NEWSLETTER

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Internationale Nachrichten

1. The Lancet: Mass imprisonment of drug users driving global epidemics of HIV, hepatitis, and tuberculosis

The War on Drugs, mass incarceration of drug users, and the failure to provide proven harm reduction and treatment strategies has led to high levels of HIV, tuberculosis, and hepatitis B and C infection among prisoners--far higher than in the general population. With an estimated 30 million people passing in and out of prisons every year, prisoners will be key to controlling HIV and tuberculosis epidemics worldwide, according to a major six-part Series on HIV and related infections in prisoners, published in *The Lancet* and being presented at the International AIDS Conference in Durban, South Africa.

"Prisons can act as incubators of tuberculosis, hepatitis C, and HIV and the high level of mobility between prison and the community means that the health of prisoners should be a major public-health concern. Yet, screening and treatment for infectious diseases are rarely made available to inmates, and only around 10% of people who use drugs worldwide are being reached by treatment programmes", says lead author of the Series and President of the International AIDS Society Professor Chris Beyrer, John Hopkins Bloomberg School of Public Health, Baltimore, USA. "The most effective way of controlling infection in prisoners and the wider community is to reduce mass imprisonment of injecting drug users."

Worldwide, between 56% and 90% of people who inject drugs will be incarcerated at some point. In parts of Europe, over a third of inmates inject drugs (38%), in Australia (55%) it is more than half. This is in stark contrast with injecting drug use the general population (0.3% in EU and 0.2% in Australia).

Data presented in the Series show that with growing numbers of injecting drug users in prison, the prevalence of infectious diseases has also increased (...). For example:

- Levels of HIV infection are 20 times higher among prisoners in western Europe than the civilian population (4.2% vs 0.2%), and around three times higher among prisoners in eastern and southern Africa (15.6% vs 4.7%) and north America (1.3% vs. 0.3%).
- While most prisoners are men, women and girls are the fastest growing imprisoned group worldwide, and in most regions of the world, levels of HV infection are higher in female inmates than male prisoners including eastern Europe and central Asia (22% vs 8.5%).
- High rates of hepatitis C are also seen among prisoners, with 1 in 6 inmates in parts of Europe and the USA carrying hepatitis C virus.
- Prevalence of active tuberculosis is higher in prisons than the general population in all settings. One study demonstrated that prevalence was 40 times higher in one prison in Brazil than the general population.

Moreover, new estimates produced for the Series suggest that up to half of all new HIV infections over the next 15 years in eastern Europe will stem from increased HIV transmission risk among inmates who inject drugs; and imprisonment could be responsible for three-quarters of new tuberculosis infections among people who inject drugs, and around 6% of all yearly tuberculosis

