



Texas Preventable Disease

NEWS

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contents:

Use of BCG Vaccines in the
Control of Tuberculosis

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USE OF BCG VACCINES IN THE CONTROL OF TUBERCULOSIS: A JOINT STATEMENT BY THE ACIP AND THE ADVISORY COMMITTEE FOR ELIMINATION OF TUBERCULOSIS*

Since 1979, when the last Immunization Practices Advisory Committee (ACIP) statement on vaccination with Bacillus of Calmette and Guerin (BCG**) was published, additional data have been published on the epidemiology of tuberculosis (TB) in the United States and on the efficacy of childhood BCG vaccines. As a result, ACIP and the Advisory Committee for Elimination of Tuberculosis have issued the following educational update on BCG vaccines.#

Immunization with BCG vaccine lowers the risk of serious complications of primary TB in children. However, BCG vaccination should be considered only for children with negative tuberculin skin tests who fall into the following categories: 1) those who cannot be placed on isoniazid preventive therapy but who have continuous exposure to persons with active disease; 2) those with continuous exposure to patients with organisms resistant to isoniazid and rifampin; or 3) those belonging to groups with exceptionally high annual rates of new infection (ie, greater than 1% per year).

INTRODUCTION

Transmission and Pathogenesis of TB

TB is a bacterial disease caused by organisms of the *Mycobacterium tuberculosis* complex (ie, *M. tuberculosis*, *M. bovis*, *M. africanum*). It is transmitted primarily by airborne droplets; infection occurs when susceptible persons inhale infectious droplets produced by the exhalations of persons with respiratory tract TB. The risk for infection is directly related to duration and intensity of exposure to air contaminated with these droplets. TB infection usually begins in the lungs and spreads to the hilar lymph nodes, then to the blood stream. Thus, disease can occur in any organ of the body. Most infected persons react to the purified protein derivative (PPD) tuberculin skin test, and 5%-40% will develop clinically apparent TB. Infection is more likely to progress to clinical disease in the presence of certain risk factors, including younger and older ages, male sex, infection within the past two years, leanness, and suppression of cell-mediated immunity.

TB can be presumptively diagnosed if acid-fast bacilli are found in sputum, body fluids, or tissue or if at least two of three other conditions are met: 1) symptoms are compatible with TB; 2) chest radiograph is abnormal or abnormalities are found on physical examination; or 3) reaction to the tuberculin skin test is positive. Definitive diagnosis requires isolation and identification of organisms of the *M. tuberculosis* complex from a clinical specimen. Diagnosis of extrapulmonary TB is more difficult because it requires tissue biopsies or body fluids (eg, spinal fluid) that usually contain only a few organisms.

Control of TB

There are four general strategies for controlling TB:

1. The most important and universally applied strategy is the early identification and treatment of persons with infectious TB. This strategy not only cures the affected person but also renders the patient noncontagious within a few weeks. Thus, case-finding and treatment programs have both clinical and public health benefits.
2. Identifying and treating persons with noncontagious TB (such as extrapulmonary disease, primary pulmonary disease in children, bacteriologically unconfirmed pulmonary disease, and

*Adapted from: MMWR 1988;37(43):663-4, 669-75.

**Official name: BCG Vaccine.

#Replaces previous recommendation on BCG vaccines (MMWR 1979;28:(241-4).

tuberculous infection) can prevent infectious cases. Therapy to prevent progression of infection to clinical disease is particularly useful in countries, such as the United States, where the risk of new infection is low.

3. Use of ventilation and ultraviolet lights will decontaminate air containing infectious droplet nuclei. Because sites of potential transmission of tubercle bacilli are numerous and difficult to identify in advance, this strategy is used routinely only where the risk of transmission is known to be exceptionally high. Some of these areas include mycobacteriology laboratories, sputum induction cubicles, chest clinic waiting areas, and selected shelters for the homeless. To be effective, ventilation systems and ultraviolet lights must be properly maintained.
4. In the United States, BCG vaccination is recommended only for uninfected children who are at unavoidable risk of exposure to TB and for whom other methods of prevention and control have failed or are not feasible.

