread through the air in microscopic droplets by coughing, spitting, talking, or sneezing. Malnourished or HIV-infected people are at a greater risk for developing active disease because of their weakened immune systems. TB and MDR-TB bacteria can spread to any organ of the body; most commonly they attack the lungs and produce a common set of symptoms: cough with phlegm, fever, night sweats, fatigue, weight loss, and pain in the back or chest.

MDR-TB and TB present with the same signs and symptoms. Examining a patient's sputum under a microscope or culturing it in a laboratory can confirm the diagnosis. MDR-TB and drug -sensitive TB appear the same on smear microscopy examinations. Cultures using drug susceptibility testing (DST) can diagnose MDR-TB by differentiating it from drug-sensitive TB. It often takes at least six weeks to complete conventional DST and requires additional laboratory testing capacities. While the basic treatment for TB is six months, MDR-TB requires a course of chemotherapy lasting at least 18 months with more expensive, potentially toxic medications, often referred to as second-line agents.[6] MDR-TB treatment can consist of either individualized treatment regimens (ITR), tailored to the resistance profile of the infecting strain, or empiric standardized treatment regimens (STR). Second-line DST is more complex and expensive than first line DST and is required for ITR.

TB was the eighth leading cause of death worldwide in 1999, and in the period from 1996-1999, 5.1% of all TB cases had MDR-TB.[7] The second report from the Global Project on Antituberculosis Drug Resistance Surveillance – a survey of 58 geographical settings, sampling 26% of the world's population from 1996 to 1999 – showed that resistance to any drug among new cases ranged from 1.7% to 36.9%. [7] In 2000, there were an estimated 273,000 new cases of MDR-TB worldwide.[8] Among previously treated cases, the prevalence of MDR-TB was six times higher than in new cases.[7] In some regions of the world, so-called "hot spots," rates of drug resistance were even higher. Deaths from tuberculosis comprised an estimated 25% of all avoidable deaths in developing countries, while 95% of all TB cases and 98% of all deaths from TB occurred in developing countries.[32]

Source: Compiled by case writer.

Exhibit 4 ***Second-line Anti-tuberculosis Drugs***

Class	Drug Name	Abbreviation	Form	Possible Adverse Reactions
Aminoglycosides	Streptomycin	S	Injection	Renal tubular damage, vestibular damage, ototoxicity
	Kanamycin and Amikacin	Km Amk	Injection	Tinnitus, deafness, vertigo, reversible nephrotoxicity
	Capreomycin	Cm	Injection	Tinnitus, vertigo, kidney damage, hypokalemia, hypocalcaemia, hypomagnesaemia, hepatitis, pain at injection site
Thiomides	Ethionamide (or Prothionamide)	Eto	Tablet	Epigastric discomfort, anorexia, nausea, metallic taste, sulphurous belching, vomiting, excessive salivation, hallucinations, depressive, hypoglycaemia, hepatitis, gynecomastia, menstrual disturbance, impotence, acne, headache, peripheral neuropathy
Floroquinolones	Ofloxacin	Ofx	Tablet	Anorexia, nausea, vomiting, dizziness, headache, mood changes, convulsions
	Levofloxacin	Lfx	Tablet	
Other Second-Line Agents	Cycloserine (or Terizidone)	Cs	Tablet	Dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression, altered behavior, suicide, hypersensitivity reaction, hepatitis
	Para-Aminosaliccyclic acid	PAS	Granules or tablet	Gastrointestinal disturbance, general skin hypersensitivity, hepatic dysfunction, hypokalemia, anorexia, nausea, vomiting, abdominal discomfort, diarrhea, hypothyroidism, goiter
	Clofazamine	Cfz	Tablet	Discoloration of skin, gastrointestinal disturbance, crystal deposition causing discoloration of the eye, phototoxicity reactions, malabsorbtion, severe abdominal distress (No longer widely used.)

Source: Adapted by case writers from multiple sources.

Exhibit 5 *Brief Summary of WHO TB Treatment Guidelines, 1991-1997*

1991 The World Health Assembly adopted Resolution WHO 44.8, recognizing "effective case management as the central intervention for tuberculosis control" and recommending the strengthening of national tuberculosis programmes by introducing short course chemotherapy and improving the treatment management system.

1993 *Treatment of Tuberculosis: Guidelines for National Programs* published, categorizing patients according to their priority for treatment (highest to lowest), and providing recommended regimens.

