New Challenges from an Ancient Disease – Drug-Resistant Tuberculosis

Maggie Fox
Hello and welcome to One World, One Health. with the latest ideas to improve the health of our planet and its people. I'm Maggie Fox. Planet Earth faces problems such as pollution, climate change, and new and reemerging infectious diseases, and just like all of us on this planet, they're all linked. This podcast is brought to you by the One Health Trust with bite-sized insights into ways to help.

Tuberculosis, or TB, has been around for about as long as human beings have been around. It was once called consumption, and it kills more people every year than the AIDS virus, malaria, or more dramatic sounding infections such as Ebola. Only COVID has killed more people in recent years. And like any other bacterial infection, TB can evolve resistance to the drugs used to treat it.

Dr. Jeffrey Tornheim, Assistant Professor of Medicine, Pediatrics, and International Health at Johns Hopkins University School of Medicine and the Bloomberg School of Public Health, is studying ways to better predict who's been infected with one of these superbug TB bacteria. Jeff, thanks so much for joining us.

Jeffrey Tornheim
Really happy to be here. Thank you.

Maggie Fox
First off, can you just give us a very quick overview of what tuberculosis is and how long has it been around?

Jeffrey Tornheim
Tuberculosis, or TB, is a bacterial infection. It's caused by a bacterium that's referred to as *Mycobacterium tuberculosis*, which is, sometimes I like to describe as, halfway between normal bacteria and fungi. Just because it's so slow to grow, it likes to take hold, and it gets a little bit sticky.

It's a bacterial infection that is transmitted between people who share the same airspace. It's breathed in through the lungs, can be expired or breathed out when somebody coughs, sings, is talking very loudly or shouting -- many of the same things that we've all become familiar with because of COVID or other airborne disease. It infects people in the lungs and can get in through the lungs and spread to other body parts. Most people can control that initial phase of the infection, their body finds a way to keep it at bay in one particular site -- we call that latent

TB, or TB infection is the term people are moving towards. And that's about a quarter of the people in the world. That's a very common phenomenon, very common.

This bacterium has been around with us for millennia. There's evidence of it with mummies and in Egypt and elsewhere. There are strains and lineages found all over the world wherever we have human civilization. Most people control it, as I mentioned, but about 10 percent of people who have been exposed to TB at some point in their life will develop an active TB infection where it's a disease that's affecting them. They have symptoms, cough, fevers, unintentional weight loss, night sweats, or if it's in some other part of their body, problems there like meningitis, and that's about 10.6 million people per year.

This before COVID was the number one infectious disease killer in the world. COVID had its time to take over TB in that role, but we expect that TB is going to be coming back in a big way once COVID starts to wane a little bit. As I mentioned, 10.6 million global cases, 1.6 million global deaths, and just under half a million or 450,000 cases that are multidrug-resistant tuberculosis, so a major problem for the world's population.

Maggie Fox
So what you're describing is a bacterial infection. I think sometimes tuberculosis is caused by what's called a bacillus and I think people get mixed up, but it's treated with antibiotics, correct?

Jeffrey Tornheim
Yeah, so it is a bacillus, it's rod-shaped and referred to often as an acid-fast bacillus or AFB because of the specific features of this bacteria, how well it rose and how hard it can be to look at using normal testing, normal staining under a microscope, but it is a bacterial disease that spread through the air. It used to be referred to as consumption, if people have heard that term, and there was a long period where it was a very romantic, Moulin Rouge sort of situation within the romance poets but these days, that's not generally how we think.

Maggie Fox
So multidrug-resistant TB, MDR TB: what is it, how's it developed, who said a threat to?

Jeffrey Tornheim
So like most bacterial infections, we have some sense of how the bacteria grow, how they live, and what medicines can kill that bacteria. For tuberculosis, we do have good and effective treatments both for TB infection and for TB disease. About 86 percent of people globally get treated effectively with a combination of our first line drugs.

