NEWSLETTER

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Internationale Nachrichten

1. US tuberculosis cases drop almost 20 percent among foreign-born entrants from 2007-2011

The reasons behind a 19% drop in US tuberculosis (TB) cases among foreign-born people between 2007-2011 vary depending on the person's country of origin and when they entered the U.S., according to a study published February 10, 2016 in the open-access journal *PLOS ONE* by Dr. Brian Baker from the U.S. Centers for Disease Control and Prevention and colleagues.

While the overall number of TB cases in the U.S. has declined over the past two decades, TB morbidity among foreign-born people remains persistently elevated. Beginning in 2007, scientists observed a sharp decline in TB cases among recent U.S. entrants. The authors assessed whether this decrease was because of changes in population size or through decreased incidence of TB. Specifically, they looked at TB case counts, TB case rates, and population estimates by time since U.S. entry, using the U.S. National Tuberculosis Surveillance System and the American Community Survey.

During 2007-2011, there was an overall 19% decline in TB cases among all foreign-born people in the U.S. The authors found that TB cases decreased in recent entrants from each of the top five countries with largest number of cases diagnosed in the U.S.: Mexico, Philippines, India, Vietnam, and China. However, the causes for the decline varied by country of origin; among recent entrants from Mexico, 80% of the decline was attributable to a decrease in population, while the declines among recent entrants from the Philippines, India, Vietnam, and China were almost exclusively the result of decreases in TB case rates. The authors also observed an unexpected decline in TB cases during 2007-2011 among non-recent entrants, who account for ~75% of TB cases among the foreign-born each year. The authors suggest that strategies that will impact both recent and non-recent entrants are necessary to further reduce TB morbidity in the U.S.

"These results are important because they help guide future TB control strategies. To accelerate the decline of TB in the U.S., it will be important to invest in TB control overseas as well as provide testing and treatment to those with TB infection among the ~43 million foreign-born persons currently living in the U.S."

Source: Medical Xpress, http://bit.ly/21h3TNU (11.02.2016)

2. Antibiotic resistance growing menace in BRICS

The urgent need to boost investment in development of new vaccines and other alternatives to antibiotics is the focus of a latest report released Thursday by a British government-commissioned review of the superbug threat.

The Review on Antimicrobial Resistance (AMR), chaired by British Treasury Minister Jim O'Neill, was announced by UK Prime Minister David Cameron in July 2014.

Although there are many new areas of scientific research emerging that could become alternatives to antibiotics, the report warns "the current pace of progress and funding offers little to no hope that new products will be available in the next five to ten years".

The UK report says any use of antibiotics promotes the development and spread of multi-drug-resistant infections, or superbugs.

"Drug-resistant infections, in particular tuberculosis, already have a huge human and economic impact in the so-called BRICS countries. As the latest report from my Review sets out today, vaccines and alternative approaches have a key role to play in preventing infections so we use less antibiotics – which reduces drug-resistance. Without global action to tackle this problem it is sadly likely that the human and economic cost will grow far higher, for the BRICS and the rest of the world, with 10 million worldwide deaths a year predicted by 2050, and more than 30% of those alone in the BRICS countries," Jim O'Neill told *The BRICS Post* on Thursday.

Research by scientists at the Guangzhou Institute of Geochemistry of the Chinese Academy of Sciences shows China consumed 162,000 tons of antibiotics in 2013, or more than half of the global total. About 52 per cent was used on livestock and 48 percent by humans. More than 50,000 tons ended up in the water and soil.

AMR or 'antimicrobial resistance' is the term used to describe drug-resistant infections, sometimes referred to as 'superbugs'. Antimicrobials include antibiotics (which act only on bacteria), antivirals, antiparasitics and antifungals.

AMR UK said last year research and development must be aimed at producing about 15 new licensed antibiotics every 10 years.

O'Neill has proposed a global innovation fund of $2bn over five years to boost research into new drugs and diagnostic tests, with most of the money going to universities and small biotechnology companies. The big pharmaceutical companies would be asked to make substantial contributions to the fund.

"To contain the emergence of drug resistance globally, all these interventions will need to be designed to deliver access to the patients who need them, wherever they are and regardless of levels of income. No single country can insulate its citizens from emerging superbugs if they are left to proliferate somewhere else," the report warns.

