NEWSLETTER

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Internationale Nachrichten

1. TB: Why SA is testing new 'poster-child' drug to beat it

The approval in South Africa last year of the first new TB drug in 50 years was celebrated as a milestone in the fight against the global epidemic.

The drug – bedaquiline – is a new class of TB drug with the potential to tackle drug resistant strains of TB. Trials showed that, when combined with other multi-resistant-TB drugs, bedaquiline was more successful and shortened treatment time.

Though no magic bullet, bedaquiline has provided rich lessons about the challenges posed in global efforts to curb an epidemic that still notches up nine million new cases per year and causes 1.5 million deaths worldwide. Of these, 1.4 million cases were in Africa. More than 32,000 people in Africa suffer from Multiple Drug Resistant TB (MDR-TB). The number is rising, accompanied by worsening trends in the even deadlier extensively drug resistant TB (XDR-TB). This has significantly complicated the treatment of TB, as has the fact that at least 40% of patients in Africa are also infected HIV.

Bedaquiline was hailed as the poster child for new TB drugs when it was approved by the US Food and Drug Administration in 2012. Local approval was granted shortly after to allow the first South Africans to benefit from the drug under a programme put in place by the manufacturer, Janssen Pharmaceutica. Early access, or compassionate use programmes, allow a limited number of patients access to a medication under strict criteria.

In late 2014 South Africa's drug regulatory body the Medicines Control Council registered bedaquiline, paving the way for wider access to the drug. This decision was taken after concerted lobbying by the National Department of Health, Right to Care and Médecins Sans Frontières.

The Department of Health is aiming to roll out access to 3000 MDR-TB patients later this year, offering new hope to those who most desperately need it. But cost is preventing a more robust and comprehensive roll-out.

A six month course of bedaquiline costs around $1 000 per patient, even with concessional pricing for low and middle income countries. The already stretched Department of Health can ill-afford the additional costs.The current estimates are that multiple drug resistant TB accounts for three percent of the disease burden in South Africa but consumes over 30% of the national TB programme budget.

The cost challenge is compounded by the fact that bedaquiline is only successful if administered as part of a cocktail. There are very few alternatives that can be used and the cost of at least one – linezolid – is also prohibitive.

Patent restrictions have hampered access to cheaper generic versions. Last year Médecins Sans Frontières was granted special permission to use a substantially cheaper generic version of linezolid in its drug resistant TB programme in Khayelitsha, a peri-urban township in the Western Cape, South Africa. However, even this drug costs over $1 400 for a six month course.

Administering bedaquiline is a tricky business. One of its side effects of is impaired heart function This means it cannot be used with another new TB drug, delamanid, which also affects cardiac

function. There are also concerns about using bedaquiline in conjunction with anti-retrovirals.
There is another reason for extreme caution. Shortly after its introduction, reports of resistance to bedaquiline emerged. While this does not rule the drug out as a valuable component of the anti-TB toolbox, it does mean that its use must be closely monitored.
This means that access to the drug must be controlled, nurses need to be trained and patients monitored and tested continuously. Accurate reporting of the information collected is also essential. This underscores the critical need for effective health care systems and sustained funding.
South Africa has the dubious honour of having first put XDR-TB on the world map in 2006 when an outbreak was reported in a rural area in Kwazulu-Natal on the Indian Ocean Coast. Subsequently over 100 countries have reported cases.
The treatment success rate for MDR-TB in Africa are in line with global trends, at only around 50%. However, for XDR-TB, Africa fares poorly with treatment success rates of only 16%. This is not surprising given that fewer than half of the confirmed MDR-TB cases were started on appropriate treatment.
Attempts to reverse the rates of infection, and the rise in resistant strains are being confounded by lengthy and complex treatment regimens. Treatment of drug-susceptible TB can take a minimum of 6 months and involve a combination of drugs. Naturally, it is very difficult for patients to stick to them, increasing the risk of treatment failure and newly drug resistant strains.
The call for new TB drugs is increasingly urgent. The drug development pipeline is long, leaky and expensive. TB, in particular, poses a monumental challenge because certain strains persist even when exposed to reasonably effective drugs. How it does this is not fully understood and is one of our own research interests. Solving this puzzle may pave the way for more effective and more rapidly acting anti-TB drugs.
The chances of this happening are greater than they have ever been. Decades of research seem finally to be paying off, and several new TB drugs are being licensed for clinical use.
The use of bedaquiline should be viewed in this light. By adding to our body of knowledge and providing TB researchers, health care workers, activists and patients with valuable insights, it will hopefully pave the way for more effective treatments to come.
Source: BizNews, http://bit.ly/1BpNDOh (02.06.2015)

