NEWSLETTER

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Inhalt

Internationale Nachrichten

1. Tuberculosis mortality nearly halved since 1990 - But TB ranks alongside HIV as a leading cause of death worldwide

The fight against tuberculosis is paying off, with this year's death rate nearly half of what it was in 1990. Nevertheless, 1.5 million people died from TB in 2014. Most of these deaths could have been prevented, according to WHO's *Global tuberculosis report 2015*, which was released today in Washington. To reduce TB's overall burden, detection and treatment gaps need to be closed, funding shortfalls filled and new diagnostics, drugs and vaccines developed, according to the report. Most of the improvement has come since 2000, the year the Millennium Development Goals (MDGs) were established. In all, effective diagnosis and treatment saved 43 million lives between 2000 and 2015, according to the report, the 20th in a series of annual evaluations produced by WHO.

"The report shows that TB control has had a tremendous impact in terms of lives saved and patients cured," said WHO Director-General Margaret Chan. "These advances are heartening, but if the world is to end this epidemic, it needs to scale up services and, critically, invest in research." Those advances include the achievement of the MDG that called for halting and reversing TB incidence by 2015. The goal was reached globally and in 16 of the 22 high-burden countries that collectively account for 80% of cases. Worldwide, TB incidence has fallen 1.5% per year since 2000, for a total reduction of 18%.

"Despite the gains, the progress made against TB is far from sufficient," according to Dr Mario Raviglione, Director of WHO's Global TB Programme. "We are still facing a burden of 4 400 people dying every day, which is unacceptable in an era when you can diagnose and cure nearly every person with TB." In 2014, TB killed 890 000 men, 480 000 women and 140 000 children. The disease ranks alongside HIV as a leading killer worldwide. Of the 1.5 million people killed by TB in 2014, 400 000 were HIV-positive. HIV's total death toll in 2014 was estimated at 1.2 million, which included the 400 000 TB deaths among HIV-positive people.

This year's report describes higher global totals for new TB cases (9.6. million) than in previous years. However, these figures reflect increased and improved national data and in-depth studies rather than any increase in the spread of the disease. More than half of the world's TB cases (54%) occurred in China, India, Indonesia, Nigeria and Pakistan. Among new cases, an estimated 3.3% have multidrug-resistant TB (MDR-TB), a level that has remained unchanged in recent years.

The report highlights the need to close detection and treatment gaps, fill funding shortfalls, and develop new diagnostics, drugs and vaccines. The detection gap is significant. Of the 9.6 million people who fell ill with TB in 2014, 6 million (62.5%) were reported to national authorities. That means that, worldwide, more than a third (37.5%) of the cases went undiagnosed or were not reported to national authorities. The quality of care for people in the latter category is unknown. Detection and treatment gaps are especially serious among people with MDR-TB, which remains

a public health crisis. Of the 480 000 cases estimated to have occurred in 2014, only about a quarter – 123 000 – were detected and reported to national authorities. The 3 countries with the largest numbers of cases are China, India and the Russian Federation.
Treatment initiation for those diagnosed with MDR-TB substantially increased and almost all cases detected in 2014 started treatment. Forty-three countries reported cure rates for MDR-TB patients of more than 75%. Nevertheless, globally, data shows an average cure rate of only 50% for treated MDR-TB patients. Treatment is improving, with 77% of patients known to be co-infected with HIV and TB getting antiretroviral medicines in 2014. The number of people living with HIV who were given TB preventive therapy was nearly 1 million in 2014, an increase of about 60% compared with 2013. More than half (59%) of these people were in South Africa.
“A primary reason for detection and treatment gaps is a major shortfall in funding,” said Dr Winnie Mpanju-Shumbusho, WHO Assistant Director-General for HIV, TB, Malaria and Neglected Tropical Diseases. This shortfall amounted this year to US$ 1.4 billion of the US$ 8 billion needed to fully implement interventions. In addition, an annual funding gap of at least US$ 1.3 billion must be filled for research that would include the development of new diagnostics, drugs and vaccines.
From 2016, the global goal will shift from controlling TB to ending the global TB epidemic. The End TB Strategy, adopted by all WHO Member States, serves as a blueprint for countries to reduce TB incidence by 80% and TB deaths by 90% and to eliminate catastrophic costs for TB-affected households by 2030. “Ending the TB epidemic is now part of the Sustainable Development Goal agenda” said Dr Eric Goosby, UN Special Envoy on Tuberculosis. “If we want to achieve it, we’ll need far more investment – at a level befitting such a global threat. We’ll also need progress on universal health coverage and poverty alleviation. We want the most vulnerable communities worldwide to gain first, not last, in our efforts.”
Source: WHO, http://bit.ly/1HbyP8Q (28.10.2015)

