NEWS

Driving a Stake Into Resurgent TB

Eighty years after the first tuberculosis vaccine, health leaders say they need a new one. Scientists have several promising candidates—but who will pay for them?

Tuberculosis is an anachronism to many Westerners. It conjures up images of hollow-eyed writers and artists wracked by "consumption," or Swiss sanatoriums where patients are wheeled outside to be cured by fresh mountain air. From a scientific viewpoint, tuberculosis (TB) also seems out of place in the 21st century. Most cases are now curable with antibiotics, and a cheap vaccine is administered to some 100 million newborns each year, making it the most widely used vaccine ever made. TB shouldn't be a threat any longer.

But TB still ranks among the world's most deadly infectious diseases, killing 2 million to 3 million people a year. An astonishing 2 billion people—a third of the world's population—may carry a latent TB infection, and roughly 10% of them will develop a life-threatening form of disease. The vaccine, it turns out, is no match for *Mycobacterium tuberculosis*, the bacterium that causes the disease. Treatment is problematic as well; indeed, the bacterium has evolved deadly new strains, resistant to the most powerful drugs. "TB is arguably the most successful pathogen on the planet," says William Jacobs, a researcher at the Albert Einstein College of Medicine in New York City.

The only effective way to control TB, researchers have concluded in the last decade, is to develop new vaccines. The challenges will be daunting, because much about the disease is still unknown. But optimism, a rare commodity in TB research, is rising: Molecular biology is providing new tools for the battle and, for the first time in decades, money is pouring in to support new research.

The big scientific leap came in 1998, when researchers sequenced the genome of *M. tuberculosis*. Obtaining the DNA for all the TB genes at once was like walking into "a candy store," says Stanford University geneticist Peter Small. And the mounting death toll, as TB teamed up with AIDS, helped stimulate global awareness of the disease. In 1993, for instance, the World Health Organization (WHO) declared TB a "global health emergency." In response, the European Union launched a $4.3 million TB Vaccine Cluster research program in 1999. In the United States, a $25 million grant from the Bill and Melinda Gates Foundation has energized a new round of vaccine development projects, coordinated by the Sequella Global Tuberculosis Foundation in Rockville, Maryland. Created in 1997, Sequella's goal is to get vaccine candidates far enough along in clinical trials to make them interesting for drug companies. The foundation hopes to take three candidate vaccines into the first small-scale safety trials in humans over the next 12 to 18 months—a step few would have thought possible 3 years ago. A British group, meanwhile, plans to start human trials as early as September.

Old foe. Tuberculosis has been controlled in wealthy countries through a combination of screening, antibiotics, and vaccination.

Even WHO, which has traditionally focused on how to deliver drugs to people who need them—and ensure that they take them—is rethinking its strategy. It is examining the logistics of future large-scale clinical trials, says Michael Brennan, a TB vaccine researcher at the U.S. Food and Drug Administration, who is now advising the international agency.

A deadly partnership

Veterans in the field trace the beginnings of the turnaround to the late 1980s, when TB suddenly surged, and drug-resistant strains emerged in the United States, riding on the heels of the AIDS epidemic. The outbreak drove home the point that even in industrialized countries, TB remained a large if hidden threat, says Marcus Horwitz of the University of California, Los Angeles.

TB is tough to control because it can lurk in the body for years, out of reach of the immune system. After the initial infection, *M. tuberculosis* goes into a latent phase, hiding inside a class of blood cells called macrophages. An intense course of multiple antibiotics, administered for 6 to 8 months, is needed to rid the body of the bug, even though the symptoms usually disappear within weeks. Patients tend to drop their antibiotic treatment too early, which fuels the emergence of drug-resistant strains.

U.S. public health officials mounted a strong offensive against resistant TB, imposing new regimes to ensure that patients finish their therapy. After peaking in 1992, the U.S. outbreak declined by the end of the decade. Last month, the Centers for Disease Control and Prevention in Atlanta announced that in 2000, the number of new cases compared to 1999 had dropped by 6.6%, reaching an all-time low of 16,377.

