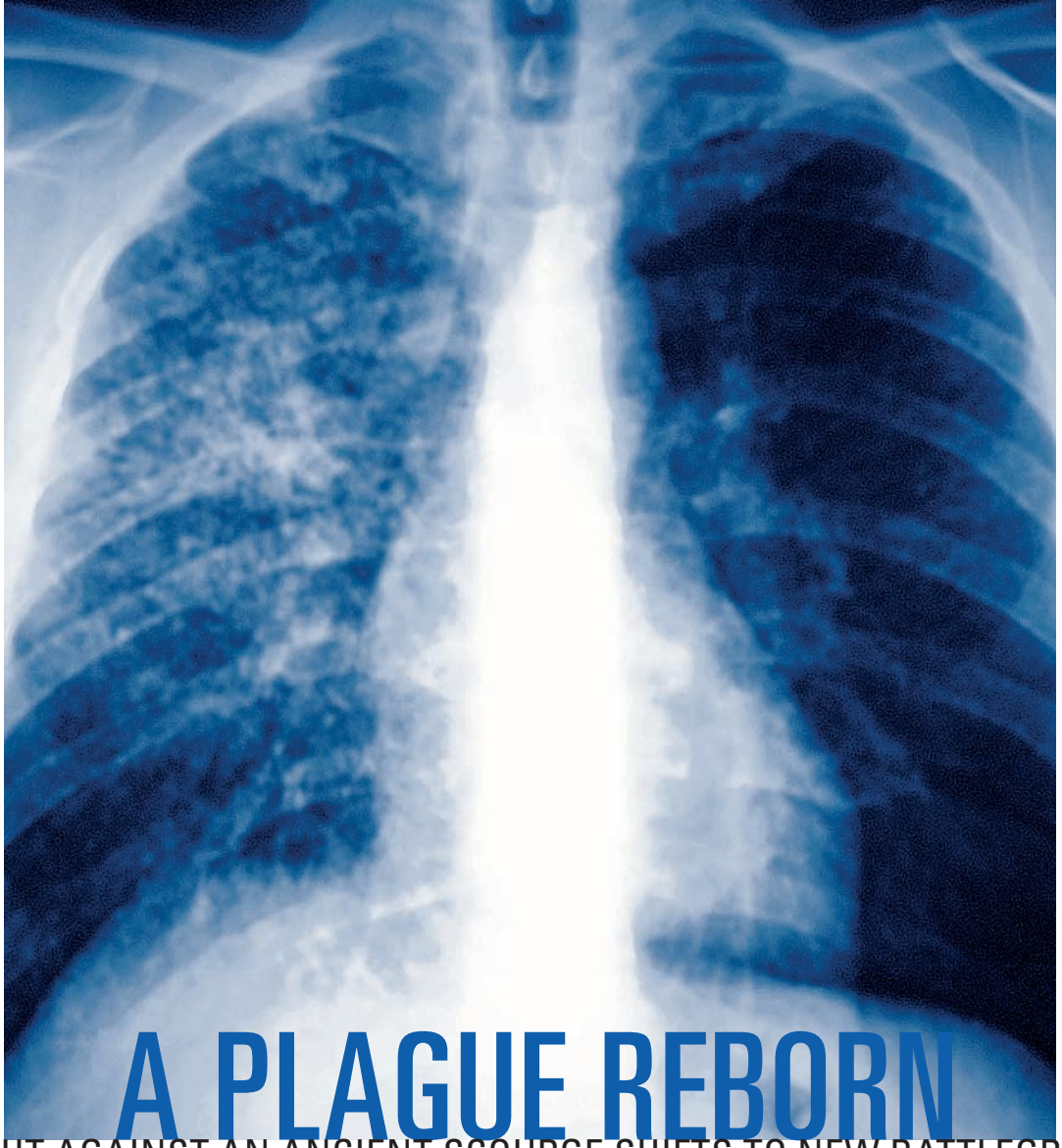


A PLAGUE REBORN

THE FIGHT AGAINST AN ANCIENT SCOURGE SHIFTS TO NEW BATTLEGROUNDS.

by JONATHAN SHAW

JAMES CAVALLINI / PHOTO RESEARCHERS, INC.