2. Staff deaths at leading hospital put India's TB battle in spotlight
Campaigners and a former official overseeing Asia's largest tuberculosis hospital in Mumbai say staff deaths there are being under-reported, highlighting India's growing struggle to contain multi-drug resistant forms of the contagious, airborne disease.
Many of India's toughest TB cases end up in the metal cots of the state-run Sewri Hospital, where on a recent Reuters visit open wards were lined with emaciated patients, many left alone by families scared by the disease and its stigma. Medical Superintendent Rajendra Nanavare, Sewri's top doctor, says an average of six patients a day die at the 1,200-bed hospital. Nanavare says a dozen hospital workers had also died from TB in the last five years. But others say the real number of staff deaths is higher - although they could not give a precise figure - pointing to a public health crisis at the heart of one of the world's most densely populated cities. "A lot of class 4 workers like the sweepers and the cleaners at the hospital leave work after they get the infection," said Prakash Devdas, president of the local workers' union. "We don't know if they're alive with the infection or dead. Nobody tracks them. That's why I said the actual number would be much higher."
Campaigners blame weak infection controls, poor oversight and infrequent checks on workers in a country where the shame of TB alone drives people to suicide. "There is so much interaction between the patients and staff. They become more vulnerable... especially if they have weak immunity," said former TB officer Mini Khetarpal, who supervised the hospital for Mumbai authorities until earlier this year.
Nanavare said 69 employees has been diagnosed with TB since 2011, of whom 12 had died while 28 had been cured. A lot of staff continue to work at the hospital long after being infected.
India has the world's largest number of TB patients - an estimated 2.6 million Indians live with the bacterial lung disease, which is spread through coughs and sneezes. The country is second only to China in the number of patients with drug-resistant TB, a major threat to TB control with repercussions well beyond India. In July this year, a Mumbai woman who flew to Chicago was found

to have the extremely drug resistant TB (XDR TB). She has since been quarantined and is under treatment there. "Globally, XDR TB presents the greatest threat to TB control," said Brian Katzowitz, a spokesman at the Centers for Disease Control and Prevention, the leading national public health institute in the United States. Nerges Mistry, director of the Mumbai-based Foundation for Medical Research, investigated conditions at the Sewri hospital at the behest of city authorities in 2011. That report - seen by Reuters but not released publicly - found about 65 hospital staff died between 2007 and 2011, many of them cooks.

It also highlighted serious problems including inadequate record-keeping, sanitation and hygiene problems. Doctors failed to wear N-95 disposable masks, it said, a basic form of infection control recommended by the World Health Organization. Mistry said it was unclear if any of the proposals made were implemented. "It's a last ditch thing. You go there and you never come out," she said.

Nanavare says the hospital has brought in changes to ensure better staff protection, though masks remain an "individual decision".

Prime Minister Narendra Modi's manifesto ahead of last year's election accorded "high priority" to the health sector, and promised a universal health assurance plan. But he has been forced to tightly control healthcare spending as India battles to spend its way out of slow-moving recovery. In the latest high profile case at the Sewri hospital, a nurse died in September from drug-resistant TB, prompting staff protests to demand better working conditions.

High profile campaigners such Leena Menghaney, an HIV and TB activist, say still not enough is being done. "Despite increased investment in prevention and treatment of drug resistant TB over the last decade, local authorities, the National TB Programme and policymakers in India are not directing sufficient attention to infection control," she said.