We usually use four drugs at the same time to prevent resistance and we choose our first line drugs based on the best combination that maximizes benefit for treatment and minimizes the toxicity or minimizes the side effects from the treatment. For normal TB or drug-susceptible TB, that's four drugs for about six months for most forms and newer treatments can provide that within four months and still achieve similar rates.

Drug-resistant TB is when something happens and we lose the ability to make use of those drugs and primarily the drug that we look at, which is the one we have a fast test for, is a drug called rifampicin. That's one of the two main drugs that's used to treat TB. And the second one that's most effective, and that's isoniazid, the combination of resistance to those two things is referred to as multidrug-resistant TB and or MDR TB. And after that occurs, there's sort of a cascade of resistance that can occur when people have some drug resistance and get the less effective combination of therapy, more dominoes can fall over time. And we can end up with more extensive drug resistance with an actual classification system referring to extensively drug-resistant TB as a common phenomenon.

We're lucky in TB because this resistance isn't with drugs that are generally shared for other diseases. But because of the large global burden of disease, that means a large number of people, as I mentioned, just under half a million people a year, about 450,000 a year, with rifampicin or multidrug resistance. This can develop because either individual people can take medicines inconsistently or get the wrong doses or take them in the wrong way, or because of limited access to testing, end up having drug resistant TB that isn't recognized when they start therapy. So they get medicines that aren't effective, with less support to prevent future resistance, and then they develop resistance.

That resistance gets encoded in the DNA of the TB bacillus, and then it sticks around permanently. So that isolator strain is a resistant strain in a particular individual. So then if you catch TB from me and I'm infected with resistant TB, then you, just for bad luck, start out with a drug-resistant TB strain. And that's actually the case for most drug-resistant TB in a lot of parts of the world.

Maggie Fox
Why do people have to stay on TB treatment for so long?

Jeffrey Tornheim
TB is a tricky bacterium. It's a very slow bacillus to grow. So when it grows, for example, in culture, if I were looking for a bloodstream infection or a UTI, usually I would collect my sample, put it into the lab, and wait up to five days. And if it didn't grow in five days, I'd say cool, that's not what's going on for you, there's nothing growing. For TB, that can be up to 10 weeks, depending on the culture mechanism. It just grows so slowly that you have to wait a lot. And that puts us in a position where to effectively eradicate the bacteria in your body, you have to wait for that long period of time for these bacteria to wake up, become metabolically active, and then susceptible to therapy.

They have a lot of ways to sustain themselves energetically, which can take time to actually make the drugs effective against them. So you have to keep the medicine around long enough to kill all the bacteria as they wake up and are ready to be killed.

Maggie Fox

And so this probably helps explain why people often don't like having to undergo treatment for TB.

Jeffrey Tornheim
Well, because it's such a slow disease and because it takes so long to treat, a lot of us are busy and have a lot of other things to worry about in our lives. Doing something consistently every day, it's hard, even if it's something that you want to do and recognize the importance. I should go to the gym more often, but I don't exercise every day. Because that treatment is so long, many people are on board with the first parts of therapy over the first few weeks. And then as they start to feel better, [they] start to get a little more energy and feel back to themselves, but still have many months to go. It doesn't always sustain the same goal as the priority and the same importance to make sure that happens.

For drug-resistant TB, like I mentioned, the treatment comes with pretty bad side effects. These are not our first choice medicines. The first choice medicines are the most effective ones, that are the least toxic. But as you run out of drugs that are in that first line class, you go to more second or third line choices that have more side effects. And the more your medicine hurts, the less you want to take it.

Maggie Fox
Can you tell us what some of those side effects are?

Jeffrey Tornheim
So it does depend on the drug class. For a lot of our first line drugs, we focus more on making sure that the liver is okay. Some people experience joint pains, some people experience some vision challenges. When we go into these more toxic drugs, we often end up finding people having more problems either by losing their hearing when we were more frequently using injectable TB drugs that are damaging both to the hearing and to the kidneys. So people would have either kidney injuries or loss of some of their hearing. Some of the newer drugs that have been refurbished for TB have more nerve damage as part of their problems. So people will either have painful or burning or tingling sensations in their hands or their feet, or similarly can have nerve injury to their eyes.