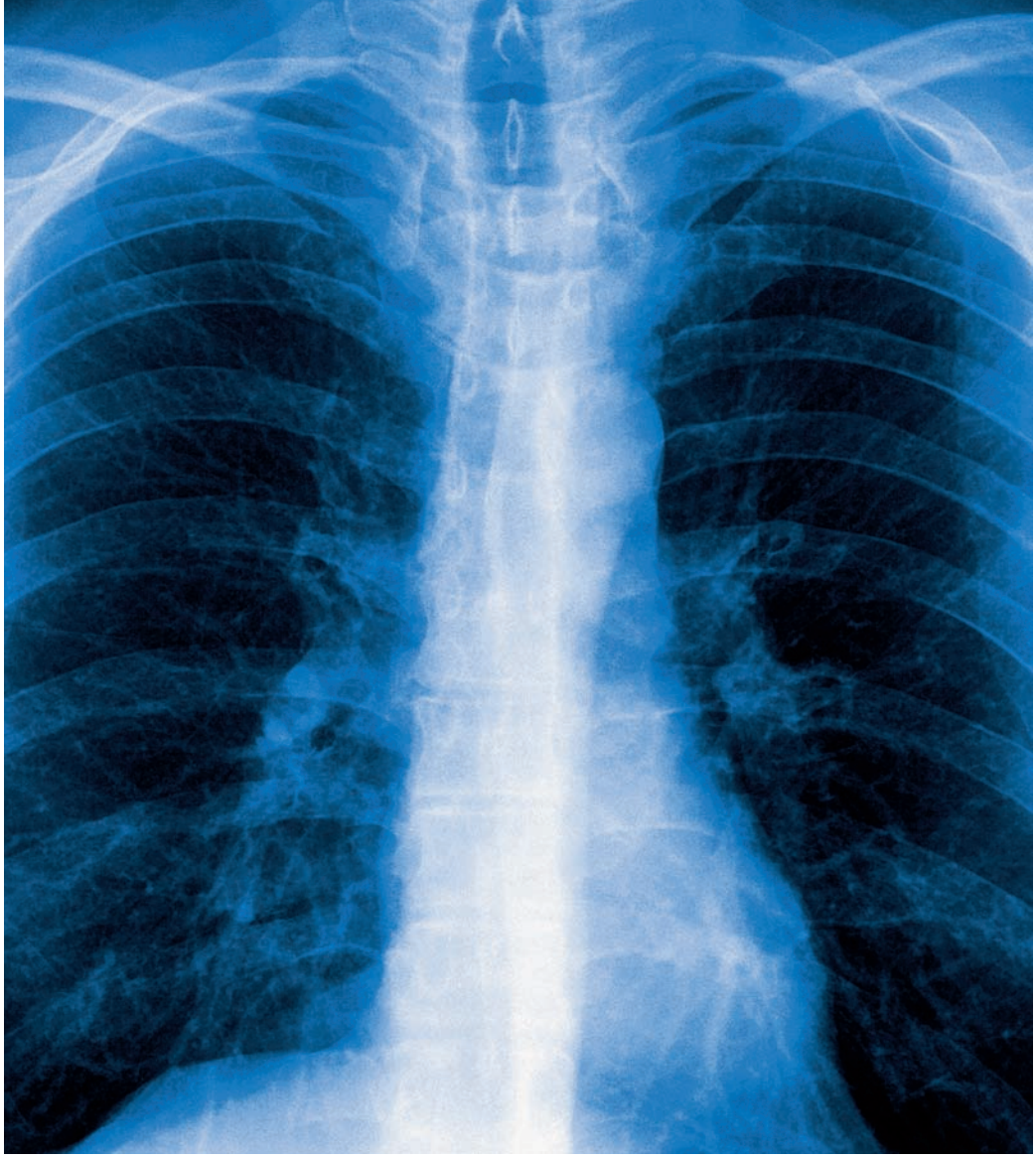
THERE IS A TENACIOUS LITTLE BUG that infects one in three people worldwide, hiding within their immune cells. Other microbes use the same strategy to evade detection, but this one is unusual because most of the two billion people who carry it don't even know it—and never will. One in 10 carriers, however, will get sick, and require months or years of persistent treatment with simultaneous doses of multiple antibiotics to be cured. A like number will appear healthy until, decades later, they suddenly fall ill of a long-latent and potentially fatal disease. Scientists who study the bacterium can't answer even the most basic biological questions about its life cycle—where does it hide for so long? why is it so hard to eradicate?—even though it has killed more people in human history than any other disease by far: one billion in the last century; two million last year. The microbe is *Mycobacterium tuberculosis*—TB for short—and it has, in the last 15 years, become increasingly resistant to antibiotics.

TB's resurgence as a serious threat to global health has brought together professors from Harvard's public-health, medical, and business schools to tackle the disease. Since the 1998 appointment of Barry Bloom, himself a TB researcher, as dean of the Harvard School of Public Health (HSPH; see page 64), the University has assembled a deep bench of research scientists focused on the bacterium. And in the field, Harvard works with Partners in Health (PIH), a nonprofit founded to bring Western medicine to partner organizations caring for the world's poor; PIH offers clinical expertise in treatment strategies that have proven effective in even the most difficult circumstances.

Yet TB presents a host of unsolved problems, ranging from the lack of a basic understanding of the bug's biology, to the absence of a simple way to diagnose infection, to the frustrating pace of vaccine and drug development, to complexities of clinical treatment. To make matters worse, TB synergizes with HIV wherever the two meet: each disease makes its carriers more susceptible to the ravages of the other. The impossibility of treating the two separately has underscored the need for a new way of thinking about the organization and delivery of global healthcare interventions.

A Contemporary Killer's Reach

IN THE UNITED STATES, TB is often thought of as a nineteenth-century disease. Known then as consumption, in its pulmonary form it led to cavities in the lungs, weight loss, and slow death in 50 percent of cases. But TB can also infect the skin, bones, and other parts of



ALFRED PASIEKA / PHOTO RESEARCHERS, INC.

Pale blotches on a chest x-ray (opposite) indicate pulmonary tuberculosis. Cavities form within these light areas. Healthy lungs (above) appear clear.

the body. The hunchback of Notre Dame probably had tuberculosis of the spine. Today, in parts of the world where HIV is prevalent and antibiotics in short supply, the TB mortality rate and the rate at which it awakens from dormancy are soaring, while the number of drugs still effective against it is shrinking. In parts of the former Soviet Union, for example, drug-resistant strains now represent about 20 percent of all new cases.

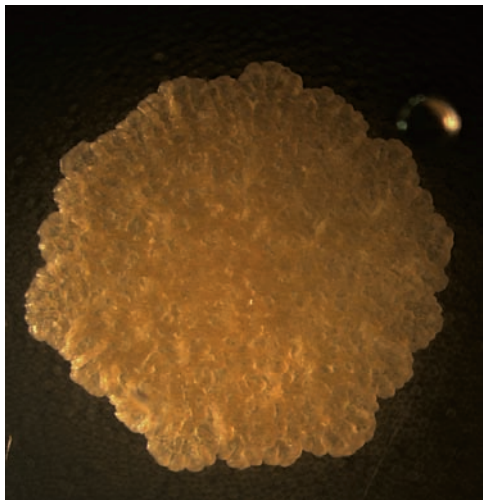
Transmitted by the simple act of breathing, TB is a social disease whose spread is closely linked to the conditions in which people live and work. "It was the HIV of the 1600s," says Eric Rubin, an HSPH associate professor of immunology and infectious diseases. Poor ventilation, malnutrition, and cramped living and sleeping quarters aid in its transmission. The Industrial Revolution's factories, teeming with workers, brought unprecedented levels of urban density, creating ideal conditions for TB's spread. That pattern is being repeated in different parts of the world today: epidemics rage in China and India.

As living standards improve, however, rates of infection drop. In the United States and Europe, TB rates declined rapidly from the 1870s through the 1920s, even before the discovery of antibiotics. The "sanatorium movement"—the practice of sending patients to clinics in the mountains where they could breathe fresh air—may have had something to do with that, says HSPH associate professor of epidemiology Megan Murray, in part because it isolated carriers. "But more likely," she adds, "the decline was caused by cultural and socioeconomic change: less crowding or lower vulnerability to infection."

Sunlight can kill the bacteria, making open-air transmission rare. But TB spreads quickly in darkened mines, prisons, and even hospitals without proper infection control. Recent research, on which Bloom collaborated with Robert Modlin of UCLA, suggests that lack of sunlight may also compromise the host immune system's antimicrobial capabilities. Vitamin D, produced when sunlight hits the skin, appears to be a vital link in a chain that promotes secretion of cathelicidin, a powerful microbicide that may prevent TB infection by increasing a person's innate immunity. Lab studies have shown that dark skin pigmentation absorbs ultraviolet light and thus lowers Vitamin D production below the critical threshold level necessary to produce cathelicidin.

