Overseas Treatment of Latent TB Infection in US–Bound Immigrants

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Amera Khan, a technical officer at the Stop TB Partnership in Geneva, Switzerland. We'll be discussing treatment of latent TB among US-bound immigrants in Vietnam.

Welcome, Dr. Khan.

[Amera Khan] Hi, Sarah. Happy to be chatting with you. Thanks for giving me this opportunity.

[Sarah Gregory] Let's start with TB. There's so many respiratory diseases and viruses now: TB, pneumonia, RSV, COVID. How is it different and what are the symptoms?

[Amera Khan] Well, to start with, TB is caused by a bacterium, not a virus, and that bacterium is called *Mycobacterium Tuberculosis*. And actually, TB is a very ancient disease that has plagued humans for centuries. We even have evidence of TB dating back to ancient Egypt. But most importantly, until the recent emergence of SARS-CoV-2 (the virus that causes COVID-19), TB was the number one killer by infectious disease in the world. And right now, it's the number two killer by infectious disease in the world, but it is preventable and treatable. So that is really a big problem that we aren't able to get those numbers down yet.

You had asked about symptoms. Possible symptoms of TB disease are night sweats, fever, chills, a cough lasting longer than three weeks, fatigue, weight loss, lack of appetite, among some other symptoms. Pulmonary TB disease develops in the lungs while extrapulmonary TB disease can develop in other parts of the body, and the symptoms can vary depending on the type of TB disease you have.

[Sarah Gregory] And how is it spread?

[Amera Khan] Like COVID-19, TB is an airborne disease, so it spreads from person to person. So basically, when a person with TB coughs, speaks, or sings, people who are nearby and exposed, they may inhale the bacteria and become infected themselves.

[Sarah Gregory] Your article talks about latent TB. What is latent TB?

[Amera Khan] Yeah, that's a good question. So not everyone who is exposed to and infected with the TB bacteria becomes sick with TB disease. They can have what is referred to as latent TB infection. So in this condition, the TB bacteria are in the body in a dormant inactive state—so basically your immune system is able to keep the bacteria under-control. So people who have latent TB infection, they're not sick from TB disease and they actually have no signs or symptoms and they cannot spread the disease.

[Sarah Gregory] How does latent TB turn into active TB?

[Amera Khan] Well, the thing is that many people who have latent TB infection, they actually may never develop TB disease. Their bodies are able to keep the bacteria under control. But about 5-10% of people with this latent infection will develop TB disease at some point during their lifetime, and this happens when the immune system weakens and is no longer able to keep that bacteria under control, and then the bacteria start to multiply. The risk of developing TB disease is higher for those who are living with HIV, as well as those who have diabetes or any

other condition that can weaken the immune system, such as cancer, malnutrition, substance abuse, or other conditions. But the important thing to note is that there is treatment that can be taken to prevent latent TB infection from developing into TB disease.

[Sarah Gregory] I think you already answered this, but can latent TB still be spread to others, even if those with it are not showing symptoms? Right? You said you could not.

[Amera Khan] Correct. Yeah, people who have latent TB infection are not sick from the disease, and the bacteria are not actively multiplying so they will not be able to spread the disease, nor do they have signs and symptoms of the disease.

[Sarah Gregory] And how is TB diagnosed?

[Amera Khan] TB is diagnosed through a combination of clinical and laboratory exams. First, exposure and signs and symptoms are assessed clinically. And then you can have a skin test or a blood test that is used to detect an immune response to TB infection. But these tests cannot confirm or exclude that you have active TB disease. So then you would next will get a chest x-ray, which will show if there are any abnormalities, and then you would have the microbiological laboratory tests on sputum samples to detect the actual presence of the bacteria. Tests are also conducted to see if a person has drug-sensitive TB or drug-resistant TB, which will then determine the course of treatment. So you can see there's quite a bit of work involved to determine if someone has TB.

[Sarah Gregory] Okay. So drug-resistant or not drug-resistant, how is it treated?

[Amera Khan] Yeah. There are a few treatment regimens available in the United States for drug-sensitive TB. For drug-sensitive TB, the treatment can take anywhere from four, six, or nine months depending on the regimen used. The four-month treatment regimen is fairly new and consists of four drugs: rifapentine, moxifloxacin, isoniazid, and pyrazinamide. And the six-to-nine-month treatment regimens, which are more commonly available, also consists of four drugs: rifampin, isoniazid, pyrazinamide, and ethambutol. And because there are concerns for development of drug resistance, if medication is not adhered to, TB treatment is often delivered by what we call DOT (directly observed therapy). So this is, depending on the country context, where a healthcare worker or a family member provides support to ensure that the person with TB takes their medicine as prescribed. And if a person has drug-resistant TB, the medications are for a longer timeframe and can be a bit more complicated.

