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## Internationale Nachrichten

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### 1. Remove TB stigma to better fight the disease

Tuberculosis, or TB for short, is an ancient disease of man caused by the bacterium *Mycobacterium tuberculosis*, first discovered in 1882 by the celebrated German microbiologist Robert Koch.

It is in many ways a slow infection. TB is typically spread by prolonged and close contact with a person with active pulmonary (lung) TB. The majority of infected persons clear the bacterium spontaneously, while a minority contain it without any outward manifestation of the disease. This is termed latent TB, which is non-infectious.

Only a minority of persons with latent TB progress to develop active symptomatic TB in their lifetime, usually months to years after the original exposure. Because the most common presenting symptom of active TB - coughing - is shared by many other viral and bacterial infections, the disease is often diagnosed late, giving the bacterium further opportunity to spread despite its relative inefficiency at doing so.

Singapore has been a model for TB control, reducing the incidence of this contagious airborne disease almost tenfold between 1960 and the mid-2000s. However, the local burden of disease remains significant, with 1,498 newly diagnosed cases of active TB among Singapore residents last year. The challenges of maintaining and improving on past results are manifold, and include ensuring that persons with active TB complete a protracted (usually six months) course of a cocktail of anti-TB drugs, as well as improving on contact investigations - a process to identify persons who have been exposed to the TB germ and are at high risk of infection.

Comprehensive contact investigation helps prevent further spread of TB by offering a window of opportunity for preventive treatment of infected individuals prior to the development of active contagious TB. However, the public fear and stigma of TB in Singapore has not fallen to the extent that persons with active TB infection will divulge their close contacts or voluntarily ask these people to go for TB screening for fear of being identified and stigmatised.

Multidrug-resistant TB (MDR-TB) is a term used to describe a drug-resistant form of the infection where the two "backbone" drugs of the anti-TB cocktail - isoniazid and rifampicin - are no longer effective against the bacterium. The phenomenon of MDR-TB did not arise spontaneously, but is a consequence of numerous instances of incomplete adherence to TB treatment, facilitated in several parts of the world by the rising HIV epidemic in the 1980s to 90s.

MDR-TB compounds the challenges of TB control drastically. Treatment of active MDR-TB infection results in lower success rates compared with drug-susceptible TB despite a treatment regimen that is more toxic, costly and which takes twice as long to complete. For persons with latent MDR-TB infection, there is also insufficient evidence that preventive treatment is effective. Singapore is fortunate in that our MDR-TB rates have remained low, at less than 1 per cent of all TB cases last year. The majority of our MDR-TB cases are imported, with no reported subsequent secondary infections locally.

Given what we know of TB, the recent cluster of cases at a Housing Board block in Ang Mo Kio is



unique for several reasons. Firstly, it is MDR-TB, which escalates the stakes for prevention of further transmission. Secondly, the infected persons appear not to have any focal point of prolonged close proximity usually necessary for the transmission of TB.

Many would presume that the TB transmission occurred in common lifts or because of the "crowded" living conditions in an HDB block. However, if such assumptions are true, we would have seen more reported TB case clusters in apartment blocks previously. Yet, according to the Singapore Tuberculosis Elimination Programme's registry, with the exception of case clusters within a single household, less than 2 per cent of TB clusters (defined via molecular fingerprinting of the bacterium) over the past 10 years actually share identical housing block addresses. That living in the same apartment block is not a risk factor for the spread of TB is also borne out by international experience. Moving forward, the unique features of this Ang Mo Kio MDR-TB cluster warrant more detailed and extensive investigation in order to determine how it has occurred as well as to identify others who may have been infected.

We need better public education and communication to increase awareness of TB, and remove the stigma from TB, which in turn will lead to better contact investigations and reduction of the spread of the bacterium. Better community support, especially from employers, will be welcome and will help improve treatment adherence of patients on anti-TB therapy, which will reduce the risk of the emergence of drug resistance.

