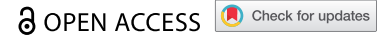


SHORT REPORT



First vaccination after birth: serious adverse events of Bacillus Calmette-Guérin (BCG) in real-world

Jinmiao Lu ^a, Xunjie Zhang ^a, Hong Xu ^b, and Zhiping Li ^a

^aDepartment of Clinical Pharmacy, National Children's Medical Center, Children's Hospital of Fudan University, Shanghai, China; ^bDepartment of Nephrology, National Children's Medical Center, Children's Hospital of Fudan University, Shanghai, China

ABSTRACT

The Bacillus Calmette-Guérin (BCG) vaccine is a free vaccine in China, and more than 300 million newborns have been vaccinated. Inevitably, the BCG vaccine will have some rare adverse events on the first day of life (24 hours after birth), but related reports are extremely rare. In this commentary, the authors searched the Chinese legal documents database for documents related to serious adverse events caused by BCG from January 2010 to January 2022. Fourteen pediatric cases were identified, including 7 preterm infants and 7 full-term infants. The events included 4 cases of interstitial pneumonia, 3 cases of lymphadenitis, 3 cases of septicemia, 1 case of myocarditis, 1 case of muscle atrophy, 1 case of epilepsy, and 1 case of disseminated BCG vaccine. The mortality rate of preterm infants was 100% and that of full-term infants was 28.6% (2/7). All deaths occurred within one day. The BCG vaccine has good safety for the vast majority of newborns.

CLINICAL IMPLICATION

- To our knowledge, we present the largest case series of BCG vaccine-induced serious adverse events in neonates.
- The BCG vaccine has good safety for the vast majority of newborns.
- The incidence of serious adverse events with BCG vaccine may be as low as eight per million.

ARTICLE HISTORY

Received 7 March 2022
Revised 6 May 2022
Accepted 18 May 2022

KEYWORDS

Serious adverse; Bacillus Calmette-Guérin; vaccine; premature; neonate

Introduction

Tuberculosis is one of the leading causes of death worldwide, affecting 12% of children.¹ Bacillus Calmette-Guérin (BCG) is the most widely used vaccine globally since 1921 and the only vaccine against tuberculosis. Recent evidence suggests that the nonspecific effect of BCG vaccination may also protect patients from COVID-19.² The WHO recommends the universal use of single-dose BCG vaccination at birth in areas with a high prevalence of high tuberculosis risk. Since 2002, the BCG vaccine has been used free of charge in Chinese newborns, and so far, more than 300 million children have been vaccinated.

BCG is a live attenuated vaccine administered intradermally, slightly below the middle of the upper arm deltoid muscle, on the first day of a healthy infant (within 24 hours after birth). For preterm infants with gestational age ≤ 31 weeks, vaccination should be completed within 3 months of birth. A common side effect of the BCG vaccine's injection is a red, swollen, infiltrating papule at the inoculation site, followed by ulceration and scarring, leaving a permanent scar. This side effect can last for up to 6 months. It is generally self-limiting and does not require treatment.³ Serious adverse events requiring hospitalization, including lymphadenitis, tuberculous osteomyelitis, and disseminated tuberculosis infection, were rarely reported.⁴ This study collated 14 serious adverse events related to the BCG vaccine's vaccination in China from the China legal documents

website database. A causality assessment, patient presentation, and treatment history for all cases are listed in Table 1.

Method

The authors searched the database (<https://wenshu.court.gov.cn/>) from January 2010 to January 2022. Pediatric cases with serious adverse events after BCG vaccination were included. The adverse event is defined as serious if the outcome of the patient is dead, life-threatening, requires hospitalization, prolongation of hospitalization, permanent disability, or require interventions to prevent these consequences. There is a complete process for the identification of vaccine disputes in China. First, once a drug or vaccine case is identified as an "adverse reaction," human errors have already been ruled out by professionals. Second, according to legal requirements, expert group identification needs to start within 5 days after the incident, so that experts involved in the identification could obtain first-hand clinical data on all patient's basic medical conditions. Finally, all five participating experts were drawn randomly and anonymously. Therefore, judges believe that the panel's conclusions are prudent and reliable. The expert used the subjective evaluation method to judge the causality of adverse reactions to vaccines in China, which was consistent with the evaluation method adopted by the Swedish regulatory agency.⁵ The panel members evaluated causality by considering seven factors: time sequence, medicine information,

Table 1. Summary of severe adverse reaction due to Chinese BCG vaccine (n = 14).

