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Received: June 12, 2020  
 Accepted: July 28, 2020

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No potential conflict of interest relevant to this article was reported.

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# Investigation of adverse events following bacille Calmette-Guérin immunization using immunization safety surveillance system in Korea Centers for Disease Control and Prevention

**Purpose:** The report of adverse events following immunization (AEFI) in Korea has continued since 1994, and the most frequently reported cases of AEFI of Korea Centers for Disease Control and Prevention (KCDC) is bacille Calmette-Guérin (BCG). Meanwhile, various inoculation methods and strains have been used in the past 6 years in Korea. Therefore, we investigated AEFI of BCG by strain types and inoculation methods using immunization safety surveillance of KCDC.

**Materials and Methods:** We reviewed BCG AEFIs registered in the KCDC from January 2013 to June 2018.

**Results:** There were 336 AEFI cases during the period, and average time interval from vaccination to symptom onset was within 2 months. AEFI proportion was 6.4 cases per 100,000 doses for BCG percutaneous Tokyo strain, 41.6 cases per 100,000 doses of BCG intradermal Danish strain, and 25.9 cases per 100,000 doses of BCG intradermal Tokyo strain. Intradermal type was more reported AEFI than percutaneous type in the same strain. The most common adverse events were local reaction like BCG lymphadenitis and severe adverse reactions such as osteomyelitis or disseminated BCG disease were 0.1 to 0.2 cases per 100,000 doses which are correlated with the range of World Health Organization published AEFI rates.

**Conclusion:** The AEFI reporting rate does not equal the actual proportion of AEFI occurrence. Because AEFI monitoring is a passive surveillance system, various factors might influence the number of events reported. Nevertheless, it is important to analyze BCG AEFI by vaccine strains and inoculation method using surveillance data of KCDC.

**Keywords:** BCG vaccine, Adverse event following immunization, Surveillance

## Introduction

The bacillus Calmette-Guérin (BCG) vaccine is the live attenuated vaccine and the most widely used vaccine in the world. Since it was first developed by Calmette and Guérin in 1921, it has been vaccinated by more than 3 billion people worldwide [1]. BCG vaccine is useful to protect tuberculosis (TB) especially, effective against active TB disease as like TB meningitis and disseminated TB disease in children [2]. In Korea, BCG vaccinations have been conducted all over the country since 1952 [3]. As National Immunization Program (NIP) was only authorized for intradermal BCG, the number of vaccination registrations or reports of adverse events for percutaneous inoculation

has not been accurate compared to those for intradermal inoculation. In addition, intradermal strains used were changed from Pasteur to Danish in 2007 and have continued to be used until 2015 [1]. But in 2015 and 2017, when the supply of intradermal vaccine was suspended, percutaneous Tokyo strains were inoculated with a temporary preventive inoculation [3]. During that period, intradermal Tokyo strains are used as regular preventive inoculation and percutaneous Tokyo strains are used as temporary preventive inoculation. Various inoculation methods and strains have been used in the past 6 years in Korea, and especially, there has never been a previous study on adverse reaction of Tokyo strains in Korea. As a result, we need to find out about the incidence or types of adverse events for BCG. Therefore, the purpose of this study was to analyze adverse events following immunization (AEFI) of BCG was reported to the Korea Centers for Disease Control and Prevention (KCDC) from January 2013 to June 2018 and to examine the characteristics of adverse events, such as the period from vaccination to occurrence of AEFI, the reporting rate of adverse events, the type and frequency of reported adverse events by strains and inoculation methods.

## Materials and Methods

### Subjects and data collection

From January 2013 to June 2018, we reviewed all AEFIs registered in the Integrated Management System of Disease and Public Health (<http://is.cdc.go.kr>). Among them, BCG AEFI cases were collected that meet the conditions suitable for the “scope of adverse reactions after vaccination (Appendix 1) that should be reported” after regular and temporary national preventive inoculation. The number of BCG vaccinations administered was collected through the National Immunization Registry Integration System of the Division of Vaccine-Preventable Disease Control and the NIP at KCDC. The research period was set up from January 2013 before the use of the intradermal Tokyo and percutaneous Tokyo strains for vaccination projects to June 2018 to compare adverse reactions by inoculation strains.

The BCG AEFI registered in the Integrated Management System of Disease and Public Health were analyzed by year, by inoculation method, and strains. It also examined the reporting rates of adverse events by inoculation year and the period after vaccination to occurrence of adverse events from the information listed on the report of adverse events (Appendix 2). We also looked what is the types of adverse reactions that are

reported mainly by analyzing the types of reported adverse reactions. This research was exempted from deliberation by the Institutional Review Board (115288-202005-HR-039-01).