**Source:** The Straits Times, <http://bit.ly/29ahOXQ>, 17.06.2016

## **2. Antibiotic Resistance Requires Global Response Similar to AIDS, Climate Change**

Addressing antibiotic resistance will require a global political response similar to the way the world has reacted to climate change or HIV / AIDS, Sweden's Minister of Public Health Gabriel Wikstrom, told IPS recently. "(These problems) began with a small group of experts discussing and trying to warn the rest of us and it was not until it was politically addressed that it really became an issue that was solvable."

"Of course (with antibiotic resistance) we have many technical issues still to solve, and medical issues, as well but it's foremost a political issue," said Wikstrom.

Antibiotics have helped extend the average person's life by 20 years, yet by failing to use them with care we have already begun to render them useless.

Heads of State and Government will discuss the pressing issue of the decreasing effectiveness of antibiotics at a high level meeting scheduled to take place at the UN in September.

Earlier this week, experts and political leaders from the health, agricultural and economic sectors spoke at an event convened by the UN's Every Woman Every Child at the Yale Club of New York about what needs to happen at the September summit.

"What is clear is that all countries around the world need to stop treating antibiotics as if they are sweets," Lord Jim O'Neill, Chairman of the Review on Antimicrobial Resistance (AMR) told IPS. "It's true in humans, and it's true in agriculture."

Incorrect use of antibiotics in both humans and farm animals is contributing the rapid increase in bugs which are resistant to the drugs we currently have.

A study led by O'Neill has found that if the problem is not addressed an additional 10 million people will die every year by the year 2050.

The fact that no new antibiotics have been found since the 1980s makes these new drug resistant infections even more worrying, says Sally Davies, the United Kingdom's Chief Medical Officer.

"We've essentially got a dry pipeline of no new drugs coming through," Davies told journalists at a press briefing here, Tuesday.

Already 700,000 people already die every year from drug resistant infections, a low estimate, according to the report.

One of the diseases which is most linked to drug resistance is Tuberculosis (TB). According to the WHO an estimated 480 000 people developed multidrug-resistant TB in 2014.

Aaron Motsoaledi, Minister of Health of South Africa and Chair of the Stop TB Partnership told



journalists that the only drugs available to address multidrug-resistant TB are extremely toxic, and that even after long courses of these drugs, there is only a 50 percent cure rate, Addressing drug resistant TB requires both investment in new drugs and investment in health care systems in developing countries, said Motsoaledi.

“It is a market and moral failure at the same time for most pharmaceutical companies not to be investing in finding effective cures for this world leading cause of death from infectious diseases,” he said.

Motsoaledi added that AMR is not the only emerging global problem putting additional strain on healthy systems in developing countries and their ability to address infectious diseases.

“It’s not only AMR that might come ... it’s also climate change, we’re not sure what it’s going to be bring, (and) we’re encroaching on the habitats of other organisms in the animal kingdom,” said Motsoaledi, in a possible reference to Ebola.

Strengthened health care systems can help address AMR by preventing infections, through measures such as immunisation, hygiene.

Training more doctors and nurse will also lead to the more appropriate use of antibiotics. However Davies emphasised that appropriate use does not necessarily mean reduced use overall.

“We must not forget that at this time more people die because they didn’t get access to the appropriate antibiotic than because of resistance so it is also a development issue.”

Taking less than the full course of antibiotics can also lead to resistance. In her book, *The Drugs Don’t Work*, Davies describes how bacteria become resistant to drugs when a person doesn’t take antibiotics for long enough. If the drugs are not given enough opportunity to fully kill the bacteria it may survive while also learning how to resist future treatment with the same drug. This is why it is important that antibiotics are only taken exactly as prescribed by a trained medical professional. (...)

Addressing AMR requires the health and agricultural sectors to work together, said Wikstrom.

However around the world, lack of regulation in the agricultural sector has seen antibiotics abused as growth hormones or as prophylaxis.

“All too often around the world antibiotics are used for growth promotion in animals,” said Davies.

Resistance to one powerful antibiotic, Colistin, which has been used in the agricultural sector, has recently reached the United States, after beginning in China.

Despite the importance of such drugs there are no global agreements around their use in agriculture, something which may potentially change at the UN meeting in September.