BCG VACCINES

BCG was derived from a strain of *M. bovis* attenuated through years of serial passage in culture by Calmette and Guérin at the Pasteur Institute in Lille, France. It was first administered to humans in 1921. Many BCG vaccines are available worldwide; all are derived from the original strain but vary in cultural characteristics and in ability to induce sensitization to tuberculin. BCG vaccines vary because of genetic changes in the bacterial strains and because of differences in techniques of production, in methods and routes of vaccine administration, and in characteristics of the populations and environments in which BCG vaccines have been studied.

Production standards for BCG vaccines, set by the Food and Drug Administration, specify that they be freeze-dried products containing live bacteria from a documented strain of BCG. The strain must demonstrate various specified characteristics of safety and potency in animals and induce tuberculin sensitivity in guinea pigs and humans. The vaccines currently available in the United States have been evaluated only for their ability to induce a delayed hypersensitivity state.

Vaccine Efficacy Studies

BCG vaccines vary substantially in efficacy. Different preparations of liquid BCG used in controlled community trials conducted before 1955 gave estimated efficacies ranging from 56% and 80%. In 1969, a large controlled trial was begun in Madras (Chingleput) in south India to estimate the efficacy of two strains of freeze-dried BCG vaccine at two different doses. After 15 years of follow-up, the risk of sputum-positive pulmonary TB in persons vaccinated with BCG was not lower than that in persons given placebo.

Data from studies show that the incidence of tuberculous meningitis and miliary TB is 52%-100% lower and that the incidence of pulmonary TB is 2%-80% lower in vaccinated children less than 15 years of age than in unvaccinated controls. However, because vaccination is not allocated randomly in observational studies, disproportionate exposure to TB may distort the estimates of vaccine efficacy.

Side Effects and Adverse Reactions

BCG rarely causes serious complications. Side effects vary by vaccine strain; they also vary for the same strain over time. Side effects occur in 1%-10% of vaccinated persons and usually include severe or prolonged ulceration at the vaccination site, lymphadenitis, and lupus vulgaris. The risk of side effects is greater with more potent vaccines. Some vaccine strains have caused osteomyelitis in one case per million doses administered. Disseminated BCG infection and death have occurred in one to ten cases per ten million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity.

In persons with tuberculous infections, the response to BCG vaccine is accelerated. This accelerated response is generally characterized by the appearance of induration >5 mm in diameter within 24-48 hours after vaccination, formation of a pustule within 5-7 days, and scab formation and healing in 10-15 days. The normal response to BCG vaccine begins 2-3 weeks after vaccination. Scar formation and healing occur within 3 months.

Interpretation of Tuberculin Test Following BCG Vaccination

The size of tuberculin skin test reactions caused by BCG vaccination (ie, postvaccination sensitivity) varies by strain and dose of vaccine, age and nutritional status at vaccination, number of years since vaccination, and frequency of tuberculin testing. Mean size of skin test reactions in BCG-vaccinated children range from 3 mm to 19 mm. The presence or size of

post vaccination tuberculin skin test reactions does not reliably predict the degree of protection afforded by BCG.

After BCG vaccination, it is usually not possible to distinguish between a tuberculin skin test reaction caused by virulent mycobacterial infection or by vaccination itself. Therefore, TB should be included in the differential diagnosis of any TB-like illness, especially if the person has been recently exposed to a person with infectious TB or received BCG several years before being tuberculin tested.

General guidelines exist for interpreting tuberculin skin test reactions in BCG vaccine recipients. The probability that a skin test reaction results from exposure to *M. tuberculosis* increases 1) as the size of the reaction increases, 2) when the patient is a contact of a person with TB, especially if that person has infected others, 3) when there is a family history of TB or when the patient's country of origin has a high TB prevalence, and 4) as the length of time between vaccination and tuberculin testing increases. For example, a positive skin test (>10 mm) usually can be attributed to *M. tuberculosis* infection if the vaccinated person is in a group at high risk for TB or has known exposure to a person with infectious TB. However, in vaccinated persons who do not belong to groups at high risk for infection and have no known exposure, a positive skin test reaction probably does not indicate recent infection with *M. tuberculosis*.

