NEWSLETTER

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Internationale Nachrichten

1. Philippines 'winning' fight against tuberculosis

Based on 2010 health statistics, the Department of Health (DoH) said that TB ranked as the 8th leading cause of sickness and as the 6th leading cause of death. (...) Since 2013, the DoH has noted this marked decline in TB. The progress is linked with the achievements of the "directly observed treatment short-course" (DOTS) strategy adopted by the Philippines in 1996. TB cases and deaths have been reduced by more than 50%, from the 1990 baseline. The Philippines has developed and put in place the 2010-2016 Philippine Plan of Action to Control TB.

In 2011, rapid diagnostic tools to combat TB were introduced by the DoH TB experts in a bid to improve and lessen the turnaround time of multi-drug resistant TB diagnosis. The DoH has continuously expanded services for drug resistant TB cases, with at least one treatment center or satellite treatment center per province and highly urbanized city.

The success of the Philippines' national TB program is also due to the previous campaigns and efforts, such as the implementation of the DOTS Strategy or "*Tutok-Gamutan*," management of the multi-drug resistant TB, initiation of public-private mix DOTS, implementation of the TB in children program, the enhancements of DOTS through the adoption of the World Health Organization (WHO)-endorsed STOP TB strategy, and expansion of services to vulnerable groups like inmates and people living with HIV.

On a global scale, the WHO's "End TB Strategy" envisions a world free of TB with zero deaths, disease, and suffering. This sets targets and outlines actions for governments and partners to provide patient-centered care, pursue policies and systems that enable prevention and care, and drive research and innovations needed to end the epidemic and eliminate TB. The WHO is at the forefront of calling on governments, affected communities, civil society organizations, health care providers, and international partners to join the drive to roll out this strategy and to reach, treat, and cure all those who are ill today. The past several years have witnessed impressive progress in the fight against TB, with over 37 million lives saved globally. Despite these achievements, much more needs to be done. An estimated 1.5 million people still die of tuberculosis each year. TB also has devastating economic consequences for affected families, reducing their annual income by an average of 50% and aggravating existing inequalities, the WHO said. Controlling, managing, and eradicating TB is a "matter of social justice," fundamental to the WHO goal of universal health coverage.

All Filipinos afflicted with TB and every person with TB all over the world must be given equal and unhindered access to the innovative tools and services they need for rapid diagnosis, treatment, and care. The "End TB Strategy," adopted by governments at the World Health Assembly in 2014, is designed to drive action in three key areas: integrated patient-centered TB care and prevention for all in need, including children; bold policies and supportive systems; and intensified research and innovation.

Source: Business World Online, http://bit.ly/1JAQo23 (22.08.2015)

2. Kenya battles new Tuberculosis strain

Two patients in the last one year have been diagnosed with a new borderline strain of Tuberculosis (TB) in Kenya, The Standard on Saturday has exclusively learnt.

Known as pre-XDR TB, this strain is resistant to one form of the drugs used to treat Multi-Drug Resistant TB and could graduate to the more infectious form known as XDR-TB if left untreated.

Head of the National Tuberculosis, Leprosy and Lung Disease programme (NTLD) Enos Masini told the Standard on Saturday that the first case of a patient with unique strain of the respiratory disease was diagnosed last year and investigations done revealed that they were resistant to one form of TB medicines.

"This particular strain of TB is a stage between MDR-TB and XDR-TB (extensively drug-resistant TB) where the patient is resistant to either an injectable drug or a type of antibiotic called fluoroquinolone- the two key drugs used for MDR-TB treatment ," said Dr Masini noting that treatment for both MDR and XDR requires treatment with other drugs that are less potent, more toxic and much more expensive. "One of them began treatment for pre-XDR TB in May this year whereas the other is waiting for an additional new drug called bedaquiline to bolster his treatment," said Dr Masini adding that due to the specificity of the type of drug required to treat Pre-XDR TB of the respiratory disease, the drug takes longer to be available.

These two cases come at a time when Kenya is carrying out a national TB survey with the pilot ending tomorrow (Sunday) before the campaign kicks off nationally on 26th September beginning in Machakos and Kiambu Counties for ten days.

