JANUARY 2021 | VOLUME 1 | ISSUE 2

Tuberculosis Newsletter

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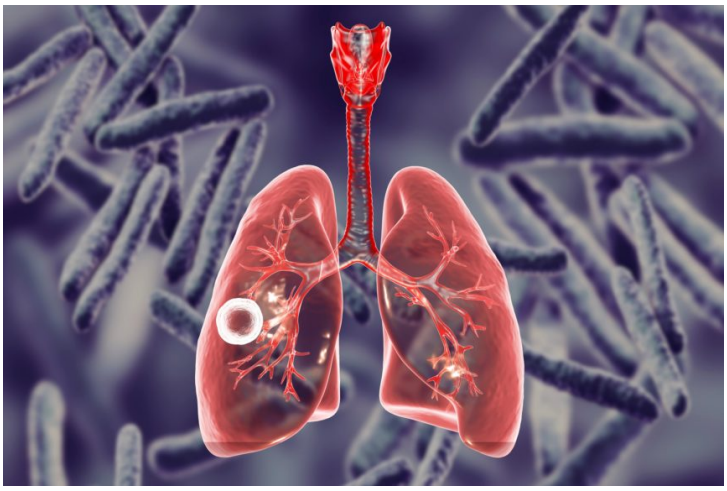
Articles



Cover image of newsletter from https://www.pulmonologyadvisor.com/home/meetings/chest-2019/prophylaxis-with-moxifloxacin-may-prevent-incident-tuberculosis-infection-in-high-risk-people/

The Clock is Ticking: It's Time to END TB

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

World TB day is observed on 24th of March every year. This year's theme is "The Clock is Ticking". This day is designed to raise public awareness about the TB epidemic, which is still the number one killer globally among infectious diseases. Tuberculosis is a curable and preventable disease. The global burden of the disease attributes to delay and poor diagnostic and inadequate treatments, which leads to the severity of the disease with an increase in mortality rate and the spike in transmission and development of drug resistance. TB does not spare any country in the world, even though it unreasonably impacts LMIC (lower- to middle-income countries). A total of 3% of global TB cases occur in the WHO European Region. In the US, about 13 million people live with latent TB.

If we look at the response and aggressiveness the world has laid down to address the Covid-19 pandemic, the same show has not been put up for TB even though it is a century-old problem globally. Both Covid-19 and TB has the capacity to stress healthcare systems. The current pandemic has seen rapid diagnosis and public awareness for disease control and containment, whereas insufficient and inadequate diagnostics in Tuberculosis keeps fuelling the on-going disease transmission in many settings. The critical ingredients of infectious disease control are creating an ecosystem of trained healthcare workers in recognizing the disease and an effective surveillance system to monitor the behaviour. This requires a tremendous effort from the regional and central level and must be backed by financial and human resources. Tuberculosis at large has never seen a data and knowledge sharing platform that Covid-19 has witnessed. The lack of coordination and sharing of information and data at the national and international level has created barriers to informative datasets that could have facilitated and accelerated quality research in Tuberculosis. TB has seen a long-standing paucity of funding to address different issues associated with the disease ranging from surveillance, reporting, diagnosis, treatment, policy and research, to name a few. The current pandemic will change the future of vaccine discovery and development. There is a paradigm shift in vaccine technology. The accelerated speed at which multiple vaccines have come up to address the current pandemic is overwhelming. It has shown when all the resources are at their disposal how fast vaccine development can proceed when there is a global emergency. Can we imbibe this learning for other neglected diseases such as Tuberculosis?

There is a critical need for new TB vaccines that are more effective than the Bacille Calmette-Guérin (BCG) vaccine in preventing pulmonary and extrapulmonary forms of TB in all age groups. THE century-old BCG vaccine is immunoprotective against extra pulmonary paediatric TB, including meningitis. However, the protection provided against pulmonary TB in adults is variable. New vaccines are also required keeping in view the slow decline in TB incidence globally and the persistent threat of MDR-TB. The article from Prof Madhukar Pai in this issue is an eye-opener, as he rightly said, “It’s time to use Covid-19 innovations and systems to reimagine TB care”. The long duration of the current TB treatment and side effects associated with it leads to non-compliance, ultimately resulting in MDR and XDR TB. There is a greater need for developing a shorter regimen. Article by Drs Shingar and Pawan Sharma has thrown light on the current effort on shortening the treatment duration from 6 months to 4 months as shown by a phase 3 clinical trial study (Study 31/A5349). The study included eight weeks of daily treatment with high-dose rifapentine, isoniazid, pyrazinamide, and moxifloxacin and nine weeks of daily treatment with rifapentine, isoniazid, and moxifloxacin. The treatment was well-tolerated and found to be non-inferior in efficacy to the standard six-month regimen (2RHZE/4RH), which includes eight weeks of daily treatment with rifampin, isoniazid, pyrazinamide, and ethambutol and 18 weeks of daily treatment with rifampin and isoniazid. The world is overwhelmed by vaccine development to address the current pandemic. The article by Dr Saheed Jawahar has reflected the current advancement in vaccine development for Tuberculosis. Countries with high levels of Tuberculosis face a significant comorbidity burden from

both non-communicable and communicable diseases. Prof M V Hosur article talks about the syndemic nature of TB and HIV and how the mortality rate is three-fold higher than just Mtb infection. Tuberculosis is not restricted to human; it is seen in animal too. Dr Rudrodip Majumdar article has emphasized Tuberculosis in captive elephants, which has emerged as a serious infectious zoonotic disease in the past few decades.

The "Clock is Ticking", and we need to put our act together before it's too late.

It's Time To Use Covid-19 Innovations And Systems to Reimagine TB Care

Prof. Madhukar Pai, Canada Research Chair in Translational Epidemiology & Global Health, Associate Director, McGill International TB Centre, Dept. of Epidemiology, Biostatistics & Occupational Health, McGill University

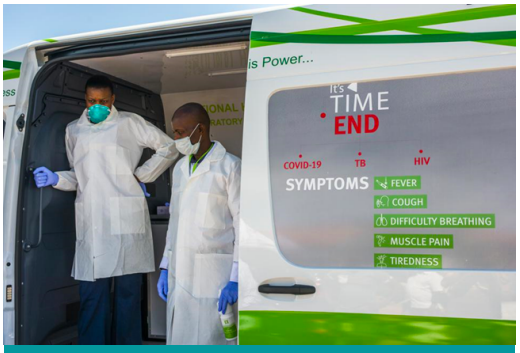
***It's Time To Use Covid-19 Innovations And Systems to Reimagine TB Care* (*forbes.com*)**

Even as the world comes to grips with the mounting death toll due to the Covid-19 pandemic, the WHO released its 2020 Global Tuberculosis Report last week. The news is not good. Nearly 1.4 million people died from TB in 2019. Of the estimated 10 million people who developed TB that year, some 3 million were either not diagnosed, or were not officially reported to national authorities.

As expected, the Covid-19 pandemic is making things worse, with 25-30% drops in TB notifications reported in 3 high burden countries – India, Indonesia, the Philippines – between January and June 2020 compared to the same 6-month period in 2019. These reductions in case notifications and ongoing disruptions to TB services could substantially increase TB deaths.

As I previous wrote, together, Covid-19 and TB pose a deadly, dual threat - a syndemic. Tremendous catch-up work, advocacy, and funding is needed, to get back on track, even as the pandemic is pushing millions of people into extreme poverty. That cannot be good for TB, since Poverty and TB are old pals.

In the early days of the pandemic, there was optimism that TB technologies and systems could help end the Covid-19 pandemic. Indeed, molecular technologies widely used for TB are being used to test for Covid-19, and the BCG vaccine for TB is being tested for Covid-19. National TB program staff (e.g. contact tracers) are engaged in the Covid-19 response. TB wards have been re-purposed to serve as Covid-19 wards.



Mobile testing for Covid-19 in South Africa. Photographer: Waldo Swiegers/Bloomberg, © 2020 BLOOMBERG FINANCE LP

But now, given the massive setback to progress in reaching any of the TB targets, it's time for the TB community to ask: are there Covid-19 innovations and systems that can be effectively leveraged to reimagine TB care?

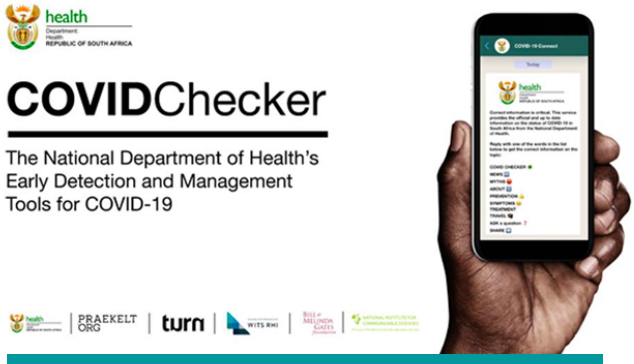
"In many low- and middle-income countries, TB programs became the foundation of an effective early response to Covid-19. Now, as we are urgently rebuilding disrupted core health services for TB and other conditions, we have an opportunity to draw on the toolbox of innovations that have been created for Covid-19," said Catharina Boehme, CEO of FIND, Geneva.

By speaking with a large number of experts, I could indeed identify several opportunities for the TB field (and vice-versa).

Education, risk assessment & screening

Mobile apps & services (e.g. using Whatsapp & chatbots) are being widely used for public education on Covid-19, for risk or self assessment, screening and linkage to testing, for contact tracing and mapping.

For example, South Africa, building on its success with Mom Connect, has reached over 7 million people using a suite of digital tools (e.g. COVID-19 Health Alert & COVID-19 Health Check). India's open-source Aarogya Setu mobile app has been downloaded by over 150 million individuals. If these apps can enhance TB contact tracing, that would be a huge advance, since contact investigation is an effective but underused intervention in many high TB burden countries.



In South Africa, the National Department of Health's COVID-19 digital responses have connected the ... [+] DEPARTMENT OF HEALTH, SOUTH AFRICA

According to Zameer Brey, a Senior Program Officer at the Bill & Melinda Gates Foundation in South Africa, these platforms and technologies are being repurposed for TB. "The 'disruptive' innovations that emerged during the Covid-19 pandemic were waiting beneath the surface to really enhance patient-centered care across the most vulnerable communities. The biggest tragedy would be to quickly bury those innovations and bury the hope of a more patient centric system," he said.

Another way to screen for TB and Covid-19 is to use digital chest x-rays (highly portable systems now exist), with artificial-intelligence (AI) solutions to make the interpretation easier and less reliant on expert radiologists. Such AI-based solutions already exist, for TB as well as Covid-19. AI-based algorithms can also identify CT scans with COVID-19 associated pneumonia.

