NEWSLETTER

Ausgabe 8/2016

Inhalt

Internationale Nachrichten

1. Scientists explain why Russian tuberculosis is the most infectious

A collaborative of Russian researchers conducted a large-scale analysis of the proteins and genomes of mycobacterium tuberculosis strains that are common in Russia and countries of the former Soviet Union and found features that provide a possible explanation for their epidemiological success. A paper detailing the results has been published in the prestigious journal *Scientific Reports*.

Up until the 20th century, tuberculosis was considered an incurable disease, and despite newly developed methods of treatment during its early stages, the death rate is still high. There are 22 countries, including Russia, in which the infection rate is four times greater than in the rest of the world. It is important to note that the term "tuberculosis" covers a wide range of bacteria strains that cause the disease. Strains of the Beijing family, a genotype that was first discovered in Beijing, are prevalent in Russia—every year, about 150,000 people are infected with it. To understand the reason behind the success of this strain, scientists compared proteins produced by Beijing B0/W148 with a control strain. In order to do this, separated bacterial proteins were enzymatically cleaved into smaller fragments—peptides and their mass and relative abundance were measured precisely using mass spectrometry.

After analysing the data, the scientists knew which and how many proteins there were in each strain. They found that in Beijing B0/W148 strains, 266 proteins were differentially abundant compared with the control strain. Fifty-seven of them were entirely absent in the study group and 17 were unique to it, while others differed quantitatively. Analysis of the functions associated with differing proteins revealed that in Beijing B0/W148 strains, there are more proteins producing long-chain fatty acids and fewer proteins destroying them. Bacteria use these acids to produce mycolic acids, which integrate themselves in the bacterial cell membrane and make it waxy, which is why mycobacteria can survive and even reproduce in macrophages (special human cells that destroy foreign substances).

Normally, if a bacterium is eaten by a macrophage, it dies. However, mycobacterium tuberculosis strains have evolved to reproduce within macrophages, and in doing so, they hide from the immune system. Mycolic acids not only protect bacteria, but also play a crucial role in synthesizing substances that inhibit macrophages so they stop fighting disease. These newly discovered features of lipid metabolism could explain the success of Beijing B0/W148 strains in relation to other tuberculosis mycobacteria.

Source: Medical Xpress, http://bit.ly/2bMFHDB (23.08.2016)

2. Eugene Bell Foundation calls for support to treat more TB patients in North Korea

Stephen Linton, chairman of the charity group, said the foundation faced "serious" disruption in running its program to treat North Korean patients with multidrug-resistant tuberculosis in early 2016 due to tension on the divided peninsula.

He said that a delay in South Korea's approval of its medication shipment to the North and

Pyongyang's issuance of visas delayed the delivery of its regular spring shipment by about a month.
"Unless our program can transcend politics and tensions, maintaining a responsible program becomes impossible," Linton said at a press conference in Seoul that touched on the trip to North Korea earlier this month.
The foundation has long provided medical humanitarian assistance to North Korea, especially for multidrug-resistant tuberculosis.
Linton said that the delay in the medication delivery has made it impossible for the charity group to accept 500 new TB patients which it had hoped to enroll this spring.
The group has so far provided TB medication to about 1,500 patients in North Korea with plans to register an additional 1,000 patients this year.
Seoul has suspended civilian inter-Korean exchanges and South Koreans' visits to North Korea since Pyongyang's fourth nuclear test in January.
He said that the group has recently earned the Seoul government's approval to deliver TB medication to the North slated for November.
Linton called for South Koreans and the Seoul government to provide support for non-government exchange programs with North Korea despite high inter-Korean tension.
"Ultimately, people in South and North (Korea) must decide if vital private sector exchanges can be protected from the chronic tensions on the Korean Peninsula... Koreans should remember that people die because of tensions as well as direct conflict."
Source: TB Online, http://bit.ly/2c0qOwC (18.08.2016)

