NEWSLETTER

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Internationale Nachrichten

1. Diabetes — a serious threat to ending TB

Tuberculosis continues to be a major public health challenge, affecting 9 million people and claiming 1.5 million lives annually. Several risk factors have been associated with TB including HIV, smoking, malnutrition, poverty, and others. A fast emerging addition to this list is diabetes, which significantly increases the risk of TB. With rapid urbanization, economic development and related lifestyle changes, diabetes is on the rise. It is estimated that around 600 million people will be affected by diabetes in the next two decades — and most of these will be from lower- and middle-income countries, which are already struggling with around 80 percent of all the world's TB cases.

What threats does diabetes pose to TB control and what can be done to address this issue?

The Millennium Development Goals have been successful in halving the prevalence and mortality and reversing the incidence of TB in most regions of the world. This has been possible with the efforts of the national TB programs supported by various technical agencies — including the World Health Organization and The Union — and donor agencies — including The Global Fund, World Bank and others.

However, this is not sufficient to control the TB epidemic, which continues to affect millions of people globally and causes economic losses in the billions. The forthcoming sustainable development goals will build on the MDGs and propose ambitious and holistic targets to address poverty and hunger; ensure education, health, gender equality, human rights, environmental sustainability, global partnerships and economic development; and provide a framework for U.N. member states to develop their agendas and policies for the next 15 years. TB remains an important component of this agenda and the post-2015 global framework — the End TB Strategy, which focuses on integrated patient-centered TB care and prevention, supportive system, and intensified research and innovation — aims for a world free of TB, with targets to reduce TB deaths by 95 percent, to cut new cases by 90 percent and to ensure that no family is burdened with catastrophic expenses due to TB by 2035.

But are we facing down a TB-diabetes co-epidemic?

The International Diabetes Foundation estimates the prevalence of diabetes to increase to 10 percent in the next couple of decades. This could result in a situation similar to the rising incidence of HIV in the 1990s, which fuelled the TB epidemic in several African countries and led to unimaginable mortality, morbidity and financial losses from which these countries are yet to recover.

The similarities with the HIV-TB co-epidemic are striking. Like HIV, diabetes weakens the immune system and accelerates the breakdown of those infected with TB to active disease. Diabetes, while causing significant morbidity by itself, is likely to flare up the TB incidence further in rapidly developing countries like India, China, Indonesia, Pakistan and Brazil, which already have high TB burden. However, unlike the TB-HIV epidemic, where delayed response took its toll, there is still an opportunity to control the TB-diabetes co-epidemic — provided we act rapidly.

The first step is to implement the The Union-WHO recommended collaborative framework on prioritizing countries at higher risk and advocates for collaboration of the national programs on TB

and diabetes at all levels of the health system. All patients should be screened for diabetes and all the diabetes patients should be screened for symptoms of TB periodically — and managed accordingly.

So what are the challenges of implementing this framework?

First, it will require institution of policies by countries to provide a platform to integrate diabetes and TB control programs as a priority. Second, while most of the countries have a robust and well-functioning TB program, many diabetes programs are still rudimentary. The diagnostic and treatment services for TB are widely available at little or no cost to the patients, whereas those for diabetes are limited and expensive which makes bidirectional screening and management of those with both diseases challenging. Additional resources will be required for strengthening the diabetes programs, including developing standardized protocols for management, training of health staff, providing test kits and drugs, and establishing a recording, reporting and follow up mechanism.

There are several opportunities in these challenges. The strengths of the already established TB programs can be leveraged to serve as an entry point for identification of diabetes patients and create the demand that diabetes programs can match gradually as they scale up.

TB programs can also pragmatically allocate resources for collaborative activities to serve as seed money to strengthen diabetes programs. This will encourage further investment from conventional and nonconventional donors as they begin to see the value. The success of the TB program anchors on the simple and standardized management protocol, decentralized services and a robust recording, reporting and follow-up mechanism — something that diabetes programs can learn from and replicate.

So what is our call to action for the global development community?

The implementation of the collaborative framework will require commitment and resources. During the last World Lung Conference in Barcelona in 2014, a historic report on the looming TB-diabetes co-epidemic synthesized the scientific evidence on how TB and diabetes are linked, promoting the global policy framework as a way to address the two diseases together. This scientific document can be the starting point for advocating the integration of TB and diabetes control programs.

The upcoming third International Financing for Development conference in Addis Ababa in July is an opportunity to discuss how multilateral development agencies can assist governments in aligning TB and diabetes programs in LICs and MICs — and encourage investment of funds and other resources towards strengthened collaboration along the same lines as the TB-HIV implementation model. This will be a major leap towards ensuring ending TB for good.