[Sarah Gregory] Is it more difficult to test for and treat latent TB compared to active TB?

[Amera Khan] Well, the tests for latent TB infection include either the skin test or the blood test, also known as the IGRA (interferon gamma release assay). These are designed to detect an immune response to the bacteria that causes TB. They don't actually tell you if you have TB disease versus TB infection. But the tests are also not perfect, so neither of these tests can confirm the actual presence of the bacteria. So for a variety of reasons, there can be both false positives and some false negatives, but more so with the skin test than with the blood test. But the other challenge is even with the better blood test, these tests cannot yet identify who with TB infection is most likely to progress to TB disease and most in need of preventive treatment, because remember: not everyone with latent TB infection will progress to developing TB disease.

So ideally it would be great to have a test that can accurately predict who with infection will progress to disease. I mean, it is still complicated, but in terms of treatment, TB infection

treatment can vary from six to nine months of isoniazid to the newer shorter treatment regimens that are three to four months and include a rifamycin. So it's beneficial to take TB infection treatment to prevent TB disease, but one of the major challenges with treating LTBI is that treatment initiation and completion rates are often really low. And that's because people don't feel sick so they may not want to take medicines for months, and while the regimens are relatively safe, they do have some side effects, which can be barrier for some people.

So the real challenge with latent TB infection treatment is often treatment completion. But we are seeing better treatment completion rates with the shorter and more tolerable three-to-four-month regimens that we have now compared to the six- or nine-month isoniazid regimens.

[Sarah Gregory] Okay. So latent versus active, it's a little complicated because some people get it active, and some people don't. What are the long-term health effects of untreated latent TB if you don't even know you have it, say?

[Amera Khan] The big thing you want to do here is prevent developing TB disease. So untreated latent TB infection can result in TB disease, which can itself cause long-term permanent lung damage. And without treatment, TB disease can ultimately lead to death. So this is really about preventing developing TB disease.

[Sarah Gregory] TB, as you said, is a global disease, but where is it most prevalent?

[Amera Khan] Yeah. As I mentioned before, TB is one of the leading causes of death by infectious TB globally. So an estimated 10 million people around the world develop TB disease annually, and it is most common in low to middle income countries (primarily in Asia and Africa), but TB can occur anywhere and it can affect anyone.

[Sarah Gregory] In 1989, the US Advisory Council on the Elimination of Tuberculosis declared a goal to eliminate tuberculosis in the United States by 2010. How did that go?

[Amera Khan] Well, we clearly missed that goal since we are sitting here and discussing this in 2022, but progress has been made. So in 1989, like you mentioned, the goal was set to eliminate TB in the US by 2010, with elimination being defined as less than one case per million. While the US has made a lot of progress with a continued annual decline in TB incidence, we currently are at an all-time reported low of approximately 7,000 cases in the last year, but the current case rate remains at 22 cases per one million—so a lot higher than the elimination goal that we are seeking. The main challenge for meeting this goal has been that the percentage of TB cases occurring among non-US-born persons in the United States continues to remain high. So roughly

70% of TB cases in the United States occurred among non-US-born persons who likely acquired their infection prior to moving to the United States. So what we are seeing are these latent TB infections starting to develop into TB disease post-US arrival for these non-US-born persons. And if we don't address that, many people who could benefit from preventive treatment are at risk for developing TB disease and we won't be able to reach the TB elimination goal.

[Sarah Gregory] So global health partners have clearly been working tirelessly for a lot of years here towards the elimination of TB. Theoretically, how close are we to elimination globally?

[Amera Khan] You know, we have been working tirelessly for quite some time and we were making a lot of progress towards the END TB goal, but unfortunately the COVID-19 pandemic has reversed the years of global progress in tackling TB. And in the first time in over a decade, we actually have seen TB deaths increase, according to the WHO 2021 global report. So this is

mainly due to the disruptions caused by the pandemic, and we saw many resources being diverted and people were not able to access care due to COVID-19 restrictions. We are now seeing some improvements, but there's still a lot of work to be done to catch up and move closer to our END TB goals.

