NEWSLETTER

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Internationale Nachrichten

1. Europe's tuberculosis hub Britain seeks to wipe out the disease

Health authorities launched an 11.5 million pounds ($17.4 million) plan (…) to tackle Britain's persistent tuberculosis (TB) problem, seeking to wipe the contagious lung disease out altogether. Britain has one of the highest TB rates in western Europe and London is known as the continent's "TB capital". TB rates in the United Kingdom are nearly five times those in the United States. If current trends continue, England alone will have more TB cases than the whole of the U.S. in two years.

"TB should be consigned to the past, and yet it is occurring in England at higher rates than most of Western Europe," said Paul Cosford, a director at the government's health agency, Public Health England (PHE). "This situation must be reversed." Often thought of as a disease of the past, when it was dubbed "the white plague" for rendering its victims pale and feverish, TB has stubbornly persisted in Britain. It occurs mainly in areas of poverty and deprivation. The bacterial disease is hard to treat and contagious, passing on via the coughs and sneezes of an infected person.

In 2013, 7,290 TB cases were reported in England, an incidence of 13.5 cases per 100,000 of the population. TB cases are concentrated in urban "hot spots" in London, Leicester, Birmingham, Luton, Manchester and Coventry. PHE officials say TB clinics in London manage more cases a year than those in all other western European capitals together. Drug resistant TB is also an increasing problem, with cases of multi-drug resistant (MDR) TB rising from 28 cases in England in 2000, to 68 in 2013. PHE's plan is to work with the National Health Service (NHS) to target the most vulnerable people, improving access to screening, testing and treatment services as well as outreach programs such as "Find and Treat" mobile health units. Bruce Keogh, NHS England's medical director, said the NHS would focus its 10 million pounds contribution on screening and treatment. "Our goal is to eliminate TB as a public health problem," he said.

Source: Reuters, http://www.reuters.com/article/2015/01/19/us-health-tuberculosis-britain-idUSKBN0KS00120150119 (21.01.2015)

2. Explaining Singapore´s TB Rates

After a generally downward trend from 2000, the number of tuberculosis (TB) incidences in Singapore has been increasing since 2008, with incidence rates higher among the elderly and Malay residents. The study documenting these findings has been published in *BMC Pubic Health*. Initiated by National University of Singapore (NUS) researchers and conducted together with researchers from the Singapore Tuberculosis Elimination Programme and the Singapore General Hospital, the study contained a time series analysis of demographic and temporal trends of tuberculosis in Singapore.

By virtue of its location, Singapore lies on a key maritime route and serves as a major transit hub for travel in Asia. It is also a part of a region which accounts for 29 percent of global TB incidence. Finally, although most developed countries are classified as low-risk TB incidence countries, Singapore is classified as an intermediate TB incidence country.

The research team examined four hypotheses for the recent surge of TB cases, with the first relating

to TB transmission from foreigners to locals, and the second and third hypotheses involving the country's gross domestic product (GDP) and HIV notification rates. Their statistical analyses showed that transmissions from foreigners to locals, GDP and HIV incidence rates could not be attributed to the mounting number of TB cases among Singaporean residents. Instead, the fourth hypothesis— Singapore's ageing population— appeared to have contributed to the recent rise of TB cases.
As a disease, TB is more prevalent among the elderly, and despite declining incidence among seniors, the growth in the number of elderly has resulted in a higher overall incidence rate among the population as a whole. (...) Fortunately, although the TB incidence rate at the population level has been increasing, when broken down by age groups, incidence rates showed a consistently downward trend. (...)
Source: Asian Scientist, http://www.asianscientist.com/2015/01/general/explaining-singapores-tb-rates/ (15.01.2015)

