Invited Review

Historical Review of BCG Vaccine in Japan

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SUMMARY: Bacillus Calmette and Guérin (BCG) was introduced to Japan in 1924 by Kiyoshi Shiga and has been propagated for research purposes ever since propagation is accomplished using a glycerin-bile-potato mixture in the same manner used by Calmette and Guérin. To prepare a stable and safe freeze-dried BCG vaccine, several joint research projects were organized in 1949. At the National Institute of Infectious Diseases (formerly the National Institute of Health), the 172nd passage of BCG from the first culture was freeze-dried in 1961 and was used as the origin of the Japanese BCG strain, Tokyo-172. The Tokyo-172 was registered as an International Reference Strain in 1965 by the World Health Organization. In 1967, a multiple puncture method for BCG vaccination using a plastic cylinder implanted with nine fine needles at one end was introduced to Japan; thereafter, percutaneous administration replaced intradermal injection. The efficacy and adverse reactions of BCG vaccines as well as recent knowledge on the genetic characterization of BCG is also discussed.

1. Introduction

Tuberculosis (TB) is a pandemic disease that represents a major public health and economic problem throughout the world. Mycobacterium tuberculosis, the causative agent of TB, is estimated to have infected nearly one-third of the world’s population, with an annual incidence of approximately eight million and two million tuberculosis from deaths each year.

Robert Koch (1843-1910) first discovered M. tuberculosis in 1882; his discovery prompted numerous lines of research to create prophylactic and therapeutic vaccines against tuberculosis. In 1908, Albert Calmette (1863-1933) and Camille Guérin (1872-1961) at the Pasteur Institute in Lille, France, started working with a virulent strain of Mycobacterium bovis that had been isolated by Edmond Nocard (1850-1903) from a cow with tuberculosis mastitis. Calmette and Guérin subcultured the organism every 3 weeks on potato slices cooked in beef bile, supplemented with glycerol. In 1921, after 230 successive passages over the course of 13 years, they found that the resulting culture was stable to reversion to virulence but retained limited invasiveness in experimental animals. The first human vaccination using this attenuated strain, named the bacillus of Calmette and Guérin (BCG), was applied to a newborn whose grandmother had pulmonary tuberculosis in Paris in 1921. The BCG vaccine was adopted by the Health Committee of the League of Nations in 1928, and the mass vaccination of children was begun and was adopted by many countries, after newer and safer production processes were implemented. Since then, more than one billion children throughout the world have been vaccinated.

2. BCG vaccine in Japan

2-1. Freeze-dried vaccine

The BCG strain, which was donated by Calmette himself, was brought to Japan by Kiyoshi Shiga (1890-1957), one of the discoverers of the dysentery bacillus, in November 1924. The strain was maintained and utilized for research by Professor Imamura at Osaka University, while Professor Sato was charged with the maintenance of the strain at the Institute for Tuberculosis (RIT) of the Japan Anti-tuberculosis Association in 1940, where Ken Yanagisawa was charged with the monthly propagation of the strain using a glycerin-bile-potato medium. In 1947, the strain was transported from RIT to the National Institute of Infectious Diseases (NIID) (formerly known as the National Institute of Health [NIH]) and was maintained in the same manner as that used by Calmette and Guérin. The BCG strain has been utilized for the production of vaccine and for research ever since.

Tuberculosis became endemic in Japan after World War II as a result of social confusion and the critical status of national sanitation programs. Consequently, the mortality rate of tuberculosis increased to more than 250 per 100,000 population, peaking among individuals aged 25 to 29 years. Accordingly, a BCG vaccination program was considered an urgent priority, and a safe, stable and reliably potent vaccine—such as a freeze-dried form—was needed. Research on a freeze-dried BCG vaccine had begun in Japan in 1943, and the mass production of dried BCG vaccine was initiated in 1947. BCG vaccination using the freeze-dried vaccine became compul-
sory under the Immunization Law in 1948 for all tuberculin-negative individuals aged 25 years or under. Subsequently, BCG vaccination emerged as a national policy for the control of tuberculosis; since 1949, the usage of all freeze-dried BCG vaccine has required official approval by the NIH in Tokyo.

