NEWSLETTER

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Inhalt

Internationale Nachrichten

1. Global Plan to Stop TB 2016-2020 Regional Consultation in Europe: Why we need to change now if we want to End TB

24 July 2015 – Istanbul, Turkey – The third regional consultation on the Global Plan to Stop TB 2016-2020 ended this week as participants gathered at the Global Plan to Stop TB & Eastern Europe and Central Asia Consultation on Sustainable Impact in Istanbul. The need for a change in policy and health systems in the Region in order to End TB was central to the main discussions during the two-day meeting. The meeting was opened by Professor Dr Eyup Gumus, Under-Secretary at the Ministry of Health, Turkey and was attended by Dr Mark Dybul, Executive Director of the Global Fund to Fight AIDS, Tuberculosis & Malaria, Dr Masoud Dara, Senior Advisor, WHO Office at European Union, Dr Paula Fujiwara, Scientific Director for The Union and Chair of the Taskforce for the Global Plan, in addition to Dr Lucica Ditiu, Executive Director of the Stop TB Partnership.

The first day was devoted to discussions and debates on the Global Plan to Stop TB 2016-2020 and the second day was dedicated to discussions on Global Fund investments, transition, sustainability and scale-up of TB and HIV interventions in the region. The current Global Plan represents the investment case and the advocacy tool of the first five years of the WHO End TB Strategy that goes up to 2035. As outlined by colleagues from WHO EURO, the European region has special challenges to face: high MDR and XDR-TB rates, lengthy hospital stays, and the need for changes in health, human rights policies including decriminalization, real civil society and community engagement. The participants suggested the need for rapid change in the way business is done in TB – giving the right voice and engagement of communities and civil society, including key populations, integration of TB/HIV interventions, boosting the human rights component and the need for a multidisciplinary approach in paving the way forward as well as putting the patients at the center of all interventions.

The group work-centred sessions focussed on several key issues. On MDR-TB, participants identified the importance of early diagnosis and universal access to DST, the importance of using present tools better, the need for new drugs and regimens as well as the crucial need for a change in policy and implementation. The need for proper human resources plans and actions was also outlined.

On health systems and financing, discussions centred around the importance of domestic funding, the need for programmes and activities to be backed by financial allocations, working with and involving other Ministries, more consideration given towards what could be decentralized care, as well as flexibility from the Global Fund for the eligibility of countries.

On Key Populations, the specific groups that need greater attention were identified and the role of NGOs as well as government agencies in reaching these groups were highlighted. Recommendations were made to collect disaggregated information on the priority groups to measure progress.

On innovation and research, much more needs to be done to improve both tools and systems in order to fast track the path from diagnosis to cure. Civil society have a key role to play here in demanding the creation, awareness, and facilitating the access and delivery of services. Health systems reform and innovative use of ICT systems were highlighted. The group also touched on

addressing infection control, social science research and preventive treatment research among others. The rich discussion in Istanbul concluded with topline comments around costing of the Global Plan, creating a real investment framework and making the case for priority investments. This third regional consultation follows the discussions and endorsement that was given at the inaugural regional consultation held in May in Addis Ababa, and then in Bangkok in June. The fourth and last regional consultation will be held in Buenos Aires, Argentina on 2 September.
The online public consultation of the Global Plan to Stop TB 2016-2020 is now open to everyone to share information, ideas and experiences, and, will run through 10 August 2015. Participants are very much encouraged to provide comments -- based on the top line questions asked -- on the introduction and the seven main chapters that make up the Global Plan.
The Global Plan will launch at the end of the year in Cape Town, South Africa at the 46th Union World Conference on Lung Health.
Source: Stop TB Partnership, http://bit.ly/1SB9xLM (03.08.2015)

