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Original Article

The Active Surveillance of BCG-related Adverse Events

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Abstract

Bacillus Calmette-Guérin is a live attenuated vaccine. It protects children from mortality due to tuberculosis meningitis and disseminated tuberculosis disease, and the World Health Organization suggests that BCG vaccination should be completed in infancy. In Taiwan, with the decline in the prevalence of tuberculosis, as well as the dramatic drop in birth rate, both the number and incidence of tuberculosis in children have reached a new low. BCG vaccination brings about a certain percentage of serious adverse events, such as disseminated BCG-related disease and BCG-related osteomyelitis/osteitis, which start to be taken seriously with the low number of tuberculosis in children. After weighing the mortality and long-term side effect caused by tuberculosis meningitis and disseminated tuberculosis disease, as well as the impact of disseminated BCG-related disease and BCG-related osteomyelitis/osteitis, the public health department and medical experts propose routine neonatal BCG vaccination according to the recommendation of the International Union Against Tuberculosis and Lung Disease. Taiwan Centers for Disease Control will continue monitoring the serious adverse events due to the BCG quality and vaccination actively; moreover, promote the relevant units to establish the active reporting system of vaccine adverse events by the public and medical institutes. In addition, we will help the related units to assist the family of children suffered from vaccine adverse events to claim for vaccine injury compensation. The long range goal of the national tuberculosis policy is to promote TB contacts to receive treatment for latent infection, and further decrease the tuberculosis incidence in young generation and work for the stop of BCG vaccination.

Keywords: tuberculosis in children, Bacillus Calmette-Guérin, surveillance of vaccine safety, public health strategy

History of BCG vaccination

BCG vaccination in Taiwan follows the footsteps of the World Health Organization (WHO). The first use of BCG is a liquid vaccine, which was certified by the WHO since 1953. It was prepared from old Pasteur strain in Pasteur Institute, France. The BCG vaccine was switched to a new Pasteur strain from 1956 and Tween 80 was removed from BCG vaccine in 1971 based on the suggestions from experts [1], since Tween 80 in BCG will increase the risk of lymph node enlargement. In 1979, BCG was changed to freeze-dried vaccine manufactured from Japan Tokyo 172 strain. In the past 30 years, the BCG vaccine targets are mainly preschool children aged between 1 and 5 years. There are around 20-30 ten thousand doses of BCG vaccination in infants and newborn each year. However, the number of vaccination had dropped to below 20 ten thousand from 2008 onwards because of the decline in the birth rate [2].

The effectiveness of BCG vaccination

BCG is one of the most widely used and the oldest vaccines in human history, but the protection against tuberculosis infection shown in research done in different areas varies, and which brings about a debate [3]. However, the meta-analysis of the published literature proved that the BCG vaccine can actually protect against tuberculosis meningitis and disseminated disease in infants, effectively decrease infant deaths or complications due to tuberculosis [4]. By the late 1930s, the double blinded randomized control trial of BCG vaccine in Alaska, US, indicated that, after 60 years, there was 52% difference in TB incidence (including pulmonary tuberculosis) between community with vaccination and community without vaccination, suggesting the protection and effectiveness of BCG vaccine for pulmonary tuberculosis. In countries with high prevalence of tuberculosis, BCG vaccination is an effective and inexpensive measure to protect infants from tuberculosis. At US$2–3 per dose, BCG vaccination costs US$206 (US$150-72) per year to save one with tuberculosis meningitis or disseminated TB-related life [5]. Therefore, the WHO made an appeal that BCG vaccination should be completed in infancy. In 2009, the global BCG vaccination coverage was about 88%, and the Western Pacific region where Taiwan belongs, has the highest coverage rate among all regions [6]. In relation to the data in Taiwan, there are three reasons to support the neonatal BCG vaccination [7]. Firstly, from 1965 to 1970, neonatal BCG vaccination was promoted in Taiwan and the coverage rate was reached to 70-80%. In the meantime, there was a significant decrease in the children mortality rate of pulmonary and extra-pulmonary tuberculosis under five years old. Secondly, in accordance with the data in the late 1990s, although the incidence of tuberculosis in Taiwan was 10 times more than in the United States, the incidence of tuberculosis under five years old in Taiwan was the same as that in the US (5/100,000), showing that the neonatal BCG vaccination given in Taiwan but not in the US, provides protection in children. Finally, based on the number of live births between year 2002 and 2007 in Taiwan, children without completing the BCG

vaccination had 16 times higher incidence of tuberculosis meningitis than children with BCG vaccination.