Category I: newly diagnosed cases of smear-positive pulmonary tuberculosis and other newly diagnosed seriously ill patients with clinically severe forms of tuberculosis.

Recommended treatment regimen: 2HRZS (E)/4H_3R_3 or 6HT[•]

Category II: relapse and smear-positive treatment failures suspected of having INH-resistant and or S-resistant disease.

Recommended treatment regimen: 2HRZES/1HRZE/5 H_3R_3 E_3

"… If patient is not smear negative by the end of 12 weeks, the initial phase can be extended by 4 weeks. If patient is still smear positive at the end of the fourth month, all drugs should be stopped for two to three days and a sputum specimen tested for DST. The patient should then start the continuation phase. If pre-treatment DST showed patients fully susceptible to all the drugs, then the continuation phase of Category I patients should follow the initial phase. If the pretreatment studies showed resistance to H or R, then the patients should start continuation under close supervision. If the pretreatment studies showed resistance to both H and R …. the chance of achieving sputum conversion is limited. If the patient remains smear positive after the completion phase, he or she is not longer eligible for the re-treatment regiment."

Category III: pulmonary smear negative tuberculosis with limited parenchymal involvement and extra pulmonary tuberculosis (this category usually includes children for whom pulmonary disease is almost always smear negative).

Smear negative pulmonary cases that will eventually become smear-positive are a higher priority than those with more benign forms of extrapulmonary tuberculosis.

Recommended Regimen: 2HRZ/2H_3 R_3

Category IV: chronic tuberculosis

"Management of these patients who have a high likelihood of MDR-TB is highly problematic. Even with optimal therapy, cure may be possible in only half of such cases. Second-line drugs are very expensive, are generally more toxic and are significantly less effective than conventional regiments

[•] Treatment regimens for TB have a standard code. Each anti-Tuberculosis drug has an abbreviation: isoniazid (H), rifampicin (R), pyradinamide (Z), streptomycin (S), ethambutol (E), thioacetazone (T). TB treatment consists of two phases; the number before a phase is the duration of that phase in months. Letters in parenthesis represent fixed-dose combinations. Subscript numbers indicate the number of doses per week of the letter they follow. No subscript number following a letter represents daily (6 times a week) doses of that drug. For example, 2HRZS (E)/4H_3R_3 represents two months of some dose of isoniazid, rifampicin, pyradinamide, and streptomycin with a fixed dose of ethambutol daily followed by four months if isoniazid and rifampicin three times a week.

in drug-susceptible cases. More over, the patients must remain in the hospital for several months. If possible, the drug sensitivity of the bacilli should be established and a re-treatment program should be attempted with second-line and experimental drugs. However, in countries, with limited resources, treatment of patients with chronic tuberculosis should be given the lowest priority and should not divert resources from higher priority patients. One option, available to programs with limited resources, is to prescribe lifelong isoniazid for such patients, in the hope that this will diminish their infectivity and reduce the transmission of resistant organisms."

1995 WHO Tuberculosis Control Workshop held in Geneva discussed simplifying the patient treatment categories and the use of second-line drugs. Participants "recommend that a country prepared to go to this expense should only provide these second-line drugs for a specialized unit (or units in large countries), in close connection with a laboratory able to carry out cultures and reliable susceptibility tests."

1997 *Treatment of Tuberculosis Guidelines for National Programs 1997, 2nd edition* published to "to update the guidelines in the light of the experience gained since the first edition in assisting NTPs." The same basic regimens remained in place with some alternatives and flexibility to acknowledge variations in resources and circumstances across countires.

Guidelines for the Management of Drug-Resistant Tuberculosis published to advise "more economically prosperous" countries with "resources for second-line drugs" on how to "give some hope of cure" to patients who remain sputum smear-positive following fully supervised WHO retreatment regimen.

Source: World Health Organization, *Guidelines for the Management of Drug-Resistant Tuberculosis*. 1997, WHO: Geneva; World Health Organization, *Treatment of Tuberculosis: Guidelines for National Programmes, 2nd Edition*. 1997, WHO: Geneva; and World Health Organization, *Treatment of Tuberculosis: Guidelines for National Programmes*. 1993, WHO: Geneva.