But in Eastern Europe, where funds are lacking and public health services are inadequate, multidrug resistance has become rampant. And in Africa, TB and HIV have combined in a deadly spiral. In AIDS patients, latent TB has a much higher chance of becoming active, and when it does, the symptoms are much more severe. As a result, most African AIDS patients die of TB. TB also appears to speed HIV's replication rate. Although several new drugs are in the pipeline, none is expected to make a big dent in the epidemic. "I think everybody now agrees that we won't substantially reduce the burden of TB without new vaccines," says Brennan.

The existing vaccine was developed by Albert Calmette and Camille Guérin of the Pasteur Institute in Paris some 80 years ago from a bovine cousin of *M. tuberculosis*. Initially, it seemed to work well. But over the

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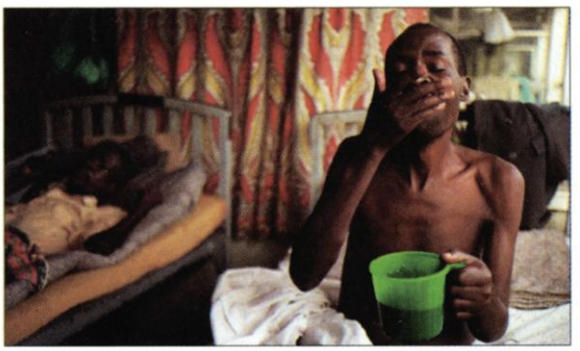
decades, the efficacy of Bacille Calmette-Guérin (BCG), as the vaccine is known, has come into question. Large-scale trials have produced wildly conflicting results, varying from 80% protection to none at all. "There's no other vaccine for which the results are so inconsistent," says Paul Fine, a BCG expert at the London School of Hygiene and Tropical Medicine in the United Kingdom.

In most parts of the world, BCG's protection doesn't seem to extend beyond childhood, during which it generally protects against TB's most severe forms. Young adults, however, remain at risk of the disease. Except for the United States and the Netherlands, which have never used BCG, almost the entire world has followed WHO's recommendation to vaccinate every child with BCG at birth. "It's not a perfect vaccine," explains Fine, "but it's doing some good and it's dirt cheap—so we give it."



Shaky support. Drug treatments requiring months of therapy are difficult to sustain in the developing world.

The new generation

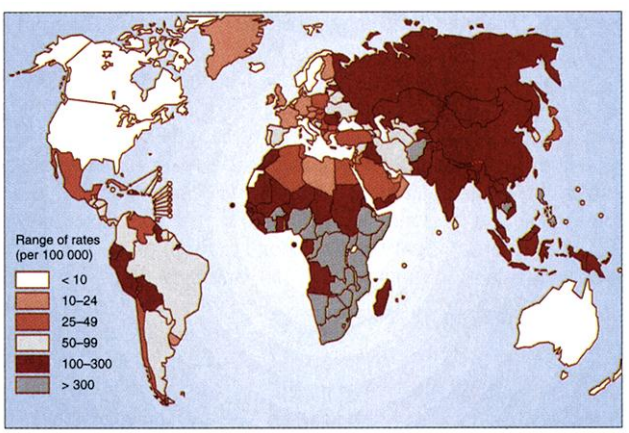
Coming up with alternatives, however, has proved tough. For one, the world may need several vaccines: a preventive type to immunize children at birth, as well as "therapeutic vaccines" to protect the 2 billion latently infected from actually developing symptoms and cure those who already have active TB. Researchers still understand little about the complex ways in which *M. tuberculosis* thwarts the human immune system. It's unclear how the bug manages to persist for decades, for example, or why some people eventually get sick, yet the majority stay healthy. "At the end of the day, we need to know the answers if we want to make a very good, very effective vaccine," says Jacobs.