"Another key to global access will lie in more academic teams and companies developing new products where most patients live and at prices they can afford, such as India, China, South Africa, Russia or Brazil," it adds.

AMR UK will produce its definitive recommendations to Cameron in May 2016, setting out a package of actions to tackle drug-resistant infections globally.

In O'Neill's first report, he estimated antibiotic and microbial resistance could kill an extra 10 million people a year and cost up to $100 trillion by 2050 if it is not brought under control.

Source: The Brics Post, http://bit.ly/1ROS1jH **(**12.02.2016)

Forschung & Entwicklung

1. Revamped, safer, and with greater punch

A potent vaccine against tuberculosis is getting readied at the Pune-based Serum Institute of India Limited. The institute started a 'Phase 2b' clinical trial in neonates in South Africa late last year using a novel, recombinant BCG (bacillus Calmette-Guérin) vaccine. The new TB vaccine (VPM1002) is based on the BCG vaccine in use today, but what makes it more powerful is that it contains a gene which makes it easier for the vaccine to be better recognised by cells of the immune system.

The 'Phase 2b' trial will be studying 416 babies (newborns) whose mothers are HIV-positive and negative. A single dose will be administered to babies immediately after birth and will be followed up for a year. The trial, to be completed by mid-2017, will study safety and the level of cellular immune response (which does not involve antibodies) produced by the vaccine.

A 'Phase III' trial involving newborns will begin in India once 'Phase 2b' ends. By the end of this year, the institute also plans an independent 'Phase III' trial, again in India, involving nearly 2,500 adult TB patients who have been successfully treated.

The rationale for targeting this high-risk subset of the adult population is because each year in India, TB recurrence (reinfection and relapse) is seen in at least 2,00,000-2,50,000 people who have been successfully treated. According to the medical director at the institute, Dr. Prasad S. Kulkarni, it will be easy to clinically prove the vaccine's efficacy as the study will be restricted to a relatively fewer number of people.

The recombinant vaccine, which was developed by a group headed by the founding director of the Max Planck Institute for Infection Biology, Berlin, Stefan H.E. Kaufmann, has already shown promise in animal and small-scale human trials. Prof. Kaufmann said the amount of bacteria reduced 100-fold in all animals studied when the recombinant vaccine was administered. Studies in two separate 'Phase I' human clinical trials in 80 adults in Germany (2009) and 50 adults in South Africa (2010) and one 'Phase 2a' trial in 50 newborn infants in South Africa in 2012 have confirmed safety and sufficient strengthening of the immune system against TB, thus raising hopes for a higher efficacy vaccine.

The trials in Germany and South Africa were carried out by Vakzine Projekt Management GmbH (VPM), Hanover, Germany. The Max Planck Institute holds the patent and has licensed the vaccine to VPM; VPM, in turn, has out licensed it to the Serum Institute.

The recombinant BCG vaccine is intended to protect children and possibly adults against drug-sensitive and drug-resistant TB. The hope is that the vaccine will be able to protect against pulmonary and extra-pulmonary TB. In comparison, the classical BCG vaccine can only protect against severe forms of the disease in children but cannot prevent pulmonary TB in all age groups, including children.

Besides better efficacy, the recombinant BCG vaccine has been found to be superior safety-wise. Unlike the currently used vaccine that causes BCG-related disease in HIV-positive babies (as they have reduced immunity), the recombinant vaccine is expected to be safe in this population. Better safety of the new vaccine was demonstrated even during animal trials — immuno-compromised mice died when the existing BCG vaccine was administered but not when the recombinant vaccine was used. Prof. Kaufmann and others strongly believe that a difficult pathogen like *Mycobacterium tuberculosis,* which expresses some 3,000 different antigens, cannot be dealt with by a vaccine containing one or a few antigens. "Since BCG shares almost all antigens with tuberculosis, we decided to improve BCG with respect to its ability to provoke an immune response," he said. "Indeed, our strategy has been termed by others as [a] rational vaccine design".

The hypothesis was that the vaccine would induce broader cellular immunity (that does not involve antibodies) but something unexpected happened. "Antibody response was also seen in animals. This was unexpected and is good," he said.

"The vaccine being tested is intended to replace the current BCG vaccine and will be administered to young children to protect them against tuberculosis. Adults may also be able to benefit from it later," Prof. Kaufmann added.

Since its use in 1921, BCG has become the "most widely administered vaccine in history with approximately 4 billion doses administered worldwide".