2. TB treatment programme may be generating more MDR cases

The Joint Monitoring Mission 2015 has come down heavily on the Revised National Tuberculosis Control Programme (RNTCP) and the Ministry of Health and Family Welfare for their inability to handle the MDR-TB crisis in the country. The report released last month reflects on the findings, conclusions, and recommendations made by it in 2012.
Despite its inability to diagnose drug-resistant TB, the national programme's heavy dependence on the century-old, insensitive smear microscopy as a primary diagnostic tool has been strongly criticised. Besides the lack of sensitivity, the microscopy is ill-equipped to diagnose drug-resistant TB. This is particularly worrying as the number of drug-resistant cases is steadily increasing.
The Standards for Tuberculosis Care in India (STCI) — a document drawn up by the Central TB Division in consultation with the WHO and national TB institutes — advocates drug sensitivity testing for all presumed MDR-TB cases. However, this may not become a reality in the near future. "Progress is threatened by slow uptake of the new molecular test" the JMM says. "Procurement of these tests is unaccountably delayed."
"The RNTCP currently treats patients without knowing their resistance profile," states the Joint Monitoring Mission report. This along with its current regimen of thrice weekly drugs even to those with prior resistance has been associated with "failure and amplification" of resistance to rifampicin drug. "It is therefore likely, under programme conditions, to be generating more MDR cases," it says.
While private doctors treat patients with daily dosing, the RNTCP follows a thrice weekly strategy. The report has emphasised the need to "accelerate implementation of the transition to daily dosing."
According to the report, turning to "universal drug susceptibility testing and switching to a daily

regimen with adherence support" can go a long way in addressing the problem of unwittingly exacerbating TB drug resistance in the country.

According to Dr. Soumya Swaminathan, Director of the Chennai-based National Institute for Research in Tuberculosis, the RNTCP is planning to start daily dosing using fixed dose combination in 5-6 States and then expand it to the rest of the country. "RNTCP is currently procuring drugs to make this shift," she said.

Another failing of the TB programme pertains to the mandatory TB notification by the private practitioners. "In spite of mandatory notification, TB patients [treated by private doctors] are not notified to the RNTCP," the report says. It wants the Ministry to develop e-Nikshay, an advanced version to the existing Nikshay system for notifying TB patients.

The national strategic plan (NSP) for TB control for 2012-17 developed by the Union Ministry of Health & Family Welfare had raised the bar for tackling the rapidly growing TB epidemic in the country. The main goals of the strategic plan are to provide universal access to early diagnosis and treatment and improve case detection.

Due to faltering on both counts, the JMM reports that the "implementation of the NSP for 2012-2017 is not on track — projected increases in case detection by the RNTCP have not occurred, vital procurements are delayed and many planned activities have not been implemented."

Worse, about two-thirds of the recommendations made by the Joint Monitoring Mission 2012 have "not been fully implemented." For the most part, the Central TB Division has "completed the policy work requested. Work is held up for lack of timely decisions, especially at central level," it states.

With the cost of treating a person with TB going up to 39 per cent of the household's annual expenditure, the report has recommended that the Ministry of Health minimises the out-of-pocket expenditure by families by "supporting the cost of TB testing and [providing] free drugs." It also wants the government to eliminate taxation on TB diagnostics and drugs considering TB as a public health emergency.

In order to ensure that patients receive the standards for TB care for India, the JMM has recommended that the government establishes a "state-of-art TB surveillance system for capturing all TB cases, public and privately-treated." This is essential for the country to "capture and respond to local and focal epidemics."

Source: The Hindu, http://bit.ly/1FDTlzW (02.06.2015)

3. HSE runs out of vaccine that protects babies from TB

Ireland's supply of the BCG vaccine that protects newborn babies against tuberculosis (TB) has run out, with a new batch not expected until July at the earliest. The HSE has admitted that it is experiencing delays with the supply of the vaccine and says it is a European-wide issue.

There is only one licensed manufacturer of the BCG vaccine in the EU and it has told the health authority that it could take eight weeks or more before new stock could be delivered. Because the BCG vaccine stock in all areas of the country expired last month, BCG vaccination clinics in HSE clinics and maternity hospitals have been postponed. The HSE has said its staff would arrange appointments for BCG vaccination clinics when the supply of the vaccine is restored.

There were 107 reported cases of tuberculosis reported to the HSE's Health Protection Surveillance Centre so far this year, compared to 116 over the same period last year.

Latest HSE immunisation uptake statistics show that at 12 months the uptake of the BCG vaccine has fallen from a high of 97% in 2010 to 86% during the third quarter of last year. However, the BCG update data was only available for five of the eight HSE areas and data from the HSE Southern are only related to Kerry data.

Laura Haugh, mother-in-residence for MummyPages.ie, said the HSE should have looked elsewhere for the BCG vaccine. "This is not a new problem. The HSE has been experiencing supply difficulties for the last 10 years and it seems to happen year in, year out, at various intervals," she said. Ms Haugh said parents should not worry that their child is at risk if they do not receive the vaccine at birth, or it is delayed by a number of months, as the risk of TB was very low. "A baby does not need to have the

BCG vaccine before getting any of the other vaccines that are included in the very comprehensive immunisation schedule," she said. A child needs five visits to a GP to complete their course of vaccines and Ms Haugh said parents would be reminded at each visit about the BCG vaccine. The public health nurse would also remind parents about the vaccine when making initial checks during the first three months of their child's life. Ms Haugh said arrangements could be made for a baby to receive the BCG vaccination as well as other vaccines on the same day. While the situation was not ideal, children who had not received the BCG over the first 13 months of their life would be picked up by the health system. "I know it is something that first time mums worry about but any concerns they have would be alleviated by talking to their GP," said Ms Haugh.
Source: Irish Examiner, http://bit.ly/1JVLvVr (02.06.2015)