Maggie Fox
And so I would imagine if people are reluctant to take these drug regimens for long enough to cure themselves, that too can help drive the evolution of these resistant bacteria.

Jeffrey Tornheim
That's true. And I do want to underscore that while we previously had a lot higher proportion of the drug resistance development for tuberculosis occurring because of challenges, making sure that people took all of the medicines all along the way, a lot more of the drug-resistant TB that people have gotten in the last few years through more recent studies of epidemiology are finding that people are just getting infected with that strain that has the permanent DNA change indicating drug resistance.

Maggie Fox
This is something you're working on, right? Testing, so that you know right away if you're infected with one of these resistant strains or not.

Jeffrey Tornheim
That's right. So I've been very fortunate to find some great mentors and colleagues who are world experts in TB testing and in TB treatment, especially for those drug-resistant TB situations. So what we've done is a combination of cohort epidemiology and diagnostic test development where we generate these cohort studies. We work together to build cohorts of people who are coming into clinics and being treated for drug-resistant tuberculosis, and we ask them to allow us to keep track of the things that happened to them during standard of care therapy. What drugs are they getting? What side effects do they have? How does that see both their subjective and objective experiences of the disease change? And then looking to see if there are different factors of their treatment or diagnosis that impact either their good outcomes, their benefits, or their bad outcomes from their side effects.

Building on top of those cohorts, we've collected additional samples where we can do evaluations either upfront with newer diagnostic tools, such as using whole genome sequencing or targeted next generation sequencing of the genes and the bacteria at the start of treatment to identify drug resistance, or looking at other markers of treatment response. That includes looking at how people's genes are expressed during the course of their therapy. That's included looking at drug levels to see how the drug is moving through their body, if it seems like it's going to be at an effective level by combining people's experience over time with the knowledge that we get from these new diagnostic tools, as well as using the presence of resistance markers in the genome in bacteria to predict how much drug we think somebody will need. We can get a sense of how to get somebody the right amount of treatment with the right drugs as soon as possible without subjecting them to the medicines they don't need and might be hurting them.

Maggie Fox
And if you can test people more quickly, how does that help?

Jeffrey Tornheim
I think that one other space that is really exciting to me, is the idea that we can move towards implementing some of these newer diagnostics to allow for a more personalized medicine approach. One thing that we've been working on has been developing rapid molecular tests, faster tests to look at these resistance markers over the last couple of years that can be used in the first week of treatment without waiting for that TB bacterium to grow so slowly. Once those markers are identified, we can get a sense of how resistant your particular bacterial infection is to a given drug and can make an upfront decision about whether you should or shouldn't get that regimen or should get your dose adjusted in a particular way.

We can then use confirmatory tests to ensure that we're getting you to that right place all at once. And I think that this combination of new tools with the new drugs is going to make therapy

quite a bit more effective for people moving forward and quite a bit more palatable to get them through that.

This is a really exciting time for such an old disease to be able to take advantage of new treatments and new diagnostics. The availability of a test really impacts how quickly you identify a disease and how quickly you get somebody on treatment.

Over the last 15 to 20 years, there has been development of a lot of carbon-based nucleic acid tests, the most common one being the Xpert MTB/RIF, or the Xpert Ultra, which is the later generation test, and these are quick tests that have largely been redeployed for COVID but within an hour, you can identify the presence of TB from somebody's sputum without waiting for it to grow, as well as the markers of resistance to Rifampin, one of the major drugs used to treat TB. Implementing that and rolling it out worldwide as a screening tool has been associated with a dramatic increase of identification of TB that's drug-resistant, but has also been associated with a great opportunity to be able to get people on therapy right away.

So quickly deployable, rapid tests like that are really going to make a big difference in terms of disease control, and again, letting us all get back to our lives.

Maggie Fox
Jeff, thanks so much for joining us.

Jeffrey Tornheim
Absolutely. Thank you guys.

Maggie Fox
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