**Tuberculosis: how it infects, how it is currently treated, and the future of treatments**

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Tuberculosis, caused by *Mycobacterium tuberculosis*, is the deadliest bacterial disease in the world. In most patients (around 2 billion), it remains latent in their lungs, but in others, it is an active infection, especially in those who are immunocompromised. There are very few treatment regimens that can be followed, all including taking at least four antibiotics at once over a months-long period. Antibiotic resistance has become a massive issue when treating tuberculosis, which means more effective medications need to be found to fight these resistant strains. Many efforts are being made to approve new drugs to treat tuberculosis, especially those in which a genetic target, such as a gene or enzyme involved in transcription, ATP synthesis, or stability of the cell wall, is selected, and then experiments are done to see what antibiotics affect it the best. Some of these medications are in the earlier stages of experimentation while others have reached clinical trials, which could eventually lead to the first approved antibiotic to fight against tuberculosis in ten years.

**Introduction**

Up until the COVID-19 pandemic, tuberculosis was the number one most deadly disease on Earth (Alsayed et al., 2023). As of 2022, around 2 billion people are infected with the disease, and those numbers went up during the height of the recent pandemic. It is caused by the bacteria *Mycobacterium tuberculosis* (Mtb) and is easily spread via contaminated aerosols, which spread through talking, coughing, and sneezing. These aerosols are inhaled by the recipient, then the bacteria travel through the respiratory tract.

What happens after the initial infection can vary. Typically, the bacteria will stay in the lungs as either an inactive or latent form of infection, living safely in a granuloma, causing the host to be asymptomatic and an unknowing carrier. The host can go the rest of their life without becoming symptomatic, or the bacteria can escape the granuloma and the infection becomes active. The latter scenario mostly occurs in immunocompromised hosts, especially those with HIV (Alsayed et al., 2023).

One thing that makes tuberculosis so deadly is that it is very hard to treat. The basic treatment regimen is a mixture of four antibiotics taken in a six-month period, and this can change depending on whether the certain strain of Mtb infecting the host is resistant to some of those typical antibiotics. There are many efforts around the world to find new treatments for the disease, whether that be from figuring out what a known effective antibiotic target is within the cell or selecting a genetic target and discovering what antibiotics affect it.

**Recent Progress**

The four antibiotics used in the typical treatment regimen for tuberculosis are rifampicin, ethambutol, isoniazid, and pyrazinamide (Alsayed et al., 2023). Each medication targets different areas of the cell, such as the permeability of the outer membrane of the cell, the structure of the cell wall, the ability to transcribe DNA, and the ability to survive within a granuloma. While these drugs are effective, they have many side effects, and their usage has taken part in “the emergence of (drug resistant) Mtb strains.” (Alsayed et al., 2023)

There are fifteen alternative antibiotics that can be used to fight drug-resistant Mtb infections. Different ones can be used to replace one or more drugs from the typical treatment, but the timeline is much longer (as of 2020, it is 9-11 months) and includes more medication (Alsayed et al., 2023). If a patient does not meet the many requirements to follow this 2020-approved plan and is infected with drug-resistant Mtb, then they must follow an even longer secondary (18-20 months).

There has not been a discovery of a new drug to treat Mtb since 2014, but there are many efforts to find new ones (Alsayed et al., 2023). There are two “discovery cascades” that are used to find treatments, the “target-to-drug” pathway, which identifies a gene target and tries to come up with a safe treatment that can effectively kill an Mtb cell, and the “drug-to-target” pathway, which screens for already effective drugs and then discovers what it targets. The latter has been the most successful, but the former can help with more particular replacement in therapies.

There are many genetic targets of interest that could lead to new antibiotics being approved for treatment. DNA gyrase, an enzyme essential for transcription, replication, and recombination, is made up of GyrA and GyrB subunits. Fluoroquinolones are a validated drug that targets GyrA, but treatments that affect GyrB (which promotes ATP hydrolysis) have been less explored. In 2015, a group discovered VXc-486, an aminobenzimidazole, that effectively inhibited the growth of Mtb *in vitro* for many strains, as well as non-tuberculosis *Mycobacterium* strains, by targeting GyrB (Locher et al., 2015).

