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The Path to TB Elimination: Challenges, Innovations, & Future Horizons

Announcer:
This is ReachMD, and you're listening to Tackling TB, sponsored by Qiagen.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Although tuberculosis has maintained its global epidemic status since 1993, its mortality rate fell by 42% between 2000 and 2018. But what developments made this progress possible? And are we on the path to eliminating this disease? That topic, and more, to come on today's discussion.

This is *Tackling TB* on ReachMD, and I'm your host, Dr. Jennifer Caudle, and joining me to consider the current challenges and innovations towards eliminating tuberculosis is Dr. Masae Kawamura, practicing internist in San Francisco and Senior Director of Scientific and Medical Affairs for QIAGEN. Dr. Kawamura, welcome to the program.

Dr. Kawamura:
Thank you, Jennifer, I'm really happy to be here.

Dr. Caudle:
Well, I'm happy that you're here, as well. So, to get us started, I want to recognize the progress made toward controlling the spread of TB, because it's really been remarkable. But can you just level-set for our audience what the journey has looked like over the past several years from your vantage point?

Dr. Kawamura:
Well, the global journey has been really slow and delayed. In the United States, because of the excellent public health system and really, I think, world class TB control programs, you're not seeing active disease in the U.S. And so the U.S. is actually an example of what good TB control looks like. Our national rate is under three cases per 100,000. The global rate is way over 100 cases per 100,000, and much, much higher in certain countries. And that's because we do all of it. We have a comprehensive strategy of finding cases and preventing cases and treating all the cases effectively. So, it's a find, treat, and prevent strategy. And we have guidelines for every kind of scenario in terms of TB screening healthcare workers, long-term care facilities, very strict immigration policies. Before COVID-19, there was about a million people coming into the United States from overseas or 500,000, and half of that million adjusting their status. Even with all of this movement, and this really is a global community, we still managed to maintain control. But globally, it was in a passive case-finding mode. You have to have TB and show up to the doctor after all the contagion had passed, right? The damage was done basically. But now it's a more proactive approach; we have also included prevention and latent TB infection. So the globe is in a new phase, and it's following in the footsteps of what we're doing in the United States.

Dr. Caudle:
Fast forwarding to today, why has eliminating TB become such a point of focus for clinicians and public health experts recently?

Dr. Kawamura:
I think that the numbers are so horrendous. A quarter of the world's population is infected with TB. That means you have this massive reservoir, that will continue to, reactivate and give you TB cases, over the future unless you actually reduce that reservoir through prevention.

Dr. Caudle:

So, let's consider some of the challenges that have slowed down or, frankly, stood in the way of making TB a thing of the past. Starting with our evaluation and diagnostic practices for patients with suspected TB, what are some obstacles that you and your colleagues have encountered?

Dr. Kawamura:
In the U.S., active TB is not encountered very often. So, in the private sector, if you're not thinking TB, it could be anything, because TB is considered the great masquerader, and 80% of the time it's in the lungs, but it can affect any part of the body. I've even seen TB thyroiditis, believe it or not. It –can be very difficult to diagnose if you're not thinking about it. And so, really the key is to think TB risk. Where was this patient born? Is there a chance of TB infection in this individual? And then putting it into the differential diagnosis, particularly when you have a chronic respiratory illness, because TB is a contagious airborne disease, as well. It's difficult to diagnose, so people need to think TB. The diagnostics we have today are remarkable. PCR testing of sputum can give you a turnaround of 24 hours. You can get the drug susceptibilities within days to maybe two weeks, which is really remarkable. When I started my career, it took 8 to 12 weeks to rule out tuberculosis, and then another 3 months beyond that for the drug susceptibilities, and so everything you did was actually empiric. And now, you're actually acting on real results, and knowing what you're doing, and knowing what drugs to use. So it's really hopeful.

Dr. Caudle:
Excellent. You know, shifting to therapeutic considerations, what are some of the most pressing challenges that have hampered treatments for TB, both here and abroad?

Dr. Kawamura:
The most pressing challenges in the United States actually has just been the duration of treatment and the perception that the drugs you're using are toxic. For active TB, it's no problem. I believe in the hands of experts who are usually treating patients, the patient being sick, they want to get better, even though it's more toxic to take multiple drugs for six months. But adherence even with that is problematic, and that's why the gold standard is directly-observed therapy to ensure that the patient completes their treatment, not only to protect the public and to get these patients healed, but also to prevent acquired drug resistance, which is extremely low in the United States because the programs and the doctors do such a great job at the completion of treatment. But for latent TB infection where you're asymptomatic and you really have a choice to refuse because you're not ill, the duration of treatment, the six to nine months of isoniazid, was a real, obstacle. There is some toxicity. The older you are, if you drink, if you have underlying liver disease, if you take medicines that have cross reactions with isoniazid, you can have liver problems. Sometimes you have, rashes, as well. So that was I think the biggest obstacle and if it's true in the United States, it's a big problem elsewhere. But now with the newer, much shorter regimens; the three-month regimen of isoniazid and rifapentine once a week, you can get it done, with a single dose each week at the office in three-months' time. Now, outside of the United States, adherence is the biggest issue in manpower and programs. They can barely keep up, and they don't have enough outreach or capacity for the support. And acquired drug resistance, is truly a big problem globally. And multidrug-resistant TB has much worse outcomes, 50% in treatment success, which is not very good. It's almost as good as not treating TB. So adherence is really the biggest problem, and global programs themselves, are just not in place; not yet anyway.