3. Ignorance leads to TB spreading in Assam´s tea gardens
Tuberculosis (TB) has become a major problem in Assam's tea gardens, often leading to the death of workers. Experts say ignorance among workers and poor management response are to blame. The disease affects nearly 40 per cent of the tea workers and doctors say the situation is going from bad to worse.
According to R.N. Roy, district TB officer (under the Revised National Tuberculosis Control Programme) in Sonitpur, there has been no significant improvement in the status of TB among the tea garden workers over the years mainly because of "ignorance" and "no management support".
"TB is a big problem [in the tea gardens]. But there has been no significant improvement in the situation over the years. From 2005 until today, the data has been more or less the same. There has been no control over the spread of infection because proper preventive measures are not taken," Roy told IANS. Of the 8.6 million cases globally, 2.2 million cases are in India — the country with the world's highest TB burden. According to Roy, if one looks at the numbers of registered cases in the tea gardens, 30-40 per cent of the workers in every tea estate are affected by TB. "But what is even more worrisome is that drug resistant TB is now becoming common. Almost 80 per cent of all drug-resistant TB cases come from the tea estates," Raoy pointed out.
Although the WHO-recommended Directly Observed Treatment, Short Course (DOTS) programme, relaunched as the Revised National TB Control Programme, has achieved success, leading to a slight decline in numbers, experts say that HIV co-infection and multidrug-resistant TB (MDR-TB) are adding a new dimension and keeping the numbers high.
Mintu Phukan, a doctor in one of Sonitpur district's tea estates, told IANS: "TB is a serious health concern and despite being curable, people continue to die because of it." "Since it is highly contagious, it is difficult for family members of a patient to escape it unless they are very careful. In tea garden workers' colonies, overcrowding and unhygienic living condition aid the spread of the infection, and ignorance further fuels it." Rajeev Sharma, another doctor, agreed. "Overcrowding is a major factor for the spread of infection. The workers live in one-bedroom houses with big families ... since TB is contagious, family members of a patient immediately become vulnerable. Plus the level of awareness is low, so the patient is not isolated," Sharma told IANS. Phukan said while most tea garden hospitals are equipped to provide treatment, the management can do more to control the problem. Another doctor said: "Better housing facilities, proper drainage and better living conditions can go a long way in improving the situation in the tea gardens." "But not enough is being done. There is pressure on plantation managers to increase productivity and cut costs, and in the bargain, medical expenditure always get the axe first."
Most of the tea garden workers in Assam are adivasis, or tribals, who hail from Odisha, Andhra Pradesh, Jharkhand and West Bengal, whose ancestors were brought to work in the plantations by the British more than a century ago. Hardly anything has changed ever since as far as the lifestyle of those living in the plantations is concerned — the estate executives continue to lead luxurious lives in

British-style bungalows, while the workers continue to live in poor conditions in their well demarcated "labour lines" (colonies), where diseases thrive.
A healthy workforce, however, brings better productivity and Roy said TB hits the productive age-group the hardest. Women, especially, are among the most vulnerable lot. According to a study conducted by Unicef, almost 96 per cent women workers in tea gardens are anaemic. Malnourishment, also among children, is high — all of which makes them specially vulnerable to infections. "Half of all TB cases from the gardens are women," Roy said. Another study concluded that the female reproductive system is very vulnerable to TB infection, causing infertility, menstrual irregularity, pregnancy loss — and increased risk of morbidity of both mother and child in pregnant women. Richa Misra, research associate at CSIR-Institute of Genomics and Integrative Biology, New Delhi, said women are more at risk in their productive years. "Although biological mechanisms may account for more men being affected in low-income countries, socioeconomic and cultural factors leading to barriers in accessing health care may cause under-notification in women," Misra told IANS in an email interaction. "Tuberculosis control programmes should be sensitive to the constraints faced by women in accessing health care in order to empower women to commence and complete treatment. The fear and stigma associated with tuberculosis have a greater impact on women than on men, often leaving them in a more precarious social and economic position," she added.
The disease, however, is not just a health problem. Since it hits the productive age group the most, absenteeism from work because of ailing health is high, putting stress on the meagre family income of the daily wage earners. Then again, with one or both parents ill, many times children drop out of school to work and supplement the family income. "There have been heart breaking cases in which families have been wiped out because of TB. In one such case, the father got the infection first, then his wife, and then both their sons," Roy said. "Treatment in the garden hospital is free of cost, but detection of the disease was late. Over a short span of time, the whole family was dead," Roy said.
"The situation can be improved, the disease can be controlled, but concrete steps at the community level and by the management need to be taken for that," he added.
Source: Gulf News, http://gulfnews.com/news/world/india/ignorance-leads-to-tb-spreading-in-assam-s-tea-gardens-1.1443007 (28.01.2015)

Forschung & Entwicklung

1. Combination TB therapy showed comparable efficacy, superior completion rate vs. Single therapy

Rifapentine and isoniazid in combination had comparable efficacy to isoniazid alone and had a higher treatment completion rate for preventing tuberculosis among children, according to recent findings.
M. Elsa Villarino, MD, MPH, of the CDC, and colleagues compared treatment efficacy, discontinuation rates and adverse events among 552 children who received 12 once-weekly doses of a combination of rifapentine and isoniazid for 3 months and 506 children who received 270 daily doses of isoniazid over 9 months. Children were aged 2 to 17 years and were eligible for treatment of latent tuberculosis infection. Participants were from the United States, Canada, Brazil, China and Spain. Children assigned isoniazid only self-administered the therapy without physician supervision; combination treatment was given by directly observed therapy. Study participants were followed for 60 days after their last dose.
Children in the combination therapy group had a treatment completion rate of 88.1% vs. 80.9% in the isoniazid-only group (*P*=.003). Three influenza-related adverse events, three cutaneous events and two gastrointestinal events led to treatment discontinuation in the combination therapy group. One cutaneous and one gastrointestinal adverse event resulted in discontinuation of isoniazid-only therapy. No study-related adverse events occurred among the five children with HIV. Two deaths occurred, including one due to cardiac arrhythmia, in the isoniazid-only group.
Of the 471 children who received combination therapy and were available for follow-up, none were

