AUGUST 2020 | VOLUME 1 | ISSUE 1

Tuberculosis Newsletter

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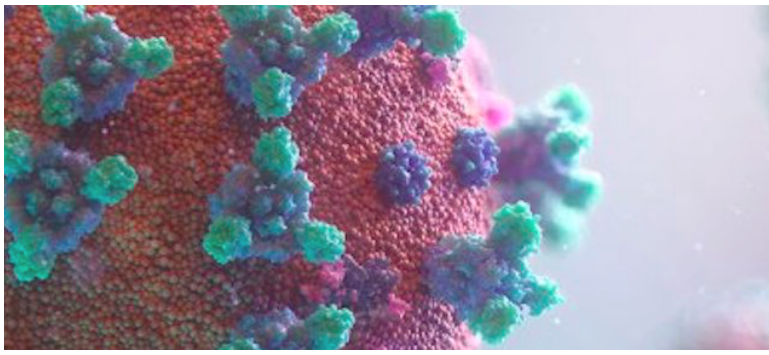
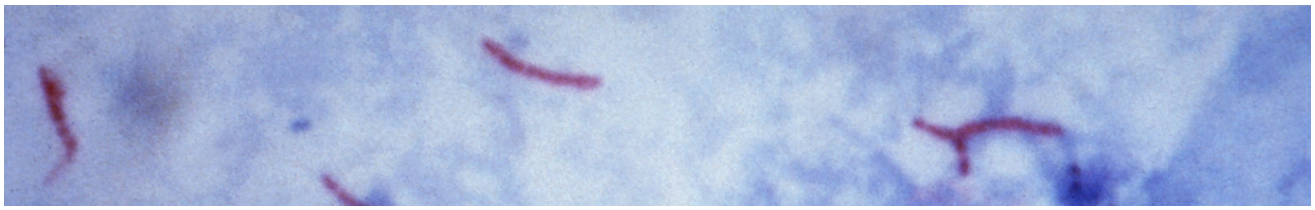


Let's Make the Worldwide Fight Against COVID Transformative for Other Global Threats like TB

Dr. Nibedita Rath, Scientific Director, Open Source Pharma Foundation, Bengaluru

Currently, the world is reeling from COVID-19 pandemic. The awareness campaigns to reduce the spread of this highly contagious virus have made some impact. The pandemic has affected us as individuals, communities, countries and continents. On the hindsight, the pandemic is teaching us how to prepare ourselves in a worldwide threat like this. It is heartening to see a country as diverse as India waking up to the challenge in a united way both at the government and citizen level. The efforts to bring solutions both in terms of treatment and vaccine have unfolded a few new ways of collaboration among big pharma, biotech, non-profit organizations and Governments. Furthermore, the model of partnership with manufacturing companies across the globe has opened another avenue to meet demand and affordability. The rapid innovation of a novel vaccine or drug used to be unthinkable during the pre-COVID era. Can it be a tipping point for the fight against chronic infectious diseases that are even deadlier, such as tuberculosis (TB)? Is this the time to make our efforts towards fight against TB transformative? I strongly believe so.



Currently, the world is reeling from COVID-19 pandemic. The awareness campaigns to reduce the spread of this highly contagious virus have made some impact. Retrospectively, post the epidemic in China and the loss of more than 3,000 lives; everybody probably apprehended it becoming a global threat. But never have imagined the magnitude to be this big. In a global economy where the cross-border business has been the hallmark of success and survival, lockdowns, travel restrictions, closure of non-essential services etc. have become a norm across the globe in the past six months and still counting. The pandemic has impacted us as individuals, communities, countries and continents. On a positive note, it brought us together to fight and help each other. It is heartening to see Asian countries like Taiwan, Singapore and South Korea showed the world the way by their proactive measures to contain the spread of the virus and minimize the casualties. We sincerely hope this testing phase will pass and we will be back to normalcy sooner than the later.

On the hindsight, the pandemic is teaching us how to prepare ourselves in a worldwide threat like this. Of course, the advent of technology in terms of electronic media is playing a vital role in this. The phrases like 'social distancing', 'stay home, stay safe', 'self-quarantine' etc. are not words from health workers or medical practitioners or government, they are widely used and practised by citizens and communities. We are becoming more and more aware of the precautionary measures against this novel coronavirus.

It is heartening to see a country as diverse as India waking up to the challenge in a united way both at the government and citizen level. The efforts to bring solutions both in terms of treatment and vaccine have opened up a few new ways of collaboration among big pharma, biotech, non-profit organizations and Governments. The ongoing clinical trial of the coronavirus vaccine that has emerged from the University of Oxford-AstraZeneca collaboration is a great example. Furthermore, the model of partnership with manufacturing companies across the globe has opened another avenue to meet demand and affordability. The rapid innovation of a novel vaccine or drug used to be unthinkable during the pre-COVID era.

Can it be a tipping point for the fight against chronic infectious diseases that are even deadlier, such as tuberculosis (TB)? TB is a global health problem and has been responsible for the loss of millions of lives worldwide every year (https://www.who.int/en/news-room/fact-sheets/detail/tuberculosis). The current standard of care is long and stressful for the patients leading to non-compliance that results in drug-resistant TB. Additionally, social reaction and isolation against TB patients put unnecessary psychological pressure on patients to come out and seek help. While the pharma, government and non-profit research organizations are working towards finding novel drugs and treatment for TB, we as global citizens can hugely benefit the cause by talking about it. This magazine is a small effort towards this direction.