In 1961, the 172nd passage of BCG from the first culture was freeze-dried and selected as the origin of the Japanese BCG strain, Tokyo-172. This lot has been kept at the NIID. Tokyo-172 was registered as an International Reference Strain in 1965 by the World Health Organization (WHO). Thereafter, commercial laboratories began producing and distributing the BCG vaccine nationwide and also internationally, after in-house and national assessments. Today, only the Japan BCG Laboratory produces BCG vaccine in Japan. In 1951, BCG vaccination was enforced by the Tuberculosis Prevention Law so that all persons under the age of 30 years and employees of all of ages were required to be vaccinated intradermally if they exhibited a negative to tuberculin reaction. In 1974, the Tuberculosis Prevention Law was revised so that all infants and children under the age of 4 years were primarily vaccinated and all 1st grade students of elementary school or junior high school were revaccinated if they exhibited a negative tuberculin reaction. The Tuberculosis Prevention Law was further revised in 2003 so that only infants under the age of 6 months are primarily vaccinated, and no tuberculin tests have been conducted since then. The Tuberculosis Prevention Law was integrated into Infectious Diseases Prevention Law in 2007.

2-2. Percutaneous administration

In Japan, although intradermal BCG vaccination successfully achieved high tuberculin conversion rates, complaints of side reactions—mainly local lesions like ulcers, abscesses and ugly scars—mounted up to such an extent that an improved vaccination method was urgently requested. After more than 10 years of cooperative studies examining percutaneous BCG vaccination, a multiple puncture method using a plastic cylinder implanted with nine fine needles at one end was finally chosen in 1967. Thereafter, the multiple puncture vaccination method completely replaced intradermal injections in Japan. Local lesions noticeably decreased, both in intensity and duration, compared with those produced by intradermal vaccination.

To produce the vaccine, an ampoule containing 80 mg, 40 mg or 12 mg of dried BCG is reconstituted with 1.0 mL, 0.5 mL or 0.15 mL of physiological saline, respectively. A drop of suspended vaccine with a concentration of 80 mg BCG per mL is spread over an area about 15 × 30 mm in size on the upper arm; then, two strong pushes are separately made using the needle-implanted cylinder, producing a total of 18 punctures. The intensity of the skin punctures was found to be correlated with the tuberculin-positive rate and the appearance of local lesions following vaccination. The viability of the vaccine was also correlated with the tuberculin conversion rate and the mean size of the tuberculin reaction 1 month after vaccination: an 80% positive rate and a tuberculin reaction with a mean size of 15 mm would be expected when a vaccine with 15 million culturable particles in 1 mg of BCG was used, and a 60% positive rate and a mean size of 12 mm would be expected for a vaccine with a 10 million viable count. Although small pustules and crusts were induced by the multiple puncture method at 1 month after vaccination, hypertrophic scars—particularly ugly keloids—were relatively infrequent (less than 1%), even after revaccinations using the new puncture method because most of the pustules healed leaving tiny flat and sometimes depigmented slight scars. Lymph node involvement almost did not occur. A total of 114 newborn babies in a maternity hospital were vaccinated using the multiple puncture method and were followed for 1 year; an 89.5% tuberculin-positive rate and a reaction diameter of 14.0 mm was obtained 1 year after vaccination in this cohort, with only one case of lymph node swelling. The swollen lymph node was about the size of a soybean and was observed 3 months after vaccination; however, the swollen lymph node was no longer palpable after 6 months. The formation of keloid was not reported as a troublesome side reaction in this series, and the scars had disappeared in 40% of the vaccinated infants 1 year after vaccination. These results suggested that newborn babies could be easily and effectively vaccinated using a needle-implanted cylinder and percutaneous dried BCG vaccine made from the Japanese BCG strain (the multiple puncture method) without troublesome side reactions.

3. Vaccine production

The tuberculosis mortality rate, which had been the leading cause of death in Japan for several years, decreased steadily after the war from over 200 per 100,000 population in 1951 to half that rate and falling as low as 1.8 per 100,000 population in 2004, to become the 25th leading cause of death in Japan. The reduction in the mortality rate was most dramatic among younger age groups.

Freeze-dried BCG vaccine is one of the most beneficial achievements of medical science in Japan. The purpose of BCG vaccination is to provide resistance to tuberculous infection in the form of cellular immunity; this has been shown to be induced most effectively using living BCG, but not dead bacilli, in humans. Therefore, each dose of BCG vaccine should contain as many viable organisms and as few dead bacilli as possible to ensure a high potency. To perform the necessary basic and applied studies on freeze-dried BCG vaccine and its administration, several joint research projects have been successively organized since 1949 to concentrate on the production, control and vaccination method for the dried vaccine.