diagnosed with TB. Three of the 434 children who received isoniazid-only were diagnosed with tuberculosis during follow-up.
"We found that combination therapy with rifapentine and isoniazid was well tolerated and safe in children aged 2 to 17 years who were treated for latent tuberculosis infection," Villarino and colleagues wrote. "Our study also demonstrated that, in children, directly observed, once-weekly therapy with rifapentine plus isoniazid for 12 doses was as effective was isoniazid that was mostly self-administered daily for 9 months. The shorter regimen might encourage more treatment starts because of the promise of a briefer time commitment."
Source: Healio, http://www.healio.com/pediatrics/respiratory-infections/news/online/%7B36e1f26d-5843-4760-bfc9-6f8020357e3c%7D/combination-tb-therapy-showed-comparable-efficacy-superior-completion-rate-vs-single-therapy (15.01.2015)

2. Ein Newcomer schlägt endlich diesen Keim
Versteckt sich tief im Erdreich die nächste Generation von Antibiotika? Hoffentlich, denn seit Jahrzehnten verlieren die Allzweckwaffen der Medizin ihre Wirkung gegen gefährliche Bakterien. Die Keime haben sich an die Wirkstoffe gewöhnt, sie sind resistent geworden.
Ärzte und Forscher wissen darum. Doch noch immer werden Antibiotika viel zu häufig und unbekümmert verschrieben, zum Teil sogar falsch verwendet. Die Mittel sind so weit verbreitet, dass sich rasant mutierende Krankheitserreger immer effizienter vor ihnen schützen können. Recherchen von ZEIT ONLINE, DIE ZEIT und CORRECT!V haben erst kürzlich ergeben, dass allein in Deutschland jedes Jahr wohl Tausende mehr Menschen an den Folgen solcher Keiminfektionen sterben als offiziell bekannt. Das Auffinden neuer Antibiotika drängt.
Wissenschaftler um die Genetikerin Losee Ling hat die Suche nach den dringend gebrauchten neuen medizinischen Waffen nun zurück zu den Ursprüngen der Antibiotikaforschung geführt. Sie blickten wieder in die Natur, genau genommen ins Erdreich und haben Tausende Bakterienstämme, die dort leben, durchforstet, um geeignete Killer für krankheitserregende Keime zu finden. Der Ansatz ist nicht neu. Aus Mikroben im Untergrund fischten Forscher schon erfolgreiche Bausteine für spätere Antibiotika. Nun könnte sich das erneut als hilfreich erweisen.
Denn Ling und ihr Team von der US-amerikanischen Pharmafirma NovoBiotic haben im Erdreich ein neues Antibiotikum entdeckt, das gegen einen der am weitesten verbreiteten Krankheitserreger Wirkung zeigte: *Staphylococcus aureus*, zu denen auch der Krankenhauskeim MRSA gehört (Ling et al., 2015). Der isolierte Wirkstoff namens Teixobactin ist möglicherweise so potent, dass infektiöse Keime wieder Jahrzehnte bräuchten, um sich breit gegen ihn zur Wehr zu setzen. Teixobactin attackiert krankmachende Bakterien anders als die meisten Antibiotika. Oft greifen die Antibiotika die Eiweiße von Keimen an. Diese verändern sich aber rasant, mutieren und entwickeln Resistenzen. Teixobactin hingegen schädigt die starre, schützende Hülle von Bakterien, wodurch diese nicht mehr überlebensfähig sind. Getestet haben die Forscher den Stoff nicht nur an *Staphylococcus aureus*, sondern auch an dem Keim *Streptococcus pneumoniae*, der Lungenentzündungen auslöst.
Im Labor gelang es den Teixobactin-Entdeckern zudem nicht, gezielt resistente Bakterien gegen den neuen Wirkstoff zu züchten. Damit sei das Mittel aus dem Untergrund ähnlich widerstandfähig wie Vancomycin, mutmaßt der Biochemiker Gerard Wright in einem Begleitartikel zur Studie von Ling im Magazin *Nature*. Dieses ist dafür berühmt, dass sich erst 30 Jahre nach seiner Entdeckung 1953 und seinem Einsatz in der Klinik erste Resistenzen entwickelten (Leclercq et al., 1988). Neueren Mitteln widerstehen Keime schon nach wenigen Jahren.
Unbeteiligte Forscher werten die Entdeckung als Erfolg – mit Einschränkungen. "Es ist ein Schritt nach vorn", sagt Neil Woodford, der im britischen Gesundheitswesen die Abteilung für Antimikrobielle Resistenzen leitet. Allerdings helfe Teixobactin nicht gegen Infektionen von Bakterien wie *E.coli* oder *Klebsiella*, die bereits für eine Vielzahl heutiger Resistenzen verantwortlich sind. Bislang hat Teixobactin sein Können nur im Mausversuch gezeigt. Giftige Nebenwirkungen beobachteten die Forscher dabei zwar nicht, ob der Wirkstoff auch in menschlichen Zellen Keime abwehrt, ist aber noch nicht untersucht. Bis dahin, wird noch einige Zeit vergehen. "Potenzielle