infections (...).
High rates of injecting drug use in some settings, lack of access to condoms, unsanitary conditions, and gross overcrowding have made prisons and detention centers high risk environments for spread of these infections. Almost half of countries in sub-Saharan Africa report that prisons are at 150% capacity or higher. Increased frequency and duration of imprisonment increase individual risk for these infections, particularly HIV and tuberculosis.
But these health issues do not remain confined to prisons. With around 10.2 million people imprisoned worldwide at any given time (nearly 2.2 million in the USA alone), and an estimated 30 million passing in and out of prison each year, substantial numbers of undiagnosed and untreated infections in prison can spread to the community when prisoners return home. Treatment interruptions upon release threaten former prisoners and their communities.
The Series brings together a wealth of evidence to show that countries can reduce and even reverse infectious disease transmission by scaling up proven harm reduction and treatment strategies in prisons like opioid agonist therapy (OAT), antiretroviral therapy (ART), hepatitis B vaccination, condom distribution, and sterile needle and syringe exchange.
Modelling conducted for the Series suggests that reducing mass incarceration of people who use drugs, in this case lowering the number of prisoners who inject drugs by 25%, could result in a 7-15% drop in new cases of HIV among injecting drug users in the community over 5 years. Similarly, scaling up OAT (eg, methadone and buprenorphine) to all those in need in prison, and after release, could prevent over a quarter (28%) of new HIV cases in people who inject drugs in just 5 years (...).
Although such interventions have proved successful in prisons and are required by international human rights law (...), they are severely underfunded and are often impeded by discrimination and restrictive prison rules in all countries--both in high- and low- income countries. The fact that in many countries, prison health services are isolated from national public health programmes and the ministry of health has exacerbated the issue.
The authors reviewed six of the fifteen key interventions for the prevention and treatment of infectious diseases in prisons recommended by WHO/UNOCD: information (education, communication), counselling and testing, sterile needle exchange, OAT, condom provision, and ART. Yet, globally, only eight countries (Moldova, Armenia, Kyrgyzstan, Germany, Luxembourg, Portugal, Spain, and Switzerland) provide all six interventions (...).
In 2014, only 43 countries offered OAT in at least one prison and less than 1% of prisoners worldwide who need it actually receive this treatment. In western Europe, only a third (10 of 29) of surveyed countries reported hepatitis C screening programmes for prisoners; and in 2012, ART was available to prisoners in just 43 countries worldwide.
But, several countries have achieved success. For example, in Iran, where more than 60% of prisoners are incarcerated for drug-related crimes, HIV prevalence among injecting drug users in prisons reduced from 18.2% in 2003 to 2.3% in 2007 due to a combination of voluntary HIV testing, OST, condoms, and needle and syringe exchange programmes (...).
"The response to the HIV, tuberculosis, and hepatitis epidemics in prisons has been slow and piecemeal, and the majority of governments continue to ignore the strategic importance of prison health care to public health", says Professor Beyrer. "Most strategies for dealing with infectious diseases in prisons focus on a zero-tolerance approach to drug users. The fact that infection rates are still climbing confirms that this approach does not work."
He adds, "Reforming laws and policies that criminalise drug use and sexual behaviours will be crucial to reducing prison populations that put large numbers at risk of potentially life-threatening infections, and which can be more effectively prevented and treated in community settings. Non-violent drug-offenders, especially women, should be offered treatment as an alternative.
The authors make several recommendations to improve access to health care for prisoners--leading with the urgent need to recognise the contribution of prison health to health inequalities, and to make prison health a priority by convincing governments that health policy must be based on the best available evidence. Other recommendations include addressing the fundamental right of

prisoners to a minimum standard of health care at least equivalent to the wider community; and to increase cooperation and coordination between criminal justice and public health systems.
In an accompanying Comment, Series authors Professor Chris Beyer, Professor Adeeba Kamarulzaman from the University of Malaya, Kuala Lumpur, Malaysia and Professor Martin McKee from London School of Hygiene & Tropical Medicine, London, UK as well as co-authors from *The Lancet* HIV in Prisoners Group call for urgent reform. They write, The Nelson Mandela Rules provide benchmarks to achieve meaningful reform in access to health care for those detained. We can, and should, do better to reduce both the numbers of those incarcerated and the length of their sentences, and to improve prevention, treatment, and post-release linkage to care for prison-associated infectious diseases. Meeting community standards of care in correctional settings, especially in low-income and middle-income countries, will require political will, financial investment, and support from medical and humanitarian organisations across the globe, but it can and must be done. Global control of HIV, viral hepatitis, and tuberculosis will not be achieved without addressing the unmet health needs of prisoners."
In a Comment introducing the Series, Dr Pam Das, Senior Executive Editor and Dr Richard Horton, Editor-in-Chief at *The Lancet* say, "As Archbishop Desmond Tutu's message "Don't forget the prisoner" reaffirms, we have a moral and human imperative to provide treatment to prisoners since we have limited their ability to access care except through prison health. Only by fully including them and other marginalised populations in the global HIV/AIDS response, will the fast-track to accelerate the fight against HIV and to end the AIDS epidemic by 2030 become a reality."
Source: Eurekalert, http://bit.ly/29VAfwN (15.07.2016)