Any potential global regulations should be able to draw on positive examples from countries which have successfully regulated the use of antibiotics in farming.

Countries like South Korea and the Netherlands, show that it is possible to regulate antibiotic use on farms without having an economic impact on the agricultural sector, says O’Neill.

It is also important to remember that small holder farmers are particularly vulnerable to the global consequences of AMR because they live and work closely with animals, Carla Mucavi, Director of the Food and Agriculture Organization (FAO) New York Office told IPS.

**Source:** Inter Press Service, <http://bit.ly/1YnmaLr> (14.06.2016)

### 3. India - Medicos trained on use of new TB drug

With a new drug – Bedaquiline – all set to be rolled out as part of the treatment regimen for patients with Multi-Drug Resistant (MDR) Tuberculosis, district TB officers, medical officers and workers involved in TB control are now being trained in the implementation of this additional drug.

On Tuesday, 64 persons from six districts – Vellore, Tiruvannamalai, Krishnagiri, Dharmapuri, Salem and Namakkal – participated in the Bedaquiline implementation training held at the Government Vellore Medical College Hospital (GVMCH), Adukkamparai.

Raja Sivanandam, deputy director of medical services (TB control), Vellore said that patients suffering from MDR TB would have the benefit of this additional new drug – Bedaquiline – in their existing treatment regimen soon.

“After the discovery of streptomycin in 1940s and Rifampicin in 1960s, there was no major



breakthrough in the discovery of new drugs for the treatment of TB. After a lull for so many decades, recently, Bedaquiline holds out tremendous promise to TB patients," he said.

He pointed out that the new drug is seen to enhance culture conversion rate, thereby improving the cure rate of MDR TB. As of now, there are 108 patients with MDR TB in Vellore district.

"When patients with normal type of TB fail to get cured with conventional first line anti-TB drugs and return culture positive, they move on to the next stage of MDR TB, that is they are found to have developed resistance to the two principal drugs," he explained.

MDR TB, which continues to remain a challenge to healthcare providers in TB control, has a cure rate of 50 per cent and attrition rate of 30 per cent in the district, he added.

With Bedaquiline, he added that they would be able to do away with attrition rate, boost culture conversion rate and improve cure rate.

The Central TB Division, New Delhi had given its nod for launching Bedaquiline at six places in India – two in New Delhi, Assam, Gujarat, Maharashtra and Tamil Nadu.

Dr. Sivanandam said it was proposed to extend the drug implementation in all districts of the State.

After getting administrative, legal and ethics clearance, training in the implementation of conditional access programme under the Programmatic Management of Drug Resistant Tuberculosis (PMDT) has been completed at the national and State level.

Regional level implementation trainings were being conducted, with the one-day training for Vellore zone (comprising six districts) held on Tuesday.

The training programme focused on how to administer the drug to patients, problems that the medical personnel could encounter, adverse reactions, monitoring of patients, safe delivery of drugs for optimal use to control MDR TB.

District-level training would be organised and implementation of the drug in PMDT would be launched soon, he added. E. Theranirajan, head, Department of Paediatrics, GVMCH inaugurated the training programme.

**Source:** The Hindu, <http://bit.ly/295cHSz> (08.06.2016)

#### **4. Diabetes patients will now be tested for TB**

CHENNAI: Patients who test positive for diabetes at government facilities will now also be referred to undergo examination for tuberculosis. The new guideline was recently framed by the central TB division after studies showed that people with diabetes have 2-3 times higher risk of contracting TB. At present, under the revised national tuberculosis control programme (RNTCP), TB patients are asked to check their sugar levels too. Through the new framework, health officials hope to detect more TB cases.

"Our estimation of people suffering from the bacterial infection is 22 lakh, but we are able to reach only 14 lakh patients. We don't know if the 'missing' population is getting the right diagnosis and treatment," said Dr Sunil D Khaparde, deputy director general in the ministry of health and family welfare, who also heads the central TB division. As a pilot project, the new framework was implemented in 100 districts across India.

