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## Original Research Article

# BCG-SSI<sup>®</sup> vaccine-associated lymphadenitis: Incidence and management

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## ABSTRACT

**Background and objective:** There is a high incidence of childhood tuberculosis in Latvia, including children aged less than 1 year, while BCG-associated lymphadenitis is one of the most frequent adverse events requiring surgical treatment. The aim of this study was to analyze the incidence of purulent BCG adenitis through-out the population of Latvia after the introduction of BCG-SSI<sup>®</sup> vaccine and to evaluate the treatment results.

**Material and methods:** The study included 194 patients. All patients had received the BCG-SSI<sup>®</sup> vaccine during the first week of life routinely or at a later time according to the indications. The indications for surgical treatment were lymph node destruction also affecting the skin. All patients in this study received surgical treatment – the affected lymph node extirpation.

**Results:** The mean age of the patients was  $5.12 \pm 0.96$  months. A total of 172 patients had purulent axillar lymphadenitis, 14 had purulent supraclavicular lymphadenitis, 8 patients had lymphadenitis at both localizations. During the whole study period the incidence of BCG adenitis varied from 0.02% to 0.36%, while the mean rate was  $0.11\% \pm 0.08\%$  from 184,068 vaccinated children during the study period. We observed an increasing trend in the incidence of BCG lymphadenitis during the study period. The primary and complete healing rate at the end of period was 99.5% ( $n = 193$ ) following an affected lymph node extirpation. The mean hospitalization time after the operation was  $3.71 \pm 0.18$  days.

**Conclusions:** The incidence of BCG-SSI<sup>®</sup> vaccine associated purulent lymphadenitis varied widely with an increasing trend, followed by the return to the product characteristic limits. Indications for the surgical treatment should not be changed. Extirpation of the purulent BCG adenitis is a safe treatment method and leads to the primary wound healing in the majority of cases.

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## 1. Introduction

Bacillus Calmette–Guerin (BCG) vaccination is a part of the immunization programs in the countries with a risk of childhood tuberculosis [1–4]. In different countries there are different schedules for BCG vaccination, starting from the maternity home [5] to the 6th year of life [6]. The vaccine was recommended in Europe in 2005 for children under one year of age in 12 different countries, for older children in 5 countries, only at risk groups in 10 countries, and no routine vaccination in 7 countries [6]. The early BCG vaccination between 2 and 5 days after the birth is a part of the compulsory childhood immunization program in Latvia, due to the high incidence of childhood tuberculosis, including the children under one year of age [7,8].

BCG lymphadenitis is one of the BCG vaccination's adverse events, related to the Category NR1 – Abnormal BCG primary complex [9,10]. Its incidence differs depending on the particular vaccine, the age of the child at the time of vaccination and probably some other factors [6,9].

The treatment of BCG lymphadenitis is still controversial [5,11–14]. While indications for the surgical treatment are rather clear, particular treatment methods are still discussed and opinions differ among different countries, centers and authors [5,15–18].

Today there is only one BCG vaccine available in the European Union – BCG-SSI<sup>®</sup> vaccine from Staten's Serum Institute (M Bovis, Danish Strain 1331), which is distributed in vials, containing 10 doses of 0.1 mL of vaccine for children over 12 months of age and adults, or 20 doses of 0.05 mL for infants under 12 months. The BCG-SSI<sup>®</sup> vaccine has been the only one used in the Republic of Latvia since the year 2005.

The clinical effects and the elevated number of the adverse reactions of the BCG-SSI<sup>®</sup> vaccine have been described in a number of publications. Those about the adverse reactions give different results, and try to concentrate mostly on the vaccine-related reasons [5,6,10,19–21]. A sudden increase in incidence of the purulent BCG adenitis was recognized also in Latvia in 2010 and 2011. It led to a tri-lateral discussion among the State Drug Agency (the Government's Pharmacovigilance Office), the Statens Serum Institute and the Latvian Association of Paediatric Surgeons, followed by the implementation of the BCG-SSI<sup>®</sup> vaccine manufacturing changes and an instruction campaign about the vaccination procedure, performed by The State Drug Agency in the first part of 2012 [22]. After this successful campaign we observed a decline in the incidence of BCG adenitis in the subsequent years.

The aim of this study was to analyze the incidence dynamics of purulent BCG adenitis through-out the population of Latvia after the introduction of BCG-SSI<sup>®</sup> vaccine and to evaluate the treatment results.