"The efforts to bring solutions both in terms of treatment and vaccine have opened up a few new ways of collaboration among big pharma, biotech, non-profit organizations and Governments."

There has been concerns and rightly so, that the COVID-19 pandemic is adversely affecting the TB services in prevention, case-detection and management. This might be inevitable considering the unprecedented pressure the health care system is facing now and the need to mobilize the resources.

The pragmatic approach however is our preparedness to deal with this kind of situation and make sure our long term commitment to STOPTB (http://stoptb.org/news/stories/2020/ns20_014.html) has not taken a back seat. The article from Dr. Ansu Bhardwaj in this issue is an eye opener. At the same time the response from digital technology to support the communities and health care system during COVID has been rapid and innovative. Add the innovations from big pharma and non-profit organizations to fight against cancer to our learning. The article from Dr. Peter Kapitein from the company Inspire2Live is inspirational in this regard. The article from Dr. Shailesh Nayak has emphasized that India needs to take the lead in developing a strategy to enhance its efforts to eradicate TB. Dr. V Bhujanga Rao's article talks about new technological intervention such as SAFE (Satellites for Epidemiology) for better surveillance of TB. Regarding invention in treatments, Dr. Urmi Bajpai's has emphasized on exploring the possibility of phage therapy in the battle against drug-resistant TB. Dr. Rudrodip Majumdar's article has cited the need for new vaccines towards achieving Millennium Development Goal of eliminating TB globally by 2050. Is this the time to make our efforts towards fight against TB transformative? I strongly believe so.

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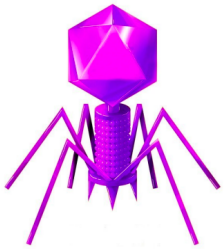

Bacteriophages as Therapeutics for Managing Drug-Resistant Tuberculosis?

Dr. Urmi Bajpai, Associate Professor, Acharya Narendra Dev College, DU

The world health organization has predicted high mortality rates due to infection by drug-resistant pathogens and has called for taking urgent measures to mitigate the crisis (WHO Report , 2019). While several national and international bodies have taken initiatives for finding new antibiotics, a less enthusiastic R&D by pharmaceutical companies towards antimicrobial drug discovery has aggravated the crisis globally. The alarming rate of occurrence of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) therefore mandates pacing up the efforts to discover new drugs as well as explore alternative options with open mind.

The world health organization has predicted high mortality rates due to infection by drug-resistant Mycobacterium tuberculosis and has called for taking urgent measures to mitigate the crisis (WHO Report, 2019). While several national and international bodies have taken initiatives for finding new antibiotics, a less enthusiastic R&D by pharmaceutical companies towards antimicrobial drug discovery has aggravated the crisis globally. The alarming rate of occurrence of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) therefore mandates pacing up the efforts to discover new drugs as well as explore alternative options with open mind.

In this piece, I am aiming to highlight the role bacteriophages (phages for short) can play as potential alternative or adjunct to antibiotics and why higher participation by the research and the medical community is required to examine them as effective anti-mycobacterial agents. Phages are virus of bacteria and are estimated to be the most abundant biological entity (1031) on the planet. They are highly specific predators to their bacterial hosts and have a benign presence in the environment. These simple facts make them a useful and inexpensive resource for developing new antibacterial solutions, especially against drug-resistant chronic infections. Also, the phage-encoded lytic enzymes such as endolysins, ectolysins, depolymerases are gaining attention as potential alternate /complement to antibiotics (Hatfull et al., 2012; Fischetti 2018). Bacteriophage therapy is already being practised in Poland, Georgia, Russia since about a century (A. Sulakvelidzeet al., 2001; LL Furfaroet al., 2018; T Parfittet al.,2005). Recently, a successful case study from United States (Schooley et al., 2017) where a terminally ill patient, suffering from a chronic multi-drug resistant Acinetobacter baumanii infection was rescued by phage therapy, has catalysed the research on clinical applications of bacteriophages.

From L to R: Doctor Helen Spencer, Prof. Gram Hatfull, the patient Isabelle who undertook phage therapy for mycobacterial infect ion and her mother. https://www.sciencemag.org/news/2019/05/viruses-genetically-engineered-kill-bacteria-rescue-girl-antibiotic-resistant-infection

Phage/lysin therapy for treating tuberculosis (TB) doesn't exist so far. The challenging part of using phages for treating TB is the intracellular location of M.tuberculosis (Mtb), which impedes the targeted delivery of phages. Also, only limited Mtb-specific lytic phages have been discovered so far. However, these are not intractable impediments; a greater number of Mtb-specific phages should be discovered and their variants can be created by genetic engineering to expand their host range or to meet the other therapeutic requirements. A major impetus to the cause came from a recent successful case of phage therapy against a non-tuberculous mycobacterial infection (M.abcessus) in a young patient of cystic fibrosis who had undertaken lung transplant and had developed chronic infection and the prognosis was poor (Dedrick et al., 2019). This case has served as a convincing proof of concept and drawn world's notice to the therapeutic potential of phages in treating mycobacterial infections. This was also the first instance, where a cocktail of genetically engineered mycobacteriophages (lysogenic genes were edited) were used in human therapy.

