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ORIGINAL ARTICLE

A case series of bacillus Calmette-Guérin scar reactivation after administration of both mRNA and viral vector COVID-19 vaccines

Leontine van Balveren | **Eugène P. van Puijenbroek** | **Linda Davidson** | **Florence van Hunsel**

Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

Correspondence
Leontine van Balveren, Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands.
Email: l.vanbalveren@lareb.nl

Aim: Reactivation of the scar resulting from intradermal injection of bacillus Calmette-Guérin (BCG) is a common specific reaction in Kawasaki's disease. It has also sporadically been associated with viral infections, multisystem inflammatory syndrome in children, influenza vaccination and mRNA COVID-19 vaccination. In this case series, characteristics of BCG scar reactivation after different COVID-19 vaccinations are presented and possible mechanisms are discussed.

Methods: Data were collected from the spontaneous reporting system of the Netherlands Pharmacovigilance Centre Lareb. Descriptives were made for the case reports in which a BCG scar reactivation was detected.

Results: Since the start of the COVID-19 vaccination campaign in January 2021, the Netherlands Pharmacovigilance Centre Lareb has received 22 case reports of BCG reactivation after vaccination with a COVID-19 vaccine. In 20 case reports, it concerned mRNA COVID-19 vaccines Moderna (14) and Pfizer (6). In two case reports, the viral vector COVID-19 vaccine AstraZeneca was administered. Erythema and pain were the most frequently reported symptoms and the size of the inflammation was between 1.5 and 5 cm. BCG scar reactivation occurred with a median time to onset of 2 days after the second or booster COVID-19 vaccination, whereas the median time to onset was 7 days after the first COVID-19 vaccination. None of the BCG scar reactivations were treated.

Conclusions: The exact mechanism of the occurrence of BCG scar reactivation remains unknown, but involvement of heat shock protein 65 is suggested. BCG scar reactivation is a nonserious, self-limiting reaction that can occur after vaccination with both mRNA and viral vector COVID-19 vaccines.

KEYWORDS
bacillus Calmette-Guérin scar reactivation, bacillus Calmette-Guérin vaccine, COVID-19 vaccines, vaccine safety

1 | INTRODUCTION

In early 2021, a mass vaccination campaign against COVID-19 vaccination started in the Netherlands. Four vaccine brands were used: mRNA

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vaccines from manufacturers Pfizer (Comirnaty) and Moderna (SpikeVax) as well as viral vector vaccines from manufacturers AstraZeneca (Vaxzevria) and Janssen (Jcovden). Although these vaccines were tested for efficacy and safety in large clinical trials,[1–4] not all adverse events (AE) were known at the moment of (conditional) marketing approval.

Bacille Calmette-Guérin (BCG) vaccination is not part of the National Immunisation Programme for children in the Netherlands. However, BCG vaccination is offered to children of parents who come from countries where tuberculosis is endemic. Additionally, BCG vaccination is indicated for travellers to one of these high-incidence countries.[5] After intradermal vaccination with the BCG vaccine, an ulcer appears at the injection site. Consecutively, this ulcer develops to a characteristic scar.[6] Sometimes the scar inflames later on in life. This so-called reactivation of the former inoculation site is a very specific reaction. BCG scar reactivation presents as a local inflammatory reaction and may consist of symptoms of erythema, induration, ulceration or crust formation.[7] It may occur as an (early) symptom of Kawasaki's disease (KD).[7,8] BCG scar reactivation has also been described after infection with measles and human herpesvirus 6, and recently after multisystem inflammatory syndrome-children (MIS-C).[9–12] In addition, some cases of BCG scar reactivation occurred after vaccination with influenza vaccine,[13] and one case has been described following adalimumab.[14] Since the start of the COVID-19 vaccination campaigns worldwide, a few cases of BCG scar reactivation have been described as adverse events following immunization (AEFI) of an mRNA COVID-19 vaccine.[15–20] As far as we know, no case reports of BCG scar reactivation after administration of COVID-19 viral vector vaccines have been reported in the literature.