Source: Devex, http://bit.ly/1BwJH3v (30.06.2015)

2. XDR-TB patient in U.S. highlights global reach of infectious disease

If an argument is needed against prioritizing United States medical research dollars simply on the basis of disease burden in the U.S., global health advocates in Washington, DC didn't have to look any farther this week than the National Institutes of Health campus in Maryland. That's where a woman who recently flew from India to Chicago and has since been diagnosed with extensively drug-resistant tuberculosis is now being treated.

While the U.S. Centers for Disease Control and Prevention is notifying passengers on the woman's international flight, and working with local health officials to find other people who spent time with her in Illinois, Tennessee and Missouri, as the *New York Times* reported Monday, the agency also has issued a statement saying the woman's case posed little risk to the public. Why the concern then?

Because even with low risks of transmission and high cure rates, ordinary tuberculosis demands months of difficult and harsh treatment before it is cured and stops posing a threat to individual patients and to public health. The strain of tuberculosis the woman is sick with — also known as XDR-TB — resistant to at least two first line drugs, and at least one injected second line drug, requires years of harsh and closely supervised treatment with less likelihood of success. While ordinary tuberculosis has about a 90 percent cure rate, the CDC estimates that a cure is possible in about 30- to-50 percent of patients with extensively drug resistant disease. In parts of the world

where the disease is more common, the toll (in India, home to the world's highest TB burden and where the current patient at NIH traveled from, tuberculosis has been estimated to kill one person every two minutes, and 750 people a day) is exacerbated by the resources treating and controlling the disease demands.

"You can treat 25 patients with regular tuberculosis for every one patient with XDR-TB," Dr. Lewis Schrager said Tuesday. Dr. Schrager is an infectious diseases and vaccine specialist and vice president of Scientific Affairs at Aeras, a nonprofit biotechnology outfit working to develop new tuberculosis vaccines. The challenge of treating extensively drug resistant tuberculosis is difficult in the U.S., he notes, and overwhelming in developing countries.

On the other hand, what makes tuberculosis bacteria resistant to treatment drugs would not make it resistant to a vaccine. While distance offers diminishing protection in an increasingly mobile world, "vaccines are the ultimate game-changer," Dr. Ann Ginsberg, Aeras chief medical officer said. "Tuberculosis is airborne," Dr. Ginsberg notes, adding that includes by coughing, sneezing or shouting. "People travel all over the world. There is nothing to prevent us getting tuberculosis either at home or abroad."

That's why while one tuberculosis patient has attracted attention in the U.S. this week, the worldwide nine million people diagnosed with active tuberculosis and 1.5 million who die of the disease each year also should, the way global health advocates and researchers see it.

Source: Center for Global Health Policy, http://bit.ly/1IfpgFB (15.06.2015)

3. New report shows that 400 million do not have access to essential health services

A WHO and World Bank Group report launched today shows that 400 million people do not have access to essential health services and 6% of people in low- and middle-income countries are tipped into or pushed further into extreme poverty because of health spending.

"This report is a wakeup call: It shows that we're a long way from achieving universal health coverage. We must expand access to health and protect the poorest from health expenses that are causing them severe financial hardship," says Dr Tim Evans, Senior Director of Health, Nutrition and Population at the World Bank Group.

The report, Tracking Universal Health Coverage, is the first of its kind to measure health service coverage and financial protection to assess countries' progress towards universal health coverage.

The report looked at global access to essential health services—including family planning, antenatal care, skilled birth attendance, child immunization, antiretroviral therapy, tuberculosis treatment, and access to clean water and sanitation—in 2013, and found that at least 400 million people lacked access to at least one of these services.

"The world's most disadvantaged people are missing out on even the most basic services," says Dr Marie-Paule Kieny, Assistant Director-General, Health Systems and Innovation, at the World Health Organization. "A commitment to equity is at the heart of universal health coverage. Health policies and programmes should focus on providing quality health services for the poorest people, women and children, people living in rural areas and those from minority groups".

The report also found that, across 37 countries, 6% of the population was tipped or pushed further into extreme poverty ($1.25/day) because they had to pay for health services out of their own pockets. When the study factored in a poverty measure of $2/day, 17% of people in these countries were impoverished, or further impoverished, by health expenses. "These high levels of impoverishment, which happen when poor people have to pay out of pocket for their own emergency health care, pose a major threat to the goal of eliminating extreme poverty," says Dr Kaushik Basu, Senior Vice President and Chief Economist at the World Bank Group. "As we transition to a post-2015 development era, we must act on these findings, or the world's poor risk being left behind." WHO and the World Bank Group recommend that countries pursuing universal health coverage should aim to achieve a minimum of 80% population coverage of essential health services, and that everyone everywhere should be protected from catastrophic and impoverishing health payments.