Besides using the whole virulent phages, the phage-derived lytic enzymes such as lysins can also be effectively used in the treatment of bacterial infections. Unlike standard-of-care antibiotics which are broad spectrum, endolysins are specific and hence are safe for the commensal microflora. Lysins can target drug-resistant strains with same specificity and sensitivity. Also, the occurrence of bacterial resistance against these enzymes is less probable since bacteria are less likely to modify peptidoglycan, which is one of the most essential components of the bacterial cell wall. For these reasons, a spurt in interest in phage derived endolysins, also called as enzybiotics, is being witnessed and several of them have been scaled up for commercial purpose (Fischetti, 2018). For example, Staphefekt(TM) is an endolysin-

ibased aseptic solution (Schmelcher, Mathias, et al., 2015), manufactured by Micreos company (Netherlands) and Ecto-LysinTMP128 is an ectolysin (Shankaramurthy C. et al., 2017) from Ganagen Inc. Both the enzymes target skin infections caused by methicillin resistantStaphylococcus aureus(MRSA) Another successful example of a lysin effective against S. aureusinfections is CF-301 developed by ContraFect Corporation (NY, USA)(Schuchet al., 2017).

Mycobacterial cells have a complex cell wall (envelop) consisting of a cytoplasmic membrane and peptidoglycan layer, which is covalently linked to the arabinogalactan-peptidoglycan (mAGP) complex and mycolic acids (Chatterjee 1997). Mycobacteriophages usually encode two endolysins, Lysin A and Lysin B, which act on the peptidoglycan layer and the mycolic acid-arabinogalactan layer, respectively and help phages lyse the mycobacterium for the release of viral progeny. Phages and the endolysins can also be used synergistically with antibiotics. The combination can help to treat late-stage, drug-resistant infection by reducing the MIC (minimum inhibitory concentration) and delaying the occurrence of antibiotic resistance (Kalapala et al., 2020).

Hence, in the grim state of growing antimicrobial resistance, the natural killers of bacteria need to be brought in centre-stage and studied extensively to utilize their antibacterial potential. By using the modern tools for culture techniques, phage purification, high throughput screening, for genome & proteome analysis and understanding their pharmacokinetic/ pharmacodynamics, the century-old therapy can meet the rigours of modern-day medicine. There is a vast reservoir of untapped bacteriophages and their derived lytic enzymes. What is required is to build repositories of well-characterized lytic mycobacteriophages and endolysin (natural and/or engineered) specific to drug-sensitive and resistant Mtb strains, devise efficient phage delivery mechanisms and develop procedures for effective phage therapy against tuberculosis. For this to happen, the scientists, clinicians and regulatory authorities need to work in tandem. Ultimately, framing guidelines for compassionate use of phages/phage-encoded lysins in treating drug-resistant infections and clinical trials should not be far-fetched to our imagination!

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It's Time to Act!!

Awareness of the Stakeholders Patients Centered **C**are **T**echnology driven solutions

Dr. Anshu Bhardwaj, Senior Scientist, CSIR-Institute of Microbial Technology, GN Ramachandran Protein Center, Chandigarh, India

The Pandemic has caused severe damage to the progress made in addressing Tuberculosis. An interdisciplinary collaborative framework is needed to address the ongoing and anticipated pandemics.

"'The Biggest Monster' Is Spreading. And It's Not the Coronavirus" - This is the title of a recent article in The New York Times[1]. The article refers to the unbridled spread of the perennial Mycobacterium tuberculosis infection that causes Tuberculosis (TB). Tuberculosis was the first infectious disease to be declared a global emergency by WHO in 1993. Ever since countries have made consistent efforts and developed novel interventions saving millions of lives. However, despite the progress made and the fact that most TB programs have 100% DOTS (Directly observed treatment, short-course) coverage, the TB infection management and treatments are far from adequate[2].

The Pandemic and its Impact on TB Tuberculosis disease burden in India and rest of the world demanded a global concerted effort to develop new treatment and prevention strategies. This realization led the world leaders and organizations to come together and commit to End TB. The proposed strategy of the End TB mission aims to reduce TB deaths by 95% between 2015 and 2035[3]. However, latest reports from WHO clearly indicate that the progress made to achieve this goal has been hit hard by the COVID-19 pandemic. Two scenarios have been analyzed to predict TB mortality in the pandemic context. In the first scenario, it is estimated that TB detection decreases by 25% over a three month period. This translates to a 13% (1,90,000) increase in TB deaths in 2020, similar to what it was in 2015. In the second scenario the detection drops by 50% leading to a 26% increase in TB mortality, as was in 2012[4]. Irrespective of which scenario mimics the reality, these estimates clearly indicate that the pandemic has caused severe damage to the progress made in TB control strategies over the past 2-3 decades.

