Problems with BCG Vaccination Program in Current Tuberculosis Control

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Abstract: The importance of BCG vaccination as a measure for tuberculosis control has traditionally been recognized in Japan. According to the current system, routine BCG vaccination is administered to infants of three and under, and to primary school and junior high school entrants. The overall BCG vaccination coverage rate among infants is estimated at approximately 97%, although the rates in certain prefectures are lower than 90%. This variation is attributable to differences in the policies of the local autonomies that are responsible for the BCG vaccination program, as well as to the technical level of tuberculin skin testing prior to BCG vaccination. The method of administering the BCG vaccination in Japan is the percutaneous method employing a multipuncture technique that has a drawback in its lack of technical uniformity. For example, the tuberculin positivity rate among primary school entrants who have been vaccinated in their infancy varies widely among prefectures, ranging from less than 30% to more than 70%. The speed of decline in the case rate of tuberculosis among Japanese infants is greater than that in Europe and the USA; Annual rates of decrease during 1976 through 1986 were 10% for 0–4 year olds in Japan, 11% for 5–9 year olds, and 4% for all ages, with the corresponding figures for the US being 5%, 4% and 6%, respectively. These figures may suggest the overall effectiveness of the BCG vaccination in Japan, however, the revaccination as currently practiced in Japan is considered to be of extremely limited effectiveness, if any. We therefore consider it necessary to maintain a higher coverage of the primary vaccination for the time being and higher quality standards in the vaccination technique.

Key words: BCG vaccination; Tuberculin test; Tuberculosis control program

The tuberculosis control program is a controversial issue in Japan because of the re-emergence of the disease in epidemics and in this situation, the necessity of reconsidering the tuberculosis control program has been indicated. Much attention has been focused on the policy of Directly Observed Treatment, Short course (DOTS) the core of which is intensive

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case management to ensure regular drug taking by patients. This policy has been adopted as a standard tuberculosis program strategy throughout the world, in both developing and developed nations. The remarkable progress in the treatment program in developing countries has even provoked enthusiastic discussion over the possibility of introducing individualized treatment for drug resistant tuberculosis based on the results of drug sensitivity testing (DOTS plus), which was effectively a dream for such nations until recently.

As is well known, a large-scale field trial on the efficacy of BCG vaccination conducted in South India during the late 1960s through the mid-70s produced negative results. This sent shock waves throughout the world in the 1980s, and gave rise to the subsequent controversy over BCG, however, in recent years, the controversy appears to have abated. When Indian researchers reported the results of the study in 1978, some TB experts were extremely satisfied with the results, whereas others were highly embarrassed, and heated debate continued between the two groups for many years thereafter. In the 1990s, a surge in the incidence of TB in the USA and other developed countries accompanied by increases in drug resistant TB and the nosocomial outbreak of TB again led to a discussion of the efficacy of the BCG vaccination. In 1996, Centers for Disease Control and Prevention (CDC), USA, concluded that the BCG vaccination was effective, although its necessity was limited given current circumstances in the USA.[1)] This conclusion was based on the results of meta-analysis, a mathematical methodology that was developed comparatively recently and which has gradually come to be accepted as a useful method of analysis.

On the other hand, tremendous efforts are being made to develop novel vaccines superior to BCG, exploiting new biomedical technologies. The author will review the problems with the BCG vaccination program as a measure of tuberculosis control in Japan in light of the current tuberculosis problem and its control together with a discussion of its related problems and prospects for the near future.

Current Conditions of Implementation of Mass Vaccination and Issues of Technical Assessment

Under the existing scheme, the BCG vaccination (the periodic vaccination) is administered to infants of three years and under (infants are advised to receive BCG vaccination as early as possible after the age of three months). BCG revaccination is to be administered to first-grade primary school and junior high school students (second-grade students who were vaccinated in the previous year may also be vaccinated again). Only those who have a negative reaction to a tuberculin test are eligible for BCG vaccination or revaccination.

In addition to the issues pertaining to the BCG vaccination technique, which is an unavoidable part of the percutaneous vaccination method, the tuberculin test also presents technical problems. Thus, the BCG vaccination program is unique in terms of the need for quality assurance and assessment. Accordingly, we need to be more careful in shifting from the mass vaccination system to the system of vaccination on an individual basis.

1. BCG vaccination coverage and area differences

The nationwide BCG vaccination coverage rate has been maintained at levels near 100%, and was 97.3% for 1997, according to a rough estimate based on the total number of infants who received BCG vaccination divided by the total number of births within a year. This high level of coverage may be maintained via the widespread adoption of the mass vaccination system, even after the introduction of the new vaccination program where a system for individual vaccination is being encouraged for other vaccines. However, prefectural variations in the coverage are apparent as shown in Fig. 1.