3. Invisibility, TB's deeper malaise
The number of tuberculosis (TB) cases in India could well be two to three times higher than the current estimates, says a study from London's Imperial College, suggesting that the actual number is going "vastly under-reported".
The findings are disconcerting as India already has the highest number of tuberculosis cases, accounting for a quarter of all cases worldwide. But even this is under-reported suggests the latest study, indicating that there was an "additional" 2.2 million TB cases in the private sector in 2014.
The study is one of two India-oriented research papers that will be published in *The Lancet Infectious Diseases* on Thursday. The other study was on antibiotic use in India. (...)
The under-reporting of TB was because people opt for private health care, who fail to report to public health officials, the study said. And this, scientists warn, could fuel drug resistance, where the medicine given to treat TB becomes ineffective.
Tuberculosis is a bacterial infection, spread through inhaling tiny droplets from the coughs or sneezes of an infected person. In 2014, 9.6 million people (reported and unreported cases) fell ill with tuberculosis and 1.5 million died from the disease, a note on the study said.
Nimalan Arinaminpathy, lead author of the research from the School of Public Health at Imperial told *BusinessLine* in an email interaction, that of the six million odd cases, globally reported in 2014, India reported over 1.6 million. "There is an *additional* burden of TB that is 'invisible' to public health authorities - much of this burden is managed by the private sector. So the 2.2 million should be regarded as additional to the 1.6mn reported by India," the author said. The team arrived at the estimate from a calculation of nationwide sales of tuberculosis drugs across the private sector.
In fact, the Government had mandated private doctors to notify them when they treat a TB patient at their clinics. Arinaminpathy, however observed, that making TB a notifiable disease was a valuable step, but was not sufficient for such a large and fragmented private healthcare sector as in India. "We already know that the private sector is only reporting a small fraction of their TB cases, but the present study highlights that the problem is bigger than we had previously recognised," the researcher said.
Against the backdrop of drug resistance, the author pointed out that tuberculosis treatments need to be taken for six to nine months. But patients feel better within a couple of weeks and often stop taking the medication, when in fact, completing the course was key to effective treatment. Mumbai,

for example, faces a worrying epidemic of drug-resistant TB and many would argue the private sector has a role in this, the researcher said.
Arinaminpathy said that the findings highlight the need to re-double efforts to address the burden of tuberculosis in India, and urgently increase surveillance in the private sector, besides improving its cooperation with the public sector in India.
The study was funded by the Bill and Melinda Gates Foundation (BMGF), with other collaborators being IMS Health Inc; Central TB division (Government of India) and the India offices of the World Health Organization and BMGF.
Source: The Hindu Business Line, http://bit.ly/2bMLs6a (25.08.2016)

Forschung & Entwicklung

1. Development of medicines to treat tuberculosis. Comments on draft guidance invited until 31 January 2017
The European Medicines Agency (EMA) has launched a public consultation on revised guidance on the development of new medicines to treat tuberculosis (TB). The guidance is an addendum to EMA's guideline on the evaluation of medicines to treat bacterial infections.
Stakeholders can send their comments to the Agency until 31 January 2017.
TB is caused by a bacterium called *Mycobacterium tuberculosis.* In Europe, approximately 340,000 new TB cases and 33,000 deaths were reported in 2014, mostly from eastern and central European countries. While TB is slowly declining worldwide, the burden of the disease is still very high with approximately 1.5 million deaths per year. Moreover, multidrug-resistant tuberculosis (MDR-TB) still poses a serious public health challenge. It often affects people from the most vulnerable communities, including migrant workers, refugees, displaced persons, prisoners or drug users.
Today's existing TB treatments cannot effectively combat the disease because they are lengthy, complex, and generally show reduced efficacy against MDR-TB, imposing a heavy burden on patients, families and healthcare systems. New TB medicines and regimens (a combination of medicines) that are simpler to administer, are of shorter duration, and can overcome drug resistance are urgently needed.
In recent years, there has been a shift towards developing entirely new regimens to treat TB, rather than focusing on single medicines. The revised guidance takes into account this development.
The guidance also clarifies the European Union's regulatory requirements with regard to data that should be generated to support the approval of new medicines or combinations of medicines, and provides direction on the following topics:

- evaluation of the efficacy of individual new medicines and regimens in light of recently approved medicines;
- evaluation of new regimens including at least one new medicine;
- role of biomarkers to predict the effectiveness of the medicine(s) during clinical development.