Adverse reactions of BCG vaccination

BCG is a live attenuated vaccine, and which causes a papule at the site of injection after vaccination in 7 to 14 days. After that, the papule will keep growing without fever. The papule may develop into pustules or ulcers after 4 to 6 weeks and heal between 2 and 3 months later, leaving a small scar [8]. Mostly BCG-induced adverse reactions are local reactions. In addition to ulcers near injection site, the most common are local lymphadenitis or suppurative lymphadenitits, located in axilla area on injection site (left side in Taiwan) or near clavicle area [9]. Studies have shown that these local adverse reactions are related to the strain of viable bacilli, techniques of injection, doses of vaccine and individual physical condition [10]. The Pasteur and Copenhagen strains have generally been found to be more reactogenic than the Tokyo, Glaxo or Brazilian strains, and vaccinated persons are more likely to have local reactions [10]. Moreover, if the inoculator gives subcutaneous injection instead of intradermal injection, meaning inject too deep, it is not likely to have a bulge and local pus formation is more likely. Since local reactions are mild reactions, only a small number of suppurative lymphadenitis needs debridement and medical treatment. The vast majority will resolve itself or drain discharge automatically without drug use.

Nevertheless, BCG vaccine may cause severe adverse reactions, such as BCG osteomyelitis/osteitis and disseminated BCG infection. So far there is no evidence that these severe reactions are correlated with the methods and technique of injection. However, BCG osteomyelitis/osteitis is related with the change of vaccine strains [11], whereas the disseminated BCG disease is highly related to immunodeficiency. From 1998, there had been a series of cases of BCG osteomyelitis/osteititis and disseminated BCG infection in children reported in Taiwan [12-17]. Most of the BCG osteomyelitis/osteitis patients were children < 2 years old and healthy before the onset of the disease. After diagnosis, there was no evidence that people with the same disease received the same batch of vaccine, and these diseases were not relevant to the method and technique of injection or doses of vaccine. It seems severe adverse reactions has occurred by chance. Most of the published cases of disseminated BCG diseases have identified causes of immune deficiency [18], including two infants with severe combined immunity deficiency (SCID) having the deletion or mutation of interlukin-2 (IL-2). Children with clinical manifestation as disseminated BCG diseases were further diagnosed as severe immunodeficiency, and the mortality of the immunocompromised children was reduced through matched cord blood/bone marrow transplantation. Research also points out that some children with multiple skin lesions caused by BCG vaccination have primary autoimmune neutropenia or chronic mucocutaneous candidiasis through immunoassay [18]. Some of the patients with deficiency of IL-2 would be infected by non-tuberculous mycobacterium sooner or later, depending on the degree of deletion or variation.

Active and passive surveillance of adverse reaction after BCG vaccination in Taiwan

In 1988, the Taiwan government established "Rules for the establishment of Compensation Fund for Vaccine Injury ", and the “Rules for the Vaccine Injury Compensation ” was implemented in 1992. After some amendments, the compensations are classified into death benefits, disability benefits, serious diseases benefits and other payments due to vaccination associated adverse reactions according to the impact of clinical adverse reactions. The suspected victims or their families have to claim for compensation from local health authorities, and the claim will be reviewed by the committee of Vaccine Injury Compensation.