2. Localized transmission significantly drives MDR-TB epidemic in Peru
Local "hot spots" of increased risk appeared to play a key role in disease transmission during a multidrug-resistant tuberculosis epidemic in Lima, Peru, according to recent data. In the population-based, prospective cohort study, researchers identified 3,286 patients aged older than 15 years with incident pulmonary tuberculosis (TB) diagnosed at one of 106 participating public health centers in Lima Ciudad and Lima Este between September 2009 and August 2012. Within 1 month of diagnosing TB in the index patients, the researchers visited their homes and asked all other household members to participate in a baseline assessment of TB infection and disease. These individuals were monitored for incident infection and disease for 12 months. Smear and culture were used to assess all index cases and suspected cases for TB disease. Using handheld GPS units, study nurses gathered spatial data on affected households. Strains were further tested from culture-confirmed cases for drug resistance, and extracted and genotyped DNA by 24-loci MIRU-VNTR. The researchers constructed maps illustrating per-capita rates of drug-resistant, drug-sensitive and MDR-TB at the health center level.
The overall per-capita incidence of culture-confirmed tuberculosis was 74.12 per 100,000 (95% CI, 71.59-76.61). There was significant geographic disparity in the per-capita rate of TB and the rate of MDR-TB across the 85 evaluated areas. Some health center catchment areas had especially high overall rates of TB and MDR-TB, and the most severely affected areas had per-capita disease rates that were much greater than those of the least affected area (Rate ratio = 89; 95% CI, 54-185). The researchers reported an average ratio of MDR to non-MDR cases of 0.12 (95% CI, 0.12-0.15). Overall, 12 of 35 of the largest genotypic clusters demonstrated patterns of spatial aggregation, indicating localized transmission. However, the researchers sometimes observed that most cases of a particular genotype fell outside a highlighted area of genotype-specific risk. "Our findings provide additional detail on the spatial distribution of MDR-TB and identify areas where transmission of particular genotypes appears to be spatially concentrated," the researchers wrote. "We also expanded on the results of previous analyses of administrative data which raised concerns about elevated risk of transmitted MDR-TB risk in Lima Este. We found that the increased risk of MDR due to transmission associated with living in this area was comparable to the increased risk of MDR associated with previous TB treatment in the study population as a whole."
Source: Healio, http://bit.ly/1K0ViG6 (30.07.2015)

3. Study finds strong link between diabetes and TB in tropical Australia
A 20-year study by James Cook University scientists has found a strong link between diabetes and tuberculosis in tropical Australia.
Despite massive improvements in sanitation and antibiotic coverage over the last century, TB still remains the leading bacterial cause of death worldwide. Previous studies conducted in developing countries where TB is endemic have demonstrated the connection between the two diseases. But

the study by JCU and Townsville Hospital researchers, published in the *American Journal of Tropical Medicine and Hygiene*, has for the first time established a connection between diabetes and TB much closer to home.

Scientists looked at data from the Townsville Hospital over a 20-year period (1995-2014) and found patients with diabetes were much more likely to develop TB than the general population. The study also revealed Indigenous Australians and overseas-born patients, primarily from Papua New Guinea, were over-represented in both the stand-alone TB group and in the TB-diabetes group. "If a person has diabetes they are up to seven times more likely to contract TB compared to the general population," said Tahnee Bridson, a researcher involved in the project. According to the Director of Microbiology at Townsville Hospital, Dr Robert Norton, people with diabetes suffered from "immune dysregulation" and were more prone to contracting the deadly infection. "You can have TB your whole life and not know it, but if you suffer from diabetes and your immune system is not functioning well, it can flare up."

It had been assumed that higher standards of care for diabetic patients in Australia and the relative rarity of TB meant there was not as strong a link between the two ailments. But the JCU study showed that while the overall numbers were lower, the proportion of diabetics developing TB was the same as in less-developed countries. Dr Norton said the findings support the view that there must be screening of patients with diabetes for latent TB in any setting.

"It is especially important because the prevalence of type two diabetes is increasing at a very significant pace," he said. Scientists at JCU are developing experimental models that will enable them to study the interaction between the bacteria that causes TB and immune cells with similar properties to those from patients with diabetes. "Without such models we will not be able to study the defects that make patients with diabetes more susceptible to TB," according to Professor Natkunam Ketheesan. "Such models are useful in developing treatment protocols and prevention strategies."

It is estimated that if diabetes could be reduced by 35% globally, 1.5 million TB deaths and 7.8 million infections could be prevented, making this an important area where further local research is warranted.

