NEWSLETTER

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Inhalt

Internationale Nachrichten

1. Azerbaijan brings quality tuberculosis care to prisons

Tuberculosis (TB) is a major public health problem in many prisons and infection rates are often more than 10 times higher than in the general population. Frequently overcrowded and poorly ventilated, many prisons also lack early detection and sound treatment programmes to combat the disease. Moreover many prisoners come from population groups that are already at high risk of TB infection and disease, such as people who inject drugs, are homeless or mentally ill.

But, in Azerbaijan—a country bordering Russia, Georgia, Armenia and Iran—a tuberculosis programme in the country's prisons is helping reverse the spread of the disease. Fifteen years ago, 7 in every 1000 Azerbaijan people were ill with TB. By last year, rates had fallen to 1 in every 1000 people, which is major progress. Still, there is substantial work ahead to end the general epidemic and address multidrug-resistant disease. Part of the response is addressing TB in vulnerable groups, including prisoners.

In 1995, supported by the International Committee of the Red Cross, the country introduced the WHO DOTS approach to enable TB care and control in all of the country's prisons. The approach has fostered political commitment and financing for TB efforts in prisons as well as linking to the wider national TB programme and health services; enabled earlier diagnosis; provided standardized treatment with supervision and patient support; provided effective drug supply and management; and monitored and evaluated the programme.

Routine screening of detainees has been a key element of the successful programme in Azerbaijan. Once a year, the country's prisons hold dedicated TB days to screen all detainees and raise awareness about risk-factors and symptoms of the disease. Those prisoners who test positive are transferred to a centralized TB prison hospital for treatment and additional support.

"We've made sustained efforts to actively detect TB in prisons for more than a decade now," says Elmira Gurbanova, from the Central Medical Department of the Azerbaijani Ministry of Justice, who is responsible for coordinating TB control programme in prisons. "We set up a specialized TB hospital for detainees, with infection control measures and a new laboratory that uses all the diagnostic techniques recommended by WHO, including molecular-genetic testing."

However, it is not just the prison's detainees and health personnel who play a role in the programme. Prison officers and other non-medical staff are taught about the symptoms, risk factors and treatment of TB through mini-plays, performed in the country's prisons by a state theatre group.

"Most prison officers are not medical workers, so they need to be educated about TB. We train them so that they understand the basics of the disease and convey consistent messages to detainees about the importance of TB control," explains Gurbanova.

The importance of rigorously completing TB treatment is reinforced to all infected prisoners who start a course of medication. In addition, with so many detainees released from prison part-way through treatment, a local nongovernmental organization provides a vital service offering support to newly- released detainees to ensure they complete the medication regimen.

Azerbaijan's national programme has developed in line with the WHO European Office's Consolidated Action Plan to Prevent and Combat M/XDR-TB 2011-2015 which promotes integrated care, and collaboration across health and justice ministries.
WHO is helping the country strengthen programmatic management of drug resistant TB, improve TB drug management, expand access to rapid diagnostics and further develop its laboratory network. In addition, the country receives support for TB control in prisons from the Global Fund to fight AIDS, Tuberculosis and Malaria.
"In order to support Member States improve their health services, we facilitate and nurture intercountry exchange of know-how and good practices. Azerbaijan's successful implementation of state-of-the-art TB care in prisons can be used as a model for other countries.", highlights Dr Masoud Dara TB and M/XDR-TB Programme Manager of WHO Regional Office for Europe. The prison programme has achieved recognition for its work in protecting the health of detainees, including an award from the International Corrections and Prisons Association (ICPA) in 2013. "The Azerbaijani Ministry of Justice has achieved solid TB cure rates and is implementing WHO recommended approaches to case finding and treating tuberculosis in prisons," says Dr Fuad Mirzayev, medical officer from the WHO Global TB Programme.
In 2012, a demonstration centre was set up within an Azerbaijan TB prison hospital to train international health workers and prison staff on how to implement similar programmes in their prisons. Last year, WHO officially recognized the facility as a WHO Collaborating Centre on the prevention and control of tuberculosis. In May 2015, the centre will host its first international training event. It has already trained more than 100 representatives from countries across Central Asia.
Source: WHO, http://bit.ly/1CebAbx (24.03.2015)

2. Missing the big picture in TB control
India's TB control programmes turn a blind eye to historical experiences which reveal that in much of the advanced world today, the infection was controlled through enhanced nutrition, better housing design, socio-economic advancement opportunities and cleaner environments.
The rampaging and terrifying face of tuberculosis in India today with a thousand deaths every day has a complex history. India's TB control efforts have for long suffered from not being able to see the wood for the trees or the big picture — a cardinal failure of control programmes where health-care professionals assume the role of sole resolvers of the disease. Not surprisingly, even today India's TB control programme continues to clamour for more diagnostics, newer drugs, augmented human resources and the technological magic bullet to kill TB forever. They turn a blind eye to historical experiences which reveal that in much of the advanced world today, TB was controlled through enhanced nutrition, better housing design, socio-economic advancement opportunities and cleaner environments.
A withering contrast is the way in which nutrition for TB patients is handled at the ministerial level in India — a game of handball between the Ministries of Health, Social Justice and Labour. While convergence in governance is utterly lacking even within health systems, scant attention is paid to more basic issues. A country that sends missions to Mars is unable to guarantee basic TB drugs to even its most vulnerable. Nowhere is this more evident than in the lack of availability of paediatric TB drugs even in large cities and the lethargic inclusion of new life-saving drugs for patients (many of them young) doomed to die from unresponsiveness to the existing drugs.
One of our greatest limitations in TB, however, has been a de-motivated workforce and poor care in the public health system. Ill-managed financial pipelines between the Centre and the States choke the receipt of funds at Ground Zero, where health workers struggle in slums, remote villages and hazardous health facilities. The cadres often get deprived of their salaries for months as funds fail to arrive.
Hardly 20 per cent of our overall population utilises public health services. Study after study attributes this to the poor quality of services at its facilities. The huge gaps in human resources and

