New Diagnostics Sought To Replace TB Skin Test

BY BRUCE JANCIN
Denver Bureau

LISBON — Better diagnostic tests are seen as essential in the campaign to control the global tuberculosis epidemic—and help is on the way.

The archaic, nearly 100-year-old tuberculin skin test was until recently the sole tool available for diagnosis of latent TB infection. The skin test has several limitations, chiefly its low specificity due to cross-reactivity with the BCG vaccine and false-positives in persons infected with non-TB mycobacteria, Dr. Karin Weldingh said at the 12th International Congress on Infectious Diseases.

Major international aid organizations including the Foundation for Innovative New Diagnostics, the Stop TB Partnership, and the World Health Organization have declared development of faster, simpler, more convenient, and more accurate TB diagnostic tests to be a high priority.

Recently, two novel cell-mediated immune response–based assays have become widely commercially available as alternatives to the skin test for detection of latent TB. The in vitro assays—the QuantiFERON-TB Gold and T-SPOT.TB assay—measure interferon-γ released by sensitized T cells following stimulation by antigens specific to *Mycobacterium tuberculosis,* including culture filtrate protein-10 (CFP-10) and early secreted antigenic target-6 (ESAT-6).

Studies show these assay kits have better specificity for detection of latent TB and are at least as sensitive as the skin test for active TB; plus, they're interpreted more objectively, with results available in a day, said Dr. Weldingh of the Statens Serum Institute, Copenhagen.

The QuantiFERON-TB Gold assay was first to win approval by the Food and Drug Administration. Late in 2005, the Centers for Disease Control and Prevention recommended its use in all situations where the skin test has been used, including serial evaluation of health care workers.

The downsides of using these assays in the developing world are that they require living cells and ready access to a lab for enzyme-linked immunosorbent assay.

"This means you have to process blood samples within 12 hours. You have to be careful with the blood. It's sensitive to temperature. You can't put it in the fridge and leave it for the weekend. You cannot leave it out in the car. You cannot mail the blood sample to a lab," she explained at the congress sponsored by the International Society for Infectious Diseases.

For these reasons, Dr. Weldingh sees the assays ultimately being most useful for latent TB case-finding via contact tracing and screening of high-risk groups in low-endemic, highly developed areas such as Western Europe and the United States. The tests should also prove useful in areas with an intermediate TB incidence and good infrastructure, such as parts of Brazil.

In places where TB rates are high, roads poor, and laboratories hard to come by, these tests aren't practical. The ultimate solution in such places is probably an improved skin test that utilizes *M. tuberculosis*–specific antigens rather than the traditional purified protein derivative; such tests, which are simple, low-tech, and low-cost, are now under evaluation in field studies.

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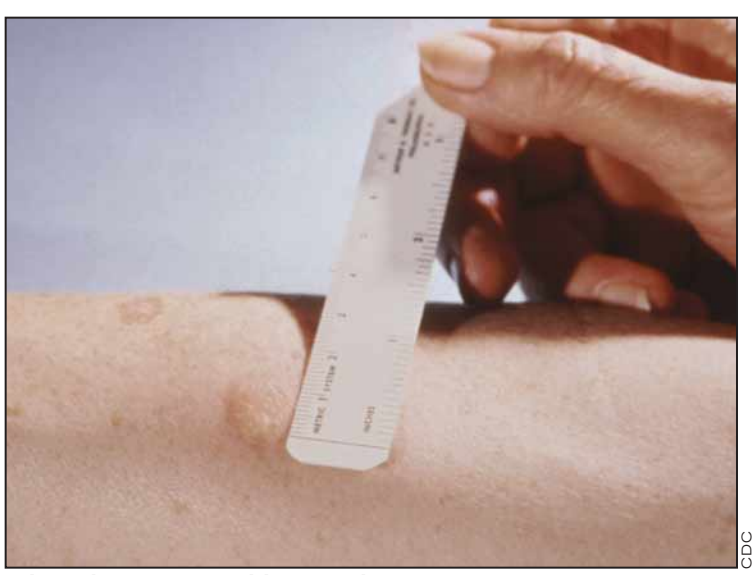
DR. GODFREY-FAUSSETT

Another approach involves serologic antibody tests. These offer several potential advantages. They're much less temperature-sensitive and fragile than the interferon-γ tests, they don't require living cells or access to a laboratory, and they yield results in 15-30 minutes.