The national survey that seeks to identify challenges in testing and treating TB is the first since Independence to ascertain Kenya's actual TB burden and is expected to inform on more effective ways to prevent infections and recurrence. "The field team targets persons above 15 years and we are testing for TB by asking for sputum and x-rays and any cases of TB will be referred to treatment," said Dr Masini adding that 120 field workers are collecting the data in two counties simultaneously and expected to complete the exercise in eight to ten months. The target is 72,000 respondents from 47 counties in a campaign themed, 'Assessing Kenya's TB burden,' South Africa currently accounts for the highest XDR-TB in Sub-Saharan Africa with outbreaks being reported in various provinces since 2006.

Closer home, Kenya has had 5 cases of XDR TB; one was cured, two are on treatment and two died from the complications of this extreme form of TB that costs Sh2 million to treat per patient for a period of two years.

For MDR TB, Kenya has successfully treated 1,500 patients who were on treatment for at least 20 months for a treatment regime that included eight months of injections alongside oral medications at a cost of Sh1.5 million each. XDR treatment for TB takes two years at a cost of two million shillings to treat each patient. Globally, TB is a major public health problem with drug resistant strains of the disease threatening to destabilise its control and eventual elimination.

Source: The Standard, http://bit.ly/1PA9pHa (18.08.2015)

3. Quality Control Improves TB Rates

A new study shows that redesigning medical services for tuberculosis can dramatically reduce the death rate. The research was conducted in a local health district in the West African nation of Togo.

TB is blamed for two million deaths every year. Most of them are in developing countries. It's also the second leading cause of death among infectious diseases.

Over the years, TB and HIV have been closely linked because TB easily infects those with weakened immune systems. Also, new drug resistant strains of TB have arisen, often making treatment difficult and painful and sometimes ineffective. But a study in Togo reports a 10 percent drop in TB deaths following changes in services in the Lacs Health District. It's located in the country's southern Maritime Region.

Dr. Kossivi Afanvi works for Togo's Ministry of Health. He was health director of the Lacs District from 2008 to 2015. He said when he arrived there was much room for improvement in the treatment of

TB. “The treatment rate of tuberculosis was very, very low at 80 percent. And the death rate was very, very high at 13 percent.”
Afanvi is the lead author of the Togo study appearing in BMJ Quality Improvement Reports. He had received training from the Boston-based Institute for Healthcare Improvement, a non-profit organization. In 2012, Afanvi implemented – what’s called -- a System Quality Improvement Model in Lacs. “So, we decided to increase the treatment success rate to at least 85 percent and to reduce the mortality rate to five percent,” he said.Two years later, the program exceeded its goals. The mortality rate quickly fell from 13 to three percent. And by the time he took a new job early this year, he said there were no TB deaths in Lacs District.
There’s a hospital and more than 30 health clinics in Lacs. The model called for increasing TB screening in every location where there was a registered nurse. If a test is positive, it’s followed by intensive treatment. What’s more, screening was also done for HIV. Treating those infected with the AIDS virus can strengthen their immune systems and in turn make them better able to defend against TB.
Dr. Afanvi is now in charge of the neighboring Vo Health District, where he’s also implemented the System Quality Improvement Model. “In my new district, I decided to use the model to manage other programs. I came here in February and according to the immunization program the rate was at 75 [percent].But actually we are at 91 [percent] for vaccinating or immunizing children,” he said. And the TB death rate has also dropped sharply in Vo.
Afanvi has recommended to Togo’s Ministry of Health that the model be applied to the entire country. He’s working on a doctorate on public health using the quality improvement model. Dr. Afanvi is also seeking a fellowship at the Institute for Healthcare Improvement.
Source: Voice of America, http://bit.ly/1F2xWy8 (28.08.2015)