### Definition of an abnormal response

Since the causality of vaccination is not assessed for reported adverse events, it was defined as adverse events after BCG vaccination for symptoms that occurred within the period, i.e., time-related symptoms, referring to the information listed in Appendix 2. This is a separate concept from epidemiological investigations for compensation for the damage, and would conform to the definition of adverse reactions under the “Infectious Disease Control and Prevention Act” [4] or the World Health Organization (WHO) definition [5].

Usually, lymph node swelling is considered to occur within a year with a diameter of more than 1.5 cm, but the adverse event declaration form does not contain any information on the size of the lymph nodes. Therefore, an adverse event in accordance with BCG is considered to be an adverse event within 1 year. The occurrences of osteitis, osteomyelitis, disseminated BCG disease, and local reactions within 6 months are considered abnormal responses, and no time limit is required for any other suspected adverse events. Whether or not there is an association with adverse reaction were referred to the data in the WHO’s BCG information sheet [6]. We compared whether there was a difference in the period of occurrence of adverse event by gender and inoculation strains. We identified the reporting rates of adverse event by organizing the number of adverse reactions reported by inoculation year and strains through the reported number of BCG vaccinations and adverse reaction data.

We divided the types of adverse events into localized reaction (suppuration, lymphadenitis, injection sites symptom) and systemic abnormalities (allergy, anaphylaxis or anaphylactoid reaction, fever, osteomyelitis, osteitis, disseminated BCG disease, etc.) according to the declaration form (Appendix 1) and looked at the frequency. We also looked at the number of BCG vaccinations, the type and frequency of adverse events per year and strains. Lastly, we investigated whether there are differences in adverse events by strains.

### Analysis

The collected data of adverse events were divided into strains (Danish strains, Tokyo strains) and inoculation methods (intradermal, percutaneous). The report of adverse events is a passive reporting system, and some does not report adverse

events to KDCD in cases of inoculation other than NIP (for BCG percutaneous). In addition, the history of vaccinations may not be registered if they are not included as NIP. Therefore, we compared only BCG vaccinations regular (BCG intradermal) and temporary (BCG percutaneous, specific period) performed on NIP to meet the same conditions. In addition, the number of inoculations per 100,000 inoculation cases was calculated as an AEFI rate for comparison, because the number of inoculations varies by strain and method of inoculation.

**Results**

**The sex/age distribution of the subjects**

Among 1,847 AEFI are registered in the Integrated Management System of Disease and Public Health from January 2013 to June 2018, 464 were reported adverse reactions from BCG vaccinations (302 [65%] for male). Among the 464 cases, 336 cases correspond to the definition of an adverse events and the period of the NIP, intradermal BCG and two temporary preventive inoculation periods. There were 218 cases for male (65%), and 275 (82%) were vaccinated within 4 weeks of the standard inoculation period (range, 0 to 44 months) (Table 1).

**Period from bacille Calmette-Guérin vaccination to adverse events**

AEFI was most common in 2 months after BCG inoculation

**Table 1.** Children characteristics

Variable	Value
Gender	
Male	218 (65.0)
Female	118 (35.0)
Total	336 (100.0)
Median age at immunization (mo)	0 (0–44)
Median time from onset symptom (mo)	2 (0–12)

Values are presented as number (%) or median (range).

**Table 2.** Onset of symptom after BCG vaccination (months)

BCG strain	0 mo	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8–12 mo	Total
Percutaneous, Tokyo	7 (24.1)	6 (20.7)	8 (27.6)	7 (24.1)	-	1 (3.4)	-	-	-	29 (100.0)
Intradermal, Danish	26 (10.9)	35 (14.7)	51 (21.4)	53 (22.3)	27 (11.3)	20 (8.4)	11 (4.6)	4 (1.7)	11 (4.6)	238 (100.0)
Intradermal, Tokyo	16 (23.2)	18 (26.1)	11 (15.9)	9 (13.0)	1 (1.4)	7 (10.7)	3 (4.3)	2 (2.9)	2 (2.9)	69 (100.0)
Total	49 (14.6)	59 (17.6)	70 (20.8)	69 (20.5)	28 (8.3)	28 (8.3)	14 (4.2)	6 (1.8)	13 (3.9)	336 (100.0)

Values are presented as number (%).  
BCG, bacille Calmette-Guérin.