GENERAL RECOMMENDATIONS

In the United States, the general population is at low risk for acquiring tuberculous infection. Furthermore, TB can be controlled successfully in most high-risk groups by modern methods of case detection, chemotherapy, and preventive therapy. In most population groups, prevention of TB is most reliably accomplished by periodic Mantoux testing with PPD tuberculin for high-risk children and adults and with administration of preventive therapy to those whose skin test reactions convert from negative to positive. Preventive chemotherapy should also be given to tuberculin-positive persons who are contacts of persons with infectious TB and to other high-risk tuberculin-positive persons. Therefore, a BCG vaccination policy for the entire population is not indicated. However, BCG vaccination may contribute to TB control in selected population groups. For example, it may benefit uninfected children who are at high risk for continuous or repeated exposure to infectious persons who remain undetected or untreated.

Recommended Vaccine Recipients

Exposed tuberculin skin-test-negative infants and children. BCG vaccination is strongly recommended for infants and children with negative tuberculin skin tests who 1) are at high risk of intimate and prolonged exposure to persistently untreated or ineffectively treated patients with infectious pulmonary TB, cannot be removed from the source of exposure, and cannot be placed on long-term preventive therapy, or 2) are continuously exposed to persons with TB who have bacilli resistant to isoniazid and rifampin.

Groups with an excessive rate of new infections. BCG vaccination is also recommended for tuberculin-negative infants and children in groups in which the rate of new infections exceeds 1% per year and for whom the usual surveillance and treatment programs have been attempted but are not operationally feasible. These groups include persons without regular access to health care, those for whom usual health care is culturally or socially unacceptable, or groups who have demonstrated an inability to effectively use existing accessible care.

Discontinued Recommendation for Health-Care Workers

In the past, BCG vaccine was recommended for health-care workers, who as a group experienced high rates of new infection. However, BCG is **no longer recommended** for this group. Instead, health-care workers should be protected by adequate surveillance by periodic tuberculin skin testing and isoniazid preventive therapy for all skin-test-positive health-care workers who are at high risk for developing disease. These persons include recent skin test converters and workers who are close contacts of TB patients or those who have medical conditions such as diabetes, renal failure, or immunosuppression associated with therapy or disease. In addition, hospital infection control measures, especially the prompt identification and implementation of precautions for patients with suspected TB, will help reduce the risk of TB transmission to health-care workers.

Vaccine Availability

Two BCG vaccine strains licensed in the United States are available. The Glaxo strain is available from Quad Pharmaceuticals, Inc., Indianapolis. The Tice strain is available from Bionetics Research, Inc., Chicago, or Antigen Supply House, Northridge, California.

Vaccine Dose and Administration

BCG should be reserved for persons whose skin test is negative to 5 tuberculin units of PPD tuberculin. The Glaxo strain is administered intradermally and the Tice strain percutaneously. Vaccination should be administered only by the route indicated in the package labeling and only in the suggested dose.

Infants <30 days old should receive one half the usual dose. If the indications for vaccination persist, they should receive a full dose at 1 year of age.

Freeze-dried vaccine should be reconstituted, protected from exposure to light, refrigerated when not in use, and used within 8 hours.

Contraindications to Use

BCG should not be given to persons 1) whose immunologic responses are impaired because of congenital immunodeficiency, HIV infection, leukemia, lymphoma, or generalized malignancy or 2) whose immunologic responses have been suppressed by steroids, alkylating agents, antimetabolites, or radiation.

BCG vaccine should be administered with caution to persons in groups at high risk for HIV infection. An AIDS patient was reported to have developed disseminated *M. bovis* disease after vaccination with BCG. Three infants with symptomatic HIV infection were reported to have developed BCG adenitis after vaccination; however, disseminated BCG disease has not been reported in persons with asymptomatic HIV infection.

Theoretically, persons with asymptomatic HIV infection may be at greater risk for complications from BCG vaccine, but data are inconclusive regarding this elevated risk. The World Health Organization has recommended that in populations where the risk of tuberculosis is high, HIV-infected children who are asymptomatic should receive BCG vaccine at birth or as soon as possible thereafter. BCG vaccine should not be given to children with symptomatic HIV infection. In populations where the risk of TB is low, BCG vaccine should be withheld from persons known or suspected to be infected with HIV. The latter recommendation would apply to most populations in the United States for whom BCG might be considered.

Use in Pregnancy

Although harmful effects of BCG on the fetus have not been observed, women should avoid vaccination during pregnancy.

SURVEILLANCE

All suspected adverse reactions to BCG should be reported to the manufacturer and to the Office of Biologics Research, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland. These reactions occasionally occur >1 year after vaccination.

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