Source: News Medical, http://bit.ly/1JHoeHv (03.08.2015)

4. New Figures Show Alarming Trends in TB Financing

The Stop TB Partnership is calling on the world to renew commitments to funding the global fight against tuberculosis as the UN Financing for Development Conference in Addis Ababa concludes, where leaders discussed financing for the Sustainable Development Goals (SDGs). A new TB financing fact sheet released by the Partnership, 'Racing to the End TB Finish Line', shows that low-income high-burden TB countries (HBCs) need increased international support, while many lower-middle income HBCs are failing to step up with the needed domestic investments. In the eight low-income HBCs, domestic funding represents less than 7% of National TB budget needs, and in the nine lower-middle income HBCs, domestic funding represents less than 26% of National TB budget needs.

"The Financing for Development Conference was a key moment for the global community to confirm its commitment to financing global health" said Dr. Lucica Ditiu, Executive Secretary for the Stop TB Partnership. "Tuberculosis kills 4000 people every day and if we want to end TB, we must ensure that domestic investments step up to address TB challenges".

"While the BRICS countries have benefited from strong economic growth and have prioritized domestic investments in TB, other countries with major TB burdens are still heavily dependent on external financing for their TB programs. Tuberculosis has devastated the economies of many of these countries, where the treatment of one person with drug-resistant TB can cost over $10,000 and primary health care systems struggle to cope with the TB epidemic."

"It's the responsibility of all of us to ensure the world has the needed resources to meet the goal to end TB by 2035. It is alarming that domestic investments are low where they are needed the most. In addition, new figures released by the IHME show a worrying 9.2% decrease in international support

for TB at a time when the world has agreed to the most ambitious goals against TB in history."
Source: Stop TB Partnership, http://bit.ly/1SB8mMc (19.07.2015)

Forschung & Entwicklung

1. New treatment principle for tuberculosis activates the body's own defence system
Widespread resistance to antibiotics requires new, expensive medicines with various side-effects to be used against tubercle bacteria. However, many affected countries lack access to such medicines. Researchers are therefore trying to develop new strategies for effective treatment of tuberculosis, which continues to be a major worldwide problem.
The researchers behind the new study are investigating how to activate the body's own antibiotics, antimicrobial peptides, which form a part of the innate immune defence system. The peptides are produced in all mucus membranes and also in granulocytes and macrophages, two types of white blood cells that are recruited to the site of infection.
"We have focused particularly on increasing the body's production of the body's own peptides with the help of existing drugs. LL-37, a human antimicrobial peptide that we discovered in 1995, is highly effective against TB bacteria," says Birgitta Agerberth at the Department of Laboratory Medicine at Karolinska Institutet, one of the researchers who has led the study.
Researchers have already shown that the drugs vitamin D and phenylbutyrate increase the production of LL-37. They have now demonstrated that LL-37 plays a key role in the manner in which these drugs kill the TB bacteria. It is already known that vitamin D can trigger a process known as autophagy which is important for killing pathogenic bacteria inside macrophages and other cells. In this study, researchers have shown that phenylbutyrate also activates autophagy and that vitamin D and phenylbutyrate work even more effectively when used in combination. In addition, the underlying mechanism of the activation has been clarified.
In an another study from the same research group it is shown that supplementary treatment with phenylbutyrate and vitamin D had positive results when combined with standard antibiotics in the treatment of newly diagnosed tuberculosis patients in Dhaka, Bangladesh.
"The results show that we can thus strengthen the body's defence against serious infections such as tuberculosis by increasing the production of antimicrobial peptides. Both these studies provide combined support for a new treatment principle for infectious diseases with the activation of the body's own defence system combined with traditional antibiotic treatments. This new treatment strategy as we name "Host-Directed Therapy" has many advantages: it minimise the risk of developing resistance, it strengthens the effect of regular antibiotics and controls the often damaging inflammation that occurs commonly in different infections," says Birgitta Agerberth.
The research is funded by the Swedish Foundation for Strategic Research, Swedish Heart-Lung Foundation, the Swedish Research Council and SIDA, among others.
Source: Karolinska Institutet, http://bit.ly/1fZX0Qc (31.07.2015)