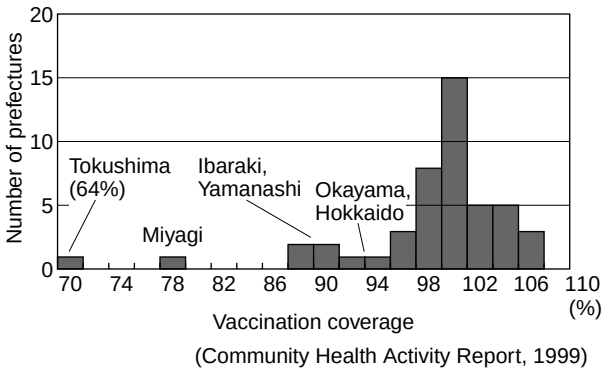

Fig. 1 Distribution of prefectures by BCG vaccination coverage among infants (1997)

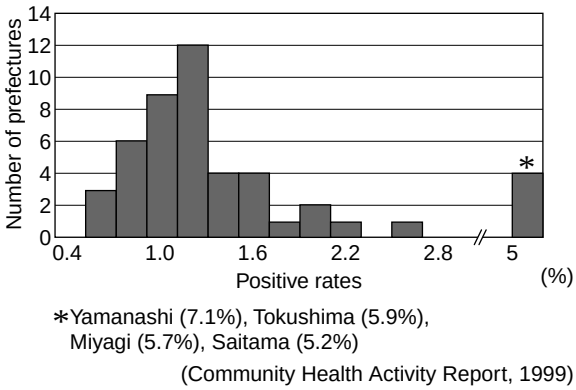

Fig. 2 Distribution of prefectures by tuberculin positive rate of unvaccinated children (1997)

In many prefectures the coverage rate is almost 100% (in some areas it exceeds 100% due to the estimation formula), whereas there are prefectures with rates of around 90%, or even with rates as low as 80% (Fig. 1). In view of the existence of prefectural disparities in BCG vaccination coverage, wider differences may be seen at the levels of public health centers, and municipalities (cities, towns and villages).

This gap in BCG vaccination coverage among areas is mainly attributable to differences in the policies adopted by municipalities including cities, towns, and villages, including methods of public relations, actions taken to address non-attenders, the number of opportunities for mass BCG vaccination in a year, and the accessibility of the sites for mass vaccination. Furthermore, attention needs to be directed to the tuberculin skin testing technique, which is conducted prior to BCG vaccination.

Figure 2 gives the distribution of prefectures according to the tuberculin positivity of the infants tested prior to the vaccination. The national positive rate is 1.4%, which is considered reasonable, whilst conceding that most of the positive tests are so-called false positive reactions. However, some prefectures report figures as high as 5% or more. There are two possible causes for this abnormally high positive rate. One is a technical problem in the testing, specifically, over-reading reactions, such as reading intra-dermal or subcutaneous bleeding due to injection as erythema. The other cause is that tested subjects are older in relative terms, i.e., including those aged two or three years of age. The tuberculin tests given to these "older" infants are more likely to produce "non-specific" reactions than those given to young infants, which may inflate the positive rate.

2. Variations in the technical level of tuberculin testing

According to the report of the tuberculin test results in infants by the Okinawa Branch of the Japan Anti-Tuberculosis Association, an association considered to have a very high technical level of testing, infants under one year who had erythema measuring 10 mm or more in diameter accounted for 1.0% of those tested, while the proportion for those aged one, two, and three years was 2.1%, 4.2%, and 7.1%, respectively. Since the prevalence of tuberculosis infection among these infants is estimated to be less than 0.1%, so-called "positive" tests in these age groups are considered to be mostly false positive reactions. Infants who have a "positive" reaction to the test are referred to a further examination that includes X-ray and tuberculin re-testing. As a result, some of them can be given chemoprophylaxis without any certain evidence of tuberculosis infection.

Because BCG works by conferring immunity

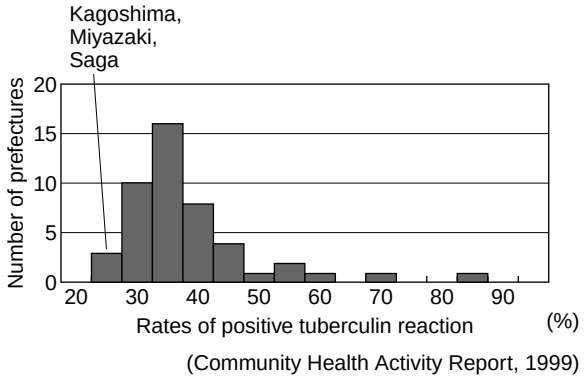

Fig. 3 Distribution of prefectures by tuberculin positive rate of primary school entrants (1997)