Forschung & Entwicklung

1. New online tool to predict genetic resistance to tuberculosis drugs
Finding out what drugs can be used to treat a patient with tuberculosis (TB) can be sped up by days or weeks, thanks to a new free online tool. The TB-Profiler tool, developed by a team of scientists led by Dr Taane Clark at the London School of Hygiene & Tropical Medicine, analyses and interprets genome sequence data to predict resistance to 11 drugs used for the treatment of TB. This rapid tool only takes a few minutes and means that sequence data can now be used without delay. Importantly, it also removes dependence on specialised bioinformatics skills that are not readily available in clinical settings. Data on how the tool works is published in open access journal Genome Medicine. Speeding up the process to find appropriate drugs when treating a patient with drug-resistant TB improves the likelihood of cure. By enabling the optimum course of treatment to be selected without delay, toxic drugs found to be ineffective because of resistance can be disregarded, relieving patients of damaging, unpleasant, and often long-lasting side effects. Researchers say the TB-Profiler tool will aid control of drug resistant TB, the emergence of which currently threatens to derail global efforts to control the disease. The World Health Organisation estimates that 5% of the world's 11 million TB cases have multi drug-resistance disease (MDR-TB), with approximately 480,000 new MDR-TB cases and 210,000 deaths in 2013. The TB-Profiler was developed using global data and refers to a library of 1,325 mutations to M. tuberculosis (the bacteria that causes TB), making the tool the most comprehensive and accurate data source to date. Dr Taane Clark, Reader in Genetic Epidemiology and Statistical Genomics, said: "Sequencing already assists patient management for a number of conditions such as HIV, but now that it is possible to sequence M. tuberculosis from sputum from suspected multi-drug resistance patients it means it has a role in the management of tuberculosis. We have developed a prototype to guide treatment of patients with drug resistant disease, where personalised medicine and treatment offers improved rates of cure." Traditional lab-based methods of determining resistance involve growing the bacteria to see if it survives the drug, a process that can take weeks and sometimes months, and requires stringent safety measures to protect the laboratory personnel. The researchers highlight that their research demonstrates the potential of whole genome sequencing to increase the accuracy of molecular tests for resistance, with improved sensitivity and specificity. The tool also provides data on the genotype of the bacteria which can be used in epidemiological studies and by public health experts to track chains of disease transmission. Co-author Dr Ruth McNerney of TB Alert added:"This is a welcome step forward in our battle against drug resistance. It is now time to take sequencing out of the research lab and into the clinic. Patients with drug resistant disease have to endure many months of treatment with toxic drugs with no guarantee of success. Personalised treatment will increase their chances of survival while minimising the horrible side effects."
Source: London School of Hygiene & Tropical Medicine, http://bit.ly/1KqZwZx (02.06.2015)

2. Neglected disease research and development: a smart use of aid dollars

Governments treat neglected disease product research and development (R&D) as they would treat products for commercial diseases – with the expectation that the pharmaceutical industry will take early stage and basic research, and translate it into new health technologies. Due to the nature of neglected diseases, this is not the case. Aid agencies can respond to the pharmaceutical industry gap and make smart investments in neglected disease R&D by balancing funding for health programs that use ineffective tools, with funding to best-in-world developers to create new and better tools.

Neglected diseases such as malaria, tuberculosis (TB) and other, lesser known, poverty-related illnesses affect over a billion people, and result in 6 million deaths each year, almost exclusively in the developing world. Much of this disease burden could be prevented if more effective drugs, vaccines and diagnostics existed.

Most people who suffer from neglected diseases live in developing countries and do not have the resources to pay for health products. The lack of market forces to encourage investment in neglected diseases means that R&D is primarily a public responsibility, with industry and not-for-profit funders providing additional philanthropic investments to supplement government contributions.

Funding R&D is a high impact investment for governments. Once a new product has been developed, that product has the potential to change the lives of thousands. For example, TB Alliance's three-drug combination therapy for TB and multidrug resistant TB (MDR-TB), PaMZ, which is currently in Phase III clinical trials, has the potential to revolutionise MDR-TB treatment. Current MDR-TB treatment can take up to two years to complete, and requires the patient to take up to 12,600 pills throughout the treatment, as well as daily injections for the first four months. The full course of treatment can cost up to $5000 per patient in the developing world. PaMZ has the potential to reduce treatment time for MDR-TB to just six months, reduce the number of pills required throughout the full course of treatment to 360, and eliminate the need for injections. The treatment has been designed and priced for the developing world, so a full course will cost 10% of the existing therapy price. PaMZ could be available by as early as 2018.

Governments provide two-thirds [PDF] of all funding for neglected disease R&D. This funding is predominantly delivered through two different types of agencies: science & technology (S&T) agencies, such as the National Health and Medical Research Council (NHMRC); or aid agencies, such as the Department of Foreign Affairs and Trade (DFAT) (formerly AusAID). 13% of global government funding in neglected disease R&D since 2007 has come from aid agencies.

S&T agencies like NHMRC predominantly invest in domestic universities and research institutes that focus on basic and early stage research. Translating these early stage research discoveries into a new drug or vaccine ('product development') requires specialist expertise and high levels of investment. For 'commercial' diseases such as cancer and diabetes, pharmaceutical companies who are looking to develop a product they can sell for profit have a natural incentive to provide this expertise and investment. In the case of neglected diseases, this incentive is missing. For these diseases, product development is largely the domain of not-for-profit Product Development Partnerships (PDPs), who combine pharmaceutical company expertise with public and philanthropic sector funding.