"Besides assured supply, [the] Serum [Institute] manufacturing the vaccine will mean that [the] cost will be reasonable," said the Director-General of the Indian Council for Medical Research, New Delhi, Dr. Soumya Swaminathan.

With a capacity of 100 million doses, the Pune institute meets the global demand for BCG vaccine and is well equipped to supply the new vaccine when the trials are completed. This will mark the end of a long journey that began when the recombinant vaccine was constructed in the late 1990s and tested in different animal models to determine its safety and protective effect.

Source: The Hindu, http://bit.ly/1UNckRh (25.02.2016)

2. Slight change to antibacterial drug may improve tuberculosis treatments

Researchers with Vanderbilt University have discovered that one small chemical change to an existing antibacterial drug results in a compound that is more effective against its target enzyme in tuberculosis.

Not only does the new compound—a derivative of the fluoroquinolone moxifloxacin—work better against the wild-type tuberculosis enzyme, it maintains activity against resistant forms of the enzyme, said Neil Osheroff, Ph.D., John Coniglio Professor of Biochemistry.

The findings, reported in the *Proceedings of the National Academy of Sciences*, could lead to a more effective treatment for tuberculosis.

"We're really excited about the translational potential of this work," Osheroff said.

Tuberculosis (TB) is one of the world's deadliest diseases. One third of the world's population is infected with TB, and in 2014, 1.5 million people died from the disease, according to the World Health Organization.

Although TB is considered curable, the six-month multi-drug regimen is difficult to complete—particularly in low-income parts of the world—and resistance to drugs in the first-line regimen is growing.

Broad-spectrum fluoroquinolone antibacterials, such as levofloxacin and moxifloxacin, are used in second-line tuberculosis treatment regimens, and they are being tested as part of a newer first-line regimen. But resistance to fluoroquinolones, which are commonly prescribed for a wide variety of infections, is also on the rise.

To understand how bacteria become resistant to fluoroquinolones, Osheroff and his team have studied the interaction between the drugs and their target enzyme, a bacterial type II topoisomerase.

"By understanding how the drugs interact with the enzyme, we can learn how resistance occurs and then hopefully develop strategies for overcoming that resistance," he said.

Topoisomerase type II enzymes cut DNA and stitch it back together to manage knots and tangles and facilitate DNA replication. The fluoroquinolones bind the enzymes and stabilize the cut DNA-enzyme complex, resulting in a chopped up genome.

Graduate student Katie Aldred, Ph.D., now a faculty member at the University of Evansville, characterized the interaction of fluoroquinolones with the tuberculosis topoisomerase II enzyme, called gyrase.

She confirmed the importance of certain gyrase amino acids to the interaction, and demonstrated how mutations that change those amino acids weaken or eliminate the interaction and result in resistance to the drug.

The researchers discovered that a certain position in the fluoroquinolone molecule was particularly important to the drug-gyrase interaction and that chemical changes at the critical position impacted the interaction.

Changing moxifloxacin at the critical position resulted in a compound (8-methyl moxifloxacin) that was more potent against the wild-type gyrase. The new compound was also effective against gyrase containing clinically relevant resistance mutations—even more effective than moxifloxacin itself was against the wild-type gyrase.

"By making one small change in moxifloxacin, we've come up with a much better drug against the wild-type gyrase enzyme; it maintains activity against resistant enzymes; and in all cases, it forms more stable DNA strand breaks," Osheroff said.

The hope, he added, is that the modified moxifloxacin will be an effective drug that results in a better treatment for tuberculosis.

"This project has been a lot of fun; we get to do highly mechanistic biochemistry that has really important ramifications," Osheroff said.

Source: Medical Xpress, http://bit.ly/20Dqwvy (17.02.2016)

3. Startup develops quick breath test for TB based on UNM tech

Doctors could soon determine if patients have tuberculosis in less than 10 minutes with a simple breath test being developed by a local startup company with technology from the University of New Mexico.

Avisa Pharma Inc., which licensed the testing process from UNM in 2010, and has been working to develop and market it, conducted its first field test on patients in South Africa last fall. The trial, which included nearly three dozen people in a region where co-infection with HIV and tuberculosis is common, produced rapid results that in some cases were even more accurate than standard sputum smear tests, said Avisa President and CEO David Joseph.