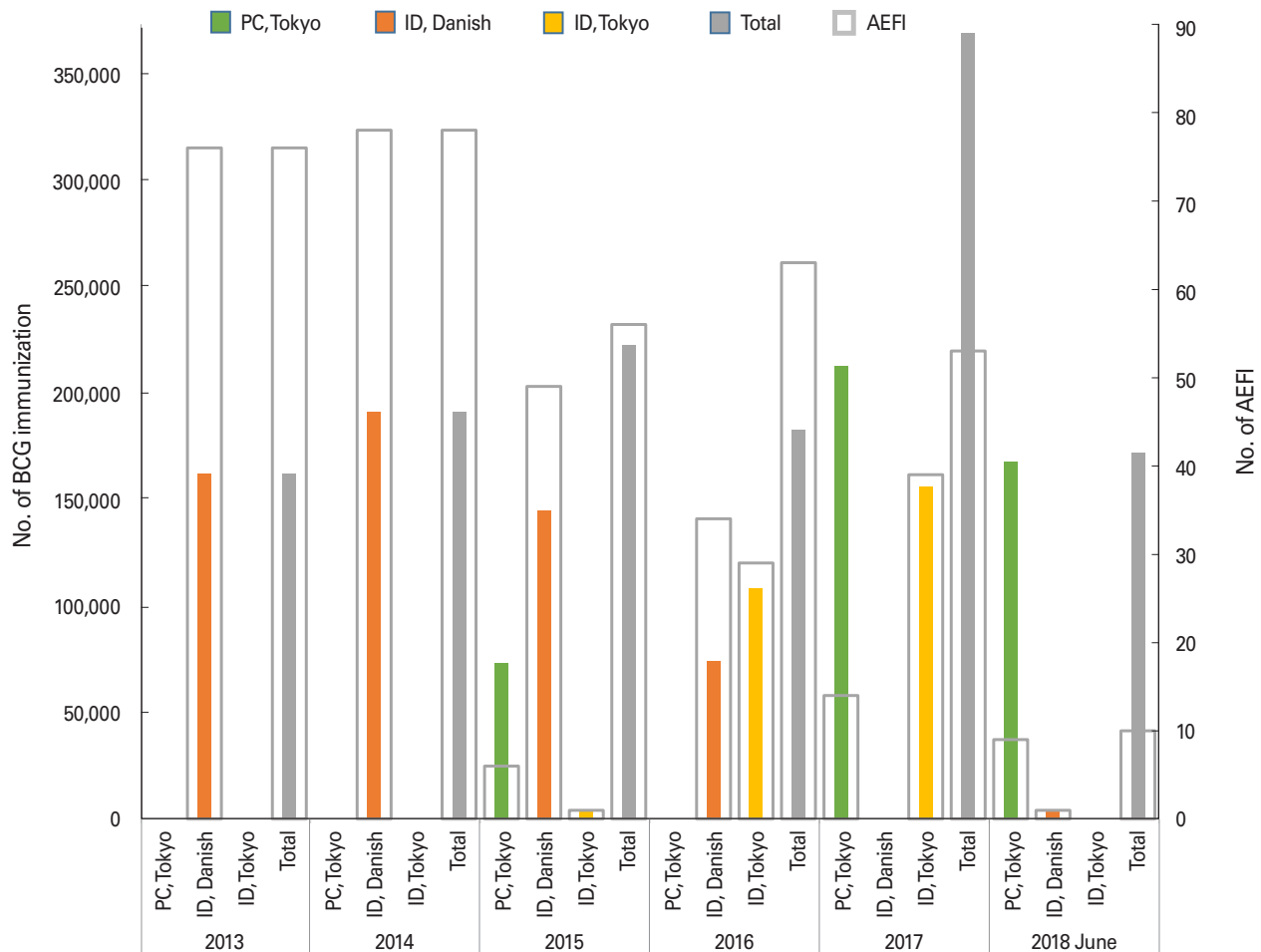
(20.8%), and more than 70% of the adverse events occurred within 3 months of vaccination. The percutaneous Tokyo strains had the most adverse events in 2 months after inoculation (27.6%) and most occurred within 3 months of vaccination. The intradermal Danish strains had the most adverse events in 3 months after inoculation (22.3%) and also occurred 12 months after vaccination. The intradermal Tokyo strains had the most adverse events in 1 month after inoculation (26.1%) and occurred until 11 months after vaccination. In other words, the percutaneous method had fewer AEFI than the intradermal method, mainly occurred early after being vaccinated, and the intradermal method had AEFI up to 12 months (Table 2).

**Reporting rate of adverse events according to the stains**

The number of BCG vaccination registered in the Integrated Management System of Disease and Public Health is shown (Fig. 1). The 336 cases to be analyzed were divided into the inoculation year. The adverse events are often not reported to the KCDC, if it is not properly received as a NIP. Therefore, it was analyzed only for reports of adverse events to regular and temporary NIP cases for fair comparison (Fig. 1). In comparison with the number of vaccinations registered, 26 cases per 100,000 doses were reported. When investigated by strains type, the incidence of adverse events per 100,000 doses was found to be 6.4 for percutaneous Tokyo strains, 41.6 for intradermal Danish strains and 25.9 for 100,000 intradermal Tokyo strains (Fig. 2).