Exhibit 6 ***Select Results from WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, 1997***

Country	Patients Tested	Overall		Resistant to:				Poly Resistance	
		% Suscept.	% Resist.	1 drug	2 drugs	3 drugs	4 drugs	Any	MDR
Peru	*	81.5	18.5	11.0	4.9	1.8	0.7	7.5	4.5
Argentina	*	82.0	18.0	7.7	3.9	3.6	2.9	10.4	8.0
Bolivia	*	71.6	28.4	23.2	5.8	0.2	0.1	6.2	2.1
Botswana	*	95.2	4.8	3.8	0.5	0.1	0.4	1.0	0.8
Brazil	*	91.0	9.0	6.5	2.4	0.2	0.0	2.5	1.3
Dominican Rep.	*	57.6	42.4	25.2	10.9	4.2	2.0	17.2	8.6
France	*	90.4	9.6	6.3	2.6	0.5	0.2	3.3	0.9
India (Delhi state)	2,240	67.6	32.4	10.9	10.9	7.1	3.5	21.5	13.3
Latvia	*	58.4	41.6	7.0	13.5	14.2	7.0	34.7	22.1
USA	14,344	87.1	12.9	8.4	3.0	0.8	0.7	4.5	2.0
MEDIAN**	n/a	87.4	12.6	7.5	3.1	0.9	0.6	5.0	2.2
minimum	n/a	57.6	2.3	1.2	0.0	0.0	0.0	1.0	0.0
maximum	n/a	97.7	42.4	25.2	14.0	14.2	7.0	34.7	22.1
WEIGHTED MEAN***	n/a	83.3	16.7	9.1	4.6	2.1	1.0	7.7	4.3

* Combined drug resistance prevalence was calculated from primary and acquired figures; except for countries with surveillance of virtually 100% of TB patients, acquired drug resistance prevalence was weighted by the proportion of cases for retreatment.

** All medians, minimums and maximums apply to the complete study including Australia, Benin, Cuba, Czech Republic, England & Wales, Estonia, Ivory Coast, Kenya, Lesotho, Nepal, Netherlands, New Zealand, Northern Ireland, Portugal, Puerto Rico, Republic of Korea, Romania, Russia (Ivanovo Oblast), Scotland, Sierra Leone, Spain (Barcelona), Swaziland, Thailand, Viet Nam and Zimbabwe.

*** Arithmetic mean weighted by the estimated number of smear-positive cases of TB in 1995 for country or region surveyed.

Source: World Health Organization, *Anti-tuberculosis drug resistance in the world*. 1997, WHO: Geneva.

Exhibit 7 *Incidence of Smear Positive TB in Peru by Department, 2000*

Department	Population	Area (KM²)	Density (habitants per KM²)	New smear positive cases	Incidence (per 100,000)	Urban population (%)
Cajamarca	1,411,942	33,318	42	243	17	27.9
Apurímac	426,904	20,896	20	88	21	37.9
Huancavelica	431,088	22,131	19	105	24	29.7
Amazonas	406,060	39,249	10	105	26	39.0
Puno	1,199,398	71,999	17	333	28	41.3
Piura	1,545,771	35,892	43	453	29	71.4
San Martín	743,668	51,253	15	297	40	63.5
Pasco	247,872	25,320	10	114	46	61.1
Tumbes	193,840	4,669	42	99	51	88.7
Huánuco	776,727	36,887	21	409	53	41.2
Ancash	1,067,282	35,877	30	581	54	59.0
Junín	1,190,488	44,197	27	666	56	66.4
Ayacucho	527,480	43,815	12	344	65	49.5
Cusco	1,158,142	72,104	16	762	66	48.6
Arequipa	1,072,958	63,345	17	758	71	86.6
Lambayeque	1,093,051	14,231	77	775	71	78.6
Moquegua	147,374	15,734	9	115	78	83.6
La Libertad	1,435,970	25,500	57	1,262	86	70.1
Loreto	880,471	368,852	2	930	106	59.3
Ucayali	424,410	102,411	4	470	111	66.8
Ica	649,332	21,328	30	774	119	84.3
Tacna	277,188	16,076	17	382	138	90.2
Lima	7,466,190	34,802	215	11,123	149	96.9
Callao	773,701	147	5263	1238	160	99.9
Madre de Dios	84,383	85,183	1	154	183	60.6

Note: KM² indicates square kilometers.

Source: Ministerio de Salud, *Informe 2000*, in *Tuberculosis en el Perú*, República del Perú, Editor. 2000, Dirección General de Salud de las Personas: Lima.