This is where aid agency funding for neglected disease R&D is critical. Insufficient funding for product development creates a bottleneck situation, in which the fruits of S&T agency investments in basic and early stage research are not translated into products. Aid agency funding to best-in-world product developers (such as PDPs) increases investment in the product development stage of the pipeline, relaxing the bottleneck and helping translate research into life-saving tools.

Australia ranks fifth highest out of all national governments for investment in neglected disease R&D between 2007 and 2013, with average funding of USD$35 million per year. The majority of this funding (82%) came from the NHMRC.

Just 4% of Australia's neglected disease R&D funding came from AusAID/DFAT between 2007 and 2013. As a result, Australia's aid for neglected disease R&D ranks 14th out of all aid agencies globally. Prior to 2012, Australia was unique for the fact that it did not give any aid funding at all to product development for neglected diseases. But in 2012, in response to the 2011 Independent Review of Aid

Effectiveness [PDF], the Australian Government implemented the Medical Research Strategy (MRS). The MRS committed AUD$40 million to medical and operational research for neglected diseases, disbursed over five years, with the first AUD$10 million committed to PDPs for TB and malaria.

After just one funding round, following aid budget cuts in December 2013, the MRS was put up for review, and funding disbursements were put on hold. R&D did not leave the agenda though. A replacement aid funding scheme for medical R&D and operational research for neglected diseases was committed in June 2014, with the announcement of the new aid paradigm. This commitment was honoured in March of this year, on the eve of World TB Day in Canberra, with an investment of AUD$30 million to TB Alliance, FIND and Medicines for Malaria Venture to help bring new diagnostic tests and drugs for TB and malaria to market, to be used over three years.

DFAT's most recent investment in neglected disease R&D is commendable and is testament to the cost-effectiveness of R&D for neglected diseases. Neglected disease R&D is one of the only areas that received a bump in funding in the aid-unfriendly 2014-15 federal budget, and one of the few to be protected in the 2015-16 budget. In fact, Australian aid will report its highest level of funding to neglected disease R&D this year, despite massive aid cuts across the board.

Despite improvements, Australia's aid program still lacks balance between funding programs that utilise existing tools, and funding new, more effective products. For example, DFAT recently announced AUD$15 million in funding to support TB programs in Papua New Guinea (PNG), bringing Australia's TB control funding in PNG up to nearly AUD$60 million over three years. This funding is predominantly targeted at MDR-TB. There were an estimated 560 new MDR-TB cases in PNG in 2013 out of 25,000 new TB cases in total. Drug sensitive TB and MDR-TB patients in PNG and globally could benefit from TB Alliance's PaMZ drug; yet R&D for new TB drugs will receive just over AUD$10 million over the next three years.

Balancing investments in this way is a high impact and cost-effective use of budget that can eventually create savings in other health programs. New and improved technologies enable operational programs to function more efficiently, freeing up more funding.

Until the World TB Day 2015 investment of $30 million, Australia's only aid funding for neglected disease product development was $10 million in 2012 [PDF]. In that year, R&D investment made up just 0.2% of the aid budget. A smart balance of investment could be a commitment of just 1% of the aid budget to neglected disease R&D. This would still leave the vast majority of the aid budget for operational activities, and contribute substantially to development of more effective products.

Aid agencies have an important role to play by investing in product development. DFAT should continue to invest in best-in-world organisations that specialise in product development. Focussing funding in this way increases opportunities for valuable research to be translated into products that could save lives across the developing world.

Source: Devpolicy Blog, http://bit.ly/1FiCPmG (02.06.2015)

3. TB: India study confirms Xpert diagnostic test's superiority

For the first time in India, the superiority of Xpert MTB/RIF over smear microscopy for bacteriological confirmation of pulmonary TB and in diagnosing MDR-TB (Multi Drug Resistant-TB) patients before initiating any treatment has been proved in a large-scale study undertaken in 2012-2013.

The latest study, the largest in the world, found that using Xpert molecular test as an initial diagnostic test for TB in public health facilities "increased the rate of TB case notification by 16 per cent and of bacteriologically confirmed TB by 39 per cent." Also, the rifampicin-resistant TB case notification increased by "fivefold," notes a paper published recently in the journal *PLOS ONE*. Dr. K.S. Sachdeva, Additional Deputy Director General of the Central TB Division, New Delhi is the first author.