Wirkstoffe in die Zulassung zu begleiten, ist ein langer, kostspieliger und schwieriger Prozess." Der aber nötig sei, sagt Woodford.
Bedeutender als Teixobactin selbst ist ohnehin die Geschichte seiner Entdeckung. Neue Wirkstoffe zu finden, ist aufwändig und teuer. Kaum ein Pharmaunternehmen investiert in diesen Bereich größere Summen. Was, wenn ein neues Medikament nach kurzer Zeit schon wieder wirkungslos ist? Damit lässt sich kein Geld verdienen. Bemerkenswert ist daher, dass Ling und ihr Team eine neue Methode genutzt haben, mit der sich die Bausteine für künftige Antibiotika rascher und günstiger auffinden lassen als mit den gängigen Verfahren. Mit einem relativ neuen Laborgerät namens iChip analysierten die Wissenschaftler rund 10.000 Bakterienstämme (Nichols et al., 2010).
Die Zellen der Mikroben können im iChip gedeihen, ohne aus ihrem natürlichen Umfeld gerissen zu werden. Zuvor zogen Forscher potenzielle Antibiotika-Lieferanten vor allem aus solchen Stämmen heran, die sich ohne großen Aufwand im Labor kultivieren ließen. Die überwiegende Mehrheit von Bakterien im Erdreich blieb deshalb unangetastet. Die neue Methode eröffne nun neue Wege. Mit ihr können Bakterienspezies analysiert werden, die "Bedingungen benötigen, die sich mit bisherigen Methoden im Labor nicht nachbilden lassen", schreibt der Biochemiker von der McMaster Universität im kanadischen Hamilton. So ließen sich gerade auch schwer zu züchtende Mikroben aus dem Erdreich untersuchen, die vielleicht Lagerstätten für ganz neue Varianten von Antibiotika sind.
Die systematische Suche nach künftigen Antibiotika könnte sich auszahlen. "In einem Forschungsbereich, der vor allem von Untergang und Trübsinn geprägt ist, gibt die Arbeit von Ling und Kollegen Anlass zur Hoffnung", schreibt der Biochemiker Wright. Teixobactin sei möglicherweise ein erster Hinweis auf eine neue Klasse von Antibiotika. Wie genau sie wirken, ob es sich gar lohnt, auf ihrer Basis neue Medikamente zu entwickeln aber, ist noch völlig offen.
Teixobactin ist ein Erfolg der Grundlagenforschung. Nicht mehr und nicht weniger. Gegen die Antibiotika-Krise kann der Stoff vorerst nichts ausrichten.
Source: DIE ZEIT, http://www.zeit.de/wissen/gesundheit/2015-01/antibiotika-resistenzen-keime-entdeckung/komplettansicht (15.01.2015)

3. Scientists find drug candidate for TB, malaria

Indian scientists have created a common drug candidate capable of tackling tuberculosis (TB) and malaria–the nation's two most common health problems–though it will take several years before the breakthrough in the laboratory is translated into a medicine. A common drug against the two big killer diseases was a dream for scientists for years. But biologists in Delhi have successfully tested the candidate–a peptide (type of protein) molecule called M5–in the laboratory and found that it reduces the diseases load by 80 per cent in TB and malaria."It is promising, but several years of research is required before we come anywhere close to trying this molecule as a drug. In the next step, we will test this protein in malaria infected mice to see the response," Anand Ranganathan, one of the principal investigators at International Centre for Genetic Engineering and Biotechnology (ICGEB), Delhi, told Deccan Herald. When studied in the laboratory, M5 not only inhibits pathogen's entry to human cells by 80 per cent in case of TB and malaria, but it was also effective against drug resistant-strains of malaria causing Plasmodium Falciparum parasite that has emerged as a public health concern. Drugs available at present for treatment of both these infections have been failing in cases with resistant strains of pathogens, causing wide-spread alarm. While globally there was 8.6 million new cases of TB with 1.3 million deaths in 2012, the incidence of malaria, too, is equally staggering at 207 million cases with 6, 27,000 deaths."We were looking at an universal target and found M5 is promising. We will keep on modifying the molecule," said Gobardhan Das, one of the team members from Jawaharlal Nehru University (JNU). Besides Ranganathan and Das, the team includes Pawan Malhotra of ICGEB and several young researchers from ICGEB, JNU and All India Institute of Medical Sciences. The research findings have been published in the January 14 issue of "Nature Communications". "It is a fantastic paper, though drug development is a log way off. Four young groups have come together for this important discovery, breaking the boundary of academic institutions," said Samir K Brahmachari, former director-general of Council of Scientific and Industrial