Following long collaborative efforts, DOPASI, Stop TB and Fujifilm launch TB screening of 400, 000 ... [+] DOPASI ORGANIZATION FOR SUSTAINABLE DEVELOPMENT, PAKISTAN

"While TB needed AI interventions, the development of such technologies was slow because TB was (and still is) a poor person's disease. Covid-19 has not only ushered more adoption for existing AI interventions, but forced us to think what we can build beyond usual offerings," said Prashant Warier, CEO of Qure.ai. "Initially, while a lot of TB solutions were repurposed for Covid-19, now there is an opportunity to reverse-purpose several Covid-19 solutions for TB," he added.

Automated recognition of cough duration and sound patterns might help encourage care-seeking and potentially screen for conditions such as TB and Covid-19. Indeed, innovative R&D around this is happening (e.g. Hyfe cough tracker app). "How could the ability to detect and classify coughs not be transformational?" asked Peter Small, a TB expert and innovator at Global Health Labs.

Raghu Dharmaraju, a VP at Wadhwani AI is hopeful about cough-based screening as well as greater use of data science or pandemic response. "My deepest hope is that we use this crisis to accelerate the shift to truly data-driven health systems," he said.

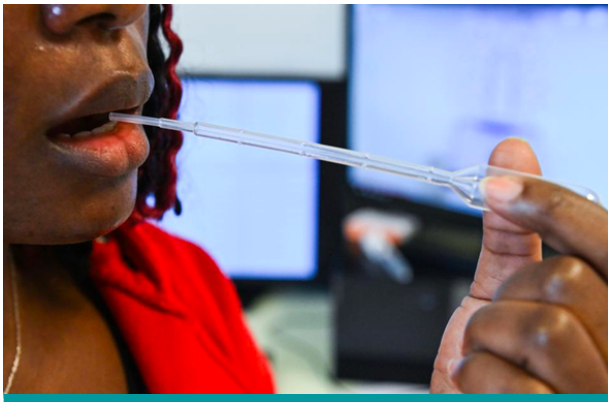
Innovative sample collection and diagnosis

"Innovative community-based (decentralized) testing and enhanced case finding can be lessons learned from Covid-19 and scaled up for TB," said Antonio Flores, a HIV/TB specialist with Médecins Sans Frontières.

Puneet Dewan, a physician and TB expert with Global Health Labs agrees. "There has never been so much enthusiasm and money in diagnostic testing," he says. He hopes some good can come out of the current crisis. "We have to ensure we end up with products and systems that meet TB control needs," he said.

The demand for rapid and simpler Covid-19 testing has pushed companies and health systems to innovate around what samples to collect, where to collect them, and how to make testing easier to access. For example, samples such as saliva, rinse and gargle, oral swabs, and even sampling of face masks are being actively tried out. Better and cheaper swabs have been developed (e.g. polyester-based Q-tip-type swab).

Tremendous effort is being made to develop home-based, self-tests for Covid-19. Mobile testing sites, drive-through testing, and sample collection via community health workers, neighborhood pharmacies, schools and workplaces are all happening.



A researcher from the Sys2Diag laboratory, from the biotechnology company SkillCell, takes a saliva ... [+] AFP VIA GETTY IMAGES

Currently, TB testing is highly reliant on sputum, a sample that is not easy to collect and process. TB testing is also not easily accessible at the primary care level. So, if some of the innovative approaches around Covid-19 sample collection & near-patient access can be applied to TB, this might help reduce the massive diagnostic gap in TB.

"The unprecedented speed with which Covid-19 tests have been developed is proof that even technically challenging diagnostics can become reality in record time," says Morten Ruhwald, Head of TB at FIND, Geneva. He believes there is huge potential to expand Covid-19 technologies across a spectrum of respiratory diseases.

There are several rapid molecular diagnostic platforms that are currently running Covid-19 and TB tests. Some of them are designed for point-of-care use (e.g. GeneXpert and TrueNat), while others are meant for high-throughput, centralized laboratories (e.g. BD Max, Abbott m2000, Roche Cobas). Wider use of molecular technologies and bi-directional testing can only be good for TB, and help the field get rid of suboptimal tools such as smear microscopy.

In addition, great progress has been made with rapid, point-of-care antigen testing for Covid-19. Adapting this to develop simpler POC tests for TB would be a massive advance.

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Rapid, high-sensitivity urine LAM antigen detection technology holds great promise and will benefit from all the technology development around Covid-19 rapid testing.

"Simple self-sampling (e.g. from face masks) appears within reach – and in combination with cutting-edge molecular detection assays like CRISPR, this could make at-home diagnosis of respiratory infections not just as straightforward as a pregnancy test, but as accurate as conventional diagnostic methods," said Morten Ruhwald.

"I am very enthusiastic about the possibility of porting true point-of-care, non-sputum based diagnostic systems for use in TB. It's not just the instrumented platforms, but non-instrumented disposables that have taken a flying leap forward," said Puneet Dewan.

Innovations in care delivery

"Remote service provision has come to stay due to Covid-19," said Ifeanyi Nsofor, CEO of EpiAFRIC and Director of Policy and Advocacy at Nigeria Health Watch. And everyone now sees the value of care close to home (primary care).

Indeed, because of lock-downs and physical distancing requirements, tremendous advances have been made in the area of tele-health, online consultations, house calls by doctors, use of call centers, e-pharmacies, use of digital adherence technologies (e.g. smart pillboxes, video observed therapy), and home delivery of medicines using health workers, ride-sharing services, etc. All of these can and should be leveraged for TB, at a larger scale than what is currently happening.

Coronavirus emergency (Covid 19). Volunteers of the Italian Red Cross engaged in the delivery of ... [+] MONDADORI PORTFOLIO VIA GETTY IMAGES

"Covid-19 is providing a huge boost to the at-home delivery market for medicines," said Prashant Yadav, a supply chain expert and professor at INSEAD. "The infrastructure that many privately funded startups & social enterprises are creating could be extremely useful for TB patients especially if sometime in the future we transition to even shorter treatment regimens which can be self-administered with a tele-consult follow-ups," he added.

Indeed, we now have hopes for a 1-month treatment for latent TB infection, a 4-month treatment for active TB, and a 6-month oral treatment for drug-resistant TB. If these can be combined with tele-consults and at-home delivery of medicines, it could revolutionize TB care.

According to Yadav, Covid-19 has created a sudden and growing interest in improving healthcare supply chains. "Many of the initiatives are focusing on resolving system bottlenecks in procurement, distribution and supply chain information systems. These will go a long way in ensuring healthy supply chains for all medicines," he said.

Better data, data visibility and usage

Most TB programs still rely on annual reports and paper-based reporting systems that are no longer fit for purpose. Covid-19 shows us the power of real-time data aggregation, analysis and usage.

During this pandemic, an astounding number of real-time Covid-19 trackers, vulnerability indices, geospatial mapping tools and dashboards have been launched, often by collaborative networks of scientists and citizens. This has provided real-time data for public health and personal use. Rapid data sharing has also provided early epidemiological and clinical insights. Most countries are conducting rapid prevalence and infection surveys, to enhance routine surveillance. Covid-19 has also accelerated the use of electronic medical records.

TB has never seen this level of investment in data systems. Lack of good data has always blunted effective TB response and made it harder to ensure accountability.

UKRAINE - 2020/04/29: In this photo illustration the Coronavirus COVID-19 Global Cases world map by ... [+] SOPA IMAGES/LIGHTROCKET VIA GETTY IMAGES

"Investments on data systems and tools like vulnerability indices are key to deploying a more precise response (for Covid-19 or TB)," says Sema Sgaier, Director of Surgo Foundation. "Vulnerability indices can be powerful predictive tools that enable policy makers to identify geographies that will have the hardest time to mitigate the health, social, and economic impacts of a disease like TB, and guide policy makers to the types of mitigation interventions they should be betting on," she added. Machine learning and big data can also help precisely target those who need extra support.

Infection control & behavior change

Despite being an airborne respiratory infection with high risk of occupational transmission, TB infection control has received little attention in high-burden countries. Covid-19 shows that healthcare systems can find ways to protect healthcare workers and people can change their behaviors to reduce risk, for themselves and others.

"The overlooked story is how human behavior change can interrupt transmission. A no holds barred attack on how we change behavior should be essential response to this pandemic and TB," said Peter Small.

Routine use of personal protection equipment by healthcare workers, large-scale use of face masks by the public, better triaging and cohorting within health facilities, safer disposal of respiratory secretions, and advances in research into aerosols & airborne transmission (and engineering controls) can all help interrupt TB as well as Covid-19 transmission.

Because of Covid-19, the use of face masks has become less stigmatized, and there is wider acceptance that anyone can get a respiratory infection. Hopefully, this will make TB less stigmatized.

Social safety

Covid-19 has taught the world about the importance of social safety nets that include paid sick leave, unemployment benefits, direct cash transfers, food supplements, and a heightened focus on social determinants. Greater education of the public and community engagement is also evident in many settings. And public health investment is now clearly understood as a 'social good.'

Since TB is primarily a disease of poverty and is highly correlated with social determinants such as malnutrition and poor housing, such social security benefits must be more widely available to all persons with TB, especially in low- and middle-income countries. A purely biomedical approach to TB is unlikely to succeed. In the same vein, greater engagement of communities most affected by TB is critical for success.

Public-private partnerships for care delivery

During this crisis, governments across the world have found a variety of mechanisms (e.g. price caps, strategic purchasing of services, better regulation) to tap into the private health sector for Covid-19 testing and treatment. As noted by WHO, many LMICs have a large and growing contingent of private sector health service delivery actors that have historically been weakly governed and poorly coordinated. "Now more than ever LMICs need a whole-of-government and whole-of-society approach as they immerse in the battle against COVID-19."

A recent survey showed wide variations in the cost of Covid-19 testing in the private health sector across LMICs. However, some countries have successfully made Covid-19 testing more affordable and accessible via private laboratories. Similar private-provider initiatives are also underway for TB, and deserve to be taken to scale, since the private health sector is a major source of TB care in several high TB burden countries.

Global partnerships & collaborative research

The pandemic has transformed medical research and publishing. We now have rapid access to information via pre-prints and open access publications. Most medical and scientific conferences are now free and easily accessible to people around the world.

"Now more than ever LMICs need a whole-of-government and whole-of-society approach as they immerse in the battle against COVID-19."

There are many open data platforms to foster research collaborations & R&D. "Despite TB being the biggest infectious diseases burden, and especially affecting LMICs, many publications are still sitting behind a paywall," laments Muge Cevik, a clinical lecturer in infectious diseases at the University of St Andrews.

The pandemic has also inspired several multilateral global collaborations and partnerships (e.g. ACT Accelerator, COVAX), pooling of funding for new tool development & delivery, patent pools to increase access, and other approaches to increase access to new tools.