HIV makes people more vulnerable to TB infection. The origins of an epidemic that struck New York City in the late 1980s and early 1990s have been linked not only to increasing rates of HIV infection in the prior decade, but to fires. One study showed that as fire stations were closed, surrounding neighborhoods

began to fall into disrepair. An advancing "fireline" that discouraged reinvestment by landlords in these neighborhoods led to the destruction of 150,000 to 200,000 housing units. The consequence was a "vast internal migration"—about 600,000 people over a five-year period—to adjacent neighborhoods. The overcrowding that ensued made the city fertile ground for an epidemic. By the time the outbreak ended in the mid 1990s, the cost to control it had exceeded $1 billion.



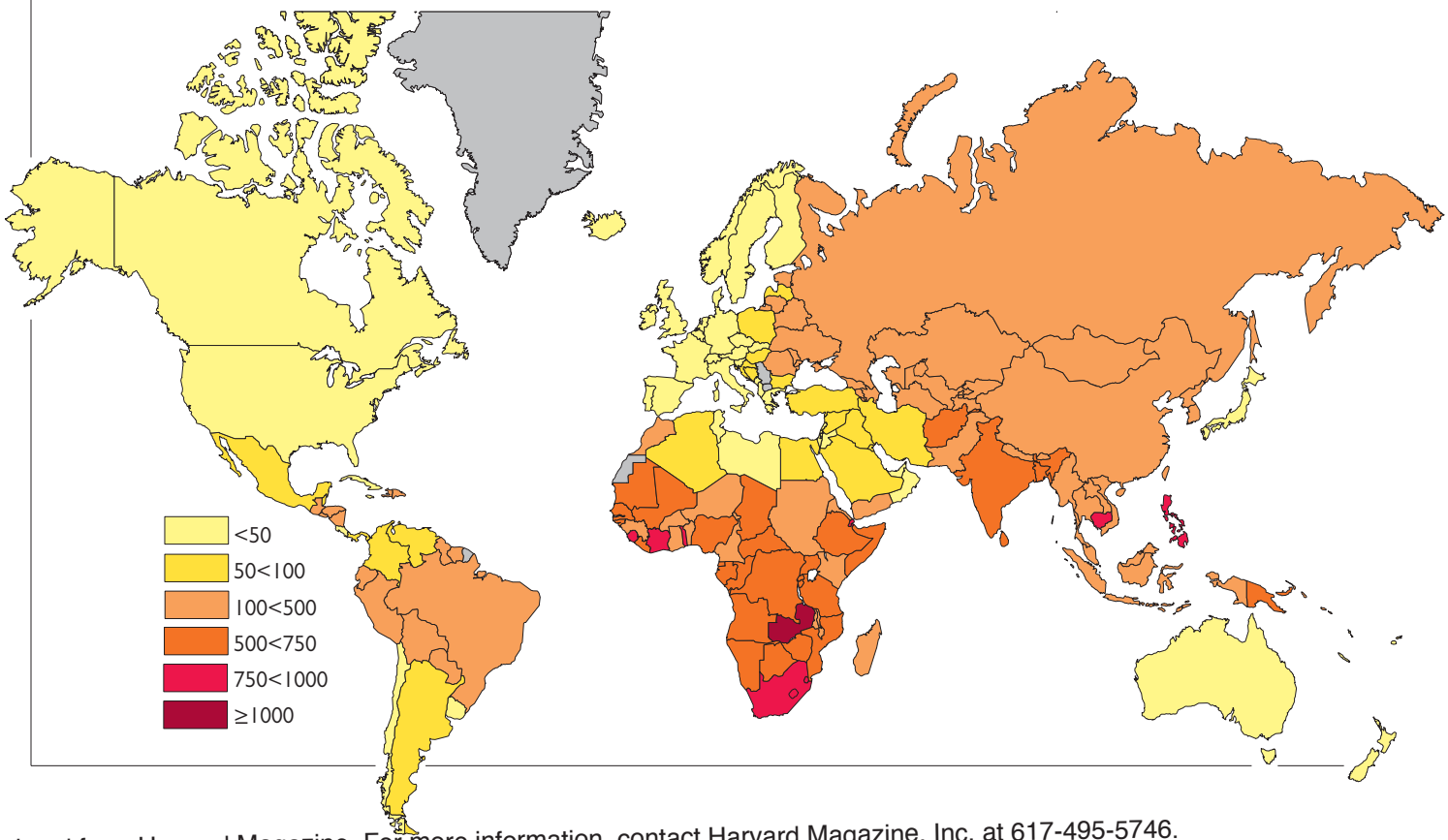
More recently, the ease with which TB can travel internationally overnight was underscored in May 2007 by the Andrew Speaker incident. Speaker, a young American diagnosed with drug-resistant tuberculosis, subsequently took multiple international plane flights as part of his wedding and honeymoon celebration. Although the likelihood of infection due to a single such exposure is low, and the prospect of a U.S. epidemic has seemed unlikely due to this country's social and economic stability, "If you got on a plane," points out Murray, "and sat by somebody who had extensively drug-resistant TB and coughed on you and gave you a disease that couldn't be treated, you wouldn't be happy about it."

The average carrier infects 20 other people over the course of a lifetime, which suggests that the risk of transmission at any particular moment is low. But TB can be highly contagious—inhaling a single bacterium is enough to cause infection. In a carefully documented case in the United States, a young man passed the disease widely and rapidly to even the most casual of contacts: co-workers, people who had a meal with him, and even a person who stood near him for a few minutes at a bus stop.

The symptoms at first are easy to ignore. A cough may be the only early sign of active pulmonary disease. Victims often experience fever, night sweats, and loss of appetite that eventually leads to weight loss. They may cough blood and grow fatigued easily, but in some countries, because of the social stigma associated with the disease, they may successfully hide their symptoms. In a quarter of cases, TB spreads from the lungs to infect other parts of the body, causing illnesses like scrofula, characterized by weeping sores of the neck, or Pott's disease, which causes a humpback.