Comments on the draft guideline should be sent to idwpsecretariat@ema.europa.eu using the form provided. EMA will host a workshop in November 2016 to discuss stakeholders' comments on the revised guidance. Comments will be taken into account in the finalisation of the guideline. The workshop will be broadcast live.
Source: EMA, http://bit.ly/2apzXi9 (02.08.2016)

2. Simple test could quickly detect tuberculosis in developing countries
Tuberculosis (TB) is one of the biggest scourges there is among infectious diseases, killing nearly 2 million people a year, most in developing countries. It is also notoriously hard and slow to detect in places without top-flight health care systems. Yesterday, researchers reported at the American Chemical Society (ACS) meeting here that they've devised a simple new way to diagnose TB, and

even distinguish living TB cells from dead ones, which could give doctors an easy way to see whether their anti-TB medications are working. The researchers are now putting their diagnostic through its paces with samples from patients in South Africa, which has one of the world's highest incidences of TB, and they hope to launch a clinical trial of their test soon.

According to the World Health Organization, nearly 10 million people contract TB every year. That happens when someone infected with *Mycobacterium tuberculosis* coughs, or even speaks, and others nearby inhale tiny, bacteria-laden droplets. In wealthy countries, doctors take lung x-rays of patients suspected of having TB and test their sputum (mucus and spit) for DNA markers of the bacterium. But in developing countries, where there is limited access to these technologies, technicians often turn to a procedure known as the Ziehl–Neelsen (ZN) test.

Developed more than a century ago, the ZN test spritzes dye-laden liquids onto a sputum sample. After extensive processing, those dyes latch onto water-excluding "hydrophobic" compounds that are abundant in *Mycobacteria* membranes. But the test is slow to administer, not particularly sensitive, and gives many false positives, because many bacterial membranes contain hydrophobic compounds, says Carolyn Bertozzi, a chemist at Stanford University in Palo Alto, California.

Bertozzi and her colleagues wondered whether there wasn't a better way to flag TB. Her team had spent more than a decade studying how different organisms, including pathogenic bacteria, attach a wide variety of sugar compounds to the proteins and fatty molecules called lipids that make up their cell membranes. In their early studies they found that unlike most other bacteria, and most other organisms, *Mycobacterium tuberculosis* and its close relatives use a type of sugar known as trehalose to carry out this construction. "We wondered whether we could use this to mark TB cells," Bertozzi says.

The researchers designed a series of different trehalose sugars tagged with a fluorescent dye abbreviated DMN. The dye glows bright green when it absorbs light—but not always. If it's surrounded by even the slightest bit of water it doesn't shine. When water is excluded, as it is in the hydrophobic interior of a cell membrane, the dye lights up. Bertozzi's hope was that if her team fed their dye-labeled sugars to the TB bugs, the microbes would take them up and append them to their cell membrane lipids, turning them green. That wouldn't happen for dead TB cells that can't take up the sugar, nor for the cells of most other organisms, making it possible to spot a live TB infection in highly diverse sputum samples.

In lab studies the researchers found just that. Bertozzi reported at the meeting that live *Mycobacterium* samples shone bright green under a fluorescence microscope, whereas those containing common bacteria, such as *Escherichia coli* or *Staphylococcus aureus*, didn't fluoresce at all. What's more, the live TB cells begin to glow in as little as 5 minutes after being fed the sugar, and turn bright green within 1 hour. ZN tests, by contrast, can take hours and often miss low levels of infection. Another standard test, wherein TB proteins are injected under the skin and doctors look for an immune response that shows a person has been infected, can take 3 days to produce a result.

Bertozzi and her colleagues also collaborated with Bavesh Kana, a biochemist at the University of the Witwatersrand in Johannesburg, South Africa, who provided sputum samples of patients suspected of having TB. Lab tests on those samples not only quickly flagged live TB, but showed a close match with more exacting DNA studies. Bertozzi says that she and her colleagues are hoping to launch a clinical trial of their diagnostic to test its success under real-world conditions.

"It's pretty spectacular," says Dale Boger, a chemist at the Scripps Research Institute in San Diego, California, who attended Bertozzi's session. Boger adds, however, that even if TB is detected rapidly its resistance to current medications continues to be a major problem. Bertozzi notes that if the new test proves successful, it could help fight such resistance by allowing doctors to determine what medications are and aren't working to defeat one of the most vexing and dangerous infectious diseases.

Source: Science Mag, http://bit.ly/2bk86Al (24.08.2016)

3. **HIV not a super-spreader of drug-resistant tuberculosis**

While the human immunodeficiency virus (HIV) pandemic fuels tuberculosis (TB) outbreaks, it does not drive the development and transmission of multidrug-resistance in TB patients as previously suspected, according to a study published in *eLife*.