These research teams performed a joint study on the correlation between viable numbers of dried BCG vaccine preparations and the tuberculin conversion rate following intradermal vaccination after completing a pilot field study that had indicated a positive correlation. The researchers found that the tuberculin conversion rate at 1 and 3 months after inoculation was well correlated with the number of injected viable units. On the basis of these results, they concluded that one dose of BCG vaccine should contain as high a number of viable bacilli and as few dead organisms as possible to increase the vaccine’s immunizing ability. With this in mind, the researchers concentrated their efforts toward the mass production of dried BCG vaccine so as to achieve the highest proportion of viable bacilli in 1 dose of BCG vaccine as possible and to maintain this level of viability until inoculation. The joint research projects exploring these production objectives concentrated on the following points.

Resistance of young BCG cultures to freeze-drying: To improve the viability of the freeze-dried BCG vaccine, the sensitivity of growing BCG to the freeze-drying process was examined. As a result, younger cultures in the logarithmic growth phase were found to be highly resistant to the freeze-drying process, compared with cultures in the stationary
Phase—during which large quantities of bacterial mass were being harvested to prepare the liquid BCG vaccine. When younger Sauton cultures of 8 or 9 days were used for the mass production of vaccine, the potency of the Japanese freeze-dried BCG vaccine improved. The dried vaccine produced from the younger BCG cultures was found to have a superior immunizing potency in humans. In addition, the Japanese strain of BCG (Tokyo 172) was shown to be considerably more resistant to freeze-drying, compared with other BCG strains used in various countries.

**Addition of preservatives to the dried BCG vaccine to protect viable bacilli from freeze-drying:** The discovery that sodium glutamate could be used to produce heat-stable, freeze-dried BCG vaccine in place of sucrose or lactose was a remarkable advance in stabilizing the potency of freeze-dried BCG vaccine. BCG vaccine can remain sufficiently viable when stored at 5°C for 2 years or even at 37°C for 4 weeks, with typical survival rates of over 50%. Thus, dried glutamate BCG vaccine can be transported and used even without refrigeration for short periods of time, even in tropical environments. The effect on the allergenic potency of storing dried sucrose or glutamate BCG vaccines at 5°C or 37°C was compared. When both vaccines were stored at 5°C, the resulting tuberculin allergy was similar. However, when the two vaccines were stored at 37°C for the same period of time, the allergy induced by vaccination with the glutamate vaccine was much stronger.

**Moisture content of dried BCG vaccine:** The storage of dried BCG vaccine for long periods of time, even at low temperatures, requires a low moisture content in the freeze-dried powder. The optimal moisture content for living BCG organisms to survive in mass-produced vaccines in Japan was less than 3%, as measured using the Aberhalden method. At higher moisture contents, the dried vaccines lost their viability more rapidly, especially at higher temperatures. Dried glutamate BCG vaccine with a moisture content of less than 3.0% could be maintained at a satisfactory level of viability at 5°C for 2 years and at 37°C for 1 month. During the freeze-drying process, the BCG vaccine can be heated up to around 37°C in vacuo to reduce the residual moisture to less than 3.0%. For freeze-dried BCG vaccine intended for vaccination using the multiple puncture method, which requires a high bacterial content of 12, 40 or 80 mg per ampoule, a higher moisture content may be recommended for the preparation of vaccines with a high viability and sufficient stability during storage.

**Protection of dried BCG vaccine from sunlight:** BCG is essentially sensitive to both direct and indirect sunlight. Viable BCG in both liquid and freeze-dried vaccines is killed by sunlight within a short period of time: the viability decreases to 1/15 in 60 min in reconstituted BCG vaccine and to 1/10 in 60 min in dried BCG vaccine. Therefore, the interior of the vaccine production facility should not be exposed to any sunlight. To prevent the exposure of the dried vaccine to sunlight during transport or at the vaccination clinic, the vaccine should be either covered with black paper or sealed in brown-colored ampoules. These countermeasures can successfully prevent the harmful effects of indoor daylight on reconstituted BCG vaccine. Although the effect of sunlight on freeze-dried BCG vaccine seems to be comparatively mild, its bactericidal effect was much more obvious in the reconstituted BCG suspension if it was not protected.

**Necessity of vacuum-sealing of vaccine ampoules:** Since normal air pressure has been found to harm the viability of dried BCG vaccine, the vaccine container must be sealed under a high vacuum for maximum viability. The replacement of air with dried nitrogen has been useful for maintaining viability. The viability of freeze-dried BCG decreases very rapidly under normal air pressures, even when stored at 4°C. Consequently, sealing freeze-dried BCG vaccine ampoules in vacuo is indispensable.