“Our success rate was very high,” Joseph said. “Three of the patients had negative smear tests, but our tests confirmed that those same patients did have tuberculosis. That shows that this test can detect disease with even more sensitivity than today’s standard tests.”

A rapid breath test for tuberculosis could provide an immense boost in global efforts to combat the disease, particularly in Africa and other developing regions where tuberculosis is rampant and access to modern medical facilities is limited.

A report from the World Health Organization released last fall called tuberculosis the world’s leading infectious disease killer, alongside HIV/AIDS, with about 1.5 million deaths in 2014. The organization said a new, rapid diagnostic system is urgently needed to help stem the disease, which currently infects nearly 10 million people globally.

The problem is lack of a reliable testing method for early detection of tuberculosis and to rapidly monitor patient progress on antibiotics to determine if treatments are working, Joseph said. Today’s sputum smear tests generally take days or weeks to confirm disease. The results can be erroneous because the sputum samples don’t provide a full examination of the lungs. And children or patients sick with AIDS and other diseases often can’t produce enough sputum for an effective test.

“We can detect tuberculosis in less than 10 minutes and it doesn’t require sputum,” Joseph said. “Since the test takes just minutes, doctors can also monitor antibiotic treatments to see if they’re working or need to change.”

The breath test was originally developed by Graham Timmins, a UNM professor of medical chemistry and toxicology, and Vojo Deretic, chair of the Molecular Genetics and Microbiology Department.

They created a urea-based drug that turns to carbon dioxide when it comes in contact with bacteria. That happens because a lot of bacteria in the lungs contain an enzyme that breaks down urea to absorb the nitrogen and other elements in it, leaving carbon dioxide behind.

The drug acts as a biomarker for the enzyme. Patients breathe the compound in and, when they exhale, the carbon dioxide levels are measured.

“The breath test shows the presence of the enzyme in the lungs, which shouldn’t be there, and the system says something is wrong and you need to probe further,” Timmins said. “It’s almost like a bacterial thermometer for the lungs.”

The compound can detect the presence of bacteria anywhere in the lungs, making the breath test more accurate than culture-based sputum samples, which examine only limited regions of the respiratory tract, Joseph said.

Since 2010, Avisa has built a portable device to measure carbon dioxide levels as patients breathe in and out. The laptop-sized machine is fairly simple to use, making it ideal for remote, rural locations, said David Karshmer, vice president for technology development.

“It’s a small, lightweight, battery-powered sampling system with a simple user interface,” Karshmer said. “We went into the field to clinics and hospitals to come up with a simple, easy-to-use design that you can put in a backpack and carry anywhere.”

The company now has a prototype, which it used in the South Africa trials, and, by midyear, Joseph expects to send the design to a contract manufacturer in Texas.

Avisa is now preparing for a large, clinical trial for approval by the U.S. Food and Drug Administration and regulatory agencies in other countries. That trial, which would likely take place in summer of 2017, would include up to 1,000 people in the U.S., Europe, China and South Africa.
Once that trial concludes, it could take up to a year to receive FDA approval, potentially paving a path to market by 2018, Joseph said. At that point, Avisa would initiate more trials to apply the technology to detection of other lung diseases, such as cystic fibrosis and chronic obstructive pulmonary disease. That diversity in potential market applications has helped attract venture investment in the company.
Avisa has raised about $8 million in private equity to date, including a $4 million round of venture investment that closed last year. It's now raising a later-stage, $10 million round of investment to carry the company through to its clinical trials.
Santa Fe-based Sun Mountain Capital – which manages the State Investment Council's $150 million co-investment fund for direct investments in startup companies – has contributed several million dollars to Avisa Pharma, said Sun Mountain managing partner Brian Birk.
"We originally got interested in the technology because it has a number of different applications, not just tuberculosis," Birk said. "And the technology itself is relatively simple, giving it a shorter path to commercial development with a reasonably low amount of capital compared with other pharmaceutical startups. Avisa is one of those local companies that's been flying under the radar, but really doing some great stuff."
The company now employs seven people at a 2,000-square-foot office in Santa Fe. It expects to ramp up its workforce over the next year in preparation for the clinical trial.
Source: Albuquerque Journal, http://bit.ly/1SDnpTw (08.02.2016)