The protocol of differential diagnosis of BCG strains was established in 2004 by the National Reference Mycobacterial laboratory in Research and Diagnostic Center (6^{th} division), Taiwan Centers for Disease Control (Taiwan CDC). The laboratory is responsible for specimen testing and strain differentiation which is suspected due to BCG vaccination from hospital. The laboratory not only provides reports to people who claim for vaccine injury compensation but also feedback to hospitals. Since 2007, the laboratory offers the examination for extrapulmonary tuberculosis strain in children <5 years old or pathological specimens which cannot be isolated. At the end of 2007, the Advisory Committee on Immunization Vaccination Practices (ACIP) realized that the passive surveillance would inevitably underestimate the incidence of vaccine adverse events, and suggested active surveillance of BCG-related adverse events at Taiwan CDC (Table). Therefore, hospitals are asked quarterly sending extra-pulmonary tuberculosis strains in children <5 years old and pathological specimens which cannot be isolated to the National Reference Mycobacterial laboratory for further examination. The Committee also requested to improve the quality control of vaccines, training on inoculators, and the quality control of technical evaluation of inoculation. After promotion and revision, the active surveillance increased the ratio of testing to reporting. For children < 5 years old, the percentage of sending strains or specimens in reporting cases of extra-pulmonary tuberculosis increased from 26% in 2006, 19% in 2007 to 86% in 2008 and 94% in 2009, respectively [19]. Most importantly, the specimens of 14 reporting cases of tuberculosis arthritis and osteomyelitis/osteitis in 2009 were 100% sent to the laboratory and 64% of them were confirmed to be BCG-related diseases. Preliminary analysis of data shows that in addition to infants with SCID or immunocompromised patients with leukemia

Table The Methods and results of passive and active surveillance of BCG-related adverse events in Taiwan

Year	Surveillance system	Methods (Stragegy)	Results
2004~2007	Passive surveillance	Taiwan CDC provides clinical laboratory testing and receives specimens from hospitals	In children < 5 years old, the percentage of sending specimens or strains in reporting cases of extrapulmonary TB is 26% in 2006 and 19% in 2007
2008~now	Active surveillance	Performed by public health unit, reviewing laboratory testing of reporting cases quarterly from 2008 and monthly from 2010	In children < 5 years old, the percentage of sending specimens or strains in reporting cases of extrapulmonary TB is 86% in 2008 and 94% in 2009

underwent chemotherapy may contract disseminated BCG diseases and even lead to death. Most of the adverse reactions caused by BCG are local and self-limited without sequela. Some cases of BCG osteomyelitis/osteitis attack joints, which needs debridement for diagnosis and short-term rehabilitation to restore function. However, after completion of medical treatment course, it has no long-term effect on movement and development.

During 2005 through 2007, 13 bacterial isolates and 6 biopsy samples of suspected BCG-infection TB cases were sent to the laboratory. Eight cases were confirmed as BCG-related bone and joint diseases and they were all children aged younger than 2 years [20]. One of the strains was from a 9-year-old child with primary autoimmune neutropenia who had suppurative lymphadenitis due to immune deficiency [18]. At the end of 2009, Taiwan CDC reported the results of active surveillance to the ACIP, and which showed that the incidence of BCG-related osteomyelitis/osteitis in 2008 birth cohort was approximately 41 per million estimated by medical chart review and laboratory diagnosis. In addition to maintaining the original vaccination policy, the Committee decided to expand the targets of active surveillance of BCG-related adverse events to children with extra-pulmonary tuberculosis under the age of 15. From 2010, Taiwan CDC started to review the samples monthly. Samples from BCG-related bone and joint diseases in children <5 years old were 100% collected. Seventy-five percent of samples from children aged 5-14 were sent to the laboratory and none of them was BCG related. This surveillance will continue until the end of 2011 under the recommendation of the Committee. The incidence of BCG related osteomyelitis/osteitis in 2008 birth cohort is estimated nearly 50 per million till the end of 2010. The incidence of disseminated BCG diseases in 2003, 2004, and 2006 birth cohort is 4 per million (one case each year) and there was no case in 2005 and 2007-2009.