Rapid diagnosis of TB infection is made using a skin test. But these tests are poor tools, because they can't distinguish among active disease, latent infection, and disease that has already been cured with antibiotics. (A vaccine exists that protects children, but less so adults; its effectiveness reportedly varies from country to country for reasons that are not understood. It, too, causes a false positive skin test, so the fact that the vaccine is not used in the United States has proved an advantage in the control of modern TB outbreaks: it is easier to discover who really is infected.) The other diagnostic, the culture of sputum, is not only costly and slow, but even if the patient coughs up sputum, says Murray, "there is a reasonably good chance that the physician won't actually get any bacilli."

Treatment, meanwhile, is prolonged, and some of the drugs, particularly those used to treat resistant cases, are not tolerated well. Kidney failure, depression, and psychosis are among the most debilitating side effects.



AN EVASIVE BACTERIUM

Mycobacterium tuberculosis remains a black box, and scientists have begun to wonder if it operates by a different set of biological rules than those they are familiar with. Last year, the director of the National Institutes of Health awarded a special "New Innovator" grant to a young Harvard School of Public Health (HSPH) faculty member, Sarah Fortune, to investigate this possibility.

Fortune, an assistant professor of immunology and infectious diseases, asks how TB escapes detection by the immune system—a fundamental question with ramifications that extend all the way to the structure of treatment programs, whose difficulty reflects the complex biology of the bug.

"The canonical model," she says, "is that TB goes into the macrophage [a form of white blood cell], is sequestered, becomes dormant and drug resistant, and lives there protected forever." But other bacteria, including those that cause salmonella, legionnaires' disease, and typhoid fever, have "at least conceptually similar lifestyles in a protective vacuole in a macrophage," and are treatable. Typhoid, for example, can be cured with ciprofloxacin in three days. With TB, she says, "It takes at least six months—nine if the case is latent."

Furthermore, a typical macrophage lives only about two years, while latent TB can persist for 30. This implies that the bacteria periodically move on to other cells to escape the host animal's immune response. "Malaria does something similar on a much smaller time scale," Fortune explains. "You get waves of disease when the malaria is escaping and replicating, and then it becomes quiescent, whereas with TB, it is not clear that there are real expansions and contractions of populations." The implication is that a very few bacteria become very adept at surviving in the host across generations.

The grand problem with *that* possibility, Fortune explains, is that it flies in the face of traditional evolutionary theory. Typically, bacteria resist host immune defenses or drug therapies by random mutation within *large* populations. Those few individual bacteria with genetic changes that make them resistant survive these selective pressures and found new populations. If their bacterial progeny face new pressure—a second antibiotic, for example—there is a chance, if they are numerous enough, that one or more will carry an additional mutation conferring resistance to the second antibiotic. But genome sequencing of drug-resistant TB strains carried out at the Broad Institute (in a project co-led by HSPH associate professor of epidemiology Megan Murray) suggests that TB has little genetic plasticity—all strains seem to share a basic blueprint—and doesn't mutate especially quickly. "Is it mathematically even possible," Fortune asks, "that a few bacteria that mutate very slowly could actually develop resistance to eight antibiotics?" (as strains of extensively drug-resistant TB repeatedly do). This suggests TB may use some other strategy to survive.

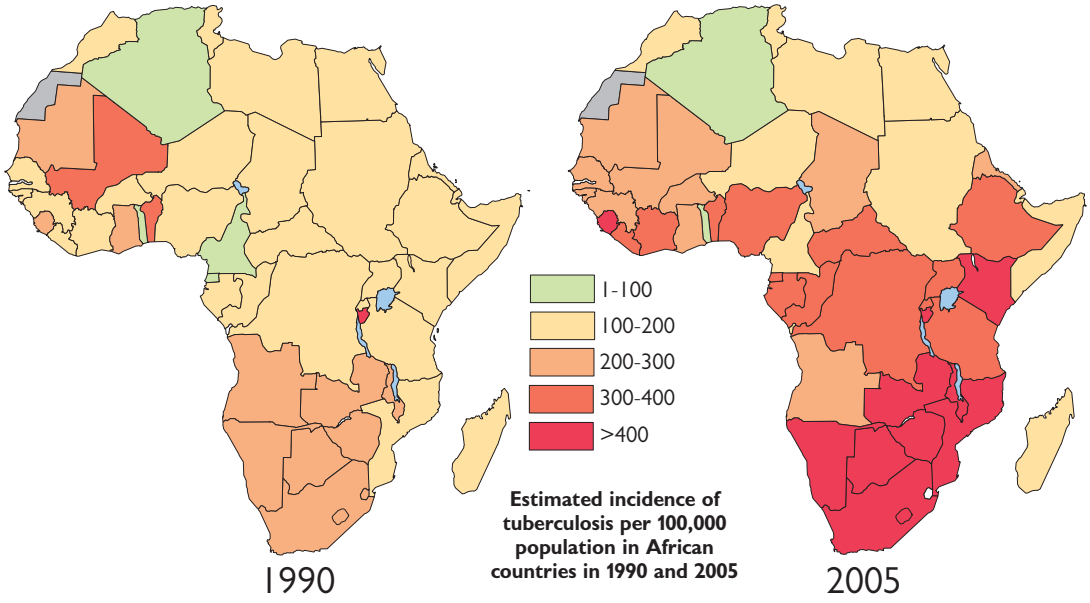
One possibility is horizontal gene transfer, in which whole "cassettes" of genes that confer resistance to environmental pressures are exchanged among bacteria. Many bacteria do this, including at least one species of *Mycobacterium*.

Fortune has chosen to investigate a different possibility. If there are generations of bacteria living in humans that somehow become drug resistant, but their numbers are too small to achieve this through random mutation and selection, she asks whether the ability to adapt to a changed environment can be acquired and then passed from one generation of bacteria to the next in ways that are not genetic. Mechanisms of "post-genetic" inheritance have been described in animals, plants, and fungi, and Fortune hopes to discover if TB uses them, too. That could explain the microbe's ability to persist latently for decades even in people with healthy immune systems. —J.S.

"Is it mathematically even possible that a few bacteria that mutate very slowly could actually develop resistance to eight antibiotics?"

Sarah Fortune

Portraits by Stu Rosner



Estimated incidence of tuberculosis per 100,000 population in African countries in 1990 and 2005

A Recalcitrant, Adaptable Opponent

Simply doing TB research is difficult as well, because there are few good animal models of the disease. Researchers can infect mice, but the disease takes a different course than it does in humans. Only macaques, which cost $20,000 each, develop latent infection. And although cows get TB (the existing vaccine is based on *Mycobacterium bovis*), genetic studies indicate the bovine strain was contracted from humans thousands of years ago, not the other way around. In fact, it appears that *Homo sapiens* is the animal reservoir of the disease—which makes it harder to study in vivo.