2. Research charities help marry two major South African HIV/tuberculosis institutes
As the International AIDS Conference kicked off in Durban, South Africa, today, two of the nation's most prominent biomedical research institutions announced that they will marry and combine resources to attack the raging coepidemic of tuberculosis (TB) and HIV in the region.
The new Africa Health Research Institute, backed by the deep-pocketed U.K.-based Wellcome Trust and the equally flush U.S.-based Howard Hughes Medical Institute (HHMI), plans to connect basic research to population-level studies and clinical trials. "This is something very strong," says Bruce Walker, an immunologist at Massachusetts General Hospital in Boston who is an HHMI investigator.
Many fundamental questions remain about why HIV spreads so fiercely in South Africa, which has more people infected with the AIDS virus than any country in the world. South Africa also has a huge burden of TB, caused by a mycobacterium that thrives in an HIV-compromised immune system, and badly needs both better diagnostics to detect cases and more effective treatments to combat widespread multidrug-resistant TB strains. The Africa Health Research Institute promises to attack these overlapping problems—both of which are at their worst in the province of KwaZulu-Natal where the institute resides—with a unique combination of high-powered basic research and biological samples, such as blood or lung tissue, from tens of thousands of people who have carefully documented health histories. "We've got significant funding and significant expertise and it really has a huge potential," says clinical virologist Deenan Pillay, who will head the new institute. "There's nothing like it as far as I can see anywhere in the world."
The creation of the Africa Health Research Institute also provides a solid home for two institutions that each have faced uncertain futures. One of the partners in the merger is the KwaZulu-Natal Research Institute for TB-HIV (K-RITH), which HHMI created in 2008 at the suggestion of Walker. The idea was to create a strong basic research institution at the heart of the HIV/TB coepidemic that would bring in world-class researchers and train a new generation of African scientists. HHMI spent $40 million building a state-of-the-art biomedical facility, including a biosafety level 3 lab that can handle dangerous pathogens such as drug-resistant TB and HIV. "In terms of facilities, I don't think there's any place that comes close in sub-Saharan Africa," Walker says.
But K-RITH ran into trouble soon after it opened its doors in 2012. Its first director, William Bishai, a TB investigator from Johns Hopkins School of Medicine in Baltimore, Maryland, ended up resigning a

year later after HHMI, which emphasizes "fundamental research," told him not to pursue clinical trials. HHMI feared that this would veer from its mission and also could make the philanthropy vulnerable to lawsuits, says developmental geneticist Dennis McKearin, an HHMI administrator in Durban who ran K-RITH after Bishai left.

Several others familiar with the episode told *Science*Insider, and Bishai confirms, that HHMI also had concerns that he inappropriately used its funds to pursue clinically related projects. Bishai insists he did nothing wrong and is "very proud" of how he ran K-RITH. "Why put in $100 million to study TB and HIV and put the right hand in a sling and prevent it from reaching out to the patients?" he asks. Barry Bloom, a TB researcher at Harvard T.H. Chan School of Public Health in Boston, who led the search committee that selected Bishai for the job, says HHMI did not have a policy about clinical research when K-RITH opened, but it was clear to him that the philanthropy blanched at the idea from the outset. "Howard Hughes said they would not have anything to do with patients," Bloom says. "What Bill didn't understand is they were serious. I told him 100 times over. He was a bull in a china shop."

"When Bill left it had an enormous negative backlash on K-RITH," notes Kristina Wallengren, an epidemiologist and molecular biologist who was clinical adviser at the institute but formally tied to Johns Hopkins. "It was enormously damaging to the scientists." (Wallengren now heads a nonprofit in Durban, the TB & HIV Investigative Network, that stages clinical trials.)

The other partner in this new union, the Africa Centre for Population Health, embraces clinical research, but it too has gone through upheavals. Established by the Wellcome Trust in 1996 in Somkhele, about 235 kilometers north of Durban, it has focused on observational studies that track HIV's spread through entire communities, creating elegant spatial epidemiological maps. All told, the institute says it has "detailed population data" on more than 100,000 people. It also has led clinical studies of mother-to-child transmission of HIV and the impact antiretroviral treatment has on AIDS prevention.

But in 2013, the Wellcome Trust brought in Pillay, a clinical virologist from University College London, to head the center, a leadership change that signaled a desire to conduct more research that directly helped the local community. "One of the reasons I became director of the Africa Centre in 2013 was the wish of the Wellcome Trust as the main funder to see a very different scientific agenda," Pillay says. "There's been increasing pressure and need for the Africa Centre not just to observe the epidemic but to do something about it. How long can you be producing bloody maps?"

Pillay says Bloom effectively rescued the Africa Centre. "The sense I got from Deenan and others is that if he didn't take the job, Wellcome would have shut the place down," he says. Bloom, a former HHMI investigator who for a time chaired the scientific advisory board for K-RITH, is optimistic Pillay will also be successful in his new challenge. "Deenan has the insight and the enthusiasm to pull together the basic research and the clinical studies."

The Wellcome Trust, which, unlike HHMI, strongly supports clinical trials, has promised the new institution $50 million over the next 5 years in a renewable grant. HHMI, for its part, plans to give a total of $80 million to the Africa Health Research Institute (in addition to the building) by 2018, after which it plans to cut back its contribution, McKearin says.