"As more countries make commitments to universal health coverage, one of the major challenges they face is how to track progress," says Dr Ties Boerma, Director of the Department of Health Statistics and Information Systems at the World Health Organization. "The report shows that it is possible to quantify universal health coverage and track progress towards its key goals, both in terms of health services and financial protection coverage." This is the first in a series of annual reports that WHO and the World Bank Group will produce on tracking progress towards UHC across countries.
"As the saying goes, 'what gets measured, gets done.' With countries around the world taking steps to provide universal health coverage, the ability to identify gaps and effectively measure progress will add critical momentum to this global movement," says Michael Myers, Managing Director at The Rockefeller Foundation. "This an important tool for countries to achieve universal health coverage and build more resilient health systems."
Source: WHO, http://bit.ly/1Fdl8ne (30.06.2015))

4. The Trans-Pacific Partnership — Is It Bad for Your Health?
International trade deals once focused primarily on tariffs. As a result, they had little direct effect on health, and health experts could reasonably leave their details to trade professionals. Not so today. Modern trade pacts have implications for a wide range of health policy issues, from medicine prices to tobacco regulation, not only in the developing world but also in the United States.
The Trans-Pacific Partnership Agreement (TPP) is a case in point. A massive trade deal now reportedly on the verge of completion, the TPP has nearly 30 chapters. A draft chapter on intellectual property (IP) alone runs 77 single-spaced pages.
The full health implications of the TPP are hard to judge, not only because its provisions are complex but also because the draft text is a closely held secret. Even members of the U.S. Congress can see it only if they agree not to talk publicly about it and if they leave their pens and phones (and, until recently, their expert staffers) at the door. But several key chapters have recently been leaked and reveal that the TPP could have a substantial impact on health.
Groups including Médecins sans Frontières and Oxfam warn, for example, that the agreement could threaten the lives of millions of people in developing countries. Their concerns stem primarily from the leaked IP chapter and the effect that patents have on the prices of medicines. In the context of human immunodeficiency virus, for example, patents increase the annual cost of antiretroviral therapy from around $100 per person to $10,000 per person. The TPP could impose obligations on developing countries that go far beyond any existing trade agreement. Indeed, some proposals in the leaked IP chapter seem directly targeted against innovative measures that developing countries have used to maximize the use of low-cost generic medicines.
For example, India allows patents on new drugs but not on new uses of old drugs or new forms of known drugs that do not increase therapeutic efficacy. These provisions have paved the way for generic versions of lifesaving drugs such as the cancer treatment imatinib mesylate (Gleevec) in that country. But such limits on patent eligibility could be outlawed by the TPP. Reports suggest that there may be some kind of phase-in period for developing-country members, but only for some parts of the agreement. And at best, a phase-in period would merely postpone some of the TPP's effects for a few years. India is not a party to the TPP negotiations, which have been conducted by 12 Pacific Rim countries: Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the United States, and Vietnam. Why, then, would India's laws — sometimes word for word — be targeted in the TPP negotiations? For one thing, other developing countries have started to follow India's lead. For another, the TPP is a platform agreement designed for other countries to join, and it will establish a new baseline for future international negotiations. The risk regarding access to medicines in developing countries is real. Though it is less widely recognized, the TPP could also have a direct effect on health in developed countries. For example, the leaked IP chapter contemplates major extensions of "data exclusivity" provisions. These laws prevent drug regulatory agencies like the Food and Drug Administration from registering a generic version of a drug for a certain number of years — and as a result can substantially affect the prices of medicines.

In recognition of this fact, President Barack Obama's fiscal year 2016 budget proposes rolling back the data-exclusivity period for biologic drugs in the United States to 7 years from 12 years, yielding a projected savings of more than $4 billion over the next decade. In the TPP negotiations, however, the United States is proposing a 12-year term of exclusivity. Such a requirement would lock the United States into a policy that many observers, including, apparently, the President himself, believe inflates the cost of medicines unjustifiably. Even if the number of years required by the TPP is negotiated downward, the lock-in effect remains a concern, because trade agreements can be extremely difficult to amend.

The cost of medicines is no small concern in the United States today: spending on prescription drugs in the United States jumped 13% in 2014 alone. The recent experience with new hepatitis C treatments shows that even lifesaving cures may be rationed in the United States — whether implicitly or explicitly — if we fail to contain drug costs and promote more efficient innovation. The TPP, however, could make moves toward more rational drug pricing in the United States difficult and even imperil existing provisions that help to contain costs for government programs.

A 2011 “annex” to the TPP, apparently proposed by the United States, would have mandated that all countries use “competitive market-derived prices” or benchmarks that “appropriately recognize the value” of the drug in question when establishing drug prices. A just-leaked December 2014 draft omits these provisions but still contemplates substantial procedural obligations for governments and makes clear that these rules apply to the Centers for Medicare and Medicaid Services (CMS). The text is difficult to decipher and still in flux. But consumer groups argue that the annex could create opportunities for interference in the decisions of CMS and render health programs in all TPP countries more vulnerable to drug-company influence and more difficult to reform.