TB control programs are designed as a part of the public health systems which are critically impacted during the pandemic. The recent WHO reports highlight the reallocation of TB resources to COVID-19 testing. Also, the magnitude of COVID-19 pandemic has exposed the fragile health care systems across the world. Recent articles also highlight the potential risk of covidization without long term strategic planning[5]. To maintain the momentum of TB control programs in the context of the pandemic, WHO has developed an accelerated action plan [6]. However, this requires proactive participation of stakeholders with clear understanding of their roles and potential contributions in the accelerated response framework.

Were we doing enough before the Pandemic? Looking back in time in the pre-pandemic era, the issue of patient-centered care for TB remained unmet. Patient-centered care refers to all the aspects from disease diagnosis to treatment. Several studies in past years have highlighted the complex route a suspected TB patient needs to take in order to receive appropriate diagnosis and treatment. These studies highlight the challenges and gaps resulting in patients not being provided the right guidance on diagnosis and not being referred to settings which are equipped to handle TB diagnosis and subsequent treatment options. Such gaps in implementation of TB care are the

reasons for delayed diagnosis and treatment. A recent study from 30 high-burden countries shows that one in two TB patients (50%) successfully complete treatment[7]. The situation is worse for DR-TB (drug-resistant -meaning forms of TB that do not respond to 1 or more antibiotics) patients. It is reported that fewer than 1 in 4 individuals with DR-TB patients receive treatment[8]. This clearly indicates that coverage does not reflect TB treatment out comes. The Lancet Global Health Commission on high-quality health systems reported that poor-quality care is a bigger killer than insufficient access to care[9]. In the Lancet TB Free World report, the authors recommend patient-centered services as the top most priority for achieving better TB control. The report is based on how the quality of care stands globally and what specific gaps exist. The report recommends adopting the HQSS framework (High-quality health systems in the Sustainable Development Goals era) to achieve quality TB care[10].

What should we do now? A global framework with integrated approach is needed to build public health systems to expand access and improve the quality of care in an accelerated mode. Though TB is one of the major killers in the world from an infectious agent, there are other drug resistant infections which are increasing at an alarming rate and it will not be an exaggeration to state that all these are pandemics in the making and have been recognized as potential pandemics as early as in 1999[11]. If we do not act now and address the ongoing and anticipated pandemics through an integrated approach the progress made over the last several decades in addressing the same will be seriously jeopardized. We therefore need to look at interventions which engage all stakeholders in real time. We need to ACT:

Awareness of the Stakeholders Patient Centered Care Technology Driven Solutions

New means of generating Awareness are the need of the hour. These methods should be engaging as well as provide platforms for generating evidence of what the grass root level issues are so as to provide proper Care. These solutions should be Technology driven (telemedicine, interactive apps for ecological momentary assessments, digital DOTS, smart pill box, etc).The decreasing rate of internet connection and the expansion of smart phone availability provides an unprecedented opportunity for better and precise management of TB control programs. Last and the most critical step is to invest in science of disease biology, development of new methods of point-of-care affordable diagnosis, discovery and development of shorter and targeted treatment regimens, adoption of evidence based prescription and use of data analytics in achieving all these goals in an interdisciplinary collaborative framework.

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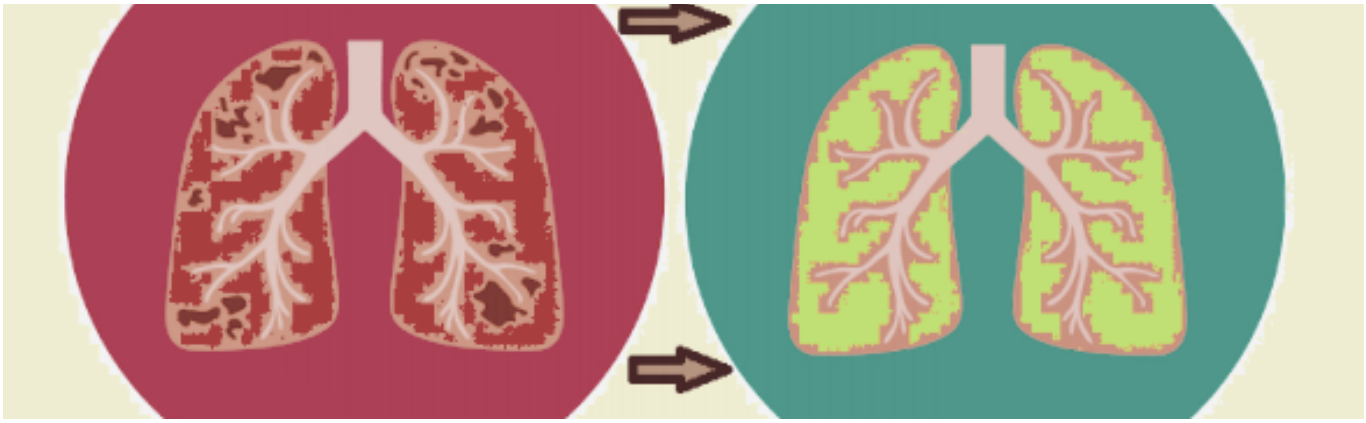

Tuberculosis: A Brief Overview and Recent Advancements in Clinical Treatment

Dr. Rudrodip Majumdar, Energy and Environment Programme, School of Natural Sciences and Engineering, National Institute of Advanced Studies, Bengaluru

Brief overview about TB infection:

Tuberculosis, which is also popularly called as TB, is one of the most ancient diseases that has stayed and co-evolved continuously with the human beings, with the earliest record being more than 17000 years old[1, 2]. TB is caused by the bacterium named Mycobacterium tuberculosis. Broadly, TB can be categorized into two different classes: (a) active disease and (b) latent infection. The most common form of active TB is pulmonary TB, but it can manifest in other organs as well, and those instances are termed as "extra pulmonary TB"[3]. Depending on the degree of infection, a person with active pulmonary TB disease may exhibit the symptoms like chest pain, cough, phlegm, weight loss, weakness, fever, chills and sweating at night; and the active patients are prone to spreading the disease by coughing the infectious particles into the air. An aggressive form of active TB is known as miliary TB, which may take place if TB bacteria find their way into the bloodstream. In this rare form, the bacteria quickly spread all over the body in tiny nodules and affect multiple organs, leading to the fatality of the concerned patient[4].

On the other hand, the patients with latent TB do not develop the overt disease, and in many of the cases, even the chest x-ray images may appear to be normal. One proven and effective way to detect latent TB is to look for the reaction to the tuberculin skin test (TST) or interferon-gamma release assay (IGRA). However, the latent TB infection in asymptomatic individuals may escalate to the active disease at any time during their lives due to a compromised immune system arising from other illnesses such as HIV or special medications (e.g. the medication following organ transplants to prevent organ rejection)[5, 6]. To curb this TB escalation, the United States devised a preventive therapy for latent TB infection. Vaccination for TB has always been inadequate, as only one vaccine (Bacille Calmette-Guérin (BCG) TB vaccine) developed way back in 1921 is available for helping the immune system towards developing necessary protection from the disease. The vaccine is usually administered to the infants of the at-risk populations. In some of the advanced countries, like the United States, BCG vaccine is not generally recommended as variable effectiveness of the vaccine has been found against adult pulmonary TB, and there is a chance of the vaccine's potential interference with TST reactivity[7].

"The World Health Organization (WHO) data shows that about 10 million people were infected with TB in 2017"

The emergence of drug-resistant tuberculosis (DR-TB): With the advances in the mainstream medical sciences, the number of reported tuberculosis patients experienced a decline. Further, the ability to treat some forms of TB effectively with drugs led to the collective perception amongst the general population, as well as, the medical community that TB is no longer a disease of morbidity and mortality. However, the recent discovery of multidrug-resistant tuberculosis (MDR-TB) in the US-American centres for the HIV patients, as well as, in a few other countries that regularly sees a large influx of migrants with TB syndromes, highlights the importance of continued research and innovation towards curbing the TB outbreak[6]. The World Health Organization (WHO) data shows that about 10 million people were infected with TB in 2017, and about 1.6 million succumbed to the disease. Data-based evidence brought forth 558,000 new cases with TB infection that exhibited resistance to the most effective first-line antibiotic. Among the patients with drug-resistant TB, about 82% were resistant to multiple antibiotics[8]. Therefore, we should get rid of the sense of complacency and large-scale research should be directed towards the innovation of an effective drug, as well as, an advanced treatment regimen.

Treatment Regimen for TB and Recurrence of Infection: The prevalent treatment regimen for the infected people is quite lengthy with tuberculosis symptoms lasting for a duration of six months to a year, and sometimes even more for the drug-resistant TB variants[9]. Relapse of TB for people undergoing treatment is also very common, as many of the patients fail to stick with the daily schedule of medications that typically comprises of multiple pills[9]. Recurrence of TB infection may arise due to multiple reasons. Data show that the trends and signatures are also specific to the geographical locations in this context. For example, in the United States and Canada, most of the recurrent tuberculosis cases were found to be a relapse of the original infection, presumably because of the insufficient treatment; whereas, in a study done in the TB-prone city of Cape Town in South Africa, 18% of the 612 participants exhibited tuberculosis reinfection and 14% of those patients were infected again with a different strain of TB following a successful treatment[9].

Latest Advancements in the Research: Recently, in a clinical trial conducted on the 3,330 participants living in active tuberculosis disease centres in Kenya, South Africa, and Zambia, doses of the Glaxo SmithKline inoculation called M72/AS01E was administered. The vaccine trial was found to have a 50% efficacy rate. However, William Schaffner, an infectious disease specialist and a professor of preventive medicine and health policy affiliated with the Vanderbilt University School of Medicine in Nashville, Tennessee mentioned that the scaling up of such research activities is required, and the vaccine will not be available to the public for at least a decade or so[10]. In another major effort in 2019, a team of researchers at RCSI (Royal College of Surgeons in Ireland), funded by the Health Research Board (HRB) and the Royal City of Dublin Hospital Trust, claimed to have developed small, safe-for-consumption particles packed with all trans-retinoic acid (atRA), a derivative of Vitamin A, so that they can be used in an inhaler. Upon being inhaled by a patient, the atRA-loaded particles would reduce the load of TB bacteria in the lungs and improve the patient's immune system leading to an increased chance of recovery[8]. In a further advanced study at the University of Michigan, Artificial Intelligence (AI) is being used to create a software tool to enable prediction of suitable combinations of pharmaceutical drugs, from the pool of both likely, as well as, unlikely candidates, to facilitate more effective treatments without requiring exhaustive clinical trials that are typically time-consuming[11].