**Procedure for freeze-dried BCG vaccine production:** At the BCG production laboratories, the Tokyo 172 strain is used in a seed lot system to transfer the BCG culture to a Sauton medium for vaccine culturing. The second Sauton culture is usually harvested after 7 to 10 days. After washing with the suspension fluid, the dehydrated bacterial mass (approximately 70% moisture content) is homogenized in a round flask containing crystal or stainless-steel balls rotating at a high speed. The moist bacteria is triturated homogeneously, and suspended in a solution of sodium glutamate at not higher than 15 w/v% to make the moist bacterial concentration to 80 mg/mL to serve as the final bulk. The final suspension is dispensed into brown-glass ampoules in aliquots of 0.15 mL, 0.5 mL or 1.0 mL, depending on the desired doses, prior to pre-freezing. The freeze-drying is carried out in a chamber-type freeze-dryer at freeze-dried and hermetically at a pressure not higher than 13.3 Pa. After being taken out of the freeze-dryer, the dried ampoules are handled under precautions against moisture absorption and contamination and are then sealed hermetically. Suitable numbers of ampoules extracted at random from the final products are submitted by lot to in-house and national assessments before use.

**Characteristics of the Japanese freeze-dried BCG vaccine:** The freeze-dried BCG vaccine produced from the Tokyo 172 strain has a high potency in humans, as demonstrated by the size of the tuberculin reaction and the local lesion. However, the Japanese strain has been reported to have a lower residual virulence and a weaker immunogenicity. Since the Japanese strain characteristically has a much higher viability before and after freeze-drying, compared with other strains, the weaker antigenicity of the living vaccine might have been supplemented quantitatively by the relatively high number of living bacilli present in the vaccine at the time of vaccination. In addition, the Japanese freeze-dried BCG vaccine generally produces less lymph node involvement, probably because of the reduced residual virulence. As vaccines for human use should be evaluated with regard to both efficacy and side reactions, the Japanese freeze-dried BCG vaccine is considered to exhibit favorable characteristics.

**4. Quality control**

Extracted samples of bulk BCG suspension prior to freeze-drying and ampoules of freeze-dried BCG vaccine representing each lot are submitted to the National Institute of Infectious Diseases for national quality-control checks, in addition to in-house assays by the manufacturer in accordance to the Minimum Requirements for Biological Products (Ministry of Health, Labour and Welfare, Japanese Government). The crude bulk BCG suspension is subjected to a guinea pig test to ensure the safety of the vaccine and the absence of virulent mycobacteria. Control tests on the freeze-dried BCG vaccines, including the above-mentioned safety test, were first established in 1949 in Japan and include the following tests. Freeze-dried BCG vaccines have been examined using this national assay for almost 60 years.
Color and physical characteristics of BCG vaccine:

Dried BCG vaccine is a white powder-like substance that can be easily moved by shaking; it should be easily dissolved when diluted with physiological saline to produce a homogeneous suspension. The pH of the dissolved vaccine should be within the range of 5.5 to 7.0.

Staining test: Smears are made directly from undiluted suspensions or from diluted specimen in physiological saline. Smears are stained by Gram’s procedure and the acid-fast procedure, and examined microscopically to verify the morphological appearance of the bacteria. The Ziehl-Neelsen staining test is applied to identify and determine the homogeneity of the bacteria in the vaccine under a microscope. The Japanese BCG vaccine usually shows many aggregates of acid-fast bacilli in various sizes in addition to single bacilli after reconstitution.

Safety test for free from virulent mycobacteria: A test sample of 2.5 mg/mL is injected into six normal guinea pigs weighing between 300 and 400 g; the injections are performed intramuscularly into the thighs of three animals and subcutaneously into the lateral abdomens of the other three animals. The sample is injected at a dose of 1.0 mL (2.5 mg of moist bacteria), and all the inoculated animals are observed for at least 6 weeks before autopsy. None of the animals should show any abnormal signs, other than lesions at the site of injection and regional lymph nodes with an apparent tendency toward recovery at the time of autopsy. No animal should show progressive tuberculous lesions or other abnormal changes, except mild lesions with a tendency toward recovery at autopsy performed at the end of the observation period. At least two-thirds of the animals must survive the observation period. All of the lots examined during the past nearly 60 years have been proven to be safe and free from virulent mycobacteria based on the above criteria.