In March 2015, a third bombshell dropped: a draft chapter on “investor-state dispute settlement” (ISDS). It would empower foreign companies to sue member countries for hundreds of millions of dollars in damages in a wide range of cases in which they argue that their expected future profits have been undermined. These challenges would be heard by “arbiters” — typically private lawyers, many of whom cycle in and out of industry — with no prospect of independent review by a national court. Such provisions have been included in trade agreements before. But the scale of the TPP would substantially increase the number of companies that could bring such challenges. Firms have already used provisions like these to challenge an astonishing range of laws, from minimum-wage laws in Egypt, to tobacco regulations in Uruguay and Australia, to core aspects of patent law as they apply to medicines in Canada. The ISDS provisions alone could interfere with domestic health policy for decades to come. Under their auspices, policies covering a wide range of issues, from food and tobacco labeling, to patent law, to drug-pricing rules, to environmental protection could be challenged in participating countries — including, of course, the United States.

The course that the TPP takes is not yet set in stone. Negotiations continue, and the Obama administration could work toward an agreement that excludes provisions such as ISDS and the health care “annex” or that incorporates robust safeguards to protect health. Congress has an important role, too. As of early June, it was in the midst of a fierce legislative battle over whether the TPP and deals like it should be “fast-tracked.” If Congress takes this route, its ability to influence the treaty will be much diminished: fast tracking allows passage of a trade treaty with only a simple majority vote in Congress and also denies Congress any opportunity to make changes to the agreement's text.

Much hangs in the balance in the coming weeks and months. If the TPP includes robust ISDS provisions and the expansive provisions proposed in the IP chapter and the health care annex, the United States could be signing away its authority to regulate critical aspects of health policy for years to come.

Source: NEJM, http://bit.ly/1HvvZRg (30.06.2015)

Forschung & Entwicklung

1. Durchbruch in der Tuberkuloseforschung: Erbgut des Erregers als Schlüssel für optimale Behandlung

Wissenschaftlerinnen und Wissenschaftlern des Forschungszentrums Borstel, des Deutschen Zentrums für Infektionsforschung, des Oxford Biomedical Research Centre und des South African National Institute for Communicable Diseases haben eine neue genetische Methode entwickelt, mit der sie nicht nur voraussagen können, gegen welche Antibiotika Resistenzen bestehen, sondern auch welche Präparate gegen den jeweiligen Tuberkulose (Tb-)-Erreger wirksam sind. Die Ergebnisse werden am 24. Juni in der Onlineausgabe der internationalen Fachzeitschrift The Lancet Infectious Diseases veröffentlicht.

Der Nachweis von Tb-Erregern und die genaue Ermittlung von Antibiotikaresistenzen erfolgt bisher in Kulturverfahren. Diese Methode benötigt bis zu sechs Wochen, bis ein Ergebnis vorliegt. Wertvolle Zeit, die häufig eine effektive Behandlung verzögert. Zudem sind die Kulturverfahren relativ fehleranfällig. Sie müssen sehr präzise sein, um verlässliche und vergleichbare Ergebnisse zu erhalten. Solche optimalen Laborbedingungen sind jedoch insbesondere in Ländern mit hohen Tuberkuloseraten oft nicht vorhanden. Auch die in den letzten 20 Jahren eingesetzten molekulardiagnostischen Schnelltests können lediglich eine Aussage über eine begrenzte Anzahl von Mutationen und die daraus resultierenden Resistenzen treffen.

„Wir wollten einen Schritt weitergehen und therapeutische Hinweise geben, welche Kombination von Antibiotika sich zur Behandlung eines bestimmten Erregers eignen“, fasst Professor Stefan Niemann, Leiter der Forschungsgruppe Molekulare Mykobakteriologie am Forschungszentrum Borstel und Mitglied des Exzellenzclusters Entzündungsforschung, den Forschungsansatz zusammen. „Wir bewegen uns dazu von 130 Jahren Tb-Kultivierung zu einer neuen, digitalen Ära in der Mikrobiologie.“

Dazu untersuchte das Team mittels Gesamtgenomsequenzierung das Erbgut von rund 3500 Tb-Stämmen. Die Forscherinnen und Forscher konzentrierten sich dabei auf Veränderungen im Erbgut, die sie mit Antibiotikaresistenzen und -Empfindlichkeit in Verbindung bringen können. „Wir haben eine Art Lexikon für Mutationen im Erbgut der Tb-Erreger ermittelt“, erklärt Niemann. „Findet man Veränderungen im genetischen Code eines Erregers, sind bestimmte Medikamente nicht mehr wirksam und sollten daher nicht für die Therapie verwendet werden. Das ist ein enormer Fortschritt, insbesondere für die Behandlung von multiresistenten Erregern!“

