Adverse Events Induced by BCG Immunization in Taiwan

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Abstract

The Pasteur strain 1173 P2 was originally used for Bacillus Calmette-Guerin (BCG) vaccine production in Taiwan and was substituted by the Tokyo strain 172 in 1979. The lymphadenopathy investigation proceeded from 1969 to 1982 revealed that the side effect of lymphadenopathy caused by Tokyo 172 was lower than Pasteur strain 1173 P2. From 1998 to 2007, there were 14 cases applied for compensation on BCG-caused adverse reaction, and six of them were confirmed after investigation. BCG vaccination caused five cases of humeral or sternal osteomyelitis and one death resulting from disseminated BCG infection. Between 2002 and 2006, the incidence of BCG osteomyelitis was 3.68 cases per million doses and the incidence of disseminated BCG infection was 0.9 case per million doses. In order to understand the real situation of adverse reaction caused by BCG vaccination, to establish the BCG safety profile, and to improve the BCG production in Taiwan, long-term systematic investigations of adverse reactions caused by BCG vaccination is recommended.

Key words: suppurative lymphadenitis, BCG osteitis/osteomyelitis, disseminated BCG infection.

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Introduction

Bacillus Calmette-Guerin (BCG) is a live attenuated bovine mycobacterial vaccine produced by French scientists Calmette and Guerin, using *Mycobacterium bovis* isolated from cows with mycobacterial mastitis which was subcultured 230 times over a 13-year period (subcultured once every 3 weeks) using culture medium containing potato, bovine bile fluid, and glycerine [1]. BCG was first used orally on human infants in 1921. Subcutaneous vaccination began in 1923 and intradermal vaccination in 1927. BCG is broadly used for tuberculosis prophylaxis since then and about 100 million children receive BCG vaccination every year [2].

BCG is a vaccine that is widely used and has been in use the longest, but the effectiveness has been questioned in the last 30 years [3]. In Europe, the incidence of tuberculosis had decreased obviously because of widespread use of BCG. The incidence of tuberculosis in North America with low usage of BCG also showed natural decrease. No obvious decrease of the incidence rate of tuberculosis was reported in Asia, such as India and China, which had massive use of BCG. Many epidemiological studies were also unable to prove that BCG can prevent tuberculosis. Currently, BCG has only been confirmed to prevent progressive primary tuberculosis, such as tuberculous meningitis, in infant children.

Adverse effects induced by BCG

Adverse effects may be found in some people after BCG vaccination. Studies revealed that the incidence of these adverse effects may be related to the strains of BCG vaccine, the method, technique and dose of the vaccine, and human physique [4]. BCG is contraindicated in patients with the following: 1. high fever; 2. severe, acute disease and immune deficiency; 3. severe congenital

diseases; 4. infants weighing less than 2500 grams; 5. suspected tuberculosis or have positive in tuberculin skin test; 6. severe eczema; 7. HIV-infected patients with clinical symptoms or patient on immunosuppressive treatment; 8. pregnant. Malnutrition is not a contraindication for BCG vaccination.

Normally, small, red nodules may be found at the injection site 7-14 days after BCG vaccination. The nodules may become larger, but the vaccinee should not have fever. The vaccinee may feel locally mild itch and pain. After 4-6 weeks, the nodules may progress into pustules or even ulcerate. No medication or bandaging is necessary except to keep this area clean and clear the pus with sterile cotton or gauze when needed. The ulceration may heal in 2-3 months after vaccination and leaves a pale red scar.

Mild adverse reactions caused by BCG are usually localized and lymphadenitis is most commonly seen. The incidence was 0.01~17.2 cases per 1000 doses in Europe [5]. The incidence in Asia and Africa is higher than other areas in the world and mostly found in neonate immunization. Axillary and supraclavicular areas are most commonly recorded within 5 months after vaccination, and the nodules are usually 1-2 centimeters in size. Lymphadenitis in these areas usually healed spontaneously. If the lesions show no adhesion, it is not necessary to treat the lesions.