Forschung & Entwicklung

1. A novel toxin for M. tuberculosis
Despite 132 years of study, no toxin had ever been found for the deadly pathogen Mycobacterium tuberculosis, which infects 9 million people a year and kills more than 1 million.
Now, Michael Niederweis, Ph.D., professor of microbiology at the University of Alabama at Birmingham, and colleagues have described the first known toxin of this pathogenic bacterium. This toxin—Tuberculosis Necrotizing Toxin, or TNT—is the founding member of a novel class of previously unrecognized toxins present in more than 600 bacterial and fungal species, as determined by protein sequence similarity. Before the Niederweis discovery, those toxins were identified only as the "Domain of Unknown Function 4237."
Bacteria with those newly recognized toxins include Yersinia pestis, the pathogen that caused the bubonic plague known as the Black Death in Medieval Europe, and Listeria monocytogenes, one of the most virulent and deadly food-borne infections and the cause of Blue Bell Creameries recalls this year.
The lack of an identified toxin in M. tuberculosis had contrasted with nearly all other pathogenic bacteria whose toxins contribute to illness or death.
M. tuberculosis is notable for its survival inside macrophages, the immune cells that ingest and destroy infectious bacteria. The newly identified TNT, Niederweis says, plays a key role to induce necrotic death of the infected macrophage. Thus, TNT enables the M. tuberculosis bacteria to escape from the macrophage and disseminate to other host cells in a person infected with tuberculosis, thus contributing to the survival of M. tuberculosis and spreading the disease.
"The battle between M. tuberculosis and the human immune system to control the fate of infected macrophages is critical in determining the outcome of the infection," Niederweis wrote in the TNT paper. "The control of host cell death is of utmost importance for the survival, escape and dissemination of M. tuberculosis."

The paper, "The tuberculosis necrotizing toxin kills macrophages by hydrolyzing NAD," was published online Aug. 3 in *Nature Structural & Molecular Biology*.

How did this toxin evade discovery for more than a century? First, it is produced in vitro only in very small quantities—the Niederweis lab could detect it only in a cell culture filtrate that was concentrated 1,000-fold, equivalent to concentrating a gallon of milk to about one-third of a teaspoon. Second, the toxin is deadly only when it is inside the host-cell cytosol; if the toxin is in the bloodstream or is added to the culture medium of in vitro host cells, it has no effect. Third, the toxin has no similarities to any other known toxin.

Niederweis discovered TNT while searching for something completely different. He was hunting for outer-membrane proteins that can act as a door to let nutrients outside the bacteria pass through the extremely impermeable, outer-membrane barrier of M. tuberculosis. The Niederweis group thought they had found such a porin protein; but it had an unusual property—the end portion of the protein broke off after the pore formed in the outer membrane, and that end portion was extremely toxic, both in simple prokaryotic cells like bacteria and in the more complex eukaryotic cells of yeast, mammals and fish. In a paper published in *Proceedings of the National Academy of Sciences* in 2014, Niederweis said this discovery "challenges the paradigm that M. tuberculosis is one of few bacterial pathogens that does not produce toxins."

The current paper fully establishes this new paradigm by identifying the mechanism of TNT-induced necrotic cell death at the functional and structural levels. Like an optical illusion where at first one sees a vase, and it then appears to be two faces peering at each other, Niederweis initially he believed he had found an outer-membrane porin that lets nutrients in and carried an artefact. Now he sees the pore part of that protein as a bacterial autotransporter (similar to those seen in other bacteria) that exports its TNT protein cargo to the outside of the outer membrane. After that export is done, the transporter pore remains in the outer membrane.

The similarity of the tnt gene to DNA sequences in more than 600 other bacterial and fungal species will enable research on how this novel class of toxins may function in other pathogens, especially in microorganisms that depend on induction of necrosis to survive or spread.

In a laborious search for the molecular function of TNT, Jim Sun, Ph.D., a postdoc in the Niederweis lab, found that TNT hydrolyzes the essential co-enzyme nicotinamide adenine dinucleotide (NAD+). This explains why it kills every type of cell it is cloned into, because NAD+ is necessary for the cell's normal metabolism. Researchers were able to clone the TNT gene only by placing it next to an inducible promoter that tightly represses transcription until induced. The TNT enzyme hydrolyzes NAD+ inside of cells and in vitro. It is blocked by antibodies against TNT, and specific TNT point mutations that eliminate all enzymatic activity.

That noncatalytic TNT mutant is not able to kill macrophages, showing that the hydrolase activity is required for TNT-induced cell death.

If TNT were produced inside M. tuberculosis, it would kill the cell. Niederweis and colleagues found that M. tuberculosis, similar to the bacterial pathogen Streptococcus pyogenes, produces an antitoxin to its toxin. The TNT antitoxin binds to the toxin and blocks its hydrolase activity, thus making it harmless inside the bacteria. The researchers have named the antitoxin immunity factor for TNT (IFT).