Bis die Methode im praktischen Arbeitsalltag von Medizinerinnen und Medizinern angewendet werden kann, dauert es aber noch etwas. Dennoch habe die Methode großes Potential, glaubt Dr. Thomas Kohl, Zweitautor der Publikation: „Auf längere Sicht ist die Genomanalyse erheblich einfacher durchzuführen und kostengünstiger als konventionelle Verfahren. Vor allem im Hinblick auf die EndTB-Strategie der WHO, die vorsieht, dass die Tuberkulose bis zum Jahr 2035 erfolgreich eliminiert werden soll, sind diese neuen diagnostischen Ansätze von großer Bedeutung.“

Tuberkulose (Tb) ist die weltweit häufigste tödliche Infektionskrankheit. Vermutlich ist etwa ein Drittel der Menschen weltweit mit dem Erreger infiziert. Bei den meisten Betroffenen bricht die Tuberkulose aber nie aus. Pro Jahr erkranken 9 Millionen Menschen an Tb – ca. 1,5 Millionen sterben an den Folgen dieser Krankheit. Insbesondere die stark zunehmenden Antibiotikaresistenzen der Erreger sind dabei ein immenses Problem. Diese verlängern die Behandlungsdauer erheblich und verursachen hohe Kosten.

Source: Forschungszentrum Borstel, http://bit.ly/1FNta6C (27.06.2015)

2. New hope in the fight against tuberculosis

According to figures of the World Health Organization, some 8.7 million people contracted tuberculosis in 2012 and this disease is fatal for approximately 1.3 million people throughout the world each year. One of the main problems is that the tuberculosis pathogens have become resistant

to the antibiotics used to fight them. Scientists from the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken, the Helmholtz Centre for Infection Research (HZI) in Braunschweig and the German Center for Infection Research (DZIF) joined forces with scientists from Sanofi, a global health care company, and identified a new agent, which might potentially remedy these problems. The scientists just described this agent and its unique mechanism of action in the highly renowned scientific journal *Science*.

Mycobacterium tuberculosis is the main cause of tuberculosis. The treatment for drug-susceptible tuberculosis consists of the daily administration of multiple drugs for a minimum of six months. Lack of adherence to this regimen can result in treatment failure and the emergence of drug resistance. "Complexity and duration of the treatment are true issues and the main reasons for the development of resistant pathogens," says Prof Rolf Müller, who is the Executive Director and head of the Microbial Natural Substances department of the HIPS, an institution jointly sponsored by the HZI and Saarland University.

Consequently, there is an urgent need for new medications and therapeutic approaches to both fight the resistant pathogens, as well as to shorten the duration for the treatment of drug-susceptible organisms. Based on earlier reports, Müller, in collaboration with Prof Jacques Grosset from the Johns Hopkins University School of Medicine in Baltimore, and his colleagues from the HZI and Sanofi scientists, initially focused on the natural substance called griselimycin. The potential of this natural substance, was discovered in the 1960s. However, due to the success of other tuberculosis medications and its low efficacy in an infection model, the substance was not developed any further at the time.

"We resumed the work on this agent and optimised it such that it shows excellent activity in the infection model - even against multi-resistant tuberculosis pathogens," says Müller. In the course of their work, the scientists discovered that cyclohexylgriselimycin, a variant of griselimycin, is particularly effective against Mycobacterium tuberculosis, both in cells and in the animal model. Importantly, cyclohexylgriselimycin was effective when administered orally, which is key in tuberculosis treatment, non-orally available drugs are extremely burdensome to administer daily during the many months of treatment. Moreover, combining this substance with current TB antibiotics increases the efficacy compared to the antibiotic cocktail that is usually administered.

The scientists were not only able to demonstrate the efficacy of cyclohexylgriselimycin against tuberculosis, but they also elucidated the underlying mechanism of action. "In the tuberculosis pathogen, the substance binds to the so-called DNA clamp and thus suppresses the activity of the DNA polymerase enzyme, which multiplies the genetic information inside the cell," says Müller. Neither DNA replication nor efficient DNA repair can proceed in the absence of the DNA clamp, which means that the bacterial pathogens are prevented from proliferating in the body. Structural biologists at the HZI successfully elucidated the detailed structure of the DNA clamp in a complex with cyclohexylgriselimycin bound to it. "This allowed us to elucidate the special mode of action of the new antibiotic at high resolution," says Prof Dirk Heinz, Scientific Director of the HZI, who was also involved in the study.

Since this mechanism is different from the mechanism of action of the antibiotics used previously against tuberculosis and all other bacterial pathogens, the risk of resistance developing is low for now. In addition, the scientists were able to show that the development of resistance in mycobacteria, which include the tuberculosis pathogen, albeit possible, is associated with a drastic decrease in the growth of the pathogens such that the potential of the development of resistance is estimated to be low. "We hope that cyclohexylgriselimycin will become an agent that can even be used against resistant tuberculosis pathogens in the future and contributes to a more successful fight against this dreadful disease," says Müller.

