A dozen vaccine candidates bring shot of hope to TB epidemic

The best hope of eradicating tuberculosis (TB) is to prevent it with mass vaccination. Trouble is, those vaccines don't exist—at least, not yet.

The World Health Organization (WHO) has set a goal for a new vaccine by 2015. That may be a bit ambitious: scientists are still trying to pin down the immune factors that would protect people from TB bacteria.

The existing vaccine, bacille Calmette-Guérin, protects children from disseminated TB, the form of the disease that spreads throughout the body. It's powerless against adult disease and childhood pulmonary TB.

"The current control of TB is largely a testament to how much committed people can do with fundamentally lousy tools," says Peter Small, senior program officer for TB at the Bill & Melinda Gates Foundation.

One of the foundation's biggest grantees, Maryland-based Aeras Global TB Vaccine Foundation, is developing about a dozen vaccine candidates, most of which are in preclinical stages. But the furthest along is the Wellcome Trust's MVA85, which is being tested in South Africa and could be in the clinic by 2012.

Many of the candidates follow the prime-boost strategy, in which antigens are introduced twice into the body, first by BCG or an improved recombinant BCG and then by another method, so that the immune system reacts to the antigens rather than the delivery system. A key technique in designing the prime is to edit out the tricks the bacteria uses to dampen down the host immune response.

"We're taking the features of the bug that it uses to turn off the immune response and disabling them," says Jerry Sadoff, president and chief executive officer of Aeras.

Another strategy is to build with only the proteins that provoke good responses rather than the whole bacterium. One Aeras candidate called M-72 is a recombinant of two TB proteins fused together, mixed with an adjuvant to pump up the cellular response.

The key to good vaccine may be in understanding those who get infected with the TB bacteria but never get sick. Only about 10% of infected individuals become ill, half at the time of infection, the other half after some interval of latency.

> TB is infectious and spreads through the air; if not treated, each person with active TB infects on average 10 to 15 people every year.

In the healthy 90%, the immune systems imprison the TB bacteria in a little granuloma that keeps the bacteria from spreading. In mice, immune cells that secrete a protein known as interferon-γ seem to be key, and many vaccines try to boost the number of these cells. There are other candidates, but the exact number and proportion of these various types of immune cells remains unknown.

One of the only teams focusing on this aspect is part of the South African TB Vaccine Initiative. Those researchers have collected samples from thousands of infants as they are inoculated with BCG. These children are being followed to see who goes on to get TB.

The rest of the field is moving forward on what amounts to educated guesses.

"Considering the fact that we don't have an animal model or an assay that we know correlates with protection, we think we are doing very well," says Sadoff.

All of the vaccines being investigated are designed to keep the infection latent. New approaches would prevent the bacteria from gaining a foothold in the lungs at all.

For Chris Dye, coordinator of TB monitoring and evaluation at the WHO, the dream is a dual vaccine. "But that is going to be at least 10 years down the line, probably 20 or 30 years down the line," says Dye. "It is not clear that we are ever going to have an understanding of the immunological problems."

Emma Marris, Washington, DC

When the vaccine causes disease

For decades, the World Health Organization (WHO) has recommended that every newborn at risk of tuberculosis (TB) should be protected with a single dose of the bacille Calmette-Guérin (BCG) vaccine as soon after birth as possible.

But in late November, the WHO's Global Advisory Committee on Vaccine Safety reviewed mounting evidence from Argentina and South Africa and concluded that for infants infected with HIV, the risks of BCG vaccination outweigh the benefits.

"If you know that a child is infected with HIV, this child should not receive BCG," says Paul-Henri Lambert, the committee's chair.

In rare cases, BCG can itself make children ill, triggering a swelling of the lymph nodes and mimicking the symptoms of TB. In HIV-infected children, the risk of this disease is estimated to be as high as 400 for every 100,000 vaccinated children (*Vaccine* **25**, 14–18; 2006).

"That's a very high risk. In fact, that's about half the incidence of TB in this age group," says William Hanekom, laboratory director of the South African Tuberculosis Vaccine Initiative. And the benefit of BCG vaccination to HIV-infected children is as yet unknown.

Hanekom has just wrapped up a trial to compare the immune effects of BCG vaccination on HIV-infected children with its effects on healthy ones. The results are expected later this year.

The WHO's new policy says that wherever possible, children born to HIV-infected mothers should be tested for HIV—which cannot be done till the infant is at least six weeks old—and only vaccinated if they are uninfected.

Most African countries have the resources neither to test every child nor to make sure that the mothers bring their children back for the vaccine, but may decide to postpone vaccination anyway, Hanekom warns.

"It's a high-risk policy and it may have been done in relative haste," he says. "I think it's going to result in a lot of HIV-negative kids getting TB."

Apoorva Mandavilli, New York

WHO