their poor skilling are not so much a resource issue but one of lack of inspirational leadership in the sector. Apart from remuneration, hardly any motivational incentives are offered to public health sector staff; nor are their services recognised when work is undertaken in difficult conditions. A de-motivated workforce cannot be a harbinger for effective TB control.
The overall decision-making pathways for the control programme (this is not restricted to TB) are ill-informed since the country has poor survey and surveillance mechanisms. Nikshay, touted and celebrated as a transformational health management information system for TB, is horribly slow in its development. It is an electronic registry at best, but hardly an epidemiological tool. If the grounds of decision-making are so shaky and incomplete, then erroneous decisions are a natural consequence.
Ultimately, achieving a resolution of the big-issue gaps in TB requires both political will and vision — that seem to be lacking. The decision to cut health budgets or to continue not to engage India's vast private sector where millions seek care, will not reduce India's TB burden; nor will constantly stalling the urgently needed nutritional support, new drugs and technologies for diagnosis that TB patients need. What we need is an entire transformation of the system and its entrenched red-tapism which is making us lose a battle against a critical infectious disease that is putting India's growth and development at grave risk.
It is unlikely that our choices will bring a 40 per cent drop in TB prevalence that has been achieved by neighbouring China. It seems the elephant, unlike the dragon, will continue to lumber on, loaded with 25 per cent of the world's TB patients, several avatars of progressive drug resistant disease (an under-counted minimum of 1,10,000) and omnipresent social injustices and basic insecurities that fuel the fires of this deadly disease.
Source: The Hindu, http://bit.ly/1CmRIlA (25.03.2015)

3. Peru: Study aims to reveal how TB spreads
Dr. Leonid Lecca was fast asleep in the darkness of a Sunday morning when his phone rang. A nurse was calling for help. In one of the Lima households she was monitoring, a little girl had fallen sick with fever and coughing. Her mom was worried that she'd been infected with tuberculosis from her uncle, and she didn't know who else to call at 4 a.m. Would Dr. Lecca come see her?
Making house calls was not part of Lecca's job description as the local principal investigator of the EPI study, an effort between Partners In Health in Peru and Harvard Medical School to understand how TB spreads from one person to another. But in his nearly 10 years working with Socios En Salud (SES), PIH's sister organization, he had come to prize solidarity with people who are poor and sick. Groggy, he began the drive into the far reaches of Lima, where shantytowns climb hillsides like vines.
"I sat for an hour with them, talking about TB and how they could protect themselves. No one had explained it to them," Lecca said. "They were very grateful, because they lived in a remote hillside, and no one else came to see them."
For five years, nurses like the one who called Lecca that morning had been visiting TB patients and their families in their Lima homes, checking on their health and referring them for care when needed. The visits were part of an unprecedented study to understand the transmission of tuberculosis, both the type that can be treated with standard antibiotics and its more fearsome offspring, multidrug-resistant tuberculosis, which requires a much longer, more difficult treatment.
Scientists have long debated the dynamics of how tuberculosis spreads in people, including whether MDR-TB is as likely to spread as drug-sensitive TB. The epidemiologists behind the study hope that answering this question will better equip public health professionals to stop tuberculosis in all its forms. Researchers have already published some results of the study and expect more to come out this year, including the relative transmissibility of MDR-TB and drug-sensitive TB.
"When we designed this study almost 10 years ago, no one had actually measured TB transmission in people," said Megan Murray, the Harvard epidemiologist leading the study. "We wanted to do a really systematic study where we observed what happened in people exposed in drug-resistant cases and drug sensitive-cases. We hope this will close the door on the discussion."

The little girl Lecca visited that morning turned out to be okay—her uncle's TB had not spread to her. But others in Peru and around the world are not so lucky. In 2013, TB sickened 9 million people and killed 1.5 million around the world. Its more fearsome offspring, multidrug-resistant tuberculosis, caused disease in at least 480,000 people that same year—probably more, based on recent research from the same group of Harvard epidemiologists.

The treatment for MDR-TB is much more difficult for patients: It takes two or more years of daily treatment and causes side effects such as nausea, diarrhea, and even deafness.

Despite the deadly toll of tuberculosis, scientists are still working to understand some of the factors that affect the spread of TB. They debate questions such as: What genetic strains of the bacteria are most virulent? What factors about the infected people—living conditions, smoking habits, immune systems—make them more likely to pass it to others? When the sick person comes into contact with others, what factors about those people—age, vaccinations, prior TB exposure—make them more susceptible to infection? How much does early diagnosis and treatment, which lessens the infected person's contagiousness, help prevent the spread of the disease?

To answer these questions definitively, epidemiologists at Harvard Medical School studied tuberculosis transmission in a huge sample of people. Peru has a large TB epidemic, centered in Lima, with about 32,000 people suffering from TB nationwide—60 percent of whom live in or near Lima. Peru also has the highest rate of MDR-TB infection in Latin America.

