# Tokyo-172 BCG Vaccination Complications, Taiwan

**To the Editor**: BCG (*Mycobacterium bovis* BCG) is a vaccine for preventing childhood tuberculosis (TB), especially military and meningeal TB. Because Taiwan has an annual TB incidence rate of ≈70 cases/100,000 persons, the National Immunization Program has included neonatal BCG vaccination since 1965. The coverage rate has remained at 97% since 2001. According to the Taiwan Tuberculosis Registry, the median rate of TB infections diagnosed in patients <10 years of age during 2005–2007 was 0.39% (60 cases) (*1*). The risk of developing childhood extrapulmonary TB without lung involvement is highest among children <5 years of age.

In 1965, the World Health Organization registered freeze-dried Tokyo-172 seed lot as an international reference vaccine strain (*2*). Tokyo-172 BCG is currently used in Taiwan, Japan, and South Korea. The vaccine is recommended as less reactogenic. Because intradermal injection is recognized as a more effective BCG administration route (*3*), it is practiced in Taiwan, while a multiple puncture method is used in Japan and South Korea. In addition, 10% BCG (Danish strain) vaccinations for infants are administrated intracutaneously in South Korea (*4*). Although BCG is effective in preventing progressive primary TB, adverse reactions to the vaccine do occur. A systemic review of adverse reactions has been established in Japan (*5*) but not in South Korea (*4*) and Taiwan (*6*).

During 1951–2004, a total of 39 cases of severe adverse vaccine reactions were reported in Japan, with an incidence rate of 0.182 cases of reactions/million vaccinations. Of the 39 cases, 27 patients (69.2%) had bone and joint involvement, and 13 (33.3%) had primary immunodeficiency (*4*). One patient had both complications. The BCG vaccine was initially produced in Taiwan using Pasteur-1173 P2 strain (0.025 mg/0.1mL) and changed to the less reactogenic Tokyo-172 strain (0.05 mg/0.1 mL) in 1979. From 1998 through 2007, 14 patients applied for compensation through the vaccine injury compensation program for BCG-caused adverse reaction, and 6 claims were confirmed. Of the 6 confirmed BCG complications cases, 5 patients had humeral or sternal osteomyelitis and 1 patient died from a disseminated BCG infection. Accordingly, in 2002–2006 the risk for BCG osteitis/osteomyelitis and disseminated BCG infection was 3.68 and 0.9 per million, respectively (*6*). Incidence of severe complications was higher than that documented in Japan.

Because Taiwan lacks diagnosis and postmarketing surveillance system, BCG-related complications might be underreported. As part of initiating a comprehensive adverse events surveillance, a laboratory program to differentiate *M. bovis* BCG from other species of the *M. tuberculosis* complex was established to monitor local adverse events (injection-site abscess, lymphadenitis) and severe complications (suppurative lymphadentitis, BCG osteitis/osteomyelitis, and disseminated BCG infection) among vaccinated children.

During 2005–2007, 19 clinical specimens (6 biopsy samples and 13 bacterial isolates) of suspected BCG-infection childhood TB cases were sent to the Taiwan Centers for Disease Control. To differentiate among *M. tuberculosis*, *M. bovis*, and *M. bovis* BCG, DNA samples were initially screened using a GenoType kit (Hain Lifescience GmbH, Nehren, Germany), multiplex PCR (*7*), and pncA sequencing (*8*). In addition, spoligotyping was performed with a commercial kit (Isogen Bioscience BV, Maarssen, the Netherlands). An additional multiplex PCR (*9*) was used to differentiate vaccine strains. Medical charts were reviewed to determine sites of involvement and severity of complications.

Of the 19 patients, 1 (5.3%), 2 (10.5%), 15 (78.9%), and 1 (5.3%) were infected with *M. tuberculosis* complex, *M. tuberculosis*, *M. bovis* BCG, and *M. abscessus*, respectively. All identified *M. bovis* BCG isolates had the same spoligotype as the Tokyo-172 vaccine strain. The median age of BCG-related complication patients was 2 years (range 1–9 years), and the male:female ratio was 1.5. Of the 15 *M. bovis* BCG–infected patients, 14 had extrapulmonary sites of involvement, including 8 bone and joint, 3 suppurative lymphadenitis in axillary lymph node, 2 subcutaneous abscess away from the injection site, 1 injection-site abscess, and 1 disseminated BCG infection (Table).

According to an international survey, the estimated rate of osteitis/osteomyelitis is 1–700/1,000,000 vaccinated newborns or infants with different strain-derived BCG (*10*). In Taiwan, the estimated incidence of BCG osteitis/osteomyelitis was 12.9 cases (8/621,853; 95% confidence interval 4–21.8) per million vaccinations during 2005–2007. Previously reported complications of BCG osteitis/osteomyelitis related to Tokyo-172 strain might be underestimated. The association between administration route and osteitis/osteomyelitis with Tokyo-172 BCG remains obscure. The potency and safety of BCG prepared from Tokyo-172 stain are under reevaluation as one of the action plans of National TB Program. The stability and quality control of vaccines strain, production processes, and intradermal injection techniques are being reappraised.