Dr Khaparde, who was in the city to deliver the 31st edition of Professor Viswanathan Medical Oration on Sunday, said the guidelines will be followed by all government facilities with the RNTCP setup.

A recent study by Dr Vijay Viswanathan, chief diabetologist at M V Hospital for diabetes, and University of Massachusetts Medical School, found that 54.1% of the 209 patients they surveyed with pulmonary tuberculosis were diabetic, while 21% were pre-diabetic. "According to data, every fourth person has latent TB, which surfaces when the immune system is weak," said Dr Viswanathan. Diabetes, he explained, increases the risk of progression to active TB disease in people infected with Mycobacterium tuberculosis, the bacteria that causes TB. Conversely, TB has an effect on diabetes. It can not only worsen blood sugar control but also complicate clinical management of diabetes.

Dr Khaparde said earlier studies had shown that treatment failure rates of tuberculosis patients were higher if they had poorly-controlled diabetes. Chennai is estimated to have a diabetes prevalence of



18.5%, and TB prevalence of 0.25 %. "Although the evidence on the link between TB and diabetes has been around for a while now, it has been assessed and consolidated only recently. Now we have compiled enough evidence, and need to act fast and implement bidirectional screening," said Dr Khaparde.

**Source:** The Times of India, <http://bit.ly/29aA6Xo> (20.06.2016)

## 5. European Members of Parliament convene to accelerate political progress against tuberculosis

Parliamentarians from 12 European and Central Asian countries convened in Bratislava from 24-26 June for the European TB Summit, issuing a united call for governments to put tuberculosis (TB) back on the political agenda.

This inaugural meeting of the Eurasian Parliamentarian Group on TB brought together 15 Members of Parliament (MPs) from 12 countries to discuss one of the most pressing health threats to the European Region: TB. Despite widespread belief that TB is no longer a threat in Europe, the region has the highest rate of multidrug-resistant tuberculosis (MDR-TB) in the world, comprising 25% of all MDR-TB cases globally. That fact, coupled with the rising rate of HIV in Europe and diminishing political and financial support, puts the region at greater risk of suffering a serious – and preventable – resurgence of TB.

Representatives from The Union, the Stop TB Partnership and civil society joined together to drive home these points, and underline the urgency of the situation to the MPs in attendance.

Co-chaired by MPs Dr Stephan Albani, Germany and Dr George Khechinashvili, Georgia, the summit engaged the MPs in open discussion about the reality of TB in Europe. MPs visited a homeless shelter, which highlighted issues of TB infection and the difficulties of infection control amongst vulnerable populations, and had the opportunity to speak to TB clinicians in a lung disease clinic.

The event culminated in the signing of a European Call to Action, which urged Slovakia to use its Presidency of the EU Council to prioritise TB and facilitate discussion on TB and MDR-TB throughout the EU. All 15 MPs pledged their support to return to their countries, speak to their colleagues about TB and push for increased government action.

The Summit was held immediately after The Union Europe Region Conference, which was attended by over 600 delegates, including government representatives, healthcare professionals, medical experts, TB survivors and organisations.

The Union has supported the Global TB Caucus since its inception in Barcelona at the 45th Union World Conference on Lung Health.

**Source:** The Union, <http://bit.ly/29dFdp9> (30.06.2016)

## Forschung & Entwicklung

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### 1. Faster detection of pathogens in the lungs

What used to take several weeks is now possible in two days: Thanks to new molecular-based methods, mycobacterial pathogens that cause pulmonary infections or tuberculosis can now be detected much more quickly. Time-consuming bacteria cultures no longer need to be taken from the patient samples, meaning that a suitable therapy can be started quickly.

Mycobacteria cause various illnesses. Mycobacterium tuberculosis, the main representative of this genus, is the causative agent of tuberculosis, which killed around 1.5 million people worldwide in 2014. Nontuberculous mycobacteria can trigger pulmonary infections, lymph node infections and skin diseases in patients with compromised immune systems. On account of more and more people with chronic lung diseases and the success of transplants, these difficult-to-treat infections have been on the rise continuously in recent decades.