[Sarah Gregory] What are some barriers that public health needs to overcome in order to achieve elimination?

[Amera Khan] Yeah. I just mentioned the issues with the COVID-19 pandemic, but even prior to COVID-19, we had a huge funding gap of nine billion US dollars that is needed to be able to respond to TB adequately. And in fact, this year's World TB Day theme is "Invest to end TB. Save lives", and this is a call for attention to address this funding gap.

Additionally, we need more affordable, better, and easy to use diagnostic tests as well as shorter and more tolerable treatment regimens. I had mentioned before how long these treatments can be. There have been advances, but they have been slow. And you look at the amazing response to COVID-19 in terms of the quick development of rapid tests and vaccines these past couple of years, and you look at TB and you wonder why is it taking so long for TB to have these types of technological advances. For example, in TB we have the BCG vaccine, but that vaccine is over 100 years old, and it actually doesn't work that well. So it would be really great to see TB getting the investments and that kind of attention since it is also an airborne deadly disease that has needlessly taken many lives over the years.

But even with the tools we have, there are still other barriers (like access to care) and we need to do a better job providing treatment support and addressing stigma that persons with TB face during their long course of treatment. And additionally, we need to continue to focus on and expand and scale-up the use of preventive treatment for those with latent infection if we want to further progress towards our END TB goals.

[Sarah Gregory] Yes, considering, as you said, it used to be before COVID the number one killer. It would be good if there were some dedicated resources to this more than we have right now.

In your study, you looked at voluntary uptake of latent TB infection testing and treatment by Vietnamese residents immigrating to the US. Is TB particularly a problem in Vietnam?

[Amera Khan] Yeah, and there are a few reasons why we chose Vietnam as the study site. So according to WHO, Vietnam is considered a high TB burden country with an incidence of about 180 cases per 100,000 population. Approximately one third of Vietnam's adult population has latent TB infection. The national TB program in Vietnam is very much interested in scaling up their TB infection preventive treatment through the use of shorter treatment regimens like 3HP, which was used in our study. So the 3HP regimen consists of isoniazid and rifapentine and is given once weekly for three months. This study that we did marks the first time that this shorter treatment regimen has been used in Vietnam.

To add to that, from the US perspective, we chose Vietnam as the site because it is in the top five countries of birth for non–US-born persons with TB in the United States. So targeting that site can have a big impact on our US TB epidemiology. And lastly, we really had incredible partners at the Cho Ray Hospital Visa Medical Department in Vietnam who conduct these overseas medical exams for US-bound immigrants.

[Sarah Gregory] Is TB testing mandatory for all people immigrating to the US, whether or not they are showing symptoms?

[Amera Khan] Yeah. So all immigrant visa applicants who are seeking permanent residency in the USA are required to undergo a medical examination prior to their US arrival. The purpose of these overseas medical examinations are to screen for communicable diseases of public health significance as required by the US Immigration and Nationality Act and the Public Health Service Act. Because TB is transmissible, screening and treatment for TB disease are essential components of this examination. So this medical examination is only required for those seeking permanent residency and is not yet required for persons seeking temporary visas to the US, like students or tourists or other business-type visas.

The current focus of the TB component of the medical exam is just on identifying and treating active TB disease, not latent TB infection, as that's not a condition that is transmittable.

[Sarah Gregory] I see, okay. So I guess it seems fairly obvious, but what's gained by treating people with TB before they come to the US?

[Amera Khan] Well, these overseas medical examination platforms, they really provide an opportunity to find and treat people who have TB disease. Most importantly, they get people on treatment who need it. And then having people complete their treatment prior to arriving in the US helps ensure that they are not continuing to transmit the disease and they aren't lost to follow up when they arrive to the US. It can be really resource intensive and challenging for health departments to follow up with people after they arrive to take their treatment.

[Sarah Gregory] So tell us briefly about your study. How did you go about doing it?

[Amera Khan] Yeah. So I used to work at the CDC's Division of TB Elimination, so the big strategy there right now is to really focus on finding and treating people with latent TB infection. And you can see that with the US data, most TB cases in the US likely come from people who acquired their infection prior to migrating to the United States. But historically the strategies that the US has used that have tried to address latent TB infection within high-risk communities, including the non-US-born, after they arrive in the US have come with challenges. They have been resource-intensive, and they've suffered from low treatment initiation and completion rates for a variety of reasons. Again, as previously mentioned, people with latent TB infection don't feel sick so they may not want to be on preventive treatment. Their providers may not feel like that's necessary, either. But this was more of a problem when the only options were the six-to-nine-month treatment regimens, but we are seeing some improvements again with the shorter course treatment regimens that are available now.