The Netherlands Pharmacovigilance Centre Lareb has received a high number of adverse events following COVID-19 vaccination. So far, over 225 000 case reports of AEFI have been reported since January 2021. Case reports in which a BCG scar reactivation was reported after vaccination with a COVID-19 vaccine were identified. We describe the characteristics of the BCG scar reactivations in reported cases and discuss a possible pharmacological mechanism.

What is already known about this subject

- Bacillus Calmette-Guérin (BCG) scar reactivation is a common and early sign of Kawasaki disease.
- BCG scar reactivation may be observed after several viral infections and has been described in multisystem inflammatory syndrome in children.
- Case reports have been published on BCG scar reactivation after mRNA COVID-19 vaccination, but none after COVID-19 viral vector vaccination.

What this study adds

- BCG scar reactivation can be an adverse event after both mRNA and viral vector COVID-19 vaccination.
- We present the first two cases in which BCG scar reactivation was associated with COVID-19 viral vector vaccination.
- The time between COVID-19 vaccination and BCG scar reactivation was longer after the first than after the second or booster dose.

2 | METHODS

Pharmacovigilance (PV) Centre Lareb maintains the spontaneous reporting system for drugs and vaccines in the Netherlands. By collecting and analysing AEFIs, more knowledge is acquired on the occurrence of AEFIs in daily practice. We included cases that had been reported to our PV centre from January 2021 (start of the COVID-19 vaccination campaign in The Netherlands) until 12 April 2022. All AEFIs are coded with the Medical Dictionary for regulatory Activities (MedDRA versions 24.0 and 24.1).[21] All case reports coded with the term "Bacille Calmette Guérin scar reactivation" were included in our study. To detect possible misclassified cases, the database was screened by a free-text search of the primary source description and additional information fields using the terms "tuberculosis," "TBC," "BCG," and "scar." In case a BCG scar reactivation was discovered, the reported AEFI in these cases was recoded to "Bacille Calmette Guérin scar reactivation" and included in this case series. Data enrichment was attempted by asking follow-up questions concerning diagnostic procedures, treatment and outcome of BCG scar reactivation as well as the reporters age at time of BCG vaccination.

The following aspects were retrieved from the spontaneous safety reports: seriousness (according to CIOMS criteria), brand of COVID-19 vaccine, age and sex, description of the reaction at the BCG scar, latency period between vaccination and onset, outcome, duration, burden (based on a five-point Likert scale) and presence of other AEFI.

3 | RESULTS

A total of 22 cases of BCG scar reactivation were reported to Pharmacovigilance Centre Lareb between January 2021 and 12 April 2022. Table 1 summarizes the characteristics of the case reports. Of the 22 case reports, 14 reactivations were associated with the Moderna COVID-19 vaccine, six with the Pfizer COVID-19 vaccine and two with the AstraZeneca COVID-19 vaccine. In 21 case reports (96%) women were involved. The mean age was 38 years (range 12-70 years, median 34 years).

The reactivation occurred after administration of the first, second or third (booster) dose in eight, 10 and four cases, respectively. In none of the cases the occurrence of a similar reaction after re-exposure to a next COVID-10 vaccine (rechallenge) was reported.

TABLE 1 Summary of 22 case reports of bacillus Calmette-Guérin (BCG) scar reactivation