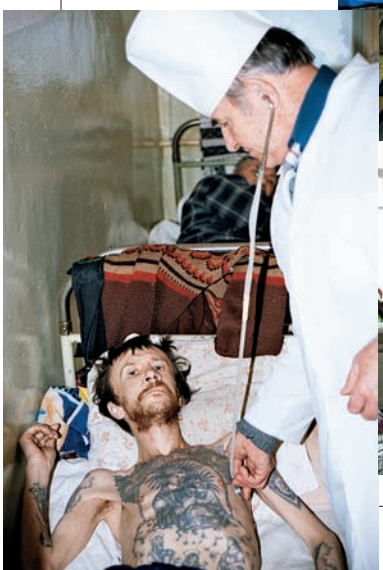
Fortunately, in vitro analysis is thriving. Several Harvard labs are engaged in efforts to identify key components of TB's genetic makeup that could be targets for vaccines or drugs. Eric Rubin is working to establish which genes are critical to TB's survival—he estimates the number at about 800, any one of which could become the target of drugs. He has also discovered that a protein called resuscitation promoting factor, once thought to be a signal that woke TB from latency, is in fact involved in breaking down and making a new cell wall for the bug when it replicates. These cell walls are a little unusual, he says. "The bacteria are covered by this huge, greasy coat—they're disgusting, and nothing can get in." Colonies of *Mycobacterium smegmatis*, a related mycobacterium, share this trait: in a petri dish they resemble lumps of fat—and smell like Limburger cheese.

"There may be a clue here," says Rubin. Although a thick lipid coating can't confer antibiotic resistance (only a genetic mutation can do that), it may increase the bacteria's tolerance—"meaning that for a certain amount of time, they're not killed by antibiotics, because you have to get drugs into the cell through that waxy coat." Rubin's lab has recently been able to demonstrate that such tolerance seems to originate in a subpopulation of the bacteria.

If scientists better understood the permeability of the cell wall, their drugs might be made more effective at killing the bacteria. "Nobody knows exactly how drugs get into a cell," Rubin notes. But his colleague and collaborator Deborah Hung, an assistant professor of microbiology and molecular genetics at Harvard Medical School (HMS) and a core member of the Broad Institute (a genomics research center), has been trying to define the rules that determine how small molecules (drugs) enter cells.

Taking a chemical biological approach to many of the same questions that Rubin studies, Hung has been testing a range of ideas. Because the mathematical assumptions underlying mutation and selection don't seem to explain TB's rapid acquisition of drug resistance (see "An Evasive Bacterium," page 41), Hung wonders if those assumptions are wrong. Maybe the bacteria mutate at a much higher rate in a host—where there are all kinds of pressures, from drugs or the immune system to lack of food or oxygen—than in a Petri dish. In humans who have been infected but whose immune systems successfully control TB, the bacteria are walled off in tiny nodules in the lungs called granulomas. Research has shown that little if any oxygen gets inside. Mimicking the hypoxic conditions inside a granuloma, Hung has demonstrated such "hypermutability" in one species of *Mycobacterium* in low-oxygen environments. That, in concert with the protection bestowed by a thick lipid coating, might buy this group of bugs time enough to develop true genetic resistance to antibiotics. While Rubin searches for genetic controls that might switch such hypermutability

MIKHAIL METZEL/ASSOCIATED PRESS



VALERY KASATKIN/PARTNERS IN HEALTH

ARACHU CASTRO/PARTNERS IN HEALTH

Top: TB spreads easily in crowded prisons like this one in Moscow. Left: In Tomsk, Siberia, a healthcare provider monitors patient adherence to a lengthy, complicated drug treatment regimen through the UN-advocated program of "directly observed therapy." Far left: The emaciated appearance of TB patients gave the disease its nineteenth-century name: consumption.

on and off, Hung takes an opposite, but complementary, path: she tests libraries of drugs seeking chemical compounds that will affect mutation rates. "Then we can use that," she says, "to dig into regulatory pathways and mechanisms" that determine the TB organism's success and life cycle.

But there are other explanations for TB's adaptability, and Hung hopes to explore those, too. She has generated a lot of excitement advocating the idea that one might disarm a bug without killing it. Antibiotics are a blunt, lethal instrument. Bacterial survivors are resistant. But if a drug targeted only the aspect of a bacterium that triggers disease, and not its survival, resistance to the drug would not be generated, a so-called "anti-virulence strategy." Drugs would target only "the weapons or toxins that [the bacteria] need in order to cause disease," rendering them harmless. "We're covered with bugs that are benign," Hung points out. "By not selecting for survival, you might not engender resistance in the same way."

"The policy argument was that drug-resistant TB might kill people, but it didn't spread well."