(...) A research group from the Institute of Medical Microbiology at the University of Zurich and the National Centre for Mycobacteria used a large-scale study with more than 6,800 patient samples to examine molecular-based methods for the detection of mycobacterial pathogens. Because many



mycobacteria only grow at a very slow pace, routine detection using bacteria cultures in highly specialized and expensive high-safety labs takes several weeks to complete. The subsequent susceptibility test to determine the appropriate medicine also takes one to two weeks. "For patients and doctors, this long waiting period is an unnecessary test of their patience", says Dr. Peter Keller from the Institute of Medical Microbiology at the UZH. "By comparison, with molecular detection methods, most patients know after one or two days whether they have an infection with tuberculosis pathogens or with nontuberculous mycobacteria."

For their study, the researchers developed a diagnostic algorithm to detect mycobacteria directly from the patient sample using genetic analysis. With this ultra-fast molecular detection method, the patient samples were examined continuously over three years and compared with the results from the bacteria cultures for more than 3,000 patients. The new molecular-based methods were found to be just as accurate as the lengthy culture-based techniques used to date. (...)

In addition, the molecular analysis makes it possible for the first time to also detect the nontuberculous mycobacteria directly from the patient sample within just a few hours. This means that suitable therapeutic measures can be initiated much more quickly. By contrast, if the patient has a tuberculosis infection, a further molecular assay is carried out to test susceptibility to the main tuberculosis drugs "rifampicin" and "isoniazid". "This also showed that the molecular-based method reliably predicts the culture-based resistance results. It is possible to obtain certainty much sooner of whether the therapy with standard medicines chosen is likely to be successful", explains Keller.

**Source:** Medical Xpress, <http://bit.ly/297IFzF> (24.06.2016)

## 2. UQ research hones in on new TB drugs

University of Queensland scientists are honing in on drug-resistant tuberculosis (TB) in a project which could lead to new antibiotics.

The UQ team has identified four new classes of compounds which act against TB bacteria, and hopes commercialisation activities could begin within two to three years. Dr Antje Blumenthal from the UQ Diamantina Institute (UQDI) said the team would now build on that research by prioritising and optimising the most promising potential drug candidates.

"This will include an assessment of these compounds to identify which are the most effective, safe and unlikely to be compromised by drug resistance," Dr Blumenthal said. Professor Rob Capon from UQ's Institute for Molecular Bioscience said the compounds were identified by screening thousands of extracts from microorganisms and marine organisms.

"Activity against TB bacteria including multi-drug-resistant strains is being confirmed," Professor Capon said. "Importantly, these new chemicals hold out the prospect of acting in new ways against TB, so they are not compromised by existing drug resistance mechanisms."

TB remains a global health emergency with nine million new cases of active disease and 1.5 million deaths registered every year.

Current treatment for TB is a combination of four drugs developed in the 1940s and 1960s which have significant side effects and must be taken for at least six months to achieve a cure. Dr Blumenthal said this contributed to poor patient compliance, particularly in the developing world. "That is why we are seeing recurring disease and multi-drug-resistant TB becoming such a serious problem," Dr Blumenthal said.

The Australian Government Australian Tropical Medicine Commercialisation program has co-funded \$250,000 for the \$500,000 University of Queensland project.

Dr Blumenthal said the grant had come at a critical time. "Many innovative research discoveries do not become new drugs because of difficulties in funding pre-clinical and proof-of-concept studies, so we are excited that this support will enable us to conduct these critical studies."

Once the most promising candidates are identified, the UQ team will work with UQ's commercialisation arm UniQuest on options for drug development.

**Source:** The University of Queensland News, <http://bit.ly/28Su6lr> (22.06.2016)





### **3. Advocates commend Johns Hopkins University for pursuing a public health driven path for sutezolid's development**

In an open letter sent to Johns Hopkins University on May 31, 2016, TB advocates acknowledge and congratulate Johns Hopkins University's decision to enter negotiations with the Medicines Patent Pool (MPP) regarding the licensing of worldwide non-exclusive rights to sutezolid. Sutezolid is a promising candidate for the treatment of TB. The letter also commends the university for responding to requests from the TB community to pursue a public health driven path for sutezolid's development. "As the first academic institution to contribute to the MPP under its new mandate in TB, Johns Hopkins University is showing important leadership in global health. The inclusion of appropriate terms and conditions in the licensing agreement under negotiation will help to expedite the development of sutezolid, which has been stalled in phase II for several years, by enabling interested researchers and institutions to access and investigate sutezolid as a component of desperately needed novel regimens for TB; and if proven, ensure equitable access for TB patients and treatment providers."