Cloning the genes for both TNT and IFT into E. coli, where IFT protects the bacteria from death, allowed the researchers to produce milligram quantities of TNT and IFT. In a collaborative effort, Gino Cingolani, Ph.D., a professor from the Thomas Jefferson University, produced crystals of the purified protein complex and determined its molecular structure to an astonishing resolution of 1.1 Å in a matter of weeks. The TNT molecule is shaped like a grasping hand, with fingers on one side and an extended thumb on the other. The IFT fits into the TNT like a ball held in a hand.

When pathogenic M. tuberculosis grows inside a macrophage phagosome, the TNT rapidly gains access to the cytosol of the infected macrophage and hydrolyzes NAD+, depleting that essential co-factor. This initiates necrotic cell death through downstream signals that are not yet characterized.

Curiously, a literature search revealed that an uncharacterized, heat-stable NAD+-glycohydrolase activity in M. tuberculosis cell extracts had been described half a century ago, as well as an uncharacterized heat-labile inhibitor of that hydrolase activity. Several biochemical characteristics of TNT and IFT found by the Niederweis lab match those of the uncharacterized proteins described in the reports from the 1960s.
However, the lack of the modern equipment and antibodies of today, and the very low levels of TNT present in M. tuberculosis, prevented those researchers from finding the toxin.
Source: Phys.org, http://bit.ly/1Uh3XcX (05.08.2015)

2. Tuberculosis R&D "grossly insufficient" according to new report
The global tuberculosis response and TB research and development remain weak and inadequate despite approval of the first new TB drugs in decades and a new global strategy to reduce TB incidence and mortality, according to Treatment Action Groups' latest report.
With just $255 million spent on TB research and development each year, funding is currently just one-third of the annual target set by the Global Plan to Stop TB 2011-2015, the report says, forcing TB treatment researchers to do more with less.
"TB treatment researchers are making the most of what they have, cobbling together combinations and treatment strategies to better use existing medicine combinations and the few new and experimental drugs available," the report says.
There are studies underway testing new drugs in smarter combinations for shorter drug-susceptible TB regimens and multidrug-resistant TB regimens, "but for the most part, these research efforts won't bear fruit for years," the report says. "Drug sponsors are slow or unwilling to collaborate, pharmaceutical investment is minimal, and TB treatment trials remain lengthy."
Meanwhile, nearly half a million people develop multidrug-resistant TB every year but only one in three are diagnosed and one in five receives treatment, the report notes. While bedaquiline was approved nearly three years ago, fewer than 1,000 people have received it outside of a clinical trial, and fewer than 200 patients have received delaminid one year after approval, the report says.
TAG's pipeline report also provides an update on the antiretroviral pipeline, calling it "surprisingly encouraging."
Source: TB Online, http://bit.ly/1WWndAB (12.08.2015)

3. Heading Off The Looming Diabetes-Tuberculosis Epidemic
Tuberculosis (TB) has recently made headlines in the U.S. And news of these cases remind us once again that TB is far from conquered. This disease infects about 8.6 million people every year and kills 1.5 million, more than any other infectious disease except human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS).
Increasingly, TB's spread is fueled by rising rates of diabetes—as with HIV, diabetes weakens the immune system, making a person more vulnerable to TB infection and illness—particularly in emerging economies like India and China, which are the source for much of the TB seen in the U.S.
Globally, it is now estimated that 15 percent of people who develop TB are also living with diabetes — equating to over 1 million people worldwide. We appear to be ignoring this trend at our peril. TB and diabetes need to be addressed together — immediately. If not, this problem will grow to epidemic proportions and ultimately claim the lives of millions.
Diabetics have difficulties in processing insulin. This dysfunction weakens their immune system and makes them more susceptible to contracting TB, which is an airborne bacterial infection. Most people living with a TB infection never develop the full-fledged disease. But a weakened immune response makes it easier for TB bacteria to turn "active," making it contagious and potentially fatal.
In fact, having diabetes increases a person's chances of developing the fully fledged TB disease by two to three times. And global diabetes rates are rapidly rising. Over the next three decades, the

total number of people with this illness is expected to jump from just under 400 million to nearly 600 million. That rise will fuel TB's spread.