4. Blood test could transform tuberculosis diagnosis, treatment in developing countries
A simple blood test that can accurately diagnose active tuberculosis could make it easier and cheaper to control a disease that kills 1.5 million people every year.
Researchers at the Stanford University School of Medicine have identified a gene expression "signature" that distinguishes patients with active tuberculosis from those with either latent tuberculosis or other diseases.
The technology fills a need identified by the World Health Organization, which in 2014 challenged researchers to develop better diagnostic tests for active TB.
A paper describing the work will be published online in *Lancet Respiratory Medicine* on Feb. 19.
Globally, tuberculosis infects 9.6 million new patients each year and kills 1.5 million. Yet the disease remains difficult to diagnose. "One-third of the world's population is currently infected with TB. Even if only 10 percent of them get active TB, that's still 3 percent of the world's population—240 million people," said Purvesh Khatri, PhD, assistant professor of medicine and senior author of the paper.
Traditional diagnostic methods, such as the skin prick test and interferon assays, can't separate patients with active TB from those who are no longer sick or have merely been vaccinated against TB (and most countries vaccinate everyone against TB). These older diagnostics can miss a case of TB in patients with HIV.

A common way to test for TB is to look for the disease-causing bacterium in sputum samples coughed up by patients. But sometimes it's hard for people to produce sputum on demand, said research associate Tim Sweeney, MD, PhD, first author of the paper. "If someone can't produce adequate sputum, or if you have a kid who can't follow directions," it's hard to diagnose them, he said. And the sputum test is almost useless for monitoring how someone is responding to treatment. As people start to get better, they can't produce sputum for the test.
The new test developed in the Khatri lab works on an ordinary blood sample and removes the need to collect sputum. It can signal a TB infection even if the individual also has HIV. And it won't give a positive response if someone only has latent TB or has had a TB vaccine. It also doesn't matter which

strain of TB has infected a person, or even if it has evolved resistance to antibiotic drugs. The test works in both adults and children.
WHO has called for a test that would give a positive result at least 66 percent of the time when a child has active TB. The Khatri test is 86 percent sensitive in children. And if the test comes up negative, it's right 99 percent of the time. That is, of 100 patients who test negative with the Khatri test, 99 do not have active TB.
The requirements of the test are simple enough that it can potentially be done under relatively basic field conditions in rural and undeveloped areas of the world. Any hospital should be able to perform the test. Villages without electricity could likely use ordinary blood samples and a solar-powered PCR machine, which multiplies strands of DNA, to accurately test people for active TB.

When pathogens infect the cells of the body, the infection sets off a chain reaction that changes the expression of hundreds of human genes. Khatri's team identified three human genes whose expression changes in a consistent pattern, revealing the presence of an active tuberculosis infection. The team validated the new three-gene test in a separate set of 1,400 human samples from 11 different data sets, confirming the diagnostic power of the test.
The new test not only accurately distinguishes patients who have active tuberculosis, it could also be used to monitor patients to see if they are getting better and how well they are responding to different treatments. Thus, it can be used not only for diagnosis and to inform treatment, but also to study the effectiveness of different treatments. The test's hugely accurate negative response would be especially helpful in monitoring the effectiveness of treatments during clinical trials, said Khatri.
He has already begun collecting funding to develop the test for widespread use, both to diagnose TB in patients and to monitor recovery in clinical trials, allowing for more rapid development of better and cheaper treatments.
The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.
Source: Medical Xpress, http://bit.ly/21h3TNU (20.02.2016)

Reportage

1. When my brother got TB, doctors said there was no hope. How could that be?
Two years ago a hospital administrator confirmed that my brother Gary had tuberculosis. Then she told us the bad news.
“It’s worse than we thought,” she said. “There might not even be any medication to help him.”
I didn’t understand. It’s the 21st century, not the 1800s or even early 1900s. We have sophisticated machines and advanced robotics; surely we know how to cure TB? But the doctors at the Southern California hospital where Gary was being treated kept trying new antibiotics — and nothing was working.
Gary’s symptoms had started a few weeks before, with a 103-degree fever. We took him to the emergency department, where he was admitted to the hospital and diagnosed with pneumonia. In the hospital, he continued to lose weight, and his fever would not go down. He looked so frail; I worried he would break if I touched him. It was hard to watch the big brother who had always protected me, who was then only in his mid-30s, waste away in front of me.
Gary was tested for TB, but the results were confusing. First, we were told Gary had TB, then that he didn’t have it, then again that he did. But pneumonia and TB are treatable, so why wasn’t my brother getting better? I demanded to speak with his nurses, his doctors and the county health department.
That is when the hospital health administrator told me there was no hope.
The hospital had isolated Gary in a tiny room with a bed and a bathroom. I had to wear a cloth mask when I visited, and his doctors wore full hazmat-like suits.

