Why yearly TB testing of health care workers is a waste

Sherrie Rice

January 2022—The United States and the rest of the world can expect to see an uptick in active tuberculosis cases brought about by impaired access to care and delays in diagnosis and treatment during the pandemic, says Wendy Thanassi, MD, MA, medical review officer and chief of occupational health, VA Palo Alto Health Care System, and associate professor of population health and preventive medicine at Stanford.

Testing is the path to eliminating TB, but it has to be done in the right population, she says, and health care workers are the wrong group.

Before Dr. Thanassi began her CAP TODAY webinar on TB testing in health care providers in the age of COVID-19 (made possible by a special educational grant from Qiagen, captodayonline.com), the audience was asked if their institutions were requiring annual TB testing for employees. The result: About 40 percent work for institutions that test all employees yearly, and at least another 10 percent say their institutions test only patient-facing employees. And all that testing runs counter to U.S. policy, Dr. Thanassi says.

The United States carries only 0.00005 percent of the global tuberculosis burden. The United Nations, World Health Organization, and CDC have as a goal the eradication of TB by 2030, and doing so will require identifying where the people are who have latent TB.

Fifty-two percent of U.S. TB cases are in four states: New York (nine percent), Florida (six percent), Texas (13 percent), and California (24 percent). “That is not on a per capita basis; that’s on a purely case basis,” she says. “New York is getting a huge amount of immigration, as is Florida, Texas, and California. It’s our southern border with Mexico that’s bringing most of the TB in, and then also with California’s proximity to the Pacific Islands.”

The highest per capita incidences are in Alaska (primarily among indigenous peoples with nomadic lifestyles who are difficult for public health officers to reach) and Hawaii (large population from Asia, where TB is endemic, and the Pacific Islands). And about 72 percent of people who have latent TB were born outside the United States.

Dr. Thanassi

For years the U.S. made progress in eliminating TB, but in the late ’80s and early ’90s there was backward movement in those TB elimination efforts. “It was because of HIV, and I bring that up,” she says, “because we’re going to see the same thing with COVID-19.” In the HIV era, all of the public health efforts shifted, and “diagnostics on tuberculosis declined, treatment declined, and we saw very rapidly the rates of TB go up in the U.S.”

The CDC and National Tuberculosis Controllers Association reported in July 2020 that more than 90 percent of TB programs had deployed their personnel to the COVID-19 response, and 60 to 72 percent of public health TB efforts in the U.S. had experienced a partial or high impact on their staffing. TB cases in the U.S. dropped between 2019 and 2020.

“Either we weren’t making as many diagnoses” because attention to TB was diverted, “or there were real reasons TB dropped off,” Dr. Thanassi says. “Did our decreased immigration for a few years mean we brought in less TB

than we had in years before? Was there decreased transmission because everybody was using PPE and staying indoors and separated? Was it because of decreased diagnosis?" She says she suspects it was "all of the above."

A paper published in August reported a dropoff toward 2020 in TB-associated hospitalizations and deaths after COVID-19 shelter in place went into effect in San Francisco (Louie JK, et al. *Emerg Infect Dis.* 2021;27[8]: 2227–2229). Hospitals in San Francisco saw a decrease in the number of TB patients receiving treatment by month. "And their report is that in the first few months after the pandemic, the numbers of patients newly diagnosed with TB decreased compared to the prior 14.5 months. Then by July 2020, just six months into the pandemic, the number of patients newly diagnosed with TB did begin to increase. And now a higher proportion of them required hospitalization or had TB-related death."

This population in San Francisco is "like the canary in the coalmine," Dr. Thanassi says.

"We are seeing an increased number of hospitalizations and deaths from tuberculosis because we were not seeing diagnosis and treatment of latent tuberculosis infection. We're also seeing late recognition of tuberculosis because," as a pulmonary disease, "it looks like COVID."

Turning to health care personnel, she says the number of active TB cases in the U.S. in 2016 (the latest year for which data are available by job type) was 8,600, and only 3.4 percent of them were in health care workers. "That means 96.6 percent of tuberculosis in the U.S. was not in health care workers. This is how I want you to go back to your leadership and be able to argue the science against doing annual TB testing, but rather focus on the right populations," Dr. Thanassi says. "If 96.6 percent of active TB in the United States is not in health care workers, why are we testing up to 20 million a year?"

"And then you spread that out—your basketball coach, your babysitter, your school nurse, and your teacher, all needing to do TB testing because there's this trickle down from the sense that it's lurking out there as a secret infection. But it's not. We know where it is."

The incidence of tuberculosis in health care workers between 2003 and 2007 was lower than in the general population, as it was from 2010 to 2016. To Dr. Thanassi, this is understandable. "Who's a health care worker? We are in the prime of our lives," or slightly post-prime, she says. "That means we're in our 20s to 60s-ish. We're not babies. We're not the elderly. We also tend as health care workers not to be homeless, incarcerated, or drug users," and to rarely have had organ transplants or be undergoing chemotherapy. "It's not a big population compared with the elderly. If you were to look at it from the outside, we would be exactly the wrong population to be tested for TB, unless you believe employees are still getting TB from their patients, which we're not." That is known, she says, because annual TB testing has been done "forever."

