Another Look at the TB Vaccine

Should the United States use BCG widely?

By DAMARIS CHRISTENSEN

In spite of conflicting evidence of its ability to prevent infection, the tuberculosis (TB) vaccine is, surprisingly, the most widely used vaccine in the world. Its rise to prominence began in 1908, when Albert Calmette and Camille Guérin at the Pasteur Institute in Paris developed a weakened strain of a bacterium that causes TB in both cows and humans. They first tested this vaccine in people in 1921; since then, more than 3 billion people have received the BCG (bacille Calmette-Guérin) vaccine.

Although BCG is recommended by the World Health Organization's Expanded Program on Immunization, doubts about its effectiveness remain. Some clinical trials have shown it to protect 80 percent of those vaccinated; others have found it to offer no protection at all. Numerous theories have been proposed to explain these conflicting results, including the possibility of subtle differences in the BCG vaccines used.

The relatively low incidence of TB in the United States, coupled with uncertainties about the effectiveness of the BCG vaccine, has led the U.S. Public Health Service to recommend TB testing and drug therapy for those infected, rather than vaccination. But TB cases are on the rise, and the spread of the hard-to-treat multidrug-resistant tuberculosis (MDR TB) has encouraged the Centers for Disease Control and Prevention (CDC) to take another look at BCG.

Tuberculosis kills more people than any other infectious disease. Annually, there are an estimated 8 million new cases of TB and 2.9 million deaths worldwide. Last year, there were 26,673 new cases in the United States, a 20 percent increase over 1985.

In the United States, the tuberculin skin test is the primary means of identifying TB. This is another reason the CDC does not recommend BCG: Both vaccination and infection cause positive skin tests. Anyone with a positive skin test is treated with antibiotics for 6 to 12 months. In patients with drug-susceptible TB, antibiotics prevent active, contagious TB from developing about 90 percent of the time.

The problem is, says microbiologist Barry R. Bloom of the Albert Einstein College of Medicine in New York City, "even *doctors* can't take their medicine that long." Indeed, the difficulty of getting TB-infected individuals to finish a complete course of therapy is one of the main reasons for the rise in MDR TB. When TB is only partially treated, just the most susceptible bacteria are killed; the remaining bugs can generate a drug-resistant strain.

In a study published in the March 2 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, CDC medical epidemiologist Alan B. Bloch reported that of 3,313 TB cases tested between January and March 1991, 472 (14.2 percent) were resistant to one or more drugs. Bloch also found that people with MDR TB were more likely than those with the drug-susceptible version to have tuberculosis bacteria in their saliva, making them more likely to spread the disease.

Bloom confirms in the June 16 NEW ENGLAND JOURNAL OF MEDICINE that MDR TB spreads more easily. "The premise of the whole [TB] policy — which I agreed with up till now — is that if someone does become skin-test positive, you can then treat it with one drug. That premise has completely collapsed with the rise of MDR TB," he says.

The CDC recently sponsored a review of 14 prospective trials and 12 case-control studies of the BCG vaccine. After analyzing these studies, Graham A. Colditz of the Harvard School of Public Health in Boston concluded that the vaccine protected just over half of those inoculated.

"It's on the lower end of efficacy [for a vaccine], but it still provides protection [for some people]," he says. "This shows us that BCG is effective, and we really need to reconsider where and if we use it in the U.S."

In 1988, CDC's Advisory Committee for Elimination of Tuberculosis recommended that the BCG vaccine be used only in children who did not test positive for TB but who were unavoidably exposed to the disease and could not be treated with preventive therapy. BCG was *not* recommended for use in health care workers or in adults at high risk of developing the disease.

The spread of TB can be limited in other ways. Early identification and treatment of people who develop positive skin tests is important, notes Lawrence Geiter, chief of the clinical research branch in CDC's department of tuberculosis control. Hospitals, prisons, and homeless shelters — places with high rates of TB transmission — can also prevent the spread of drug-susceptible and drug-resistant TB with improved ventilation, filtration and UV radiation of air, and early isolation of TB patients, he adds.

These steps, plus greater use of "directly observed therapy" (watching TB patients take their drugs) and involuntary detention for patients who would not otherwise take medication, led to a 15 percent decline last year in new TB cases in New York City, reports Steven J. Matthews, associate commissioner of the city's public health department.

"So long as these procedures are adhered to correctly and consistently, we believe there's no need for the use of BCG," he says, adding that "the analysis so far supports only further study."

Balancing the risk of MDR TB against questions of the vaccine's effectiveness and concerns about the risk of administering a live vaccine to people with weakened immune systems — those most likely to develop TB — is a knotty problem. The CDC hopes to issue new recommendations on the use of BCG sometime after late June, following a meeting of public health officials and vaccine experts.

BCG ought to be an option for people who are exposed to TB — especially MDR TB — on the job, says Bloom. "Whether BCG is 100 percent effective or 50 percent effective, it's still better than treating a drug-resistant organism with a drug that doesn't work," he says.

On the other hand, Bloom argues, "I don't think everybody in the country or even in New York needs [BCG]. . . . My hope would be that something better is developed in the next 5 to 10 years."

Researchers are working to develop new vaccines against TB. They are also tinkering with the BCG vaccine. And despite concerns about its effectiveness, BCG has many advantages. It has a long safety record and is the only live vaccine that can be given to children at birth. In addition, BCG triggers such a strong immune reaction that researchers are using it to boost the body's response to other vaccines.

BCG can be genetically manipulated to act as a carrier for vaccines against other diseases. For example, MedImmune, a biotech company based in Gaithersburg, Md., is beginning to test a BCG-Lyme disease vaccine in people and has already begun studies of a combined BCG-DPT (diphtheria, pertussis, and tetanus) vaccine in animals.

Use of these combined vaccines remains a long way off, but they may eventually affect the U.S. tuberculosis control strategy. "If you could vaccinate against many diseases in one fell swoop, would the advantages of BCG outweigh the disadvantages?" asks Geiter. "I don't know; we'll have to make that decision when and if we get there." □