The Rise of Drug Resistance

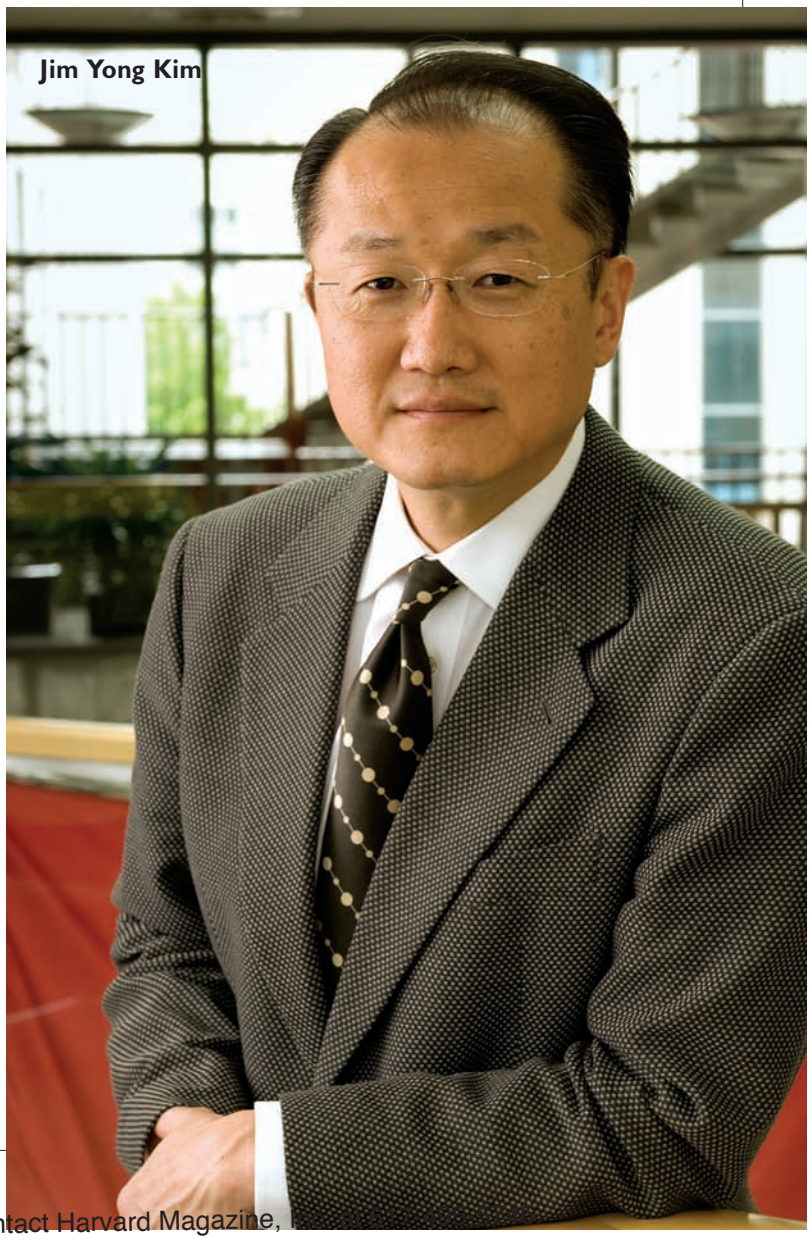
With support from the Harvard Initiative for Global Health, basic scientists like Hung and Rubin meet monthly for a TB research seminar that draws on about 20 labs in the Boston area. At this year's annual retreat, says their colleague Sarah Fortune, an HSPH assistant professor of immunology and infectious diseases, the group plans to bring in four or five heads of TB field sites from around the world to foster collaboration: "We are trying to enable the basic community to move ideas into the field and then give field sites access to the Harvard TB research community, advancing the translation of research into practice."

Harvard has deep connections with several of these field programs, the best known of which is Partners in Health (PIH), founded by Paul Farmer, now HMS's Presley professor of social medicine. PIH treats patients in Haiti, Peru, Russia, Rwanda, Lesotho, and Malawi—and has encountered different strains of TB in each place. A $14-million National Institutes of Health project led by HSPH's Megan Murray is combining field studies of transmission in Peru (looking, for example, at the risk factors among people who get sick) with molecular laboratory analysis of the strains and epidemiological study of transmission and interventions. The project's focus is multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, which are difficult and costly to treat.

Failure to recognize TB's growing drug resistance was a hallmark of doomed global efforts to control the disease in the 1990s, and helped fuel the epidemics now raging in China, India, Russia, and Africa (see map of prevalence, page 40). In 1993, the World Health Organization (WHO) began advocating a new strategy for controlling TB worldwide—directly observed therapy-short course, or DOTS—which cut the time required for treatment from one to two years to six to nine months, and mandated that healthcare workers observe patients taking their medicines. By and large, the program's results were excellent. "This was a good thing to promote," Murray says, "but it didn't identify or treat people with drug-resistant (DR) TB." Simplicity was an underpinning of the DOTS approach, and treating DR TB was thought to be too complicated and expensive, if not impossible. But the architects of DOTS had little reason to worry: the dogma was that any genetic change that caused drug resistance would also make the organism less fit and unable to propagate. "The policy argument was that drug-resistant TB might kill people, but it didn't spread well," Murray says.

The first contrary evidence appeared the very same year, when then-HMS junior faculty members Jim Yong Kim and Paul Farmer, the leaders of Partners in Health, were working on a small childhood-nutrition project in Peru, hoping to expand PIH's impact beyond its original base in Haiti. The two went at the invitation of a friend, a Catholic priest who had moved to Lima from Roxbury. When he fell ill, they sent him to Boston for treatment, where he died of what turned out to be a drug-resistant strain of tuberculosis.

"At around that time," says Kim (now professor of social medicine at HMS and Bagnoud professor of health and human rights at HSPH), "in the northern Lima community where he had been living, we started finding people dying of TB—in the middle of what was supposed to be the best TB control program in all of the developing world." Almost immediately, they thought, "This has



Jim Yong Kim

to be drug resistance.” They began going house to house, patting residents on the back and getting them to cough into a cup. Back in the United States, lab analysis of the sputum confirmed their suspicions. This was resistant disease, and clearly, as the death of their friend proved, it was being transmitted. “The DOTS protocol without question is one of the great public-health achievements of all time,” Kim says. “It took countries from random, chaotic treatment to an organized approach that had much better results. It detected and cured many, many more patients.” But when initial treatments with first-line drugs failed, DOTS called for adding a single additional antibiotic. “The one thing you never do in TB treatment,” says Kim, “is to add a single drug to a failing regimen—never. If you do, the great risk is that you are going to develop resistance to that drug as well.”

> “We started finding people dying of TB—in the middle of what was supposed to be the best TB-control program in all of the developing world.”

At the time, drug-resistant tuberculosis was considered too difficult and too expensive to cure in resource-limited settings. Kim and Farmer’s answer was to increase the pool of resources by making sure the whole world knew what was happening in Peru. They also developed lower-cost treatment protocols, using mostly community-health workers and nurses, and in their first cohort of 45 patients, achieved a cure rate of more than 80 percent. When they presented their results at the American Academy of Arts and Sciences in 1998, WHO leaders were astounded, and soon adopted a new policy dubbed “DOTS plus” that allowed for treatment of MDR TB.

Still, the cost of the necessary drugs was high, as critics of their “healthcare for all” approach frequently pointed out. In 1999 Kim went a step further, and worked to get TB drugs, all but one of which were off-patent, manufactured inexpensively in China and India. Eli Lilly and Company, which makes two of the most important drugs for MDR TB, made large donations of these drugs, transferred the technology to China, Russia, and Africa, and trained people in those countries to make the drugs, spending $200 million on the effort—“pure philanthropy,” Kim says. In a single year, the cost of treatment dropped 95 percent, from $25,000 to as low as $1,500 per patient. Says Eric Rubin, “Jim, as much as anyone, is responsi-

TACKLING TB IN THE FIELD

Lesotho is a country of breathtaking beauty and heartbreaking poverty. The twin epidemics of HIV and drug-resistant tuberculosis may also make it the site of the most devastating pandemic of the twenty-first century.