2. Delamanid for extensively drug-resistant tuberculosis
Our evaluation of delamanid in a single cohort proceeded with a 3-month randomized, controlled trial (a 2-month treatment period with a 1-month follow-up) (Trial 204), a 6-month open-label trial (Trial 208), and a 24-month follow-up study (Trial 116). In all three trials, patients also received an optimized background treatment regimen recommended by the World Health Organization (WHO). In the analysis population, infection with XDR-TB was confirmed at baseline. In Trial 204, the primary end point was 2-month sputum-culture conversion, which was defined as a negative culture for 5 consecutive weeks. Sustained sputum-culture conversion was defined as sputum-culture conversion without positive culture results through the remainder of treatment (the follow-up period was 24 months from the date of randomization). Investigators assessed treatment outcomes with the use of WHO cohort definitions aggregated into two groups: successful treatment, defined as cure plus

treatment completion, and unsuccessful treatment, defined as treatment failure, default (the interruption of treatment for any reason for 2 consecutive months without medical approval), or death. Microbiologic assessments were performed with the use of solid media. For treatment outcomes, patients were stratified according to receipt of treatment with delamanid for 6 months or more (i.e., those participating in Trials 204 and 208) and receipt of treatment for 2 months or less (i.e., only those participating in Trial 204).

Patients receiving delamanid for 2 months had a higher rate of 2-month sputum-culture conversion than patients receiving placebo (7 of 16 [44%] vs. 1 of 10 [10%], P=0.10). Mortality was lower among patients treated with delamanid for 6 months or more than among patients treated with delamanid for 2 months or less (0 of 17 vs. 2 of 9 [22%], P=0.11), with one death occurring at 181 days and the other at 309 days after randomization into Trial 204 (the cause of death was not recorded for either patient since the deaths occurred outside the timeframe of the trial). Rates of sustained sputum-culture conversion were higher, but not significantly so, among patients treated for 6 months or more than among those treated for 2 months or less (13 of 17 [77%] vs. 4 of 9 [44%], P=0.19), and rates of successful treatment outcomes were higher, but not significantly so, among patients treated with delamanid for 6 months or more than among patients treated for 2 months or less (11 of 17 [65%] vs. 4 of 9 [44%], P=0.42). Patients with 2-month sputum-culture conversion were 2 times as likely to have sustained sputum-culture conversion as those without conversion (P=0.02) and 2.6 times as likely to have a successful treatment outcome (P=0.007).

These data are hypothesis generating and offer insight into discussions of the predictive value of early sputum-culture conversion, which the Food and Drug Administration has described as "reasonably likely to predict clinical benefit," although the specific time points for early sputum-culture conversion in XDR-TB are unknown. The study was limited by sample size and the potential for bias; however, it provides initial indications of 2-month sputum-culture conversion as a surrogate end point and provides data on treatment outcomes among patients with XDR-TB who were treated with delamanid.

The studies in this analysis were approved by institutional review boards at each site and written informed consent was obtained for patients in all studies.

Source: TB Online, http://bit.ly/1VWAAAq (03.08.2015)

3. Linezolid for XDR-TB — final study outcomes

We previously reported 4-month culture conversion rates among patients with chronic extensively drug-resistant tuberculosis (XDR-TB) who received linezolid. By 4 months, 15 of 19 patients (79%) in the immediate-start group and 7 of 20 (35%) in the delayed-start group had conversion to a negative sputum culture (P=0.001). After 6 months of linezolid treatment, 34 of 39 patients (87%) had negative sputum cultures. Here, we report final study outcomes for these patients 1 year after the end of treatment, 36 months after they began the study.

Among 39 patients who were enrolled in this trial, 38 received linezolid. Of these patients, 27 had negative results on sputum culture 1 year after the end of treatment, 3 were lost to follow-up, and 8 withdrew before the end of the study, including the 4 patients in whom linezolid failed, as reported previously. The median duration of tuberculosis treatment was 789 days overall, with 781 days of linezolid. Final regimens included any remaining active second-line drugs (as described in the Supplementary Appendix of our original article, available with the full text of the article at NEJM.org).

Among the 27 patients who completed the study, 4 had a dose reduction from 600 mg to 300 mg of linezolid per day before the second randomization. Among the 13 patients who were assigned to continue receiving the 600-mg dose, 9 had a subsequent reduction in the dose to 300 mg. All the dose reductions were due to adverse events. Additional serious adverse events beyond our original report included 3 patients with optic neuropathies and 1 with anemia; all these conditions resolved after the discontinuation of linezolid.