This is the first time the two organizations have collaborated on a global health institution. "Bringing together HHMI and the Wellcome Trust into funding this unified institution is a great match," McKearin says. "It would be very difficult to even imagine a better outcome."

Source: Science, http://bit.ly/29JIKse (19.07.2016)

3. Pricing dispute hits supply of TB drugs in Pakistan

As in many developing countries, the Drug Regulatory Authority of Pakistan (DRAP) sets prices for about 320 critical medicines. But pricing caps have not been significantly raised since 2001, making it unviable for firms to make many of the drugs.

The issue has become particularly acute for TB drugs. Of 18 companies licensed to manufacture TB drugs in Pakistan, only four, including Novartis, were making them this year, said Ayesha Haq,

executive director of Pharma Bureau, a trade group representing 20 firms in Pakistan.
Doctors and public health officials said shortages could lead to a rise in drug-resistant strains of TB with tens of thousands of patients missing doses mid-treatment. The drugs include combinations of antibiotics as well as substitutes for patients with complications.
"It's an emergency in the making," said Naseem Salahuddin, an infectious disease doctor in Karachi.
With a population of 190 million, Pakistan has around 500,000 TB patients every year, according to the World Health Organization.
Rana Iftikhar Anjum, a resident of Multan in Punjab province, said it took him weeks to track down TB drugs for his 15-year-old niece, and Muhammad Rafiq, a pharmacist at a leading Islamabad hospital, said he had to pay 2,000 rupees ($19) in bribes to get the drugs for his brother, who suffers from multi-drug resistant TB, from a government hospital.
Novartis spokesman Dermot Doherty said the company, which controls around 30 percent of Pakistan's TB drug market, was looking to exit the business, and Ahsan Raees, in charge of the company's regulatory affairs in Pakistan, blamed the production halt on the price dispute. "If they had given us the price increase, we would never have done this," he said.
Pfizer Inc, which controls another 30 percent of the market, has also seen supply disruptions in recent months, adding to shortages, spokeswoman Trupti Wagh said. She did not elaborate on the disruptions, but said they were resolved last month. She declined to say whether the pricing dispute was a factor. A local TB drug maker, Schazoo Zaka, also partially cut production because of the pricing dispute, said Ejaz Qadeer, who heads Pakistan's anti-TB program. Schazoo Zaka did not respond to a request for comment.
While TB medicine is available in government hospitals, at least a third of patients rely on private clinics, where the drugs are hard to come by, health officials and patients said.
DRAP Chief Executive Muhammad Aslam said he has recommended a workaround to the health ministry for companies to raise prices for some critical medicines, and a decision could come next month.
Pakistan has raised critical drugs prices on an ad hoc basis over the past 15 years when companies have asked, but drugs firms say those increases have not been enough. Haq, the lobbyist, said companies were seeking an average 30 percent increase for regulated drugs to make production viable. Formed in 2012 to oversee drug regulation, DRAP this month instituted a first annual price increase since 2001, with increases pegged to inflation, which last year was at a 46-year low of 2.86 percent. Last month, DRAP also allowed for an 8 percent increase in TB drug prices under a hardship clause, which drug companies can apply for once every three years. DRAP's Aslam acknowledged that price increases so far were not enough. About 18 months ago, DRAP recommended that at least three dozen drugs be put under a new 'orphan drug' policy - for medicines developed to treat rare diseases, and typically with no price cap, so as to give manufacturers an incentive to produce for a small market. "Anti-TB drugs, cardiac drugs, anti-cancer drugs - these are critically needed," Aslam said. TB is not classified as a rare disease in Pakistan, but listing it as an orphan disease would allow companies to get around current regulations and sell TB drugs at cost price. Sajid Hussain Shah, a ministry spokesman, said work was ongoing on the policy.
Source: TB Online, http://bit.ly/2aJBmTa (28.07.2016)