I am in the capital, Maseru, wearing a face ventilator and standing with Partners in Health (PIH) director Jim Yong Kim—professor of social medicine at Harvard Medical School and François-Xavier Bagnoud professor of health and human rights at the Harvard School of Public Health—outside a new 24-bed hospital devoted to the most serious and infectious of Lesotho’s extensively (XDR) and multidrug-resistant (MDR) TB patients. It is Kim’s first visit in more than a year, and the PIH hospital, four months old and the first in the country with state-of-the-art infection control, bears witness to the devastation of the disease.

Take Molahlehi (not his real name), a patient on the wards who used to work in the South African mines. HIV-positive and now, after intermittent and incompetent treatment for tuberculosis, resistant to all of the most important drugs, he is a classic XDR TB case. The stigma associated with his condition is such that his village won’t have him back, nor would his children when he tried to return home over Christmas. He called PIH to pick him up again when he realized the extent of his isolation. While PIH is caring for his family members (his wife left him) and educating his village about his condition, PIH’s MDR-TB program director, physician Hinda Satti, is praying that he will respond to treatment. The outlook is grim; a cure rate of 50 percent is deemed the highest success.

“These are, hands down, the most complicated patients I’ve treated in my life,” says Jen Furin, PIH’s country director in Lesotho and a physician at Harvard-affiliated Brigham and Women’s Hospital in Boston. Furin has worked on MDR cases at PIH sites from Haiti to Peru. But in Lesotho, where the incidence of HIV and TB co-infection is among the highest on earth, the patients are far sicker—and far more likely to stay that way.

The challenges extend far beyond clinical treatment of the condition. As patients move from the hospital wards to PIH-run halfway homes, and, finally, back to their villages, community health workers trained and employed by PIH help them navigate their twice-daily drug cocktails—more than 20 pills a day for many, for a minimum of two years—and educate community and family members.

The success thus far has been astonishing. Of the 94 patients who have made their way through the wards since November, Satti says, not one has defaulted on therapy. The hospital is already attracting international attention: a contingent of doctors from the South African province of KwaZulu Natal—doctors who, given their own country’s wealth, medical infrastructure, and history with XDR TB, should be training Basotho (as citizens of Lesotho are called)—were learning from the hospital staff the day I arrived. And Kim, after visiting the newly reno-

Photographs by Justin Ide/Harvard News Office

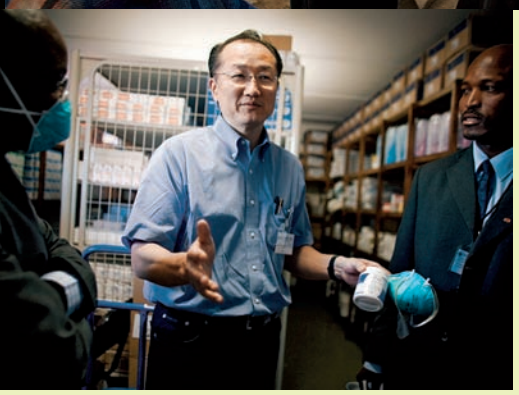
ble for driving down the prices of drugs that are required to treat MDR TB—personally responsible—even though he wouldn't take credit for it."

In 2000, with a $45-million grant from the Bill and Melinda Gates Foundation, Kim and Farmer scaled up PIH's program. Today, the Peruvian government has taken it over and everybody has access to care. "Half the people who have been treated for drug-resistant TB in the developing world have been treated in Peru," says Kim. "That is the one place where we really achieved universal access to MDR TB treatment. It doesn't yet exist in other places."

Yet even as their efforts in Peru were rewarded, a new disaster loomed. In a 2000 report funded by the Soros Foundation, PIH predicted that the problem of drug-resistant tuberculosis was going to explode in two places: "South Africa, where TB and HIV were coming together," Kim recalls, and in the former Soviet Union, "where there were huge prison populations, the health systems had been destroyed, and there was a long history of using single drugs" for treatment. Still, there were some who argued that DR strains would never become a big problem.

Eight years later, the development of clusters of new cases indicating active transmission of rampant drug-resistant disease in both places has essentially settled the matter, and genetic work has confirmed that they do maintain fitness: after a mutation confers drug resistance, some of the resulting strains remain fully capable of reproducing and infecting new patients, while others are enfeebled. The fit strains survive and soon grow to become a significant proportion of cases in a population. At the molecular level, the bugs that acquire mutations conferring drug-resistance *are* weakened at first. They languish and fail to divide and reproduce as well as normal strains. But these sacrifices in function don't appear to last long. Within a few bacterial generations, compensatory mutations at other locations in the genome rescue the bug and restore its vigor. Megan Murray, with the support of HMS professor of systems biology Eric Lander, director of the Broad Institute, and a team of Broad scientists, has been sequencing some of these drug-resistant strains to ascertain what makes them hard to kill.

"Two years ago," Lander says, "the greatest barriers to progress were technology and the lack of communities of young scientists who were committed to these problems. Both of those things are changing, so now it is a question of all of us putting our support behind this generation of visionary scientists." He predicts that "in the next five to 10 years we will understand the processes that TB uses both to infect us and to avoid our immune system and our drugs. That doesn't mean we are going to cure TB, but it is an amazing foundation."



In Lesotho, Partners in Health (PIH) has set up a modern laboratory and treatment center for the care of patients with drug-resistant TB. Many are also infected with HIV. Clockwise from left: At a rural clinic, PIH's Jen Furin admits a patient with AIDS, TB, and meningitis; a recovering TB patient lives in a home near the hospital where doctors monitor her care; PIH leader Jim Kim (right), with Furin (center), meets Moses Phakis, a local clinic administrator, in Bobete; Kim in the new PIH-affiliated hospital pharmacy in the capital, Maseru.

vated TB and microbiology lab (which eliminates sending specimens to South Africa for testing), was as excited by its capacity to help Lesotho as by the precedent set for other countries: "I was talking to the director of the TB department at the World Health Organization about your work here," he raved to lab head Mathabo Mareka, "and he is so excited about it."

As important as these TB projects are to PIH's healthcare-delivery and capacity-building efforts in Lesotho, they are far from the whole story. Unlike organizations that pursue narrower aims or are restricted in their use of funds, PIH owes some of its success to its commitment to comprehensive care: not just to the most serious XDR cases, but to any patient in need.