According to the data presented by the World Health Organization (WHO) (Table 1) [2], severe side effects caused by BCG include the following:

(1) Localized suppurative lymphadenitis

The incidence of localized suppurative lymphadenitis is 100~1000 cases per million doses, but the incidence had decreased in recent years. Well-trained staff using standard freeze-dried vaccine and proper individual dose depending on the age of the vaccinated subjects could decrease the incidence of these harmful

side effects [6].

(2) BCG osteitis/osteomyelitis

The incidence of this adverse reaction is 1-700 cases per million doses. It is particularly reported in Eastern and Northern Europe (Sweden, Norway, Denmark and Iceland) [7]. Typically it is associated with the changes in BCG vaccine strain. [8]. The incidence of BCG osteitis was increased to 35 cases per million doses in Czechoslovakia after the BCG strain, the Prague strain, was replaced by the Russian strain. The incidence of BCG osteitis was increased in Finland and Sweden after switching to the Gothenbury strain produced in Denmark in 1971. The incidence rate in Sweden was as high as 1 case per 3000 doses. The incidence decreased rapidly after the national vaccination policy shift to using Copenhagen 1331 strain.

According to the report presented by Kroger et al [9], the incidence rate of this adverse effect was 15-73 cases per 100,000 doses. The frequency was between 0.1-30 cases per 100,000 doses quoted by Dittmann in 1992 [10]. However, the incidence was much rare after injection of the Pasteur or Japanese strain.

(3) Disseminated BCG infection

Disseminated BCG infection is a recognized but rare adverse effect of BCG vaccination. The incidence rate is 2 cases per million doses, usually found in infants with severe immunodeficiency [11, 12]. Recently, an investigation by multicenter confirmed this syndrome mainly occurred in patients with severe combined immunodeficiency (SCID), chronic granulomatous disease, DiGeorge syndrome, and children with interferon- γ -receptor deficiency [13,14]. Its frequency was less than 5 cases per million doses, reflecting its rarity. However, it could be lethal if not treated properly.

According to Mande et al [15] in 1980, the first case of disseminated BCG infection was recorded in 1953, 30 years after BCG was first applied on humans. 34 cases of disseminated BCG infection were found in global literature during 1954-1980. Lotte et al [16] estimated that the incidence rate of this adverse effect was 2.19 cases per million doses. Yet, Canada reported recent three more cases in 1998. Severe and disseminated BCG infection patients with immunodeficiency should be treated with drugs including isoniazid and rifampicin.[17]

The relation between the BCG strain and adverse reaction

Current BCG strains were distributed to laboratories world wide from the original isolate in 1921. These strains were developed into distinct BCG strains and preserved through series of culture. Monosodium glutamate was added as stabilizer, but the adjuvant or preservative was not added. The diluent is saline solution or distilled water.

WHO indicates that the four main strains of BCG have been widespread in use: (1) Pasteur strain 1173 P2; (2) Danish strain 1331; (3) Glaxo strain 1077 in England (derived from the Danish strain); (4) Tokyo strain 172. About 66% of the BCG strains used in 1996 were the first 3 strains listed above and BCG vaccines currently in use are over 90% when Tokyo 172 strain was included [2]. WHO attempted to use stabilizer and freeze-dry techniques to standardize the production and quality of the vaccine. However there is still $5x10^4$ to $3x10^6$ bacterial particle differences remaining between each dose due to different characteristics of each strain.

Studies revealed that the vaccine-induced adverse reaction may be different for each strain. The discussion is followed.

(1) Pasteur strain 1173 P2

At the end of the 1980s, there were several reports of adverse events, such as large ulceration and localized or suppurative lymphadenitis, exhibited in the supplementary information on vaccine safety by WHO in 2002[2]. Switch of the vaccine strain, from less reactogenic Glaxo strain 1077 to more reactogenic Pasteur strain 1173 P2,and failure to inform the vaccination personnel to modify the vaccine dose were responsible for those events.

