PIDSP Journal, 2002 Vol. 6 No. 1

BCG: Revisited

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Tuberculosis (TB) claims approximately 2 million lives a year, almost 3 million if the estimate include individuals with HIV who die with active TB. In the Philippines, data from the Philippine Health Statistics in 1998 lists TB as the 6th leading cause of mortality and morbidity. Worldwide, the case fatality rate is 23% with a greater than 50% rate reported from some African countries with a high prevalence of HIV infection. Approximately 10% of immunocompetent individuals infected with *M. tuberculosis* will develop active TB some time in their lives.

BCG (live attenuated *Mycobacterium bovis* BCG) represents the only vaccine currently available against tuberculosis. This vaccine was developed by Calmette and Guerin in the early 1900s, by attenuation of virulent *M. bovis* via serial passage. In 1921, BCG was first administered per orem to a newborn whose mother died of TB and who was going to live with a grandmother suffering from the disease. This child throughout his life has remained free of tuberculosis. Between 1921 and 1927, reported mortality was higher among those unvaccinated compared to those highrisk children given BCG. Because of this, in 1928, the League of Nations recommended widespread vaccination with BCG. At present, it is the most widely administered of all vaccines in the WHO Expanded Programme for Immunization.

However, inspite of its extensive use, several studies have shown variability in its efficacy. In 1994 Colditz et al. did a meta-analysis of the efficacy of BCG involving 1264 published articles[4]. Results showed that 7 trials indicated a protective efficacy from death of 71%, five trials showed protection from meningitis of 64%, 3 studies, protection from disseminated disease of 78% and 3 protection from laboratory confirmed disease of 83%. Trials indicated that BCG is 80% protective in one place and 20% in another. Thus, the authors concluded that geographical site of the study explained 66% of variability.

Studies done in PGH on the protective efficacy of BCG against tuberculosis meningitis by Galicia in 1994 and against extrapulmonary/complicated tuberculosis by Javier et al. in 1996 revealed almost similar findings of BCG scar rate of 45.44% and 45% respectively[6,7].

Other reasons for variability are not fully comprehended. A number of theories have been put forward but none seem to provide a total explanation.

Reasons cited were:

1. Methodological. All studies varied slightly in the way they were designed.
2. Different vaccines. The original BCG was not cloned and distributed strains have been propagated throughout the world under varying conditions. This process has created a variety of related "BCG" vaccines that today have varying genotypic and phenotypic characteristics. These different vaccine strains were used in the trials and are in use across the world today.
3. Tuberculin status of subjects. In some trials, tuberculin status have not been considered. Some individuals in both control or vaccinated may have been tuberculin positive and therefore had "natural" protection.
4. Different strains of *M. tuberculosis*. It is possible that in different parts of the world have different strains of the bacterium which may vary in virulence. This has been demonstrated by new molecular techniques.
5. Genetic differences in population. There is variation in individual susceptibility to TB. This could have caused the disparity in results. In the United States, BCG is not recommended because studies have shown that it has no protective efficacy.
6. Intensity of infecting dose. Infection and susceptibility to disease may be affected by the quantity of bacteria inhaled.
7. Nutritional differences. It is known that different nutritional status can vary susceptibility to disease. The more malnourished patients, the more susceptible they are to TB.
8. Protection of controls by environmental mycobacteria. Free living mycobacteria which resembles *M. tuberculosis* sometimes cause disease. They may be responsible for infecting individuals therefore providing partial immunity to *M. tuberculosis*.

Citing these reasons, the question now is, "Is the efficacy of BCG waning?" Some authors (Behr, 1997) believe that it is[5]. This is because the BCG vaccine is continuously being reproduced as part of the

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Key words: Tuberculosis, clinical practice guidelines

manufacturing process which is common with other live vaccines that undergo this process. This may be a factor for the less virulent vaccine and therefore less able to provide immunity to those who are vaccinated.

But the importance of BCG can not be over emphasized. These findings in the variability in its efficacy has led to numerous researches in tuberculosis particularly in the development of potential vaccines namely: recombinant BCG vaccines, live attenuated strains of *M. tuberculosis*, nonpathogenic mycobacteria, non-mycobacterial microbial vectors, subunit vaccines and DNA vaccines. However, while TB vaccine development is underway and the issue of varying efficacy, should we abandon our current recommendation of giving BCG at birth? Most countries give BCG at birth to provide protection in the early years when infection can often lead to devastating widespread disease such as miliary tuberculosis or tuberculous meningitis. This is particularly important in high prevalence countries like the Philippines where the chance of being infected in very early life is high. Thus, so as not to add to the menace brought about by tuberculosis, giving of BCG at birth should be continued.

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