Exhibit 8 *Select Results of WHO's Random Sample Survey in Latin America, Initial Drug Resistance by Cluster*

	NUMBER OF CULTURES				RESISTANCE (%)			
Cluster	**Received**	**Excluded**	**Retained**	**Susceptible**	**1 drug**	**2 drugs**	**>2 drugs**	**Total resistance (%)**
Callao	23	1	22	10	4 (18.2)	4 (18.2)	4 (18.2)	12 (54.5)
Ica	21	1	20	12	4 (20.0)	2 (10.0)	1 (5.0)	7 (35.0)
Lima	79	2	33	20	12 (36.4)	1 (3.0)	0 (0)	13 (39.4)

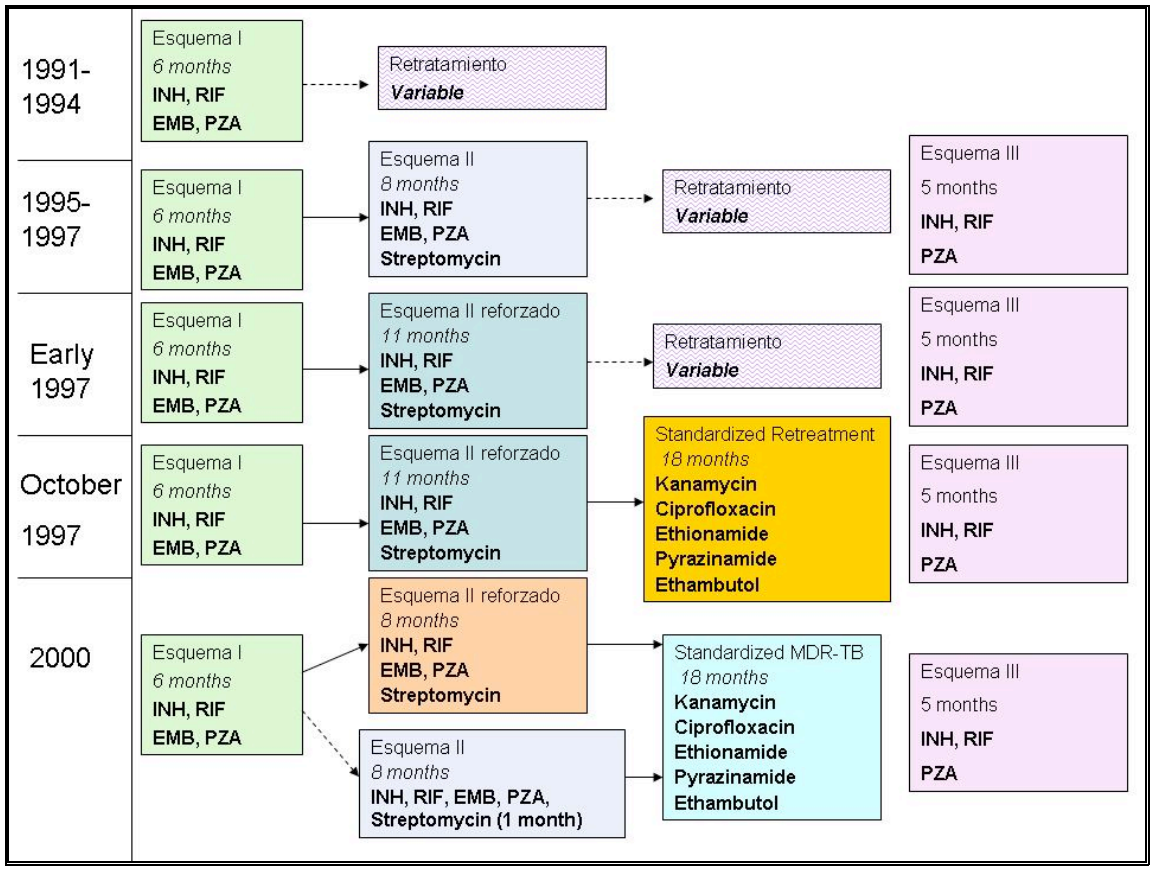
Source: Laszlo, A. and I.N. de Kantor, *A random sample survey of initial drug resistance among tuberculosis cases in Latin America*. Bulletin of the World Health Organization, 1994. 72(4): p. 603-610.