Discussion

Through the implementation of active surveillance of BCG-related serious adverse reactions, the incidence of disseminated BCG disease in Taiwan is around 0-4 per million, consistent with the statistic data of vaccine-related adverse events reported by WHO [10], which was less than 5 per million doses. According to WHO, the incidence of BCG-related osteomyelitis/osteitis is around 1-700 per million doses. In Taiwan, the incidence is 50 per million based on the surveillance data from 2008 birth cohort, and this incidence rate is in the acceptable scope. In the past, most of the cases reports were found in Northern Europe and Eastern Europe [21], which was considered to be related to the change of BCG strain [11]. However, the reported incidences of BCG-related adverse events from Tokyo and Pasteur strains are very low [22]. In Taiwan, Tokyo 172 strain vaccine had been used for 30 years and there was no change in vaccine strains or manufacture process. The research on quality control of BCG vaccine shows the stability of quality as well [23]. We will keep monitoring the incidence of BCG-related adverse events in order to make sure there is no abnormal increase in adverse events.

As for other BCG-related adverse events, the WHO statistics shows that the incidence of suppurative lymphadenitis is between 100 and 1000 people per million doses [10]. The incidence of adverse events can be effectively reduced by trained personnel using standard freeze-dried vaccine and administering BCG vaccines with appropriate dosage in accordance with the age of each individual [24]. Currently, the vaccinators in Taiwan are requested to have initial training and the validation of intradermal injection, as well as receive the technical evaluation every two years in order to perform BCG vaccine administration. In addition to neonatal vaccination, the tuberculin skin test, used for diagnosis for latent tuberculosis infection, needs the specific technique as well. Since the strategy of expanding the targets of diagnosis and treatment of latent tuberculosis infection in contacts of TB, it needs the efforts from both central and local health units to implement the evaluation of technique and further maintain the high-standard inoculation technique.

The International Union Against Tuberculosis and Lung Disease proposed that countries with detailed tuberculosis reporting system and being able to reach one of the following criteria may consider the strategy such as selective BCG vaccination [25], meaning that routine neonatal BCG vaccination may not be required if the prevalence of infectious tuberculosis is very low. The first criterion is that the annual incidence of smear positive cases should be less than 5 per 100,000 people. In Taiwan, the current annual incidence of smear positive cases is 25 per 100,000 people [26]. The second is the notification rate of TB meningitis in children under five years old is less than one per ten million people in the past five years. In Taiwan, there were three reporting cases and two confirmed cases (no mortality) of TB meningitis in children under five years old between 2006 and 2010. However, there were 17 cases reported and 10 of them were confirmed as TB meningitis with 3 mortality cases during 2002 and 2005. The last criterion is that the annual infection rate is less than 0.1%. According to the results of tuberculin skin test in non-vaccinated first-grade students in primary schools, the annual infection rate is estimated to be 1%.

According to the above information, the ACIP made a resolution to continue routine neonatal BCG vaccination. Hence, Taiwan CDC closely and actively monitor the few serious adverse reactions caused by BCG quality and vaccination, in particularly for the extra-pulmonary tuberculosis children <5 years old, whose specimens and strains are sent for examination compulsively to exclude BCG-related adverse reactions. Currently the incidence of adverse reactions is fairly stable. The targets of surveillance system expanded to children <15 years old with extra-pulmonary tuberculosis from 2010 and will continue till 2011. Taiwan CDC will keep reviewing samples monthly and conducting complete and comprehensive surveillance system of BCG-related adverse events. The Food and Drug Administration (FDA) was established in 2010. The development of active reporting system of vaccine adverse events for the public and medical units is one of the priorities in the discussion between FDA and Taiwan CDC. A consensus is reached that in addition to other routine childhood immunization, BCG should be included in the active reporting system as well. Meanwhile, Taiwan CDC

entrusts to handle the annual training of BCG inoculators, teaching the trainers, and routine technical evaluation for people with credentials every two years. For the household with adverse events, the local health units will home visit and provide care and help the family to confirm the diagnosis in order to claim the vaccine injury compensation.