Looking at these recent advancements, it would be reasonable to conclude that along with malaria, HIV, and universal flu vaccine, an effective TB vaccine is going to be a major discovery and such a breakthrough innovation could prevent many serious illnesses and reduce the mortality that is owed to the insufficient medical intervention.

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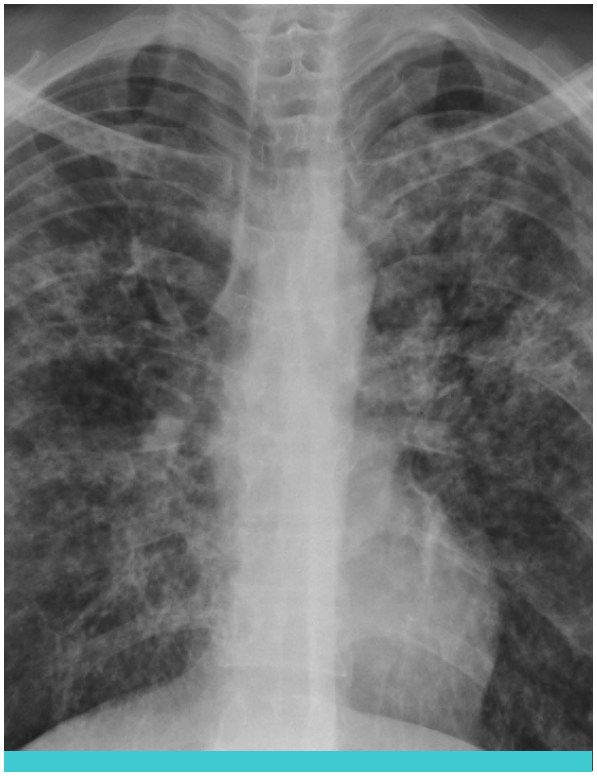
"About 25% of total TB patients are in India and 600 people on an average die from TB every day. At the same time, TB is curable and preventable."

Awakening to Crises of the TB Endemic

Dr. Shailesh Nayak, Director, National Institute of Advanced Studies, Bengaluru

Tuberculosis or TB is one of the major causes of death worldwide. India is worst affected, followed by China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa. About 25% of total TB patients are in India and 600 people on an average die from TB every day. At the same time, TB is curable and preventable. The death rate in India is falling due to improved diagnosis and treatment, though slowly. We have a long way to go before we can eliminate TB endemic by 2025, a target set by India.

The recognition of the elimination of TB as one of the sustainable development goals is a testimony of its importance to humanity. The goal of the free world from TB has to be linked with other sustainable developmental goals as well. The most important goal in this regard relates to ending poverty from the world. Each human being should get adequate support for fulfilling its basic needs. Balanced economic growth and inclusive growth are key to reduce poverty. Improved nutrition to the poorest is vital as undernourished are at increased risk, almost three times more. Access to affordable health care for early diagnosis and treatment of TB patients is another critical issue. The 'Aayushman Bharat' program is the right step in this direction. The National Tuberculosis Control Program has also focused on increasing access to health care for TB patients.The current standard of care is long and stressful for the patients leading to non-compliance that result in drug-resistant TB. Other socio-economic conditions, availability of clean fuel for cooking, air pollution, unemployment, poor built-environment and crowding in homes and lack of awareness especially among women need to be addressed at the earliest. Most patients are socially marginalized people. Dis-empowerment and stigma put unnecessary psychological pressure on patients to come out and seek help.



India, recently, has eradicated polio, by very innovative approaches for reaching to each and every chi ld. Similarly, India needs to take a lead in developing a strategy to greatly enhance its efforts to eradicate TB. One of the most important steps is to develop an information system based on GIS for monitoring and reporting each and every case and how the implementation of the national program is being carried out at local, state and district levels.Adequate investment in research and innovation for developing affordable drugs, providing access to diagnosis, treatment, care and research has to be ensured. Though India has almost quadrupled its funding from Rs 800 to Rs 3300 crore during 2016 to 2018, It may need more than Rs 10,000 crore per year to achieve the target. India has to show great political will and involve all stakeholders, pharma companies, civi l society and the private sector and commit themselves towards achieving the task of eradication of TB. I am sure this magazine is a small but very critical effort towards realizing this goal. My compliments to them and wish very best for this noble initiative.

Tuberculosis: The Quest for a Better Approach

Dr. h.c. Peter Kapitein, Patient Advocate, Inspire2Live, Amsterdam

As a patient advocate from Inspire2Live, the Dutch and international organization of patient advocates that aims to get cancer under control, it's not a weird question to write an article about tuberculosis. It is particular not weird because I was asked about how to come to a better approach of setting up research for a better treatment of tuberculosis. To be honest, I know almost nothing about tuberculosis. I know a lot about cancer and about how to organize settings, workshops and brainstorm sessions for realizing new approaches to deal with it. I'm convinced it works for other diseases as well. We call our approach 'The Discovery Network'(DN). Let's see how this goes.