The findings, from a collaboration between Norwegian, British and Argentinian scientists, also show that TB drug resistance is not more likely to evolve in HIV-positive patients compared to HIV-negative patients.

"It is already known that a parallel HIV pandemic amplifies the TB epidemic, with ongoing efforts around the world to tackle these potentially fatal diseases," says lead author Vegard Eldholm, a research fellow at the Norwegian Institute of Public Health.

"Among the estimated 1.5 million people who died from TB in 2015, about 200,000 cases involved multidrug-resistant TB and 400,000 were HIV co-infected. However, it is not clear exactly how much of an effect HIV has had on drug resistance in the most common form of TB, Mycobacterium tuberculosis (Mtb)."

To explore the impact of HIV co-infection on Mtb drug resistance, Eldholm and his team analysed the genomes of 252 TB isolates from patients belonging to the largest outbreak of multidrug-resistant TB in South America to date.

The isolates were collected from patients with known HIV status from the mid-1990s until 2009. The team used the genomes to create a time-labelled phylogenic tree, a diagram showing the inferred evolutionary relationships among the mutations within the sampled patients. They then applied a new mathematical model optimized for TB to reconstruct how the disease spread among individuals. Finally, they combined the results of both methods to estimate the length of the TB latent period -- the time from infection to infectiousness -- and identify the patients in who TB strains evolved drug-resistance mutations.

"We saw no significant differences in the rate at which mutations occur in the genomes of strains in HIV-positive and negative patients. This suggests that drug resistance is not more likely to evolve in HIV-positive patients," says co-corresponding author Francois Balloux, Professor of Computational Systems Biology at University College London.

While the team's reconstruction of disease transmission among individuals did not reveal a significant impact of HIV co-infection on the ability of patients to transmit TB, their estimates of TB latency confirm that HIV co-infection accelerates the development of active TB.

"HIV prevents some cells from doing their job in the immune system, meaning the body is unable to fight off a large number of infections," Eldholm explains.

"The disease therefore provides TB with a pool of susceptible hosts, amplifying the rate of co-infection. Indeed, for this reason, HIV patients at a major hospital in Buenos Aires, Argentina, played a central role in fueling South America's largest multidrug-resistant TB epidemic in the early 1990s," he adds.

Source: Science Daily, http://theatln.tc/2aICpQr (10.08.2016)

4. HHS forges unprecedented partnership to combat antimicrobial resistance

To address one of the greatest modern threats to public health — antibiotic resistance — the U.S. Department of Health and Human Services (HHS), the Wellcome Trust of London, the AMR Centre of Alderley Park (Cheshire, United Kingdom), and Boston University School of Law will create one of the world's largest public-private partnerships focused on preclinical discovery and development of new antimicrobial products.

Made possible through a cooperative agreement, the partnership promotes innovation and could provide hundreds of millions of dollars over five years to increase the number of antibiotics in the drug-development pipeline.

The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, represents a global innovation project for antibiotic products research and development. CARB-X brings together multiple domestic and international partners and capabilities to find potential antibiotics and move

them through preclinical testing to enable safety and efficacy testing in humans and greatly reducing the business risk, which can make advanced development more attractive to private sector investment.
The Biomedical Advanced Research and Development Authority (BARDA), within the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), and the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health will join the Wellcome Trust and the AMR Centre in joint oversight of the project. Two U.S. non-profit life science accelerators — Massachusetts Biotechnology Council in Cambridge, Massachusetts (MassBio), and the California Life Sciences Institute (CLSI) of South San Francisco, California, will provide support for early-stage antibiotic development projects.
ASPR's BARDA will draw on its extensive experience of successfully advancing promising medical countermeasures through late-stage development and provide $30 million during the project's first year and up to $250 million during the five-year project.
The AMR Centre, a public-private initiative formed in February 2016 to drive the development of new antibiotics and diagnostics, aims to provide $14 million to support CARB-X projects in year one and up to $100 million over five years. The Wellcome Trust, a global charitable foundation focused on biomedical research, will contribute further funding and its expertise in overseeing projects of this kind.
NIAID, which leads the U.S. government in biomedical research on infectious and immune-mediated diseases and developing better means of preventing, diagnosing and treating these illnesses, will provide in-kind research support, including preclinical research expertise, to projects that CARB-X supports. NIAID will also provide technical support related to early-stage antibiotic drug discovery and product development.
"Increasingly, it is becoming clear that partnerships of global reach and efficiency are needed to address complex problems like antimicrobial resistance," said Dr. Richard Hatchett, acting BARDA director. "The establishment of CARB-X is a watershed moment; governments, academia, industry, and nongovernment organizations have come together to operate under a common strategic framework to tackle a monumental public health threat of our time."
"Antibiotic resistance is a major public health problem that will only get worse without the creation of new antibiotic drugs to combat bacterial infections," said NIAID Director Anthony S. Fauci, M.D. "NIAID is enthusiastic about being a part of this effort to accelerate the discovery and development of a new generation of life-saving antibiotics."