Case	Sex Age Source (physician or patient)	Vaccine Dose order Date of administration vaccine	Reported AEFI (MedDRA version 25.0)[21]	Time to onset of the BCG scar reactivation	Outcome duration or time from onset to reporting BCG scar reactivation
1	F 38 Patient	Moderna vaccine 2 22-04-2021	BCG scar reactivation Chills Headache Myalgia Arthralgia Malaise Fatigue Injection site erythema Injection site swelling Injection site inflammation Pyrexia	2 days	Not recovered at the time of reporting day of onset
2	F 36 Patient	Moderna vaccine 2 27-02-2021	Headache Nausea Myalgia Malaise Fatigue Injection site pain BCG scar reactivation Injection site swelling Injection site inflammation	3 days	Recovered 4 days
3	F 30 Patient	Moderna vaccine 1 10-05-2021	BCG scar reactivation	1 day	Recovering 7 days after onset
4	F 25 Patient	Moderna vaccine 1 15-05-2021	Injection site erythema Injection site warmth BCG scar reactivation Injection site inflammation	7 days	Not recovered at the time of reporting day of onset
5	F 30 Patient	Moderna vaccine 2 21-05-2021	BCG scar reactivation	2 days	Not recovered at the time of reporting day of onset
6	M 27 Patient	Moderna vaccine 2 28-06-2021	BCG scar reactivation	2 days	Not recovered at the time of reporting 2 days after onset
7	F 33 Patient	Moderna vaccine 1 27-06-2021	BCG scar reactivation Injection site erythema	8 days	Not recovered at the time of reporting 1 day after onset

(Continues)

TABLE 1 (Continued)

Case	Sex Age Source (physician or patient)	Vaccine Dose order Date of administration vaccine	Reported AEFI (MedDRA version 25.0)[21]	Time to onset of the BCG scar reactivation	Outcome duration or time from onset to reporting BCG scar reactivation
8	F 28 Patient	Moderna vaccine 1 27-05-2021	BCG scar reactivation Erythema Pruritus Feeling hot	8 days	Not recovered at the time of reporting 3 days after onset
9	F 53 Patient	Moderna vaccine 2 19-06-2021	BCG scar reactivation myalgia Injection site swelling Injection site induration	4 days	Recovered 7 days
10	F 40 Patient	Moderna vaccine 2 13-07-2021	BCG scar reactivation Chills Headache Nausea Myalgia Arthralgia Malaise Fatigue Body temperature increased	1 day	Not recovered at the time of reporting 1 day after onset
11	F 40 Patient	Moderna vaccine 1 12-05-2021	BCG scar reactivation Injection site erythema Arthralgia Malaise Fatigue Injection site induration Injection site pain Injection site swelling	9 days	Recovered 15 days
12	F 63 Patient	AstraZeneca vaccine 1 12-05-2021	BCG scar reactivation	5 days	Not recovered at the time of reporting 1 days after onset
13	F 12 Health professional	Pfizer vaccine 1 22-07-2021	BCG scar reactivation	2 days	Not recovered at the time of reporting Day after onset
14	F 35 Patient	Pfizer vaccine 2 22-07-2021	BCG scar reactivation Headache Myalgia Pyrexia	1 day	Recovering 3 days after onset

TABLE 1 (Continued)

Case	Sex Age Source (physician or patient)	Vaccine Dose order Date of administration vaccine	Reported AEFI (MedDRA version 25.0)[21]	Time to onset of the BCG scar reactivation	Outcome duration or time from onset to reporting BCG scar reactivation
15	F 25 Patient	Pfizer vaccine 2 31-07-2021	BCG scar reactivation Injection site erythema Injection site pain Injection site haematoma Injection site inflammation Pain in arm Fatigue	1 day	Recovered 7 days
16	F 17 Patient	Pfizer vaccine 2 11-08-2021	BCG scar reactivation Injection site erythema Injection site swelling Injection site pain Injection site pruritis Injection site inflammation	1 day	Recovered 4 days
17	M 61 Patient	Moderna vaccine 3 22-12-2021	BCG scar reactivation Injection site irritation Injection site erythema Extensive swelling of vaccinated limb	1 day	Not recovered at the time of reporting 2 days after onset
18	F 70 Patient	Moderna vaccine 3 22-12-2021	BCG scar reactivation Injection site erythema Injection site swelling Injection site warmth Injection site pruritis Injection site inflammation	1 day	Recovered 5 days
19	F 62 Patient	Moderna vaccine 3 29-12-2021	BCG scar reactivation Lymphadenopathy Myalgia Nausea Headache Chills Fatigue Injection site erythema Injection site warmth Injection site pain Injection site haematoma Injection site swelling Injection site inflammation	2 days	Recovered 3 days
20	F 32 Patient	Pfizer vaccine 3 14-01-2021	BCG scar reactivation Headache	2 days	Not recovered at the time of reporting 2 days after onset