For the man with a hammer the whole world looks like a nail. When you never deal with other people, opinions, businesses and approaches, you will be convinced of yourself and find out that you can do the same thing over and over again and that you are always right. However, people around you see no chance and even worse, no progress at all. Arguments like 'change needs time' are needed to justify your way of working. When dealing with diseases this is not the right thing. In healthcare, we have a strong responsibility, we need change and progress.

People don't want to change. They talk about it a lot and adapt. But they only adapt when there is an urgency. And that's what lacking in the decision-making process in healthcare: there is no urgency. We say there is and that the patient is important, but we do not act upon it. The approach that Inspire2Live chose for improvement in treatments and change the way science works is to combine emotions with arguments. The emotions come from our fellow patient advocates; they are sick and dying. This brings the urgency we need: better hurry

because we're dying. With emotions alone we did not get where we want to be. We need arguments: science, knowledge and facts. Patient advocates need to know what they talk about when working with the stakeholders in the Medical Industrial Complex: patient organizations, doctors, scientists, industry, government and health insurance.

When working on change and improvements we have to keep 4 maxims in mind. Let me explain (Reference 1).

Bring a range of people together
Invite someone who does not understand your field of expertise, but who is smart. Ask her to ask questions that you have never thought about before and look for the answer. You will be amazed by your lack of knowledge in your own field. You'll be amazed how much you take for granted, but what (for an outsider) is not self-evident. 'I don't know who discovered the water but it certainly wasn't the fish.' And always elicit someone's opinion: 'I want your opinion, even if I do not like it.' We are looking for the truth and for that everything has to be on the table.

Look for the real cause
'Johnny fits into the trouser. The trouser fits into the bag. Therefore, Johnny fits into the bag.' This is the logical fallacy of assuming the conclusion. This statement is clearly nonsense, but in practice there is often evidence that could hardly, if at all, be called evidence. I am referring to the fumbling with data that supports scientific articles and that in a number of cases simply is neither verifiable nor repeatable. Continue and ask penetrating questions (with the various people and their diverse backgrounds) as far as irritation point and the pain threshold, and beyond. Only once we know the real cause is a solution really possible.

Upscale Quickly
Think big, start small and upscale quickly. You don't solve cancer by thinking small. Cancer is a global problem and that requires great ideas, grand theories and sweeping approaches. This piece of knowledge comes from France, that insight from an American. And look what an essential contribution India is making on this point.

Be independent
We are never independent, because we always act because of something or someone. The only permissible dependency that stakeholders have in healthcare is dependence on the patient. In this, we must be vigilant. If we see otherwise, then it is our duty to correct it. All those involved in the Medical Industrial Complex must ask themselves seriously whether this is the only permissible dependency, or whether there is another dependency at play. Everyone is obliged to answer this question in good faith and to weigh up that answer in the discussions they have with the other parties concerned about the patient's problems: 'Am I serving you or someone else?' The four maxims help in determining the right route to reach a solution. And the nice thing is that they are placed in a certain order in which the various points influence and reinforce each other in their application. You bring together different people with different opinions, who jointly search for the real solution and find it. What they find must then be brought to all patients as quickly as possible. This solution can only be found and implemented if there are no interests at play other than those of the patient.

The DN concept
The DN creates an open environment for those who are in this structure to pursue a common goal and to better reach that common goal. Patients are an integral part of this open environment. The DN will facilitate at least three levels of cooperation in the area of research and treatment.

- Better sharing of better observations
- Better utilization of better treatments
- Better organization of better networks

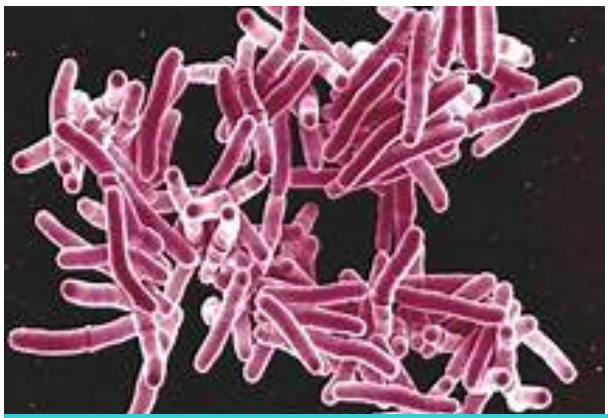
To function as a full-blown information science, with connected brains, the DN must incorporate all levels of cooperation. An inherent problem in this kind of system is that the DN must enable the need for both openness to novelty and closure when disciplined research and/or treatment regimens are required.

Without better sets of high quality observations of groups and individual patients, better treatments will not be discovered and utilized. In fact, without capturing better quality data of treatment effects and sharing them, we will not be able to distinguish good from bad, better from worse or better from really better. At some point, strict regimens of diagnostics, treatment and observation of treatment effects are necessary to make progress at.

At the end of the day, treatments are central. Introducing better treatments also means adapting existing regimens and replacing existing regimen with better regimen at the level of well-defined groups and in given cases, at the level of the individual patient.

But we also need better networks (research groups, cooperating institutes, teams of clinicians and lab researchers, et cetera). We need to change the way we work within and between groups of researchers, physicians, engaged patient and all relevant others. Here data sharing and the fluent creation of problems focused networks of researchers, clinicians and engaged patients is crucial.