Already, countries with the highest TB rates are also suffering from severe diabetes burdens. Sub-Saharan Africa, for example, has the highest concentration of TB in the world. And over the next two decades, the region's diabetes rates are expected to jump by over 100 percent.

Likewise, over half of the countries predicted to have the highest diabetes rates by 2035—China, India, Brazil, Indonesia, Pakistan, and Russia—also have the highest rates of TB. These are countries with historically high prevalence of latent TB infection, have large urban centers that facilitate transmission of TB disease, and are experiencing the changes in diet and lifestyle that predispose individuals to diabetes. In some parts of India, evidence suggests that one out of every five people with TB also has diabetes.

It's evident that the global diabetes epidemic now threatens to undermine the tremendous progress we've made against TB. Since 1990, the global TB mortality rate has been cut by almost half. This pernicious cross-partnership threatens to boost it back skyward.

The global health community must act. And the first step is for health care providers in high TB areas to implement what's called "bidirectional" screening. This protocol simply requires that any patient that tests positive for TB be referred for diabetes testing, and vice versa. This ensures patients suffering from TB and diabetes receive the proper treatments. Their diseases can be managed and prevented from accelerating negative effects.

Global health officials have witnessed such a deadly partnership before. Back in the early 90s, TB and HIV/AIDS worked together in a similar way, with the latter weakening people's immune systems and making them more susceptible to infection. HIV/AIDS helped quadruple the number of TB cases in many parts of Africa.

Despite ample evidence of this relationship, international officials failed to act quickly. It took years for them to mobilize. Finally, the World Health Organization declared an emergency, integrated its treatment protocols, and started to drive down infection rates. The solution was straightforward and essentially mirrors the bidirectional screening now needed for TB-diabetes: provide HIV counseling and testing for people diagnosed with TB, provide TB screening for people living with HIV/AIDS, followed by appropriate care that is convenient for patients to access.

There was a severe human cost to this lag. Poor countries suffered greatly. In Swaziland, which has the world's highest rate of TB-HIV co-infection, average life expectancy dropped from 59 years in 1990 to a low of 46 years in 2004.

In November, the Indonesian Ministry of Health, together with the World Diabetes Foundation, the International Union Against Tuberculosis and Lung Disease, and leaders from the United States and other countries will co-host a summit in Bali to catalyze the action needed to fight TB and diabetes together. They'll take lessons learned from health officials in countries like India, which has begun piloting bidirectional screening, so they can replicate those activities in their home countries. In southern India especially, clinics have begun reporting high yields of patients diagnosed with diabetes and TB through bidirectional screening. By convening now, these leaders are attempting to do something that we see too little of these days: to get out in front of a looming epidemic before it does its worst damage.

The global health community must not let history repeat itself. The relationship between diabetes and tuberculosis is clear. Now is the time for action, starting with bidirectional screening in places where it's needed most.

Source: Voice of America, http://bit.ly/1F2xWy8 (28.08.2015)

Reportage

1. **The digital game that could cure TB**

A unique collaboration between two Scottish universities has produced a digital game that fights tuberculosis. A team of undergraduates from Abertay University in Dundee has created Sanitarium, a game that invites people to play doctor. Using scarce resources they must treat as many TB patients as they can.

Behind the game lies a mathematical model developed at St Andrews University that uses data from human interactions to simulate a drug trial. The data collected by the game could help deliver new drug treatments to the developing world quicker and cheaper than ever before.

Tuberculosis (TB) is a global killer that is increasingly resistant to antibiotics. The global TB Alliance has been formed to fight it. Prof Stephen Gillespie, who holds the Sir James Black chair of medicine at St Andrews University, is part of that fight. "For a lot of the poorer parts of the world it remains a common problem," he says. "There are about eight million new cases ever year and about two to three million deaths."

Innovative approaches are called for. Which is why Professor Gillespie found himself issuing a brief to a group of third year computer game students at Abertay. They call themselves Radication Games.

Their task: to develop a game about curing TB in a virtual world that could lead to the same thing happening in the real one. Their first hurdle: to make a game people would actually want to play.

The team's lead programmer James Warburton led me through it. "The player is presented with a doctor screen - the doctor they'll be playing," he said. "It gives them information about how many patients they've got to cure and how many patients are still in treatment.