Such partnerships are urgently needed for TB, where slow access to new tools is a long-standing concern. 'We have demonstrated that with global solidarity, a lot can be achieved in a short time. Open data, open access research and (to some extent) pooling of technology have all become the norm and should be continued for global threats like TB," said Soumya Swaminathan, Chief Scientist at WHO.

Rapid, multi-centric trials & evaluation studies (e.g. Solidarity trial, Recovery trial), faster regulatory approval processes, greater cohesion among scientists for evidence-driven interventions (e.g. John Snow Memorandum), and multi-sectoral responses within and across countries have all been noticeable during this crisis. "Wouldn't it be great to see the same concerted efforts to develop TB drugs and tests as we've seen for Covid-19?" asked Antonio Flores.

Muge Cevik would like TB researchers to be more open to adaptive clinical trial designs. "It seems like we are constantly stuck in long phase 3 studies of single drugs," she lamented.

Jennifer Furin, a TB physician and advocate, laments that TB has received almost no attention compared to Covid-19, despite the fact that TB kills millions of people each year. “Research predicts a gloom-and-doom scenario for TB as a result of Covid-19, but if we are smart, persistent, and creative in adapting some of Covid-19's successes, this could actually become our finest hour,” she argued. Along with her colleagues, she has listed potential collateral benefits from the Covid-19 pandemic to TB and HIV services.

Aakriti Pandita, an infectious diseases physician at the University of Colorado has survived both Covid-19 and TB. “Covid-19 is unclogging many novel pathways towards medical advancement that otherwise would have taken a lifetime to develop. In fact, in time, Covid-19 may actually prove to be one giant leap in medical science and global health if we use it our advantage,” she said.

Beyond disease silos

While the Covid-19 crisis has brought a great deal of attention to health, it is unclear whether such interest will sustain when the crisis dies out. Will Covid-19 create more disease silos, or will we finally see stronger health systems that can offer better primary healthcare? Will countries continue to invest in public health?

Daksha Shah, Deputy Executive Health Officer for the Municipal Corporation of Greater Mumbai in India has coordinated services for both TB and Covid-19. “Right now, the health system is most receptive (she highlighted the “My Family, My Responsibility” campaign in her state as an example) and we should build on this for improving care for TB, non-communicable diseases, and other conditions,” she said.

Grania Brigden, Director of the TB Department at The Union agrees. “I, personally, do not want to see another vertical disease program established with separate funding streams/ donors/ multinational organizations,” she said. “I think there is a benefit to thinking how/if TB integrates with the Covid-19 response and in high burden contexts becomes the cornerstone of a comprehensive approach to lung health,” she added. Since Covid-19 has put the spotlight on the importance of comorbidities, she hopes a similar attention will be paid to addressing comorbidities that often accompany TB (e.g. HIV, diabetes, malnutrition).

Yogan Pillay, country director of CHAI in South Africa, sees great potential for leveraging Covid-19 innovations for TB. The problem, he said, is “none of these are new to the TB community. How to get everyone to take TB seriously as they are with Covid-19?”, he asked.

Jennifer Furin has similar concerns. “The dazzling list of innovations for Covid-19 only happened because wealthy nations are just as at risk of Covid-19 as poor nations,” she said. “So we need to be fierce advocates to make sure these tools for Covid-19 are applied to TB because rich countries have revealed themselves for what they are: self-interested to the core,” she added.

Jennifer Furin is right - the billions of dollars invested in Covid-19 vaccines is orders of magnitude higher than the investments made in TB vaccine development since the dawn of humankind. We might have Covid-19 vaccines within a year, but will still be using a 100-year old vaccine for TB next year.

Saurabh Rane, a drug-resistant TB survivor and advocate has a compelling message. "I don't want to know why the world didn't respond this way for TB when it kills over a million people every year. But now that we are building tools to fight Covid-19, I beg everyone to use them to fight TB as well," he said. I agree wholeheartedly with him. There cannot be a more opportune moment for the TB community to leverage Covid-19 innovations to reimagine TB care, and make universal health coverage a reality.

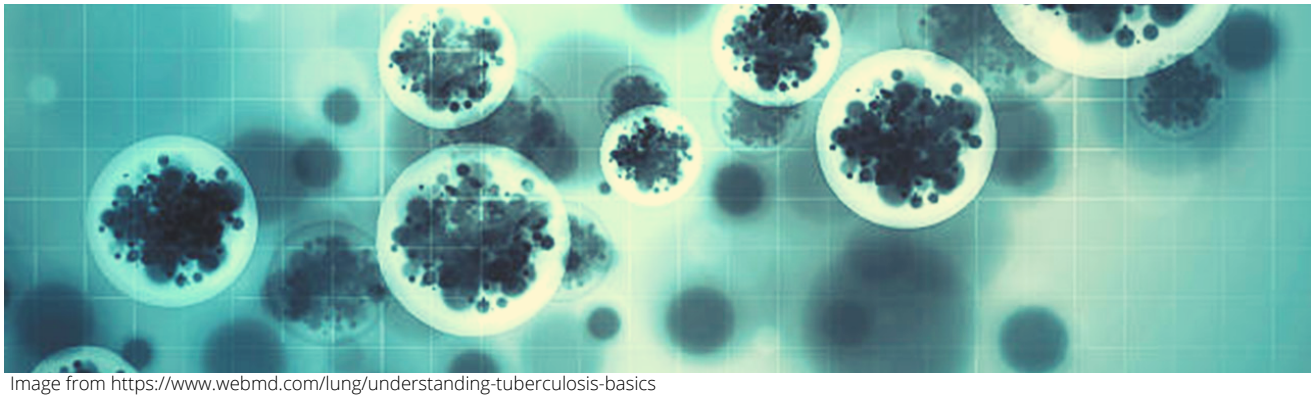


Image from https://www.webmd.com/lung/understanding-tuberculosis-basics

Ground Breaking Advancement in TB Treatment Regimen

Dr. Shingar Sharma, Formerly Grant Advisor, WT-DBT India Alliance, New Delhi & Dr. Pawan Sharma, Formerly Senior Research Scientist, ICGEB, New Delhi

A six-month-long duration of TB treatment under the DOTS programme is fraught with issues like non-compliance by patients, mix up of drugs, etc., contributing to the emergence of multi-drug-resistant TB. Shortening the duration of treatment has been a priority area in the TB drug discovery research efforts. In a recent Phase 3 clinical trial (Study 31/A5349), a 4-month regimen is as efficacious as the 6-month regimen for treatment of drug-susceptible tuberculosis in patients. This landmark breakthrough is expected to strengthen the global efforts for the elimination of TB by 2030.

The need to find game-changing yet feasible solutions to overcome the TB problem has taken on even greater importance in unprecedented times like these.

According to the WHO Global TB report, there were an estimated 10 million new cases of TB worldwide in 2019 and approximately 1.5 million people died due to the disease. India accounted for 26% of the global TB burden, the highest among all countries. Though the numbers have been falling over the past years, the progress is too slow. Disruptions in health services and case reporting due to the COVID-19 pandemic have caused a setback in the efforts to achieve the Sustainable Development Goals and can derail the ambitious End TB Strategy which aims to reduce TB deaths by 90% by the year 2030. The ongoing Covid-19 pandemic has not only laid bare the abject unpreparedness of countries across the world to effectively deal with such a massive health emergency but also poses a grave threat to the gains made in combating other major global diseases, such as Tuberculosis (TB). TB continues to be a leading cause of death worldwide and has not halted its grim march even as Covid-19 is taking a toll on health systems everywhere.

The need to find game-changing yet feasible solutions to overcome the TB problem has taken on even greater importance in unprecedented times like these. Drug-resistant TB remains a formidable threat and radical approaches are required to stem its onslaught. India had the largest number of drug-resistant cases in 2019, amounting to 27% of the global burden (WHO report 2020)[1]. Although the current new TB drug pipeline reflects impressive international effort in developing new anti-TB drugs {Table}, research on cutting down the duration of a long treatment schedule is equally important.

Putative New TB Drug Pipeline 2020: Based on www.newt bdrugs.org/pipeline/discovery

