A New Life for a Deadly Disease

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You can hear it before you see it. Most of the time, it starts with a wracking cough. Damage to the lungs advances; if infection enters the bloodstream, it may spread throughout the body. Then the patient grows weak, and as the infection advances, the body seems to melt away. When the end comes, as it does for more than a million each year, death arrives like a train wreck of blood and phlegm and spit. It used to be called "consumption," or "the White Death." Don't think of Camille, lounging in soft focus whilst romantically fading away. Tuberculosis is a ferocious killer.

Tuberculosis is caused by an infection of one of a handful of members of the Mycobacteria family, usually Mycobacterium tuberculosis, though four other related bacteria can also cause it. It is a disease of crowds. An infected person coughs, sneezes, or spits—or even sings with gusto—he can release an aerosol of thousands of tiny droplets. It doesn't take many bacteria to produce an infection: some estimate that fewer than ten can be enough to set the disease process in motion. Those most at risk are people living packed together (in range of sneezes) and those who spend a great deal of time with an actively contagious person.

Mere contact with M. tuberculosis doesn't mean that an active case of tuberculosis will follow. After inhalation, the invaders travel until they reach cavities deep within the lungs. There they invade cells involved in immune response; those cells then invite reaction from other types of cells in the immune system, forming clumps in which the infected cells can fall into dormancy, becoming a latent TB infection. Most otherwise healthy people will never develop active disease. But for about one in ten, the infection flares, producing tissue damage around each clump. Sometimes the immune system can mount another counterattack, and the disease may wax and wane. Left untreated, active TB is the stuff of nightmares: up to two-thirds of its victims will die if no help comes to them.

That help has been available for almost sixty years. But not for seventeen desperately ill people in the Eastern Cape province of South Africa whose fate suggests that we may not enjoy our sense of invulnerability in the face of TB—and other infectious diseases we've conquered—for that much longer. Those afflicted suffer from a strain of tuberculosis that seems to resist every drug available to treat it. Seventeen is a tiny number, but the question those desperately ill people embody is whether we will do what is necessary to keep their numbers so small.

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The rise of drug-resistant tuberculosis should come as no surprise. Drug resistance is a natural phenomenon, the outcome of the long, long story of bacterial evolution. In any microbial population, there is some variation, differences in the way one bacterium or another responds to the challenges in its environment—including the test posed by a new drug. Some of those flukes of genetics allow their possessors to survive an antibiotic assault, or at least to hang on long enough to persist if someone stops taking drugs too soon. Such resistance is then passed to new generations. For M. tuberculosis, naturally occurring resistance to the most common drugs occurs at rates that

range from one in ten million to one in ten billion. People with active TB in their lungs will harbor up to a trillion tuberculosis bacteria, which means that as a matter of pure statistics, they can face as many as ten thousand resistant bacteria before they take a single drug. That's why the standard treatment for TB calls for the use of combinations of drugs; mixing and matching compounds that take different routes to destroy the disease-bearing bugs.

The dangers posed by such antibiotic resistance were recognized from the start of the antibiotic era. Alexander Fleming discovered the first modern anti-bacterial compound—penicillin—in 1928. He saw it work its miracles, as story followed story of patients resurrected by his drug when they were halfway through death's door. But even in those first days, Fleming grasped the basic principles of microbial ecology. As early as 1945, just two years after the new compounds entered broad application, he used his Nobel Prize lecture to sound a warning:

Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why, Mr. X, whose negligent use of penicillin changed the nature of the microbe. Moral: if you use penicillin, use enough.

Just the next year, 1946, the *American Journal of the Medical Sciences* reported the cases of four soldiers infected with gonorrhea resistant to penicillin—a big deal, given that one of the first major uses of the drug was to keep soldiers, sailors, and marines available for duty, no matter what adventures they'd enjoyed on leave. (Jerome Groopman covered the rise of drug-resistant gonorrhea for the magazine last October.) Soon, staph infections started turning up that similarly resisted treatment, leading, ultimately, to genuinely threatening drug-resistant epidemics. From its first appearance in the United States in a single hospital in 1968, MRSA—methicillin-resistant Staphylococcus aureus, a staph infection that shrugs off first-line antibiotics—has spread into the ordinary settings of everyday life, where it kills as many as nineteen thousand Americans each year. (See Maryn McKenna's essential, relentless "Superbug" for the full, sad story.) More recently, outbreaks of C.R.E., carbapenem-resistant members of the Enterobacteriaceae family, seem to be following the same path. C.R.E. is still largely confined to hospitals and long-term care facilities—but the C.D.C. warns that it, too, may be able to leap beyond the wards into the community at large.

For decades, though, TB seemed to be an unequivocal success story. With the discovery of streptomycin, in 1943, the terrifying odds TB's victims had faced for nearly all of human history began to improve. As the antibiotic revolution advanced, more and more easily administered drugs became available that could attack M. tuberculosis at any identifiable weak point, making possible the seemingly invincible multi-drug approach to combatting naturally occurring resistance. One frontline drug, isoniazid, blocks the formation of its cell walls; another, rifampicin, interferes with the transmission of the bacterium's genetic information; a third, ethambutol, has a mechanism of action that is still imperfectly understood—but has been shown to attack active M. tuberculosis—and still others interfere with yet more intricate aspects of bacterial metabolism. This growing antibiotic arsenal proved so effective that what had been an implacable scourge became over the first decades after the Second World War a trivial matter of medical management. By 1968, the disease seemed so utterly tamed that health officials in New York City, once a TB hotspot, believed the disease was on the verge of eradication and began to close its clinics. (Within twenty years, two-thirds of its TB clinics were closed.)