PIH has worked with our sister organization, SES, for nearly two decades to support Peru's Ministry of Health in fighting the epidemic. In 1996, SES pioneered a model for treating MDR-TB in the shantytowns of Lima. That model proved highly effective in curing MDR-TB, and has since been published as an international standard, known as DOTS-Plus. The community-based model places the patient at the center of a network of community agents who provide clinical, socioeconomic, and social support in addition to accompaniment and dose supervision.

The size of Peru's TB epidemic, coupled with SES's deep ties to affected communities, made it the ideal location to study TB transmission. "In the end, we went to almost 4,500 households and collected data on 18,500 people," Murray said. "We couldn't have done that without the history of Socios working in the community, and having learned how to work in the community. The follow-up level is unprecedented in a big TB study. I'm not sure we could do it anywhere else."

In designing this study, Murray and her Harvard colleagues wanted to settle the debate about whether MDR-TB is as transmissible as drug-susceptible TB. In 2007, they won a grant from the National Institutes of Health and two years later the team began implementing the study. Gathering the data in Peru cost about $6.5 million—a low cost relative to other epidemiological studies of this size. The epidemiologists aimed to include 25 of Lima's 45 districts, representing more than half of the sprawling city and the areas where TB was most common. They hoped to monitor every person diagnosed with TB in those districts and everyone they lived with for at least a year. Data collectors would gather information on participants' HIV status, history of illness, nutritional condition, smoking habits, and, most importantly, the presence of latent tuberculosis infection and active disease. By observing which of the healthy people became sick after their exposure to the TB patients they live with, epidemiologists could identify risk factors and make it easier to prevent the disease in the future.

"There were huge operational challenges, because it is a huge study," Murray said. "I don't think we actually understood how big the study was until we started doing it." To collect data for the study, PIH/SES drew on its extensive experience working with TB patients in Lima's poorest neighborhoods and with the Peruvian health system. In 2006, SES hired Lecca to be in charge of the implementation. Lecca is a doctor who previously worked for the Peruvian Ministry of Health, and had worked closely with SES on prior research about MDR-TB. He began recruiting and training young nurses and other health professionals to join the staff of the study.

In 2009, the study began enrolling participants. Study staff were assigned to Peruvian Ministry of Health-run clinics and health centers, totaling about 100 facilities. Every day, they showed up at the health centers along with the regular staff there. When clinicians diagnosed a patient with TB, they

would introduce the patient to study staff, who would invite them to participate in the study. It wasn't an easy ask—but critical to the study's success.

"For these patients it was a difficult moment," said Melissa Guevara, a nurse who has worked on the study since 2010. "They've just been diagnosed with an illness. We tried to approach them with sympathy and sensitivity. When they see this type of empathy, they had more trust in us."

Guevara said that many of these conversations happened while patients were in tears, just moments after their diagnoses. Study staff were as ready as they could be to handle these situations—they were trained by PIH/SES on how to work with people in such difficult conditions, not only facing months or years of treatment, but also living in great poverty. Study staff invited them into a private room and used specially designed educational materials to explain to them why the study was being done, what they would have to do to participate, and how their participation could help fight the disease.

Some of the procedures required by the study—including taking blood samples from them and their families—put them off. Some patients were distrustful of the study altogether—they thought it was some sort of experiment being performed on sick people. But if they declined to participate at first, they were still eligible to enroll until several days later. The patients had to return to the health center every day to take their medicine under the supervision of Ministry of Health clinicians, and each day they saw the study staff, who worked alongside the health center staff they trusted, and always greeted them and asked after their health. Many times, the patients came to trust them and decided to enroll. "At first the participants had a lot of prejudice against the word 'investigation,'" said Jhudyd Cruz, another nurse who worked in health centers. "Slowly they realized that we weren't there with bad intentions. We treated them like old friends, and once we had their trust, they agreed to participate." After a patient agreed to enroll, study staff would follow up with a visit to his or her home, where they enrolled everyone who lived in the household. They returned three months, six months, and a year later to perform tests. If a member of the household tested positive for TB or any other illness, the study staff member referred them to the health center for treatment.

In all, the study ended up enrolling about 18,500 people—including about 4,500 TB patients and 14,000 household members. And the team managed to retain more than 90 percent of participants in the study from beginning to end. At the peak of data collection, the study was employing 200 people and enrolling 1,000 new participants each month. They even adapted an open-source electronic medical record system to facilitate data collection on specialized smartphone apps. The scope of the work meant that PIH/SES was running a small army for more than three years, concluding most of the work in 2012.

"We were working 24 hours a day," Lecca explained. "Many of the participants left home at 5 or 6 a.m. to go to work or school, so our team had to be there before then. This meant that we had to leave from the office at 3 or 4 a.m. If we needed to take a blood or sputum sample, we had to bring a cooler and other supplies. So if someone left the office at 4 a.m. to do a home visit, another staffer had to be in the office even earlier to prepare the coolers. We had shifts in our warehouse day and night." Once blood and sputum samples were collected, they had to undergo various kinds of testing that helped make a diagnosis of TB or MDR-TB and identify the genetic strain, so that researchers could study the virulence of the specific bacteria. PIH/SES started out using Peru's regional laboratory, but the volume of samples quickly overwhelmed it. PIH/SES thought the country needed greater lab capacity anyway, so it built a new lab that can run tests more quickly than any other lab in the country.

The staff worked so hard, and cared for their patients so much, that many were at risk of burning out. Lecca recalled that PIH/SES tried to inspire a sense of unity and purpose in the team through all-staff meetings that included icebreaker activities. Once he even hired a clown to cheer them up.

