Safety of the Polish BCG-10 Vaccine During a Period of BCG Vaccine Shortage: An Australian Experience

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Abstract: Bacille Calmette-Guerin vaccine is widely administered to reduce the risk of severe tuberculosis disease in children. Recent global vaccine supply issues have led to the use of alternative products, which may vary in side effect profile. We report on the safety of the Polish (Moreau strain) "Bacille Calmette-Guerin-10" vaccine in an Australian cohort. Using active surveillance, we identified an adverse event rate of 54.6 per 10,000 doses (95% confidence interval: 38.5–75.2), which was comparable to that reported with the Danish Sanofi-Pasteur and Connaught strains.

Key Words: adverse events following immunization, Bacille Calmette-Guerin, vaccine safety

(Pediatr Infect Dis J 2020;39:e66–e68)

The bacille Calmette-Guerin vaccine (BCG) is an attenuated form of Mycobacterium bovis, administered to reduce the risk of severe tuberculosis disease in children. In Australia, a country with low tuberculosis disease incidence, BCG vaccine is recommended for high-risk populations: children younger than 5 years who are travelling to countries with high tuberculosis prevalence, children of Aboriginal and Torres Strait Islander descent living in communities with high disease incidence, and those with a family history of leprosy.1

The BCG vaccine is very immunogenic, with potential for localized and systemic reactions that may take weeks to months to resolve.2 Common adverse events following immunization (AEFI) with BCG include abscess formation and regional lymphadenitis. While BCG is considered a relatively safe vaccine, disseminated BCG disease and osteitis can occur. This is of particular concern in immunocompromised children.1 Following initial development of BCG, repeated subculture of the vaccine has led to multiple BCG strains, which may vary in immunogenicity and side effect profile.3 Previous reviews of BCG safety have shown heterogeneity in the side effect profile according to geographical region, BCG strain used and the mode of administration.2,5

Since 2012, a worldwide shortage of the Danish Sanofi-Pasteur BCG strain has led vaccine providers to utilize alternative strains. In the Australian state of Victoria, the Polish “BCG-10” vaccine derived from the Brazilian Moreau strain has recently been utilized since February 2, 2016.

BCG-10 has been manufactured and utilized in Poland since 1955.6 However, there are limited reports of this strain’s safety. Given suspected variation in BCG strain immunogenicity, we have closely monitored AEFI patterns following the use of this vaccine strain in Australia.

METHODS

In Australia, BCG vaccine provision is funded through state programs. In the state of Victoria, BCG vaccine is largely administered through the 2 tertiary pediatric hospitals, The Royal Children’s Hospital (RCH) and Monash Children’s Hospital (MCH). Most vaccine recipients are younger than 12 months of age, though the vaccine is recommended in children up to 5 years of age in Australia. To assess the safety of BCG-10, vaccine recipients were prospectively monitored for AEFI. Children who received BCG vaccine at RCH were reviewed via an email survey 6 months post BCG administration. Children who received the vaccine via MCH were sent an SMS 6 months postvaccination prompting families to report AEFI. AEFI was then reported via Surveillance of Adverse Events Following Vaccinations in the Community (SAEFVIC), a state-wide immunization safety service through which community members and healthcare providers are able to report any reactions postvaccination. Additionally, a search of MCH records was performed to identify any patients who had “BCG reaction” entered in their medical records. These records were reviewed to identify any children who may have had AEFI that were not reported to SAEFVIC.

All RCH, MCH and SAEFVIC reports made during the period of BCG-10 usage, from February 2016 to December 2018, were reviewed. The SAEFVIC reports included those identified through active follow-up of RCH and MCH vaccine recipients, alongside a small number of external AEFI reports (children vaccinated in the community or overseas).

AEFI was defined according to Lotte’s classification,2 with localized AEFI including abscess or necrosis. Lymphadenopathy included enlarged lymph nodes that were fluctuant or adherent to the skin. Redness at the injection site, nodule formation and skin ulceration which resolved spontaneously were not considered an AEFI, but rather an expected local reaction.7

The incidence of AEFI was calculated using the total number of vaccine doses administered through RCH and MCH as the denominator. Statistical analysis was performed using SPSS.

RESULTS

During the study period, 6779 children received BCG vaccine (3484 at MCH and 3295 at RCH). There were 75 reported side effects (21 identified through active surveillance at RCH, 47 via SAEFVIC and additional 5 from review of MCH records), as shown in Figure 1. Children who received a different BCG vaccine strain (ie, not BCG-10) and those assessed to have an expected, local reaction were excluded. The remaining 37 were classified as AEFI, an incidence of 54.6 AEFI per 10,000 doses (95% confidence interval: 38.5–75.2). The median age of this group was 12.1 months (range 3.2–52 months).
In this cohort, the most common AEFI was local abscess (25/37, 68%). Only one case required incision and drainage. Three children were treated with antibiotics (in cases where treatment was specified, cephalexin and flucloxacillin were administered). No children received antituberculous therapy. Potential risk factors in our cohort included eczema (7/37,
18.9%) and immunosuppression (one child had known neutropenia).

**DISCUSSION**

This is the first profile of BCG-10 safety since its introduction in Australia. The only previous passive surveillance study of this strain of BCG was from Poland reported an AEFI incidence of 20–60 per 10,000 doses. In the cohort of this Polish study also appeared to have more severe AEFI, as a quarter of children with AEFI required hospitalization, which may suggest more severe reactions or differing hospitalization practices.6

The incidence of AEFI for this cohort of 54.6 per 10,000 doses is comparable to AEFI profiles of other BCG strains. An Australia-wide study of BCG (Connaught or Denmark SSI) recipients from 2009 to 2014 reported an AEFI incidence of 33–68 per 10,000 doses.7 Another Victorian study of the same strains reported a lower incidence of 11.6–15.4 per 10,000 doses.8 The spectrum of AEFI in these studies was similar, with abscess, injection site reaction and lymphadenopathy/lymphadenitis being the most commonly reported. The number of children with lymphadenopathy was small, consistent with a previous review that suggested the Brazilian Moreau strain was rarely associated with lymphadenitis.5

The variable results of these studies show wide variation of reported BCG effects, which may relate to variation in defining and diagnosing AEFI. For example, the distinction between an expected injection site reaction and abscess formation may vary between clinicians. Additionally, technique with administration technique may also influence rates of AEFI.9 Reporting patterns may also vary.

These factors introduce limitations into our study. During this time period, vaccine providers and healthcare workers may have been more likely to report reactions in the setting of a new product. Additionally, the use of active follow-up for AEFI may have resulted in more sensitive reporting, compared with previous passive surveillance studies.

Finally, it is likely that additional doses of vaccine were administered through private providers and travel clinics; hence, the denominator used to calculate incidence is likely to be an underestimate. As BCG vaccine is not funded in Australia via the national immunization program, there are no specific incentives for private providers to register BCG administration and BCG administration is rarely reported on the Australian Immunization Register. As such, it is difficult to ascertain the true incidence of BCG-10 vaccine use. While we believe that adverse reactions sustained through these providers would be captured via the SAFEVIC reporting system, the number of total BCG vaccine doses administered state-wide would be underestimated, resulting in an overestimated AEFI incidence rate.

Despite these limitations, we believe our study provides a reflection of the safety of BCG-10. The prospective nature of surveillance and generous estimates of AEFI incidence have nonetheless shown a safety profile comparable to that documented with previously used strains. In addition, the severity of AEFI in this cohort was low, with few cases requiring intervention.

**REFERENCES**