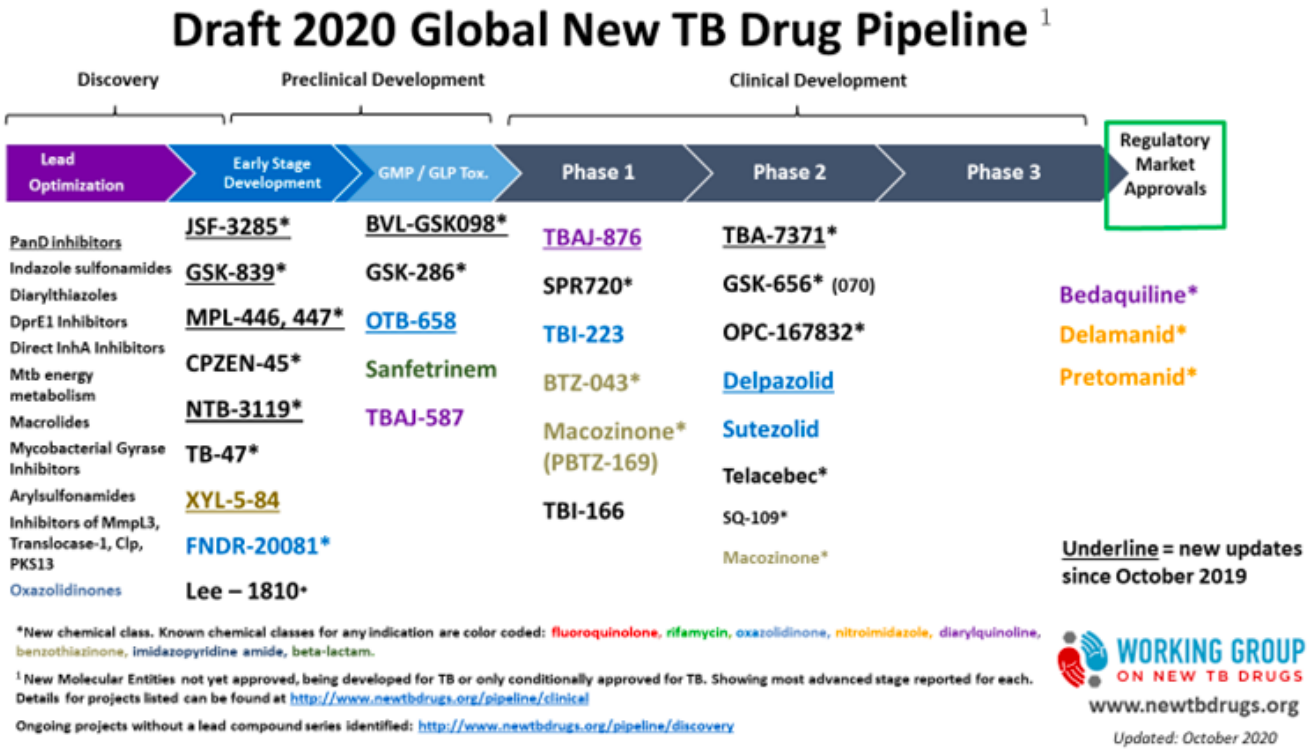
Pre-clinical	Phase 1	Phase 2	Phase 3
Sanfetrinem GlaxoSmithKline, Bill & Melinda Gates Foundation **BVL-GSK098** BioVersys AG, GlaxoSmithKline **GSK-286** GlaxoSmithKline, TB Drug Accelerator, Bill & Melinda Gates Foundation **TBAJ-587, Diarylquinoline** TB Alliance, University of Auckland, Merck & Co., Inc. **Spectinamide 1810** Microbiotix, Inc.	**TBI-223** TB Alliance, Institute of Materia Medica **SPR720** Spero Therapeutics, LLC, Bill & Melinda Gates Medical Research Institute ·Phase 1 Safety, Tolerability, and Pharmacokinetics of SPR720 **BTZ-043** University of Munich, Hans-Knöll Institute, Jena, German Center for Infection Research (DZIF), European and Developing Countries Clinical Trials Partnership (EDCTP), Radboud University ·BTZ-043 Multiple Ascending Dose / EBA **TBAJ-876 Diarylquinoline** TB Alliance, University of Auckland ·Evaluate Safety, Tolerability, PK of TBAJ-876 in Healthy Adults **TBI-166** Institute of Materia Medica, CAMS & PUMC **TBA-7371** TB Alliance, Bill & Melinda Gates Medical Research Institute, Foundation for Neglected Disease Research ·Phase 1 Study to Evaluate Safety, Tolerability, PK, and PK Interactions of TBA-7371 **Macozinone (MCZ, PBTZ-169)** iM4TB - Innovative Medicines for Tuberculosis, Bill & Melinda Gates Foundation	**Telacebec (Q203)** Qurient Co., Ltd, Qurient Co. Ltd. / LLC "Infectex", a portfolio firm of Maxwell Biotech Venture Fund ·Q203 Phase 1b Q203-TB-PI-US002 ·Phase 2 Telacebec (Q203) EBA **Rifampicin** PanACEA, EDCTP, NIAID, NIH, DHHS, USAID ·ReDEFINe High-Dose RIF for Meningitis ·High-Dose Rifampin **Macozinone (MCZ, PBTZ-169)** Nearmedic Plus LLC ·Phase 2a Study of PBTZ169 **OPC-167832** Otsuka Pharmaceutical Development & Commercialization, Inc. ·OPC-167832 Phase 1 / 2 EBA **GSK 3036656** GlaxoSmithKline, European Union Horizon 2020, NIAID, NIH, DHHS ·EBA, Safety and Tolerability of GSK3036656 in Subjects With Drug-sensitive Pulmonary Tuberculosis **Bedaquiline, Pretomanid, Moxifloxacin, Pyrazidamide (BPaMZ)** TB Alliance ·SimpliciTB **SQ109** Sequella, Inc **Sutezolid**	**TRUNCATE-TB** University College, London, SPRINT TB (National University of Singapore) **Delamanid** Otsuka Pharmaceutical Development & Commercialization, Inc. ·Delamanid with OBR for MDR TB ·Pediatric PK and Safety Trial Delamanid in MDR TB ·OPC-167832 Phase 1 / 2 EBA **Bedaquiline** Janssen Research & Development, LLC ·STREAM Trial Stage 2 ·Nix-TB (B-Pa-L) ·SimpliciTB **Rifapentine** CDC TBTC, Sanofi ·TBTC Study 31 ACTG 53494-month treatment regimens **BEAT-TB** **Bedaquiline - Pretomanid - Linezolid** TB Alliance ·Nix-TB (B-Pa-L) ·ZeNix (B-Pa-L) NC-007 **endTB** Médecins Sans Frontières **Clofazimine** Novartis **Rifampicin** St. George's Hospital University of London RIFASHORT **Bedaquiline - Linezolid**

	Sequella, Inc, TB Alliance **Delpazolid (LCB01-0371)** LegoChem Biosciences, Inc. ·NCT02836483 A Prospective, Randomized, Open, Active-controlled, Interventional, Exploratory, Phase II Trial of LCB01-0371. **TB-PRACTECAL** Médecins Sans Frontières **Auranofin** The Aurum Institute NPC, Calibr, The Scripps Research Institute ·TB Host Directed Therapy (TBHDT) **PredictTB** NIAID, NIH, DHHS, Bill & Melinda Gates Foundation, EDCTP **Levofloxacin** CDC TBTC, NIAID, NIH, DHHS, Boston University ·TBTC Study 32, Opti-Q **INH, RIF, PZA, MOX** ·NexGen EBA **Bedaquiline - Delamanid with MBT for MDR** ·ACTG 5343 Bedaquiline - Delamanid with MBT for MDR	**ifampicin** St. George's Hospital University of London RIFASHORT **Bedaquiline - Linezolid - Levofloxacin with OBR** ·Bedaquiline - Linezolid with OBR MDR (NExT Trial) **Pretomanid, Moxifloxacin, Pyrazidamide (PaMZ)** TB Alliance ·STAND

Current treatment regimens for TB are prolonged, intensive and complex, and often result in mismanagement by healthcare providers (the wrong combination of drugs prescribed or inappropriate length of treatment) or non-compliance by patients. In some regions, drugs may not be readily available or may be of poor quality. These issues of mismanagement and non-compliance have given rise to several drug-resistant strains of Mycobacterium tuberculosis. Given this situation, there is a great emphasis on developing shorter regimens. Though research on this front has been going on for several decades, it is only this year that a major breakthrough has been reported. An international, randomized, Phase 3 clinical trial called Study 31/A5349, has shown that a shortened four-month daily treatment regimen is as safe and effective as the standard six-month daily drug therapy. The trial, led by the U.S. Centers for Disease Control and Prevention's (CDC) Tuberculosis Trials Consortium (TBTC) in collaboration with the AIDS Clinical Trials Group (ACTG) was conducted at 34 clinical sites in 13 countries with more than 2,500 participants, including 214 people with HIV. The study tested the safety and efficacy of two four-month regimens containing high doses of rifapentine to treat drug-susceptible TB. Out of the two regimens, the one that included moxifloxacin (2PHZM/2PHM) showed promise. It included eight weeks of daily treatment with high-dose rifapentine, isoniazid, pyrazinamide, and moxifloxacin and nine weeks of daily treatment with rifapentine, isoniazid, and moxifloxacin. The treatment was well-tolerated and found to be non-inferior in efficacy to the standard six-month regimen (2RHZE/4RH) which includes eight weeks of daily treatment with rifampin, isoniazid, pyrazinamide, and ethambutol and 18 weeks of daily treatment with rifampin and isoniazid.

These findings, presented at the 51st Union World Conference on Lung Health[2], (held virtually on Oct. 20-24, 2020), are nothing short of ground-breaking. A shortened course would be more convenient, economical and most likely boost patient compliance. The shorter duration would hopefully mitigate the dire consequences of interruptions in the longer standard regimen and thus prevent emergence of drug-resistant cases. However, it remains to be seen how well these findings translate to actual clinical practice. It would be important to examine the safety and efficacy of the short-course treatment in different ethnicities and more vulnerable populations. TB disease is a wide spectrum and manifests in highly varied forms in individuals. Moreover, the current uncertainty and socio-political instability in many parts of the world can also have an enormous impact on the ability of countries to implement new treatment regimens for the masses. Nevertheless, the success of this trial will surely generate immense buzz in the TB research community and also serve to strengthen the hope that other advancements in TB treatment are still very much possible even if the journey is extremely arduous. The TB drug clinical pipeline has many candidates, existing and novel, as well as novel regimens being tested in various trial phases. The outcomes of these trials are eagerly anticipated and further success could tremendously bolster TB control programmes around the world, especially in high burden countries like India.

In some regions, drugs may not be readily available or may be of poor quality. These issues of mismanagement and non-compliance have given rise to several drug-resistant strains of Mycobacterium tuberculosis.



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Vaccines for Tuberculosis

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Vaccines have played a major role in our efforts to control many bacterial and viral infectious diseases. Smallpox is the classical example of a viral disease that has been eradicated primarily by using an effective vaccine.

India has a comprehensive immunization programme for infants and children under the National Health Mission (1). The Expanded Programme on Immunization launched in 1978 was renamed as Universal Immunization Programme (UIP) in 1985 and has been an integral part of the National Rural Health Mission from 2005. It is one of India's largest public health programmes targeting close to 2.67 crore newborns and 2.9 crore pregnant women annually. Under the UIP, immunization is providing free of cost against 12 vaccine preventable diseases: diphtheria, pertussis, tetanus, polio, measles, rubella, severe form of childhood tuberculosis (TB), hepatitis B, meningitis & pneumonia caused by Hemophilus Influenza type B, rotavirus diarrhoea, pneumococcal pneumonia and Japanese Encephalitis. The two major milestones of UIP have been the elimination of polio in 2014 and maternal and neonatal tetanus in 2015.

Unfortunately, for TB, an ancient scourge that has afflicted mankind since antiquity and that still affects more than 10 million persons annually with 1.4 million deaths (2). We do not have an effective vaccine.

BCG (Bacillus Calmette Guerin), the only licensed vaccine for TB currently, was developed by Frenchmen Albert Calmette, a physician and microbiologist and Camille Guerin, a veterinarian, by attenuating Mycobacterium bovis over 230 cycles between 1908-1919 (3). BCG was first used for human immunizations as early as a century ago in 1921 by the oral route. The League of Nations, the precursor of the World Health Organisation (WHO) adopted BCG as a standard vaccine for human TB in 1928. However, the use of BCG suffered a setback in 1930 when 207 of 252 children who received the vaccine in Lubeck, Germany, developed active TB and 72 of them died. The vaccine came from Pasteur Institute in Paris but was contaminated with Mycobacterium tuberculosis in the TB laboratory in Lubeck. Although BCG vaccine itself was eventually exonerated, its use declined for several years thereafter.