Dr. Caudle:
For those of you who are just tuning in, this is *Tackling TB* on ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Masae Kawamura about the path towards eliminating tuberculosis. So, Dr. Kawamura, we've spent some time focusing on the roadblocks you've seen on this path, but let's look at the other side of it and zero in on any recent innovations putting that goal of eradicating TB within reach. So, on the diagnostic front, do we have any new tools or tests available to us? And are they nice-to-haves? Or are they need-to-haves?

Dr. Kawamura:
All the diagnostics that have been developed for TB have really been need-to-have. Rapid diagnosis is really the key to better patient care, to accurate treatment, and safety. So these new diagnostics that have been available for awhile , have been game-changers for active TB and also for latent TB. So on the active TB side, you have these rapid molecular tests that can identify MTB genome in a sample within a day , or two. Depending on how long it takes for the sample to get there. Through genetic methods, you can detect the drug susceptibility, whereas the old standard method was growing the TB in culture. And TB is one of the slowest-growing bacteria. It takes a full day to double, you know. So, it took weeks to months for you to get an answer, unless you had a positive smear. And even if you had a positive smear, which is finding the acid-fast bacilli on the smear, doesn't mean it's the right organism, because there are obviously other kind of mycobacteria that are acid-fast positive, as well. So from the active TB side, it's just been a game changer. From the latent TB side, you have a much more accurate blood test that eliminates the second visit from the skin test for a reading. These are all immunoassays, so it measures the immune response to someone who has had TB infection. You can't tell them it's active or latent, but that's what the chest x-ray does after you get a positive result. So these tests have actually eliminated the need for a lot of

chest x-rays. And the accuracy of testing has really changed. It's a much better time right now to practice because of these tools that we have for diagnosis.

Dr. Caudle:
Excellent. And coming back to the treatment side, have there been any developments here, as well?

Dr. Kawamura:
The drugs for standard drug-susceptible active TB have not really changed all that much. It's a six-month regimen with a two-month up-front intensive, using usually three to four drugs and then two drugs for the last four months. But with drug-resistant TB, if you have multidrug resistance, it can be 18 months to 3 years. It really depends on the severity of the disease and the level of drug resistance. And going through MDR TB treatment, these patients are my heroes. It's so difficult. It's toxic, and the road is hard. It used to involve injectable agents. Today, there are non-injectable treatments for multidrug-resistant TB. There are new drugs that are making it easier. And these regimens are getting shorter and shorter and being tested globally right now. And so I think in a couple of years, you're going to see the regimens change even more drastically, and we're going to be saving a lot more lives for those with MDR TB. From the prevention side patients are healthy, they don't want to take medicines, and the isoniazid and the rifamycins were the standard, but mostly isoniazid for six to nine months. And now there is a longer-acting rifamycin called rifapentine, and the regimens that are being commonly used now in the United States is isoniazid and rifapentine one dose per week for 12 weeks. So, you have a three-month regimen; 12 doses. There's a recent study that was published in *JAMA*. They looked at individuals who were HIV-positive, and it's a global multicenter study showing that the one-month daily isoniazid/rifapentine regimen was as effective as a nine-month isoniazid regimen. This is in, you know, our highest-risk individuals, people living with HIV. So I'm even more hopeful that, in the future, this shorter regimen will be recommended at least for certain groups.

Dr. Caudle:
Excellent. So, looking ahead, Dr. Kawamura, what are some upcoming directions in the TB landscape that you're really excited about?

Dr. Kawamura:
Well, there is a new U.N. proclamation and support for TB elimination, and that has never happened before. And so, with that, I think the momentum for programs to really beef it up and have a more comprehensive strategy will change around the world. And, as you know, we live in a global society, and that means that whatever good happens outside of the United States will really be good for the United States. What we're doing is great, but we ourselves cannot impact the globe. And that's the situation. So, with this new strategy, new support globally, new funding, I'm really hopeful the new diagnostics, the new treatments, if they can be implemented as they have been in the United States, we have a very bright future and– the reality of eliminating TB , becomes, something we can actually really believe in.

Dr. Caudle:
Absolutely. Well, Dr. Kawamura, those are really great insights for us to look forward to, and I'd really like to thank you for joining me today. It was great having you on the program.

Dr. Kawamura:
Thank you. I enjoyed it too.

Announcer:
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