"I don't know how to help you," one doctor told us. Another apologized. "I've just never seen a case like yours," he said.
Finally, the hospital staff told me that Gary didn't have just multi-drug-resistant TB: He had "extensively drug-resistant" TB. Later I would learn he had one of the most drug-resistant forms of TB ever diagnosed or treated in the United States, among the most drug-resistant in the world.
Tuberculosis has haunted humans for thousands of years. In the late 1880s, when the bug that causes TB — *Mycobacterium tuberculosis* — was first identified, the airborne disease was responsible for killing 1 of every 7 people in the United States. The bacteria can attack any part of the body but usually attacks the lungs. It wasn't until antibiotic treatment was developed in the mid-1900s that the disease was brought under control.
Between 1953 and 1985 the number of new TB cases in the United States dropped by 74 percent. People began to believe that it had been eradicated, and resources were diverted from TB surveillance, treatment and prevention to other areas of health care.
When the HIV/AIDS epidemic hit in the 1980s, TB rates began to increase once again in the United States. TB is the most common opportunistic infection affecting HIV-positive people. Increased federal resources and programs were devoted to those with HIV/AIDS, and by the mid-1990s rates of TB were decreasing again.
In 2014 there were 9,412 reported new cases of TB in the United States — or three new cases per 100,000 people. While this is a 2.2 percent decrease from 2013, it represents the smallest decrease in the rate of the disease in more than a decade. This alone is not cause for alarm, but there are worrying trends — health systems' limited experience with and institutional knowledge about the disease, the lack of new TB medications, the toxicity of drugs used to treat drug-resistant TB, and the lengthy and disruptive treatments that drug-resistant TB requires. While the overall TB incidence in the United States is declining, the incidence of multi-drug-resistant TB is not.
Worldwide, TB is the No. 1 killer of people with HIV. One-third of the world's population has latent TB, meaning that they have TB in its dormant state but that the disease has the ability to reactivate.
Individuals with TB have the potential to infect up to 10 to 15 people each over the course of a year. According to the World Health Organization, only 1 in 4 of the estimated 480,000 people who developed multi-drug-resistant TB globally in 2014 were diagnosed and notified. India, China and Russia accounted for more than half of those 480,000 patients.

I grew up in Hollywood, but Gary and my two older sisters grew up in Russia and Armenia. Our family is Armenian and moved to the United States while I was still young. Gary later returned to the former Soviet Union and was living in Russia with his own nuclear family in 2009 when he developed a cough. Doctors there diagnosed pneumonia.
It wasn't the first time that Gary had been sick. In his 20s he had been diagnosed with ankylosing spondylitis, an inflammatory disease that can result in the spinal vertebrae fusing together, causing a hunched-forward posture. He was given immune-suppression medication, something I now believe may have made him more vulnerable to developing TB.
Gary continued to suffer bouts of pneumonia on and off for the next several years. At the hospitals in the United States, doctors occasionally mentioned "seeing something on his lungs" when they X-rayed them. In the end, they always concluded it was scar tissue from his past bouts of pneumonia and sent him home with more antibiotics.
In December 2013 Gary developed the fever that would not break. But this time, the doctors also tested him for TB. It was the third time he had been to the emergency department for a cough that fall. And the first time he was tested for TB.
Gary, a musician, was divorced by this time, and his son and daughter were living in Russia. It fell largely on me and my sisters to care for him. After much lobbying on my part, Gary was transferred to Olive View–UCLA Medical Center in Los Angeles. Caitlin Reed is the medical director of the inpatient TB unit there, and I truly believe that if it wasn't for Reed, Gary would be dead right now.

As the incidence of TB in the United States declines, fewer doctors are familiar with the disease and are often late to diagnose it, according to Reed. In 2000, a study from Johns Hopkins University's Center for Tuberculosis Research Laboratory reported that TB had become rare enough in the United States, and its treatment complicated enough, that doctors in private practice often did not get the treatment right. The Hopkins authors suggested that these doctors were responsible for most of the country's new drug-resistant cases. A patient faces better outcomes when treated by a public health physician such as Reed, who has seen more cases of the disease.