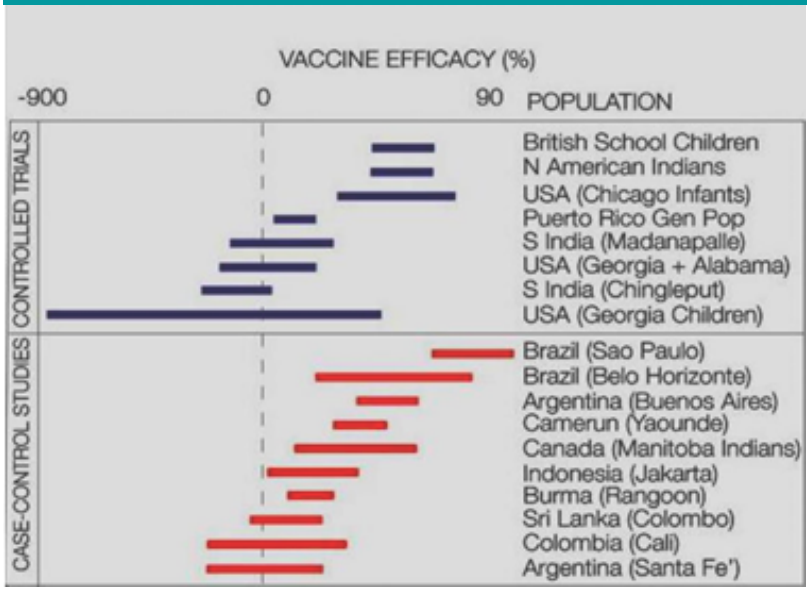
In India, BCG vaccination was first introduced on a limited scale in May 1948. The BCG Vaccine Laboratory was set up in Chennai (then called Madras) in the same year and in 1949 BCG vaccination was extended to schools in almost all the States of India. The International TB Campaign helped to scale up by conducting BCG vaccination demonstrations in five centres starting with Madanapalle in Andhra Pradesh. The Programme was expanded through mass campaigns in 1951 supported by the United Nations International Children's Emergency Fund (UNICEF) and WHO. By 1956 the campaign covered all the States of India. BCG became part of the National TB Control Programme in 1962.

Even though BCG is the most widely used vaccine (120 million/year) in the world, its efficacy against TB is one of the most debated issues. To test its efficacy in the Indian population a randomized clinical trial (RCT) was started in Chengleput in South India by the Tuberculosis Chemotherapy Centre (TCC), later renamed the Tuberculosis Research Centre (TRC) and subsequently as the National Institute for Research in Tuberculosis (NIRT) of the ICMR, in 1968. The Chengleput trial was the world's largest BCG vaccine study. It was a double blind, parallel-arm, placebo controlled RCT covering a population of 3,66,000 individuals in Chengleput district of South India close to Madras. Two strains of BCG (French and Danish) and 2 doses (0.1 mg; 0.01 mg) of each were used and compared to a placebo. The study population was followed up for 15 years by resurveys every 30 months. Two reports (7.5 years and 15 years) were published (4,5).

The results of the study came as a surprise to the Indian and international community. It showed overall, that neither of the two strains of BCG in either dose offered protection against adult forms of pulmonary TB. However, a modest protection of 21-32% was seen in children 1-9 years of age. These results were hugely disappointing and prompted further research to identify the causes of the failure of the vaccine. A rigorous evaluation by Indian and International experts of the methodology of the trial did not reveal any methodological flaws.

The efficacy of BCG vaccination has varied in different populations ranging from 0-80% (Figure 1). In RCTs in British school students, infants in Chicago and in North American Indians the efficacy has been as high as up to 80% whereas in other states in the USA (Georgia, Alabama) and in South India the vaccine has offered no or little protection. However, case control studies over different geographic locations have shown modest to significant protection, especially against military and disseminated TB.

Figure 1: Efficacy of BCG vaccine in randomized clinical trials and case-control studies in different populations



A systematic review and meta analysis of RCTs in pulmonary and meningeal and miliary TB showed higher protection with increasing latitude. Protection was greater when BCG was given in infancy or at school age, when prior sensitization was excluded. Protection against meningeal and miliary TB was greater than for pulmonary TB. Protection was also higher with a lower likelihood of diagnostic detection bias. There was little evidence that other study characteristics or vaccine strain was associated with protection (6).

It was assumed that the possible reasons for the variable efficacy of BCG could be:

a) Genetic variability among the strains of BCG. Six BCG strains are in use in international immunization programs (BCG Pasteur 1173 P2, BCG Danish1331, BCG Glaxo 107, BCG Tokyo 172-1, BCG Russia-I and BCG Brazil). These six BCG strains exhibit different characteristics of attenuation and protection in animal models.

b) Genetic variation in populations.

c) Prior exposure to non-tuberculous mycobacteria could result in a nonspecific immune response against mycobacteria that could interfere with efficacy of BCG by a process of either 'Masking', as already there is a level of immunity and BCG is not adding to this, or by 'Blocking' that prevents BCG from replicating and stops it from producing an immune response.

d) Interference by concurrent parasitic infection. Th1 response is required for an effective immune response to TB infection. Concurrent infection with parasites can produce a simultaneous Th2 response that could blunt the effect of BCG.

In view of these varied responses the WHO has made the following recommendations (7):

a) In high TB burden countries, a single dose of BCG vaccine should be given to all infants soon after birth. Revaccination is not recommended.

b) BCG vaccine should not be used in HIV infected children, even if they are asymptomatic.

c) Low TB burden countries may choose to limit BCG vaccination to neonates and infants of high-risk groups for the disease or to skin-test negative older children.

d) BCG vaccination of adults is not recommended.

The End TB Strategy of the WHO based on the United Nation's Sustainable Development Goals (SDGs) envisages a Vision of a world of 'zero' deaths, disease and suffering due to TB', and aims at a 95% reduction in deaths, 90% reduction in the incidence of the disease by 2035 compared to 2015 (8). The National Strategic Plan of the Government of India to eliminate TB (9) is even a more ambitious, planning to reach these goals set by WHO by the year 2025. The current rate of decline of TB incidence globally is a mere 2% per year (Figure 2). To reach these goals set by the WHO this rate of decline has to be steeply increased and for this to happen new vaccine(s) against the disease are desperately and urgently needed. However this is easier said than done as there are many challenges to be faced for the development of a new TB vaccine. Our knowledge and understanding of the immune system in TB is still inadequate. As yet there is no good correlate for protection and there is no suitable animal model. Funding is available primarily from governments and charitable organizations as TB is not high priority for pharmaceutical companies that are profit oriented. And many TB endemic countries lack the infrastructure for large-scale clinical trials that will be required to evaluate vaccine candidates.

New TB vaccines

However, driven by the compulsions and urgency of the global need to rein in and reverse the TB epidemic there has been a welcome and concerted effort in the research and development of new vaccines against TB in the last two decades (10). Under the aegis of aeras and later the International AIDS Vaccine Initiative (IAVI), funded in main by the Bill and Melinda Gates Foundation, many thousands of potential TB vaccine candidates were identified and have gone through the stages of preclinical evaluation in animal models and a handful have qualified for clinical studies in humans to date. Similarly in Europe, the research promoted by the different European Commission Framework Programs has resulted in several potential TB vaccine candidates. The European TB Vaccine Initiative (TBVI) is a non-profit organization that facilitates the discovery and development of new, safe and effective TB vaccines and biomarkers that are accessible and affordable for global use.

Efficacy trials of new prophylactic TB vaccines could target either the prevention of infection against Mycobacterium tuberculosis (POI), or the prevention of acquiring TB disease (POD) and the prevention of recurrent TB disease (POR). POR trials evaluate therapeutic vaccines administered as an adjunct to drug treatment to increase the effectiveness and shorten the duration of TB treatment in patients undergoing TB treatment for active disease.

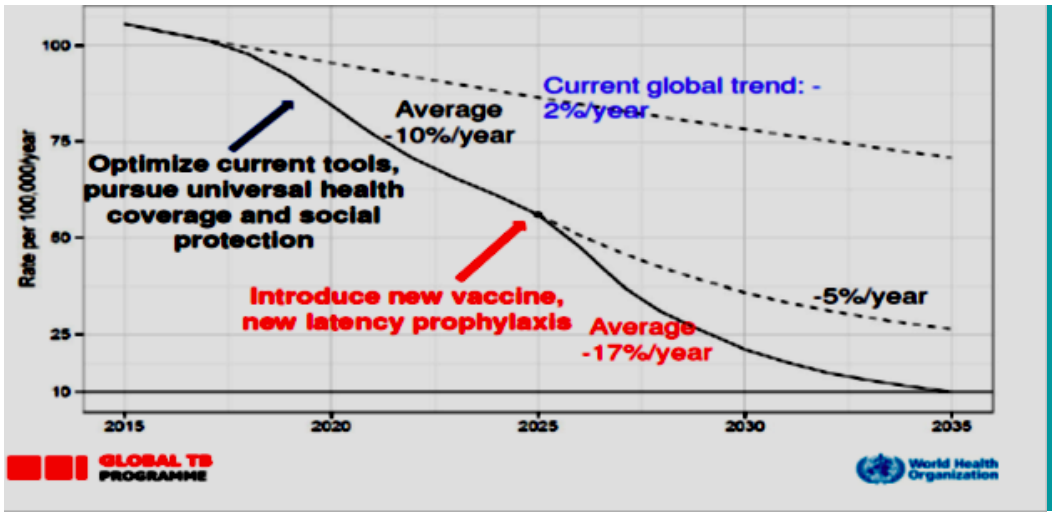


Figure 2

New TB vaccine candidates in clinical trials can be either whole cell vaccines, consisting of a) live or attenuated Mycobacterium tuberculosis strains, b) Mycobacterium bovis BCG, c) recombinant BCG, d) killed mycobacterial vaccines formulated from other saprophytic mycobacterial species or Mycobacterium tuberculosis; or subunit vaccines that contain Mycobacterium tuberculosis antigens expressed as a) recombinant proteins formulated with different adjuvants or b) expressed by recombinant viral vectors used as vehicles for the administration of antigens.

Currently, 14 TB vaccine candidates are being studied in Phase 1 to Phase 3 RCTs in children and adults (11). Of these, eight are based on whole-cell mycobacteria and six on subunit candidates (Table). Of the whole-cell mycobacterial candidates, four are based on live attenuated mycobacteria (BCG revaccination, recombinant BCG (VPM1002), attenuated Mycobacterium tuberculosis (MTBVAC and GamTBVac), and four are based on inactivated/ extracts of mycobacteria (MIP, DAR-901, RUTI, AEC/BC02). Of the subunit candidates, three are mycobacterial fusion protein(s) in new adjuvant formulations (ID93:GLA-SE, H56:IC31 and M72:AS01E) and three are based on recombinant live-attenuated or replication-deficient virus-vectored entities expressing one or more Mycobacterium tuberculosis proteins (Ad5Ag85, ChadOx1.85/ MVA85A and TB/FLU-04L).

Recently there has been encouraging news that in infected adults, the adjuvant vaccine M72/AS01E has shown 54% protection against active pulmonary tuberculosis disease, without evident safety concerns (12). Of particular interest to us in India is a Phase 3 multicentre double blind, placebo controlled RCT that is studying the safety and efficacy VPM1002 and Mycobacterium indicus pranii (MIP) in preventing TB in household contacts of TB patients on treatment. VPM1002 is a live-attenuated, recombinant BCG and results from phase 1 and 2 clinical trials have confirmed the pre-clinical data and have shown that VPM1002 is at least as safe and immunogenic as BCG. MIP, earlier known as Mycobacterium w, is a non pathogenic mycobacterial species known to be protective against leprosy. The origin of the proposed name is a combination of the site of isolation of the bacterial species from India (indicus), discovery by Pran Talwar (pranii) and characterization at the National Institute of Immunology, India (pranii). The trial has completed recruitment of 12000 participants (13). Results are eagerly awaited.