Mumbai city officials in charge of overseeing the hospital say sub-standard private care before patients are sent to Sewri must share the blame for its travails. A Reuters reporter found cats wandering around wards and few visible instructions to keep visiting relatives safe. None of the nurses wore masks and two said they were encouraged not to, on the grounds that they were already exposed to TB bacteria. One patient, 12-year-old Kamala, wore a light green muslin mask, untied at one end. "I just removed it because I was coughing too much," she said. A group of about 60 health experts and activists including the U.S.-based Treatment Action Group, wrote a letter in August to the state, federal and city authorities highlighting what they described as "dismal" conditions at the hospital. They have yet to receive a response.

Sunil Khaparde, a health ministry official in New Delhi who oversees India's TB control program, said the hospital had been asked to tighten procedures and more training was planned. "The Sewri Hospital is in urgent need for a facelift," said Zarir Udwadia, a chest physician at Hinduja Hospital in Mumbai and one of India's best-known TB experts. "More funds, more staff and more commitment are needed."

Source: Reuters, http://read.bi/1SjpdPY (12.10.2015)

3. Trading posts brought tuberculosis to Quebec Arctic: genetic study

Genetic research suggests the arrival of permanent trading posts in Arctic Quebec meant more than easier access to flour and metal cookware for Inuit families. A newly published paper from McGill University concludes that's how tuberculosis was introduced into the region as well.

"It would appear that the tuberculosis epidemic dates to permanent interaction with some outside people," said lead author Marcel Behr. Although TB is a distant memory in most of Canada, it still stalks the North. Last year, Nunavut recorded 83 cases, although that was an improvement. There were 100 cases in 2010, a rate of infection 63 times higher than that in the south.

In 2008, a study found Canada's four main Inuit regions had a tuberculosis incidence rate of 157.5 for every 100,000 people. The rate in southern Canada was 0.8 per 100,000. In an attempt to understand why the respiratory disease remains so persistent in Arctic Quebec, Behr and his colleagues examined the genetic structure of tuberculosis bacilli found in 163 cases from the region known as Nunavik. They found the great majority of them were very similar. Using known rates of genetic

mutation for the TB bacillus, they were able to derive a pretty good idea of when the bug arrived among the Inuit -- about 1919.
"The Inuit of northern Quebec had long-standing casual interactions with whalers and fishermen and explorers for probably about three centuries," Behr said. "We do not see any evidence that those three centuries led to (TB taking hold). "After the early 1900s, you actually start to see formal installations and villages and trading posts. You have a much more permanent interaction."
The good news is that Behr's team couldn't find any evidence that Nunavik's TB strain is more virulent than others. Although some strains elsewhere on the globe are harder to treat or more antibiotic-resistant, Nunavik's is not among them. "We could find absolutely no traces of a hyper-virulent bacteria. It is a relatively ordinary bacterium." That suggests the disease's persistence is due almost entirely to social conditions such as overcrowded, substandard housing. "It should be a controllable strain."
Behr said public health agencies have two ways to address the issue -- treating the disease itself or treating the conditions under which it flourishes. "You can either see TB as the problem, and then your goal is controlling TB, or you can see TB as a symptom of the problem, and then your goal should be broader. "What we need is not brand-new interventions, but to scale up things that already exist and we have to apply them better."
Tuberculosis has left an indelible mark on Inuit culture. In the '50s and '60s, thousands of infected Inuit were sent south for treatment, many never to return.
Source: Toronto Sun, http://bit.ly/1XK6OP8 (20.10.2015)

Forschung & Entwicklung

1. Researchers discover potential treatment for tuberculosis
Deakin University scientists have discovered a potential new treatment for tuberculosis, a disease rapidly gaining resistance against current medical therapies.
The discovery, a group of molecules which appear to block the growth of the bacteria which leads to the disease, was made by a researcher while investigating a new treatment for a completely different condition – prostate cancer.
The finding has generated excitement among the medical world, frustrated by a rise in tuberculosis, which the World Health Organisation estimates has now infected 30 per cent of the globe's population and is becoming increasingly resistant to current treatments.
Dr Luke Henderson, a Senior Research Fellow within Deakin University's Institute for Frontier Materials said his discovery came about while his team was researching the value of the same group of molecules for prostate cancer treatment.
"While we were working on a group of 25 to 30 compounds, six of the most active components proved to be able to inhibit the growth of TB," Dr Henderson said. "The good thing about these molecules is that we can easily generate and modify a lot more. We can synthesise them in one day, which means that we can speed up the research process.
"While there is still a long road ahead before a drug would be ready for commercialisation, we are very excited about its potential as current treatments are just not getting on top of the global pandemic. Dr Henderson said that while annual TB fatalities were declining, resistance to the disease was increasing, which could soon prove disastrous.
"The disease is evolving resistance to the two frontline drugs that have been used to treat TB for almost 30 years, Isoniazid and Rifampicin," he said. "Now, around half a million of all TB cases are multi-drug resistant and around 10 per cent of these are extremely drug resistant.
"The first new drug in 30 years, Bedaquiline, was made available in 2012, but unfortunately it has a 'black box' warning, which is the most serious warning in relations to side-effects able to be given by the FDA."
In 2013, TB killed 1.5 million people, with more than half of these deaths occurring in the South East