The best way to avoid the damage of BCG-related adverse events to children is to reduce the risk of tuberculosis transmission from adults to children, which gives a chance to stop national routine BCG vaccination and shift to selective BCG vaccination policy [23]. Now we are in the sixth year of the “halving tuberculosis in ten years”¸ and the risk of tuberculosis infection in Taiwan is reducing gradually based on the three indicators of selective BCG vaccination policy suggested by the International Union Against Tuberculosis and Lung Disease. The policy in 2008 decided that TB contacts younger than 13 years of age should be subjected to evaluation and treatment of latent infection is likely to be expanded to contacts in all children even young adult in 2012. The purpose of this lifelong education is to decrease the incidence of tuberculosis in the young generation and effectively lower the risk of being exposed to tuberculosis in children [27]. Furthermore, we can fulfill the criteria of discontinuing routine BCG vaccination and have the discussion about the likelihood of selective BCG vaccination later.

Conclusion

After weighing the mortality and long-term side effects caused by tuberculosis meningitis or disseminated tuberculosis disease and the impact from sporadic BCG-related disease and BCG-related osteitis, the public health department and medical experts follow the recommendation of the International Union Against Tuberculosis and Lung Disease about routine neonatal BCG vaccination. Taiwan CDC will continue actively monitoring BCG quality, and the very few serious adverse events triggered by BCG vaccination. The long range goal of the national tuberculosis policy is to promote TB contacts to receive treatment for latent infection, and further decrease the tuberculosis incidence in young generation and work for the stop of BCG vaccination.

References

1. Provincial Chronic Disease Control Bureau. A review of the tuberculosis control program in Taiwan, 1949–1989: chronological development of the program, BCG vaccination. Taipei, Taiwan: Provincial Chronic Disease Control Bureau 1991:4-37.
2. Sheu GC, Yang SL, Lee CD, et al. Adverse Events Induced by BCG Immunization in Taiwan. Taiwan Epidemiol Bull 2008;24:357-71.
3. Tripathy SP. Fifteen-year follow-up of the Indian BCG prevention trial. Bull Int Union Tuberc Lung Dis 1987;62:69-73.
4. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. JAMA 1994;271:698-702.

5. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006;367:1173-80.
6. WHO/UNICEF coverage estimates 1980-2009, July 193 WHO member states, Date of slides, 6 July 2010.
7. Chan PC, Huang LM, Kuo SH. Is Neonatal Bacillus Calmette-Guérin Vaccination Protective in Taiwan? J Formos Med Assoc 2008;107:195-7.
8. Taiwan CDC. Chapter 16. BCG vaccination. The Tuberculosis Working Manual. Available on http://www.cdc.gov.tw/public/Attachment/021951571.pdf. Accessed on April 27, 2011.
9. Fine PEM, Carneiro IAM, Milstien JB, et al. Issues relating to the use of BCG in immunization programmes. WHO/V&B/99.23. Geneva, Switzerland: World Health Organization, 1999.
10. WHO 2000. Supplementary information on vaccine safety: Part2: Background and rates of adverse events following immunization. Available at:http://whqlibdoc.who.int/hq/2000/WHO_V&B_00.36.pdf
11. Lotte A, Dam HG, Henderson R. Second IUATLD study on complications induced by intradermal BCG vaccination. Bull Int Union Tuberc Lung Dis 1988; 63:47-59.
12. Yan JJ, Chen FF, Jin YT, et al. Differentiation of BCG-induced lymphadenitis from tuberculosis in lymph node biopsy specimens bymolecular analyses of pncA and oxyR. J Pathol 1998;184:96-102.
13. Lin CJ, Yang WS, Yan JJ, et al. Mycobacterium bovis osteomyelitis as acomplication of Bacille Calmette-Guérin (BCG) vaccination: rapid diagnosis with use of DNA sequencing analysis: a case report. J Bone Joint Surg Am 1999;81:1305-11.
14. Wang TC, Tzen CY, Su HY. Erythema induratum associated with tuberculous lymphadenitis: analysis of a case using polymerase chain reactions with different primer pairs to differentiate bacille Calmette-Guérin (BCG) from virulent strains of Mycobacterium tuberculosis complex. J Dermatol 2000;27:717-23.
15. Huang CY, Su WJ, Perng RP. Childhood tuberculosis presenting as an anterior chest wall abscess. J Formos Med Assoc 2001;100:829-31.
16. Lin WJ, Lu JJ, Chu CC, et al. Calmette-Guérin bacillus sternalosteomyelitis diagnosed by DNA sequencing analysis of PNC A. Pediatr Infect Dis J 2004;23:784-6.
17. Huang LH, Shyur SD, Weng JD, et al. Disseminated Bacille Calmette-Guérin disease as the initial presentation of X-linked severecombined immunodeficiency--a case report. Asian Pac J Allergy Immunol 2005;23:221-6.
18. Lee WI, Liang FC, Huang JL, et al. Immunologic analysis of HIV-uninfected Taiwanese children with BCG-induced disease. J Clin Immunol 2009;29:319-29.
19. Chan PC, Lee PH, Wang KF, et al. Improving surveillance of Bacillus Calmette-Guérin related adverse effects among children aged under five. The 3rd Asia Pacific Region