Gender	Gestational weeks	Postnatal age (days)	Occurrence time	Clinical diagnosis/Patient presentation	Prognosis	Caused by the vaccine*
Female	Premature (30 weeks)	61	On the day of vaccination	Sepsis/She was diagnosed with infections in multiple organs, peripheral circulatory failure, and immediate death.	Death	Yes
Male	Premature (34 weeks)	14	On the day of vaccination	Myocarditis/The cyanotic complexion, myocarditis with atelectasis, died of respiratory and circulatory failure on the same day.	Death	Yes
Male	Full-term (38 weeks)	1	2 months later	Disseminated tuberculosis/Disseminated tuberculosis, left armpit mass suppuration, fever, multiorgan failure, died on the day of hospitalization.	Death	Yes
Male	Full-term (38 weeks)	1	On the day of vaccination	Suppurative lymphadenitis/Lymphadenopathy was diagnosed as suppurative lymphadenitis of the axilla due to BCG vaccination.	Hospitalized for 5 days	Yes
Male	Full-term (38 weeks)	1	5 days later	Suppurative lymphadenitis/He had a 2 × 2 cm mass on the lower left side of his neck, which was diagnosed as suppurative lymphadenitis.	Hospitalized for 11 days	Yes
Male	Full-term (38 weeks)	1	13 days later	Suppurative lymphadenitis/He had right upper limb dyskinesia with shoulder redness and swelling. The pediatrician diagnosed suppurative arthritis, which was cured after incision and drainage.	Hospitalized for 17 days	Yes
Male	Full-term (38 weeks)	1	10 days later	West syndrome/He had three convulsions within 2 days of vaccination and was hospitalized with a diagnosis of granulocytopenia, bacterial infection, and epilepsy.	Seizures	Yes
Male	Premature (30 weeks)	60	The day after vaccination	Sepsis/Acute subcutaneous suppuration of the left upper arm resulted in Sepsis, interstitial pneumonia, and pulmonary hemorrhage. Immediate death.	Death	Inconclusive
Male	Premature (34 weeks)	20	On the day of vaccination	Sepsis/He was hospitalized for pulmonary hemorrhage and severe pneumonia on the day of vaccination but died 4 days later.	Death	Inconclusive
Male	Premature (33 weeks)	20	On the day of vaccination	Interstitial pneumonia, pulmonary hemorrhage/He died on the way to the hospital two hours after being vaccinated. The autopsy diagnosis was Interstitial pneumonia and pulmonary hemorrhage.	Death	Inconclusive
Male	Premature (29 weeks)	119	On the day of vaccination	Interstitial pneumonia, pulmonary hemorrhage/He was vomiting on the day of vaccination and then died at home four days later and was subsequently diagnosed with interstitial pneumonia at autopsy.	Death	Inconclusive
Male	Full-term (38 weeks)	1	On the day of vaccination	Interstitial pneumonia, pulmonary hemorrhage/He was found to have pulmonary hemorrhage on the day of the vaccine, and respiratory failure, and died despite rescue efforts.	Death	Inconclusive
Male	Full-term (39 weeks)	1	4 days later	Muscular dystrophy/His deltoid muscle atrophied at the injection site in his right upper arm.	Hospitalized for 3 days	Inconclusive
Female	Premature (30 weeks)	62	On the day of vaccination	Interstitial pneumonia, pulmonary hemorrhage/She died on the day of vaccination due to bilateral interstitial pneumonia with acute pulmonary congestion and edema.	Death	Inconclusive

*causal judgment by clinical panel.

dose-effect relationship, response pattern to drugs, reactivation, etiology, and combination of drugs. Then, this method evaluated outcomes as highly possible, possible, indeterminate, or impossible. The final evaluation results of all cases in this study fall into two categories: possible and undetermined.

Results

Fourteen pediatric cases, including 7 preterm infants and 7 full-term infants were identified. The mortality rate of preterm infants was 100%, and that of full-term infants was 28.6% (2/7). All premature deaths occurred within 1 day of vaccination. Similarly, a Canadian study showed that 28.6% of children with severe adverse events caused by the BCG vaccine died from the side effect.⁴ Severe adverse events that were found potentially related to BCG vaccine included 4 cases of interstitial pneumonia, 3 cases of lymphadenitis, 3 cases of septicemia, 1 case of myocarditis, 1 case of muscle atrophy, 1 case of epilepsy, and 1 case of disseminated BCG (Table 1).