Research. The Delhi team pursued an innovative approach as the target was a host (human) protein, rather than one in the pathogen. "Most drugs target pathogenic proteins. As a result, after few years the pathogen becomes resistant to the drugs. This will not happen with M5," said Ranganathan. M5, on the other hand, targets two human proteins ICAM-1 (TB) and its cousin ICAM-4 (malaria) and inhibits the invasion of human cells of two very different pathogens significantly.
Source: Deccan Herald, http://www.deccanherald.com/content/453540/scientists-find-drug-candidate-tb.html (15.01.2015)

4. Zombie bacteria in tuberculosis

Tuberculosis affects over 12 million people globally, and is usually treated with a course of four drugs over several months. However, even after completing the treatment, many patients suffer relapses. Based on studies of harmless environmental bacteria, scientists think that the tuberculosis bacterium, *Mycobacterium tuberculosis*, retreats into a bizarre "zombie" state in the patient's body, and comes back to life when the conditions permit. Scientists at EPFL have now made the first experimental observation of *M. tuberculosis* in this zombie state, which seems to be amplified by stressful conditions such as attacks from the host's immune system. The work, which points to entirely new pathways for treating tuberculosis, is published in *Cell Host & Microbe*.
Living bacteria divide and proliferate; if not, they are considered dead. However, some bacteria can go into a strange, in-between state where they are biologically active – producing energy and making proteins – but do not divide. "It's a kind of living-dead, zombie existence," says John McKinney, whose postdoc, Giulia Manina, led the study on *M. tuberculosis*. "The bacteria are somewhat active, but they're neither growing nor dividing. We refer to this state as 'Non- Growing but Metabolically Active' or 'NGMA'". This state is thought to underlie the relapse of tuberculosis: when the population of *M. tuberculosis* infecting a patient is faced with an aggressive antibiotic regimen, a part of it falls into this zombie state as a defense mechanism. However, there has been little evidence to support this theory, partly because experimental techniques for studying bacterial populations usually depend on the bacteria actually growing in the first place.
There is, however, a way in: the zombie bacteria are still metabolically active, which means that they keep making new proteins. Manina exploited this with a technique that can tag and track a gene that turns on when *M. tuberculosis* makes new proteins. The technique, developed by the lab's senior scientist, Neeraj Dhar, tags the gene with a fluorescent molecule that can be tracked with a microscope over time.
Manina grew the gene-tagged bacteria under different stressful conditions such as limited nutrients, antibiotics, and also conditions that simulate an attack by the patient's immune system. In addition, bacteria were taken from the lungs of infected mice at different stages of infection. Tracked with the fluorescent gene-tag, the bacteria were tested to see how the different conditions affected them over time. The researchers found that *M. tuberculosis* responds to stressful conditions like immune attacks or lack of nutrients by diversifying its population and pushing some it into the zombie state. "This means that this state could be a defensive response to the patient's immunity," says Manina. "What is unclear at the moment is whether it is an active bacterial response, or just a consequence of an immune attack." In addition, the researchers found that the lungs of mice with tuberculosis contained an unexpectedly large subpopulation of zombie cells. Surprisingly, these cells were not found in mice that were genetically modified to lack an immune system, further suggesting that the immune system and the zombie state are somehow related. (...)
Source: EPFL, http://actu.epfl.ch/news/zombie-bacteria-in-tuberculosis/ (27.01.2015)

5. Tuberculosis genomes track human history

From the dawn of agriculture to the fall of the Soviet Union, major events in human history have left marks in the DNA of the bacterium that causes tuberculosis (TB). A study of nearly 5,000 samples of *Mycobacterium tuberculosis* from around the world shows how a lineage of the bacterium that

emerged thousands of years ago in Asia has since become a global killer that is widely resistant to antibiotic drugs.