Table: TB vaccines currently in clinical trials in children and adults (11)

Category	Phase 1	Phase 2a	Phase 2b	Phase 3
Infants/		MTBVAC		VPM1002
Adolescents & Adults	Ad5Ag85A	MTBVAC	M72+ASO1E	VPM1002
	ChadOx1.85A	TBFlu04L	DAR-901	MIP
	AEC/BC02	GamTBVac	H56:IC31	
		ID93/GLA-SE	BCG	
Therapeutic	ID93/GLASE	RUTI		VPM1002
	H56:IC31	TBFlu04L		

	Live attenuated
	Whole cell
	Protein/
	Viral vectored

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M. Tuberculosis and HIV-Prolific Killers in Developing Countries are Syndemic Pathogens

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Mycobacterium tuberculosis (Mtb) infection accounts for the highest number of human deaths in low- and middle-income countries of the world. Mtb is also the most common opportunistic infection accompanying HIV infection. The death rate for combined Mtb/HIV infection is almost three-fold higher when compared to Mtb infection of HIV-seronegative patients, and the increase is not due simply to depletion of CD4 T cells due to HIV. The increased risk of mortality is due to a syndemic interaction between the two pathogens that leads to advanced immunodeficiency, chronic immune activation, and increased disease dissemination. Because of the synergy, eradication of MTB is dependent on the eradication of HIV. Though HIV/AIDS is often described as incurable, the recent "shock-and-kill" strategy to eradicate HIV holds promise for the eradication of MTB. Co-infection also amplifies transmission of multidrug-resistant tuberculosis (MDRTB), which besides requiring longer treatment has a very low success rate. Pending effective vaccine development, there is a need to identify newer targets for the development of drugs to treat MDRTB & XDR-TB.

Image from http://news.rice.edu/2021/02/22/study-could-explain-tuberculosis-bacteria-paradox/

Introduction

According to a World Health Organization (WHO) report, non-communicable diseases accounted for 74% of deaths globally in 2019 [1]. Major contributors to this class are neurological disorders, cancer and ischemic heart diseases. However, when only low- and middle-income countries (LMICs) are considered, communicable diseases which include tuberculosis, HIV/AIDS and malaria, are the highest killers. Though tuberculosis (TB) is one of the oldest (>4000 years?) known human diseases, it is not yet eradicated, and still is one of the major causes of mortality. This is essentially because of the lifestyle of Mtb inside the infected host cell. We still do not completely understand how Mtb manages to evade the human immune system to survive and spread within eukaryotic cells. We also do not understand how the bacterium develops resistance against drugs. The problem is further compounded by the fact that Mtb infection is facilitated in HIV-positive individuals with a 20-fold increase in the risk of infection compared with HIV-seronegative individuals. Analysis of samples from co-infected patients was found to contain more drug-resistant Mtb. Besides, millions of people are developing cancers as a direct result of preventable infections by bacteria and viruses. Hence, infectious diseases will remain a major threat to humankind, especially in LMICs. The United Nations' (UN) Sustainable Development Goal (SDG) 3 seeks to end the TB epidemic altogether by 2030. Although there is a decline in the incidence of TB, the decline has been slow, because gaps in preventing, diagnosing and treating TB remain. Without new tools and strategies, the UN targets are unlikely to be met even by 2050. We, therefore, need to completely understand at the molecular level the infection and co-infection processes to form effective strategies of treatment, and also to identify newer targets for drug development [2].

Mtb infection

Mtb is a rod-shaped bacillus with a diameter of about 300 nm (Figure 1, page 22). It is an extremely slowly growing bacterium (doubling time 18 – 24 hours compared to 20 minutes for E.coli), requires oxygen, and contains an unusual cell wall rich in mycolic acid. This special cell wall is less permeable to drug molecules, and it also makes detection of the bacterium more difficult.The DNA genome of Mtb (H37Rv) consists of 4.4 ⁄ 106 base pairs with approximately 4,000 genes, and the gene make-up equips the bacterium for survival in glucose-deficient and fatty-acid rich environment. The genome has evolved to encode proteins that help the bacterium evade the human immune response. The tubercle bacillus spreads from person-to-person almost exclusively by aerosolized particles contained in aerosol droplets, and one to five bacilli may suffice to transmit the infection by air. Macrophages, dendritic cells, and neutrophils are the predominant phagocytic cells that Mtb can infect using a variety of receptors including ten different Toll-Like-Receptors (TLRs). Each of these receptors activates different signaling pathways in the bound cell. Bacterial activation of surface toll-like receptors on phagocytes induces TNF, IFN-γ, IL-1β, IL-6, IL-12, IL-10 and TGF-β, activating phagocyte and recruited T-cell functions. Though TB is primarily a pulmonary disease, it has other variants where the bone, the central nervous system, and other organ systems are affected, especially when co-infected with HIV.

Once the presence of MTB in the alveolar space is detected by the patrolling dendritic cells, the innate immunity comprising of phagocytic immune cells tries to clear the infecting pathogen.The efficacy of the immune response, however, depends on the genetic make-up of both the host and the pathogen. For example, Mtb utilizes several tricks to derail pathogen destruction through the fusion of phagosome with the lysosome. When all infecting Mtbs are not cleared, Mtb is said to have infected the host (Figure 2). TB disease is of two different types – latent TB and active TB. In the latent TB, the bug is dormant, and there are no symptoms of infection. In the active TB, on the other hand, the bug can spread within the host, and there are symptoms like cough with sputum and blood, chest pains, weakness, weight loss, fever and night sweats.It is observed that only 5 - 10% of total Mtb infections are in the active TB category. The adaptive or acquired immunity tries to prevent dissemination of infection within the body.

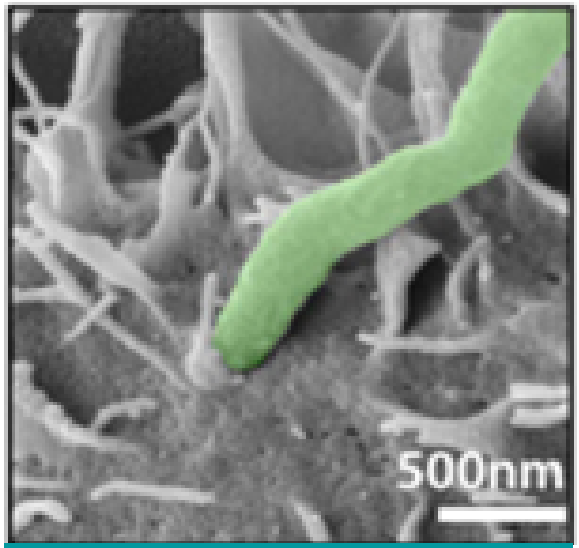

Figure 1. Electron micrograph showing the rod-shaped mycobacterium tuberculosis.

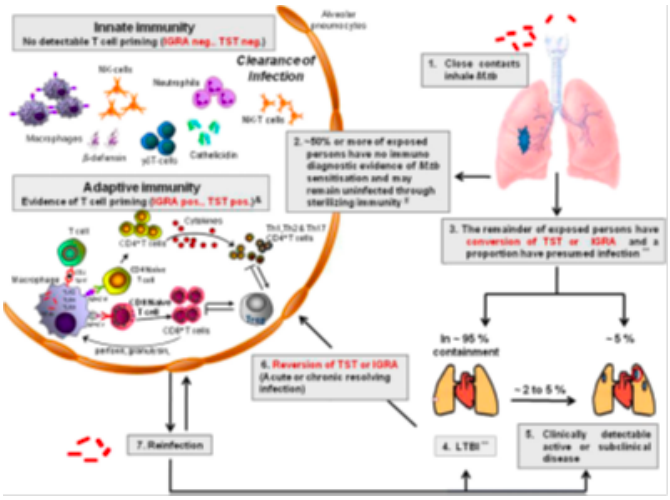

Figure 2. Mtb life cycle[13]

The outcome of a successful adaptive immune response from the host is the formation of what are called granulomas, which are organized immunological structures composed of T cells macrophages, B cells, NK cells, dendritic cells and other immune cells that surround Mtb to prevent Mtb dissemination.Formation of the Mtb granuloma during latent infection is associated with a strong localized and systemic proinflammatory response. The pathogen can stay in a latent state for many years but can be reactivated over a lifetime to cause disease and become transmissible. Disrupting the integrity of the granuloma is one way of shifting the infection from a latent state to an active disease state. Results of recent positron emission tomography and computer tomography experiments on HIV/Mtb co-infection reveal a correlation between alterations in the number and nature of granulomas and reactivation of the disease, leading to the model shown in

The extent of infection and the intra-species transmission from one individual to another depend on the population dynamics, as well as, on several geographical and climatological factors.

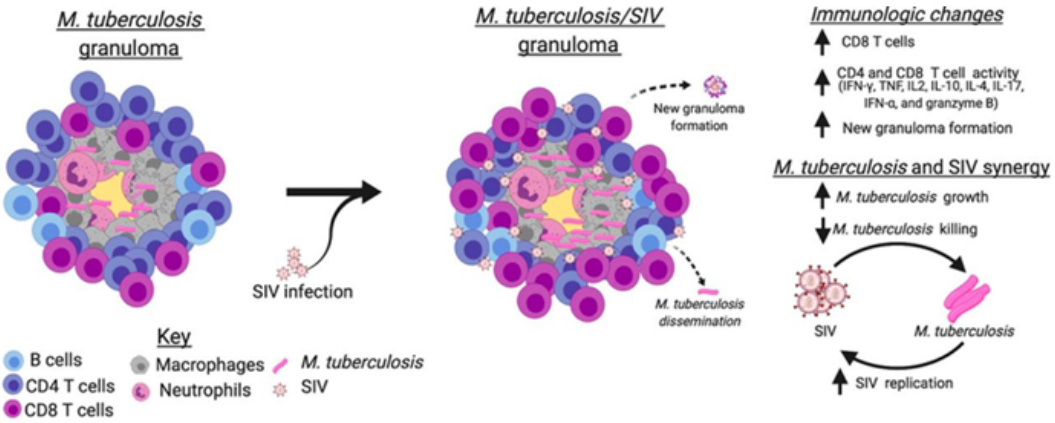

Figure 3. Granuloma in latent TB and synergistic effects of coinfection with SIV [3].