The other thing to consider is that for recent arrivals to the US, it can be challenging to navigate our health system, especially with language and transport barriers. And our health departments are often overburdened and under resourced, and so with many duties it is difficult for them to go and find and locate people after they immigrated to test and treat them for latent TB infection.

I was just going to add that we talked about the overseas medical examination, part of the study was looking at that platform, we recognized that these immigrant visa applicants already go through that, and that platform has actually been very successful in finding and treating people with active TB disease. So when these new, shorter, three month treatment regimens came out for latent TB infection, we thought this might be a great way to potentially address some of the challenges we have with trying to have these post-arrival latent TB infection strategies.

[Sarah Gregory] So what was your overall goal with the study?

[Amera Khan] So this study's overall aim was to assess if implementing a new and innovative strategy of offering latent TB infection testing and voluntary treatment during this overseas medical examination for immigrant visa applicants is feasible, and if so, should it be considered by the United States as another strategy to provide people preventative treatment who can benefit from it while progressing towards the US's TB elimination goals.

[Sarah Gregory] And what did you end up finding from your results?

[Amera Khan] Our study was able to demonstrate that this strategy of providing testing and voluntary treatment of latent TB infection is feasible and it can yield high treatment initiation and completion rates. So overall, 80% of those who started latent TB infection treatment completed their treatment, and this is higher than the completion rates which have been estimated around 40% for some of our post-arrival evaluation strategies that are currently in existence in the US.

[Sarah Gregory] I think you mentioned some of these, but were there any challenges that limited the uptake of testing and treatment among those immigrating to the US?

[Amera Khan] Yeah, for sure. I mean, you know, we don't expect to get 100%, especially since this was voluntary offering of the treatment and testing. So for our study, we did look across the different points of the LTBI care cascade of testing, treatment initiation, treatment completion to determine acceptance. So one of the challenges that we had was actually the acceptance for the TB infection test during the medical examination. It was only at 46%. But when you look at the main reasons why participants declined the actual offering of the test, it was because they were concerned about time commitment required for this study during their medical examination as well as after while they were getting ready to move to the United States. So because we were offering this test in a study context that had a lengthy consent process, it was actually a challenge for us to really determine if the visa applicants were not interested in their LTBI status or they were just not interested in participating in a study that seemed like an extra additional thing to do during this stressful time in their life.

So when you move along the cascade for those who did accept the test and were positive, 67% accepted and initiated treatment. This proportion is similar to what we see in some of our post-arrival efforts in the United States. We also did ask the folks who didn't initiate treatment some of the reasons why they didn't, and what they mentioned was, again, that they did not have enough time to complete treatment prior to immigration, especially since the way our study was setup, the treatment required clinic visits because the regimen we used (3HP), at that time of the study, it was recommend to give it by DOT (direct observation) at the clinic. So this would have required that these applicants should be coming into the clinic once a week for at least eight weeks to take their treatment, and then the remaining four weeks we would have allowed them to take self-administered treatment with a follow-up call.

So now the 3HP guidelines have actually changed. They do not require this direct observation, but now you're allowed to take these through self-administrative process. But I think with the flexibility that offers now, if we were to do this study again, I think we would probably even see higher rates of people initiating treatment with the ability to take these drugs on their own.

[Sarah Gregory] But apparently from your article, some people didn't complete the treatment course. Why was that?

[Amera Khan] Yeah. I mean, we actually did have really high treatment completion rates compared to a lot of other initiatives. Our completion rate was at 88%, so 12% didn't complete treatment and that was 36 people.18 people did not complete treatment due to minor adverse events—so basically side effects such as nausea, stomachache, from the treatment drugs—so they had to decline to continue. Five people did experience either a more significant adverse event or another medical condition that made sense for them to discontinue their treatment. And another five were found to have extrapulmonary TB or they were a contact to a drug-resistant TB case, meaning that this treatment might not be the most appropriate for them. So they also discontinued treatment. And then the remaining five participants who discontinued treatment had mentioned, again, that it was a busy time for them with the travel and the move to the US, so that they were too stressed to continue. And then three people who had actually migrated to the US were lost to follow-up. But overall, this is for a voluntary program. It's actually a quite high treatment completion rate.