Asia and Western Pacific regions. But while TB was once kept out of rich first-world nations by modern vaccinations, the disease is no longer isolated to poorer countries. The London Assembly recently reported that parts of London had higher rates of the disease than countries such as Rwanda, Eritrea and Iraq, recording more than 2,500 new cases of TB in England's capital last year – or about 40 per cent of the UK's total.

Dr Henderson said TB currently affected less than one per cent of Australia's population, due to our quality health care system and geographical isolation, but human movement across the globe and increasing drug resistance meant that TB also posed a potential risk to the country.

Dr Henderson's team's next step will be to focus on understanding how the molecules select and kill TB bacteria and whether they may cause side effects.

The team has also received support from the US National Institute of Allergy and Infectious Diseases, which tested the effect of the molecules on TB bacteria. The researchers have used the pioneering approach to chemistry called "click chemistry", introduced to the world by Nobel Laureate Professor KB Sharpless in 2001. Click chemistry enables substances to be generated quickly by joining small modular units together, like Lego, and is proving to have outstanding applications in areas ranging from materials sciences and polymer chemistry, to pharmaceuticals.

Source: MedicalXpress, http://bit.ly/1RCON1b (30.10.2015)

2. Newest MDR-TB drug prices could fall by up to 95% through generic production

The cost of newer drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) could be cut by up to 95% if generic production of patented products could be achieved in the same way as for antiretroviral drugs, according to a study presented at the 15th European AIDS Conference in Barcelona on Thursday. Price reductions might permit a tenfold increase in the number of people who can be treated for MDR-TB within current budgets, without any new funding, the study suggests.

The cost of drugs to treat MDR-TB often run into thousands of dollars, limiting how many people can be treated and leading to further spread of MDR-TB in settings where resources are limited.

Middle-income and lower middle-income countries in Eastern Europe and Central Asia have some of the highest rates of MDR-TB in the world – and some of the lowest rates of access to MDR-TB treatment. Weaknesses in diagnosis and management of MDR-TB undoubtedly contribute to low rates of treatment.

A survey comparing TB treatment outcomes in people living with HIV in Eastern Europe with those in Western Europe and in Latin America found that 34% of people diagnosed with TB in Eastern Europe had resistance to at least one drug, compared to 3% in Western Europe. MDR-TB is one contributor to poor TB treatment outcomes among people living with HIV in Eastern Europe, along with lack of integration of TB and HIV care and lack of access to antiretroviral therapy.

Voluntary licensing and the historical lack of restriction on generic production of some older antiretroviral drugs has permitted the price of antiretroviral drugs to be driven down from over $10,000 a year prior to 2000 to around $140 a year today, due in large part to the size of the market. This has encouraged generic manufacturers to invest in manufacturing generic products, because they see a guaranteed market that is profitable even at a very small profit margin.

The lack of new drugs to treat MDR-TB means that the newest agents developed against TB have been priced by pharmaceutical companies to recoup their investment in development. Voluntary licensing has not been pursued as a strategy to widen access, despite the large number of people who need MDR-TB treatment.

In order to examine whether market interventions to widen access might make MDR-TB treatment more affordable, UNITAID, the international drug purchase fund, supported Dr Andrew Hill and colleagues from Imperial College and Chelsea and Westminster Hospital, London, Liverpool University's Department of Pharmacology and Howard University, Washington DC, to calculate the scope for price reductions through generic manufacturing.