The study was undertaken in 18 TB programme units — eight in rural areas (3.9 million population), six in the urban areas (3.4 million population) and four in tribal and hilly areas that are difficult to reach (1.5 million population). The study was implemented in two phases — baseline and intervention. The baseline phase used smear microscopy to diagnose TB in over 10,500 presumptive

pulmonary TB patients; the intervention phase used Xpert diagnostic testing on over 70,500 presumptive pulmonary TB patients.
Unlike smear microscopy, Xpert has excellent sensitivity and specificity to TB and can return results in less than two hours. Besides diagnosing TB, Xpert can tell if a subject has rifampicin drug resistance.
The results strongly suggest that Xpert can substitute smear microscopy as an initial diagnostic test to diagnose more number of TB cases and also for diagnosing rifampicin resistance. The fivefold increase in identifyingrifampicin resistant cases became possible only because Xpert was used for testing drug resistance in all presumptive TB patients. Conventionally, drug susceptibility testing is offered rather selectively to patients who have already been diagnosed as suffering from TB and who run a high risk of having drug resistance.
Also, almost one-third of rifampicin resistant TB cases were detected by using Xpert in treatment naïve cases. In India, the prevalence of rifampicin resistance in new TB cases is estimated to be around three per cent. Generally, drug resistance comes up in those who have been irregular in taking TB medicines or in those who have stopped medication midway through the treatment.
"This finding demonstrates the potential impact of extending universal DST [drug susceptibility testing] to all presumptive TB cases under routine programme conditions in improving case finding of TB as well as rifampicin-resistant TB, particularly in areas where drug-resistance in treatment naïve cases is of substantial concern," the authors state. The observations may be useful in guiding the decisions on scale-up of universal DST in the country.
The study has another important implication. Regardless of prior treatment history, treatment for MDR-TB can be initiated immediately in those patients who are found to be rifampicin resistant through Xpert diagnostic testing, they note.
As per the WHO guidelines, there is no need for a repeat drug susceptibility testing for MDR-TB in the previously treated TB patients.
In the case of those who have never been on anti-TB treatment earlier, the researchers say that there is a "strong case" for initiating second-line treatment for TB when Xpert result is positive for rifampicin resistance. Though the WHO guideline requires a parallel confirmatory testing for drug susceptibility using liquid culture for new cases, the question is whether it should be done away with based on the latest study results
The current WHO guideline for a confirmatory drug testing is based on a positive predictive value of 60-65 per cent. But for the first time, this study has had a high positive predictive value of 91.3 per cent for new cases (treatment naïve cases). It is now for the RNTCP to decide whether more research is required before doing away with the need for a confirmatory susceptibility testing in new cases or to issue fresh guidelines based on the results of this study.
Source: The Hindu, http://bit.ly/1KBdfjv (02.06.2015)

4. TB Alliance Launches "Nix-TB" Clinical Trial to Test New XDR-TB Treatment
TB Alliance and its partners announced the start of a clinical trial of a new regimen to treat extensively drug-resistant tuberculosis (XDR-TB.) It is the first study to test an all-oral drug regimen, comprised of drugs with minimal pre-existing resistance, that has the potential to shorten, simplify, and improve treatment for XDR-TB.
"XDR-TB is an absolute devastation to patients, their families, and communities. The study is the first to test a novel and potentially transformative regimen for XDR-TB, which could be a valuable tool as we battle this problem on the front lines in South Africa and around the world," said Francesca Conradie, MD, the Principal Investigator of the Nix-TB (New Investigational Drugs for XDR-TB) trial and Clinical Advisor at Sizwe Hospital, in Johannesburg, South Africa. "The strategic emphasis by our National Department of Health on clinical research for drug-resistant TB coupled with a rigorous regulatory framework has enabled this trial to be conducted in South Africa."
XDR-TB is a strain of tuberculosis, airborne and infectious, that has resulted from progressive antibiotic resistance and is resistant to four commonly used anti-TB drugs. XDR-TB has been reported in 100 countries. It is complicated and expensive to treat and results in high rates of death. Today,

there are no regulatory-approved XDR-TB treatments.
Currently, healthcare providers treat XDR-TB by individualizing treatment regimens, frequently using antibiotics not normally used for TB as well as toxic medicines not meant for the long treatment duration that TB requires. People with XDR-TB can be on treatment for two years or longer, with thousands of pills and injections, extensive side effects, and little success. In a recent review of the experience in South Africa, after two years of treatment only a fraction of people—16 percent—with XDR-TB were cured.
Resistance to available antibiotics has plagued efforts to combat the TB pandemic, creating distinct drug-resistant strains of the bacteria such as multi-drug resistant TB (MDR-TB) and XDR-TB and rendering current treatments inadequate. However, the three drugs that comprise the treatment being tested in Nix-TB have novel mechanisms of action. The three-drug regimen consists of bedaquiline (B), which received conditional regulatory approval in several high-TB disease burden countries; the novel antibacterial drug compound pretomanid (Pa), which is being tested in multiple clinical trials; and linezolid, an oxazolidinone, which has been used off-label to treat TB.
If the regimen tested in Nix-TB is successful and safe in XDR-TB, that will pave the way for expanding the study, testing its potential for use in people with MDR-TB and then potentially in people with drug-sensitive TB. Having a regimen that would be usable in such a broad range of TB patients could significantly improve TB control efforts globally.
“We are testing a promising treatment for XDR-TB today, but the longer-term potential of such a regimen is even greater. We now see the possibility of a single TB regimen that can treat virtually all patients with active TB with a relatively simple and affordable regimen,” said Mel Spigelman, MD, President and CEO of TB Alliance. “The launch of Nix-TB is a critical step to achieve the vision of a truly short-course, simple, affordable and well-tolerated universal treatment regimen.”
Nix-TB is a partnership between TB Alliance, a not-for-profit organization with the mission of developing improved TB treatments and the sponsor of the trial; Janssen Pharmaceutica NV (Janssen), the originator company that in 2009 granted a royalty-free license to the TB Alliance for the development and commercialization of bedaquiline in the field of drug-susceptible TB; and the sites in South Africa where the study is and is expected to be conducted (Sizwe Hospital, TASK at Brooklyn Chest Hospital, and THINK at Doris Goodwin Hospital).
The cost for the initial phase of Nix-TB is covered by a group of long standing TB Alliance donors. TB Alliance is starting to bring together additional funding to expand the study and the number of sites.
“The availability of new TB drugs offers the unprecedented opportunity to improve treatment for people with TB. However, the existence of individual new drugs is not enough,” said TB Alliance’s Spigelman. “TB must be treated in multi-drug combinations or regimens to enhance efficacy and prevent the development of resistance. Therefore, the Nix-TB trial fills a critical gap and capitalizes on the availability of novel drugs by studying them together in the most vulnerable TB population, those with XDR-TB, and in such a way that provides clear understanding of how to use the treatments to maximize their impact on the epidemic.”
Source: TB Alliance, http://bit.ly/1AYYI8B (02.06.2015)

