Routine Childhood Bacille Calmette Guérin Immunization and HIV Infection

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(See the article by Hesseling et al. on pages 548–58.)

The safety of immunizing HIV-infected infants and children with live vaccines, including Mycobacterium bovis, bacille Calmette Guérin (BCG), was first addressed by the World Health Organization in 1987. The advisory group concluded that the benefits of BCG immunization for all children outweighed the risks among those with HIV infection, and the group recommended that routine childhood immunization be continued and that BCG vaccine only be withheld from infants with symptomatic HIV infection [1]. A 2004 World Health Organization review came to the same conclusion, adding that BCG-immunized infants of HIV-infected mothers should undergo long-term follow-up to monitor for possible adverse effects associated with BCG vaccine [2]. Two developments warrant reconsideration of these recommendations: the results of a study of BCG complications from South Africa published in this issue of the journal [3] and the identification of BCG-induced immune reconstitution inflammatory syndrome (IRIS) in children receiving antiretroviral therapy.

The benefits of BCG immunization were demonstrated in 4 controlled trials conducted among mycobacteria-naive newborns and infants, in which the collective rates of efficacy against disease and death due to tuberculosis were 73% and 87%, respectively [4–7]. Newer immunologic techniques help explain why trials that have involved older children and adults often showed lower efficacy or no efficacy. Contemporary in vitro techniques for detecting prior mycobacterial immunity have now shown that many adults have detectable in vitro responses to mycobacterial antigens, despite having negative results of skin tests for antigens derived from Mycobacterium tuberculosis and/or nontuberculous mycobacteria [8, 9]. Because trials that involved older children and adults relied on skin tests to exclude mycobacteria-experienced subjects, many subjects in these trials would have actually been mycobacteria experienced [10]. These subjects may either have had protection against tuberculosis equal to that provided by BCG vaccine and/or had sufficient immunity to prevent the replication of BCG [11], and their inclusion in the trial would therefore have reduced the apparent efficacy of BCG.

Whether the benefits of BCG vaccine also accrue in HIV-infected persons is not known. There have been no prospective studies of the benefits of routine childhood BCG immunization among HIV-infected children. Children with intrapartum or postpartum acquisition of HIV may still be capable of mounting a cellular immune response to BCG. Adolescents and adults with later acquisition of HIV may have persistence of some protection from childhood BCG immunization, but this would certainly be less than the minimal level of protection against adult pulmonary tuberculosis typically detectable among HIV-uninfected adults who received BCG vaccine at birth. Boosting childhood BCG vaccine with an inactivated mycobacterial vaccine in adulthood is a new strategy under investigation for providing protection against tuberculosis in both HIV-infected and HIV-uninfected adults [12].

After the efficacy of BCG vaccine had been demonstrated, most countries adopted routine immunization at birth. In areas of Europe where rates of tuberculosis have now decreased, BCG immunization is increasingly limited to high-risk children [13, 14]. The United States was 1 of 2 countries in the world that never adopted routine childhood BCG immunization for reasons that would no longer be valid: skepticism about its efficacy and concern about interfering with the tuberculin skin test (new in vitro tests with M. tuberculosis-specific antigens avoid this problem). Tuberculosis is now rare in the general population of the United...
States, and routine childhood BCG immunization would not be warranted. Unfortunately, however, existing US guidelines are still sufficiently restrictive, that BCG vaccine is not distributed in the United States and is not available for select high-risk groups of subjects who might benefit (i.e., health care workers who are traveling to areas where tuberculosis is highly endemic, children exposed to multidrug-resistant tuberculosis, and homeless persons and those in congregate settings at high risk of tuberculosis) [15, 16]. BCG vaccine can be obtained in Canada and Europe.

The risks of BCG immunization are attributable principally to the fact that it is a live, attenuated vaccine. Immunization leads to a usually asymptomatic but bacteremic infection. Within 8–12 weeks, a cellular immune response to mycobacterial antigens can be detected [17, 18]. Autopsy studies of BCG-immunized children who have died of other causes indicate that acid-fast organisms and granulomas are distributed widely in many organs [19]. The fact that disseminated BCG infection can occur years after immunization indicates that viable organisms may persist for long periods. The extent to which such persistence is required for maintenance of mycobacterial immunity in humans is not known.