[Sarah Gregory] Multidrug-resistant TB is clearly a great concern these days (and a concern in a lot of areas). What can be done to help promote medication adherence and completion for those with active TB infection or disease?

[Amera Khan] Yeah, you're right. Multidrug-resistant TB is a huge concern, and we are at risk of losing options for treating TB. And the treatment for it is really long and complicated, so it is a huge issue. Drug-resistance can be caused by inadequately treated TB. So there are many different reasons why people are non-adherent or they're unable to complete their treatment. The TB treatment regimens, as mentioned before, are unfortunately long in duration and they do have side effects.

There are different treatment support approaches that are used to ensure that people take their medications. TB treatment is often dispensed with an approach called DOT that we discussed a little bit earlier (directly observed therapy)—this is where the healthcare worker provides support and observes a person taking their medication. There are also now digital adherence tools that also help people...remind them to take their treatment as well as allows them to not have to go to the clinic and have a healthcare worker watching, it allows them to take their medicine at a time and place that's convenient for them. But often some of the support people need through treatment are really, you know, some basic common things that we can do to help them.

The treatment is long, and we know that people sometimes need help with nutrition, both for lack of resources but also nutrition can help them get through their treatments and is more likely to have better treatment outcomes. Some persons with TB need additional supplemental income because they're at risk for losing their job if they are out from work or if they take time to visit the clinic for their treatment. So there are different social support efforts that we can provide persons with TB to really get them through their treatment, and others also just need additional psychosocial support.

[Sarah Gregory] What do you think are the most important public health implications of your study?

[Amera Khan] Well, our study showed that we can achieve high latent TB infection treatment completion through a pre-arrival testing and treatment strategy. And so the public health implication is that this strategy has the potential to significantly impact TB rates among non-US-born persons in the US and help the US progress further towards TB elimination if it is scaled up.

[Sarah Gregory] How would you like to see your findings be used going forward?

[Amera Khan] Well, the hope is that these findings will be used to really consider this as a viable strategy to address latent TB infection and to subsequently advance US TB elimination efforts.

[Sarah Gregory] Dr. Khan, tell us about your job, what you like most about it, and how you became involved in TB prevention.

[Amera Khan] So I'll answer that last part first because I've been doing TB work for quite some time. I used to work at the CDC Division of TB Elimination, and while I was there, I was primarily working on domestic TB efforts, which, you know, included preventing TB.

In 2017, I decided that I wanted to do something a bit more global than just focus on the domestic level, so I took a job with the Stop TB Partnership in Geneva, which focuses more on global TB efforts and advocacy. And at the partnership I work on what is called the TB REACH initiative. The focus of this initiative is to fund and evaluate new and innovative approaches to find and treat people with TB. And what I like about the job is that we focus on innovations that are proposed from the ground up, from the local organizations that are working to solve the TB situation within the country. Really, it's an opportunity to help build the local capacity of our partners and it allows us to think of new ways for making progress to end TB. So I appreciate that it allows a bit of both the innovation and knowing that I'm providing some assistance to really better build capacity at the local organization.

[Sarah Gregory] Since you are living in Switzerland now, which everyone knows is a beautiful country, what are some of your favorite things about living there?

[Amera Khan] Yeah, I think it's pretty common for a lot of us here. Really, it's the chocolate, cheese, and the mountains. But definitely for me, I think the mountains—the natural beauty of this country, it's phenomenal and breathtaking. And what's really nice about it is that it is entirely accessible by train. So you can be in the mountains in the day and it's great, it's lovely.

[Sarah Gregory] Do you do hiking?

[Amera Khan] I do do hiking, yeah, especially in the summer. I am not yet a avid skier, which everyone else seems to be, so I'm slowly starting to get with that part of the culture here.

[Sarah Gregory] Hiking in Switzerland is probably...takes a lot of stamina, right? I mean, those are not...

[Amera Khan] Yeah. There are some rigorous trails, but, yeah, I think I'm more of a light weekend hiker though.

[Sarah Gregory] Yeah, the trains. That's on my bucket list—taking some of those trains around Switzerland.

Anyway, well, thank you for taking the time to talk with me today, Dr. Khan.

[Amera Khan] Thanks for having me. I really appreciate it.

[Sarah Gregory] And thanks for joining me out there. You can read the March 2022 article, Overseas Treatment of Latent Tuberculosis Infection in US–Bound Immigrants, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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