Following a methodology already employed to estimate the scope for reductions in the prices of

antiretroviral drugs and antivirals for treatment of hepatitis B and C, researchers calculated the cost of the raw materials required to make TB drugs, along with the costs of synthesis, formulation and packaging, and factored in a small profit margin as is customary for generic antiretroviral drugs.
The methodology was validated for TB drugs by calculating the costs of first-line TB drugs, for which generic versions are already available. Target prices for first-line drugs estimated through this methodology matched the lowest available prices for generic TB drugs reported to the Global Drug Facility.
Current WHO guidance on MDR-TB treatment recommends using a combination of drugs from up to five different groups, combined according to local and individual drug susceptibility patterns. The researchers found that in the case of drugs from groups 1 and 2, on which patents have expired, generic prices are already very low and there is unlikely to be further scope for savings.
In the case of the group 3 drug moxifloxacin, which came off patent in 2014, there is potential for further price reduction. A generic version of moxifloxacin costs $232 per month in the United States, compared to $38 a month in France, but the research group estimates that even if demand for a generic were low, it would be possible to bring the price down to $9 a month.
It is drugs in group 5 – products either still on patent or not yet approved for use – which offer the biggest potential for price reduction.
The researchers compared the projected costs to the current lowest prices charged for these products. They found that in most cases the lowest price achievable based on the current costs of raw materials and manufacturing was at least 80 to 85% lower than the current prices charged by manufacturers. In the case of bedaquiline, it would be possible to reduce the price of the drug from approximately $136 a month to between $8 and $16 a month – a price reduction of approximately 90 to 95%. The upper range price represents the price likely to be achievable if demand is low (>100,000 treatment courses per year), and the lower range the price if demand reaches 1 million treatment courses per year. (...)
These prices have the potential to substantially reduce the cost of several experimental MDR-TB regimens currently being tested in clinical trials. For example, the cost of experimental bedaquiline-containing regimens soon to be tested in two arms of the STREAM study could be reduced from approximately $1834 for a 40-week course to between $252 and $364, while a 28-week course could fall in price from approximately $1343 to between $176 and $257 for a course of treatment.
However, in order to achieve these savings, say the research group, patent barriers to generic production will need to be overcome, especially in middle-income countries, and demand for new drugs to treat MDR-TB will need to be increased in order to encourage generic manufacturers to develop versions of these agents. The savings implied by the model assume that it will be possible to negotiate bulk purchases for very large quantities, rather than placing multiple small national orders. Generating higher demand will require greater surveillance and case detection for MDR-TB, but not necessarily more money. Dr Hill pointed out that it would be possible to increase the numbers treated for MDR-TB tenfold within existing budgets if these price reductions could be achieved.
Source: Aidsmap.com, http://bit.ly/1Q2o155 (23.10.2015)

3. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries

Latent tuberculosis infection (LTBI) is characterised by the presence of immune responses to previously acquired *Mycobacterium tuberculosis* infection without clinical evidence of active tuberculosis (TB). Here we report evidence-based guidelines from the World Health Organization for a public health approach to the management of LTBI in high risk individuals in countries with high or middle upper income and TB incidence of <100 per 100000 per year. The guidelines strongly recommend systematic testing and treatment of LTBI in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor treatment, patients receiving dialysis, patients preparing for organ or haematological transplantation, and patients with silicosis. In prisoners, healthcare workers, immigrants from high TB burden countries, homeless

persons and illicit drug users, systematic testing and treatment of LTBI is conditionally recommended, according to TB epidemiology and resource availability. Either commercial interferon-gamma release assays or Mantoux tuberculin skin testing could be used to test for LTBI. Chest radiography should be performed before LTBI treatment to rule out active TB disease. Recommended treatment regimens for LTBI include: 6 or 9 month isoniazid; 12 week rifapentine plus isoniazid; 3–4 month isoniazid plus rifampicin; or 3–4 month rifampicin alone. (...)
Source: European Respiratory Journal, http://bit.ly/1k5uejU (19.10.2015)

4. Towards genomic prediction of drug resistance in tuberculosis

In 2014, WHO approved a new strategy for the elimination of tuberculosis,1 and recommended that countries adapt the strategy's pillars—patient-centred care, supportive systems, and innovation—as appropriate to their local contexts. The need for a novel approach to elimination of tuberculosis in low-incidence settings was further echoed in a second framework2 that laid out eight priority areas. Among the prescribed interventions were investment in new technologies and rapid drug-susceptibility testing to optimise treatments. In *The Lancet Infectious Diseases*, Timothy Walker and colleagues3 present an important study at the nexus of these areas, establishing a foundation for routine use of whole-genome sequencing in the mycobacteriology laboratory.