## 2. Material and methods

A retrospective study was undertaken and medical records of 194 children, admitted to the only reference center in Latvia for major BCG vaccination associated adverse events, from the year 2005 to 2013, were reviewed. The study included patients

from 1 to 17 months of age with the diagnosis of histologically proven purulent BCG lymphadenitis. All patients received the BCG-SSI<sup>®</sup> vaccine (M Bovis, Danish strain 1331) on the ipsilateral arm via an intradermal injection. 163 patients (84.02%) received the BCG-SSI<sup>®</sup> vaccine during the first week of life, while 31 patients (15.98%) received it later due to different medical or social reasons. Observing the signs and symptoms of BCG adenitis all patients were consulted by a pediatrician specializing in child tuberculosis and an immunologist. Indications for surgical treatment were assessed by a pediatric surgeon. The indications for surgical treatment were lymph node destruction with the overlying skin involvement. All patients in this study received surgical treatment – purulent lymph node extirpation. All patients were consulted and operated in one reference center by one pediatrician specializing in child tuberculosis, one immunologist and operated by two pediatric surgeons. All patients had postoperative outpatient follow-up controls up to 18 months. The incidence of purulent BCG lymphadenitis of less than 0.1% reported by the producer in the “Description of BCG vaccine SSI” was considered as a comparator [23]. The study was approved by the Institutional Ethics Review Board.

Data were analyzed using descriptive and analytical statistical methods. Mean values and 95% CI of the age of the hospitalized patients, time after vaccination, incidence of purulent BCG adenitis and postoperative time were calculated. The Mann–Kendall trend test was used to determine possible trends in the occurrence of purulent BCG lymphadenitis over the particular time. A *P* value of less than 0.05 was chosen as the level of significance.

## 3. Results

A total of 184,068 children had received the BCG-SSI<sup>®</sup> vaccine countrywide during the whole study period, from 17,633 to 23,123 children each year [24]. Of these 615 patients developed BCG lymphadenitis, while 194 patients aged from 1 to 17 months (the mean age was  $5.12 \pm 0.96$  months) were admitted for surgical treatment of purulent BCG lymphadenitis. The main characteristics of the study population and study findings are presented in Table. All children were healthy and none had reported close contact with any tuberculosis patient prior to hospitalization. The number of patients in each year of the study varied, and the maximum incidence was observed in the period between 2010 and 2012 with the peak in 2011 (Table). During the whole study period the incidence of BCG adenitis varied, while the mean incidence was  $0.11\% \pm 0.08\%$  (Figure). A total of 180 patients had purulent axillary lymphadenitis, from 4 to 59 each study year, 14 patients had purulent supraclavicular lymphadenitis, from 0 to 6 each study year. Of the 194 patients, 8 had lymphadenitis at both localizations.

There was a statistically significantly increasing trend in the incidence of BCG vaccine associated purulent lymphadenitis during the period 2005–2013 (Kendall's tau = 0.667; *P* = 0.013), especially in the 3-year span between 2010 and 2012 with the peak incidence in 2011 (0.36%, 95% CI 0.28–0.45, *P* = 0.05) that significantly differed from the mean incidence of the whole 9-year period.

**Table – Main characteristics of the study population and study findings (with 95% CI).**

Study year	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
No. of children vaccinated in the country	21,211	21,651	22,711	23,123	21,104	18,149	17,633	18,865	19,621	184,068
No. of patients hospitalized for operative treatment	5	13	7	17	17	30	63	24	18	194
Repeated hospitalization	3.20 ± 2.38	4.93 ± 2.28	3.43 ± 1.76	7.00 ± 3.15	6.3 ± 1.19	6.46 ± 1.21	5.58 ± 0.76	5.96 ± 1.54	4.83 ± 1.27	6
Mean age of the hospitalized patients, months	2.60 ± 0.08	4.00 ± 0.29	2.29 ± 0.45	5.11 ± 0.84	5.29 ± 0.54	3.20 ± 0.40	3.95 ± 0.43	5.08 ± 0.85	4.28 ± 0.94	3.94 ± 0.85
Mean time after vaccination, months	4	13	7	17	17	28	59	21	14	180
Suppurative axillar lymphadenitis	1	1	1	1	1	4	6	4	5	22
Suppurative supraclavicular lymphadenitis	3.80 ± 1.61	3.64 ± 0.88	4.29 ± 1.28	3.78 ± 0.57	3.59 ± 0.26	3.70 ± 0.44	3.44 ± 0.33	3.88 ± 0.36	4.33 ± 1.05	3.71 ± 0.18
Mean postoperative time, days										
Persistent lymphorrhoea						1				1

Following affected lymph node extirpation the primary and the complete healing rate at the end of period was 99.5% (n = 193). The mean hospitalization time after the operation was 3.71 ± 0.18 days.