Sterility test: The sterility test confirms the absence of microorganisms that can be detected using a sensitive medium. The fluid thioglycolate and the soybean casein digest medium have been used as test media for many years. The ampoules of dried BCG vaccine are sampled from each filling lot and are inoculated into the fluid thioglycolate medium and the soybean casein digest medium, the sensitivity of which has been confirmed. Each inoculated medium is incubated at both 30 - 35°C or 20 - 25°C, respectively, for 7 days, then checked at intervals by visual examinations.

Potency test: The potency test is performed by determining the number of culturable particles in Ogawa’s solid coagulated egg slant medium. The contents of 10 ampoules are reconstituted with physiological saline to the vaccine concentration, as indicated on the label, and further diluted in sterile water to a concentration of $0.5 \times 10^{-3}$ mg of moist bacteria per mL.

Each dilution is inoculated in a medium tube at a dose of 0.1 mL; the cultures are incubated at 37.5 ± 0.5°C for 4 weeks. At the end of the culture period, the number of colonies appearing in one medium tube is counted. The sum and unbiased variance of the square root of the value are calculated. The number of culturable particles contained in the test sample should be within a range specified upon statistical comparison of the results using the sum and the unbiased variance.

Total bacterial content test: The test sample is diluted to a concentration of 1 mg/mL in saline, and the absorbance of the dilution is measured using a spectrophotometer at 470 nm and a light path of 10 mm. The absorbance should be no more than 0.5 mg/mL. The absorbance should be no more than 0.6 kPa at 58 - 62°C for 3 h to measure the residual water content of the vaccine. The moisture content should be no more than 3.0%.

5. Vaccine efficacy

BCG is the only vaccine against tuberculosis being used throughout the world. BCG induces specific immune responses to mycobacterial antigens and appears to be able to elicit protective immunity against tuberculosis. In general, the protective effect of a vaccine is determined by an epidemiological study to compare the incidence of the disease with and without vaccination. A total of 17 controlled trials demonstrating the efficacy of BCG vaccine in humans have been reported since 1935 (1). Table 1 summarizes the results of the major trials. The first large-scale field trial of BCG efficacy was evaluated in tuberculin-negative children and adolescents between the ages of 0 - 20 years and belonging to eight North American Indian tribes. Pulmonary tuberculosis occurred in 238 of the 1,457 unvaccinated persons and in 64 of the 1,551 persons given BCG vaccination, with a protective efficacy

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<th>Area</th>
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<th>NTM exposure</th>
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<td>Vandiviere, H.M. et al. (5)</td>
</tr>
<tr>
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<tr>
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<tr>
<td>Georgia, Alabama</td>
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against active tuberculosis of 75% during the 9-11 year follow-up period (2). Another trial was performed in high-risk infants in Chicago by Rosenthal and colleagues. They found that tuberculosis developed in 59 of the 1,665 unvaccinated persons, while active disease occurred in 16 of the 1,716 vaccinated individuals (efficacy = 75%) after a follow-up period of 12-23 years (3). The Medical Research Council of Great Britain (MRC) conducted a large controlled trial of the Danish strain of BCG vaccine in 27,400 school children between the ages of 14-16 years. After a 15-year follow-up period, 243 cases of tuberculosis had developed among 13,300 persons in the unvaccinated group, compared with 56 cases among the 14,100 persons in the vaccinated group (4). Vandiviere and colleagues also found that BCG conferred a high degree of protection. A total of 3,174 villagers in Haiti were randomly assigned to either receive the BCG vaccine or to remain unvaccinated. The length of the follow-up period was 3 years. The efficacy of BCG vaccination was 80% (5). On the other hand, several trials have reported that the efficacy of BCG vaccination was low or none (6-10). One of those, co-sponsored by the Indian Council of Medical Research, WHO and the United States Public Health Service, was carried out in Chingleput, India, between 1968 and 1971. More than 300,000 villagers older than 1 month of age were randomly divided into either a BCG-vaccinated or a saline-inoculated group. During the 15-year follow-up period, vaccination provided some protection against tuberculosis in children; among adults, however, the vaccinated group had a higher prevalence of tuberculosis than the unvaccinated group. Thus, it is difficult to draw a clear conclusion regarding the efficacy of the BCG vaccine based on the results of randomized trials alone because the results of these trials have varied from 0 to 80%. Several case-controlled studies of BCG vaccination have also been performed to assess the efficacy of the BCG vaccine for tuberculosis control. The results of these studies also varied widely, with the effectiveness of vaccination ranging between 2-84% (11).