Modeling private-sector innovation accelerators:
In the private sector, start-up companies with innovative ideas can turn to venture capitalists, or accelerators, who provide the necessary funding for the research and development, and business savvy to turn the ideas into successful products. CARB-X will provide funding for research and development, and technical assistance for companies with innovative and promising solutions to antibiotic resistance.
The end goal of CARB-X is to move promising antibiotic candidates through early stages of research and development, so that they merit private or public investment for advanced development and earn approval by the U.S. Food and Drug Administration and/or the Medicines and Healthcare products Regulatory Agency of the United Kingdom.
"Our hope is that the combination of technical expertise and life science entrepreneurship experience within the CARB-X's life science accelerators will remove barriers for companies pursuing the development of the next novel drug, diagnostic, or vaccine to combat this public health threat," said Joe Larsen, Ph.D., acting BARDA deputy director. "In the same way BARDA's investment model has proven successful in advancing countermeasures through late-stage development, we believe this international partnership can identify promising candidates in the early stages of development that may offer treatment options for drug-resistant bacterial infections."

CARB-X Accelerators:
CARB-X will be headquartered at the Boston University School of Law in Boston, Massachusetts, where the CARB-X executive team will be led by Kevin Outterson, a leading health law researcher and collaborator in global projects to address antibiotic resistance who will serve as the principal investigator on the cooperative agreement. The executive team will be compromised of experts with decades of experience in drug development, including in the area of antibacterial drugs.
The four CARB-X accelerators are:

- Wellcome Trust, which will provide guidance for product developers covering a range of skillsets, including medicinal chemistry, biology, pharmaceutic formulation and clinical development. The Wellcome Trust also will help monitor project progress and provide feedback and guidance through each milestone. It also provides business development support.
- The AMR Centre, which will provide funding, capacity and capability to support programs for CARB-X product developers, and pre-clinical expertise in chemistry, analytical, microbiology, drug metabolism and pharmacokinetics, and pharmacology.
- MassBio, which will offer selectees access to capital and mentoring. This includes evaluating and providing feedback on commercial feasibility; identifying strengths, weaknesses, opportunities and threats; and teaming up to furnish industry-specific business advice for innovative ideas in therapeutics, diagnostics, medical devices and health information technology.
- CLSI, which will partner with MassBio to provide business support and mentoring services to developers selected for funding. CLSI also will work to share best practices with the Wellcome Trust and AMR Centre, expanding the scope of business support services globally.

Also under the cooperative agreement, RTI International, a nonprofit institute headquartered in Research Triangle Park, North Carolina, will be a CARB-X partner. RTI will provide research support services to product developers in the partner accelerators, and build and run the computing systems to identify, track and monitor all research programs, including real-time dashboard management information systems.
Additionally, the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, will build an antibiotics chemistry hub that product developers can access.
Source: TB Online, http://bit.ly/2cmxwR2 (03.08.2016)

Reportage

1. The danger of ignoring tuberculosis
A century or so ago, tuberculosis was everywhere. It killed babies and brides, firemen and heads of state. The colloquial term of the era, “consumption,” littered the obituary pages and underscored how ubiquitous the disease was. Tuberculosis was so pervasive it eventually *consumed* you.
Actually, “consumption” got its name from the severe weight loss that so many of the afflicted suffered. The other 19th-century nickname for tuberculosis was even more evocative: “the white plague,” on account of the ashen complexion of its victims.
The novelist Charles Dickens wrote of tuberculosis in 1838 as “a dread disease” which “medicine never cured,” and which “wealth never warded off.” An illness “in which death and life are so strangely blended, that death takes the glow and hue of life, and life the gaunt and grisly form of death.” Health officials once predicted tuberculosis would be eradicated by 1915. They were wrong. Yet in the United States, where tuberculosis has been on the decline since 1992, there’s a vague perception that it is a historic disease—long since cured and largely forgotten.
That is not the case.
Tuberculosis remains a major killer. As antibiotic-resistant strains of the disease spread across the globe, it’s getting harder to wipe out. In the next three decades, drug-resistant strains of the bacteria could drive up tuberculosis deaths by 2.4 million per year—to some 4 million fatalities annually—

according to a report published last year by the *Review on Antimicrobial Resistance.*