The re-hospitalization rate was 3.1% (n = 6). Five of these patients were hospitalized due to the repeated purulent BCG lymphadenitis in a different localization. One patient had prolonged lymphorrhoea for 14 days and had to undergo repeated hospitalization and drainage correction for another 3 days. Among the concomitant diseases in our study cohort, two patients were diagnosed with secondary immunodeficiency, four had thymus hyperplasia; three patients, iron deficiency anemia; one, asthma; one, atopic dermatitis; one, undetermined heart disease; and one patient, acute bronchitis. All patients recovered and did not show evidence of lymphadenitis or systemic tuberculosis after 6–18 months of follow-up.

#### 4. Discussion

BCG vaccination is recommended routinely for all newborns in the universal immunization program in countries where the incidence of tuberculosis infection is more than 1% [3]. Rates of notified TB among children under 15 years of age in Latvia have been increasing since 2009: from 14.9 to 19.9 per 100,000 in 2011 [8]. The increasing rate also reflects an increase in the absolute number of cases: from 40 to 61 [8]. These figures, obviously, illustrate the necessity to continue the already confirmed immunization program in countries like Latvia, which presumes to vaccinate all newborns, in the maternity home with the only exceptions being in cases where there are contraindications or where there is a refusal from the parental side.

The BCG-SSI® vaccine (M Bovis, Danish strain 1331) is the only BCG vaccine used in Latvia since 2005. A high risk of complications could lead to the loss of trust in vaccination and potentially cause a threat for children growing up in country with high incidence of tuberculosis. In our series the annual frequency of purulent BCG lymphadenitis varied remarkably (Figure). Despite the decrease in the birth-rate and therefore number of newborns vaccinated, there had been a steady increase in numbers of children with purulent lymphadenitis diagnosed since 2005–2011, which had been proved statistically.

The incidence of purulent BCG adenitis had been reported from 0% to 0.31% by different authors [2,19]. The relevance of purulent lymphadenitis to BCG vaccination was proved according to the clinical and histopathological findings [14,18]. The acceptable incidence of purulent BCG adenitis had been estimated from 0.04% to 0.1% [6,19]. Factors influencing the formation of the purulent BCG lymphadenitis are multiple [1,3,20]. They could be separated from the factors directly related to the BCG-SSI® vaccine as biological material, factors related to the indications for surgical treatment and factors related to the technical difficulties during the procedure [6]. Among the last group of factors we considered vaccination during the neonatal period, the vaccinators' skills and experience, the diameter and the tip angle of the needle and changes in the nursing care education programs and

### Annual incidence in % of purulent BCG lymphadenitis years 2005-2013

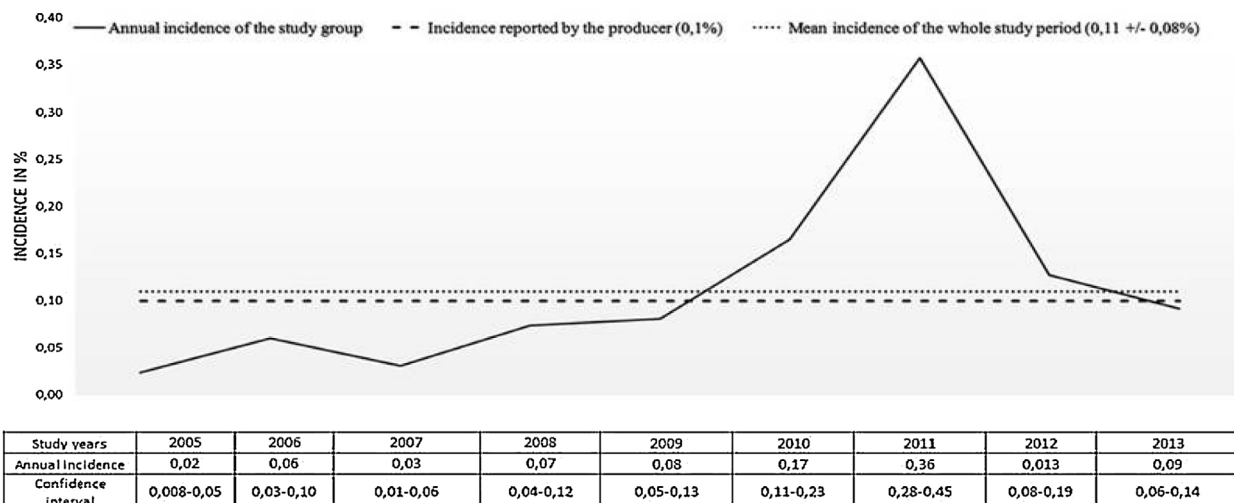


Figure – Annual incidence of purulent BCG lymphadenitis 2005–2013.

principles (i.e. the switch from the narrow specialized to broad profile nurses), which is particularly necessary for current health care of Latvia.