Human Immunodeficiency Virus (HIV)

HIV is an enveloped retrovirus that causes infectious disease HIV/AIDS. This virus was discovered in 1981, and therefore is relatively new compared to MTB bacterium. A most disturbing feature of this virus is that it attacks the human immune cells that help the body to fight infection. These cells include T-lymphocytes (also known as T cells), monocytes, macrophages and dendritic cells that express CD4 protein on their surface. The CD4 count (CD4 cells per millilitre of blood) is used to describe the severity of the disease. A count below 200is associated with full-fledged AIDS when the body immune system is badly damaged.

The glycoprotein, gp120, in the viral envelope binds to CD4 and CD8 proteins on the cell surface. Besides, a co-receptor protein is also required on the cell surface for the virus to gain entry into the cell. There are two known co-receptors, CCR5 and CXCR4, and different strains of HIV use different co-receptors. The virulence of the virus using either co-receptor appears to be different. The life cycle of HIV, shown in Figure 4, comprises of seven stages: 1) receptor-binding, 2) membrane fusion, 3) reverse transcription of the viral RNA genome, 4) integration of viral cDNA into the host chromosome, 5) production of viral RNA and proteins, 6) virus particle assembly and 7) viral budding and release.

Any molecule that can effectively interfere with these steps in the viral life cycle would be a potential anti-HIV drug [4]. The viral genome encodes for six proteins Tat, Rev, Nef, Vif, Vpr and Vpu, which play a regulatory role and control the ability of HIV to infect a cell, evade the immune response, multiply and exit to infect other cells. The viral genome also encodes for three enzymes to help in its replication: 1) reverse transcriptase – conversion of the viral RNA genome into cDNA, 2) integrase – incorporation of viral cDNA into the host chromosome, and 3) protease – cleavage of newly translated viral polyproteins into different functional proteins through cleavage of specific peptide bonds in the polyprotein.

Inhibition of these enzymes would be a scientific method of treating HIV/AIDS infection. Indeed, many of the anti-AIDS drugs developed using structural information obtained through crystallography, and used in anti-retroviral-therapy (ART), are members of these three classes of inhibitors [5 -7]. The situation, however, is not so simple. The virus can stay undetected inside the human body in the integrated state (pro-virus) for long periods. These latent-cells, which can potentially be activated to produce active virus, therefore are considered as reservoirs of the virus. These latent-cells can't be killed by the immune surveillance system, and therefore, HIV/AIDS is often described as an incurable disease. The second complication is that of drug-resistance through mutations in viral proteins [8,9].

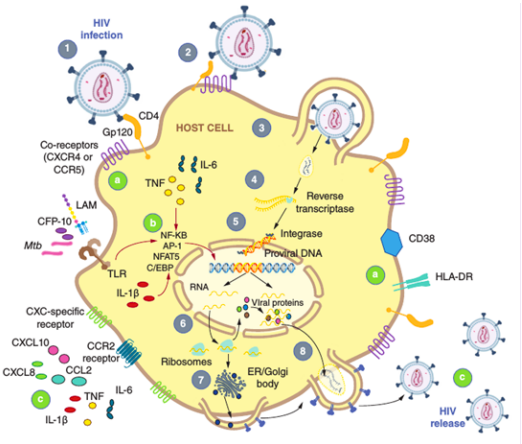

Figure 4. Effect of Mtb infection on the life cycle of HIV in co-infection [10].

The synergy between HIV-Mtb coinfection

There are several bacteria and viruses that successfully establish infections in humans when the human immune system is weakened. Such infections are described as opportunistic infections. HIV infection weakens the immune system by reducing the CD4 T-cell count to values below the normal value of about 500–1,200 cells/mm3. While many different types of bacteria can infect when CD4 count is below 200, Mtb is the only bacterium that can successfully infect an HIV-positive person even when the CD4 count is in the range 200 -500. This makes Mtb the most efficient opportunistic pathogen, and also suggests synergy between HIV and Mtb infections. The synergy is also indicated by the observation that HIV-infected patients have a 5–10% annual risk of developing TB, compared with a risk of 5–15% over the whole life-time for HIV-1-uninfected persons. The central players in this synergy are the functionally impaired T-cells and the cytokines they secrete. TB remains the leading cause of death among people living with HIV. As already pointed out, loss of protective CD4 T cells is not the sole reason for the increased susceptibility of HIV positive people for Mtb infection. The increase can be attributed to at least two mechanisms: the increased reactivation of latent TB or increased susceptibility to exogenous Mtb infection. Different experimental studies indicate the following factors as responsible for the synergistic relationship between Mtb and HIV, as shown in Figure 4 [10,11]:

1. Innate and adaptive Immune response to latent Mtb infection creates an expanded cellular niche (e.g activated CD4+ and CD8+ T-cells) susceptible to HIV-1 infection. Increased CCR5 and CXCR4 surface presentation on Mtb-antigen-specific CD4+ T-cells and increased CD38+/HLA-DR+ T-cells.

2. MTb infection Increases secretion of chemokines and proinflammatory cytokines (e.g., TNF, IL-1, IL-6) and transcription factors such as (NF-κB, AP-1, SP1, C/EBP and NFAT5) causing increases in HIV-1 replication by about 30%, even in bystander Mtb-uninfected cells.Increased secretion of CCL5 enhances replication of X4-tropic HIV-1 which causes much faster progress toward AIDS.

3. Latent TB disorients the host immune system making it easier for HIV-1 to evade the human immune system and spread quickly.

4. Mtb infection reactivates dormant HIV-1 (pro-virus) to multiply and spread in the body and enhances viral reservoir cells. Increased CXCL10 recruitment of HIV-1-infected T-cells to Mtb microenvironment. Enhanced recruitment of Mtb-specific T-cells to the bone marrow would create another niche for viral expansion and replication,

5) HIV-1 infects activated Mtb-specific T-cells, leading to their preferential depletion. HIV infection also causes a progressive loss of Mtb-specific T-cell functions, including T-cell proliferation, cytokine production, and cytotoxic capacity. HIV infects and destroys preferentially those T-cells (polyfunctional T-cells) which protect against Mtb infection.

6) This early CD4+ T-cell depletion and increase in virus-containing CD8+ T-cells on HIV infection alters the cellular composition of the granulomas surrounding the Mtb-infected macrophage (Figure 3). As a result, the granuloma becomes structurally porous and Mtb bacilli escape and spread the infection to other parts of the body.

7) HIV infection renders T-cells dysfunctional by chronic activation, and it also disturbs the desired balance between distinct T-cell populations, such as the proportion between naïve/effector/activated, Th17/regulatory T-cells (Treg).

8) HIV-infection promotes Mtb infection and active TB through up-regulation of Mtb entry receptors on macrophages. De novo Mtb reinfection in immunosuppressed HIV-infected individuals causes rapid progression to symptomatic disease with survival times as short as 14 days and fatality percentages over 85%.

9) HIV infection delays the establishment of Mtb antigen-specific immune responses by impairing TNF-mediated macrophage apoptosis.

Treatment of HIV-Mtb coinfection

There is clear evidence that providing antiretroviral therapy to HIV-infected adults during tuberculosis treatment reduces mortality. Treatment should be initiated without any delay as the probability of emergence of drug-resistant Mtb is significantly enhanced by co-infection with human immunodeficiency virus (HIV) [12]. However, the detection of Mtb infection is made more difficult by the co-infection.

Drug resistance

Several drugs, to be taken for 6 – 12 months, have been in use to treat tuberculosis, and the most popular first-line drugs are rifampicin and isoniazid. Rifampicin inhibits elongation of mRNA by binding to the β subunit of the RNA polymerase enzyme. Isoniazid is a prodrug, which once activated by the catalase/peroxidase enzyme of the host, inhibits the production of mycolic acid required for bacterial cell wall synthesis. Mycobacteria develop drug-resistance and cause MDRTB, XDR-TB and totally resistant tuberculosis. Treatment of MDRTB and XDR-TB takes longer, success rates are lower (55% and 30%) and also costs prohibitively more (5 to 6 times more). Duration of survival to death can be as short as two weeks.

Some of the mechanisms of resistance development are: 1) Target alteration – reduce drug binding through mutation of the target, 2) mimicking the target to sequester drugs e.g. MfpA mimics DNA double helix thereby sequestering DNA binding drugs, 3) inactivate drugs through chemical modification, e.g. an acetyltransferase, Eis (enhanced intracellular survival) acetylates multiple amine groups of aminoglycosidic drugs, 4) drug degradation by Mtb enzymes and 5) drug efflux – at least 18 transporters in mycobacteria have been found.

Drug-drug interactions

Treatment of co-infections is also beset with the complexity of drug-drug interactions. Drug interactions between antiretroviral and anti-TB agents are common in the management of patients with HIV and TB. Drugs for HIV and TB don't always work well together. For example, Protease Inhibitor (PI)/ritonavir + rifabutin- the combination is a prescribed treatment for HIV/TB. This treatment regimen has the following problem:

ritonavir-boosted PIs markedly increase rifabutin concentrations and reduce its clearance necessitating a reduction in the dose of rifabutin by 50% to 75%. Toxicity (neutropenia, uveitis, hepatoxicity, rash, gastrointestinal symptoms) and suboptimal rifamycin exposures with reduced dose may lead to drug-resistant bacteria. On the other hand rifampicin-induced, cytochrome P450 activity may cause sub-therapeutic levels of PIs. It is in-fact observed that co-treatment for TB and HIV significantly increased the risk for major mutations conferring resistance against PI.

Conclusions

TB remains a prime killer in the world of infectious disease. While it does enter latency in 90% of cases, reactivation is possible, and co-infection with HIV is found to be especially effective in this. HIV has a profound effect on TB, including faster rates of disease progression, higher rates of drug resistance, and increased mortality among patients with MDRTB. The co-infection disturbs the nature and structure of granulomas that isolate Mtb thereby facilitating the dissemination of Mtb. In the co-infection, the immune system is rendered dysfunctional thereby promoting propagation of each pathogen. Therefore, eradication of TB, a stated goal of the UN, becomes dependent on the eradication of HIV. Though the mechanism of HIV replication makes HIV incurable, recent research on latency-reversing agents (LRAs) is an effort to eradicate HIV by the “shock and kill” strategy [2]. If successful, this would help eradicate Mtb as well. Co-infection is also observed to lead to the emergence of MDRTB and XDR-TB, effective treatment of which requires identification of novel targets for drug development.