Forschung & Entwicklung

1. Klassisches Antibiotikum ist auch gegen die Tuberkulose wirksam
Die Anzahl von Patienten, die weltweit mit einer multiresistenten und damit schwer behandelbaren Tuberkulose (MDR-TB) identifiziert wurden, ist von 47.000 im Jahr 2009 auf 123.000 im Jahr 2015 dramatisch gestiegen. Neue Medikamente werden dringend benötigt. Ihre Entwicklung ist jedoch mit sehr hohen Kosten und wirtschaftlichen Risiken für die Pharmafirmen verbunden und dauert mindestens zehn Jahre. Hinzu kommt das Problem der Resistenzbildung: Nicht einmal zwei Jahre

nach Einführung der letzten beiden neuen Medikamente (Bedaquilin und Delamanid) gegen multiresistente Tuberkulose wurde der erste Bakterienstamm mit Resistenzen gegen diese Antibiotika identifiziert. Eine Alternative zur Entwicklung neuer Medikamente sehen die Wissenschaftler darin, bereits für andere Indikationen zugelassene Medikamente für die Tuberkulosetherapie zu testen. Lange Zeit glaubte man, dass ß-Lactam-Antibiotika, Verwandte des Penicillins, keine Wirksamkeit in der Tuberkulosetherapie haben. Ein Team aus Südafrika, Spanien, Mozambique und Deutschland hat diese Ansicht nun widerlegt.
Die Ärzte behandelten Patienten mit einer Lungentuberkulose vor Beginn der eigentlichen Standardtherapie zwei Wochen lang mit dem ß-Lactam-Antibiotikum Meropenem. ß-Lactam-Antibiotika sind vom Penicillin abgeleitet und greifen in den Zellwandaufbau der Bakterien ein. Um Abwehrmechanismen der Bakterien auszuschalten, gaben die Mediziner zusätzlich Clavulansäure; sie hemmt die ß-Lactamase, ein Enzym der Bakterien, welches ß-Lactam-Antibiotika unwirksam macht. Unter der Kombinationsbehandlung nahm die Bakterienlast im Sputum der Patienten rasch ab. „Die Behandlung war ebenso effizient wie die mit den gängigen Medikamenten Rifampicin oder Pyrazinamid“, erklärt Professor Christoph Lange, Ärztlicher Leiter der Klinischen Infektiologie Forschungszentrum Borstel und Wissenschaftler im DZIF. „Die Studie war allerdings nicht darauf ausgelegt, den langfristigen Effekt von Meropenem/Clavulansäure auf die Heilungschancen der multiresistenten Tuberkulose zu untersuchen“, dämpft Lange zu hohe Erwartungen. Mit der aktuellen Entdeckung eröffnet sich ein neues Feld in der klinischen Tuberkuloseforschung: Bereits zugelassene Medikamenten könnten auf ihre Wirksamkeit gegen die Tuberkulose getestet werden.
Source: idw, https://idw-online.de/de/news656238 (14.07.2016)

2. World first as novel test for tuberculosis developed at Cambridge Consultants
Cambridge Consultants is working with medical device start-up WaveGuide Corporation on a world first to tackle the global problem of tuberculosis, as well as other diseases.
The two companies are developing a unique portable nuclear magnetic resonance (NMR) scanner to provide fast, low-cost, point-of-care testing for disease in developing countries and geographically remote locations.
TB is one of the major killer infectious diseases worldwide. It affects nearly 10 million people each year – and 1.5 million sufferers die, according to the latest figures from the World Health Organisation. Yet the disease is curable – and its spread can be prevented – if it is caught early enough.
TB is caused by bacteria that most often affect the lungs. It is spread from person to person through the air when a victim coughs, sneezes or spits. Someone only needs to inhale a few germs to become infected. The WHO says more than 95% of TB deaths occur in low- and middle-income countries.
The traditional 'gold standard' TB test used in developing countries involves taking a sputum sample which is then cultured in a central laboratory. The process is slow, as it can take weeks for the TB bacilli to grow, and often inaccurate – sometimes picking up only 20% of cases. Such tests are also unable to detect drug-resistant strains of TB.
NMR offers the possibility of a faster, more sensitive test. But existing NMR diagnostic equipment is large and expensive – making it inaccessible to many of the populations at high risk.
In contrast, the new sputum test being developed by Cambridge Consultants and WaveGuide is affordable and no bigger than a shoebox – so it can be used in mobile clinics, for example. It will give results in less than 30 minutes, with 95% accuracy. And it paves the way for detecting drug-resistant TB. This all means that appropriate treatment can be started promptly – improving patients' chances of recovery.
“We're bringing the reliability of expensive, high-tech laboratory equipment to patients in the field, as well as in hospital, in the form of a compact POC device that gives accurate results fast," said Richard Hall, head of global medical technology at Cambridge Consultants. At the heart of the miniature NMR machine is WaveGuide's patented chipset, together with very small magnets that are a fraction of the size of those found in conventional lab equipment. “This groundbreaking

development is set to transform the detection and treatment of TB and other diseases in both the developed world and developing countries," said Nelson K Stacks, president and CEO of WaveGuide.
As well as TB diagnosis, the technology is also being adapted for the detection and monitoring of conditions such as ovarian and other cancers, where existing tests involve attaching microscopic iron particles to circulating tumour cells and using magnets to draw them out of a blood sample. It could also be used to identify counterfeit drugs – and has potential industrial applications, such as oil and gas detection and analysis.
Source: Cambridge News, http://bit.ly/29YpETK

