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## The Role of Primary Care in Eliminating TB

### Announcer:

You're listening to Tackling TB on ReachMD, sponsored by Qiagen. Here's Dr. Scott Lindquist.

### Dr. Lindquist:

Hello, my name is Scott Lindquist. I am the State Epidemiologist for Communicable Disease and the Deputy Health Officer in Washington State, and I have been in the tuberculosis world for about 20 years. And I'm here to talk to you today about risk-based TB screening. This is a nice, new approach to eliminating tuberculosis in the United States, and it's really a primary care approach to TB elimination.

And why primary care? Because CDC recommendations support that this approach to latent TB infection screening is most easily and most effectively achieved at the primary care level. This is based upon TB risk assessments as part of a standard workup. Now, I'm still a clinician. I work 1 day a week in a tribal clinic, and I really see the value of me as a primary care person being able to do a risk assessment for tuberculosis as part of a standard workup and then identify those who are patients with latent TB infection so that I can appropriately identify, triage and treat these patients.

Who should be tested? This assessment really shows us that a birth, travel or residence in a country with an elevated TB rate for at least 1 month. The easiest way to find out what countries fit this are to go backwards on this. So it includes any country other than the United States, Canada, Australia, New Zealand, or a country in Western and Northern Europe. If resources are limited in your clinic—say you see a lot of folks that are refugees, immigrants, or from countries outside of the United States, Canada, etc.—you would prioritize those patients with at least 1 medical risk for progression, and I'll talk about what those medical risks are in a moment.

The reasoning behind testing folks that were born outside of the US, Canada and these others is really about the rate in non-US-born persons versus those in US-born persons. And we know that the rate of TB in US-born cases is fairly low and has been decreasing since the early 1990s, and the same goes for non-US-born rate, but it is really much higher. We're talking about 0.7 to about 15 per 100,000 higher. This is also seen in the number of cases. We have a pretty constant number of cases in non-US-born folks, so much that in Washington State, about 80% of our TB cases are actually in foreign-born folks.

Who should be tested? Immunosuppression, current or planned, this means folks with HIV infections. So, when I said earlier you would prioritize if you had limited resources those who had a medical risk factor, immunosuppression would be at the top of the list—those who have HIV infection, those who are part of an organ transplant program or are being treated with tumor necrosis factor alpha antagonists, steroids, or other immunosuppressing medications.

The CDC really shows us who to prioritize, and priority is really given to those that will have increased risk of progression to active TB disease. And the list here includes HIV again, substance abuse, diabetes mellitus. And a quick moment on this one. If we look at some of our recent data, about 16% of the folks with TB presented also had diabetes, so diabetes really in this day and age is becoming a big risk factor for disease progression. Other things like kidney disease, low body weight, cancers, immunosuppressions, anti-tumor necrosis alpha therapy, silicosis, and organ transplants all are on this list.

When we look at estimated HIV coinfection among persons reported with TB, this has been a decrease since the 1990s. Depending on what age group you look at, it's about 10% of all those infected with TB have HIV coinfection. This is really the reason why we need to be not only testing for TB but getting an HIV test in anyone that we're testing for tuberculosis.

Other persons who should be tested include those who are residents or employees in a congregate living facility. That is places like correctional facilities, homeless shelters or long-term care facilities.

TB cases amongst persons residing in correctional facilities is also an interest for that risk factor. When we look at the numbers in people that are greater than 15 that have been in correctional facilities, really since the '90s, we see a case rate—percentage of total cases of TB that have been in correctional facilities at about 3%. This has been fairly constant through the 1990s and why this remains a risk factor for tuberculosis.

Again, when we look at the numbers for homeless persons during the previous 12 months before their diagnosis with TB, about 4.5% of all the TB cases reported homelessness—again a very significant risk factor for progression or risk factor for exposure.

The last category that is really in this assessment is: Who is a close contact to someone with infectious TB during their lifetime? Meaning if we know of an active case, who around that person had it, or in the lifetime of your patient, were they ever exposed to tuberculosis?

When we look at who should be tested, over your lifetime, the highest risk age group is in those that are over 65. That's because these folks were exposed either in their country of origin or in the workforce or in a homeless shelter during their lifetime, and as their immune systems start to wane when they are 65 and older, that's why we're seeing our highest TB case rates in this age group. This is really our target, to make sure that we're identifying these folks before they are 65 who have been infected with TB so that we can effectively treat them before they go on to actual cases.

One of the things that complicates diagnosis of tuberculosis is BCG, and BCG is a common vaccine for persons that are born in these areas where there are high rates of TB outside the United States, outside of Canada, outside of Europe, either Western or Northern Europe. And BCG is really a live mycobacterium bovis. It's not known to be super infectious, but it's effective, this vaccine, in preventing the complications in young kids. So we're talking about it won't stop you from getting pulmonary TB, but it will help prevent the more disseminated forms of TB in a country where there is a lot of endemic TB. Studies are variable. Some show good efficacy. Some show no efficacy. And clearly, with the amount of BCG that's given worldwide in our case rates of TB, it's not controlling TB, but again is probably really just preventing the complications in young kids. The WHO recommends that BCG be given to all kids born in highly endemic countries though.