"By working for EPI, I've gotten to know many districts in Lima that I never would have visited otherwise," said Guevara. "The difference from the wealthy parts of Lima to where we were working is striking. I went where people are very poor. In these areas, people are struggling to provide for large families—struggling to find something to eat, and experiencing domestic violence and crime. To

visit them, I would have to climb stairs, going up and up and up, not knowing when it would end. There are tiny houses that are very difficult to reach. And in this environment, people are trying to study and work. It helped me to see more of Lima, which was very gratifying and very difficult to witness."

Many participants ended up feeling grateful for their involvement in the study. The home visits from study staff allowed them to ask questions they otherwise might not and identify problems earlier than if they waited to go to the health center. The case where Lecca woke up in the middle of the night was not exceptional. That morning, Lecca explained a lot about tuberculosis to the family, and with that understanding, the uncle who was sick took his medicine religiously. No one else in the family fell ill. "One of the reasons for our success was that we didn't only focus on the activities of the study," Lecca said. "If we found a problem with the patient, we tried to do whatever we could to help. As a result, the study staff became very involved with the study participants—they felt like family. The participants were very grateful for the opportunities to have a visit from a medical professional. They lived in remote hillsides, and no one else came to see them."

Harvard researchers are analyzing the data that the SES team collected and plan to publish their major results in coming months. In the meantime, the study has generated new knowledge that can help fight TB. For example, the group has published a study showing that both the bacille Calmette-Guerin vaccine for tuberculosis and Isoniazid preventive therapy do help prevent active disease, which was previously less certain. They also published research showing that TB patients with HIV were less likely to transmit the infection to their household contacts, compared to TB patients who were not infected with HIV. Another finding was that TB patients who smoke cigarettes are more likely than non-smokers to transmit the disease.

As a result of genetic testing on the TB strains collected, the team now has an archive of information about which genetic strains are likely to be drug-resistant, which Murray hopes can be used to improve diagnosis of drug-resistance in patients. Right now, all tuberculosis patients are at risk of being under-treated for drug-resistant tuberculosis because clinicians lack information on what drugs their bacteria is resistant to. "We see this as a huge gold mine of data on the risk factors for infection, disease, and drug resistance in this very big cohort," Murray said.

Source: Partners in Health, http://bit.ly/1Jnpi0j (24.03.2015)

Forschung & Entwicklung

1. How the human immune system keeps TB at bay

A new tissue culture model using human white blood cells shows how people with a latent – or symptom-free – tuberculosis infection are protected from active disease by a critical early step in their immune response, researchers say.

The model also shows, however, that some TB bacteria can !nd a way to get around that protection, which helps explain how latent infections turn into active and transmissible disease.

More than 2 billion people worldwide are thought to be infected with TB bacteria, and an estimated 1.3 million people died of TB in 2012. People who are infected can harbor the bacterium without symptoms for decades, but about one in 10 will develop active disease characterized by a chronic cough and chest pain. "Many people in the United States think of TB as a distant disease that doesn't pose much of a threat. But the recent discovery of latent infections in Kansas schoolchildren who had contact with a single actively ill patient shows how widespread infection can occur with minimal exposure," said Larry Schlesinger, professor and chair of microbial infection and immunity at The Ohio State University and senior author of the study. "This research might help us better predict what puts people with latent infection at higher risk of later developing active disease."

In the study, scientists used human cells to create a model of a step in the immune response when immune cells gather together around a cluster of Mycobacterium tuberculosis cells, creating what is called a granuloma. Researchers have known granuloma formulation is vital to keeping TB at bay, but

haven't been able to observe cell behavior in these clusters until now.
Knowing more about the intricacies of this collection of cells could speed testing of experimental drugs and establish a new part of the immune response to consider targeting with therapies, said Schlesinger, also director of the Center for Microbial Interface Biology at Ohio State.
New therapies are badly needed because the antibiotics used to treat both active and latent infections are becoming less effective with the emergence of drug-resistant bacterial strains.
The researchers created granuloma-like structures in cell cultures by adding TB bacterial cells to human white blood cell samples from people with and without latent TB infection. The cells from people with latent infection started forming large clusters as early as four days after infection, while cells from uninfected people took longer to produce smaller protective structures.
Compared to samples from uninfected people, the granuloma model containing immune cells from people with latent infection was a more effective !ghter against bacteria in numerous ways: More immune cells were activated, and these cells controlled the bacterial load better. They also produced more protective proteins important to an immune response and were more capable of staving off the bacteria's efforts to use fatty acids and sugars for energy to help them grow.
But the study showed there is a downside to all of this heightened activity. Bacteria in these high-pressure immune environments were more likely to activate genes that let them adapt by changing their metabolism, giving the TB cells a place to thrive for the long term.
"This model using human cells provides evidence that there is an immune response generated during latency that reduces Mycobacterium tuberculosis growth and thus is host protective," Schlesinger said. "At the same time, we can see that bacteria are adapting early in this environment, suggesting that at least a subset can develop into what we call persisters. These persisters are the bacteria that would have the potential to reactivate later to cause active disease."
Source:

2. Oral swabs could be new frontier in TB diagnosis
Detecting the disease with a simple oral swab "could be a game changer for TB control because it could make diagnosis cheaper and easier," said Gerard Cangelosi, professor at the University of Washington.
Diagnosing TB conventionally involves collecting and testing a person's sputum - thick, gluey mucus coughed up from the lungs. Working with sputum samples is challenging due to the material's "horribly gloppy" nature, as Cangelosi called it. Sputum can hide pathogens from pathologists because it is difficult to dislodge bacteria from within the mucus' milieu, the study noted.
In search of a viable alternative to sputum samples, the scientists swabbed the mouths of 20 healthy individuals and 20 TB patients. Samples from patients with confirmed TB were taken in a clinic in South Africa. The control samples were taken from healthy individuals in Washington state. Lisa Jones-Engel , a research scientist at the University of Washington National Primate Research Center, advised the study team in applying the oral-swab method to human disease.
The researchers detected TB in oral swabs taken from 18 of the 20 confirmed patients. None of the samples from healthy volunteers tested positive. Previous efforts to test for TB in materials other than sputum, such as blood, urine or exhaled breath, have been limited by much lower accuracy, with detection rates typically below 50 percent, the study featured in the journal Scientific Reports, pointed out.
Source: Times of India, http://bit.ly/1Dj1Jox (05.03.2015)

3. Phase 2b trial results of novel TB regimen show potential to shorten treatment
A new tuberculosis (TB) drug regimen designed to improve options for TB therapy eliminated more bacteria from sputum than standard therapy and did so at a faster rate, according to data from a phase 2b clinical trial published today in *The Lancet*. These results are published just as the global phase 3 clinical trial, designed to bring this regimen through the last stage of testing, has begun.

PaMZ is a three-drug regimen comprised of two candidate drugs that are not yet licensed for use against TB: pretomanid (Pa), formerly known as PA-824, and moxifloxacin (M), and one antibiotic, pyrazinamide (Z), which is approved for use in TB treatment today. The therapy is intended for those patients whose TB infections are sensitive to the three drugs, including people with drug-sensitive and multidrug-resistant TB (MDR-TB).

"The results of this trial show the potential for the PaMZ regimen to improve treatment for tuberculosis," said Rod Dawson, MD, head of the Centre for TB Research Innovation at the University of Cape Town, South Africa, and lead author of the paper. "Especially noted is the fact that PaMZ may have a unique application as a potentially shorter, injection-free regimen for a select sub-group of patients with MDR-TB."

The Phase 2b trial, known as NC-002, tested PaMZ in an eight-week study that enrolled more than 200 patients and took place at eight sites in South Africa and Tanzania. Nearly twice (71 percent) as many TB patients treated with PaMZ had no TB in their sputum when cultured at the end of the 2-month course of the trial compared to patients treated with standard therapy (38 percent). These results are based on liquid culture, the most sensitive diagnostic method available.

Patients in the arm of the trial that tested the effectiveness of PaMZ on MDR-TB responded similarly to those with drug-sensitive TB. However, the study group for MDR-TB was small. When added to evidence from pre-clinical and earlier studies, PaMZ shows the potential to treat drug-sensitive TB and some patients with MDR-TB in four to six months.

"PaMZ is the first regimen under development to treat both drug-sensitive TB and MDR-TB," said Mel Spigelmen MD, President and CEO of TB Alliance, the trial's sponsor. "If successful, PaMZ could be a shorter, simpler, and safer treatment that would enable the scale-up of treatment."

Twenty percent of the TB patients enrolled in NC-002 also were co-infected with HIV. The PaMZ regimen appeared to be effective independent of HIV status.

Limitations in standard TB treatment remain a strong barrier to TB control. The treatment and cure of a typical case of drug-sensitive TB currently takes between six and nine months. People with drug-resistant TB require a minimum of 18 to 24 months of treatment. This more extensive therapy requires more than 14,000 pills and daily injections for at least 6 months. The long duration of MDR-TB treatment, combined with the pain and side effects that treatment causes, are major obstacles to access. Only 20 percent of all MDR-TB patients receive any treatment, and of those who do, less than half (48 percent) will be cured, according to the World Health Organization's 2014 Global Report.

On the basis of these and other data, TB Alliance and its partners have launched a global phase 3 clinical trial named STAND (Shortening Treatment by Advancing Novel Drugs) in patients who are currently considered to have either drug-sensitive or multidrug-resistant TB.

Enrollment has begun in the STAND trial. STAND researchers expect to enroll 1,500 patients in 15 countries in Africa (Kenya, South Africa, Tanzania, Uganda, Zambia), Asia (China, Malaysia, Philippines, Thailand), Caribbean (Haiti), Eastern Europe (Georgia, Russia, Ukraine), and Latin America (Brazil, Peru) in this study. PaMZ will be tested in STAND as a 4- and 6-month treatment for drug-sensitive TB and a 6-month treatment for drug-resistant TB, and also enroll those co-infected with HIV. Each patient will be followed for two years starting from the beginning of treatment. The STAND trial partners with many of the communities in which the study is conducted through its robust community engagement program.

If successful in this Phase 3 trial, the PaMZ regimen would eliminate the need for injectable drugs and reduce the cost of MDR-TB therapy by more than 90 percent in those patients whose TB organisms are sensitive to the three drugs. It also promises to be compatible with commonly used HIV drugs, helping the millions of people co-infected with TB/HIV.

Source: Medical Xpress, http://bit.ly/1ycAo7q (19.03.2015)

4. Anxiety and depression: The unseen burden of treatment-resistant tuberculosis

When Indian street-food seller Kumar Pal first began treatment for multi-drug resistant tuberculosis two years ago, he quickly spiralled into depression and gave up hope of living. Weighing just 35kg (77

lbs), shunned by his relatives and friends and in extreme pain due to the side-effects of a cocktail of medicines, 40-year-old Pal spent weeks in bed.