5. Tuberculosis among migrant populations in the European Union and the European Economic Area

(...) The World Health Organization (WHO) estimates that 4% of TB cases in 2013 occurred in the WHO European Region, with Eastern Europe particularly affected by the TB epidemic. Within the European Union/European Economic Area (EU/EEA), TB notifica- tion rates have been declining over the last decades, reaching 14.2 per 100 000 population in 2011. Despite this decline, specific subgroups of the population, such as homeless people, migrants, people living in urban settings and prisoners, remain at an increased risk of acquiring TB infection and developing active disease; this representing a challenge for TB control programmes. In particular, in many EU/ EEA settings the contribution of cases among foreign-born individ- uals to the total TB burden is increasing each year. The pathways through which migrants are at higher risk for both transmission of TB infection and

development of disease might include coming from high TB burden countries as well as being more exposed to socioeconomic and behavioural risk factors in their host countries. Migrants settled in host countries may also face legal, cultural, linguistic and socioeconomic barriers to healthcare that can delay TB diagnosis and limit access to health education and effective treatment.

Few data are available on the TB burden in migrant populations in the EU/EEA. However, understanding the diverse health needs of migrants is becoming increasingly important, not least due to the

rising proportion of migrants in the EU/EEA. From 1990 to 2010, the proportion of foreign-born individuals in the EU/EEA increased from 6.9 to 9.7% of the total population. In 2011, it is estimated that 48.9 million foreign-born residents were residing in the EU, with 32.4 million born outside it. To address the data gaps on infectious diseases among migrant populations, in 2012 the European Centre for Disease Prevention and Control (ECDC) commissioned a report titled 'Key Infectious Diseases in Migrant Populations in the EU/ EEA'. This article is based on that report and collects, critically appraises and summarizes the best available evidence on the burden of TB in migrant populations in the EU/EEA. Specific objectives are: (i) to estimate the burden of TB in foreign-born populations when compared with native populations in EU/EEA countries based on notification data, highlighting geographical patterns and time trends; (ii) to establish the burden of TB in migrants by gender, age group and country of origin as well as other relevant subgroups and (iii) to identify limitations of the available data and information gaps.

To meet the specified aim and objectives, we retrieved data using three methods: (i) a comprehensive review of the literature, (ii) analysing relevant data from The European Surveillance System (TESSy) and (iii) evidence provided by infectious disease and migration experts at an ECDC meeting on migrant health held in 2012. (...)

To our knowledge, this is the first study to use multiple sources of data—including the largest available European database on infectious disease notifications—to assess the burden and specific features of TB in migrant populations in the EU/EEA.

Overall, in the EU/EEA, the share of foreign-born subjects among notified TB cases is increasing; this percentage is higher in Scandinavian and Northern EU/EEA countries and lower in Eastern EU/EEA settings. This relative rise of TB cases in foreign-born individ- uals is due to both a real increase, as well as attributable to the sizeable drop in native cases in certain countries.2 In addition, an increase in the absolute number of TB cases should be interpreted in the context of the global migration flows between different countries (Supplementary table S1). TB incidence rates are higher in foreign-born populations as compared with native populations. However, it is important to note that interpretation of TB incidence rates in migrants remains challenging.5 Unfortunately, migration statistics do not include irregular migrants and thus denominators may be underestimated. Moreover, as ECDC does not have access to migrants' denominators figures (neither total, nor country of origin-specific denominators) surveillance data reported by the ECDC do not include incidence rates by geographical origin of cases.

The country of origin of migrants might also impact on the TB burden in selected settings. For example, the UK, in contrast to other countries with high immigration rates, hosts many migrants from high TB burden countries (10% of migrants in the UK come from countries with a TB incidence 250/100 000) which may explain the increasing trends in TB incidence reported in the country. In other countries that have experienced progressively decreasing TB notifi- cation rates, such as Germany, Italy and Spain, the greatest share of migrants come from countries with relatively low TB incidence.

Foreign-born TB cases are younger when compared with native cases. This is mainly due to the different age structure of migrant and native populations in EU/EEA, but might also be linked to the different natural history of TB in the two populations.