**Adverse events type by vaccine strains**

The total 336 reported cases from January 2013 to June 2018 were divided by vaccine strains (Table 3). Regardless of inoculation strains, the most common adverse event is local abnormalities (94.9%). Local abnormalities in each strain were the highest, with 39.9 cases per 100,000 doses with intradermal Danish strains. The following cases occurred 24.4 cases per 100,000 doses with intradermal Tokyo strains, percutaneous



**Fig. 1.** Number of BCG immunization registered in the National Immunization Program Computerized Registry and number of BCG AEFI by immunization year. BCG, bacille Calmette-Guérin; PC, percutaneous; ID, intradermal; AEFI, adverse events following immunization.

**Table 3.** Type and incidence rate of BCG AEFI by strains

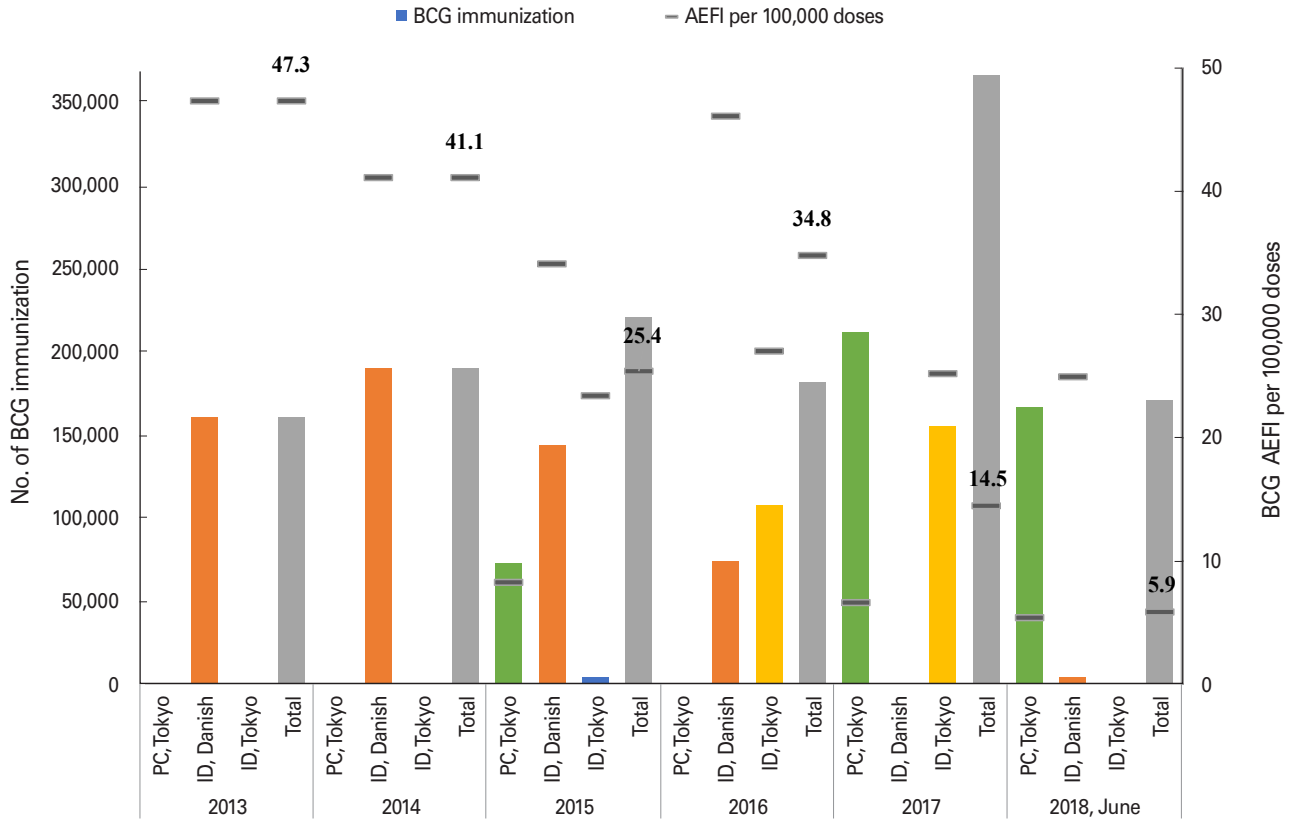
Type of AEFI	Intradermal, Danish	Tokyo	Percutaneous, Tokyo	Total
Local reaction	228 (39.9)	65 (24.4)	26 (5.8)	319 (24.8)
Suppuration <sup>a)</sup>	9 (1.6)	3 (1.1)	1 (0.2)	13 (1.0)
Injection site reactions <sup>b)</sup>	58 (10.1)	13 (4.9)	1 (0.2)	72 (5.6)
Lymphadenitis	161 (28.2)	49 (18.4)	24 (5.3)	234 (18.2)
Systemic reaction	16 (2.8)	7 (2.6)	7 (1.6)	30 (2.3)
Seizure	1 (0.2)	-	-	1 (0.1)
Allergy	1 (0.2)	3 (1.1)	1 (0.2)	5 (0.4)
Anaphylactoid reaction	1 (0.2)	-	-	1 (0.1)
Fever	7 (1.2)	2 (0.8)	3 (0.7)	12 (0.9)
Osteitis and osteomyelitis	1 (0.2)	-	-	1 (0.1)
Disseminated BCG disease	2 (0.3)	1 (0.4)	-	3 (0.3)
Others	3 (0.5)	1 (0.4)	3 (0.7)	7 (0.5)
Total	244 (42.7)	72 (27.0)	33 (7.3)	349 (27.1)

