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Adverse reactions to the Bacillus Calmette–Guérin (BCG) vaccine in new-born infants—an evaluation of the Danish strain 1331 SSI in a randomized clinical trial

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ABSTRACT

Objective: To evaluate adverse reactions of the Bacillus Calmette–Guérin (BCG) Statens Serum Institut (SSI) (Danish strain 1331) used as intervention in a randomized clinical trial.
Design: A randomized clinical multicenter trial, The Danish Calmette Study, randomizing newborns to BCG or no intervention. Follow-up until 13 months of age.
Setting: Pediatric and maternity wards at three Danish university hospitals.
Participants: All women planning to give birth at the three study sites ($n = 16{,}521$) during the recruitment period were invited to participate in the study. Four thousand one hundred and eighty four families consented to participate and 4262 children, gestational age 32 weeks and above, were randomized: 2129 to BCG vaccine and 2133 to no vaccine. None of the participants withdrew because of adverse reactions.
Main outcome and measure: Trial-registered adverse reactions after BCG vaccination at birth. Follow-up at 3 and 13 months by telephone interviews and clinical examinations.
Results: Among the 2118 BCG-vaccinated children we registered no cases of severe unexpected adverse reaction related to BCG vaccination and no cases of disseminated BCG disease. Two cases of regional lymphadenitis were hospitalized and thus classified as serious adverse reactions related to BCG. The most severe adverse reactions were 10 cases of suppurative lymphadenitis. This was nearly a fivefold increase compared to what was expected based on the summary of product characteristics of the vaccine. All cases were treated conservatively and recovered. Six of 10 (60%) families of children experiencing suppurative lymphadenitis compared to 117/2071 (6%) of those with no lymphadenitis indicated that the vaccine had more adverse effects than expected (p-value <0.001).
Conclusions and relevance: BCG vaccination was associated with only mild morbidity and no mortality. A higher incidence of suppurative lymphadenitis than expected was observed. All children were treated conservatively without sequelae or complications.
Trial registration: Trial registration number NCT01694108 at www.clinicaltrials.gov

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1. Introduction

The Bacillus Calmette–Guérin (BCG) vaccine is the most widely administered vaccine in the world, and it remains the primary prophylaxis against tuberculosis (TB). The protective effect of BCG vaccination is well studied, with highest efficacy against active disease, especially TB meningitis and disseminated TB in children, whereas there is great variation in the effect of preventing pulmonary TB [1,2]. BCG is part of the immunization program in most low-income countries with a high prevalence of TB and a recent study confirm that it is effective in preventing TB [3]. In most high-income countries BCG vaccination was discontinued as a consequence of reduced TB prevalence.

The adverse reactions (ARs) of BCG have been described thoroughly. The normal local reaction following intradermal BCG vaccination is swelling and redness which appears at the site of injection after a few weeks. This develops into a small pustule or an ulcer that heals and leaves a small scar after weeks to months. Local lymphadenopathy < 1 cm is also part of a normal reaction [4]. BCG is considered a safe vaccine and serious ARs are rarely seen [5].

Despite the fact that normal reactions and ARs after BCG vaccination are well described, studies report very different rates [6–8]. This could be due to different vaccination procedures and BCG strains. Early studies have shown that vaccination technique, dose, and preparation of the vaccine are important risk factors for adverse reactions [9–11], and that BCG strain, change of BCG vaccine, and HIV infection are also significant risk factors [12–14]. Differences in interpretation of a normal reaction and an AR could also explain the disparities; the normal local reaction and the 'adverse' local reactions represent a continuum of the same pathological process. The shift from a normal reaction to an AR is often defined by size which is difficult to assess accurately in a clinical setting.