Despite the obstacles, TB experts in recent years have identified several strong candidate vaccines that either perform significantly better than BCG in animals, appear not just to prevent but also to cure TB, or trigger a strong response in immune cells taken from infected people. The first of these to reach human testing is a vaccine developed by Adrian Hill and his colleagues at the University of Oxford, slated to enter clinical trials in September. With money from the Wellcome Trust, a large British charity, Hill is betting on a combination of BCG and a booster made of a vaccinia virus that produces antigen 85, a protein produced by *M. tuberculosis*.

The big problem with TB vaccine candidates, however, is that because most patients are poor and cannot pay for therapy, market-conscious pharmaceutical companies have little interest in them. That's why the Sequella Global Tuberculosis Foundation wants to fund researchers to help make their vaccine attractive to industry.

Sequella's goal is to get candidates ready for industrial development by putting them through small-scale tests, including phase I trials, which test for safety in healthy volunteers, and phase II trials, which probe for efficacy. After the candidates clear those hurdles, Sequella hopes to interest big pharmaceutical companies in funding large-scale phase III trials and, eventually, producing and distributing the vaccines.

Several observers credit Sequella's cofounder and director, Carol Nacy, for changing the culture and pushing researchers to apply their discoveries. "Frankly, we researchers are most interested in basic knowledge," says Jacobs. "We want that next paper in *Nature* or *Science*. But that's a far cry from getting a vaccine." One of Sequella's candidates, developed by Horwitz, builds on the original BCG vaccine strain. But Horwitz tries to beef up the body's immune response by making the BCG organism overexpress antigen 85, the same protein used by Hill and his colleagues. In guinea pig trials, the vaccine yielded 10- to 100-fold better protection than BCG itself, says Horwitz. A "turbo-BCG," as this type of vaccine has been dubbed, would have several advantages, he says. It's as safe as classic BCG, and its introduction would be relatively easy, because the new vaccine could simply take BCG's place in immunization programs.



Global problem. TB occurs everywhere, but most cases are in Africa and Asia.

Sequella's second candidate is a DNA vaccine, produced by Douglas Lowrie and his colleagues at the Medical Research Council in London. In 1999, Lowrie discovered that injecting into muscle a piece of DNA encoding a so-called heat shock protein from *M. leprae*, a bug related to *M. tuberculosis*, not only protected mice from getting tuberculosis but also cured mice that had been infected. Based on that approach, Lowrie has developed a so-called therapeutic vaccine that would be given along with drugs to patients with pulmonary TB.

An Austrian biotech company, Intercell, has developed the third candidate, a subunit vaccine. It consists of eight epitopes—key parts of *M. tuberculosis* proteins that trigger an immune response—and an "adjuvant" that fires up the body's immune response. "Everybody is getting nervous now, because they want their vaccine in the queue too," says Nacy. "You can't imagine how exciting that is."

Meanwhile, a Seattle-based biotech called Corixa plans to begin testing its own candidate in humans next year. With a $2.3 million challenge grant from the National Institutes of Health, the company has produced a "fusion protein" vaccine that combines two antigens from *M. tuberculosis*. The protein has shown "exquisitely good protection" in mice, guinea pigs, and monkeys, says Corixa's chief scientific officer, Steven Reed.

These new studies are small and preliminary; even if they produce a green light, a marketable vaccine remains years away. Sequella, for instance, has just begun long-range planning for phase II and III trials in South Africa—an ideal test case, says Nacy, "because it has a First World medical community and a Third World TB incidence." But preparing the site—collecting baseline epidemiological data and setting up the required infrastructure—will take 3 to 5 years. Then there's the biggest hurdle of all: getting a company interested. Even if researchers deliver a vaccine to a manufacturer on a silver platter, as Sequella intends to do, it's not clear that a pharmaceutical company will invest the hundreds of millions of dollars required to get the product into clinics.

For the moment, however, researchers are delighted just to see the field moving forward. "From now on, the research will be driven by the results from clinical trials," says Brennan. "That's a big change. We've really turned a corner." –MARTIN ENSERINK

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