Exhibit 9 *Growth of MINSA TB Program by Year, 1991–1997*

	1991	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**
Total health establishments	4,021	4,460	4,464	4,980	5,789	6,263	6,349
Establishments offering NTP	977	2,774	3,016	3,487	5,272	6,009	6,293
Labs doing smears	425	514	579	651	823	987	1,072
Labs doing culture	13	24	31	42	46	57	65
Sputum samples collected	978	2,460	2,369	3,238	4,441	5,022	4,964

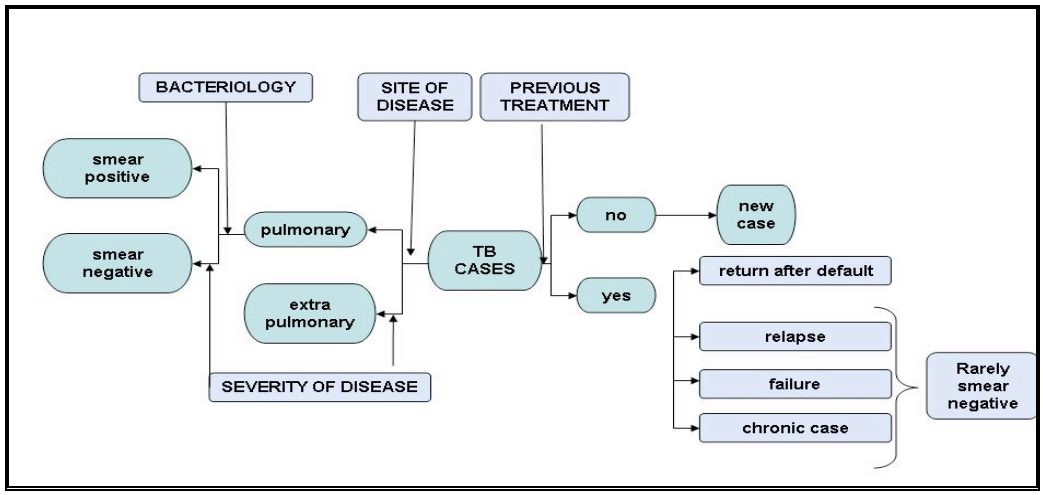
Source: Ministerio de Salud, *Informe 2000*, in *Tuberculosis en el Perú*, República del Perú, Editor. 2000, Dirección General de Salud de las Personas: Lima.

Exhibit 10 *NTP Treatment Regimens from 1991 to 2000*



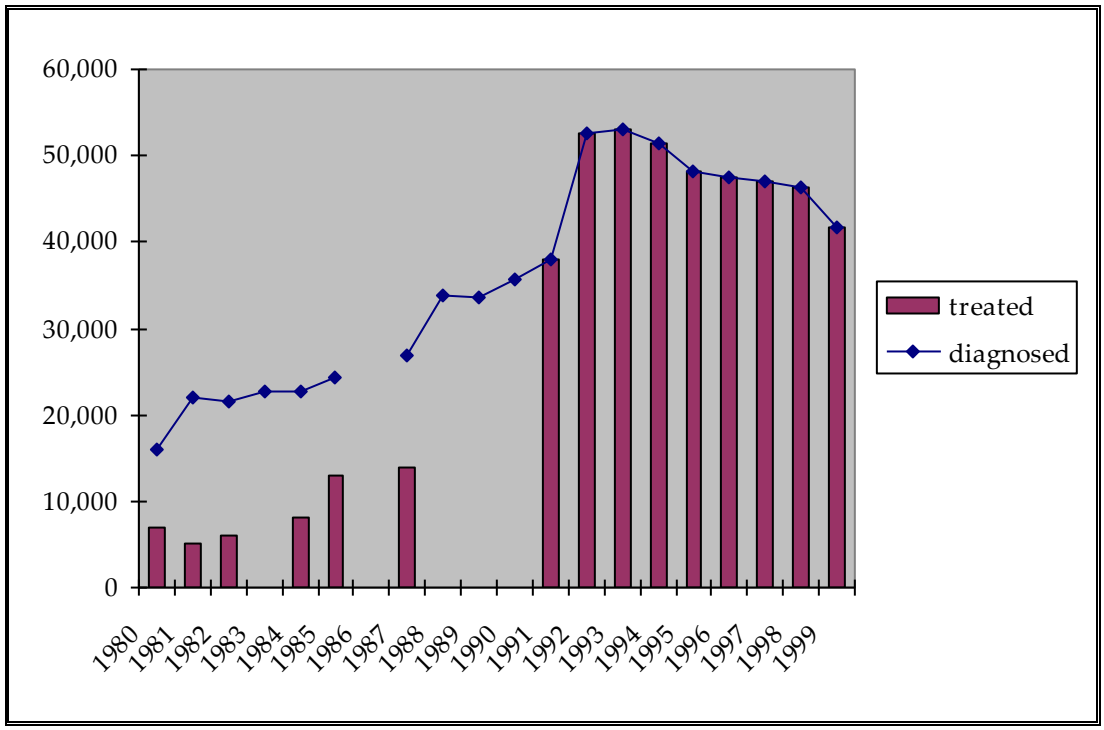
Source: Compiled by case writers.