(Continues)

TABLE 1 (Continued)

Case	Sex Age Source (physician or patient)	Vaccine Dose order Date of administration vaccine	Reported AEFI (MedDRA version 25.0)[21]	Time to onset of the BCG scar reactivation	Outcome duration or time from onset to reporting BCG scar reactivation
21	F 30 Patient	Pfizer vaccine 2 15-01-2021	BCG scar reactivation Fatigue	2 days	Not recovered at the time of reporting Day of onset
22	F 51 Healthcare professional	AstraZeneca vaccine 1 21-02-2021	BCG scar reactivation Pyrexia Headache Myalgia Arthralgia Malaise Pruritus Fatigue Limb discomfort Paraesthesia Dizziness	Unknown	Recovering Unknown time after onset

In most case reports the BCG scar reactivation was described as erythema and pain (see Figure 1). Sometimes also swelling, warmth or pruritus were reported. In one case a blister was seen at the BCG scar. Another reporter described the presence of a "red stripe" from the red BCG scar towards the inner side of the upper arm. The size of the BCG reactivation at the site of inoculation (reported in four cases) was between 1.5 and 5 cm.

The time between vaccination and the start of the BCG scar reactivation (latency time) ranged from 1 to 9 days. In one case report the latency time was not reported. Figure 2 shows the latency time of reactivation for different doses of COVID-19 vaccination. In case reports where the first dose of the COVID-19 vaccine was administered (n = 5), the median latency time was 7 days. For the second (n = 10) or third (n = 4) dose the latency time was shorter, mostly around 1 or 2 days (median of 2 days).

Recovery time was reported to be between 3 and 15 days (median 5 days) in seven cases. In three case reports the patient was recovering at the time of reporting, but the outcome was still unknown. The other patients had not yet recovered (n = 12) at the time of reporting (these cases were reported within 3 days after onset of the reaction). None of the patients was treated for the BCG scar reactivation (known at the time of reporting) and the impact of the reaction was low. Three patients reported to have quite some burden of the reactivation, for the other patients the burden was little (n = 12), no burden at all (n = 5) or unknown (n = 2).

Of 11 patients it was known that they received the BCG vaccine during childhood (under 18 years). One reporter stated that she received the BCG vaccination more than 50 years ago. Five patients reported BCG scar reactivation as the single AEFI. The other patients also reported local reactions at the COVID-19 vaccination site (n = 5), other systemic reactions, for instance myalgia or headache (n = 5), or

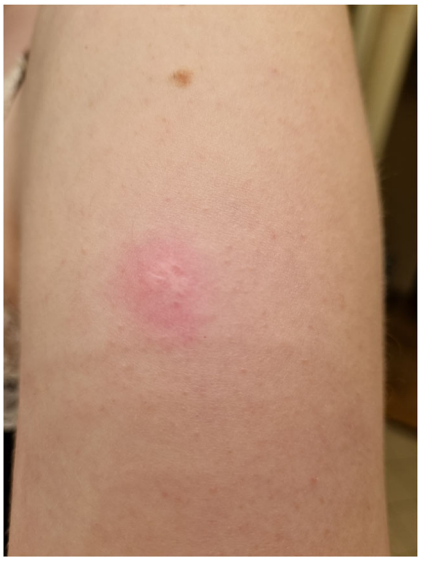

FIGURE 1 Erythema around the BCG scar after booster vaccination with Pfizer COVID-19 vaccine (with permission of the patient). This patient reported that the BCG scar was also slightly painful.