With the cost of sequencing a bacterial genome now similar to that of standard bacteriological assays such as drug-susceptibility testing (Pankhurst L, Oxford University, personal communication), a new framework is emerging in clinical microbiology, for which a single sequencing run is used to both diagnose an infection and predict its antibiotic susceptibility.4 Whole-genome sequencing is especially appealing for the tuberculosis laboratory—resistance in *Mycobacterium tuberculosis* arises largely because of point mutations, and whole-genome sequencing can yield clinically actionable predictions of antibiotic susceptibility within days rather than the weeks or months of standard approaches. Ultimately, the ability to quickly predict an isolate's drug sensitivities from genomic data will lead to faster prescribing of an appropriately tailored treatment regimen, in turn leading to a lower risk of emergent resistance and more rapid conversion to a non-infectious state, enabling a patient to resume a normal lifestyle.

The key to implementation of bespoke treatment based on whole-genome sequencing is to have a comprehensive database of resistance-associated mutations. Although some canonical mutations in genes such as *inhA* and *rpoB* bring about several drug-resistant phenotypes of tuberculosis, many other resistance mutations exist, some of which have been catalogued in databases such as TBDreamDB5 and MUBII-TB-DB,6 but many of which are unknown. Walker and colleagues present both an extended range of known resistance mutations and an algorithm to discover new mutations.3 In their study, they examine a large dataset of 3651 *M tuberculosis* genomes representing different genetic lineages, each with phenotypic results from drug-susceptibility testing. They selected 2099 isolates as a training dataset and developed an algorithm to scan for mutations in 23 genes associated with antibiotic resistance. The algorithm identified 991 mutations potentially associated with resistance; when these were combined with phenotypic data, 120 mutations ultimately emerged as being potentially predictive of resistance. Using these mutations as the basis of a classifier to predict phenotypes in the 1552 validation genomes, Walker and colleagues were able to assign nine of 10 validation cases to the correct class—sensitive or resistant—with a mean 92·3% sensitivity (95% CI 90·7–93·7) and 98·4% specificity (98·1–98·7). The investigators then re-ran the algorithm on the complete set of 3651 genomes, increasing the pool of resistance-associated mutations to 232 and improving predictive capacity—assigning 96·1% of isolates to the correct class with only a negligible decrease in specificity.

This study is an important first step towards routine genomic prediction of antibiotic susceptibility in tuberculosis. A reliable catalogue of resistance mutations is needed if whole-genome sequencing is to be standardised and validated for use in the clinical setting, as is a protocol (such as the algorithm outlined by Walker and colleagues) that can continually be retrained to identify novel resistance-associated mutations when new genomes become available. To sustain the momentum of this

approach, the community of health-care specialists in tuberculosis should commit to sharing genome sequences through public repositories, including clinical metadata such as results from drug-susceptibility testing. As sequencing moves from the research laboratory into the reference laboratory, a clash of values might occur between the open-data mindset of genomics research and public health's inherent concern with data stewardship and privacy. However, the two communities should navigate the new landscape together to create centralised, public-facing genomic repositories containing the metadata needed to train and test new predictive tools, and maintaining patient confidentiality and addressing issues of data ownership and attribution.
Can genomics ever completely replace phenotypic-resistance testing? Perhaps not, because of many reasons—the suite of resistance-associated mutations for a specific organism might not ever be completely known; compensatory mutations can be difficult to tease out from those causing resistance; and the role of minor variants and other influences on resistance, such as expression levels, has not yet been fully described. Even so, whole-genome sequencing offers the potential of rapid first-pass phenotyping and, in a world where multidrug-resistant tuberculosis is a growing problem, an opportunity to rationally tailor treatment to individuals.
Source: The Lancet, http://bit.ly/1iylUYb (07.10.2015)

