

Simple test may predict which children develop severe TB, researcher says

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A Stanford investigator and his colleagues found that a screening test for tuberculosis was a good predictor of whether children infected with the bacteria would become sick.

A simple blood [test](#) commonly used in screening adults for tuberculosis

could predict whether [children](#) infected with the TB bacteria are likely to progress to the active disease, according to a study by researchers at the Stanford University School of Medicine and five other institutions.

In an analysis of medical data from more than 2,500 South African babies, infectious disease specialist Jason Andrews, MD, and his colleagues found that a test, known as the QuantiFERON-TB assay, was a valuable predictor of which infants carrying the bacteria would become sick. The test could be particularly useful in high-risk countries like South Africa, where hundreds of thousands of young children die of the disease every year and where screening tests for TB in children are ineffective, Andrews said.

"It could be highly valuable in determining which kids will develop TB disease," said Andrews, an assistant professor of medicine who is lead author of the study.

Andrews said he hopes the study will prompt changes in World Health Organization guidelines, which currently don't recommend use of the test in children.

"Given the high rates of TB and the difficulty of diagnosing it in kids, this can be something that could be done routinely in kids to identify the high-risk ones," he said. "You could imagine in a high-burden country that at a child's 12-month visit, they could also get a QuantiFERON test and, if it's high, they'd get aggressively investigated for TB."

The test is a type of interferon-gamma release assay, or IGRA, commonly used for TB screening, both here and abroad, as it is more accurate than the older skin test.

"These new findings confirm that the IGRA test for tuberculosis infection performs differently in young children compared with adults,"

said Mark Hatherill, MD, senior author of the study and senior clinical researcher at the [South African Tuberculosis Vaccine Initiative](#). "More importantly, we now know that the IGRA test can be used to identify those children who are at highest risk of developing tuberculosis disease and who would benefit most from investigation and therapy."

The study was published online Feb. 10 in *The Lancet Respiratory Disease*.

Potentially fatal lung disease

TB is a potentially [fatal lung disease](#) caused by a bacterium that is airborne and readily transmitted by coughing. In 2015, it caused 1.8 million deaths worldwide and is one of the top 10 killers around the globe, according to the WHO. In South Africa, it is the leading cause of death among both adults and children, accounting for some 8.5 percent of the nation's fatalities, said Andrews, who has been studying the disease there for a decade.

He said [young children](#) are particularly vulnerable to TB, with up to 20 percent of those infected by the bacteria developing the active disease. While adults are commonly screened in South Africa using sputum testing, this method doesn't work in children, as they typically swallow their sputum after coughing, he said. And though children may be screened if their parents become ill, they also can become infected through contact with other infected individuals on buses, in churches, schools or other public places, he said.

So there is no effective screening tool for children, who often show up in clinics in a late stage of the disease, when it is more difficult to treat, he said.

"We really need a reliable screening test for children. It's so frustrating

to see how little progress we've made," Andrews said.

Analyzing data from trial

In the hope of finding a viable testing method, Andrews and his colleagues analyzed data from a published trial of a potential TB vaccine that had raised high hopes but proved to be a disappointment. The trial was done by the South African Tuberculosis Vaccine Initiative between 2009 and 2012 in a rural area outside Cape Town, a city of 3 million people where about 30,000 TB cases are reported every year.

The trial included 2,512 babies who were all healthy and HIV-negative, with no known exposure to the disease. Half of them received the experimental vaccine, and half received a placebo.

The researchers in the trial used the QuantiFERON-TB test, also known as QFT, to measure infection in the children, who were all tested at the start of the trial and again at one year and two years.

The assay exposes whole blood cells to the TB antigen and then measures the amount of interferon gamma, a type of cell-signaling protein, released by certain immune system cells. If the response measures less than 0.35 international units per milliliter, the person is considered negative for the bacteria, while any result higher than that is considered to be positive.

Test results at one year

When the 2,512 children in the study were tested at a year, 172 of them—6.8 percent—were found to be positive carriers of the bacteria, a very high rate of infection, the researchers reported. Of these, 30 had already been diagnosed and treated for the active disease.

The researchers more closely examined the other 142 children who tested positive but hadn't yet developed TB. They found that among those whose test results were between 0.35 and 4.0 international units per milliliter, only 2.5 percent developed the active [disease](#). But among those with values greater than 4.0 international units per milliliter, many more children—28 percent—became ill. Only 0.7 percent of those with a negative test developed TB.

"We found that as your value goes up, your risk goes up, and the risk really begins to accelerate after a value of 4," Andrews said. "The children in the high-value group had a 40-fold higher risk of getting sick, which is a very powerful marker."

He said the study is the first to show that these higher numbers matter more.

"What we are hoping is that this will show the international community—the WHO, CDC and those creating guidelines—that QuantiFERON testing can be reliable in kids, and that the quantitative values may be important so we may need to look at different thresholds than we use in adolescents or adults," Andrews said.

He said the only drawback of the test is that it is moderately expensive and requires a well-equipped laboratory and trained personnel to perform. It may be viable in a country like South Africa, with its relatively advanced infrastructure, but would be less practical to use in poorer countries. The researchers are now exploring whether it could be cost-effective to scale up testing in South Africa, he said.

More information: Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study, *The Lancet Respiratory Disease*, DOI: [dx.doi.org/10.1016/S2213-2600\(17\)30060-7](https://doi.org/10.1016/S2213-2600(17)30060-7)

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