Values are presented as number (% per 100,000 doses).

BCG, bacille Calmette-Guérin; AEFI, adverse events following immunization.

<sup>a)</sup>Presence of fluctuation on palpation or pus on aspiration, the presence of sinus, or large lymph node adherent to the skin with a caseous lesion on excision.

<sup>b)</sup>Local sub-cutaneous abscess and keloids.



**Fig. 2.** The BCG AEFI incidence rate by immunization year. BCG, bacille Calmette-Guérin; PC, percutaneous; ID, intradermal; AEFI, adverse events following immunization.

ous Tokyo strains for per 100,000 doses were the lowest with 5.8 cases. The incidence of osteitis among other major abnormalities is 0.2 cases per 100,000 doses in the intradermal Danish strains, the incidence of Disseminated BCG disease is 0.3 cases per 100,000 doses in the intradermal Danish strains.

### Discussion

When two cases of death occurred after the Japanese encephalitis vaccine inoculation in 1994, public distrusted vaccination and the vaccination rate decreased. As a result, the government investigated the link between vaccination and death through epidemiological investigations, and through the revising of the law, legislated the vaccination monitoring system (1994) and the national compensation system (1995) [7]. Since 2000, the method of reporting AEFI as electronic data interchange was introduced and 2001, the Act on the Prevention of Infectious Diseases was amended to make it mandatory for doctors to report AEFI. The report of AEFI in Korea has continued since 1994 and it has been dualized to the Korea Institute of Drug Safety and the KCDC to monitor the ad-

verse events (2012) [7]. The most frequently reported cases of AEFI of KCDC is BCG, which is more than 20% of all reported cases each year [8]. Very few previous studies have reviewed the reported adverse event after BCG vaccination. Of them, there was one survey which deals with cases registered in the Integrated Management System of Disease and Public Health similar to our research. In this study of reviewing of AEFI in all vaccine, average adverse events rate after BCG vaccination was 19.0 cases/100,000 doses from 2011 to 2016 [8]. In our study, 336 cases were reported for 6 years and the incidence of adverse events per 100,000 doses was 26 cases. Compared to previous studies reporting the number of adverse events after BCG vaccine, our study may differ in that it was subdivided and analyzed an adverse event according to the strains of BCG vaccine and inoculation methods.

BCG is a vaccine against TB that is especially effective in preventing severe TB in children. In Korea, BCG vaccinations have been conducted nationwide since 1952 [3]. The first domestic BCG vaccine was produced by the National Defense Research Institute in 1960, since 1988, the Korean Institute of Tuberculosis has been producing BCG vaccines on its own,



and has a system to produce and supply all the available doses to the people of the country free of charge [3]. But, as the BCG production facility was suspended from producing vaccines in 2006, all BCG vaccines were imported since 2007 [3]. Since 1961, Korea has been using the intradermal Pasteur strain inoculation for more than 40 years and has used the imported Danish strain since 2007. And in 2015, imported intradermal Tokyo strains were also supplied. In the mid-1990s, percutaneous Tokyo strains were imported, and nowadays many hospitals and clinics use percutaneous inoculation as well as intradermal inoculation [1]. Although this variety of strains has been used, few studies have analyzed AEFI according to strains.

Different countries have different variations in the incidence of AEFI according to BCG vaccine strains. In Poland, the frequency of adverse event after BCG vaccination was two cases per 100,000 doses from 1994 to 2000. BCG vaccine being in use in Poland was Brazilian/Moreau sub strain [9]. In Iranian hospitalized children, there were 46 cases with BCG complication after Pasteur vaccination for 2 years [10]. In Saudi Arabia, a study comparing side effects with four different vaccine strains after switching to Danish strains, the incidence rate of adverse effects during the period when the Danish strains (10.14 per 1,000 doses) were vaccinated was significantly higher than before (1.96 per 1,000 doses) [11]. In Ireland, a marked increase in the number of adverse event after change to a new strain of BCG vaccine [12]. Coincidentally, the changed strain in both studies was Danish strain. In retrospective study of Latvia, the incidence of BCG adenitis after Danish vaccination was 0.11 % from 2005 to 2013 [13].