The Australian Immunisation Handbook 8th edition [18] indicated that Pasteur strain 1173 was used for BCG vaccination. The incidence of adverse events was 5%, which includes swelling at injecting site (2.5%), lymphadenitis (1%) and hospitalization for treatment of these side effects (1%).

Canada Communicable Disease Report volume 30 published in 2004 also reported adverse events induced by Pasteur strain 1173 in 1996-2000 [19]. The adverse events induced by Pasteur strain 1173 were higher than global estimates.

(2) Danish strain Copenhagen 1331

A retrospective analysis [17] for adverse effects induced by this strain from 1979 to 1991 in Sweden showed that 1.9 cases of localized lymphadenopathy occurred per 1000 immunized children. Severe disseminated BCG infection was recorded in 4 among 139,000 vaccinees.

(3) Glaxo strain 1077 of England

Milstien et al [20] found that the adverse effects induced by Pasteur strain 1173 P2 and Danish strain Copenhagen 1331 had higher incidence of adverse events than Tokyo strain 172, Glaxo strain 1077 and Brazilian (Moreau) strain. The Department of Health in Hong Kong finally decided to adopted Glaxo strain 1077 as BCG vaccine strain because it is safer and causes fewer adverse effects, although Pasteur strain 1173 P2 has higher efficacy.

(4) Tokyo strain 172

Lotte et al [16] published a bibliography which collected over 1000 journals and articles to analyze the incidence of BCG adverse reaction in different countries between 1948 and 1974. They indicated that the incidence of BCG osteitis/osteomyelitis and disseminated BCG infection were both 0.01 case per million doses in Japan. The safety profile of Japanese BCG was the highest compared to other countries. Currently other than Japan and Taiwan, Korea is the only country using Tokyo strain 172 as BCG vaccine.

A meeting on the characterization of BCG strain [21] was held by WHO in December of 2003. The resolutions were as followed:

(1) The order of virulence was Pasteur > Russia > Glaxo, but the order of protective efficacy was Pasteur > Glaxo > Russia.

(2) It is believed that the reactogenic to Pasteur and Danish strains was stronger than Tokyo, Glaxo and Moreau strains, resulting in larger scar, and more localized or suppurative lymphadenitis.

(3) Pasteur, Danish and Goteborg strains were frequently occurred in all types of complications

(4) The incidence of adverse effects was 0.17 per 1000 doses for the first dose and increased to 0.39 per 1000 doses for second dose in Brazil using Moreau strain.

(5) Disseminated BCG infection was a rare adverse event and the incidence rate was 0.59 per million infants vaccinated in France using Pasteur strain.

(6) The quality of Tokyo strain 172 BCG production using traditional methods in Japan conforms to WHO standardization and are safe.

In 2000, South Africa changed its BCG vaccination policy to intradermal injection of Danish strain 1331 from percutaneous injection of Tokyo strain 172. The reasons were as follow: (1) WHO promoted intradermal injection; (2) only

Japan and South Africa used multiple puncture injection; (3) intradermal injection was more precise and consistent. A 3-year-period of evaluation[22] for this change indicated that the efficacy for both technique, Danish strain 1331 ID and Tokyo strain 172 PC, was equivalent (incidence of tuberculosis was 858 cases and 866 cases per 100,000 doses, respectively), showing that BCG vaccination did not decrease tuberculosis infection. However, lower incidence of disseminated tuberculosis infection (tuberculosis meningitis or milliary tuberculosis) was found using intradermal injection (4.7%) compared to using percutaneous injection (8.6%). Therefore, intradermal injection is still the main technique for BCG vaccination.