"That conversion rate was less than one percent, and that was using the skin test that had plenty of inaccuracies."

In the May 27, 2019 *MMWR* were recommendations from the CDC and the National Tuberculosis Controllers Association on TB screening, testing, and treatment of U.S. health care workers. "And this is where the sun finally comes out," says Dr. Thanassi, who was a coauthor.

It says all health care workers should be tested at hire and on transfer and at exposure and post-exposure. It says employees should be educated yearly about TB risk factors and symptoms. "The biggest change in this document is the removal of mandatory annual testing," she says, and the document makes it clear there should be no testing in any hospital population.

The authors weren't going to recommend eliminating it in all settings, she says, because there are settings in which some people should continue to be tested, such as border clinics without adequate ventilation systems that can have waiting rooms full of people with or at high risk for TB. "But in the first-world hospitals, that's not the place, not the emergency department, not pulmonary. Almost immeasurably few of those people after decades of being tested every year are converting to latent or active TB. Ideally just isolated people in each hospital should be selected for annual testing." A guidance statement from the American College of Occupational and Environmental

Medicine operationalizes the *MMWR* (Thanassi W, et al. *J Occup Environ Med.* 2020;62[7]:e355–e369).

There was a time when the CDC said a TB test cannot be done if the person had a COVID vaccine within the prior four weeks. “That never made any sense,” Dr. Thanassi says. “It was based on 1970s literature of live vaccines and their interaction with the skin test, so it’s not relevant. The COVID vaccines are not live, and nobody does skin tests, or at least most people don’t. There’s no implication or indication that getting the mRNA or the J&J or AstraZeneca brands of COVID-19 vaccines are going to affect an interferon-gamma release assay, or even a skin test. So they walked that recommendation back at the end of August,” at which time they said testing with a skin test or IGRA can be done before, after, or during the same encounter as COVID-19 vaccination (https://bit.ly/CDC-COV19-clinconsid).

“Here we are trying to hire people in a global pandemic. We’re trying to hire people into our hospitals but we have to wait four weeks from their vaccine. We want them to be vaccinated, but the requirement out of that *MMWR* is that they get tested for TB on hire. So it was causing mayhem in the hiring world for those of us in occupational health,” she says, “because if you followed that mandate, you delayed people getting their jobs by weeks. You delayed the hospital system from getting people onboarded.”

Three tests are available in the U.S. for TB diagnosis and latent TB in particular. Two are interferon-gamma release assays, both of which are whole blood assays. QuantiFeron-TB Gold Plus is the latest iteration—the fourth generation—and has four tubes. It is an in-tube interferon-gamma release assay, run as an ELISA on standard ELISA plates. The T-Spot.TB (Oxford Immunotec) also uses the same TB antigens, the ESAT-6 and CFP-10, in its assay. So both are interferon-gamma release assays using the same TB-specific antigens and both have a positive and a negative control.

Where they differ is in the technique. The T-Spot.TB is a Ficoll separation assay, and a more complicated assay. It is run primarily by Oxford’s main laboratory in Memphis (purchased by Quest).

The TB skin test is the third test and far less accurate. “I hope not many of you are using it anymore. In 2009 when I came to the VA as chief of occupational health, I came with the stipulation that we would never do this test again, and to my knowledge we haven’t.”

In the QuantiFeron test (and in T-Spot), there is a negative control, and when whole blood is drawn into that gray tube, no interferon-gamma should be released except what the body is doing in the background. “If the person has a cold, you might have a little interferon-gamma that’s measurable in the background. That’s the control on the test itself. If the gel breaks on the bottom, if the cap comes out, that Nil tube will alert you that there’s a problem with the test.” (Vigorous shaking can cause breakage of the gel, she says, so a gentle rocking motion is advised.)

The second two tubes (green and yellow) are TB antigen tubes. On the tubes themselves there is a sprayed on application of the TB-specific antigens. The fourth (purple) tube has a phytohemagglutinin slurry, and that is the mitogen tube (positive control). “The slurry that’s coated on that tube, when you add whole blood and rock the tube, is going to activate any body with a healthy immune system’s blood. And they will release a huge amount of interferon-gamma so one can see clearly that the person’s immune system is working,” Dr. Thanassi says. That’s what the positive control is—it’s on the patient’s immune system.

“In the U.S., we might have severe cancer, transplant, occasionally HIV. But worldwide, who has tuberculosis? People with AIDS, with severe malnutrition, starvation. So brilliantly, both of these companies made sure there was a positive control tube so we could make sure the immune system was working before we generate a result, negative or positive.”

