From TB tests, just a 'yes or no' answer, please

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The longer it takes to diagnose and treat an infection, the more chances those infected have to get sicker—perhaps even die—and spread the disease.

This is a fundamental tenet for any infectious disease and increasingly more urgent for tuberculosis (TB), which claims nearly 2 million lives each year. A quick and accurate diagnostic tool for TB could save up to 625,000 of those lives each year (*Nature* **S1**, 49–57; 2006).

The ideal test would be one that would deliver a quick and clear 'yes or no' diagnosis and would be easy enough for an untrained healthcare worker to use.

In Malawi, for instance, "20% of our patients die and a good half of them die in the first two weeks," notes Tony Harries, an infectious disease expert there. "We really need something that says this person has TB. At the moment it is largely guesswork."

That's because the standard test for TB, the crude 100-year-old sputum smear—in which the bacteria are spotted under a microscope—catches only half of active infections.

"You get people to cough up sputum into a pot—it is a pretty horrible process," says Christopher Dye, coordinator of TB monitoring and evaluation at the World Health Organization (WHO).

The WHO mandates multiple smears, meaning a wait of several days, during which the infection gets steadily worse. "It's that waiting time, that inefficiency that we need to cut out," says Dye.

In most individuals infected with HIV—and in some who aren't—the TB infection spreads out from the lungs and into the blood and other tissues so there are not enough bacteria in the sputum for a positive smear, making the test even more insensitive (see page 268). To cut down on waiting times, the WHO last year changed the recommended number of smears for a HIV-positive individual from three to two and is considering the change for everyone.

The next recourse is an X-ray, but interpreting the films is subjective and largely useless in cases where the bacteria are disseminated throughout the body.

A decade ago, there was little interest in developing better diagnostics. But in 2003, money from the Bill & Melinda Gates Foundation helped create the Foundation for Innovative New Diagnostics (FIND) in Geneva, which helps convince companies to invest in new diagnostic tests.

"We help them prepare a business plan and look at what the market is," says Giorgio Roscigno, head of FIND. Still, the global spending in 2005 on new tests was just $16.5 million, according to a report by the New York–based Treatment Action Group (see box, page 270).

When the TB bacteria get into the bloodstream, they produce proteins that show up in the urine. FIND is working on perfecting a urine test for HIV-positive individuals that would pick up these proteins. Two clinical trials are set to begin this year and could bring the dipstick to the market by 2009.

There are other options a bit further off, including an antibody test for blood that could be available by 2011 if scientists can first map out the bacterial proteins.

The most attractive dipstick would be a rapid test that would isolate bacterial DNA from a bodily fluid, amplify it and detect it with the right probe. "Ideally, if that platform works, you could use it for other diseases," says Roscigno.

The rising problem of drug resistance has also created an urgent need for tests that can spot resistant strains. DNA amplification might eventually be able to identify resistance in minutes, but cell cultures now used require more than a month and considerable skill.

There are more sophisticated, but expensive, versions that use liquid cultures spiked with growth enhancers in fully automated systems and cut detection time from 45 days to about two weeks. Culture time can be further shortened to about a week using microscopes to inspect the liquid medium for the characteristic shape of the bacilli in the presence of first-line drugs (*N. Engl. J. Med.* **355**, 1539–1550; 2006).

In the meantime, FIND is trying to improve smear tests by helping design affordable fluorescence microscopes that could make the tests more sensitive. FIND will field-test the new microscopes, which could be available by 2009.

These advances all focus on full-blown infections, which are a minority. For the remaining 90% of those infected, there is a skin test to detect latent TB. But those vaccinated with the bacille Calmette-Guérin vaccine—which is most of the world—can present false positives. A new blood test presents two proteins made by the bacilli but not in the vaccine (*Thorax* **58**, 916–918; 2003).

It might be years before the threat of active TB has been subdued enough to focus on latency. But that might be the wrong approach. "My conclusion is that we are never going to get to the elimination target unless we deal with the problem of latent infection," says Dye. "But it is not right at the front of [FIND's] agenda."

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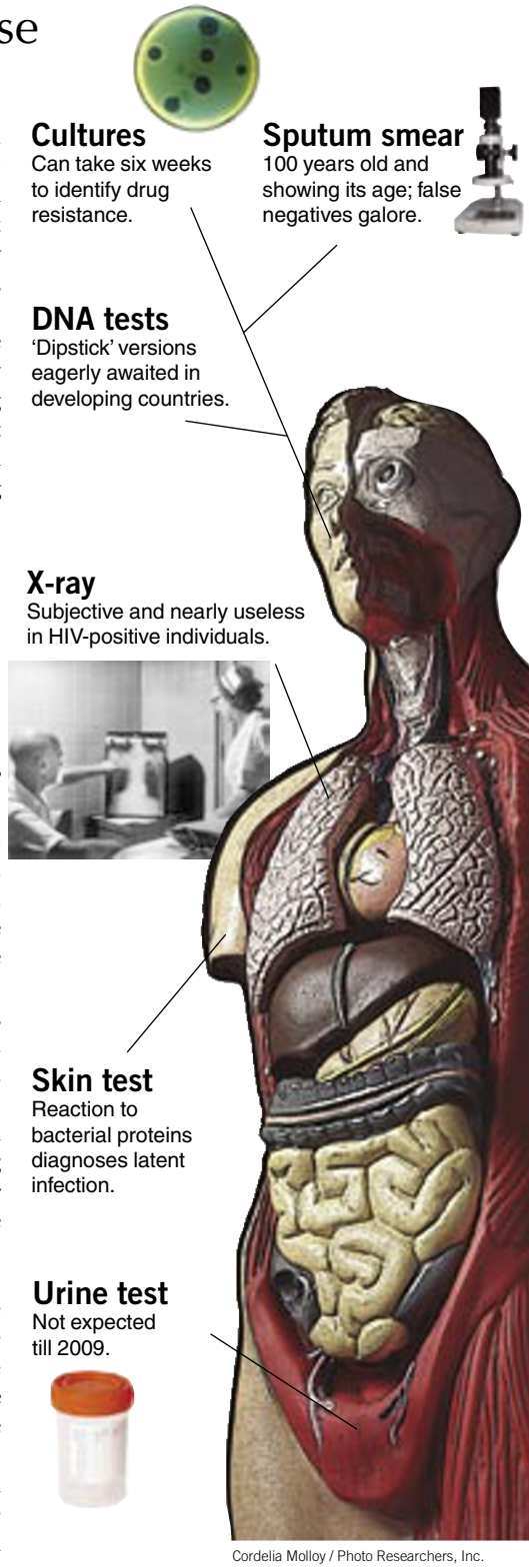

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