"There is an urgent need for new medicines to fight drug-resistant microbes," says Gary Nabel, Sanofi's Chief Scientific Officer. "This elegant study identifies a potential new therapy for tuberculosis and defines its mechanism of action, importantly targeting a genetic synthesis and repair pathway that supports the development of drug resistance. We are pleased to work with our valued academic

partners in Germany and the US to harness the collective expertise of academia and industry for the benefit of patients."
Source: Medical Xpress, http://bit.ly/1TnJup9 (30.06.2015)

3. How the tuberculosis bacterium tricks the immune system
Scientists at EPFL have discovered how the tuberculosis bacterium can trick the patient's immune cells to lower their defenses.
Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis* and it affects over 12 million people globally. When the bacterium infects a person, the body's immune response is critical to how the disease will progress; either helping the body fight the bacterium or, if certain key molecules become involved, actually exacerbating the infection. EPFL scientists now show how the tuberculosis bacterium co-opts mechanisms of the immune system to its own advantage. The study is published in *Cell Host & Microbe*.
When *M. tuberculosis* infects a person, it attacks the lungs' first-response immune cells, the macrophages. The immune response by the macrophages involves a complex of four different proteins called the "inflammasome". The main role of the inflammasome is to prepare certain immunity proteins in the macrophages, which are called "interleukins". When *M. tuberculosis* infects the lungs, interleukins from the macrophages are in the first line of defense. But if it is left uncontrolled, this defense can also cause serious damage to the patient. To prevent this, macrophages also release another group of proteins called "type I interferons". While interferons are important for defending the body against viruses, when it comes to tuberculosis they actually help the bacterium, thereby exacerbating the disease. And although the interleukin-inflammation part of the immune response is rather well understood, the part involving interferons has been elusive.
The lab of Andrea Ablasser at EPFL, in collaboration with the lab of Stewart Cole, has now discovered how *M. tuberculosis* carries out a subtle assault on our immune defenses. The key is a molecule called cGAS, which is found in the lung's macrophages, and is part of a group of DNA-sensor molecules; in short, cGAS patrols the inside of macrophages, and when it detects unidentified pieces of DNA, such as those released by *M. tuberculosis*, it triggers an immune response from the macrophages.
The tuberculosis bacterium uses a specialized secretion system to release its array of toxic proteins into macrophages. But, strangely, it also releases small bits of DNA, which are detected by sensing systems inside the macrophages, namely the inflammasome and cGAS. This causes macrophages to release two types of proteins: interleukin-1, which fights the bacterium, and type I interferons, which end up helping it. Ablasser's group used human and animal macrophages to study what happens when they are infected by *M. tuberculosis*. What they found was that the bacterium passes DNA bits into the macrophages, thereby tricking cGAS to signal the production of interferons, which reduce the immune response. In other words, the bacterium tricks the macrophages to cut back on their defense against it.
But the researchers did not stop there. They also showed that it is possible to manipulate *M. tuberculosis* in such a way that it can no longer activate the production of interferons through cGAS, while still keeping the production of interleukin-1 - and thus the body's immune response - intact.
The study is the first to identify cGAS as a sensor for *M. tuberculosis* DNA, and also suggests that this method of molecular manipulation applies to other bacteria that use specialized secretion systems to infect cells. "Our work shows that tuberculosis is a far more sophisticated disease than previously thought," says Andrea Ablasser, who is now working, among other projects, to identify the DNA pieces that *M. tuberculosis* uses to trick macrophages.
Source: Medical Xpress, http://bit.ly/1MEDxiw (30.06.2015)

4. STREAM clinical trial reaches recruitment target
The STREAM (Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB) trial, sponsored by The Union and implemented by the Medical Research Council at University

College London, is taking place at seven sites in South Africa, Ethiopia, Viet Nam and Mongolia. The sites are located a variety of settings and include patients with HIV co-infection.
In Stage 1, the objectives are to determine whether the proportion of patients with a successful outcome on the shorter treatment regimen is at least as good as that observed in the longer, control regimen.
The reason for this "non-inferiority" design of the trial is that, with its considerably reduced pill burden and duration - as well as the expected increase in adherence - the shorter regimen needs only to show that it is not less effective than the control regimen to become the new standard.
The success of Stage 1 implementation has also led to the opportunity to test two other regimens of particular public health interest and relevance: Beginning this summer, the trial will also include the evaluation of an all-oral treatment that eliminates the painful injections now required, and an even shorter, simplified regimen. These new treatment regimens will incorporate the recently approved medicine bedaquiline. This amended STREAM Protocol (Stage 2) has been approved by the US Federal Drug Administration (FDA) and the European Medicines Agency (EMA) for Bedaquiline regulatory purposes, as well as The Union's Ethics Advisory Group.
Although the original plan was to enrol only 400 patients into STREAM Stage 1, Dr I.D. Rusen, Senior Vice President for Research and Development at The Union North America, says they plan to continue to enroll patients into Stage 1 of the trial until Stage 2 is ready for enrolment. Results from Stage 1 of the trial are expected in late 2017 with Stage 2 results anticipated in 2020.
Funding for STREAM Stage 1 comes primarily from the United States Agency for International Development (USAID) with additional funding from the UK Medical Research Council and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement. Stage 2 will also include financial support from Janssen Pharmaceuticals - the makers of bedaquiline.
Source: TB Online, http://bit.ly/1JuoUk9 (25.06.2015)