5. HIV patients should be included in early clinical trials of anti-TB drugs
Tuberculosis is the number one cause of death in HIV-infected patients in Africa and a leading cause of death in this population worldwide, yet the majority of these patients are excluded from the early stages in the development of new, anti-tuberculosis drugs, according to findings presented today (29 September, 2015) at the European Respiratory Society's International Congress 2015.
Dr Florian von Groote-Bidlingmaier, director of Task Applied Science, which performs clinical trials in tuberculosis (TB) in Cape Town, South Africa, told the Congress that there was an urgent need to develop new drugs to treat TB and, in particular, drug-resistant TB. But one of the patient populations that was most in need of them, HIV patients, have been excluded from early phase clinical trials of these drugs. This resulted in slower development of new anti-tuberculosis drugs.
Dr von Groote-Bidlingmaier and his colleagues reviewed the records of 421 patients with multi-drug-resistant tuberculosis who had been referred to Brooklyn Chest Hospital in Cape Town for consideration for participation in clinical drug trials investigating a new anti-TB drug.
They found that 105 patients (24.9%) were disqualified as they had HIV with a low level of white blood cells (CD4+ cells) that fight infection or were on anti-retroviral therapy. Of the remaining eligible patients, 29 (6.9%) had died and 72 (17.1%) did not have multi-drug-resistant TB but resistance to rifampicin (an anti-TB drug) alone. Finally, of the 55 patients (13.1%) who did qualify for consideration for inclusion in the trial, only 12 (2.9%) were eventually formally evaluated.
"HIV infection with a low CD4 count and anti-retroviral therapy were the number one reasons for non-consideration for inclusion in pivotal clinical trials of a novel anti-tuberculosis drug," he said.
"We need new anti-TB drugs and we need to develop them fast. Drug development is a lengthy and expensive process and should be accelerated as much as possible. It is very, very difficult to recruit suitable patients with multi-drug-resistant TB for trials of new drugs. Inclusion of HIV patients early on would increase the number of participants and the relevance of the results."
He said the lack of effective new anti-TB drugs, especially ones that could be used by HIV patients who take other potent drugs for their HIV infection, was a problem not just for South Africa but also for all countries with a high burden of TB and a high HIV infection rate.
"South Africa has one of the highest HIV rates in adults at just under 20% of the population, and HIV patients are more likely to contract TB, which is now the number one cause of death in HIV/AIDS patients. In South Africa, more than 60% of TB patients are HIV infected, and that rate is even higher in drug-resistant TB patients.
"HIV patients who have TB are an important group, who are a lot more complicated to treat and a lot more expensive for the health systems. Some TB drugs have drug interactions with anti-retroviral drugs, and so the compatibility of new TB drugs with concomitant anti-retroviral treatment should be

investigated early in the clinical development, and HIV patients should be included in relevant clinical trials."

At present, HIV patients tend to be excluded from early phase clinical trials so that any confounding factors can be excluded in these "proof of concept" studies investigating the tolerability and efficacy of new drugs. "This makes sense from the drug development point of view. However, since HIV patients make up more than half of the TB patients, at least in South Africa, investigation of interactions between TB drugs and anti-retroviral drugs should be a priority and done early on," he said. He believes that early trials that look specifically at drug interactions may be the way forward. "If TB drugs cannot be used with anti-retrovirals, more than 60% of TB patients in South Africa and elsewhere will not be able to be treated with those drugs."

He concluded: "South Africa is one of the few countries where bedaquiline (one of the new TB drugs) is available without cost to the patient. This is a great success and a major breakthrough ten years after the first clinical trial with bedaquiline was done in Cape Town. Close collaboration between research groups and the government healthcare system is key to efficient drug development. The communities participating in these trials will benefit from that type of research directly."

Quelle: European Lung Foundation, http://bit.ly/1Ph3b0c (01.10.2015)

Reportage

1. In digital India, TB still makes public health care cough blood

The general mood in India over the past weeks has been pretty upbeat. With reports of Prime Minister Modi "conquering" the Silicon Valley, and with Satya Nadella and Sundar Pichai making it big on the global stage, we can't stop gushing about how "India's time has finally come".