Reed started testing various antibiotics to see what would work. At one time, Gary was on about a dozen antibiotics at once. The drug that probably saved his life was a new one, bedaquiline, for which the Food and Drug Administration granted accelerated approval in late 2012. Gary began taking bedaquiline in March 2014 and a few months later was deemed "culture negative," meaning he was no longer contagious.

But his battle was far from won. One of Gary's lungs was so badly damaged by TB that Reed decided on a drastic measure. Her strategy was to remove the largest burden of the disease by surgically removing the damaged lung and then using drugs to kill the remaining disease in the other lung. A method used before antibiotic treatment was available, lung surgery for TB is not as common as it used to be. John Mitchell, a surgeon at National Jewish Health in Denver who has treated many TB patients, agreed to remove Gary's lung.

After the surgery, he came back to California to recover, and we had to force him to walk. He felt as if he couldn't breathe. He'd panic and refuse to move. Gary is out of the hospital now. He uses an oxygen tank constantly and must continue antibiotic treatment for two additional years.

The treatments themselves have taken their toll. One of the antibiotics damaged Gary's hearing, and if I stand just a few feet away, he can't hear me unless I yell. Other drugs have brought on a short temper, paranoia and nerve damage in his hands and feet. There is no guarantee that the burning pain he experiences in his limbs will ever lessen or go away. If he continues to take the drug that causes the nerve damage, there's a chance he could no longer be able to walk. He takes more drugs to ease the nerve pain and slow the progression of the nerve damage. His memory is so bad we don't trust him to take his medications without supervision. He's on steroids that give him pimples all over his face and body and discolor his skin.

Yet it's a "damned if you do, damned if you don't" situation. If a TB patient doesn't take his medicine, he dies.

Gary now lives with our father and one of my sisters. He has gone from the attractive teenager whom people approached about being a model to a man who avoids going out to avoid people's stares.

Excursions are a hassle anyway: There is the loading of oxygen tanks, the packing of medication and the fact that he has to be home at 8 a.m. and 4 p.m. so the health department can watch him take his most important medications — drug resistance could result if he did not take them regularly or interrupted treatment. He wears a mask when he goes to the doctor's office or hospital, to protect him from germs. He has had several colds, and each time he ends up back in the hospital. The next one could kill him.

There was another option — one we all fought for, including Reed. The drug is called delamanid and was approved by European and Japanese regulators in 2014. It is not yet approved in the United States but is available under the FDA's expanded access, or "compassionate use," program. The program requires buy-in from the patient's physician, the FDA and the drug manufacturer. But when Reed appealed to the Japanese drug manufacturer, Otsuka, to allow her to use delamanid on Gary, it denied her request because the drug had never been tested for use in combination with bedaquiline. Reed had high hopes for using the drugs in combination. Delamanid would have replaced the drug that was causing Gary's nerve damage. However, it is unknown whether the two drugs are safe to use together; we believe it's a risk worth taking when the alternative is eventual paralysis.

In early 2015 the pain of Gary's drug regimen became too much to endure, and he told his doctors he could not bear to take the drug that was causing his nerve damage any longer. They replaced it with another drug, which caused kidney damage. He is on a third drug now, one we hope will work out better, in combination with his other medications. The nerve damage and pain continue, and he still takes medication to combat it, along with very high doses of painkillers.
Gary is almost done with his drug treatment. Following additional testing, delamanid use with bedaquiline is now allowed under limited circumstances through the compassionate-use protocol.

The last effective diagnostic for latent tuberculosis was introduced in 1891; the last vaccine for TB was introduced in 1921; and before the approval of bedaquiline in 2012, a new first-line drug for TB had not been introduced in the United States since 1967.
In the United States the small number of TB cases means that there isn't much monetary incentive for companies to stock TB drugs, which has resulted in widespread shortages of critical TB medicines and testing supplies. There is also an urgent need for new, more effective vaccines for use in preventing TB infection, disease manifestation and recurrence, internationally and even domestically.
TB has not yet been relegated to the history books. As my family's story continues to unfold, the disease's burden is very real, and the next chapters remain uncertain.
Source: Washington Post, wapo.st/1VhfOcM (16.02.2016)

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