Although *M. tuberculosis* probably first emerged some 40,000 years ago in Africa, the disease did not take hold until humans took to farming — with the consequent settling down — Thierry Wirth, an evolutionary geneticist at the National Museum of Natural History in Paris and lead author of the study. The grouping together of people in settlements made it easier for the respiratory pathogen to spread from person to person, says Wirth. A previous analysis by his team had shown that the common ancestor of all the *M. bacterium* strains circulating today began spreading around 10,000 years ago in the ancient Fertile Crescent, a region stretching from Mesopotamia to the Nile Delta that was a cradle of agriculture — enabling lots of people to live in close proximity. "It's basically a dream setting for a bug like TB," says Wirth.

But of all the *M. bacterium* strains circulating today, few strike more fear in public-health officials than the 'Beijing lineage'. First identified in greater Beijing in the mid-1990s, this lineage now circulates throughout the world and many strains are resistant to drugs that vanquish other types of TB. Wirth's team collected and analysed 4,987 samples of the Beijing lineage from 99 countries, fully sequencing the genomes of 110 of them and more limited stretches of DNA in the rest. The researchers then used the information to date the expansion of the lineage and show how the strains are related. Consistent with its name, the Beijing lineage did indeed emerge near north-eastern China, Wirth's team report in *Nature Genetics*. And it did so around 6,600 years ago, the researchers found, which coincides with archaeological evidence for the beginnings of rice farming in China's upper Yangtze River valley.

Travel along the Silk Road, which connected China with the Middle East, probably helped to spread the lineage beyond East Asia, the researchers say. So did more recent waves of Chinese immigration: a branch of the bacterium that circulates in the Pacific may have taken hold when Chinese people migrated to the Pacific Islands in the 1850s; and the rise of branches common in former Russian republics of Central Asia could be linked to the arrival and dispersal of Chinese immigrants there during national uprisings in Kyrgyzstan, Kazakhstan and Uzbekistan in the 1860s and 1870s.

Global upheavals also propelled the rise of the Beijing lineage. The team used the whole-genome sequences to model how its population changed over time and showed that numbers of the bacterium (and, therefore, people infected) shot up in the early nineteenth century, possibly because of the rise of urban populations during the Industrial Revolution. It spiked again in the early twentieth century, which Wirth says could be related to further urbanization after the First World War and exacerbated by influenza pandemics at the time, which made people more susceptible to TB. The increasing availability of antibiotics in the 1960s, meanwhile, coincides with a fall in the numbers of the bacterium. The lineage bounded back, however, in the late 1980s and early 1990s. Wirth's team notes that these dates are bookended by the rise of HIV/AIDS and the collapse of the Soviet Union. The disintegration of the Soviet health system has been widely cited as factor in the rise of TB and its multi-drug-resistant forms. Since its emerged, the Beijing lineage has become much more infectious, Wirth says, so it out-competes other strains of the bacterium. His team identified mutations related to antibiotic resistance, metabolism and evasion of immune responses that may have contributed to the success of the Beijing lineage.

Anne Stone, an evolutionary geneticist at Arizona State University in Tempe, is impressed by the number of samples that Wirth's team examined. The 6,600-year date that the team calculated for the emergence of the Beijing lineage clashes with an estimate that she and her colleagues published last year, which put the emergence at around 1,200–2,400 years ago. That study was based on TB genomes collected from 1,000-year-old Peruvian mummies and used different dating methods. But Stone now wonders if her team's estimate is on the young side. "Looking at this study, I'm thinking 'hmm we should play with this data set'," she says.

Source: Nature, http://www.nature.com/news/tuberculosis-genomes-track-human-history-1.16733 (20.01.2015)

Reportage

1. Losing the Fight Against Tuberculosis

(...) Indonesia's recently sworn-in president, Joko Widodo, takes the reins of a rising economic power poised to play a larger role on the world stage. But he also confronts a set of entrenched public health problems fueled by the poverty in which millions of Indonesians still live. None is more urgent than the spread of drug-resistant tuberculosis across this sprawling archipelago.

Thanks to support from the Global Fund to Fight AIDS, Tuberculosis and Malaria, the international financing mechanism established in 2002 to help poor countries address these diseases, Indonesia has been able to provide the costly drugs for drug-resistant tuberculosis to patients free of charge. It has also supplied laboratories like the one at Persahabatan with the Xpert MTB/RIF device, which allows health workers to diagnose suspected cases of drug- resistant disease in under two hours (conventional methods take as long as eight weeks).

These are encouraging steps, but as Indonesia is learning, the tools of clinical medicine can do only so much. "This is a social disease," Dr. Erlina Burhan, the head of pulmonology medicine at Persahabatan, told me, referring to multidrug-resistant tuberculosis. "We have 7,000 new MDR cases a year, and many of those are defaulting on their treatment."