Exhibit 11 *WHO Determinants of Tuberculosis Case Definitions, 2003*



Source: World Health Organization, *Treatment of Tuberculosis: Guidelines for National Programmes, 3rd ed.* 2003, WHO: Geneva, Switzerland.

Exhibit 12 *TB Cases Detected and Treated in Peru, 1980–1999*



Source: Ministerio de Salud, *Informe 2000*, in *Tuberculosis en el Perú*, República del Perú, Editor. 2000, Dirección General de Salud de las Personas: Lima.

Exhibit 13 *Outcome of Patients Starting* Esquema Único/Uno

	1991	1992	1993	1994	1995	1996	1997	1998	1999
Percent cured from esq. 1	76.8	82.5	85.3	86.2	87.7	91.3	92.1	92.5	92.6
Percent abandoning treatment	12.1	9.2	7.7	6.9	5.9	4	3.7	3.2	3.1
Percent dying	4.1	3.3	3.0	3.1	3.1	2.6	2.2	2.2	2.1
Percent transferring without confirmation	3.4	2.4	1.9	1.7	1.2	1.1	0.5	0.7	0.7
Percent failing	3.6	2.6	2.1	2.1	2.0	1.0	1.3	1.4	1.6

Source: Ministerio de Salud, *Informe 2000*, in *Tuberculosis en el Perú*, República del Perú, Editor. 2000, Dirección General de Salud de las Personas: Lima.

Exhibit 14 *Outcome for Patients (Relapses/Previously Abandoned) Entering* Esquema Dos

	1996 Relapsed patients	1996 Previously abandoned	1997*
Cured	82.6	68.8	--
Abandonment rate	20.1*	--	21.7
Death rate	6	4.5	5
Failure rate	4.1	2.4	4.6

* Not calculated independently for relapses and previously treated patients

Source: Peruvian Ministry of Health, National TB Control Program.

Exhibit 15 *Comparison of Health and Economic Indicators in Haiti and Peru, 1994*

	YEAR	HAITI	PERU
Population	2000	8,648,000	26,004,000
Average Life Expectancy (years)	2000	58	72
Infant Mortality Rate (Deaths per 1000 live births)	2000	109	36
GDP per capita in (2000 USD)*	1999	455	2,021
GDP per capita in - PPP (2005 international dollar)	1999	1,206	5,438
TB Prevalence (per 100,000 people)	1999	550	289

Source: Created by case writers (see table in text).

Exhibit 16 *Growth of SES's MDR-TB Treatment Program*

	Phase I: 1996	Phase II: 1997-1998	Phase III: starting 1999 until beyond 2000*
Patients enrolled	10	57	1046
DOT workers	0	18	268
SES health promoters	11	12	29
SES nurses	0	2	5
NTP physicians	1	5	6
SES physicians	2	4	6
Pharmacy personnel	0	1	4
Administrative	3	6	26

* numbers reflect size by 2002

Source: Shin, S., J. Furin, J. Bayona, K. Mate, et al., *Community-based treatment of multidrug-resistant tuberculosis in Lima, Peru: 7 years of experience*. Social Science and Medicine, 2004. 59: p. 1529-1539.

