editorial

Bacille Calmette-Guérin Vaccination in Saudi Arabia: Benefits versus Risks

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Tuberculosis (TB) continues to be a major health problem worldwide and Saudi Arabia is not an exception with a reported incidence of 18/100 000.[1] Bacillus Calmette Guerin (BCG) vaccine contains live attenuated *Mycobacterium bovis* and is the only available vaccine for TB disease since 1921.[2] There has been a long standing controversy surrounding its use and efficacy against TB with protective efficacy ranging from zero to more than 90%.[3] Neither the presence of the BCG scar nor TB test reactivity correlates with protection against TB.[4]

A meta-analysis of 12 randomized trials and 14 case-control studies showed an overall protective efficacy of 50%[5] with 56% protection against TB meningitis. Another meta-analysis that included five randomized trials on infants showed an overall protection efficacy of 74% with 78% for disseminated disease and 65% for prevention of meningitis.[6] Another analysis of randomized trials showed better protection for meningitis and miliary disease of 86% compared with pulmonary disease.[7] The most controversial aspect of BCG vaccine is the variable efficacy found in different clinical trials and that it appears to depend on geography. Trials conducted in United Kingdom showed a protective efficacy of 60% to 80%, but those conducted elsewhere have shown no protective effect and efficacy appears to fall closer to the equator.[8] The variability could be secondary to genetic variations in populations, BCG strains, and background exposure to TB. In addition to its low efficacy, BCG is associated with significant adverse effects including local ulceration at the vaccine site, lymphadenitis, osteomyelitis and disseminated disease, with variable frequency, with the most common being regional lymphadenitis, which has significant morbidity.

In this issue of the *Annals*, Al Rabiaah and colleagues attempted to study the frequency of BCG lymphadenitis at a referral hospital.[9] The study has clearly demonstrated an increasing rate of lymphadenitis from 1.96/1000 to 10.14/1000, which was associated with BCG SSI vaccine (Danish strain 1331)—this is definitely of concern. In the first component of the study, which was a retrospective chart review spanning 5 years (2002-2007), there were no cases except in 2006 and 2007 with an incidence rate of 0.76 and 1.96 per 1000, respectively. A prospective component of the study from 2008-2010 showed an increasing incidence rate from 4.30 to 10.14 per 1000. There is a possibility that some cases might have been missed in the retrospective part of the study; however, this would have been reflected throughout the retrospective part of the study including years 2006 and 2007 where cases started to be noted upon changing to the BCG SSI vaccine, which supports the idea that an increasing rate is real and not due to study design.

Another important complication, which was not addressed in this study due to the relatively small sample size, is the life-threatening disseminated BCG infection. This complication has been noted in children with primary immunodeficiency (PID) with an incidence rate of 0.06-1.59 cases per million vaccinated[10,11] and is usually associated with a high mortality of about 60%.[10,11] It is well established that severe combined immunodeficiency (SCID), chronic granulomatous diseases (CGD), complete DiGeorge syndrome (cDGS) and acquired immune deficiency syndrome (AIDS) predispose to disseminated BCG infection.[10,11-14] Such disorders account for about 50% of the cases of disseminated BCG.[10] The increasing number of disseminated BCGitis with more than two hundred cases described,[15,16] including cases from Saudi Arabia[14] are serious and warrant critical consideration.

The high rate of consanguinity in the Saudi population (56%)[17] predisposes to a high incidence of primary immunodeficiency disorders, making our population more vulnerable to BCG complications. Many cases of

disseminated BCGitis among severe combined immunodeficiency (SCID) patients and other immunodeficiency cases with significant morbidity and mortality have been seen in several hospitals in the Saudi Arabia. For example, in a single institution like KFSHRC more than 12 deaths secondary to disseminated BCGitis were encountered during the last few years, which complicated the management and stem cell transplantation of several SCID patients.

In Saudi Arabia there is no means to document cases of disseminated BCG infections. One study in the Eastern province showed that the incidence of SCID is 19 per 100 000 liver births, which is the highest incidence in the world and 20 times more than the incidence in European countries.[18] It is anticipated that disseminated BCG infection will parallel this rate since BCG vaccine is part of the routine vaccination of all newborns in the country. In populations with a high risk of SCID and at risk of TB, it is prudent to assess the benefits of BCG vaccine and the risk of disseminated BCG infections. Clark et al developed a Markov model to predict the benefits and risks of BCG among high-risk aboriginal infants in Canada who are at high risk of SCID. The model predicted that the risks outweigh the benefits if the annual risk of tuberculosis was 0.1% and the rate of SCID was higher than 4.2 per 100 000[19] Applying this model for Saudi Arabia will predict more risks than benefits since the TB rate in Saudi Arabia is 0.018% and the SCID rate is high.

Another disorder that predisposes to infection with BCG is the recently described Mendelian susceptibility to mycobacterial disease (MSMD) or online Mendelian inheritance in Man ID 209950 (OMIM 209950).[20] This is a rare genetic condition predisposing mainly to weakly pathogenic mycobacteria, such as BCG or environmental mycobacteria (EM) and non-typhoidal *Salmonella*. Those patients are also prone to *Mycobacterium tuberculosis* infection, but were apparently resistant to other infections. This syndrome is associated with mutations in the genes that control interleukin 12 (IL-12)/IL-23 dependent interferon gamma (INF-γ)-mediated microbial killing. Mutations in six genes result in 13 inherited conditions. These genes encode for the two chains of INF-γ receptor (INF-γ R_1 and INF-γ R_2), the signal transducer and activator of the transcription factor (STAT1), P40 subunit of IL12 and IL-23 (IL-12β) and β chain shared by the IL-12 and IL-23 receptor (IL12Rβ1) and the X-linked nuclear factor kappa B (NFκB) essential modulator (NEMO).[12,20-23] All of these conditions were identified after extensive study of patients presenting with "idiopathic" disseminated BCG infection from all over the world. Mycobacterial diseases in patients with complete interferon-gamma receptor deficiency (INFβR1) deficiency occur early in life and are usually severe and fatal[20] while mycobacterial infections in IL12β are often variable;[22] however IL-12Rβ deficient patients have a more favorable outcome with an overall survival of 70%.[23] There are increasing reports of these forms of immunodeficiencies that involve the IL-12/INFγ axis with the commonest reported being the the IL-12Rβ deficiency with 141 cases so far from 30 countries including 13 patients from Saudi Arabia.[23]

Added to the complications of BCG vaccine is the difficulty in treating disseminated *Mycobacterium bovis* infection since there is no standard evidenced-based regimen.[14,16,24] It is understandable that a countrywide survey that includes all complications associated with BCG vaccination will provide the best evidence of the magnitude of the problem. However, reports in the article give an alarming signal and call for the need to change the strategy of BCG vaccination, which may include decreasing the administered dose to 0.025 mL, which was proposed by the authors or changing to another vaccine product.

Based on available data on the BCG vaccine being a poor vaccine with low efficacy with serious complications and the high incidence of primary immunodeficiency disorders among Saudi children, it is wise to consider evaluating the need and efficacy of the BCG vaccine in our community or consider postponing BCG vaccination until 12 months of age. By this time most congenital immunodeficiency disorders have become apparent, so vaccination can be avoided.

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