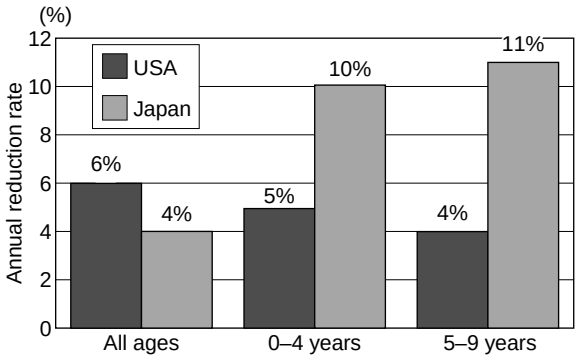

Fig. 4 Comparison of speed of decline in tuberculosis case rates, Japan and USA (All forms of tuberculosis, 1976–1986)

to those not previously infected, and because older infants have false positive reactions to the tuberculin test more frequently, earlier tuberculin testing followed by BCG vaccination is commonly recommended for infants, ideally before they reach the age of one. Regarding improvements to the tuberculin test technique the ultimate remedy would be for physicians to gain skill through experience under proper guidance and self-assessment. In some areas, only specific doctors with sufficient experience are assigned to tuberculin testing in order to secure a higher degree of technical skill.

3. Variations in BCG vaccination technique

Variations in BCG vaccination techniques is the next issue. The most serious problem with the current percutaneous vaccination method is the difficulty in securing technical uniformity, particularly uniformity in the pressure applied on the needled plunger piercing the skin. The most reliable method of technical assessment is to perform a post-vaccination tuberculin test, but for practical reasons it is also recommended to observe the local reaction at the site of vaccination. To this end, it is useful to count how many needle scars out of a total of 18 are left on the skin at 6 months after vaccination.

Within the scope of the current routine scheme, the technical level of the BCG vaccination for infants can also be assessed by observing the tuberculin reactions at the time of entry to primary school. Fig. 3 gives the distribution of prefectures by the tuberculin positive rates of first-grade elementary school students. The national positive rate was 39%. The rate was high in prefectures such as Okinawa (81%), Hokkaido (65%) and Miyagi (58%), while it was particularly low in Kagoshima (22%), Miyazaki (21%), and Saga (25%). These data demonstrate the existence of remarkable inequality in the technical level of vaccination across Japan. The reduction of such technical gap will have a significant impact on the future prospects for the BCG vaccination program, as discussed below.

Controversy Over the Effectiveness of the BCG Vaccination Program

As mentioned above, the controversy over the preventive efficacy of the BCG vaccination against tuberculosis appears to have diminished around the world. In Japan, a case-control study conducted by Takamatsu *et al.*[2] demonstrated the significant efficacy of the BCG vaccination. Moreover, a comparative study of the trends in age-specific tuberculosis case rates in Japan and the USA, where BCG vaccination is not practiced, also supports the BCG efficacy of Japan (Fig. 4). Before the reversal in tuberculosis case rates in both Japan and the USA, the rate of

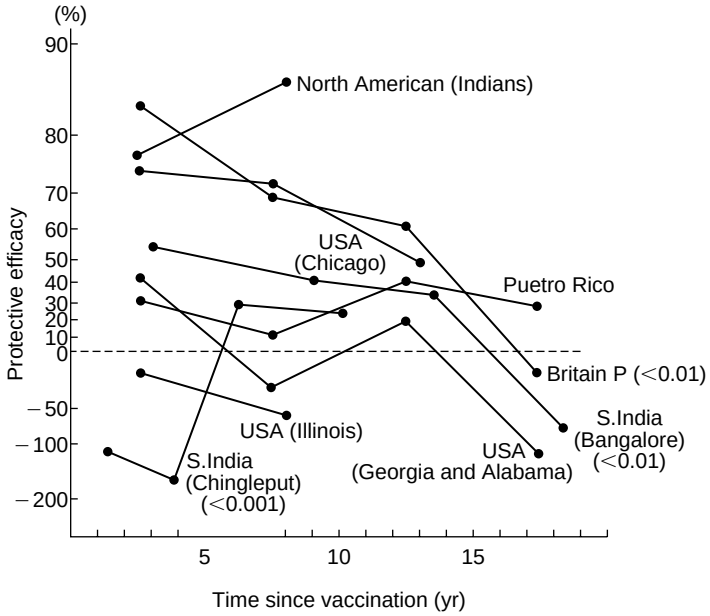

Fig. 5 Changes in protective efficacy of BCG against tuberculosis over time since vaccination, in randomized controlled trials. (p values refer to changes in efficacy over time in the years studied. No p value signifies no significant change.) (Smith PG)[3)]

decline for all ages was faster in the USA, however, it was clearly faster in Japan for infants and children. The Japanese infants' superiority can also be seen in the absolute value of the case rate. This comparison is more remarkable when it comes to comparing the rate for adults; that for Japan is several time higher than that in the USA. It should be borne in mind that this BCG efficacy is limited to the infancy and childhood, as is demonstrated in the findings from overseas studies and from the work of Takamatsu *et al.* as well. According to a famous field trial conducted in the UK, BCG vaccination efficacy lasts for 10 to 15 years after the vaccination, which fact has been confirmed by other observations (Fig. 5).

