

## **Bacille Calmette Guerin scar reactivation after administration of the Moderna COVID vaccine (Spikevax®)**

### **Introduction**

The Moderna vaccine (Spikevax®) is a COVID-19 messenger RNA (mRNA) vaccine (nucleoside modified). Single-stranded, 5'-capped mRNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2. Spikevax® is indicated for *active immunisation to prevent COVID-19 caused by SARS-CoV2 virus, in individuals 12 years of age and older* [1].

The Netherlands Pharmacovigilance Centre Lareb received 11 cases of reactivation of the scar of a former Bacille Calmette Guerin inoculation.

### **Reports**

In the period from March 7<sup>th</sup>, 2021 until October 20<sup>th</sup>, 2021 the Netherlands Pharmacovigilance Centre Lareb received 17 case reports on Bacille Calmette Guerin scar reactivation associated with administration of a COVID-19 vaccine (Spikevax® n=11, Comirnaty® n=4 and Vaxzevria® n=2).

11 case reports on Bacille Calmette Guerin (BCG) scar reactivation associated with administration of Spikevax® were included in this analysis. Case reports with the MedDRA Preferred Term (PT) "Bacille Calmette Guerin scar reactivation" were included. In one case it concerned a man and in 10 cases a woman. The average age was 34.5 year (ranging from 25 to 53 years, median age 33).

The BCG scar reactivation occurred after administration of the first dose and second dose in respectively 5 cases and 6 cases. None of the reporters reported that the scar reactivation occurred after both doses of Spikevax®. In 6 case reports the COVID vaccine was administered near or at least in the same arm as the BCG scar. In the other 5 cases it was unknown whether it was the same arm. Most of the scar reactivations were described as an inflammatory reaction accompanied by erythema, swelling, pain and sometimes pruritus. The size, if known, was ranging from 1 to 5 cm. One patient described the presence of a blister.

The latency time ranged from 1-9 days. Four cases with a latency time of 7-9 days were reported after the first dose. The latency time of all case reports after the second dose was 1-4 days.

Recovery was reported after 4, 7 and 15 days in 3 cases. The other 8 cases of scar reactivation were not recovered at the time of reporting.

In 3 case reports only the BCG scar reactivation was reported. In 6 cases also an injection site reaction on the administration site of Spikevax® was co-reported. In 2 other cases only systemic events were reported next to the BCG reactivation.

Addendum 1 contains a table with an overview of all reported cases.

### **Other sources of information**

#### *SmPC*

The SmPC of Spikevax® does not mention "Bacille Calmette Guerin scar reactivation" as an adverse reaction [1].

#### *Literature*

Scar reactivation of a former inoculation site of Baccillus Calmette-Guerin (BCG) vaccine is a common and specific early symptom of Kawasaki's disease. Kawasaki's disease is a form of vasculitis causing inflammation of small vessels. The scar reactivation is presented as a local inflammatory reaction and consists of erythema, induration, ulceration or crust formation [2]. There are also cases of BCG scar reactivation known after measles infection and herpes type 6 infection and after vaccination with influenza vaccine and COVID-19 vaccine [3-6].

Reactivation of the BCG scar is not mentioned as possible side effect of Moderna mRNA-1273 vaccine in a phase 3 randomized, observer-blinded, placebo-controlled trial. In this study 15,210 patients were enrolled who received the vaccine [7].

In the literature, 4 case reports of BCG scar reactivation after administration of mRNA COVID-19 vaccines (Spikevax® n=1, Comirnaty® n=3) are described [6,8]. The BCG scar reactivation is described as erythema and (sometimes painful) swelling at the BCG scar, with a diameter of approximately 1-2 cm. In 3 of these case reports described in the literature the scar reactivation occurred within 1 and 4 days after the second vaccination. In the other case report described in the literature the scar reactivation occurred after 7 days following the first dose. In this case no reaction was seen after the second vaccination. In all cases the reaction at the BCG scar recovered within 2 to 7 days without any treatment [6,8].

### Databases

Table 1. Cases in other databases

Database	Vaccine	ADR (PT)	Number of reports
Lareb	Spikevax®	Bacille Calmette Guerin scar reactivation	11*
Eudravigilance [9]	Spikevax®	Bacille Calmette Guerin scar reactivation	20**
WHO Vigilyze®[10]	Spikevax®	Bacille Calmette Guerin scar reactivation	65**

\*See addendum 1 for the case reports

\*\* The Lareb case reports are included

### Prescription data

Until October 2021 approximately 3,784,800 million doses of Spikevax® had been administered in the Netherlands [11].

### Mechanism

The BCG vaccine against tuberculosis is administered intradermally, and vaccination is often followed by a scar at the injection site [12]. Inflammation of this BCG scar has been described in patients with Kawasaki's disease and other immune mediated events [5].

A possible cause of this reaction is cross-reaction between mycobacterial and human homologue heat shock proteins (HSP) specifically between mycobacterium HSP65 and its human homologous protein [5,13]. Heat-shock proteins provide a natural link between innate and adaptive immune responses by combining the ideal properties of antigen carriage (chaperoning), targeting and activation of antigen-presenting cells (APC), including dendritic cells (DC) [14]. It has been suggested that HSP liberation after influenza vaccination could stimulate the immune response at the BCG scar resulting in a local inflammatory reaction [5,8]. Possibly the same mechanism occurs in the case of COVID vaccination with Spikevax®.