I encounter a vivid example on a visit to a patient with Furin. We are idling in our car along a rain-washed road, lost in the sea of shacks and shanties outside Maseru, looking for a six-year-old boy, Molise, whom we saw earlier in the week. HIV-positive and rail-thin, he hasn't been able to walk since dislocating his knee last year. His hands are swollen and elongated from shuffling around, crab-like, on the ground; his leg, permanently skewed to the side, is unusable. If PIH had a mandate, that leg would likely fall outside it. But Furin has a plan to fix not just the leg, but the leg and everything else.

An hour passes before Molise, wearing shorts and a shirt provided on our last visit, crawls excitedly toward us. As Furin examines the boy on her knee, for a moment the hospital wards, the dying Basotho isolated in the mountains, the pandemic quietly sweeping southern Africa—all fade into the humanity of the child's grin. "This [leg]," she says, the lines of exhaustion on her face fading briefly into a smile, "this is actually something, something that's savable." —SAMUEL BJORK

Ledecky Undergraduate Fellow Samuel Bjork '09 filed this report from Africa, where he worked in a Botswana AIDS clinic from August 2007 until March 2008.

Bringing Management to Global Medicine

In the meantime, stopping the spread of resistant strains will require great care. "Ultimately, what drug-resistant TB and HIV are going to force us to do is develop a new field," says Kim. "[Present] treatment is just too complicated." Patient care must be coordinated among doctors and across institutions, he believes, in order to achieve the same kind of professionalism in the field of delivery as exists already in research science and clinical medicine.

This conviction has driven him to look beyond medicine and public health for strategic expertise in management. In 2007 he asked Lawrence University Professor Michael Porter of Harvard Business School, who has conducted extensive studies of the U.S. healthcare system, for help.

Some doctors "see a problem as a series of patients. Jim's a doctor, but he sees this as an organizational problem....It's the non-sexy part of delivering care to people, and TB is full of that."

"There are a tremendous number of people who are doing biomedical research," Porter points out, "including a growing body of people who are focusing on diseases that are most common in poor countries. And that is a very good thing. There is also a lot of clinical research that [looks at] comparative effectiveness." PIH has been doing this kind of work intensively for the last 10 years: research around the treatment of TB, how it's spread, how it's treated, how patients should be managed. But now, what Kim is saying—"and what I completely embrace as well," Porter says—"is that those things are important, but they are not going to be enough."

The problem in global health, Kim has persuaded Porter, is much less about medical science and much more about the capacity to think strategically and systemically about how to deliver care in resource-poor settings. "Care is fragmented into hundreds and hundreds of little organizations," Porter explains, and is focused on interventions that are "not coordinated across diseases and medical conditions." Success is measured "more in terms of volume—how many tests, how many drugs given—than actual value, [which is] how well the patient did." "Delivering bed nets," says Kim, giving an example, "is not the same thing as saying people should be healthy and [free] from malaria over the long run. If your goal is just to deliver a bed net, you could deliver a bed net and everyone could be dead."

Porter says the key to designing a system is capturing efficiencies and effectiveness. TB is a good example, because it often occurs together with HIV. "What you learn," he says, "is that you need to treat the two together. You can't have a separate system for HIV and for TB. You'll end up dramatically reducing the value that you are delivering. And maternal health can be very closely integrated with HIV/AIDS treatment, increasing the ability to detect cases before the problem starts to proliferate."

Already, PIH has replicated its success in Peru and Haiti in other countries. In Russia, "we bring the heads of TB programs in prisons and civilian sectors into a single place, and then most of the teaching is done by our colleagues from Siberia," Kim explains. "After years of working intensely with our own doctors, who themselves learned in Peru, they are now the best teachers of drug-resistant TB management in all of the former Soviet Union. And they do it in their native language." PIH's most recent expansion was into Lesotho, where more than 80 percent of the TB patients they see are coinfected with HIV (see "Tackling TB in the Field," page 44). But Rwanda is where Kim hopes PIH, led by Paul Farmer and fellow physician Michael Rich, the country director, can build with Porter's help a model system for health delivery that could eventually be used anywhere in the world.

Kim sums up the motivation behind this push very simply: development of new drugs and vaccines is great, but "We're not even delivering the existing products." In Rwanda, Farmer, Kim, Porter, and Megan Murray are working together to develop a shared delivery infrastructure that will be flexible enough to tackle many problems at once: HIV, TB, malaria, maternal and child health, sexually transmitted infections, and even chronic diseases.

"Jim's unique genius is management," says Rubin, the molecular biologist. Some doctors "see a problem as a series of patients. Jim's a doctor, but he sees this as an organizational problem, and he is right. It's the non-sexy part of delivering care to people, and TB is full of that. How do you get the drugs to the neighborhood clinics and into people's hands? How do you make sure there is a continuous supply of it in a place where there's a war, or no roads? No refrigerators? How do you make sure that it doesn't age out while sitting on a shelf at 95 degrees?"

Academic institutions have to be involved, Kim argues from experience. From 2003 to 2006, he worked for WHO in Geneva, first as the director-general's right-hand man, and then as head of the organization's HIV program. "I really got a sense for the power of the multilateral system," he says. "When the director-general gets behind something and pushes it—it's change."

But the view from the top of WHO also gave him a keen sense of what these kinds of government organizations *can't* do. "The UN institutions aren't equipped to take on problems of this complexity," he says, and management consultants aren't set up to share and publish and teach what they learn. Working with a debilitated system in Rwanda, where existing institutions were destroyed by war (and where Porter is serving as an economic adviser to the president), Farmer and his local team are trying to build a healthcare delivery system that in some ways could be better than some health systems in the United States. "Harvard is absolutely uniquely placed to do this," he says. "We have the medical school. We have the school of public health. We have the Kennedy School, and we have the business school. We need people who study systems every day to be side by side with us thinking this through."

In the struggle against TB, there is a deep connection between what Kim and Farmer are now trying to do and the work of basic scientists. Both groups aspire to improve the lives of many, many people. In the case of "doctors who work with patients," says Rubin, "their impact is necessarily limited to the people they deal with. Not many people want to do the really boring work, which is setting drug prices and making sure that roads get built. [But] that's necessary. And that's only a tiny bit of what Jim and Paul are ultimately interested in, which is having better health as part of an entire societal framework."

Jonathan Shaw '89 is managing editor of this magazine.