The efficacy of revaccination with BCG presents another issue. This argument is highly relevant to the issue of the revaccination scheme for primary school and junior high school entrants discussed in Section 3, and also to the vaccination for health care providers in the nosocomial tuberculosis prevention program.

The latter case has a unique problem in that it concerns the vaccination of a population the majority of whom previously received vaccination more than 10 years ago, and the protective efficacy of the former vaccination is supposed to have already waned. The efficacy of the BCG vaccination for adults, young adults or adolescents in particular, has been well established by a BMRC trial in which BCG given at around the age of 14 years was shown to be potent for a period of 15 years. The problem originates from the possibility that the residual immunological effect of the previous vaccination may interfere with the subsequent vaccination, to result in a reduction in the expected efficacy. It is therefore suspected that the subsequent vaccination cannot induce the same degree of efficacy as that due to the primary vaccination. These doubts can only be dispelled by the implementation of clinical trials. This type of randomized controlled trial on the efficacy of BCG revaccination among nurses is in progress at the National Kinki Central Hospi-

tal and others. Once the results of these trials are reported, or in the event that any other strong epidemiological evidence becomes available, we will have to deal with the tuberculosis risk among young nurses which is more than double that of the general female population, using BCG vaccination as one of the emergency options. This is the recommendation of the recently published guidelines "Guidelines for Preventing Nosocomial Transmission of Tuberculosis.[4)]

Future Prospects

The future prospects for the BCG vaccination policy, including the possibility of its total abolition, have been the subject of much debate recently. The decision as to whether to abolish the BCG vaccination is dependent on what levels of infantile tuberculosis victims will be acceptable, in exchange for the pay off in costs and adverse reactions. To date, there has been no argument for discontinuation based on such considerations. At the same time, the introduction of an alternative means of complimenting the policy should also be considered.

Aside from the issue of primary BCG vaccination for infants, the revaccination of primary school pupils was recently discussed by the Tuberculosis Control Panel of the Public Health Council; There were two pressing reasons for this discussion. First, it was suspected that the benefits of revaccination under the current scheme would be very limited, even admitting the efficacy of revaccination itself. Second, the need to do more to address the problem of the strong local reaction due to Koch's phenomenon, which sometimes causes keloid formation, following revaccination. There has been a marked increase in the incidence of this adverse reaction after the revision of the scheme in 1995 to expand the target population for revaccination so that individuals with erythema measuring 5–9 mm in diameter were included in addition to those with erythema measuring 0–4 mm.

The Panel reached the following conclusion: Besides its prophylactic role, the current revaccination system is considered to play an important role in providing opportunities for those who have failed to acquire sufficient immunity to TB due to poor vaccination technique or who missed the vaccination. Therefore, the argument for discontinuation of BCG revaccination should be made having given sufficient consideration to this factor. Based on this conclusion, the establishment of a system of technical assessment of the infantile primary vaccination was recommended.

As mentioned in Section 1, the actions to be taken by the government are clear. They should include the implementation of technical training for the physicians responsible for tuberculin skin testing and BCG vaccination, appropriate technical assessment with feed back, and appropriate action for those individuals who were insufficiently vaccinated. All these actions should be incorporated into a new BCG vaccination program. This concept was not clearly recognized in the former program. One exception was the program for BCG assessment of the Yamagata prefectural government that was implemented with the cooperation of both the local medical association and the local school health authority during the 1980s.[5)] This important local experience should become a model for the establishment of a country-wide technical assessment system for BCG vaccination.

The issue of the recent incidence of straight forward technical errors in tuberculin testing and BCG vaccination requires serious attention. For example, there are still cases of incorrect vaccination with only one percutaneous shot instead of the required two shots. Unnecessarily strong action is taken for those who have a false positive reaction to tuberculin tests. Also, inappropriate treatment procedures are often used for the local reactions and the axillary lymph node swelling following BCG vaccination. Recently, the Japan Anti-Tuberculosis Association produced an educational video to be used for training in the BCG vaccination

technique and the proper treatment of these reactions.[6)]

In 1998, a total of 275 children aged from zero to 14 years developed tuberculosis, including three cases of meningitis. This apparently low figure is credited to the BCG vaccination however, there have been steady increase in the number of infection sources to which children are being exposed. Japan uses the BCG vaccination as one of the measures for protecting children from tuberculosis. There is still room for further efforts to increase the effectiveness of this measure, and to develop other preventive measures as well.

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