ATP Synthase is a target for bedaquiline, the most recently approved drug for treatment, but can cause heart issues. There are two diarylquinolines that are currently in Phase I clinical trials that also target ATP Synthase that have a lesser chance of causing cardiac problems for the patient (Alsayed et al., 2023). In relation, the cytochrome bc1 complex of the electron transport chain, specifically the b subunit (QcrB), has become a bigger target of interest in the last decade or so. This interest has led to the identification of imidazopyridine amides (IPAs) as a class of antibiotics that target QcrB, and also have a smaller risk of causing heart problems (Alsayed et al., 2023).

Decaprenylphosphoryl-β-D-ribose 2′-epimerase 1 (DprE1), fatty acyl-AMP ligase 32 (FadD32), and polyketide synthase 13 (Pks13) are all key enzymes involved with the structure and stability of the cell wall. In the past 15 years, there have been multiple discoveries of potential drugs to inhibit these enzymes, including different benzodiazepines, such as 1,3-benzothiazin-4-ones for DprE1 (Alsayed et al, 2023).

**Discussion**

Tuberculosis is expected to reclaim its spot at the top of the “most deadly disease” list very soon, so efforts to find new, more effective drug treatments must become more of a priority. There was a setback in research for Mtb treatments due to the COVID-19 pandemic, despite the increase in tuberculosis infections during this time, due to the stress of making vaccines and treatments for the virus.

Antibiotic resistance is a massive issue prevailing in many bacterial genera, but the issues with Mtb cause a lot more death than any other bacteria, and it is so difficult to find a drug that can effectively kill Mtb while having a minimal amount of side effects. The current treatment plans for tuberculosis infections involve at least four antibiotics and last anywhere from six months to almost two years, which can be detrimental to the body. A lot of these antibiotics work best in tangent with one another, but that is not always the safest option, especially in patients who are immunocompromised (Alsayed, et al., 2023). The newer efforts discussed include the consideration of the side effects of the drug, such as toxicity to the heart, but it takes so long for medicine to be approved for use that it might be years before a new tuberculosis drug is put on the market.

The positive is that there is a significant number of potential drugs in various phases of discovery, from initial experimentation to being a part of clinical trials. There are groups that prioritize creating safe and effective treatments before sending them to be tested on humans. The number of potential treatments can increase, especially since the entire genome of *Mycobacterium tuberculosis* was sequenced in 1998, which, in the realm of research, is not all that long ago (Alsayed et al. 2023). There is still the potential for new drug targets and treatments to be discovered. Additionally, Mtb does have genetic similarities with the other *Mycobacterium* species, and discoveries with any of those could also lead to discoveries with Mtb, as shown by the antibiotic VXc-486’s ability to treat respiratory infections caused by both Mtb and other *Mycobacterium* species (Locher et al, 2015).

The most significant questions that come to mind are: why has it taken so long to approve any new drug treatments for tuberculosis? It is known that experimentation and clinical trials take many years and many rounds before approval, but how has it been a decade since the last approval of a treatment? Yes, the last antibiotic put on the market does have the ability to cause cardiotoxicity, but it was still able to be approved and is still helpful in fighting Mtb. Have there been other possible treatments not mentioned above that have had even worse side effects? Are these discoveries too recent for the possible drugs that target these genes to be stable enough to use? What other possibilities are there to treat tuberculosis that have not been considered by enough people to make a significant effort in progress, or even considered at all?

No matter, this much is known: Tuberculosis is a dangerous, mutating, deadly disease that continues to be pervasive despite the different antibiotics and treatment plans available. As the decades go on, new drugs and regimens will have to be approved. Tuberculosis is not going anywhere anytime soon, so what can be done is to diagnose it, treat it, and continue to research improved treatment options, like what is being done now in laboratories across the world.

**References**

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