**Source:** TB Online, <http://bit.ly/29iDQr3> (02.06.2016)

## **Reportage**

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### **1. Ending Tuberculosis in Afghanistan: working together towards a common goal**

Afghanistan is one of 22 countries with a high burden of tuberculosis (TB) according to the World Health Organisation (WHO). The estimated number of new cases each year is a staggering 53,000 and as many as 12,000 afflicted by this curable infection lose their lives each year. For a large number of those infected, a timely diagnosis and effective treatment is out of reach due to high levels of poverty, lack of access to effective healthcare, and ongoing conflict in large parts of the country. It is not a surprise that a significant number of victims are women and children due to their vulnerable status in a society ravaged by decades of war, drought and migration. Some of these challenges such as poverty and lack of access to healthcare facilities are not unique to Afghanistan, but it is the only country, out of 22 that account for 80% of TB cases in the world, that has been utterly decimated by over four decades of war and migration.

Despite the challenges, the Afghan government and its international partners have made some progress with the implementation of the National Tuberculosis Control Program (NTCP). In 2011 an estimated 97% of people had access to TB facilities. But access to facilities is one small part of the answer. The quality of diagnosis, treatment and outreach is much more important when dealing with one of the most persistent diseases known. The causative pathogen, mycobacterium tuberculosis, can remain in an asymptomatic form for a long time. Even after treatment is started, bacteria can easily develop resistance to drugs if they are not administered appropriately. In practice, this would mean patients have not been given the correct treatment regimens and there is no mechanism to ensure that the whole course of treatment is completed. This is particularly the case in the private sector where most patients present to for initial diagnosis and treatment.

The public health challenge of treating TB in Afghanistan is that most of those affected are extremely hard to reach, public awareness of the illness and its mode of transmission is very poor, and treatment programmes are quite ineffective giving rise to a large burden of multi-drug resistant TB (MDR-TB). According to WHO, in 2014, one in four of the estimated 480,000 people worldwide with a new MDR infection received a diagnosis. The persistence of the disease in Afghanistan is in part explained by MDR-TB as those with this strain can easily infect other people.

Treatment of MDR-TB has also been extremely difficult both for patients who have to endure a long and unpleasant treatment regimen but also for healthcare workers who must ensure patient compliance, broaden access to treatment and reduce transmission rates.

Fortunately, the recently updated WHO guidelines offers hope for patients in countries like Afghanistan with shorter, cheaper treatment regimens and rapid diagnostic tests. This is an



opportunity to focus all efforts on improving the quality of diagnosis as an important public health matter and tackling the MDR-TB through this novel treatment regimen with better reported success rates.

Inadequate treatment of MDR-TB is part of the problem in fact a big part. All stakeholders must work together to address the increasing prevalence of MDR-TB and the slow progress in its detection and access to care. MDR-TB cannot be managed through national programme alone without addressing the issue of private and other healthcare providers in Afghanistan. Initiatives such as the one by the WHO to engage all healthcare providers in the fight against drug resistant TB should be rolled out across the country. Evidence has consistently shown that in countries with high burden of TB engaging all healthcare providers working in partnership through Public-Private Mix (PPM) have improved all aspects of patient care including better case detection, improved treatment outcomes, increased cost-effectiveness and more effective outreach.

The hope is that by rapid diagnosis, shorter treatment regimen and involvement of all providers through PPM initiative, Afghanistan will make significant progress towards achieving the WHO's End TB Strategy.

**Source:** PLOS Blog "Speaking of Medicine", <http://bit.ly/292TS6X> (28.06.2016)

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