TB, however, didn't disappear; in fact, it began to spread rapidly in the city's homeless population, as detailed in this study in *The Lancet*. And then there was a lethal spike in what had been an almost forgotten disease—made yet more deadly because of the politics of another, utterly unanticipated health crisis.

The first U.S. cases of the disease that became known as AIDS were reported in June, 1981. The sudden, unanticipated spread of the H.I.V. virus offered M. tuberculosis a whole new population of immunocompromised hosts to invade. As the number of infections mounted, clinicians again found what Fleming would have predicted: tuberculosis was staging a comeback. As Michael Specter reported on in the magazine, it had evolved. In New York in 1982, what became known as multiple-drug-resistant TB (M.D.R.-TB)—strains resistant to at least two frontline antibiotics—accounted for three per cent of the TB total. The armored-up bugs were lethal, especially in concert with H.I.V. Though the first numbers were too small to be definitive, the anecdotal data remain striking: non-resistant TB killed about half of those also suffering from AIDS; TB co-infections resistant to one frontline drug killed eighty per cent; and M.D.R.-TB cut still deeper, killing nine out of ten.

At least some of those deaths flow directly from an explicit public policy choice. From 1981 to 1985, Ronald Reagan's Administration formally barred its surgeon general, C. Everett Koop, from even commenting upon the emerging H.I.V./AIDS epidemic, much less doing anything about it. It took Rock Hudson's death in 1985 to persuade Reagan's Washington to take H.I.V. seriously. By then, the virus had busted past the first set of public-health responses that could have constrained its spread, and the number of Americans diagnosed with AIDS leapt from dozens in 1981 to two hundred and six thousand a decade later. And in New York, a team led by Thomas Frieden, now director of the C.D.C., reported in 1991 that M.D.R.-TB accounted for almost a fifth of the city's rising caseload. The collision between the politics of H.I.V./AIDS and the pathology of infectious disease was devastating then; there are signs now that a similar conflict may threaten public health in the midst of the current global TB epidemic—with implications that extend well beyond that one disease.

Worldwide, there were eight million seven hundred thousand new cases of TB in 2011, the last year for which comprehensive statistics are available. That same year, about one million four hundred and fifty thousand died of the disease. Most victims live in the developing world, cared for by overburdened public-health systems. Conventional multi-drug treatment with the so-called frontline antibiotics work—or could—for almost all of those people, over ninety-six per cent of the total. But the rest face a much harsher road. The WHO estimates that about 3.7 per cent of 2011's newly reported patients—over three hundred thousand cases—faced M.D.R.-TB. Absent a major co-factor like an H.I.V. infection, multiple-drug-resistant tuberculosis itself is still quite curable, but it's a rough ride. Patients must take potent and often deeply unpleasant drugs for twenty months—sometimes much longer—with no lapses in treatment. Inevitably, some people don't or can't stick with it, or lack access to the kind of care required, leading to the unavoidable sequel: populations of M. tuberculosis that display resistance to both frontline and second-line drugs. The current best estimate is that about nine per cent of those with M.D.R.-TB develop strains of the disease that doesn't respond to at least four major anti-TB drugs—extensively drug-resistant, or X.D.R., TB. X.D.R.-TB is not common (yet), but it is present in at least eighty-four countries worldwide. And it is deadly in ways that less well-defended TB bacteria are not; X.D.R.-TB kills at least half its victims.

Natural selection doesn't stop picking and choosing at four drugs, of course. The endpoint of the evolution of resistance is a bug that can shrug off all currently available antibiotics, making it totally drug-resistant—T.D.R.-TB. As 2012 came to an end, three small outbreaks of T.D.R.-TB had been described: one in in Italy, where two women died of untreatable TB in 2003, followed by another in

Iran in 2009 and another in India in 2011. That was it, until this year. In the March 3rd issue of *Emerging Infectious Diseases* came word of those seventeen South Africans suffering from what appears to be the T.D.R. version of the disease. The worldwide total of reported T.D.R. cases still stands in the dozens—a drop in the sea of new TB cases each year. But there is another way of thinking about this news. The South African outbreak marks the fourth time that an illness that was once nearly universally curable has, apparently independently, evolved into an essentially untreatable form.

Working against pathogenic microbes is not simple altruism. Keeping the lid on bad diseases in the age of air travel is a matter of self-interest, at least as much as it is a duty to our neighbors. And the invisible hand of the market is not currently taking care of this particular business. We are in the midst of a persistent antibiotic-development drought—only two new classes of the drugs have been identified in the last thirty years or so. Drug companies have been withdrawing from antimicrobial research for several reasons. Antibiotics are a lousy business, for one. While blockbuster drugs treat chronic diseases for years at a time, when antibiotics work patients take them for a little while, and then they're done. For such perfectly rational economic reasons, the pharmaceutical industry is unlikely to keep pace with the need for a social good whose benefits don't translate into profits that can be readily captured. That makes this a political matter: some other institutions will have to do the work.

But the current state of American politics doesn't look up to the job either just now. Gamesmanship over the federal budget increases our vulnerability—to TB and to the whole spectrum of resistant disease organisms. In particular, the budget sequester fixed in place by the House G.O.P. caucus increases the risks we face daily. Definitive decisions about the implementation of the sequester are still taking shape, but the Centers for Disease Control alone is losing four hundred and seventy million dollars, and estimates of the damage include the loss of TB services in eleven states. More than four hundred thousand H.I.V. tests won't get done this year. As many as twelve of the twenty border-quarantine stations the C.D.C. may close, and its Global Disease Detection centers—the front line of U.S. defenses against emerging diseases—are also under threat. In the long term, the sequester threatens to cut out a generation of basic biomedical research. All the while, M. tuberculosis continues to evolve.