Acquired linezolid resistance was observed only in the 4 patients who were originally reported (11% of the 38 patients who received linezolid). This observed rate with monotherapy may be related to

the infrequent emergence of resistance to this drug that has been observed in vitro. Thus, 27 of 38 patients (71%) with chronic XDR-TB were cured of the infection at 1 year after the termination of the study.

In the 2 years since our original report, the results of one additional prospective clinical trial of linezolid for XDR-TB have been published, with findings reported at the end of the study. Our final study results provide prospective evidence of the durable efficacy of linezolid for the treatment of XDR-TB, although our findings are limited by the small number of patients. Because relapses in TB mainly occur in the first year, the lack of relapses in our cohort is reassuring.

This report adds to the growing evidence of the efficacy of linezolid for XDR-TB, with use that was limited by side effects. Notably, these side effects were dose-related, which suggests that in future trials involving a lower dose of linezolid, the drug may have an improved side-effect profile. Newer oxazolidinones, some of which have shown potent activity against *Mycobacterium tuberculosis* in vitro, are also in development, although the side-effect profiles with long-term use are unknown. If our results are confirmed in future clinical trials, oxazolidinones may become an important part of combination regimens for tuberculosis treatment.

Source: TB Online, http://bit.ly/1IevI2o (03.08.2015)

4. Uncovering the secrets of immune system invaders

The human immune system is a powerful and wonderful creation. If you cut your skin, your body mobilizes a series of different proteins and cells to heal the cut. If you are infected by a virus or bacteria, your immune system responds with a series of cells that attack the invader and neutralize it.

But sometimes invaders find ways to exploit the very cells that are designed to protect us. Tuberculosis (*Mycobacterium tuberculosis*) and its lesser-known (and less virulent) relative *Mycobacterium avium* do exactly this, by hiding in immune cells called macrophages. A group of researchers from the Norwegian University of Science and Technology (NTNU) have now clarified one important step in the mechanism that allows these mycobacteria to trick the immune system so they can hide in macrophages. Their results are published in the 20-24 July online early edition of the *Proceedings of the National Academy of Sciences*.

Although the finding itself does not have immediate clinical implications, it adds to a greater understanding of the general mechanisms of how the immune system works, says corresponding author Trude Helen Flo, a professor of cell biology and co-director of NTNU's Centre of Molecular Inflammation Research (CEMIR). "We think this is more of a general mechanism," and not just limited to mycobacteria, she said. And because certain cancers, such as lung cancer, are linked to the inflammation that the body mounts as a first step in the immune response, the finding adds an important piece to the puzzle of understanding what regulates inflammation and how this regulation can go wrong, she said. Flo and her colleagues are interested in knowing more about how mycobacteria are able to persist in the human body because one variant, tuberculosis, remains a problem in lesser-developed countries and is becoming more of a problem in developed countries as antibiotic-resistant strains of tuberculosis spread.

Mycobacterium avium is less likely to cause illness in healthy people, but is an organism that is found everywhere, which makes it easy to study. It can, however, cause major health problems in people with compromised immune systems, such as in diabetes or AIDS, in children, or people with lung defects, Flo said. In fact, she said, during the 18th and 19th centuries, when it was considered impolite for well-to-do women to cough or spit, it was not uncommon for wealthier women to be afflicted by *Mycobacterium avium*. Infection by *Mycobacterium avium* is sometimes called "Lady Windermere syndrome," in reference to an 1892 Oscar Wilde play that pokes fun at manners and morals in upper class Victorian society.

The researchers used *Mycobacterium avium* infections of human cells to study the role of a poorly understood protein called Kelch-like ECH-associated protein, also called Keap1.