"In fact, tuberculosis is now the leading cause of death from infectious disease worldwide," Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases, told me. "It is understandable—though not excusable—that people in the United States think this is not really a problem. Most of the time people don't think beyond our borders."

Of the nearly 10 million people who get tuberculosis every year, some 1.5 million people die. And although the death rate among tuberculosis patients has plummeted since the 1990s, the rate of the decline is slowing as drug-resistant forms of the illness create new challenges for treatment. These days, half-a-million people are sickened with antibiotic-resistant tuberculosis each year, a statistic that David Perlin, the executive director of the Public Health Research Institute at Rutgers University, calls the "most troubling" aspect of an already deadly disease. "We cannot delude ourselves into believing that TB has gone away in the USA..." he told me in an email. "It always looms large."

Now, scientists and doctors are scrambling—with relatively little public research funding to support them—to prevent a catastrophic scenario in which antibiotics stop working on tuberculosis altogether. "Decades ago, before there was a a lot of multiple- and extensive-drug-resistant tuberculosis, we would be able to treat it no problem," Fauci told me. "But what we have now is the danger that if one does get infected it is a very, very difficult disease to treat."

To understand the emergence of drug-resistant tuberculosis, it helps to begin with the global distribution of the disease in 2016. About 2 billion people worldwide are already infected with tuberculosis, including 13 million people in the United States. The "overwhelming majority" of them have what's called latent tuberculosis: meaning, they're carriers of the *M. tuberculosis* bacteria, but they aren't infected with—nor can they spread—the disease.

Still, people with latent TB are at a higher risk of acquiring active tuberculosis at some point in their lifetimes; about a one-in-10 chance overall, Fauci says. Other groups, like people with HIV and other immunosuppressed patients, are also at a higher risk of infection.

In general, tuberculosis is spread through human-to-human contact and through the air, when someone who's infected coughs or sneezes. But there are two main ways that people get sick with drug-resistant TB. The first way is that people who are sick with tuberculosis fail to take a full course of antibiotics, and the bacteria develops a resistance to drugs that would otherwise knock it out. The second way is that a person is infected with a strain of the bacteria that's resistant to antibiotics to begin with. (Extensively drug resistant TB, sometimes called "total drug-resistant TB," is an even more severe category of multi-drug resistant TB.)

Drug-resistant tuberculosis in the United States is still quite rare. There were 91 such cases in the U.S. in 2014, according to the Centers for Disease Control and Prevention. But foreign-born people in the United States are much more likely to have drug-resistant tuberculosis than those born in the United States; 88 percent of the U.S. cases of antibiotic-resistant tuberculosis in 2014 were among foreign-born patients. These figures are meaningful especially in a country where immigrants face deep discrimination from wide swaths of the population.

"For the United States, the challenge is probably people coming in from immigrant populations who are already stigmatized," said Glenda Gray, the president of the South African Medical Research Council and an expert on tuberculosis and HIV. "You need an environment that's not going to be punitive [to care for] the people that are the refugees, the people that are on the fringes of society, and the people who are less educated."

Drug-resistant tuberculosis is a huge problem in South Africa. Although the precise number of cases is unknown, public health officials estimate that, of the hundreds of thousands of people who develop tuberculosis in the country each year, tens of thousands of them have drug-resistant strains. (Like South Africa, India, China, and several countries in eastern Europe are considered "high burden" areas for their outsized populations of patients with antibiotic-resistant TB, according to the World Health Organization.) The true number of those who have the disease may be much larger.

In South Africa, for instance, mineworkers are at an exceptionally high risk of catching and spreading tuberculosis due to overcrowded working and living conditions and prolonged exposure to poorly ventilated workspaces. But mine workers are also less likely to have or seek access to effective treatment for the disease. Some of them may be unaware that they have the disease, or they may resist being tested for fear of losing their jobs.