What is needed is a kind of hub connecting the relevant people and professionals, and this is the instrumental reason for creating the DN. The DN is about the discovery of better treatments: for groups and for individual patients. This needs better organization!



The functions of the DN

What is the DN? The basics are simple. The implementation and the use will be a lot harder to specify. In fact, actual use is a discovery process in itself. We enter the world of information science, because apart from the actual brains of people and the hardware, everything else should become exchangeable as information!

1. The first element: The basic idea is that we create a network, which supports the combination of ideas. This means: connecting brains and sharing all information that the brains need to reach the goal.
2. The second element relates to better observations. High quality characterizations will be needed. New imaging regimens, new imaging techniques, better reports and access to repositories will be necessary.
3. We need a map of all possibilities of treatments.
4. We need exchange with and connection to networks of scientists and clinicians. The networks include the people who operate the facilities to design animal models, screen drugs and set up trials.
5. Observations, treatments and networks must be matched. This is qua interfacing and technically the most challenging part. Human intervention will be required to get the details right. Only users from the proper networks will have the knowledge to make the right decisions.
6. Results must be studied in populations of patients and must also feed back into the DN.

Brokerage and closure

Improvement ultimately means discovery, invention, development and implementation. Quality new observations,, treatments and networks will have to be added to or replace the old sets of observations, treatments and networks. Brokerage and closure is about this dynamic process of improvement. The DN is an improvement system; ever open to falsifications, replacement of entrenched practices and better ways of working. To improve the system of discovery and speed up implementation for patients, we have to expand on the boundaries of observations, treatments

and networks. The DN connects brains and leaves to the brains what the brains are good at. It lets the network do what the network is good at. If the DN is based on any trick, this is its basic trick. It is not an Artificially Intelligent system. The Intelligence is in the interaction between brains of real people. If the people stop thinking and stop interacting, it will not make any difference at all. And this brings us to the human factor. The most important factor of all!

The central position of the human factor

The patient of the 21st century makes the importance of the patient perspective very clear (Reference 3). At the core, it is the patient who must benefit and who is smothered, because of regulations, the reputation of pharma, bad information, deliberate misrepresentation of research results (for example, reporting relative improvements in percentages instead of real improvements in terms of absolute numbers), et cetera. The human factor is the rate-limiting step. If we succeed to engage patients, funders, physicians and researchers, we make progress.

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Tuberculosis Free World

Dr. V. Bhujanga Rao, FNAE, ISRO Chair Professor, National Institute of Advanced Studies, Bengaluru

It gives me immense pleasure to wholeheartedly greet all the medical professionals, paramedical staff, researchers, patients etc. on this 'World TB Day being celebrated every year on 24 March'.

TB, as we all know, is the most infectious disease on this planet killing more than 2 million people each year. This communicable disease caused by Mycobacterium tuberculosis exists on earth since time immemorial and is intelligent enough to evade the eradication despite sustained effort and improvement in medical sciences.

Be its Mars mission, building a nuclear submarine or robotic surgery or weapons of mass destruction or the advanced jet engine or eradication of plague, polio, smallpox, human being has displayed his extraordinary ingenuity taking every challenge in his stride. Despite thousands of researchers working for the last 60 years around the globe, the disease is continued to be a threat to humanity. It takes about 2 weeks for diagnosis with an increase in complexity when we come across XDR or MDR TB cases.

The need of the hour is to relook at our efforts, redirect our research, utilize advanced technologies and find out a long lasting solution to eradicate this disease. Resistance to current drugs asks for new drugs and hence innovation in drug discovery. Additionally, TB patients suffer from social stigma, daunting and difficult treatment, lack of social support, lack of motivation to undergo prolonged treatment resulting in large unsuccessful outcomes.

"TB, as we all know, is the most infectious disease on this planet killing more than 2 million people each year."

Some of the challenges are not medical but behavioural leading to non-adherence to treatment. Failure to early diagnosis and unable to initiate on time effective treatment are some other which are indispensable for effective TB control. Expediting research using point of care Nano bio sensing based technologies which have the potential to detect even MDR TB cases with instantaneous results will be in order.

Today India has set up excellent Nano-, biotechnology centres that should be funded to undertake this research at a larger scale. Nanotechnologies are successful in drug delivery at site of action which can give nullify the challenge associated with poor absorption, metabolism and hence dosage and duration of treatment. To overcome some of the patient non-compliance and behavioral issues, digital platforms and social media can be used to create interactive communication between patients, doctors, social workers, psychologists and researchers. This may improve the awareness and hence the adherence to the treatment regimen.

India despite seriously engaged with control of TB over the last 50 years faces a mortality rate of 1200 per day. It is gratifying that GOI has set up a national programme under the chairmanship of our honourable Prime Minister and drawn up a framework to create TB free India.

ESA has funded a project SAFE (satellites for Epidemiology) which was employed for routine surveillance of TB in Georgia. This enabled better follow up of MDR cases. This has been used by Georgia national centre for TB to decentralize the way the data was collected than any other means. We can probably ask for support from ISRO to initiate such a programme in India. At the international level, the WHO has drawn up strategies at a global level to save the world from the scourge of TB by 2035 with 90 percent reduction in incidence, 95 percent reduction in deaths with affordable treatment.

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