Exhibit 17 *Incidence of Adverse Events in First Treatment Cohorts*

Adverse Effect	Patients experiencing each effect *n* (%)	Mean interval from initiation of therapy to occurrence of adverse effect in months (SD)
Mild gastritis	60 (100)	Not available
Dermatological effects	26 (43.3)	Not available
Peripheral nervous system	12 (20)	9.0 (4.6)
Depression	11 (18.3)	9.1 (4.9)
Anxiety	7 (11.7)	8.5 (4.7)
Hypothyroidism	6 (10.0)	10.8 (2.3)
Psychotic symptoms	6 (10.0)	3 (4.4)
Central nervous system (seizure or intractable headache)	5 (8.3)	6.4 (2.4)
Arthralgias/arthritis	4 (6.7)	7.8 (7.5)
Hearing loss	4 (6.7)	13.8 (7.7)
Renal toxicity	2 (3.3)	14.5 (2.1)
Hepatitis	1 (1.7)	3 (0.0)
Severe gastritis	1 (1.7)	1 (0.0)
Optic neuritis	0 (0.0)	0.0

Source: Furin, J., et al., Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. International Journal of Tuberculosis and Lung Disease, 2001. 5(7): p. 648-55.

Exhibit 18 ***Select Characteristics of the First 75 Patients at the Initiation of Individualized Treatment with SES***

Characteristic	No. of Patients (%)	Median (Range)
Sex	(n=75)	
Male	37 (49)	
Female	38 (51)	
Age (years)		26.8 (11.8 – 65.1)
Household size (no. of members)		7 (2-20)
Marital status		
Unmarried	47 (66)	
Married	24 (34)	
Parity		
0 live births	23 (61)	
≥1 live births	15 (39)	
Body mass index		19.9 (12.4-29.8)
Men		20.6 (13.1-29.8)
Women		19.0 (12.4-25.2)
Men with BMI<20	15 (41)	
Women with BMI<18.5	17 (45)	
History of homelessness, imprisonment, other institutionalization, or addiction to drugs or alcohol	17 (23)	
Months from diagnosis of TB to ITR		44.2 (2.1-383.4)
Months from diagnosis of MDR-TB to ITR		8.1 (0.2-103.2)
No. of drugs to which TB was resistant at initiation of treatment		
All drugs		6 (2-12)
First-line drugs		5 (2-5)
Second-line drugs		1 (0-7)
Parenteral drugs (SM, Km, Amk, Cm)		1 (0-4)

Source: Mitnick, C., et al., *Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru.* New England Journal of Medicine, 2003. 348(2): 119-28.

Exhibit 19 ***Suspected Causes of Death among Patients who Died during or after Individualized Treatment***

Cause	During Therapy		After Completion of Therapy
	<4 mo completed	≥4 mo completed	
Massive hemoptysis	3	0	0
Respiratory failure	5	2	1(14 wk after completion)
Sepsis (multisystem organ failure)	0	1	0
MDR-TB relapse or reinfection	0	0	1(23 wk after completion
Probable narcotic overdose	0	0	1(43 wk after completion)
Unknown	1	2	

Source: Mitnick, C., et al., *Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru.* New England Journal of Medicine, 2003. **348**(2): p. 119-28.

Exhibit 20 *MINSA Expenditure on Diagnosis and Treatment per Patient, 1999*

ACTIVITY	COST PER PATIENT (USD)	DISTRIBUTION/% OF EXPENDITURE TOTAL
Treatment	(varied)	56
Esquema uno	61.36	29
Esquema dos	107.40	11
Esquema tres	49.56	6
Esquema dos reforzado	136.92	1
Esquema MDR standard	1121.55	8
Treatment for HIV/AIDS co-infection	75.47	1
HIV/AIDS prophylaxis	24.07	1
Symptom identification	0.45	8
Control checkup	0.38	1
Culture	1.62	3
Talk	1.18	9
Referrals	0.45	Nd
Interview	0.28	1
Receipt and analysis of smear	no data	16
Vaccine	0.26	3
House visit	1.19	2

Source: Ministerio de Salud, *Impacto economico de la tuberculosis en el Perú 1999*, MINSA, USAID, and Vigía, Editors. 2001: Lima, Peru.

Exhibit 21 *Reduced Prices of Second-line TB Drugs*

Drug	Formulation	1997 Price (in USD)	1999 Price (in USD)	Decline
Amikacin	1 gm vial	9.00	0.90	90 %
Cycloserine	250 mg tab	3.99	0.50	87 %
Ethionamide	250 mg tab	0.90	0.14	84 %
Kanamycin	1 gm vial	2.50	0.39	84 %
Capreomycin	1 gm vial	29.90	0.90	97 %
Ofloxacin	200 mg tab	2.00	0.05	98 %

Source: Kim, J. Hot Topics in Global Health. Presentation. July 2008.

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