There are a few studies in Korea that examined the adverse reaction of BCG vaccine strains. According to a 2007 KCDC survey, the incidence of abnormal reaction in children with Pasteur vaccination was higher than children with the Danish vaccination [1]. As a result, intradermal strains used were changed from Pasteur to Danish in 2007 and have continued to be used until 2015 [1]. In a comparative study of adverse reactions resulting from vaccine strains from 2003 to 2009, the Pasteur strains (96.3%) were more abnormal than Danish strains (2.5%) [3]. In our study, regardless of the inoculation method, the Danish strain has more side effects than Tokyo strain when comparing the occurrence of side effects with strains. This is meaningful that the first study to compare the adverse effect of the Danish and Tokyo strains.

There are about five widely used BCG strains in the world, and each one has a different immune response aspect. Pas-

teur and Danish strains are known to have a higher preventive effect and cause more side effects than Glaxo strains, Tokyo strains, and Moreau strains [6,14]. The concentration of live particles in the vaccines varies from 50,000 to 3 million per doses, according to the strain [6]. The vaccine strains are one of the important factors affecting the incidence of abnormal reactions after BCG vaccinations [14,15]. Dose-response relationships were also observed in German and Hungary [16,17]. For proper preventive effects, the BCG germs will stay in the body for a certain period of time and induce immunity after inoculation. Therefore, low particles do not induce sufficient immune formation, and too many may cause an adverse reaction [18].

Meanwhile, there is an error in interpreting the differences in AEFI simply due to differences in vaccine strains. The variation is thought to be due to a number of factors, including the level of case finding and the diagnostic criteria employed, route of administration and technique, the age and immune status of the vaccine, and the quality, and dose of the BCG vaccine delivered [10]. Of them, one important part to investigate is how to administer the vaccine.

BCG was first used as an oral administration in 1921, but a lot of side effects have occurred, later came to administered cutaneously [19,20]. Also, cutaneous method results to better induction of delayed type hypersensitivity response to the tuberculin skin test, and lower cost [19,20]. There are two cutaneous methods (percutaneous and intradermal). BCG intradermal method is to inoculate the skin's dermis layer in the triceps to produce a 5–7 mm rash and is widely used around the world and recommended by the WHO [21]. In newborn babies, however, a significant amount of inoculation is required to administer the exact amount in the thin skin, making it difficult to inoculate. In contrast, the BCG percutaneous method is relatively simple and easy to inject a vaccine by applying a syringe to the outer skin of arm and pressing it down like a stamp with the given injection tool. However, it is not recommended by the WHO because it requires a large dose of inoculation and cannot administer the exact amount. The percutaneous method is used in a small number of countries outside Japan [1], sometimes, preferred because of less adverse events and the ease of inoculation [22,23].

One study about immune responses to intradermal and percutaneous methods showed that after 3 months of inoculation, TB-specific lymphocytes proliferative responses were only significant in intradermal injection. Also, the production of TB specific interferon-gamma was also further increased

in intradermal inoculation [24,25].

The percutaneous injection uses 50 times more bacteria than the intradermal injection, but the actual effective dose is less than the intradermal injection. Therefore, percutaneous method does not allow bacteria to pass through the cornea layer, so BCG bacteria cannot enter the proper host cell and cannot be involved in proliferating or immune response [24]. WHO also recommends intradermal BCG, and therefore KCDC also recommend intradermal BCG as national immunization [7]. Meanwhile, in Korea despite the fact that intradermal BCG vaccination is free as a national preventive vaccination business, the reason for the use of percutaneous BCG vaccination as paid, was concern about adverse reactions. In our study, when comparing adverse events according to the inoculation methods, the number of adverse events of percutaneous method per 100,000 cases has also been significantly lower than intradermal method. Although we consider that reports of adverse reactions are coming in a few years later, when compared to the reported number of cases alone, it appears that the percutaneous method has less adverse reactions than the intradermal method. However, we must consider that lymph node swelling can occur within 12 months of inoculation and that the report can last until a few years later. Also, as percutaneous Tokyo strain has been inoculated until the very latest, therefore we should consider the possibility that the reports of adverse reaction could rise later.