### Discussion and conclusion

In the period from March 7<sup>th</sup>, 2021 until October 20<sup>th</sup>, 2021 The Netherlands Pharmacovigilance Centre Lareb received 11 case reports of BCG scar reactivation after administration of Spikevax®. In addition, 6 reports after other Covid-19 vaccines were made, namely 4 after Comirnaty® and 2 after Vaxzevria®. BCG scar reactivation is a common and early sign in Kawasaki's disease, and has also been described after measles infection and herpes type 6 infection and after vaccination with influenza vaccine and COVID-19 vaccines (Spikevax® and Comirnaty®) [2-6, 8].

All cases of BCG scar reactivation after Spikevax® in the Netherlands with a late onset (after 7 days) have been reported after the first dose. A latency time within 4 days was seen after the second dose. The same pattern is seen in the case reports found in literature [6,8].

BCG scar reactivation is a very specific clinical sign and in the present cases other causes besides vaccination are considered unlikely. The clinical presentation may be of concern among patients and health care providers. It is therefore suggested to raise awareness for BCG scar reactivation after administration of Spikevax®.

#### References

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*This signal has been raised on December 20, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbq-meb.nl](http://www.cbq-meb.nl)*

### Addendum 1: Cases of BCG reactivation for the Spikevax® vaccine

Cas e	ID Sex Age Primary source Receive date	Vaccine dose Start date	Primary source text (BCG scar)	Reported PT's	Latency BCG scar reactivation	Outcome Duration (time of reporting after onset)	Concomitant medication
1	NL-LRB-00519453 F 30-40 Patient 24-4-2021	Moderna vaccine 2nd dose 22-04-2021	Redness on old TB vaccination site near site of Moderna vaccination administration	Bacille Calmette Guerin scar reactivation Chills Headache Myalgia Arthralgia Malaise Fatigue Injection site erythema Injection site swelling Injection site inflammation Pyrexia	2 days	Not recovered (day of onset)	Paracetamol
2	NL-LRB-00467197 F 30-40 Patient, 6-3-2021	Moderna vaccine 2nd dose 27-02-2021	Other reaction at or near the injection site: Under the injection site at the BCG vaccine scar (had as a baby), swelling, pain and redness present for 4 days.	Headache Nausea Myalgia Malaise Fatigue Injection site pain Bacille Calmette Guerin scar reactivation Injection site swelling Injection site inflammation	3 days	Recovered 4 days after onset	
3	NL-LRB-00546988 F 30-40 Patient 18-05-2021	Moderna vaccine 1st dose 10-05-2021	Reactivation of scar BCG vaccine	Bacille Calmette Guerin scar reactivation	1 day	Recovering (7 days after onset)	
4	NL-LRB-00552080 F 20-30 Patient 22-5-2021	Moderna vaccine 1st dose 15-05-2021	Other reaction at or near the injection site: BCG scar inflammation	Injection site erythema Injection site warmth BCG scar inflammation Injection site inflammation	7 days	Not recovered (day of onset)	
5	NL-LRB-00552730 F 30-40 Patient 23-05-2021	Moderna vaccine 2nd dose 21-05-2021	Redness and swelling at the site of the BCG vaccine I received after birth	Bacille Calmette Guerin scar reactivation	2 days	Not recovered (day of onset)	
6	NL-LRB-00606584 M 20-30 Patient 2-7-2021	Moderna vaccine 2nd dose 28-06-2021	Other reaction at or near the injection site: Inflammatory reaction from the BCG vaccine scar on the same arm	Bacille Calmette Guerin scar reactivation	2 days	Not recovered (2 days after onset)	
7	NL-LRB-00612438 F 30-40 Patient 6-7-2021	Moderna vaccine 1st dose 27-06-2021	8 days later a red spot at the site of the injection a little lower on the arm around the old BCG scar	Injection site erythema Bacille Calmette Guerin scar reactivation	8 days	Not recovered (1 day after onset)	Vitamine B Complex Forte Magnesium Visolie Collageen

8	NL-LRB-00570813 F 20-30 Patient 7-6-2021	Moderna vaccine 1st dose 27-05-2021	Redness and itching in old BCG vaccination scar	Erythema Pruritus Feeling hot Bacille Calmette Guerin scar reactivation	8 days	Not recovered (3 days after onset)	
9	NL-LRB-00629940 F 50-60 Patient 18-07-2021	Moderna vaccine 2nd dose 19-06-2021	Other reaction at or near the injection site: Reaction to old (childhood) BCG vaccination site. Redness localized and a little swollen. About 4-5 days after 2nd Moderna administration. Reaction continued for 7-10 days	Myalgia Injection site swelling Injection site induration Bacille Calmette Guerin scar reactivation	4 days	Recovered 7 days after onset	
10	NL-LRB-00626254 F 40-50 Patient 15-07-2021	Moderna vaccine 2nd dose 13-07-2021	My scar from another vaccination (tuberculosis) has turned red and is still red	Bacille Calmette Guerin scar reactivation, Chills Headache Nausea Myalgia Arthralgia Malaise Fatigue Body temperature increased	1 day	Not recovered (1 day after onset)	
11	NL-LRB-00571198 F 40-50 Patient 7-6-2021	Moderna vaccine 1st dose 12-05-2021	Also, the old scar from a BCG vaccination looked like a blister with a shiny roof. That is also fully recovered after day 15	Injection site erythema Arthralgia Malaise Fatigue Injection site induration Injection site pain Injection site swelling Bacille Calmette Guerin scar reactivation	9 days	Recovered 15 days after onset	