3. Study provides insight into why individual mycobacteria respond differently to antibiotics
Tuberculosis is one of the most common infectious diseases in the world, infecting almost 10 million people each year. Treating the disease can be challenging and requires a combination of multiple antibiotics delivered over several months. This is due, in part, to variations in antibiotic tolerance among subpopulations of *Mycobacterium tuberculosis*, the bacteria that cause tuberculosis.
Researchers from Tufts University School of Medicine have now identified specific combinations of factors that are linked to why individual mycobacteria of the same genetic background can respond differently to antibiotics. Bacteria that were smaller at birth and ones that were at the beginning or end of their cell division cycles were most susceptible to antibiotics, while larger cells in the middle of a cell cycle were the most tolerant. The findings, published in the *Proceedings of the National Academy of Science*s on June 30, 2016 shed light on the complexity of antibiotic tolerance and may improve the future design of drug regimens.
"Our study shows that bacteria in a population that we thought of as being identical are actually not. Even simple differences such as how big they are at birth correlate with differences in how they respond to drug treatment," said senior study author Bree Aldridge, Ph.D., assistant professor of molecular biology and microbiology at Tufts University School of Medicine and adjunct assistant professor of biomedical engineering at Tufts University School of Engineering. "We hope we can eventually use these insights to help engineer new, rational drug combinations that can more effectively treat tuberculosis and other diseases by specifically targeting the cells that are slower to respond to antibiotics."
Aldridge and her team, including Kirill Richardson, M.S., research technician in Aldridge's lab, based their study on *Mycobacterium smegmatis*, a fast-growing, non-pathogenic relative of *M. tuberculosis*. The researchers were able to analyze the responses of individual bacteria to rifampicin, a core frontline antibiotic used to treat tuberculosis. This was accomplished through the use of live-cell microscopy, microfluidic and imaging tools, and mathematical models.
In a previous study, Aldridge and her colleagues demonstrated that mycobacteria divide asymmetrically -- despite being genetically identical, one of the two daughter cells will usually be longer and faster growing than its twin. In the current study, the team found that these longer bacteria were least affected by rifampicin. Bacteria that inherited a mature growth pole, the cellular structure where growth originates, from its mother cell were also slower to respond to the antibiotic.
The researchers found that timing -- specifically, the phase of the cell division cycle that bacteria were in when exposed to the antibiotic -- had a significant effect on susceptibility. *Rifampicin susceptible* bacteria were small and at the beginning stages of their cell cycles, or larger and at the end stages of their cell cycles. Bacteria in the middle of their cell cycle were least affected by the antibiotic.
"By simply watching cells grow, we were able to characterize several differences between bacteria that are killed quickly and those that respond slowly to antibiotics," said Aldridge, who serves as faculty in the Immunology and Molecular Microbiology programs at the Sackler School of Graduate Biomedical Sciences at Tufts. "We hope to refine these multivariable descriptions so that we can anticipate the cyclic changes to drug susceptibility in mycobacteria, and eventually use them to shorten the long and difficult treatment course for tuberculosis."
Source: News Medical, http://bit.ly/2auf6rY (05.07.2016)

Reportage

1. Did early campfires trigger the emergence of tuberculosis?

Fire brought warmth and comfort to early humans but may also have triggered the emergence of deadly tuberculosis, Australian researchers suggest.

Smoke-damaged lungs, as well as the closeness of humans around a campfire, could have created the ideal conditions for tuberculosis to mutate from a harmless soil bacterium into our number one bacterial killer, according to the researchers' data model.

The model, published today in the Proceedings of the National Academy of Sciences, showed controlled use of fire would have increased the likelihood of tuberculosis emerging by several orders of magnitude. Mathematical biologist Associate Professor Mark Tanaka of the University of New South Wales has had a long-standing interest in the evolution of disease-causing microorganisms such as tuberculosis, but a sudden insight led him to think about the role of fire in catapulting tuberculosis into the medical limelight. This increased physical contact — which makes the spread of the disease more likely — was coupled with wood smoke, which also increases the risk of contracting tuberculosis because of damage to the lungs.