The most common adverse reaction after BCG immunization is local lymphadenitis, which occurs in less than 1% of those who have normal immunity. The incidence of occurrence of lymphadenitis is reported in some countries. In Ireland children with BCG vaccination, the most common side effect was suppurative lymphadenitis (61%), and the incidence of adverse events coincided with the introduction of a new strain of BCG vaccine (Danish strain) [12]. In Turkey, lymphadenitis is reported up to 25% [26], and it is estimated that the incidence of lymphadenitis in Korea will exceed 1.9% [27]. In this study, regardless of the inoculation strains, the most common adverse reaction was lymphadenitis (18.2 cases per 100,000 doses). When comparing according to strains, local abnormalities were highest with intradermal Danish strains, percutaneous Tokyo strains were lowest. As these are all within the WHO's published adverse events (the range of 10 to 100 cases per 100,000 doses) [6], therefore it is considered not to be worrisome. Hematogenous spread of BCG may result in osteomyelitis, but this is a rare complication. The incidence rate of BCG osteomyelitis was reported to be 1.11 cases in a million

in Europe [28]. Only rare cases of BCG osteomyelitis have been reported in Asia [29,30]. In previous study, there was one case who had been severe osteomyelitis as a complication of Tokyo BCG vaccination [31]. But In our study, osteitis did not occur in the Tokyo strain and only in the Danish strain. The incidence of osteitis was range of 0.2 cases per 100,000 doses and when compared with adverse reaction ratio shown in WHO's information sheet [6], it can be considered to be within the range of 0.001 to 30.0 cases per 100,000 doses. Disseminated BCG disease is rare complication with estimated incidence of 0.1–4.3 per one million vaccinated children, but is lethal in 50%–71% of the cases [32,33]. There have been reported 60 cases had fatal or systemic spread after BCG vaccination so far, most of which have been defective in the cell immune mechanism [34]. In our study, the disseminated BCG disease occurred in three cases. Of them, two cases occurred in intradermal Danish strain, and one case in intradermal Tokyo strain, the case had severe combined immune deficiency as an underlying disease.

There is one limitation in this study. The AEFI of BCG reporting rate does not equal the actual proportion of AEFI occurrence. Actual AEFI of BCG may be under-reported. Because the monitoring of AEFI is operated as a passive surveillance system, advertisement of AEFI report or interest in AEFI, convenience of reporting procedures or incentive of compensation for damages may affect the reporting rate. Also, there are many cases where there are errors on the reporting date or the contents of the reports alone do not reveal the causality of the vaccination. Therefore, there is a limit to simply assume that a reported event represents the occurrence rate of adverse event. Nevertheless, we consider it is meaningful to analyze AEFI data reported to the KCDC.

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Appendix 1. Scope of adverse reactions after vaccination that should be reported

[별표 3] <개정 2018. 9. 27.>

신고하여야 하는 예방접종 후 이상반응자의 범위(제7조 제2항 관련)		
신고하여야 하는 예방접종 후 이상반응자의 범위는 다음 표의 분류에 따라 이상반응이 발생한 자를 말한다.		
예방접종 종류	이상반응의 범위	예방접종 후 이상반응이 나타날 때까지의 시간
디프테리아, 파상풍, 백일해(DTaP, Tdap)	1. 아나필락시스	24시간 이내
	2. 뇌염, 뇌증	7일 이내
디프테리아, 파상풍(Td)	3. 위팔신경총 말초신경병증	28일 이내
디프테리아, 파상풍, 백일해, 폴리오(DTaP-IPV)		
디프테리아, 파상풍, 백일해, 폴리오, b형 헤모필루스 인플루엔자(DTaP-IPV/Hib)	5. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	6. 제1호부터 제5호까지의 이상반응으로 인한 후유증	기한 없음
폴리오(IPV)	1. 아나필락시스	24시간 이내
	2. 국소 이상반응	7일 이내
	3. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	4. 제1호부터 제3호까지의 이상반응으로 인한 후유증	기한 없음
홍역, 유행성이하선염, 풍진(MMR)	1. 아나필락시스	24시간 이내
	2. 뇌염, 뇌증	21일 이내
	3. 혈소판 감소성 자반증	7-30일
	4. 만성 관절염	42일 이내
	5. 국소 이상반응	7일 이내
	6. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	7. 제1호부터 제6호까지의 이상반응으로 인한 후유증	기한 없음
결핵(BCG)	1. 림프절 부기(지름 1.5 cm 이상)	1년 이내
	2. 골염, 골수염	6개월 이내
	3. 전신 파종성 비씨지 감염증	6개월 이내
	4. 국소 이상반응	6개월 이내
	5. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	6. 제1호부터 제5호까지의 이상반응으로 인한 후유증	기한 없음
B형간염(HepB)	1. 아나필락시스	24시간 이내
	2. 국소 이상반응	7일 이내
	3. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	4. 제1호부터 제3호까지의 이상반응으로 인한 후유증	기한 없음
수두(VAR)	1. 아나필락시스	24시간 이내
	2. 뇌염, 뇌증	7일 이내
	3. 국소 이상반응	7일 이내
	4. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	5. 제1호부터 제4호까지의 이상반응으로 인한 후유증	기한 없음