It's easy to understand why. For one thing, there's the financial strain; the drugs may be free, but as a recent multinational study found, the cost to patients — for everything from transportation and hospital stays to months of missed work — can amount to a year's earnings. And then there is the treatment itself: a grueling, two-year regimen of toxic drugs involving months of daily injections and possible severe side effects. And so stigmatized is tuberculosis in Indonesia that when volunteers go house to house looking for cases, families often try to hide sick relatives.

"Most of our patients don't know how the disease is transmitted," Dr. Burhan said, "so they return home and spread their drug-resistant strain to others." The World Health Organization estimates that every untreated MDR patient will infect, on average, between 10 and 15 people per year — and some of those may be their children, in whom tuberculosis is more difficult to diagnose and treat. Despite congressional calls to increase tuberculosis funding for the current year, President Obama proposed a 19 percent cut to the global tuberculosis budget of the United States Agency for International Development, which would put tuberculosis funding below $200 million for the first time in five years. The spending bill recently passed by Congress rejected those cuts and maintained level funding, at $236 million. That is still far below the $400 million per year public health advocates say is needed to combat the world's leading curable killer.

In 2013, President Obama pledged that America would contribute up to $5 billion to the Global Fund over the next three years. But by opposing increases to bilateral tuberculosis funding, the president jeopardizes this generous investment. While Global Fund grants support the purchase of drugs and diagnostics, like the $30,000 Xpert device, the agency doesn't have the in- country staff to ensure the tools' effective implementation. It's here that U.S.A.I.D. plays a vital role, by training technicians, strengthening supply chains and educating doctors and nurses about novel therapies.

Without that help, our aid dollars don't go nearly as far as they could. Between 2010 and 2012, for example, Indonesia, though a major recipient of Global Fund support, used only half of the funds allocated for tuberculosis control activities because it lacked the capacity to use that aid.

Perhaps the most tragic consequence of underfunding tuberculosis control, though, is that it undermines the fight against H.I.V. and AIDS. After billions of dollars and decades of research, antiretroviral drugs have transformed what was a death sentence into a manageable chronic disease. In spite of this monumental public health achievement, the leading killer of people living with H.I.V. today, accounting for one-quarter of AIDS deaths worldwide, is tuberculosis, a disease so neglected that the current first-line treatment is more than 50 years old. (...)

Source: NYT, http://www.nytimes.com/2015/01/06/opinion/losing-the-fight-against-tuberculosis.html?_r=1 (06.01.2015)

2. Drug resistant tuberculosis patients face dwindling treatment options

Stephanie, 29, doesn't know what to say when her brother, who has what his doctor says is the most drug- resistant tuberculosis ever diagnosed in the U.S., asks her what kind of life he is going to have if he can't walk, use his hands or hear. "I just say, 'But you're alive,'" she says. Her brother, Gary, is 37 and has extensively drug- resistant tuberculosis (XDR TB), a rare type of multidrug-resistant (MDR) tuberculosis that does not respond to almost any of the drugs used to treat TB. A year ago his family thought he would die. He still could. In November he was admitted to the hospital for a cold, a simple sickness that for Gary could prove deadly. He has only one lung, extreme hearing loss and disabling nerve damage to his hands and feet that makes it ainful to walk. He suffers from paranoia and memory loss, and his skin is covered in pimples. The disease has damaged his lungs; the treatment is destroying his body and mind. Gary and Stephanie requested that their last names not be used because of the stigma associated with the disease.

Once the leading cause of death in the United States, tuberculosis rates in the U.S. have been in decline for decades. Effective drug treatments in the 1940s all but erased tuberculosis from modern U.S. memory, until the mid-1990s, when a resurgence was blamed on AIDS, growing drug resistance and decreased funding. Renewed investment in TB prevention helped reverse the trend, and numbers once again went down, with fewer than 10,000 new cases reported in 2013. Half the cases occur in four states: Texas, New York, Florida and California. (…)

But that number is only new cases. Because of the long length of treatment, there are twice as many at any given time if you include patients still in treatment, said Dr. Jennifer Flood, president of the National Tuberculosis Controllers Association and chief of the TB control branch at the California Department of Public Health. Even doubled, the number is small, but the threat and effort to make sure it doesn't spread have more to do with the consequences than the quantity. And with MDR TB, the repercussions are both human and economic. Treatment for MDR TB takes years, not months. It is incredibly costly: about $260,000 (in 2010 dollars) in direct costs plus lost productivity for an average MDR TB patient and $554,000 for an XDR TB patient, according to a 2014 CDC study that looked at cases from 2005 to 2007. Even with treatment, 9 percent of those surveyed in the study died. Although there is not enough information to make an official comparison, "anecdotally many experts in the field feel that we are seeing greater complexity and greater drug resistance," said Mase. Dr. Caitlin Reed, medical director of the inpatient TB unit at UCLA's Olive View Medical Center, where Gary was eventually treated, said his case is the "most drug resistant that's ever been diagnosed or treated in the United States."