The TB antigen tubes are also coated on the sides with the TB antigen that’s applied, which is why when the whole blood comes into the laboratory, it must be shaken up and down at least 10 times. The walls of the tubes have to be activated to interact with the whole blood.

“We don’t have other tests that do the assay inside of the tube. It’s fascinating. It’s unique. It’s clever,” she says.

“We have a lot of information that comes out of getting the results of all four tubes so that the Nil tube should be zero. The mitogen [positive control] tube should be up near 10. The positive control should say, yes, I have a huge immune system response. And you can rest assured the two TB antigen tubes will be accurate.

“I hope,” she adds, “that your laboratories will always report out the values of all of the tubes.”

Zero to 10 is the range of results one can get on the QuantiFeron tubes. To generate a negative QuantiFeron result, “the number value in the two TB antigen tubes has to be less than 0.35. It’s hard to generate a negative test result,” she says. And in fact the FDA required that the test have a 99 percent sensitivity.

“What if someone were to test 0.36, 0.4, 0.7 on one of those TB antigen tubes? Your lab would report out positive,” Dr. Thanassi says. “But if you report out positive at 0.7 without the data being provided to the provider saying one of the tubes is negative and the other is 0.7, that provider is denied the ability to judge that test for its accuracy.” It’s crucial, she says, that those numbers be reported and that providers be told that one or the other tube was positive and that the numbers are extremely low. “Because what’s the likelihood that a 0.4 really represents TB versus a 0.34 or a 0.7? It still means that the likelihood of having TB is in the 98 percent unlikely range. So just because there’s a cutoff at 0.35 does not mean someone above that has TB.” It’s just an indicator of slightly more reaction, she says. “And what would I do as an attending? I would reorder the test on a low positive.”

What if the repeated test is also low positive? “One, I’d use your pretest probability,” she advises. “Two, I wouldn’t hurry to make a diagnosis because TB doesn’t activate quickly. Three, I would look at those exact values and see whether you have discordant tubes in both cases, with only one tube positive and one tube negative.” And she adds: “If you do decide to treat, now that we have new treatments such as 12 weeks of once-a-week antibiotic, it’s so benign that erring on the side of treating is no longer a problem.” In the past, she says, “it was a huge problem.”

When the VA made the switch from the skin test to IGRA, Dr. Thanassi did a study with colleagues at the University of Illinois Chicago. Nearly 30,000 IGRA and skin test results were obtained from the health care worker population, and all were retested once or even twice. “When we started the study, we were using skin tests and we had about a 30 percent positive rate in both institutions. When we switched to the QuantiFeron, we cut that 30 percent positive rate to 3.75 percent, and another 3.5 percent that were weakly positive, or under 1.1.

“So if you do the skin test and you can’t differentiate who has TB or who had the BCG vaccine, it’s worthless in this day and age. But if you use an IGRA, it does not interfere with the BCG vaccine. It doesn’t detect that vaccine. It only detects response to these TB antigens.”

The weakly positives keep occupational health providers in business, she says. “Because when you have a low positive, you talk to the person. You say, ‘I don’t really believe it’s positive. You don’t have any likelihood of having TB. I’m going to send it again.’ When you send it again, 86 percent of them revert to negative. So the weakly positives are important to report out to your clinicians.”

A Stanford study published in 2017 evaluated the newest QuantiFeron-TB Gold Plus in 626 health care workers with no risk factors for LTBI (Moon HW, et al. *J Clin Microbiol.* 2017;55[6]:1650–1657). Three percent were positives. “They were getting three percent with the new test versus two percent with the third generation. That is to be expected because there are now two TB antigen tubes, so if one of those two tubes just jumps over that 0.34 line, it’ll result as positive.”

“They then took their positives and said, ‘We’re not going to count you on the QFT-Plus as positive unless both of your tubes are positive, unless there is concurrence between the two tubes.’” That dropped their TB incidence rate to one percent. “It’s a way clinicians can start to look at the test to make it more accurate in this population, because we shouldn’t be using it in this population—we know we’re going to get false-positives.”

Follow-up testing of 11 health care workers with discordant results between the TB1 and TB2 antigen tubes found a reversion to negative results in 10 cases and no progression to active TB in any of the participants.

Despite the expectation of an uptick in active TB cases because of what's not being done during the pandemic, Dr. Thanassi is optimistic—about the new and improved tests and the automation that improves the consistency and accuracy of results. "But we have to use these IGRAs on the right population. We can't be out there willy-nilly doing millions and millions of negative tests. It impacts their reliability."

It also has an impact on the country's landfills, she says. "We are creating an incredible amount of carbon waste. If you do four tubes per person and you were to extrapolate that to 10 million of our health care workers, you're looking at 40 million more tubes thrown in landfills, plus all the lancets and plastic baggies and plates. So we need to be stewards of our money, our time, our landfill, and our carbon footprint." But testing must continue, she says. "We just need to do TB tests on the right people—those with a pretest probability of having disease."

Sherrie Rice is editor of CAP TODAY.