Currently, there is no gold standard to determine if a person has LTBI. There are 2 classes of tests used for screening for LTBI, the first one being tuberculin skin test, the second being the interferon-gamma release assays. This includes T-SPOT or QuantiFERON. None of these tests can distinguish between active or latent TB, and none of these tests should be used to monitor treatment to determine if the treatment has been efficacious.

When we talk about the skin tests, we're talking about an indirect test for mycobacterium tuberculosis. It's done in vivo, essentially. This is a very old test—it's been developed over 100 years ago—and it really measures delayed hypersensitivity. It requires someone to be trained and experienced on how to place the amount of tuberculin under the skin. It's an intradermal injection of tuberculin purified protein—or why we call it the PPD—and then you evaluate this in 2 to 3 days. In our clinic this is difficult to do, because if I'm in clinic on Thursday, I can't place any TSTs in the clinic because no one will be around on Saturday or Sunday to read the test.

The big limitation is, as we spoke before, is BCG. The skin test cross-reacts with BCG. Most of the antigens in BCG, depending on any of the handful that are the antigens, they all cross-react with the PPD, meaning that you get a false positive test and demonstrates that our specificity is as low as 59% in BCG-vaccinated persons. That's not much better than flipping a coin to determine if the test was accurate. It also cross-reacts with nontuberculous mycobacteria, so not only does it cross-react with BCG, it cross-reacts with a whole category of nontuberculous mycobacteria.

Other limitations of the skin test are the risk of improperly placing the PPD. There's a lot of subjectivity in reading this. The cutoffs are variable, meaning 5 mm for high-risk, 10 for intermediate and 15 for low-risk folks. And that boosting effect can impact the result accuracy, meaning that the test can be negative on the first round and positive on the second round and get bigger with each subsequent injection. It also requires 2 visits depending on the method used. If you're doing 2 tests, it's 4 patients, so this is really a limitation when you're working with a population that's hard to contact.

The other method of testing, and my preferred method, is interferon gamma release assays. This is an in vitro blood test. They are much more specific and sensitive than the skin tests for screening. What the IGRA actually does is measures the secretion of interferon gamma and is a marker of cell-mediated immune response. What the test actually does is you harvest the T-cells and you stimulate them in vitro with a specific antigen for TB. The nice thing about the interferon gamma release assays is they are measurable and they are stable, and they should be negative because you should not have a reaction with interferon gamma release assays if you have not seen tuberculosis before.

The beauty of the IGRAs are they do not cross-react with the BCG, so in your foreign-born folks who have received BCG, especially since this is a large portion of our burden for latent TB infection, this is the ideal test because it's not going to cross-react with their BCG

vaccine that they received in their home country. They do have minor cross-reactions with some of the nontuberculous mycobacterium like *kansasii*, *marinum* and *szulgai*. The rest of the environmental ones though are not affected by interferon gamma release assays.

So, when we really look at the TST versus the IGRA testing, we're comparing this modern blood test that's a single blood draw, it's unaffected by BCG, and results are available from a single visit. It's an objective test, and the nice thing is that this can be an electronic result, and there's no hunting through charts for someone's old TST or having the results of a TST be affected by BCG vaccine or nontuberculous mycobacterium.

The American Academy of Pediatrics looks at this new technology and really says, for kids 2 years and older, either a skin test or an IGRA can be used, but an IGRA is clearly preferred for those who have had a BCG vaccine or are less likely to return for a second visit for a TST. The CDC, as part of the immigration testing guidelines, as of October 1, is no longer accepting the TST as one of the civil surgeon testing methods. These updated technical instructions now, since October 1, really recognize the importance of IGRA testing in foreign-born populations. And the hope here is that by implementing IGRA, we're going to have many more true LTBI's being positive as they are identified through IGRA rather than a false positive TST.

So, in summary, LTBI identification and treatment is critical to TB elimination efforts. Our goal in eliminating TB is really going to be recognized through not only treating active cases but identifying latent TB infection, mainly through primary care and treating these to prevent these cases down the road. Primary care providers should be proactive in assessing the LTBI risk, and testing patients that have 1 or more risk factors medically or for exposure will help us hone down and target those for LTBI. Foreign-born patients, particularly those with medical risk factors, are really the highest priority and should be tested for latent TB.

IGRAs are currently preferred over skin tests, both by Academy of Pediatrics and CDC, clearly when those persons have been vaccinated with BCG. IGRA testing, such as QuantiFERON Plus or T-SPOT, is more accurate and convenient than the TST.

And with that, I thank you.

**Announcer:**

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