"I stopped taking the medicines. I was certain that I was going to die anyway. I worried about how my wife would manage with four children," says Pal, sitting in his two-roomed home in the maze of lanes in Sunder Nagari slum in north-east Delhi. "The health visitors gave me support... they used to tell me to take my medicines, do exercise, eat properly. It gave me hope for the future," says Pal, who now weighs 55kg and has recently been cleared of the disease.

Pal is one of hundreds of multi-drug resistant tuberculosis (MDR-TB) patients at St. Stephen's Hospital in Delhi who have been cured, aided by a unique programme providing psychosocial support to sufferers of one of the world's most deadly diseases. Despite a lot of progress over the past two decades, the bacterial lung disease TB, that is spread through coughs and sneezes, infected nine million people and killed 1.5mil in 2013, according to the World Health Organization (WHO).

"One of the things overlooked when it comes to curbing tuberculosis is the mental health problems of patients," says Joyce Vaghela, deputy director at St. Stephen's Hospital's Community Health Department. "The long duration of the treatment which can be more than two years, the adverse side effects of all the drugs and the social shame attached to the disease can cause patients to suffer problems like depression, anxiety, anger or even feeling suicidal... and they soon stop taking their medication." Vaghela says the hospital's home care mental health programme has treated over 400 patients with impressive preliminary success rates, proving that psychological support is crucial. Studies by the hospital in 2011 found 5.7 per cent of MDR-TB patients under the home care programme quit treatment compared to the national average of 23 per cent. The death rate under the programme was 6.9 per cent compared to the average of 23 per cent.

Each year India has 2.2mil new cases of TB, more than 300,000 deaths, and economic losses of US$23bil (more than RM84bil), prompting the nation's president to call for greater efforts to curb its spread, especially with the emergence of MDR-TB, a form resistant to front-line drugs that is hard and costly to treat. All cases of TB are hard to treat and require months of antibiotics. Symptoms include coughing, sometimes with sputum or blood, chest pains, weakness, weight loss and fever.

"TB is a major health problem which afflicts mainly the young and working population of our country. It is unfortunate that in India even today one person dies every two minutes due to this menacing disease," President Pranab Mukherjee says in a statement this week to mark World Tuberculosis Day. "There is urgent need to build public awareness about the curability and prevention of this disease."

Under a revised government TB control programme, patients must report to local TB centres six days a week to have their daily drugs administered but from the 19 million patients treated since 1993, only 3.4mil have been cured. Experts say more than drugs are needed as patients often lack employment, nutrition, decent housing, and good healthcare. "When TB is diagnosed, patients and their families must receive counselling, nutrition, and economic support," Zarir Udwadia, consultant physician at the P.D. Hinduja National Hospital in Mumbai, wrote in the *British Medical Journal*.

In Sunder Nagari slum, home to some 70,000 people, TB is common but still brings with it stigma and shame. Health workers report cases where patients are thrown out of their homes, sacked from jobs and ostracised by their community.

With no access to finance to support their families, a feeling of isolation and the harsh side effects of the drugs, patients can develop mental health problems.

"While the system is focused on the patient taking their medicines, no one stops to ask them how they are feeling inside," said Ravi Kumar Mishra, one of the eight home care health workers working in Sunder Nagari. "Many of the patients are depressed and feel hopeless. But we encourage them to continue. It's not easy but a relationship develops overtime and the patients learn to trust you and will phone regularly just to talk."

Under the programme which began in 2009, health workers fortnightly visit patients at their homes and advise and counsel them and their families about the disease and what to expect. Given the low incomes of many families, the hospital also provides supplies such as eggs and milk to patients who require a high protein diet and crèche services to help with day care. In some cases, health visitors

have also helped families gain access to government welfare schemes, soft loans and arranged skill development for family members of TB patients.
Doctors at St. Stephen's Hospital, which gets funding from the charity United Way Worldwide, say the mental health home care programme is effective and should be in the national TB programme.
"Mental health is the invisible burden of TB," said Vaghela. "Patients do not want to admit to having mental health issues and most doctors are too busy to deal with it. But if we want to end TB, we need to address this aspect of this disease."
Source: The Star Online, http://bit.ly/1Jnj7cA (26.03.2015)