History of BCG immunization in Taiwan

Liquefied BCG vaccine produced by laboratories in Manila was initially used in Taiwan. The dose was 0.1 mg/0.1 ml for intradermal vaccination. Provincial BCG manufacture laboratory was established in Taiwan in 1952. It was recognized by WHO for production of liquefied BCG vaccine in 1953. Old Pasteur Strain from Pasteur Institute in France was initially used, but was replaced by New Pasteur Strain in 1956. The dose was 0.05 mg/0.1 ml for infants under one year of age and 0.1 mg/0.1 ml for persons aged one year or older, using intradermal injection.Since batch number 1251 （September 30, 1971）, the manufacture process has been modify to removeTween 80 from BCG vaccine because it may result in higher incidence of lymphadenopathy after immunization. On September 6, 1972, the dose was altered from 0.05 mg to 0.025 mg for infants under one year old and from 0.1 mg to 0.05 mg for persons one year or older.

Freeze-dried Tokyo strain 172 (Figure 1) was used for BCG vaccine production since March, 1979. Taiwan-produced freeze-dried vaccines were

initially used for infants on July in the same year, and were expended for routinely used since fall, 1980. The dose was uniformly 0.05 mg/0.1 ml with intradermal injection. In the last 30 years, the main recipients was including 1-5 year-old children, infants and newborns. Approximately 200,000-300,000 doses of BCG vaccines were given. With decreases birthrate, the number of vaccination was also decreased.

BCG-induced adverse event in Taiwan

The incidence of lymphadenopathy after immunization of Pasteur strain 1173 P2 was 1.7-17.1% in an investigation proceeded between 1969 and 1982 (Table 2). Tokyo strain 172 was used after 1977 and the incidence of lymphadenopathy in 1977, 1978 and 1982 were 0.4%, 1.1% and 0.1%, respectively. This indicated that the adverse effect of BCG-induced lymphadenopathy was lower using Tokyo strain 172 compared to Pasteur strain 1173 P2.

There was no further investigation for adverse effect induced by BCG immunization after 1982. The regulation for Indemnification for Immunization-induced Effects was promulgated in 1991. According to the records, 14 applications were received for suspected BCG indemnification since 1998. Six cases were confirmed to be associated with the vaccines, in which humeral or sternal osteomyelitis were found in five and one death resulted from disseminated infection. From the 1.08 million infants who received BCG immunization in the 5 years between 2002 and 2006, the estimated incidence of BCG osteomyelitis was 3.68 cases per million doses and for disseminated BCG infection 0.92 case per million doses (Table 3). These results were lower than the records published by WHO (2 and 0.92 per million doses, respectively), but higher than those in

Japan (0.01 per million doses for both adverse effects) [4].

In order to understand the adverse events caused by BCG immunization, a retrospective investigation conducted by medical officers at the Taiwan Centers for Disease Control confirmed several cases of extrapulmonary tuberculosis to be adverse events induced by BCG immunization, increasing the incidence of BCG osteomyelitis and disseminate BCG infection to 6 cases and 2.25 cases per million doses, respectively. However, this was still within the range of WHO standard.

Conclusion

Lotte et al [15] published a retrospective analysis of BCG adverse effect by collecting over 1000 articles from 187 countries. This was the most comprehensive report on this topic. Although BCG immunization has been widely used in over 2/3 of the countries in the world, Lotte indicated that the information on the side effects induced by BCG was still incomplete. Only 1/3 of these countries reported cases, and some countries had only few cases. Of the cases reported, 3/4 were found in Europe, implicating that in areas other than Europe, there could be an underestimation of the incidence of the side effects after BCG immunization.

Different BCG strains resulted in different BCG-induced adverse effects. The incidence of side effects was higher for Pasteur and Copenhagen strains compared to Glaxo or Tokyo strains. More cases of BCG osteitis/osteomyelitis were found in Eastern Europe, which may be related to characteristics of the BCG strains or the shift between the BCG strain [8].