Recent studies from West Africa have found that BCG, apart from providing some protection against TB, may also have beneficial non-specific effects on childhood mortality and morbidity [15,16]. Immunological studies have supported this by showing that BCG induces epigenetic changes at the monocyte level which lead to "trained innate immunity" [17]. To investigate these possible non-specific effects of BCG vaccination in a high-income country, we conducted a randomized clinical trial ('The Danish Calmette Study') from October 2012 to January 2015 in which 4262 Danish children at birth were randomized to BCG or no intervention [18]. Within this trial, we evaluated the ARs to BCG when administered in a setting with no routine BCG vaccination and low prevalence of HIV [19].

2. Methods

2.1. Study design

The Danish Calmette Study is a randomized clinical multicenter trial investigating the effect of BCG vaccination at birth on childhood morbidity in Denmark, where BCG was withdrawn in the early 1980s, due to low prevalence of TB. The study was carried out at three Danish university hospitals, Rigshospitalet, Hvidovre Hospital, and Kolding Hospital.

At the three study sites, 4262 children were randomized after birth to BCG vaccination or no intervention. The primary outcome was child morbidity assessed as all-cause hospitalization. Secondary outcomes were obtained by telephone interviews and clinical examinations at the age of 3 and 13 months. The study is described in detail elsewhere [18].

The three study sites were organized differently with respect to the randomization and vaccination procedure. One study site had predominately one midwife vaccinating; at this site most children were vaccinated more than 24 h after birth. At the other two sites the task was split between 11 and 15 midwives, respectively; most children here were vaccinated within the first 24 h of life. All study staff were trained specifically to administer BCG vaccination correctly.

2.2. Vaccination procedure

The BCG SSI (Danish strain 1331) was used in the study. A dose of 0.05 mL of the vaccine suspension was applied intradermally on the left upper arm. A sterile 1 mL syringe with a short (25-27 G) needle was used for the procedure.

2.3. Data collection

Before giving oral and written consent and again after the vaccination, the families were informed about the normal reaction following a BCG vaccination and were advised to seek more information at the Calmette Study homepage if needed [20]. The families were encouraged to contact the study facility in case of unexpected reactions or if they felt uneasy about a reaction. To collect information regarding study outcomes the families were contacted at 3- and 13-months by telephone and were subsequently scheduled for a clinical examination at the study site. During these contacts, information on ARs was collected only when mentioned by the families and never asked for actively by the study staff.

2.4. Classification of adverse events

All potential adverse events were classified into five categories according to standard Good Clinical Practice (GCP) guidelines: adverse event (AE), adverse reaction (AR), severe adverse event (SAE), severe adverse reaction (SAR), and suspected unexpected severe adverse reaction (SUSAR). For the present study, severity was defined by hospitalization also if the hospitalization was only briefly and due to anxiousness about an AR, and assessed according to international guidelines [21]. An AE was defined as a non-severe event not causally related to BCG vaccination. An AR was defined as a non-severe event that was expected after BCG vaccination. This includes suppurative lymphadenitis when the child was not hospitalized. An SAE was defined as a severe event not causally related to BCG vaccination. An SAR was defined as a severe event that was expected after BCG vaccination and led to hospitalization. An SUSAR was defined as a severe unexpected event with suspected relation to BCG [22]. This includes disseminated BCG disease. All cases of SAR and SUSAR were discussed with the data and safety monitoring board (DSMB) and reported to the national health authorities according to Danish law.

All BCG-vaccine related events were categorized into four categories: (1) local reactions including abscess at the injection site and prolonged pustule healing (AR), (2) regional lymphadenitis (AR; SAR if leading to hospitalization), (3) suppurative lymphadenitis (AR; SAR if leading to hospitalization), and (4) others. The distinction between regional lymphadenitis and suppurative lymphadenitis was based on the clinical finding of fluctuant swelling and/or secretion from a fistula. Most cases of suppurative lymphadenitis were confirmed by ultrasound examination [23]. All cases of suppurative lymphadenitis had preceding regional lymphadenitis, but were registered exclusively in the suppurative lymphadenitis category.

2.5. Deaths

All fatalities during follow-up were evaluated for potential relation to BCG.

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