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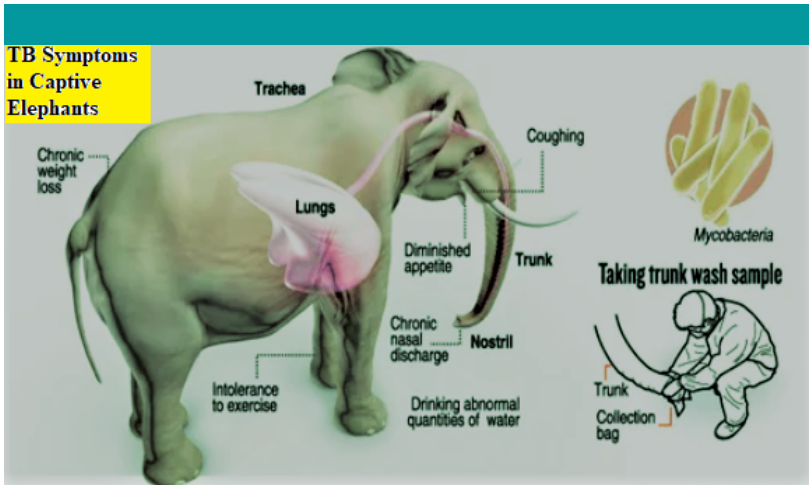

TB in Zoo Elephants and the Transmission of Infection into Zookeepers due to Extended Proximity during COVID-19 Pandemic

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Tuberculosis in captive Asian elephants has been a subject of interest among the experts and practitioners for the past few decades. During COVID -19 pandemic, the zoos remained closed and the caregivers had to spend extended hours in the enclosures to help the elephants get rid of boredom and depression. Such proximity enhanced the chance of TB transmission from elephants to human bodies. Hence, effective measures are needed for early detection of TB infection in captive elephants to curb further transmission.

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis*, and similar organisms (e.g., *M. bovis*, *M. pinnipedii etc.*) has been observed in a wide range of species encompassing non-human primates, elephants, several wild ungulates (e.g., wild boar, red deer etc.), carnivores, marine mammals (e.g., the sea-lions and the seals) and psittacine birds (especially, the parrot family) [1-5]. The extent of infection and the intra-species transmission from one individual to another depend on the population dynamics, as well as, on several geographical and climatological factors [2]. The infection can even get transmitted from one species to another (especially, in case of the wild ungulates) based on the foraging patterns. Experts and practitioners associated with the TB have mentioned that principally '*Animal TB*' is caused by the archetypical zoonotic pathogen named *M. bovis*, which can be transmitted from animals to the human bodies and *vice versa* [6, 7].

From a conceptual perspective, mere discovery of TB in wild animals in any particular environment is not sufficient to conclude whether the affected group (or species) is a self-sustaining maintenance host or a dead-end spill-over host. Moreover, based on the basic findings it is often difficult to

label those groups of wild individuals as significant source of TB infection for livestock, companion animals or humans. Such distinction is critical for the development of strategies to curb the large-scale spreading of the dangerous zoonotic infection [6].

Inclusion of wildlife disease management as an integrated part of the TB eradication programme is a complicated process, as ethical perspectives of the stakeholders and the level of engagement are directly linked with the identification of beneficiaries of the programme. These aspects lead to a certain level of difficulty in continued surveillance and systematic study of the wild species (or populations) for possible tuberculosis infection. However, representative studies conducted on the livestock, as well as the specimens living in the menageries can unearth important information about the transmission of tuberculosis infection from the captive animals to the human bodies and vice versa.

TB in Captive Animals and the Need for Adaptive Diagnostic Tools

It is important to mention that the pathogenesis of tuberculosis bacteria, the receptivity and immune responses to the infection are found to vary widely in the captive wild species living in the zoos. The variation is even more prominent when the comparisons are made between the zoo species and the domestic animals. The diagnostic tools usually used for the domestic animals tend to show limited performance for the zoo species. This necessitates the development of customized, adaptive diagnostic tools for detection of tuberculosis infection in different species [8]. Recently, diagnostic tools based on the investigation of humoral immunity have paved a promising way towards detecting antibodies directed against certain immunogenic mycobacterial antigens in various zoo species [8].

The tuberculosis in the captive elephants (Elephant TB) has emerged as a serious infectious zoonotic disease in the past few decades [9, 10]. Three elephants succumbed to the pulmonary complications caused by M. tuberculosis in an exotic animal farm located in Illinois (USA) between 1994 and 1996. In October 1996, a fourth living elephant tested culture-positive for M. tuberculosis [11]. A Swedish zoo witnessed an outbreak of TB during 2001-2003, that involved five elephants and several other species viz. giraffes, rhinoceroses, and buffaloes. Four different strains of M. tuberculosis could be separated from those infected animals [9]. Studies indicate that about 3% of captive elephants in the United States were infected with M. tuberculosis in 2000 [12, 13]. More recent estimates by Mikota indicate that the infected elephants may account for ~ 6% of the total captive elephant population housed in various US zoos [14]. It is also noteworthy that amongst the captive elephants in the zoos and the circuses, the Asian elephants (Elephas maximus) are more frequently detected to be infected with TB, as compared to the African elephants (Loxodonta africana) [14].

The extent of infection and the intra-species transmission from one individual to another depend on the population dynamics, as well as, on several geographical and climatological factors.

Elephant TB: Diagnosis, Monitoring of Treatment and Limitations

Following the untimely deaths of several high-profile captive elephants in the United States in the mid-1990s, veterinarians discovered that those animals were infected with the human strain of tuberculosis (TB) [15]. Although awareness about the TB infection in captive elephants has been gradually increasing over the past few decades, unfortunately anti-tuberculosis therapy for these animals has not been standardized yet. Currently, the most reliable diagnostic method for TB in captive elephants in the USA is based on the culture of respiratory secretions obtained by washing trunks [12]. However, the trunk wash culture method has serious limitations, as it does not facilitate rapid identification of infected individuals. Therefore, innovative and more efficient diagnostic methods are needed for early diagnosis. Early diagnosis results in timely initiation of chemotherapy leading to more effective control of TB. Although the key mycobacterial antigens responsible for elephant TB are yet to be understood completely and the optimal immunoassay formats are still not established, serological methodology has shown ample promise as a diagnostic tool towards characterizing the humoral responses associated with elephant TB [14]. In quite a few cases, anti-tubercular therapeutic doses based on the humoral responses have resulted in gradual decrease in the antibody levels to certain antigens, which hint at the possibility that the serological methodology can be effectively used for monitoring the treatment.

Usually, treatment of active TB in captive elephants involves administering combinations of Isoniazid (INH), Rifampin (RIF), and/or Pyrazinamide (PZA) orally or rectally, daily or every 48 hours for 6 months. Reported indicative daily drug dose limits are 2.5 -7.5 mg/kg for INH, 8 -10 mg/kg for RIF, and 25- 35 mg/kg for PZA. Moreover, for treating multidrug-resistant (MDR) TB, a combination of PZA, ethambutol (EMB), enrofloxacin (ENRO), and amikacin (AMK) is also used. The dosage and the duration of treatment vary from one elephant to another [14]. The preventive therapy usually continues for 6 months.

Transmission of Elephant TB infection into the Zookeepers

Following the deaths of the captive elephants in the US-based exotic farm in Illinois in the mid-1990s, twenty-two elephant handlers at the farm were screened for tuberculosis (TB) [11]. Eleven of the tested handlers showed positive reactions to purified protein derivative that was introduced through intradermal injection. One handler exhibited smear-negative, culture-positive active TB. Comparison of DNA fingerprint using IS6110 and TBN12 typing further unearthed the fact that the isolates from the four elephants and the handler with active TB belonged to the same strain.

This investigation formally brought forth the evidence of transmission of M. tuberculosis between humans and the elephants [11]. In July 2009, the routine screening conducted among the elephant handlers and caregivers at a non-profit elephant refuge in south central Tennessee, USA exhibited conversion of tuberculin skin test (TST) results from negative to positive. Further, from the records of the facility it was revealed that the trunk wash collected in December 2008 from a quarantined elephant contained M. tuberculosis [16]. Results also showed that the

susceptibility of the employees to the latent M. tuberculosis increased by more than 20 times upon working for more than 4 hours in the quarantine facility during 2009. A study conducted in 2012 on 600 captive Asian elephants in Kerala, Tamil Nadu and Karnataka exhibited high prevalence of asymptomatic TB infection of elephants in the captive Indian settings [17]. In 2019, eight caregivers dedicated to the pachyderms of Point Defiance Zoo in Tacoma, Washington tested positive for latent TB infection [18]. These observations further stresses on the need for early diagnosis in order to reduce the risk of exposure and subsequent TB transmission to the elephant handlers, other zoo inmates, as well as the visitors.

Impact of COVID-19 on TB Transmission between Captive Elephants and Caregivers

According to Adam Langer, branch chief of surveillance, epidemiology, and outbreak investigations for the CDC, depending on the environmental conditions TB bacteria can remain suspended in the air for several hours. The key deciding factors behind the exposure risk include the concentration of pathogenic load in the air, the duration of exposure, the size, and the ventilation system of the room [15]. Owing to the large lung size of the elephants, a relatively large number of bacteria are released into the surrounding air from the infected individuals during the breathing process. Therefore, sharing air space with a TB-infected elephant poses a higher risk of transmission than the same exposure to an infected person. Therefore, the handlers and caregivers, who spend substantial amount of time with the captive elephants in the indoor environment of the zoo enclosures, are highly susceptible to the TB infections. During the ongoing COVID-19 pandemic, all the zoos and the menageries with exotic collection of wild species have remained closed in order to protect the zoo inmates from the novel coronavirus SARS-COV-2. However, during this period, many captive animals have exhibited symptoms of depression that are owed to the sudden change in their respective lifestyles. Although lesser crowd during the extended lockdown period has helped some species to behave in a more stress-free manner (e.g., the deer, giraffes, kangaroos, lesser carnivores) leading to better health and reproductive behaviours; the species like the elephants that are more attached to the human beings, intelligent and responsive to the visitors, have suffered heavily in terms of the emotional health due to the extended loneliness. In order to ensure emotional wellbeing of the captive elephants, the zookeepers and caregivers have spent extended hours in the enclosures during the lockdown period. This has posed a greater risk for the zookeepers, as they have become more prone to the TB infection from the elephants.

In 2015, the United States Department of Agriculture (USDA) withdrew its policy mandating the TB testing for captive elephants in the USA, which earlier was an integral part of the standard veterinary cares for elephants. Subsequently, it has now been left to the individual facilities (private, public, or non-profit) and veterinarians to decide on the testing. The regulations for the TB testing of the elephants vary in terms of strictness and requirements from one state to another[15].

Clearly, the seriousness of the TB infection is being ignored. The COVID-19 pandemic, and the morbidity associated with it have shown the world the level of price that we have to pay due to our collective negligence. If attention is not immediately paid to the finer details associated with the critical diseases, such as the various forms of TB, it would not take a long time before another catastrophe is witnessed.

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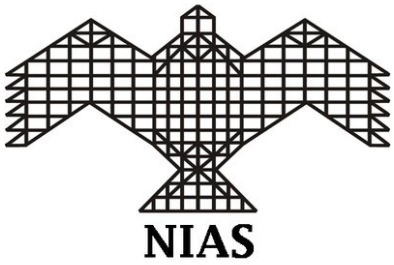

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