5. Multidrug-resistant TB appears less transmissible in households than drug-susceptible TB
Some strains of multidrug resistant tuberculosis (MDRTB) may have a lower fitness (be less capable of spreading) than drug-susceptible tuberculosis bacteria, according to a study published this week in *PLOS Medicine*. The study, conducted by Louis Grandjean of Imperial College London, and colleagues, compared new tuberculosis cases among household contacts of tuberculosis patients in South Lima and Callao, Peru to determine the relative fitness of MDRTB versus drug-susceptible tuberculosis.
The study followed 1,055 household contacts of 213 individuals with MDRTB infection (defined by resistance to the drugs rifampicin and isoniazid), and 2,362 household contacts of 487 individuals with drug-susceptible tuberculosis for up to three years. Thirty-five (3.3%) of MDRTB contacts and 114 (4.8%) of drug-susceptible tuberculosis contacts developed tuberculosis. When the authors adjusted for risk factors such as HIV status, socio-economic status, and sputum smear grade (a measure associated with higher risk of transmission) of the index case, household contacts of MDRTB cases were 44% less likely to contract tuberculosis than were contacts of drug-susceptible tuberculosis cases.
Previous laboratory findings as well as estimates of fitness based on genetic clustering of strains in the population suggested a lower relative fitness for MDRTB compared to drug-susceptible tuberculosis, but few studies have directly measured the incidence of second cases of tuberculosis among contacts of both MDRTB and drug-susceptible tuberculosis. The researchers note that they did not have genoptyping data for infections in household contacts, so some of these secondary cases may have been transmitted from someone outside the household. Additionally, transmission dynamics may be different in the community setting outside households or in different countries, and more fit MDRTB strains may emerge in the future.
Despite these limitations, the authors say that their findings are "welcome and encouraging news for tuberculosis control programs and health services attempting to contain the spread of MDRTB."
Source: MedicalXpress, http://bit.ly/1N8Xoqm (26.06.2015)

Reportage

1. Advancing TB Test Technology, Where It Matters Most

On a recent morning in a Ho Chi Minh City intensive-care unit, Cao Thi My Hanh sat crying and clutching her 5-month-old granddaughter, Nguyen Dang Thanh Phuong. More than a month earlier she had noticed the baby coughing and struggling to breathe. Hanh took her granddaughter to see several doctors in her rural province, but they all failed to give her a proper diagnosis. When she finally reached this large urban hospital, she found out that Phuong had tuberculosis, and realized the weeks of inadequate care had given the life-threatening illness time to take hold.

"I kept waiting and saw her coughing and turning pale," Hanh said over the din of crying babies. "If I had known that she had the disease, she could have taken the right medicines."

In a quiet laboratory on the grounds of this very hospital sat several gray and black machines that could have given Hanh a diagnosis much sooner. Hailed as the most significant advance in TB research in decades, this automated molecular technology called GeneXpert is more accurate and yields much faster results than traditional diagnosis methods, like smear microscopy, a basic test invented a century ago. To operate the machine, health workers deposit sputum samples they've collected from patients into cartridges that are then inserted into the Xpert machine, which is connected to a computer. The machine is able to detect the DNA of tuberculosis bacteria within 90 minutes to two hours.

When the California-based diagnostics company Cepheid Inc unveiled GeneXpert in 2010, the World Health Organization quickly endorsed it and global donors opened their purses to distribute it throughout the world. The result has been lifesaving for many patients, especially since the machine can identify multidrug-resistant forms of TB. Most recently, an Indian study published last month found that using the Xpert test increased the number of bacteriologically confirmed cases by 39 percent.

The problem is that not everyone has access to it. Not long after the rollout, health care workers began realizing that GeneXpert wasn't designed for the people who needed it most: the poor in the developing world. Even though donors were mostly paying for the $17,000 machines, the $10 cartridges were too pricey for many countries to afford on a mass scale. The setup also required electricity, computer access and refrigeration — not easy to come by in rural areas where TB is prevalent. As a result, the machines were underutilized in many hospitals and weren't being distributed to rural areas like Hahn's. In the Ho Chi Minh City hospital, for example, a mere 0.1 percent of TB diagnoses in 2013 were made with GeneXpert machines.