Gary's form of XDR TB was almost untreatable. Her colleagues suggested hospice. Instead she put him on as many as 10 to 12 often fairly toxic antibiotics at a time. She sent him to a specialist in Colorado to have a badly damaged lung removed. She urged the Japanese-based Otsuka Pharmaceutical Co. to allow him to take a new drug the company has registered in Europe and Japan but not yet in the United States. It denied her request. Gary is no longer contagious, but his health remains precarious. He could still die of XDR TB.

Reed said a fellow doctor and friend once described TB as "Ebola with wings, because you have a disease that is extremely difficult or potentially untreatable but you can spread it through the air."

In California, with MDR TB rates hovering at 1 to 2 percent of cases annually and 27 new cases in 2013, doctors are particularly concerned. Santa Barbara County Health Officer Dr. Charity Thoman considers being prepared for drug-resistant TB cases her No. 1 priority, saying it's "more important than planning for Ebola or anything else I do." But doctors as well versed in TB as Thoman, Reed and Flood are not the norm. As TB rates in the U.S. continue to decline, fewer doctors are familiar with the disease. As a result, patients are often initially misdiagnosed, said Reed, placing both the patient and the people with whom the patient interacts at risk.

Before being treated by Reed, Gary received a number of confusing diagnoses. It was not until December 2013, after years of suffering recurrent pneumonia, that he was tested for tuberculosis, said Stephanie. He had it. Then he didn't have it. Then he had a drug-resistant strain. Then he had a

strain so drug-resistant, they couldn't treat it. "We're in the 21st century. It's not like it's 18-something or even the 1920s," she said. "We've got machines for freaking machines. They have robots filling orders at Amazon. They can't figure out a way to find out what type of TB you have quicker?"

Often, they can't. Not only is diagnosis difficult because of less medical familiarity with the disease, but also treatment and diagnostic technology has been limited by a decline in funding and research. A National TB Controllers Association study revealed that 60 percent of public health TB programs in the U.S. have eliminated staff and 25 percent have restricted crucial activities, including those involved with TB outbreak response. Since 2012, three major drug companies have stopped TB research, leaving only three companies with active TB research programs. "Research into developing new treatments is sort of woefully inadequate," said Mike Frick, TB/HIV project officer with Treatment Action Group, an AIDS research group based in New York. "And the evidence of that is in the past 40 years, we've only developed two new drugs to treat drug-resistant tuberculosis."

The limited number of drugs is particularly worrying because as more of these drugs are used around the world, more resistance to them develops, said Flood. The concern is that new drugs will not be developed in time to replace those for which patients develop resistance. The lack of companies focused on developing new drugs and producing current drugs means that normal delays and recalls can lead to shortages, which can in turn lead to drug resistance.

In the last two years the Centers for Disease Control has issued seven alerts regarding shortages of TB treatment drugs and agents used in diagnostic testing, said Mase. According to a TB Controllers Association survey, 21 of 26 health departments treating MDR TB from 2005 to 2010 (representing about 75 percent of the U.S. TB burden) had trouble procuring drugs for MDR TB. The majority, 90 percent, reported resulting treatment delays and lapses, which can lead to patients' becoming infectious again. In 2013 there was a shortage of a key drug used to treat TB, said Mase, causing programs to switch regimens and start and stop treatments, all of which can lead to the development of MDR TB. "That is one of the major worries with first- and second- line drug shortages — further acquired drug resistance," said Mase. For those drugs that are available, more research is needed. In 2009, Dr. Felice Adler treated several elementary school students in Laguna Beach, California, for latent, or nonactive, MDR TB after their teacher developed active MDR TB. With latent TB, a person is infected but is not ill or contagious. About one-third of the world's people have latent TB; 10 percent will go on to develop the disease. Long and toxic drug courses similar to those used to treat active MDR TB are used to prevent latent MDR TB from becoming active. There are no separate drugs for children, and of the 26 children in Laguna Beach who underwent treatment, only 15 were able to complete it. Some of those who stopped did so because of severe side effects, including hallucinations and stress to the liver.

"We need to have more studies looking at outcomes of treating people with these long courses of antibiotics, specifically kids, because we just don't have a lot of data," said Adler, who is director of outpatient services for infectious diseases at Children's Hospital of Orange County in California. Hearing loss and nerve damage caused by the drugs can be irreversible. (...)

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