"You're not going to have people jumping up and down saying, 'Test me! Test me!'" Gray said. " It's a very complex social issue that you have to address. Particularly in America, you're going to stigmatize an already-stigmatized community, so how do you raise awareness without stigmatizing people?"

Antibiotic resistance only complicates an already daunting public-health crisis. "We don't have enough drugs to help us," Gray said. "For TB, we're running out of options."

Medicine to treat tuberculosis has existed for decades, but it hasn't changed much in that time. In order to be effective, a course of antibiotic treatment lasts for a full year, sometimes two, an unusually long duration that researchers in a 2007 *PLoS Medicine* paper described as a "fundamental problem" in tuberculosis treatment. The drugs that work are toxic to the person taking them, which makes the side effects particularly grueling.

"Oh my God, it's terrible," said the physician and humanitarian Paul Farmer, who has written extensively on community-based healthcare models as a way to quell the spread of drug-resistant tuberculosis and other diseases. "It's awful. It's been 40 years since we've had new drugs. It's so sad."

Farmer calls the lack of community-based care the "Achilles heel" of the health care system in the U.S., which incentivizes frequent and costly hospitalizations for patients with TB and other chronic diseases who have few other options for care. "They get bounced in and out of hospitals or halfway houses, where if they had a community health worker checking in on them every day, you always see decreased use of emergency rooms."

The idea behind community-based care is to set up a system where nurses and other workers visit people who need care each day, encouraging them to take medicine, taking vital signs if necessary, and so on. Eligible patients for such visits might be people who have HIV, TB, mental illness, or diabetes, he says. For tuberculosis specifically, Farmer says, community-based care would help people stay on course with their antibiotics; a crucial component of keeping drug-resistant TB at bay.

"Without community-based care, I don't see how it can work," he said. "There's not a lot of evidence that anything else works. It costs a lot more to give bad care in a facility than to give good care with community health workers."

At the same time, Farmer, Gray, Fauci, and other public health leaders emphasize the need for an infusion of research funding for development of new and better medicine to treat tuberculosis. The Bill and Melinda Gates Foundation has donated tens of millions of dollars in grant money to pursue a tuberculosis vaccine, but public funding for such research is scant. TB is now a "standout poor performer" compared with research focused on "most bacterial infections, parasitic infections, and viral infections," Farmer told me. Meanwhile, existing drugs may become obsolete due to antibiotic resistant strains of the disease. "You're facing the valley of death because there's nothing on the horizon."

Given the link between HIV and TB—a huge proportion of HIV deaths are linked to TB, as people living with HIV are up to 30 times more likely to develop active tuberculosis than people without HIV—scientists often point out how much better HIV researchers have been at securing funding for fighting that disease.

"All the things that we have with HIV are in stark contrast to what we have with TB," Fauci told me. "With tuberculosis, we don't have a good way to monitor the disease, we don't have good biomarkers, we don't have good ways to figure out the efficacy of treatment."

In other words, there's urgent need not just for newer drugs with less burdensome treatment regiments; but also a need for a faster way to diagnose TB, and drug-resistant TB in particular. But it may be impossible to secure financing for such efforts in a public funding environment in the United

States that is, many scientists told me, grossly isolationist. (See also: The Congressional failure to fund Zika research.) The United States, as a wealthy country, has a "moral obligation" to take action, Fauci says, but investing U.S. dollars in the fight against tuberculosis is also a practical matter of protecting Americans.

"We can't say, 'Because this is a problem somewhere else, we can't or shouldn't make major investments,'" Fauci told me. "Sooner or later, when you do that, it comes back to bite you."

Gray, the physician in South Africa, says the planet's "only hope" of someday eradicating tuberculosis rests with the United States, an affluent nation where cases of the disease are, for now, contained among small and somewhat predictable portions of the population. But global eradication of tuberculosis is a pipe dream too far off to even consider seriously, several scientists told me. The first step is to get the disease—and drug-resistant strains of the bacteria—under control, and to do so quickly. Before things get worse.

"It's a shame," Farmer said, "because the history of tuberculosis control is really one of forgetting. This is a transnational disease. So is Zika. So is Ebola. Without investments in the health system, the dream of rounding those last cases up? It's really not a good dream. It's more like a nightmare."

Source: The Atlantic, http://theatln.tc/2aICpQr (04.08.2016)

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