Ironically, though, those very limitations have ignited a sea change in tuberculosis care. The overwhelming excitement about GeneXpert among health officials and the substantial investments made by donors quelled doubts that there was demand for new TB technology and that it could be profitable. As a result, more companies have entered the TB market and are competing to develop diagnostic technologies that would provide the benefits of GeneXpert, without the drawbacks. The lesson? Often, it's the drawbacks, even more than the benefits, which can spur a paradigm shift.

Some context is important. Before GeneXpert, there hadn't been a major milestone in TB research for decades. Remarkably, most doctors were still using smear microscopy, which involves placing sputum samples on a slide and viewing them through a microscope. The technique is often ineffective because at times samples don't have enough TB bacteria in them to be detected visually. Because TB was largely regarded as unprofitable by the health care industry, research for new drugs was largely dormant, the development of new diagnostics tests was virtually nonexistent and the prevailing vaccine, invented in the 1920s, was proved to be largely ineffective for adults. All the while, TB remained the second-deadliest infectious disease in the world. Most troubling, millions didn't have access to adequate testing, and still don't. According to the World Health Organization, some three million cases of TB — one-third of the global total — still go undiagnosed.

"The word on the street was that TB was a disease of the poor and there wasn't enough money in it," says Dr. Madhukar Pai, director of the global health program at McGill University in Montreal.
But now, there are 81 manufacturers currently testing out 191 potential new products in TB diagnostics, according to a 2014 report by the global health organization Unitaid. Importantly, 11 of them are molecular technologies similar to GeneXpert.
"Because GeneXpert was a pioneer and showed the world we don't have to stay with this 100-year-old microscopy, that got the attention of a lot of companies," says Jim Gallarda, senior program officer at the Bill & Melinda Gates Foundation. "There is a lot of innovation now."
The Massachusetts-based diagnostics company Alere Inc., for instance, is using a $21.6 million grant from the Gates Foundation to develop a portable test that would be battery-powered, allowing it to be mobile for an entire day. The so-called point-of-care test would enable health workers to give a diagnosis to patients in the same place where they're receiving care, allowing them to make decisions about treatment on the spot. That would give it more reach than GeneXpert, which needs the electricity and air-conditioning of a health clinic to function. It would also cut down on the number of patients who never receive their test results. "This is true point of care," says Duncan Blair, director of health initiatives at Alere. "I don't want to detract from Cepheid, but that's a lab system that requires refrigeration and power." Alere is also working with Gates to make its machine and cartridges more affordable than GeneXpert's, and its increased mobility should help to reduce costs, too, Blair says. Alere is making the machine simpler to operate than GeneXpert as well, so that health workers don't need complex training. Finally, the Alere technology includes an efficient system of data collection and storage that sends results over a cellphone network to a cloud-based server. GeneXpert, on the other hand, requires a separate computer to store data, which has raised security concerns in poor neighborhoods. Alere plans to begin conducting trials on its product in 2016.
There are more technologies that could soon hit the market. The British biotech firm Epistem received certification allowing its Genedrive test, which can produce a diagnosis in 45 minutes and costs only around $4,000 per machine, to be marketed in the European Union. The Indian company Molbio Diagnostics' TrueLab technology can yield results in an hour, is battery-powered and costs only $6,000. The Chinese company Ustar received approval from its country's regulators to market its EasyNAT machine, while the British company QuantuMDx has received a grant from the Swiss-based nonprofit FIND to develop a similar test called Q-POC.
GeneXpert's limitations have also motivated Cepheid itself to make improvements. In 2012, Unitaid approved funding to reduce the price of the cartridges to $10 apiece from $17. Cepheid has also developed software called RemoteXpert, which uses cloud storage for data about TB patients. In a pilot phase in South Africa and India, the technology has allowed health workers access to real-time information from a database of nearly 2.5 million TB cases. Last year, the company announced an effort with FIND to develop a new model called Xpert Ultra, which will increase the ability to diagnose TB and H.I.V.
Still, there are questions. Cepheid has yet to make its machine more mobile. The technologies from Alere and QuantuMDx haven't been subjected to trials in the field, while the others outlined haven't had wide enough distribution to truly test their effectiveness. Alere points to a similar test it has used for H.I.V. diagnosis in several African countries. That machine has proved durable, as health workers even transport it across Lake Victoria on canoes to reach patients who live on islands. These are the sorts of portable technologies that Hanh wishes had existed in her community in Vietnam. They might have helped doctors catch her granddaughter's illness sooner. "She is still so young, and it hurts me to see the doctor operate on her," Hahn said. "I just pray the she can overcome this difficult time."
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