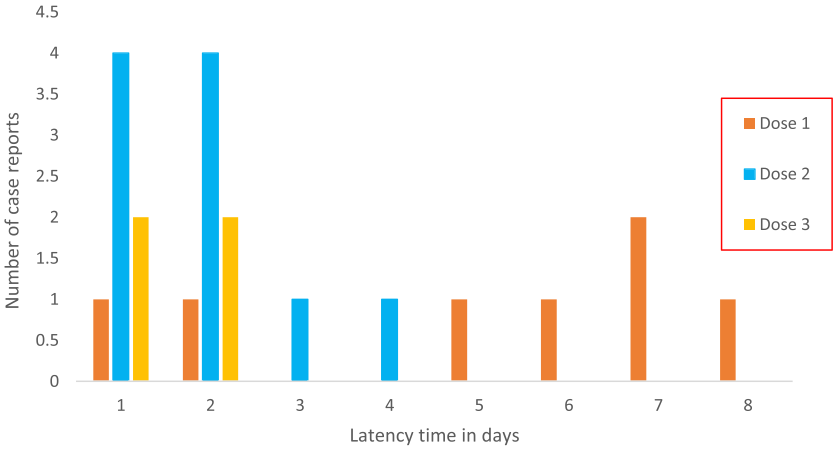

FIGURE 2 Latency time of the BCG reactivation in days after doses 1 and 2 and a first booster (dose 3).

a combination of local and systemic reactions (n = 7). None of the cases reported recent infections, medical conditions or other drugs or vaccinations as other possible causes for the reaction.

4 | DISCUSSION

This case series shows that BCG scar reactivation can occur after both mRNA and viral vector COVID-19 vaccination. It was predominantly seen in women with a median age of 38 years and most BCG reactivations were reported after the first or second dose of a COVID-19 vaccination. All BCG scar reactivations occurred within 9 days after COVID-19 vaccination. Currently this reaction is not listed as a known AEFI for the Covid-19 vaccines in the Summary of Product Characteristics.

The BCG vaccine mainly protects against the most severe forms of tuberculosis, meningeal and miliary tuberculosis. The vaccine also provides some protection against leprosy and nontuberculous mycobacterial (NTM) infections.[22–24] In addition, it has been described that BCG vaccination can enhance the immune response against some non-mycobacterial microorganisms, as illustrated by the decreased risk of pneumonia-related mortality.[6,25] Also, the phenomenon of trained immunity is described after BCG vaccination, in which immunological memory function occurs in the innate immune system, while historically immunological memory was assumed to be exclusive to the adaptive immune response.[26] Some studies showed beneficial vaccine responses in the case of previous or concurrent BCG vaccination, resulting in higher antibody levels in BCG-vaccinated participants compared to the non-BCG vaccinated group.[6,25,27] Additionally, BCG immunotherapy can be used as treatment, for instance in bladder cancer,[6] although the exact mechanism for this therapeutic effect is not yet clarified.[28] Next to the above-mentioned specific features, erythema and induration of the BCG site is an important and early sign in (especially younger) children with Kawasaki disease (KD).[8] It can be an important early sign in children with incomplete KD.[7,29]

In the literature, several mechanisms underlying BCG scar reactivation are proposed, most of which include mycobacterial heat shock protein (Hsp)65. Hsp65 is the most immunogenic component of *Mycobacterium bovis* BCG. It is responsible for inducing potent, antigen-specifc $CD4^+$ and $CD8^+$ T cell activation.[30] Consecutive production of the proinflammatory cytokines TNF-α and IL-1β shows the ability of Hsp65 to orchestrate both host defence against *M. bovis* BCG and induce tissue damage in inflammatory lesions containing high expression of Hsp65.[31] Cross-immune reaction has been suggested between Hsp65 and Hsp63 for Kawasaki disease and influenza vaccination.[13] Protein sequence analysis showed an extensive sequence similarity between Hsp65 and the spike and nuclear proteins of SARS-CoV-2.[30] These findings support the possibility of a cross-immune reaction between BCGs Hsp65 and COVID-19 vaccination. Furthermore, it has been demonstrated that BCG vaccination provides specific immunity against SARS-CoV-2 infection, although the exact mechanism is not yet elucidated.[32] In contrast, to our current knowledge no case reports of BCG scar reactivation in patients with SARS-CoV-2 infections have been published.