Local adverse effects of BCG immunization may be strain related and include persistent drainage at the site in most vaccinees [20], vaccine site abscess or lymphadenitis in 4 of 10,000 persons [21] to 1 of 100 persons [22], and osteomyelitis in 3–73 of 100,000 persons [23]. These complications usually resolve without specific therapy in HIV-uninfected children [24].

Progressive and symptomatic disseminated BCG infection is rare, but it may be fatal in children who are immunocompromised. In the era before AIDS, disseminated BCG infection was noted in <1 person per 1 million vaccine recipients, and most affected children had an identifiable immunodeficiency (often severe combined immunodeficiency). BCG lymphadenitis has also been reported after administration of antilymphocyte antibody [25] and may be expected to be a risk after administration of other immunosuppressive drugs.

In recent years, disseminated BCG infection has been recognized in children with HIV infection. In this issue of Clinical Infectious Diseases, Hesseling et al. [3] report a hospital-based study from South Africa of 25 children with complications of BCG immunization [26]. Seventeen of these children had HIV infection, including 11 children who had local or regional sites of BCG infection and 6 children with BCG infection at 1 distant site. Some children with distant infection likely had disseminated infection (i.e., infection at 2 distant sites or 1 positive blood or bone marrow culture result), but data from blood cultures and/or autopsies were not available to confirm dissemination. Five of 6 children had CD4 cell percentages \(<12\%\), and the onset of BCG infection occurred at 3–20 months of age (most commonly at 9 months of age). All 6 children received antitycobacterial therapy, 1 received antiretroviral therapy, and 3 of 6 died within 1 month, possibly from BCG infection itself. The authors recommend 9 months of antitycobacterial therapy for HIV-infected children with complications of BCG immunization.

An important new complication of BCG is IRIS in HIV-infected children who are treated with antiretroviral therapy. Previous reports of this complication have either reported single cases [27] or have involved children in Thailand revaccinated with BCG [28]. The 4 children with IRIS in the report by Hesseling et al. [3] developed culture-positive ipsilateral lymphadenitis within 3 months after they started antiretroviral therapy. The CD4 cell percentage was \(\geq12\%\) in all 4 patients, all were treated with antitycobacterial therapy, and the 1 late death did not appear related to IRIS [3]. The report from Thailand documented lymphadenitis from IRIS in 3 (2\%) of 150 children immunized with Tokyo strain BCG and who started to receive antiretroviral therapy, but 2 of these children had received BCG vaccine boosters [28].

Because childhood immunization with BCG is universal in countries with high rates of HIV infection and tuberculosis, and because the availability of antiretroviral therapy for HIV-infected children is increasing in these same areas, additional reports of BCG-associated IRIS are likely. Prospective studies are needed to determine the rate of BCG-associated IRIS and to help assess whether antibiotic prophylaxis might be beneficial. If BCG-associated IRIS proves to be common among children who start receiving antiretroviral therapy, then studies should be conducted to determine whether administration of isoniazid during the first 6 months of antiretroviral therapy will reduce the rates of both IRIS and active tuberculosis among children. Administration of isoniazid would need to be delayed until at least 3 months after BCG immunization to avoid interference with bacterial replication and induction of a cellular immune response.

Hesseling et al. [3] also propose a revision of the Talbot case definitions [29] for children with complications of BCG immunization, separating local and regional syndromes, revising the category of distant disease, and adding BCG-associated IRIS. The revisions are useful and will help standardize future reports, improve our understanding and management of the different syndromes, and refine analysis of the risk-benefit ratio for BCG vaccine. Although the article by Hesseling and colleagues does not estimate denominators for the complications they describe with Danish strain BCG, it would appear that severe or fatal complications of BCG immunization are still uncommon. Thus, data continue to support World Health Organization guidelines for universal childhood BCG immunization in areas where HIV and tuberculosis are both endemic, along with new vigilance for the detection of disseminated BCG infection and BCG-associated IRIS.
References