Reportage

1. The day we discovered the cause of the 'white death'
Of all the infectious scourges that have prowled through human history, artists and writers have deemed tuberculosis to be among the most romantic. It is, after all, the disease that carried away the poet John Keats and the scribbling Brontë sisters. It rang down the final curtain on the lives of Molière and Chekhov. Mention the word "tuberculosis" and music lovers can almost visualize Frederic Chopin trying to compose a nocturne while violently coughing at the keyboard. And of course, who can forget those powerful closing scenes of Verdi's "La Traviata" and Puccini's "La Bohème," which both feature beautiful heroines struck down by TB?
In real life, tuberculosis is a messy, agonizing and debilitating ordeal. Once the tubercle bacilli gain the momentum to proceed unchecked through the body, there is little romance to be found. The experience of active tuberculosis is one of exhaustion, not literary inspiration; drenching bouts of sweating, not hypersexual allure; irritable groaning, not lyrical arias; a relentless cough punctuated with spurts of blood, not the lover's kiss. This is the nightmarish reality of what was once referred to as the "white plague" (in contrast to bubonic plague, or the "black death").
In many respects, the modern era of tuberculosis began in the mind of a 29-year-old German physician named Robert Koch, who in 1872 was appointed the district medical officer in Wollstein (a tiny village in West Prussia, now Wolsztyn, Poland). The Koch family lived in a four-room wooden-frame home, and the doctor's consulting area was situated in the house's parlor. Using a simple curtain to divide this room in half, Dr. Koch set up a laboratory that consisted of little more than a brand new, brass microscope he had specially ordered from Berlin, an incubator, sundry glass tubes, culture plates and retorts, and a camera he had rigged to the microscope to photograph the microbes he wished to study.
Like many young physicians of this era, Koch was struck by an intense fascination with all things microscopic, a fixation some medical critics derided as "bacteriomania." Unlike his senior colleagues who ascribed epidemics to the contamination of the air with foul or unpleasant emanations, a notion referred to as the miasmatic theory, Dr. Koch sided with those who would become the scientific revolutionaries of their day by asserting and ultimately proving that specific microbes were the cause of specific infectious diseases. Because Dr. Koch practiced in an agricultural district where wool production was a major industry, he saw his share of anthrax patients. Most of the cases he treated were what we call cutaneous anthrax, painful coal-black sores (hence, the name anthrax, from anthracite) on the fingers or hands resulting from physical contact with the microbes, which resided in the wool of the sheep they tended. In the most severe situations, or inhalational anthrax, the anthrax microbes entered the lungs of unsuspecting woolgatherers who soon succumbed to raging fevers, hemorrhaging and death.
Dr. Koch hypothesized that these workers were somehow ingesting a microscopic organism living on the hides of animal carcasses but his knowledge ended there. Helpless at his patients' bedside, Koch was determined to figure out anthrax's cause and, if possible, find a cure. So every evening, after the last patient left his consulting room, the young physician retired behind his curtain, sat at his makeshift laboratory bench, peered through the barrel of his microscope and conducted his search.

Within a few months after he began this work, and countless mice later, Koch had his answer. A microbe named Bacillus anthracis, he painstakingly determined, caused the disease of anthrax.
Serendipity is often one of the most important components of a scientific discovery, yet as another great bacteriologist, Louis Pasteur, often observed, “chance favors only the prepared mind.” Three physical characteristics of Bacillus anthracis favored Koch’s discovery. The microbe has a distinctive appearance under a microscope; it is a large germ that forms even larger and hardy spores that can survive almost any manner of physical manipulation; and it is relatively easy to grow in the laboratory.
Despite his remarkable achievement of scientifically linking a specific germ to a specific disease and the ringing endorsements of many illustrious professors across Europe, the young Dr. Koch was unable to find a university position that allowed him the time and facilities to pursue his research full-time. And so he remained in Wollstein for another four years, until 1880, when he was appointed government advisor to the Imperial Department of Health in Berlin.
It was there that Robert Koch began a series of path-breaking discoveries that led to his winning the Nobel Prize for medicine or physiology in 1905. With a superb laboratory, powerful microscopes and all the assistants, experimental animals and materials he could ask for, Koch decided to investigate one of the major killers of his day: tuberculosis. His research focus was quite controversial at the time because most experts insisted that tuberculosis was a hereditary disease; after all, it did tend to “run” in families. Nevertheless, Dr. Koch was convinced that TB was infectious in nature. Working alone, without telling his colleagues, he locked himself in his laboratory every day for almost six months until he definitively isolated and figured out how to grow, or culture, the germ that we now know causes the disease: the tubercle bacillus, or Mycobacterium tuberculosis. Never a commanding lecturer, Koch had a thin, reedy voice and tended to interject his phrases with an annoying amount of “ums” and “ers.” But on March 24, 1882, when he presented his findings at a monthly meeting of the Physiological Society of Berlin, he did so with clarity and elegant logic. The medical men present were dumbstruck by Koch’s address. So spellbound and conscious of the fact that they were witnesses to scientific history, the audience could not even applaud, let alone engage in the traditional scientific attack on another colleague’s work. In the room that night was a 28-year-old dermatologist named Paul Ehrlich, who ultimately achieved great fame as the discoverer of Salvarsan 606, the first “magic bullet” against syphilis. Ehrlich later recalled the evening as “the most gripping experience” of his scientific life, and as soon as the lecture was completed he rushed home to his makeshift laboratory, where he spent the night developing a novel staining technique for the tubercle bacillus.
Seventeen days later, on April 10, 1882, Koch published his lecture, “Die Aetiologie der Tuberculose” (The Etiology, or Cause, of Tuberculosis) in the The Berlin Clinical Weekly. Given the deadly command this once mysterious disease had so long wielded over human beings, news of its cause was reported not only in all of the major medical journals of the day but also as front page news in leading newspapers all around the world. Within a few weeks, “Koch,” literally, became a household name.
Robert Koch went on to even greater heights when he discovered the cause of cholera and not a few lows, such as in 1890 when he announced a potential cure for tuberculosis he called “tuberculin.” It turned out to be not at all therapeutic, much to Koch’s embarrassment, but, in later years, tuberculin emerged as a diagnostic tool to determine those who were infected with the TB bacillus. Along the way, he made many more discoveries, mentored some of the finest bacteriologists of his era, and, in keeping with the rough and tumble world of academia, made quite a few scientific enemies.
Nevertheless, Robert Koch’s greatest evening unfolded some 133 years ago today, when at 39 he solved the riddle that had plagued doctors for centuries: what, exactly, caused tuberculosis? Although in the decades since that momentous night, modern medicine has developed an armamentarium of tools to diagnose and effectively treat this deadly malady, TB continues to stalk the planet with a vengeance. In 2013, more than 9 million people became ill with it and 1.5 million died of it, making tuberculosis one of the leading causes of infectious death in the world today (only HIV/AIDS kills more). And while global tuberculosis rates have been slowly falling since 2000, we still have much more work to do before the “white plague” truly becomes history. The great Robert Koch

would expect nothing less of the generations of talented microbe hunters who have followed in his illustrious path.
Source: PBS, http://to.pbs.org/1DUQDYB (24.03.2015)