The newer ones, which utilize *M. tuberculosis*–specific antigens, perform best. They'll never serve as a stand-alone test for diagnosis of active TB—there are too many false-positives in highly endemic areas where uninfected people are often re-exposed to TB—but they could have a role as rule-in point-of-care screening tests that trigger a visit to a clinic for definitive testing, she said.

That sounded good to Dr. Peter Godfrey-Faussett.

"I was very heartened by the work on rapid diagnostic tests with serologic agents, because I think eventually—maybe with antigen detection for screening people—that might be the way to go. We've got to be thinking about tests that can be used out in the field at the point of care, because you won't get people to come in to the health center to have a fancy test or x-ray; they can't afford the bus fare," said Dr. Godfrey-Faussett, professor of infectious diseases and international health at the London School of Hygiene and Tropical Medicine. ■



CDC

This patient had a positive reaction to the 48-hour Mantoux test, in which tuberculin is injected between the layers of the skin.

World Public Health Officials Targeting Drug-Resistant TB

BY JONATHAN GARDNER
London Bureau

International public health officials have announced actions necessary to combat deadly new strains of tuberculosis that are resistant to most drugs on the market.

Officials from the South African Medical Research Council, the World Health Organization, and the Centers for Disease Control and Prevention called for rapid surveys of the prevalence of extensive drug-resistant TB in high-risk countries, increased laboratory capacity to carry out vital culture and drug resistance testing, improved clinical capacity, infection control precautions, and research support for new drug and diagnostic tests.

To keep extensive drug-resistant TB from spreading to other patients, health care facilities need to promptly identify patients suffering from it, and then isolate them.

Of particular concern are countries with a high prevalence of HIV/AIDS, which public health officials warned has the potential to turn extensive drug-resistant TB into "an uncontrollable epidemic." They called for universal access to antiretroviral drugs in joint TB/HIV projects.

Extensive or extreme drug-resistant TB describes strains that are resistant to the two most potent anti-TB drugs, isoniazid and rifampin, and at least three of six classes of second-line drugs.

International public health leaders gathered recently in Johannesburg in an emergency session with public health authorities from 11 southern African countries to discuss how to combat extensive drug-resistant TB.

"It is an area where the global community will need to be helpful to the countries that don't have resources, but locally, there needs to be ownership of the issue," Ken Castro, director of the CDC's division of tuberculosis elimination, said in a press conference that was held in Johannesburg to discuss the threat of extensive drug-resistant TB.

New drugs and vaccines are in the works, officials said. Dr. Castro said that four agents look promising as drugs, but must still be proved through clinical trials.

Use of vaccines, including the BCG vaccine, is a possible approach, Dr. Castro said, although he added, "we will not be able to rely on vaccines to address the problem confronting us."

Infection control in health care facilities is a priority, he said. To keep extensive drug-resistant TB from spreading to other patients, health care facilities need to promptly identify patients suffering from it, separate them from the rest of the patients, and make use of respiratory devices. ■

Tuberculosis Deaths in HIV Patients Called Preventable

HIV/AIDS health workers need to accelerate efforts to prevent HIV patients from contracting tuberculosis and treat those who do, top public health officials said.

Speaking at the 16th International AIDS Conference in Toronto, leaders of the World Health Organization and International AIDS Society said a quarter of a million people with HIV die from tuberculosis every year, even though many of those deaths are preventable.

People with HIV are more vulnerable to tuberculosis than those without HIV, even if under treatment using antiretroviral therapy. More than one-third of all people infected with HIV also are infected with tuberculosis bacillus, Dr. Helene Gayle, the International AIDS Society president, said in a written statement. HIV infections number about 38.6 million worldwide.

"TB prevention, diagnostic, and treatment services must become core functions of all HIV services," Dr. Kevin De Cock, WHO's HIV director, said in the statement. "TB can be treated and cured, so most of these deaths are absolutely preventable. HIV policy makers, health ministers, and health workers all have a vital role in making sure that deaths from TB are reduced."

The officials touted a study in Rio de Janeiro that is seeking to reduce the prevalence of tuberculosis in 15,000 patients seeking treatment at 29 HIV clinics. While antiretroviral treatment can reduce the risk of contracting tuberculosis, the study aims to find out whether a comprehensive policy of screening and treatment latent tuberculosis can reduce tuberculosis incidence by an expected 60%, which would prevent 1,670 cases of tuberculosis per 100,000.

—Jonathan Gardner