No clear pattern emerged when analysing TB transmission by origin of case. It is likely that the disease develops through different pathways in foreign-born and native subjects. For migrants, clinical disease can come about through reactivation of infection acquired in the country of origin or

through recent infection acquired in the host country. Furthermore, in some cases, infection in migrants is acquired during visits to the home country. On the contrary, in elderly native subjects, the disease may be more attributed to reacti- vation of latent TB infection. No evidence was retrieved on TB trans- mission between native citizens and migrants, and fears that the presence of migrants might increase TB in native populations seem to be unjustified. As mentioned earlier, the pathways through which migrants are at higher risk for both TB infection transmission and TB disease are difficult to disentangle. To determine which risk factors are associated with TB among migrant populations would require detailed studies in every country using individual level data, for example a series of case control studies, which is beyond the scope of the current study.

Migrants are more frequently reported to have extra-pulmonary TB than the native population. No clear pattern emerged on drug resistance by migrant status, although MDR-TB is most frequently reported in migrants originating from high MDR-TB burden settings. There is however a need to get a better understanding of drug-resistant TB among migrants. Reporting completeness of HIV status among TB cases is too low to derive meaningful conclusions, and improvements need to be made to collect better data on HIV status for both the native and migrant populations.

With regard to TB in children, foreign-born children account for a lower proportion among all paediatric TB cases (15.3%), when compared with the percentages of foreign-born reported in the overall population (26%). However, data on paediatric TB by origin of cases should be interpreted with caution, as surveillance data in most countries do not distinguish between children born in the host country of foreign-born parents from those born of native parents. This is a matter for concern because children of migrants may experience similar social, behavioural and environmental risk factors as foreign-born populations.

Our study has limitations. These are mainly due to the hetero- geneity of original studies in terms of study setting, study popula- tions, data collected, methods applied and exposure and outcomes assessment which limited the potential of pooling estimates and findings. Moreover, the lack of data on denominators is a main limitation when assessing the burden of TB in migrant populations, as incidence estimates are often unreliable and tend to bias towards overestimations. In addition, only papers published in English were included in the literature review, which may limit the number of studies included from EU/EEA-Member States that do not routinely publish in English.

Available data on TB burden in migrant populations in Europe is incomplete, partly due to inconsistent surveillance and reporting systems in place in different countries and to the difficulties of properly tracing migrants in denominators when estimating incidence rates and trends. However, the collection and analysis of TB surveillance data in Europe since 2008 by the ECDC and WHO/ EURO is an important step towards harmonization of national sur- veillance systems and data sharing. The TB case definition is applied consistently by EU/EEA-Member States in their surveillance systems and much relevant information on migration status is collected. In 2010, 29 EU/EEA countries reported data on the geographical origin of TB cases, with data completeness of 97.5%.

The efforts taken in recent years to strengthen and harmonize TB surveillance systems in the EU/EEA and capture migrant-specific information have led to a greater understanding of the association between migration and TB. Nevertheless, additional steps are still needed to strengthen national surveillance systems by harmonizing and improving data completeness. In addition, better data are needed on the extent to which health determinants and living conditions in the host country influence migrants' vulnerability to TB. This information is of fundamental importance to better plan, implement and evaluate targeted TB prevention and control inter- ventions in the EU/EEA. Priority must be given to addressing migrant health and ensuring that all individuals have access to prompt, high-quality TB care.

Source: European Journal of Public Health, http://bit.ly/1dccCyO (02.06.2015)

Reportage

1. Taming one of world's oldest diseases in fast-growing Papua New Guinea

KEREMA, Papua New Guinea — Six-year-old Elisa Iboro did everything she could to avoid swallowing the 14 pills held out on a hand in front of her. She squirmed in her mother's arms. She cried. She looked sideways and simply ignored the life-saving drugs.

"Let's go, you know this is important, come on," pleaded Dorothea Deslandes, a French nurse with the medical charity Doctors Without Borders (MSF). Elisa has tuberculosis (TB), a highly infectious but curable disease that leads to fever, fatigue, chronic cough and possibly death if left untreated. But even with medication, her situation is precarious: She has developed a multidrug-resistant strain of the disease, the result of an earlier interruption in her treatment.

One of the world's oldest-known diseases, tuberculosis (TB) has essentially been eradicated in the developed world. But it remains a serious danger in poorer regions, where a staggering 1.5 million people die every year of the illness.

Papua New Guinea has the highest rate of tuberculosis in the Pacific region, where 60 percent of new cases originate, according to the World Health Organization. The epidemic there is being described as a national emergency. In many parts of the country, including vast swaths outside of the capital, health services are scarce, the result of chronic underdevelopment, along with years of government neglect and mismanagement. Elisa's situation highlights the difficulties of eliminating TB from one of the most underdeveloped corners on Earth. At the time she stopped receiving treatment for her initial case of TB, seven other members of her family were bedridden with the disease, and too ill to make the seven-hour journey from their remote mountain household to the coastal hospital to restock on pills for her. "We just couldn't return to the hospital to get another supply, when I was also sick," said Linda Paul, Elisa's mother.

In Papua New Guinea, approximately 30,000 people every year are newly infected with TB, and in many regions of the country, cases of multidrug-resistant strains are on the rise. Gulf Province, where Kerema Hospital is located, was identified by government officials as one of three "hot zones" where the disease has spiked. The TB incidence rate there can reach 1,450 per 100,000 people — more than 12 times the global average. "Tuberculosis is a constant," said Elvis Pyrikah, the provincial disease controller for Gulf Province. "Patients come every day."