Dr Tanaka and his colleagues from the University of New South Wales and Monash University said archaeological and molecular evidence indicated tuberculosis arose in humans in Africa and then spread to animals.

Just when this happened is controversial — while some research puts the date more recently at 6,000 years, others point to a date of 70,000 years. While the date of the earliest use of fire is also subject to debate, Dr Tanaka suggested that it probably came before tuberculosis.

In the study, researchers used a mathematical model to explore how a benign soil-dwelling microorganism like *Mycobacterium tuberculosis* might develop into a transmissible pathogen.

But adding fire to the mix significantly increases the risk of the bacteria hitting the mutation jackpot.

"You get multiple sporadic cases, and most of them fail in the sense that they fail to evolve and so there are multiple failed chains of transmission, but eventually the right mutations come along and the whole thing is triggered."

Paleopathologist Dr Piers Mitchell from the Department of Archaeology and Anthropology at University of Cambridge said the change from harmless soil bacteria to deadly disease would not have happened overnight. "People seem to have been using fire for hundreds of thousands of years, so it's clearly not a case of 'fire this week, tuberculosis the next week'," Dr Mitchell said.

But he said the idea that controlled fire enabled the emergence of tuberculosis was certainly plausible, and fitted with the hypothesis that human technological developments could have health consequences. "It makes sense if our invention of technologies changes our environment, and some bits of that will be good and some bits may, in unexpected ways, be bad," Dr Mitchell said.

Source: ABC Science, http://ab.co/2acrDEd (26.07.2016)

2. Madagascar: The vulnerability to tuberculosis

Ambovombe, Madagascar - Despite the heat, Manovo Edson shivers on the bed with a blanket wrapped around his small body. He is 14 years old, but looks to be only six or seven. The desperate screams of a mother who just lost her 17-month-old child in the next room echo off the walls.

Manovo is being treated for tuberculosis, or TB, in a basic hospital in Ambovombe, capital of the Androy region in Madagascar's remote and deprived south.

While many people imagine the country as a wildlife mecca, it is one of the poorest in the world, with at least 80 percent of the population living in extreme poverty and half of all children under five years old suffering from chronic malnutrition.

The associated problems, particularly the struggle for food - as malnutrition increases susceptibility to the disease, according to the World Health Organization - have contributed to TB becoming the leading infectious killer in Madagascar.

The latest estimates of the World Health Organization place the incidence rate of TB at a very high 235 cases for every 100,000 people. However, accurate figures are impossible to come by due a lack of accurate data, as well as inflicted people delaying treatment for a multitude of reasons.

By the standards of the developed world, Manovo has not eaten a proper meal in nearly two years, and perhaps never in his lifetime. His sporadic diet has mainly consisted of rice and cassava, a starchy root. His condition was grave when he arrived at the hospital 23 days ago. A weakened immune system due malnourishment made him more susceptible to the mainly airborne bacterial disease.

However, Manovo is now responding to treatment and getting stronger, according to the healthcare workers looking after him, but he will be kept under observation for at least another two months.

As the airborne disease spreads easily in cramped living conditions, TB is often associated with poverty. "Deaths at the hospital from TB are relatively rare, but patients often arrive very sick and would die if they did not receive treatment," says Melodie Paupert, a local healthcare worker. "Patients need the medicine."

In order for the family to bear the exorbitant costs of caring for Manovo, which include transport, accommodation, food and lost income, etc, they have used up most of their meagre assets, even selling one of their Zebu cows - a prized possession among many rural Malagasy. Manovo's family mostly works in farming, but long periods of drought have exacerbated the situation and increased hardships for them. Although, his illness has put an enormous strain on their income, family members have interrupted their lives as they take turns sitting by the boy's side.

Like numerous health centres in Madagascar, the staff all work voluntarily. One worker, Odille Licie, has not been paid in 10 years of working at the hospital.

Funding the fight against TB in Madagascar is a significant problem. The country's entire dedicated budget for combating TB - which has been little over $10m (PDF) for the years 2014-2017 for a population of nearly 23 million people - is now only provided by the Global Fund, a financing system established to combat aids and malaria, as well as TB. "Tuberculosis remains a big issue, despite the time we've given it," sighs Dr Martin Rakotonjanahary, deputy director of the national programme fighting TB.