Discussion

According to the China Health Statistics Yearbook (2010–2021), 167 million full-term babies were vaccinated against BCG within 24 hours of birth, while 18.56 million premature

babies were vaccinated within three months of birth. Therefore, the incidence of serious adverse events represented by 14 severe cases was 8 per 1 million. Similarly, the incidence of serious adverse events in BCG in Czech was 3.7 per 100,000.⁶ An incidence of 8 per million is much lower than the literature reported but is compatible with rare disputes in court. Developing countries require the BCG vaccine to be given to every full-term newborn at birth. China, Japan, Iran, and some EU countries have implemented this strategy. A study in Guinea-bissau showed that BCG vaccination at birth was more beneficial to survival for low birth weight preterm infants than delayed BCG vaccination.⁷ Studies in Iran have shown a positive association between the occurrence of BCG adenoiditis and the gestational age at birth (<37 weeks).⁸ On the contrary, there was a Meta-analysis that increased the risk of adverse events in the first week of life and on the first day of life.⁹ In general, BCG is safe for moderate preterm infants.¹⁰

The difficulty of identifying vaccine-related adverse reactions lies in judging the correlation between the vaccine and the events.¹¹ At the court's request, all 14 adverse event reports were reviewed by a panel of five senior clinical experts to assess the causal relationship between adverse events and BCG vaccination. The committee determined that 7 cases had a possible cause-and-effect relationship with the vaccine, including 3 lymphadenitis, 1 disseminated BCGs, 1 myocarditis, and 1 epilepsy (Table 1). The remaining 7 cases were inconclusive, mainly due

to the lack of clinical examination reports, rapid onset, and lack of detailed information. Previous studies have suggested that the immunosuppression induced by corticotropic hormone (ACTH) following treatment of epilepsy may contribute to BCG infection.¹² But no one has reported that BCG can directly cause seizures. In this case, the infant got the BCG vaccine at birth and developed 3 convulsions within 48 hours after the vaccination. He was eventually diagnosed with epilepsy. Because the child was a full-term newborn, passed the post-natal health check, and did not use any drugs, the experts concluded that the child's epilepsy was directly caused by the BCG vaccine. However, neonatal epilepsy is relatively common, and it is often difficult to determine the real cause.^{13,14} The lack of post-natal epilepsy-related testing in this child cannot rule out other potential causes of seizures. The authors believe that this cannot rule out other causes of epilepsy. One case of disseminated BCG was found in all cases, which occurred 2 months after the vaccination and resulted in death. Disseminated BCG infection is slow to develop and difficult to detect at the beginning. Early intervention or delayed vaccination may save lives.

One limitation of this case series is the lack of immunological indicators before and after BCG vaccination to determine whether the individuals had any congenital immune deficiencies. Previous studies have shown that complications from the BCG vaccine are associated with primary immunodeficiency, and early screening and diagnosis of these patients are necessary.¹⁵ In addition, this is a case series with no comparison group, so the causal conclusion is uncertain. The presumed causality in the study is the result of the subjective judgment of the clinical expert and is prone to error.

Conclusion

To our knowledge, this case series included the most amount of adverse events that resulted in death in neonates post BCG vaccination. Overall, the BCG vaccine has good safety for most newborns. The results revealed the types and outcomes of the BCG vaccine's severe and rare adverse reactions. Moreover, BCG vaccine vaccination is usually delayed in some preterm infants. A Swedish study suggests that BCG vaccination should be postponed to six months after birth in immunocompromised neonates.¹⁶

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

National Natural Science Foundation [grant numbers 81874325] and the Scientific Research Project of Science and Technology Commission of Shanghai Municipality [grant numbers 19DZ1910604/19XD1400900/18DZ1910604].