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Appendix 1. Continued

일본뇌염(IJEV, LJEV)	1. 아나필락시스	24시간 이내
	2. 뇌염, 뇌증	7일 이내
	3. 국소 이상반응	7일 이내
	4. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	5. 제1호부터 제4호까지의 이상반응으로 인한 후유증	기한 없음
B형 헤모필루스 인플루엔자(Hib)	1. 아나필락시스	24시간 이내
	2. 국소 이상반응	7일 이내
	3. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	4. 제1호부터 제3호까지의 이상반응으로 인한 후유증	기한 없음
폐렴구균(PCV, PPSV)	1. 아나필락시스	24시간 이내
	2. 국소 이상반응	7일 이내
	3. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	4. 제1호부터 제3호까지의 이상반응으로 인한 후유증	기한 없음
인플루엔자(Flu)	1. 아나필락시스	24시간 이내
	2. 위팔신경총 말초신경병증	28일 이내
	3. 국소 이상반응	7일 이내
	4. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	5. 제1호부터 제4호로 인한 후유증	기한 없음
A형간염(HepA)	1. 아나필락시스	24시간 이내
	2. 국소 이상반응	7일 이내
	3. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	4. 제1호부터 제3호로 인한 후유증	기한 없음
사람유두종 바이러스감염증(HPV)	1. 아나필락시스	24시간 이내
	2. 국소 이상반응	7일 이내
	3. 그 밖에 접종과 연관성이 있는 것으로 의심되는 이상반응	기한 없음
	4. 제1호부터 제3호로 인한 후유증	기한 없음
법 제24조 제1항 제17호에 따라 보건복지부장관이 지정한 감염병	감염병의 특성에 따라 보건복지부장관이 고시한 이상반응	감염병의 특성에 따라 보건복지부장관이 고시한 시간

Appendix 2. Report of adverse reaction after vaccination

■ 감염병의 예방 및 관리에 관한 법률 시행규칙[별지 제2호 서식] <개정 2018. 9. 27.>

예방접종 후 이상반응 발생신고(보고)서

※ 뒤쪽의 작성방법 및 신고방법 안내를 읽고 작성하여 주시기 바라며, [ ]에는 해당되는 곳에  
√표시를 합니다. (앞쪽)

예방접종 후 이상반응자 또는 사망자	성명		주민등록번호			
	(19세 미만인 경우 보호자 성명)					
	전화번호		직업	성별 [ ] 남 [ ] 여		
	주소	우편번호				
[ ] 거주지 불명 [ ] 신원 미상						
예방접종 일시	년 월 일(오전/오후) 시 분					
예방접종 기관	기관명			전화번호		
예방접종 종류 및 제품명	제조회사	제조번호	유효기간(연월일)	예방접종 부위	예방접종 방법	과거 접종 횟수
최근 4주 이내에 접종한 백신의 종류 및 접종일						
접종 전 특이사항	[ ] 5세 이하인 경우					
	※ 해당 시 접종 전 체온(°C) 출생 체중(kg)					
	[ ] 선천성 기형					
[ ] 그 밖의 기저질환						
예방접종 후 이상반응 관련 사항	이상반응 발생 일시(년/월/일/시/분)					
	이상반응 진단 일시(년/월/일)					
	이상반응 종류	국소 이상반응	[ ] 접종 부위 농양 [ ] 림프선염(화농성림프선염 포함) [ ] 심한 국소 이상반응 [ ] 연조직염			
		신경계 이상반응	[ ] 급성 마비 [ ] 뇌증 혹은 뇌염 [ ] 경련 [ ] 길랭바레증후군			
그 밖의 전신 이상반응	[ ] 알레르기 반응 [ ] 아나필락시스양 반응 [ ] 아나필락시스성 쇼크					
	[ ] 발열 [ ] 관절염 [ ] 골염 혹은 골수염 [ ] 전신파종성 비세포성비염 [ ] 혈소판 감소 자반증					

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Appendix 2. Continued

		[ ] 그 밖에 접종 후 4주 이내에 발생한 중대하거나 특이한 이상반응	
이상반응 진행상황	1. 진행 중	[ ] 생명위중 [ ] 입원치료 [ ] 외래치료 [ ] 치료 안함	
	2. 상태종료	[ ] 완전회복 [ ] 경미장애/후유증 [ ] 영구장애/후유증 [ ] 사망	
	3. 모름 [ ]		

210 mm×297 mm [백상지 80 g/m<sup>2</sup>]