A lack of funding for his department is an ongoing problem. It suffers from a 90 percent budget gap and is entirely reliant on insecure donor funding. This year, he has just $7m to fight TB in the whole country, and he doesn't know if this money will be renewed.

Widespread corruption also means money allocated to healthcare workers and facilities is skimmed little by little as it makes its way from the central administration, which, due to the size of Madagascar - the fourth biggest island in the world - is a long way.

Infrastructure issues and cultural practices, especially in the country's remote southern region, have resulted in difficulties fighting TB. Many people approach traditional healers before doctors, as they are often geographically closer and more trusted by the community. Rakotonjanahary doesn't want to fight this practice, but admits any health strategies involving traditional healers are hard to implement and must be approached with caution.

Even if people do reach proper care, their problems do not end. Lack of access to drugs due to insufficient funding and infrastructure issues can mean that TB treatment courses can be sporadic and improperly administered. Many patients also choose not to complete their long and gruelling treatment courses, which include several rounds of pills each day, and stop medicating when their symptoms have eased, only for them to return later on.

This sporadic treatment has led to another problem: multi-drug resistant TB (MDR-TB). Drug resistance, caused by mutated microbes which can fight off medicines, is a very troubling issue according to international health experts.

In Madagascar, knowledge of MDR-TB is extremely varied. While some specialist doctors are aware of its dangers, they have limited resources with which to fight it. In contrast, the Minister of Health Mamy Andriamanarivo told Al Jazeera that he was "not worried" about it.

But MDR-TB, and anti-microbial resistance (AMR) more generally, is of global concern. Already, 700,000 people a year across the world die because of AMR, according to the Review on Anti-

Microbial Resistance, a United Kingdom government-appointed task force set up to analyse the potential global impact of drug resistance. Deaths are projected to reach 10 million each year by 2050 if action is not taken.
Drug-resistant TB already kills 200,000 people each year, and will account for more than 2.5 million AMR-related deaths by 2050, according to the Review. For this reason, tuberculosis was called the "cornerstone" of the fight against drug resistance in the Review's May 2016 report on the issue.
And drug-resistant TB does exist in Madagascar, but due to poor data collection practices, the true number of cases is unknown. In the Befelatanana Hospital in the capital, Antananarivo, doctors say there have been at least 20 cases of MDR-TB since 2012.
Twelve-year-old Hortence Modesstina has been ill for six years and treated three different times for TB by local doctors in the southwestern region, where she is from. After consistent failures, she was taken to the city and has now been under treatment for eight months. It was only when she was admitted to hospital that it became known that, in addition to having a drug-resistant form of TB, she is HIV-positive. Her mother, Bao Modesstina, 43, is also HIV-positive. She has stayed with Hortence, the youngest of her five children, while she has been in quarantine. They share a room in a quite wing of the hospital and both wear face masks when they receive visitors. "I felt very discouraged, but the doctors kept counselling me, and I felt stronger after," says Bao. "It's very hard to always be kept inside, but when I see my girl getting better, it's worth it."
In the next room, 28-year-old Eternal is also beginning to feel better. He has been quarantined at the hospital since early May and had lost his job as a nurse as a result. He has been sick since 2013 with what is now known to be MDR-TB, explaining why his other treatments did not have any lasting effect. Isolated in a bare, cell-sized room, he worries about finding work when he gets out.
However, these patients may be considered fortunate, despite the harsh medications that must be carefully monitored, administered and - most crucially - uninterrupted.
Besides its inherent complexities, treating drug-resistant TB is made more problematic by the general quality of the drugs available to treat the disease. Most standard TB medicines are decades old, and there is little appetite among pharmaceutical companies to produce new ones due to the small market return on them. The most demand is from low-income countries.
Resistance to single drugs is common and doctors are forced to use more powerful combinations for many months at a time, taking a physical and mental toll on patients. The vast distances, poor infrastructure and sporadic healthcare in Madagascar mean a proper diagnosis of MDR-TB, let alone its proper treatment, are still far off as funding is still weak and heavily reliant on external donors.
Back in the isolated room, still wrapped in his blanket, Manovo rests on the bed. It's his grandmother's turn to sit by him, but 66-year-old Celestine Kasay doesn't mind. "He looks better now than when he arrived," she says. "He misses school. He wants to go back."
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