Furthermore, a policy of enhanced childhood TB surveillance was implemented in 2007, and clinicians were advised to send clinical specimens to the Centers for Disease Control in Taiwan for differential diagnosis of *M. bovis* BCG for patients <5 years of

Table. Characteristics *Mycobacterium bovis* BCG complication cases, Taiwan, 2005–2007*

| Patient no. | Sex/age at diagnosis, y | Year reported | Specimen | Diagnosis and site of involvement |
|---|---|---|---|---|
| 1 | F/2 | 2005 | Biopsy sample | BCG osteitis/osteomyelitis, right ankle |
| 2 | M/1 | 2005 | Bacterial isolate | Subcutaneous abscess, left anterior chest wall |
| 3 | M/2 | 2005 | Bacterial isolate | Severe combined immunodeficiency, disseminated BCGitis |
| 4 | M/9 | 2005 | Bacterial isolate | Suppurative lymphadenitis |
| 5 | F/1 | 2005 | Bacterial isolate | Injection-site abscess |
| 6 | M/1 | 2005 | Biopsy sample | Suppurative lymphadenitis |
| 7 | M/2 | 2006 | Bacterial isolate | BCG osteitis/osteomyelitis, right distal femoris |
| 8 | M/2 | 2006 | Bacterial isolate | BCG osteitis/osteomyelitis |
| 9 | F/1 | 2006 | Bacterial isolate | BCG osteitis/osteomyelitis, left distal femoris |
| 10 | F/1 | 2006 | Bacterial isolate | BCG osteitis/osteomyelitis, left distal radius |
| 11 | F/2 | 2007 | Bacterial isolate | BCG osteitis/osteomyelitis, right knee |
| 12 | M/1 | 2007 | Bacterial isolate | Subcutaneous abscess, left wrist |
| 13 | M/2 | 2007 | Biopsy sample | BCG osteitis/osteomyelitis, right ankle |
| 14 | F/1 | 2007 | Bacterial isolate | Suppurative lymphadentitis |
| 15 | M/2 | 2007 | Bacterial isolate | BCG osteitis/osteomyelitis, left proximal tibia |

*BCGitis, disseminated BCG infection.

age. In particular, suspected childhood TB patients without an identifiable TB contact and with normal immune status were subjected to further investigations. Multidisciplinary management, including enhanced laboratory diagnosis of atypical bony lesions in infants and children, is recommended for any suspected TB infection. Once BCG-related infection is confirmed, medical treatment has to be consistent.

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### References

1. Taiwan Centers for Disease Control. Statistics of communicable diseases and surveillance report, tuberculosis, 2005–2007. Taipei, Taiwan: Taiwan Centers for Disease Control.
2. Yamamoto S, Yamamoto T. Historical review of BCG vaccine in Japan. Jpn J Infect Dis. 2007;60:331–6.
3. Plotkin SA, Orenstein WA, Offit PA. Vaccines, 5th ed. Philadelphia: Saunders Elsevier; 2008:867.
4. Kim SH, Kim SY, Eun BW, Yoo WJ, Park KU, Choi EH, et al. BCG ostemyelitis caused by the BCG Tokyo strain and confirmed by molecular method. Vaccine. 2008;26:4379–81.
5. Toida I, Nakata S. Severe adverse reaction with Japanese BCG vaccine: a review. Kekkaku. 2007;82:809–24.
6. Sheu GC, Yang SL, Lee CD, Liu DP. Adverse events induced by BCG immunization in Taiwan. Taiwan Epidemiology Bulletin. 2008;24:357–71.
7. Yeboah-Manu D, Yates MD, Wilson SM. Application of a simple multiplex PCR to aid in routine work of the mycobacterium reference laboratory. J Clin Microbiol. 2001;39:4166–8. DOI: 10.1128/JCM.39.11.4166-4168.2001
8. Scorpio A, Collins D, Whipple D, Cave D, Bates J, Zhang Y. Rapid differentiation of bovine and human tubercle bacilli based on a characteristic mutation in the bovine pyrazinamidase gene. J Clin Microbiol. 1997;35:106–10.
9. Bedwell J, Kairo SK, Behr MA, Bygraves JA. Identification of substrains of BCG vaccine using multiplex PCR. Vaccine. 2001;19:2146–51. DOI: 10.1016/S0264-410X(00)00369-8
10. World Health Organization. Supplementary information on vaccine safety by World Health Organization: Part 2: Background and rates of adverse events following immunization. Geneva: The Organization; 2000.

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## Reemergence of Bolivian Hemorrhagic Fever, 2007–2008

**To the Editor:** Bolivian hemorrhagic fever (BHF) was first described in 1959 during outbreaks affecting isolated human communities in eastern Bolivia. However, it was not until 1963 that the etiologic agent, Machupo virus, was isolated from the spleen of a patient who died from this disease (*1*). Although no cases were reported between 1976 and 1993, an outbreak occurred in 1994 and sporadic cases have been observed since then.

In February and March 2007, at least 20 suspected BHF cases (3 fatal) were reported to the El Servicio Departamental de Salud (SEDES) in Beni,