But some Indians, for instance public health professionals, are not in a rush to celebrate. We are unfortunately too up close with the ground reality to be upbeat over media-hyped "achievements". While I am certainly not pessimistic about India's potential, I always think cautiously about the realisation of that potential, especially being aware of some of its embarrassing public health failures. One such failure is our tryst with an ancient malady - tuberculosis (TB).

As high as 40 per cent of Indians carry TB inside their bodies. In 2013, about nine million people in the world developed TB, and 2.1 million were Indians. TB has not only been annoyingly perseverant in infecting us (famously including Amitabh Bachchan), but more importantly, as we will see, it stands as a testament to the stubborn persistence of our major longstanding problems.

Some of our most serious national issues are widespread poverty; corruption and mismanagement; a problem-ridden health system; weak political will for social development; and poor sanitation and hygiene. Interestingly, our high tuberculosis rates are strongly associated with all of these. Poverty, through poor nutrition and poor living conditions, intensifies TB. Mismanagement and corruption in the public sector broadly, and the national TB programme specifically, undermine treatment of patients. The health system - the most important agency for TB control - suffers from a host of problems including neglect by successive governments, lack of human resources, and poor quality of services. Weak political will robs India of socially progressive policies and generous funding in education and health. Finally, the legendary neglect of sanitation and hygiene by citizens and local administrations augments the spread of TB bacteria.

The extraordinary aspect about TB is that it can be eliminated only when all, rather than some, of these problems are taken care of. For example, even if we somehow minimise corruption and improve sanitation, TB rates will still be high if we do little about poverty and the fragile health system. With these multiple strong associations, one can assert that the best (and the most convenient) proxy measure of India's holistic progress today is not how many foreign firms are investing in India, or how many CEOs of international companies are Indian, or how much the GDP is growing; it is the levels of tuberculosis. And for now we are faring very poorly.

There's more to TB's uniqueness - it is a highly sociopolitical disease. The six months to two years of

treatment periods put to test the robustness of health systems and strength of political will for public health; the time-tested methods of prevention, though easy and simple, demand action more at the civic level than the individual level; and the rapid wasting of the patient's body and high death rates make it more palpably lethal in popular imagination than other ailments.

The 1980s' TB epidemic in New York City revealed how politics and tuberculosis are intertwined. Many experts blamed the waning political commitment over the '70s and '80s leading to underfunding of public health activities. They coined the phrase "U-shaped curve of concern" for this phenomenon where political will and funding bring down a disease, but resurgence immediately occurs if these are withdrawn prematurely. In India now, with the national government withdrawing funding from many public health programmes, this curve of concern is a serious cause for concern.

There are more reasons to use the "TB-meter" as the perfect indicator for India's development and "greatness". The ailment's history clearly demonstrates how the West was able to tame it through sociopolitical progress - it became a menace in Europe and USA with the disorganised urbanisation and overcrowding of the Industrial Revolution, then started steadily declining with political reforms and social endeavours emphasising sanitation and better standards of living, and then briefly rose around the World Wars when general living conditions declined.

Presently too, if we look at country-wise lists of causes of health loss, only countries with low human development indices (like Burundi, Swaziland, Uganda and India) have TB among the top 10. The incidence rate of TB is 171 per 100,000 persons for India and only 3 for the USA, for example.

Thus, it is perhaps prudent to mute national pride celebrations until TB in the country comes down. Not because bringing down TB will magically set things right, but because only when things are alright with India will its TB naturally nosedive. India achieving very low TB levels will mean a whole host of highly positive developments - district and state governments showing strong commitment to citizen welfare and generously funding health systems; poverty, income inequality and corruption being minimal; and cities and villages having high levels of sanitation and hygiene. It will be the ultimate proof of our much-aspired "development". Undoubtedly, TB rates need to be taken very seriously by policymakers and citizens.

Few of today's proud Indian youth will be aware of the *Pyaasa* song "Jinhe naaz hai Hind par woh kahaan hain. (Whither are those who feel so proud about India?)" asked poet Sahir on seeing the common Indian's optimism waning just ten years into independence. That song, well, also had a subtle reference to TB - "*woh berooh kamro mein khaasi ki thhan thhan*". Today, 58 years later, as the same *thhan thhan* still reverberates in millions of Indian homes daily, Sahir's reality check assumes epic significance and offers serious food for thought regarding India and its perceived greatness.

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