When *Mycobacterium avium* invades a macrophage, the normal response of the macrophage is to send a signal - a call for help - for other cells to come help. This signal, in the form of something called inflammatory cytokines, causes inflammation in the body. "But once this inflammatory mechanism is turned on, it is so strong, the body reacts very promptly to turn down the reaction," Flo said. "Otherwise, if the reaction is uncontrolled, you can have septic shock."
The researchers found that Keap1 helps to quickly turn down the immune system reaction when a macrophage is invaded by *Mycobacterium avium* - which aids the mycobacteria in persisting in the macrophage, Flo said. "Keap1 is a negative mechanism for controlling inflammation," she said. "But this negative reaction is also what makes us susceptible to *Mycobacterium avium*. The balance (in the immune system response) has to be perfect for mycobacteria to survive."
Flo said the study underscores the importance of balancing the inflammatory response.
In addition to the risk of septic shock from an uncontrolled immune system reaction, if the immune reaction "is prolonged and not terminated, it can cause chronic inflammatory diseases," she said. However, if the immune system response "is dampened or weak, susceptibility to infections increases," she added. "Our study shows that in absence of Keap1, inflammatory responses increases and the growth of mycobacteria inside macrophages is hampered."
One distinct feature of the study was that the researchers used cells from blood donors as part of their research, rather than "cultured" immortalized cell lines that have been grown in the laboratory for decades and whose responses may be very different from primary cell isolated directly from humans. Flo said that while using human cells from blood donors made the research more difficult and time-consuming, it also made the findings more valuable in terms of eventual clinical applications. "We chose to isolate immune cells from healthy donors for our experiments," she said. "These more closely reflect what is going on in real humans, and - although they are tricky to work with - can give us findings we believe should be more relevant for real disease."
Flo said that one reason that Keap1 was of interest to her research group was because mutations in the Keap1 gene have been found in cancers that are associated with inflammation, such as lung cancer. That means that Flo or other researchers could look for mutations in Keap1 in blood samples from biobanks, such as NTNU's Nord-Trøndelag Health Study (HUNT), which has collected health and biological information and material from 120,000 individuals over the last 30 years. "We can look at patients' genes and see if they have accumulations of mutations in Keap1, which is at the core of regulating inflammation," she said. Biobanks such as HUNT that have collected data over decades allow researchers to see how different mutations are associated with different cancers, for example.
Source: MedicalXpress, http://bit.ly/1SVCfSc (21.07.2015)

Reportage

1. TB activist can hear again

Phumeza Tisile, of Khayelitsha, was 19 when she was diagnosed with drug resistant tuberculosis - a disease that would later leave her with permanent hearing loss.
But today she is not only cured of the deadliest form of TB - XDR TB - she has also regained her hearing after cochlear implants. “For five years my world was silent. I couldn’t listen to my favourite music. Suddenly I couldn’t have conversations with people… it was complete silence.”
Tisile, 24, regained her hearing four months ago after Cape Town doctors Arne von Delft and his wife, Dalene, started an online campaign to raise funds. In the campaign, “Friends of Phumeza”, the two doctors from a local NGO - TB Proof - banded together with Medicins sans Frontieres and Tygerberg Cochlear Unit TB to raise more than R200 000 that was needed for one of the two cochlear implants. Her medical scheme partly paid for the other implant.
Tisile was doing her first year in Human Resources at Cape Peninsula University of Technology when she was incorrectly diagnosed with multi-drug resistant TB and placed on a gruelling regimen of about 20 pills a day and daily injectables. One of these injections was the drug Kanamyacin - an effective TB drug. Hearing loss is one of its side effects.

"I got up one day and suddenly I couldn't hear any sound. Everything was silent. Doctors at Brooklyn Chest Hospital said I would never hear again. I was devastated," she said. Even though she became a TB activist and visited many countries around the world during the five years that she was deaf, Tisile said there was something missing. "One of the highlights for me was delivering a TB manifesto to the World Health Organisation in Geneva. But still something was missing there. I longed to hear my voice when I spoke on that mic. I remember being so curious to hear other people's accents, but it was a complete silence." Since she got her hearing back, Tisile says she's addicted to music. "I can sit with my earphones all day. Music is life to me and just having normal conversations with people and talk over the phone means the world to me. I consider myself very lucky that I never died from TB and to be able to hear again," she said. Dalene von Delft said seeing Tisile having a conversation with her mother, Nokuzola, for the first time in five years was moving. "They sat there… just chatting. We all celebrated with her."
Source: IOL News, http://bit.ly/1UhVUyw (29.07.2015)

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