Several explanations have been offered for these conflicting results, including differences in trial design, different immunogenicity of the vaccine strains, or genetic inconsistencies between individual strains. However, the most plausible explanation seems to be differences in exposure to non-tuberculous mycobacteria as environmental mycobacteria between individuals living in hot climates versus those living in cold climates (12). A meta-analysis of BCG vaccination for the prevention of tuberculosis has been performed using prospective randomized trials and case control studies (13,14). They concluded that on average, BCG vaccination was about 50% protective in preventing tuberculosis.

6. Adverse reactions

For more than 80 years, BCG vaccines have been administered to billions of individuals throughout the world, and today BCG is considered one of the safer vaccines available. Regional lymphadenitis is greater among newborns than among older infants and children, especially when a full dose of vaccine is given; therefore, the WHO recommends using a reduced dose in children younger than 30 days.

The mean risk of ostitis after BCG vaccination has varied from 0.01 per million in Japan to 300 per million in Finland (15,18-21). Fatal disseminated BCG infection has been reported to occur at a rate of 0.19 to 1.56 cases per million vaccines, occurring mostly in patients with severe defects in cell-mediated immunity, such as severe combined immunodeficiency and human immunodeficiency virus (HIV) infection (22). The safety of the BCG vaccine in children and adults who are infected within HIV is unknown. Currently, WHO recommends giving the BCG vaccine to asymptomatic HIV-infected infants who live in high-risk areas for tuberculosis. BCG is not recommended for symptomatic HIV-infected infants or for persons known to be or suspected of being HIV-infected if they are at minimal risk for infection with M. tuberculosis (23).

7. Genetic characterization of BCG strains

BCG vaccines are divided into the early strains, including the Japan, Birkhaug, Russia and Brazil BCG strains, that were obtained between 1924 and 1926, and the late strains, such as the Pasteur, Danish, Glaxo and Connaught BCG strains that were obtained after 1931 (24). Recently, the genomic compositions of the various BCG daughter strains have been studied by performing comparative hybridization experiments using a DNA microarray (25-28). Regions deleted from the BCG vaccines, relative to the virulent M. tuberculosis H37Rv reference strain, were found by sequencing across the missing segment of the H37Rv genome. Eleven regions of H37Rv were found that were absent from one or more virulent strains of M. bovis; five additional regions were present in M. bovis but absent from some or all BCG strains, and the presence of 16 deleted regions (RD1 - RD16) were confirmed (24). RD1 is missing from all BCG strains and is speculated to coincide with the attenuated virulence of M. bovis. RD2 is present in the early BCG vaccines but is missing from the late BCG vaccines. The loss of RD2 has been confirmed to coincide with the deletion of the mpt64 gene, which encodes the antigenic protein MPT64. Some of these regions are missing from only one strain; RD8 is missing from Canadian BCG strains like the Frappier and Connaught strains, while RD14 is missing from only the Pasteur strain, and RD16 is missing from only the Moreau strain. A small deletion of 22 base pairs in RD16 in the Japanese strain was uncovered by chance in a multiplex PCR-based analysis of BCG strains and was confirmed to coincide with a morphological difference (29, 30). Recently, BCG Pasteur 1173P2 has been subjected to a comparative genome and transcriptome analysis, and the 4,374,522-bp genome has been concluded to contain 3,954 protein-coding genes, 58 of which are present in two copies as a result of two independent tandem duplications, DU1 and DU2 (31).

8. Aspects of BCG vaccines

Although the current vaccine strains are all descendants of the original M. bovis isolate, subsequent passages under different laboratory conditions have resulted in a variety of BCG strains including the French strain Pasteur 1173 P2, the Danish strain 1331, the Glaxo strain 1077 and the Japanese
strain Tokyo 172; these various strains exhibit phenotypic as well as genotypic differences, as mentioned above. In terms of efficacy, no consensus exists as to which strain of BCG is appropriate for general use. Reconstituted vaccines containing both living and dead bacilli, and the number of culturable particles and the biochemical composition of the vaccines, vary considerably depending on the strain and production method of the vaccines. A clinical trial in South Africa was recently performed to examine the immune responses of vaccinated infants after percutaneous or intradermal administration of the Japanese BCG or intradermal administration of the Danish BCG. The results suggested that the BCG strain and route of delivery may determine the clinical outcome of vaccination by influencing the immune response that leads to protection against tuberculosis (34,35). Even if several daughter strains of BCG have similar protective activities to protection against tuberculosis (34,35). Even if several

REFERENCES