Tokyo strain 172 is used in Taiwan. The safety of this strain is high based on the information from Japan. The technique used in Japan is multiple puncture, but

intradermal injection is used in Taiwan. According to clinical research in South Africa, more accuracy and lower incidence of disseminated tuberculosis infection were noted using intradermal injection compared to multiple puncture [22]. No research on adverse events induced by Tokyo strain 172 using different immunization techniques was available, but past researches had shown that the BCG strain, immunization techniques, dose and physique of the recipients all effect the incidence of adverse events [5]. Because intradermal vaccination is more technically demanding, only well-trained personnel should perform the procedure. In order to understand the real situation of adverse reaction caused by BCG vaccination, to establish the BCG safety profile, and to improve the BCG production in Taiwan, long-term systematic investigations of adverse reactions caused by BCG vaccination, such as investigations performed between 1969 and 1982, is recommended.

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Table 1. Summary of rare, serious vaccine reactions, onset interval, and rates.

Vaccine	Reaction	Onset Interval	Rate per million doses
BCG	Suppurative lymphadenitis	2-6 months	100-1000
	BCG osteitis	1-12 months	1-700
	Disseminated BCG infection	1-12 months	2

Table 2. Summary of lymphadenopathy induced by BCG immunization, 1969-1982.

Year	Vaccine type	Strain	Dose	Number of dose given	Lymphadenopathy		Lymphadenopathy site		
					Number	%	Axilla	Neck	other
1969	Liquified	Pasteur 1173P2	0.05mg	9227	158	1.7	139	19	–
1970	Liquified	Pasteur 1173P2	0.05mg	4547	349	7.7	315	34	–
1971	Liquified	Pasteur 1173P2	0.05mg	5193	170	3.3	159	11	2
1972	Liquified	Pasteur 1173P2	0.05mg	5157	908	17.7	853	52	18
1973	Liquified	Pasteur 1173P2	0.025mg	3693	188	5.1	168	20	–
1974	Liquified	Pasteur 1173P2	0.025mg	3343	148	4.4	133	16	1
1975	Liquified	Pasteur 1173P2	0.025mg	4803	129	2.7	117	13	–
1977	Freeze-dried	Pasteur 1173P2	0.025mg	1237	105	8.5			
1977	Freeze-dried	Tokyo 172	0.05mg	827	3	0.4			
1978	Freeze-dried	Tokyo 172	0.05mg	856	9	1.1			
1982	Freeze-dried	Tokyo 172	0.05mg	1266	1	0.1			

Table 3. Number and estimated incidence of severe adverse effect induced by BCG vaccination.

year	Number of persons vaccinatedr	osteomyelitis		Disseminated BCG-itis	
		Number of cases	Incidence (per million doses)	Number of cases	Incidence (per million doses)
2002	240959	0	0	1	4.1501
2003	222492	2	8.9891	0	0
2004	213053	0	0	0	0
2005	204400	1	4.8924	0	0
2006	204400	1	4.8924	0	0
total	1085304	4	3.6856	1	0.9214

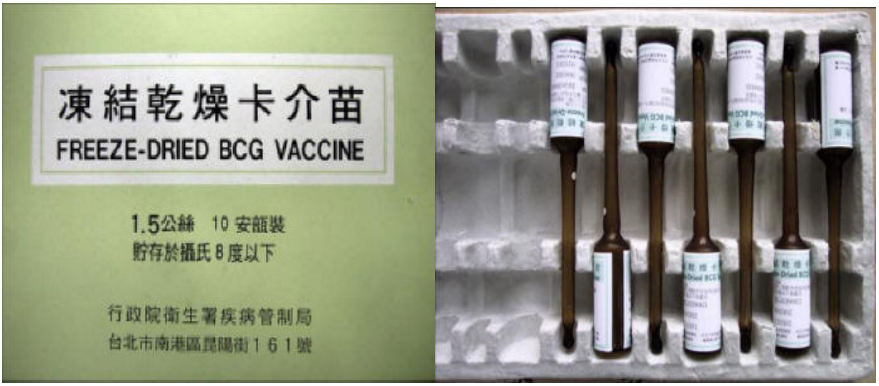

Figure 1. Freeze-dried BCG vaccines produced by Centers for Disease Control.