ORCID

Jinmiao Lu  <http://orcid.org/0000-0001-8411-2111>

Xunjie Zhang  <http://orcid.org/0000-0002-1436-5081>

Hong Xu  <http://orcid.org/0000-0002-2379-9092>

Zhiping Li  <http://orcid.org/0000-0001-6194-023X>

References

- Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, Kapata N, Mfinanga S, Hasnain SE, Katoto PDMC, et al. Global tuberculosis report 2020 – Reflections on the global TB burden, treatment and prevention efforts. *Int J Infect Dis.* 2021;113(Suppl 1):S7–S12. doi:10.1016/j.ijid.2021.02.107.
- Lobo N, Brooks NA, Zlotta AR, Cirillo JD, Boorjian S, Black PC, Meeks JJ, Bivalacqua TJ, Gontero P, Steinberg GD, et al. 100 years of Bacillus Calmette–Guérin immunotherapy: from cattle to COVID-19. *Nat Rev Urol.* 2021;18:611–22. doi:10.1038/s41585-021-00481-1.
- Greybe L, Morrison JL, Schaaf HS, Rabie H, Cotton MF. The outcome of accidental Bacille Calmette–Guérin overdose during routine neonatal immunization. *Pediatr Infect Dis J.* 2021;40(6):588–89. doi:10.1097/INF.0000000000003073.
- Deeks SL, Clark M, Scheifele DW, Law BJ, Dawar M, Ahmadipour N, Walop W, Ellis CE, King A. Serious adverse events associated with Bacille Calmette–Guérin vaccine in Canada. *Pediatr Infect Dis J.* 2005;24(6):538–41. doi:10.1097/01.inf.0000164769.22033.2c.
- Wiholm B-E. The Swedish Drug-Event assessment methods special workshop—regulatory. *Drug Inf J.* 1984;18:267–69. doi:10.1177/009286158401800312.
- Vitkova E, Galliova J, Krepela K, Kubin M. Adverse reactions to BCG. *Cent Eur J Public Health.* 1995;3:138–41. 8535371
- Aaby P, Roth A, Ravn H, Napirna BM, Rodrigues A, Lisse IM, Stensballe L, Diness BR, Lausch KR, Lund N, et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? *J Infect Dis.* 2011;204:245–52. doi:10.1093/infdis/jir240.
- Hematyar M, Chooldari A. Prevalence of BCG adenitis in infants vaccinated at birth. *J Inflammatory Dis.* 2006;9:42–46 <http://journal.qums.ac.ir/article-1-318-en.html>.
- Mostaan S, Yazdanpanah B, Moukhar R, Hozouri HR, Rostami M, Khorashadizadeh M, Zerehsaz J, Mahabadi RP, Saadi A, Khanahmad H, et al. Adverse effects of BCG vaccine 1173 P2 in Iran: a meta-analysis. *Adv Biomed Res.* 2016;5. doi:10.4103/2277-9175.183659
- Saroha M, Faridi M, Batra P, Kaur I, Dewan D. Immunogenicity and safety of early vs delayed BCG vaccination in moderately preterm (31–33 weeks) infants. *Human Vacc Immunother.* 2015;11:2864–71. doi:10.1080/21645515.2015.1074361.
- Bellavite P. Causality assessment of adverse events following immunization: the problem of multifactorial pathology. *F1000research.* 2020;9:170. doi:10.12688/f1000research.22600.1.
- Maki Y, Natsume J, Hori I, Takeuchi T, Negishi Y, Kubota T, et al. Risks of ACTH therapy for West syndrome following BCG vaccination. *Epilepsy Behavior.* 2021;118:107924. <https://www.sciencedirect.com/science/article/abs/pii/S15255052100158X>. doi:10.1016/j.yebeh.2021.107924.
- Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. *Epileptic Disord.* 2015;17:117–23. doi:10.1684/epd.2015.0736.
- Padiyar S, Nusairat L, Kadri A, Abu-Shaweeh J, Aly H. Neonatal seizures in the US National inpatient population: prevalence and outcomes. *Pediatr Neonatol.* 2020;61:300–05. doi:10.1016/j.pedneo.2019.12.006.
- Sohani M, Habibi S, Delavari S, Shahkarami S, Yazdani R, Shirmast P, Nazari F, Moeini Shad T, Mamishi S, Azizi G, et al. Evaluation of patients with primary immunodeficiency associated with Bacille Calmette–Guérin (BCG)-vaccine-derived complications. *Allergol Immunopathol (Madr).* 2020;48:729–37. doi:10.1016/j.aller.2020.04.004.
- Romanus V, Fasth A, Tordai P, Wiholm BE. Adverse reactions in healthy and immunocompromised children under six years of age vaccinated with the Danish BCG vaccine, strain Copenhagen 1331: implications for the vaccination policy in Sweden. *Acta Paediatr.* 1993;82:1043–52. doi:10.1111/j.1651-2227.1993.tb12808.x.