To clarify the underlying mechanism of BCG scar reactivation after COVID-19 vaccination, it is important to understand the type of inflammation that occurs at the BCG inoculation site. In the aforementioned hypothesis, in which an immune response against the Hsp65-resembling spike and nuclear components of the vaccine causes BCG scar reactivation, the inflammation is sterile.[33] Since lymphocytopenia is a well-defined risk factor for reactivation of latent *M. tuberculosis* infection, reactivation of latent *M. bovis* BCG bacilli causing local BCG infection (BCG-itis) during COVID-19 vaccination-induced transient lymphocytopenia could be an alternative hypothesis. Lymphocytopenia developed in 46% of Pfizer recipients during the first 3 days after vaccination and lymphocyte count returned to normal within 6 to 8 days. Grade 3 lymphocytopenia, an absolute lymphocyte count of 200 to 500 cells/μL (normal range 1000-4800 cells/μL), developed in 9% of recipients.[33] A case of BCG scar reactivation with local BCG-itis has been described in an untreated HIV patient with an absolute lymphocyte count of 2060 cells/μL and a CD4 lymphocyte count of 214 cells/mm^3 (normal range 500-1400 cells/mm^3).[34] Local and disseminated BCG-itis caused by secondary immunodeficiency following a measles infection was described in a malnourished HIV-negative infant.[35] Although the lymphocytopenia

caused by COVID-19 vaccination is transient, a self-limiting course of local *M. bovis* BCG-itis seems unlikely, therefore sterile inflammation is the most likely mechanism in 45% of our cases which reported spontaneous recovery. Unfortunately, in 55% of our cases we did not know the outcome since reporting took place within days after onset of BCG scar reactivation. There are no case reports published on reactivation of latent *M. bovis* BCG bacilli after COVID-19 vaccination.

Up to now 10 case reports of BCG scar reactivation after administration of mRNA COVID-19 vaccines have been described in the literature.[15–20] The reactivation is described as erythema and (sometimes painful) swelling at the BCG scar, with a diameter of approximately 1-2 cm. The scar reactivations occurred mostly within 7 days after the first vaccination with mRNA COVID-19 vaccine and within 4 days after the second or booster dose and they recovered spontaneously. The latency time and self-limiting BCG scar reactivations described in the literature are quite similar to the cases reported to Lareb. Unfortunately, lymphocyte count was not measured in any of our cases. In both our spontaneous safety reports and literature cases, no other possible causes, like concomitant use of immunosuppressive drugs or immunodeficiency disorder of BCG scar reactivation, were reported.

This study has some limitations inherent to the spontaneous reporting system. One of the limitations is underreporting of adverse events. As a consequence, it is impossible to calculate the incidence of the BCG scar reactivation after COVID vaccination. Additionally, it was not always possible to retrieve all relevant clinical information.

In conclusion, our case series includes the first cases of BCG scar reactivation after viral vector COVID-19 vaccination and shows that BCG scar reactivation is a nonserious, remarkable unlisted AEFI that can occur after vaccination with both mRNA and viral vector COVID-19 vaccines. Healthcare professionals should be aware of this potential adverse event to avoid unnecessary anxiety and misclassification.