"On the next screen they get presented with a world map which represents patients as red dots across the world. "They're given three mini-games which diagnose and treat the patient." For lead artist Chris Box the task was to make the game attractive. He says: "The medical world is quite a dry subject, so we wanted to make it kind of pop and interesting so that people would want to pick it up and grab it. "That's been the challenge." And has he risen to it? He smiles: "I hope so. It's been received well."

For a typical third year student project, creating an engaging digital experience would be enough. But Prof Gillespie wanted more than a game. He says: "We're in the fortunate situation now that we're starting to see new drugs coming through for tuberculosis. "But each clinical trial costs more than $50m and there may be 100 different combinations. "We can't afford to do that many clinical trials.

"So if we can have a virtual clinical trial that tests the hypothesis whether that will work, we can select a smaller number of studies that are really worth doing and worth investing in." That is why, behind the game, there lies a mathematical model.

It has been developed at St Andrews to simulate drug trials, to cut the cost and length of the real things. At Abertay the Sanitarium team, led by game producer John Brengman, took on the task of building a game around that life or death research. "With the mathematical model we have analytics running in the background that basically takes all the information happening in the game," he told me. "And we can save that and segment that and give it to the scientists and doctors to look at later.

"But if they were to come up with a new treatment for tuberculosis and a new mathematical model, we could plug that into the game. "We could get players around the world playing it. And then we could take that new dataset, compare it to the old dataset, and there you have a simulated drug trial."

That's because the people who play the game add a vital element to the theoretical model: themselves. "The most difficult thing in a mathematical model is human behaviour," Professor Gillespie says. "We can use the people who're playing the game to mimic that behaviour."

For the team's sound designer Mazen Magzoub project Sanitarium has a special resonance. He's from Sudan. "There isn't enough medication," he says. "And even when there is enough medication the nature of living in Sudan does not allow the patient to continue (treatment) for the prescribed

period. "And that makes the tuberculosis bacteria tolerant towards that certain type of antibiotic. "That's basically the challenge in the developing world."
The Radication Games team intend to stay together after they graduate to continue developing a project which brings with it a special kind of job satisfaction. The success of most digital games is measured in money. For Sanitarium it'll be in how many lives it saves. And for Prof Gillespie, working with the games team has brought another more personal benefit. He says: "They're very, very talented in every respect as you can see from the game. "Even more talented: they make my research seem cool."
Source: BBC, http://bbc.in/1Jzwitn (27.08.2015)

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Globally, it is now estimated that 15 percent of people who develop TB are also living with diabetes — equating to over 1 million people worldwide. We appear to be ignoring this trend at our peril. TB and diabetes need to be addressed together — immediately. If not, this problem will grow to epidemic proportions and ultimately claim the lives of millions.
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In fact, having diabetes increases a person's chances of developing the fully fledged TB disease by two to three times. And global diabetes rates are rapidly rising. Over the next three decades, the total number of people with this illness is expected to jump from just under 400 million to nearly 600 million. That rise will fuel TB's spread.
Already, countries with the highest TB rates are also suffering from severe diabetes burdens. Sub-Saharan Africa, for example, has the highest concentration of TB in the world. And over the next two decades, the region's diabetes rates are expected to jump by over 100 percent.
Likewise, over half of the countries predicted to have the highest diabetes rates by 2035—China, India, Brazil, Indonesia, Pakistan, and Russia—also have the highest rates of TB. These are countries with historically high prevalence of latent TB infection, have large urban centers that facilitate transmission of TB disease, and are experiencing the changes in diet and lifestyle that predispose individuals to diabetes. In some parts of India, evidence suggests that one out of every five people with TB also has diabetes.
It's evident that the global diabetes epidemic now threatens to undermine the tremendous progress we've made against TB. Since 1990, the global TB mortality rate has been cut by almost half. This pernicious cross-partnership threatens to boost it back skyward.
The global health community must act. And the first step is for health care providers in high TB areas to implement what's called "bidirectional" screening. This protocol simply requires that any patient that tests positive for TB be referred for diabetes testing, and vice versa. This ensures patients suffering from TB and diabetes receive the proper treatments. Their diseases can be managed and prevented from accelerating negative effects.
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making them more susceptible to infection. HIV/AIDS helped quadruple the number of TB cases in many parts of Africa.

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Source: Health Affairs Blog, http://bit.ly/1Jif7fO (22.08.2015)

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