Biannual Conference of IUATLD, Hong Kong, 2011.
20. Jou R, Huang WL, Su WJ. Tokyo-172 BCG Vaccination Complications, Taiwan EID 2009;15:1525-6.
21. Bolger T, O'Connell M, Menon A, et al. Complications associated with the Bacille Calmette- Guérin vaccination in Ireland. Arch Dis Child 2006;91:594-7.
22. Lotte A, Wasz-Hockert O, Poisson N, et al. A bibliography of the complications of BCG vaccination: a comprehensive list of the world literature since the introduction of BCG up to July 1982. Adv Tub Res 1984;21:194-245.
23. Yang SL, Lee TD, Zhen YF etc. The Effectiveness Evaluation of Molecular Genotyping Identification of BCG for Vaccine Quality Control. Taiwan Epidemiol Bull 2011;27:157-65.
24. Kabra SK, Jain Y, Seth MV. BCG associated adenitis. Lancet 1993;341:970.
25. International Union Against Tuberculosis and Lung Disease. Criteria for discontinuation of vaccination programmes using Bacille Calmette Guerin (BCG) in countries with a low prevalence of tuberculosis. Tubercle and Lung Dis 1994;75:179-81.
26. Taiwan CDC. Taiwan tuberculosis control report 2010. Available on http://www.cdc.gov.tw/public/data/1117169971.pdf
27. Ziv E, Daley CL, Blower SM. Early therapy for latent tuberculosis infection. Am J Epidemiol. 2001;153:381-5.

Outbreak Investigation Express

Causes of Death Associated with Complicated Influenza-Taiwan, 2011-2012 Influenza Season

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Influenza can be complicated with pulmonary and extrapulmonary diseases, secondary bacterial infection, and exacerbation of underlying chronic conditions. From July 1, 2011 to January 16, 2012, Taiwan Centers of Disease Control was notified of 587 cases of complicated influenza, including 28 (4.8%) deaths of which 20 tested positive for influenza B and 8 for influenza A (H3). Medical records were reviewed to determine the major causes of death. The 22 deceased adults were aged 48–98 years; all had underlying chronic conditions. Major causes of adult death included influenza virus pneumonia (n =14), exacerbation of chronic diseases (n

=5), *Staphylococcus aureus* sepsis from pneumonia (n=1) and skin wound infection (n=1), and *Acinetobacter baumannii* sepsis (n=1). The 6 deceased children were aged 10 months to 12 years; two had an underlying chronic condition (Kawasaki disease and hypoxic encephalopathy, respectively). Major causes of pediatric death included influenza myocarditis (n=2), influenza encephalitis (n=2), influenza virus pneumonia (n=1), and invasive pneumococcal disease (n=1). Health care providers should assess patients with influenza or influenza-like illnesses for emergency warning signs, and take influenza-related secondary bacterial infection and exacerbation of chronic conditions into consideration.

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