Treatment for the bacterial infection usually lasts six months, but with drug-resistant strains it can last a grueling 24 months and require several rounds of drugs, ongoing medical supervision and daily injections. Nearly half of TB patients, like Elisa Iboro, don't complete their course of treatment, according to the World Health Organization, leading to a much greater risk of developing a drug-resistant strain. One of the main reasons is access. More than 85 percent of the population lives in rural areas — the highest percentage in the world — and medical facilities can be hours or even days of travel away. In the country's vast landscapes, getting a correct diagnosis and monitoring treatment can be nearly impossible.

After nearly 30 minutes of coaxing, Elisa Iboro, with tears still fresh on her cheeks, eventually swallowed the bitter-tasting medicine — but only after the MSF nurse ground the pills into a fine powder and dissolved them in honey-infused water. Elisa's neck was crisscrossed with keloids, thick scars that developed after the disease escaped her lungs and infected her lymph nodes. Her mother lifted her onto a gurney for a painful injection, and the crying began anew. It is a daily routine that will await her for another two long years.

For many in the country, access to decent health care remains a broken promise. In principle, all primary and public health care in Papua New Guinea is free of charge. But the country has only one doctor per 17,500 people, compared with 302 in neighboring Australia. The vast majority of those doctors live and work in the capital Port Moresby. And despite recent economic gains, many in Papua New Guinea simply don't have enough money to afford treatment.

Per capita GDP in Papua New Guinea has nearly quadrupled in the past 10 years, the result of a

resource boom that brought the country into middle-income status. New liquid natural gas projects were recently announced, including a $6 billion investment by Inter Oil in Kerema's Gulf Province, near the hospital. The International Monetary Fund estimates the country will have the fastest-growing economy in the world in 2015. Yet development has stagnated at the local level, and in many areas, poverty and inequality has deepened. Nearly 40 percent of the population still lives below the poverty line, according to the United Nations.

"Most of them here, they don't have money to come and access the hospital," said Paul Warren, a doctor at Kerema Hospital. "This place is surrounded by swamps and a river. They can't even afford to buy food." Warren sat in one of the only air-conditioned rooms at the hospital, and explained that he is one of only two doctors at the health facility, responsible for the entire province of 160,000 people. The hospital's head doctor was evacuated last year after he was infected with TB of the spine, and without a qualified supervisor, Warren said, his teams can perform only the most basic medical procedures. "The quality of health care that we provide is maybe 10 to 15 percent," said Warren. "That means it's not good." Analysts say the lack of quality health services across Papua New Guinea points to systemic corruption at the top, and a long pattern of state neglect.

A 2013 World Health Organization review of one district indicated that health systems were "grossly dysfunctional, characterized by weak leadership and ineffective management structures and practices," according to the country's National Strategic Plan for Tuberculosis Control. The same report said that maintenance of health infrastructure across the country was a "major concern," with the majority of health facilities having intermittent or no access to electricity and water. Many remote aid posts — nearly four in 10 — have simply stopped operating, the report said.

"We have these stories of people dying of curable diseases, of people who are not having access to medical drugs, not having access to specialized doctors. It's happening on a daily basis," said Sam Koim, chairman of Papua New Guinea Anti-Corruption Task Force, which investigates corruption within the health department. "We have so much money, but that money is not trickling down to the real benefits that the people need at this time."

In recent years, the government has taking steps to reverse the situation, experts say, by rebuilding the health system from the bottom up. Recording and reporting practices are improving, and the disease is being caught earlier and more often, with case detection increasing to 89 percent in 2013 from 61 percent in 2010. Foreign governments and international donors have also stepped in to help develop Papua New Guinea's health facilities, despite the flow of cash entering government coffers. The Australian government, which is concerned about the growth of TB on its doorstep, recently pledged assistance, as well as the Global Fund and Doctors Without Borders.

Alex Paouke, an elderly subsistence farmer from the village of Koaru, sat sweating in an unventilated wood and tin shed at the rear of Kerema Hospital. It was a makeshift isolation shelter for patients like him with contagious or drug-resistant strains of the disease. He pointed to swollen, black splotches on his shoulder and back where the infection was still active, remnants from when he caught TB from his son, who died of the disease. Paouke said he had made several trips to health centers in the capital Port Moresby and near his village without ever receiving a correct diagnosis. "Some of my relatives finally told me to go to Kerema," explained Paouake. "They said, 'There are some white doctors there. Maybe they'll be able to help you.'"

Doctors Without Borders is providing additional doctors, nurses and laboratory facilities to the hospital. Since arriving in Kerema in May 2014, they have diagnosed about 50 new cases of TB per month, they said, and are experimenting with novel approaches including using drones to transport sputum samples and medicine from outer health clinics to the Kerema laboratory. The charity is also helping build a new TB ward in Geru Hospital, in the capital Port Moresby, where about 25 percent of TB patients seek treatment. "It's a very difficult situation," said George Gede, hospital manager at Geru. "If everybody thought about it and prioritized the problem, TB is a glaring problem and everybody would be helping us to do this work."

"It hasn't happened," he added.

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