The higher incidence of the local adverse reactions, including purulent lymphadenitis, associated with BCG-SSI<sup>®</sup> vaccine, has been widely discussed, however, the statistical results are still controversial [1,4–6,10,12,19]. The statistical analysis of the variable dynamics of our 9-year incidence of purulent BCG lymphadenitis obviously showed (Figure) that the true reason for the difference that we had observed could not be explained by the effect of the biological characteristics of BCG-SSI<sup>®</sup> vaccine alone. It could not also be explained by the human factors alone, related to the indications for surgical treatment, which had not been changed during the whole study period. All patients were consulted and operated in one reference center by one team of specialists. The most difficult group to estimate was the third group of procedure related factors, which could definitely contribute more to the increase of the variations in the incidence of purulent BCG lymphadenitis that we observed.

We tend to an opinion that the incidence of BCG lymphadenitis is influenced by the biological characteristics of the BCG-SSI<sup>®</sup> vaccine and by the difficulties, related in performing the correct vaccination procedure for all infants in the country during the early new-born period. We suppose that the possible proof of that is the positive effect of the activities taken during the year 2011 and 2012, the implementation of changes in the manufacture of the BCG-SSI<sup>®</sup> vaccine (formulated by the producer as “manufacturing changes, that are expected to decrease the frequency of suppurative lymphadenitis, including severe cases”) and the vaccination procedure education program [22], which have led to the return of the incidence of purulent BCG lymphadenitis to an admissible level in 2013. The mean incidence during the whole study period stayed slightly above the incidence reported by the producer, which could be a result of the increase we had in the period of 2010–2012.

Discussions were started between the State Drug Agency and the experts from pediatric surgery in the 2nd half of 2010, but the Statens Serum Institute also got involved in 2011. These corresponded with the period of the growing incidence of BCG lymphadenitis in our study. The implementation of the countrywide vaccination procedure education program started from the beginning of 2012 and the BCG-SSI<sup>®</sup> vaccine manufacturing changes were implemented later the same year. In 2012 the incidence of BCG lymphadenitis had declined, and in 2013 it returned to the authorized limits. The indications and the operating techniques were reviewed, but left without any changes so far.

Purulent BCG lymphadenitis occurs in both groups of children, in those vaccinated in the new-born period and in those, vaccinated later, so we agree with the previous published opinions [6] that the procedure related difficulties are not connected so much with the patient's age, rather than with the vaccinator's professionalism in general. However, it was not the aim of this particular study, there were hints in our material, that the patients' age and the present indications for the surgical treatment had less influence on the incidence of purulent BCG lymphadenitis, while the vaccination procedure training, instructions and education program together with close collaboration with the vaccine producer could improve the results remarkably. We suppose that the vaccination schedule and the indications for surgical treatment should not be changed, but purulent BCG lymphadenitis incidence control, vaccination procedure education activities and contact with the vaccine producer could be planned more regularly.

Treatment of BCG related purulent lymphadenitis is still controversial and there are no specific guidelines in the European Union for the treatment of BCG induced lymphadenitis [11–14,16,17]. Surgical treatment of BCG lymphadenitis is needed in cases of the formation of a skin lesion and the fixation in a region of the lymph node or the formation of fistulae with the spontaneous evacuation of pus. Medical

treatment is usually ineffective once the enlarged lymph nodes have developed the fluctuation and inflammation of overlying skin [16–18]. Incision and drainage should be avoided due to the risk of persistent draining wound [1]. In Latvia indications for surgical treatment are approved by the pediatric surgeon on the recommendation of the pediatrician specializing in childhood tuberculosis and of the immunologist. The mean time of the operation was  $3.94 \pm 0.85$  months after the vaccination. Two methods of the surgical treatment of purulent BCG lymphadenitis are accepted in the major discussions, i.e. the needle aspiration, in many cases combined with the following excision of the purulent lymph node, or the single one moment excision [1,13,16–19]. Single surgical procedure prevents further complications and gives reliable treatment results with primary healing, low recurrence rate and a relatively short postoperative hospital stay. However, the necessary attention should be paid to follow the natural course of BCG lymphadenitis and to control the indications for the cases referred for surgical treatment.

## 5. Conclusions

The incidence of BCG-SSI<sup>®</sup> vaccine associated purulent lymphadenitis varied widely during the study period with an increasing trend, followed by the return to the product's characteristic limits. Indications for the surgical treatment of purulent BCG lymphadenitis should not be changed. Extirpation of purulent BCG adenitis, despite its larger scale of intervention, is a safe treatment method and leads to the primary wound healing in the majority of cases.

## Conflict of interest

The authors state no conflict of interest.

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