2. 'How Unromantic It Is To Die Of Tuberculosis In The 21st Century'
As the Ebola epidemic in West Africa slows and falls from the headlines, there is a temptation among many to view this outbreak as an isolated event. In fact, the opposite is true. Ebola is the tip of a global health crisis: a crisis in our collective ability to deliver the essentials of modern medicine to those who need help the most, in the most timely and efficient manner.
Few diseases illustrate the ongoing nature of this crisis better than tuberculosis, a highly transmissible airborne infection that kills more than 1.5 million people every year. Many people think that tuberculosis — a disease often associated with 19th century Romantic-era poets or artists — has been eradicated. But this is not the case. In fact, the global burden of the disease is staggering.
Last year, 9 million people became sick with TB. That's more than the entire population of New York City falling ill with a disease that we have largely been able to cure since 1947. As one patient in Russia so eloquently put it a few years ago, "How unromantic it is to die of tuberculosis in the 21st century."
And although the disease is the biggest global killer of adults after HIV — hitting people at the most economically productive points in their lives — it also affects 1 million children each year.
Whereas diseases like Ebola kill swiftly and put on a horrific display of symptoms, TB consumes many of its unknowing victims over a long period. It often goes undiagnosed for months, if not years, while it multiplies in families and communities. Individuals who are sick spread the bacteria through the air. Without the correct treatment, more than 80 percent of people who fall sick will eventually waste away — coughing up blood while their bodies are ravaged by the disease — until they die.
In recent decades we've seen a surge in the number of people falling sick with strains of TB that are highly resistant to conventional treatment and that kill rapidly when left untreated. These strains — passed through the air on buses and trains, in hospitals and clinics, in places of work and in the very communities and households where people live — can be found almost everywhere, from China to Nigeria, from the U.K. to the U.S.
There is, however, an opportunity to change the course of this epidemic. More than a third of TB cases and almost two-thirds of drug-resistant cases are found in the BRICS countries — Brazil, Russia, India, China and South Africa, collectively seen as drivers of global economic prosperity and innovation that attract huge sums of foreign investment and that have burgeoning middle classes.
The BRICS countries must stop the spread of this scourge by investing in health care delivery systems that are able to find, diagnose and treat individuals exposed to and sick from TB. They must also put a priority on care for poor and vulnerable populations.
This is not news to health officials in these countries. In January 2013, the minister of health from each BRICS country gathered in India and announced they would put together a framework and collaborate on projects to expand access to treatment for tuberculosis and improve the quality of treatment. Little progress has been made toward this goal.
Stopping a TB epidemic is difficult but not impossible. New York City had an epidemic of the disease in the late 1980s, fueled by a rise in HIV, homelessness and underfunding of its public health system. At one point, the rates in parts of the city were as high as we see in India today, more than 200 cases per 100,000 people. Standard epidemic control approaches were followed: actively locating those already sick, putting them on the correct treatment immediately, using preventive therapy to protect individuals exposed to the bacteria, ensuring that patients received the clinical, economic and social supports that they needed to successfully complete therapy, and strengthening the local public health system so that it was able to deliver comprehensive care to patients outside the hospital setting. As a result, the epidemic was halted.
Similar successes have been achieved in places as far afield as Russia's western Siberian province of Tomsk. After the collapse of the Soviet Union, Russia faced an unprecedented TB epidemic, driven by

overcrowded jails and hospitals, medication shortages, and a breakdown in the state's ability to track and monitor cases. Like New York City, Tomsk embarked on a program of comprehensive care — creating patient-centered systems capable of delivering the correct therapy to people outside of the hospital setting — and successfully stemmed the epidemic.

In Tomsk, TB rates were cut in half over the past decade from roughly 120 per 100,000 population to approximately 60, and the number of deaths from the disease decreased by 80 percent from more than 25 deaths per 100,000 people to approximately five.

New York City, Tomsk and many other places have taught an important lesson: Even deadly airborne epidemics can be brought to heel if we put the correct health care delivery systems in place. Instead of pitting diseases against each other in a competition for global health dollars, we have to see today's epidemics as a harbinger of our collective failure to build 21st century health systems capable of rapidly responding to health threats new and old. This means recognizing that while having high-caliber hospitals is an essential part of a health system, it's not enough. In an age where preventable or treatable infectious diseases can spread rapidly around the globe and where large numbers of people suffer from chronic diseases that do not require hospital-based care, it is important to think about how to extend the diagnostic and therapeutic reach of our current clinic-based systems into the communities where patients live.

This challenge is as true for tuberculosis as it is for Ebola, diabetes and heart disease. And it is as true in London or New York City, as it is in Delhi, Durban, Monrovia or Moscow.

In facing tuberculosis, the BRICS countries have a remarkable opportunity to rethink how health care should be delivered in the years ahead. Proper epidemic control requires a robust health system capable of diagnosing and, where appropriate, treating patients outside of the hospital setting. In some places, this may involve community-based workers using computer-assisted mapping to identify where the most patients can be found; in others, it may involve mobile health clinics.

Such an approach will not only prevent unnecessary suffering and deaths from tuberculosis but will create better systems for addressing the communicable and noncommunicable diseases facing the world's population. We should make it unromantic to die of any treatable or preventable disease in the 21st century.

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