CONTRIBUTORS

The concept of the study was initiated by F. van Hunsel. L. van Balveren performed data analysis and description of the cases. F. van Hunsel and L. Davidson supervised the data analysis. This first draft was written by L.van Balveren and L. Davidson and reviewed by F. van Hunsel and E. van Puijenbroek. All authors were involved in the finalization of the manuscript and have approved the final version.

COMPETING INTERESTS

We have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

ORCID

Leontine van Balveren https://orcid.org/0000-0002-3815-9434
Florence van Hunsel https://orcid.org/0000-0001-8965-3224

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577
2. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111. doi:10.1016/S0140-6736(20)32661-1
3. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389
4. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187-2201. doi:10.1056/NEJMoa2101544
5. RIVM. Richtlijnen preventie BCG vaccinatie [updated 01-12-202121-07-2022]. Available from: https://www.rivm.nl/cpt/richtlijnen-preventie/bcg-vaccinatie
6. Yamazaki-Nakashimada MA, Unzueta A, Berenise Gamez-Gonzalez L, Gonzalez-Saldana N, Sorensen RU. BCG: a vaccine with multiple faces. *Hum Vaccin Immunother*. 2020;16(8):1841-1850. doi:10.1080/21645515.2019.1706930
7. Loh ACE, Kua PHJ, Tan ZL. Erythema and induration of the bacillus Calmette-Guerin site for diagnosing Kawasaki disease. *Singapore Med J*. 2019;60(2):89-93. doi:10.11622/smedj.2018084
8. Gamez-Gonzalez LB, Hamada H, Llamas-Guillen BA, Ruiz-Fernandez M, Yamazaki-Nakashimada M. BCG and Kawasaki disease in Mexico and Japan. *Hum Vaccin Immunother*. 2017;13(5):1091-1093. doi:10.1080/21645515.2016.1267083
9. Muthuvelu S, Lim KS, Huang LY, Chin ST, Mohan A. Measles infection causing bacillus Calmette-Guerin reactivation: a case report. *BMC Pediatr*. 2019;19(1):251. doi:10.1186/s12887-019-1635-z
10. Kakisaka Y, Ohara T, Katayama S, et al. Human herpes virus type 6 can cause skin lesions at the BCG inoculation site similar to Kawasaki disease. *Tohoku J Exp Med*. 2012;228(4):351-353. doi:10.1620/tjem.228.351
11. Zaki SA, Hazeem AA, Rashid A. Bacillus Calmette-Guerin scar reactivation in multisystem inflammatory syndrome in children. *Trop Doct*. 2022;52(1):222-223. doi:10.1177/00494755211051194
12. Tsuboya N, Makino H, Mitani Y, et al. Erythema and induration of bacillus Calmette-Guerin scar associated with multisystem inflammatory syndrome in children in Japan: a case report. *Front Pediatr*. 2022;10:849473. doi:10.3389/fped.2022.849473
13. Chavarri-Guerra Y, Soto-Perez-de-Celis E. Erythema at the bacillus Calmette-Guerin scar after influenza vaccination. *Rev Soc Bras Med Trop*. 2019;53:e20190390.
14. Gosse L, Dutasta F, Antoine C, et al. BCG scar reactivation on TNF inhibitors. *J Eur Acad Dermatol Venereol*. 2022;36(10):e801-e802. doi:10.1111/jdv.18283
15. Lim DW, Ng DHL, Low JG. Bacillus Calmette-Guerin scar flare after an mRNA SARS-CoV-2 vaccine. *CMAJ*. 2021;193(30):E1178. doi:10.1503/cmaj.210696
16. Lopatynsky-Reyes EZ, Acosta-Lazo H, Ulloa-Gutierrez R, Avila-Aguero ML, Chacon-Cruz E. BCG scar local skin inflammation as a novel reaction following mRNA COVID-19 vaccines in two international healthcare workers. *Cureus*. 2021;13(4):e14453. doi:10.7759/cureus.14453
17. Hung TK, Leung D, Duque JSR, Lau YL. Bacillus Calmette-Guerin scar erythema in a 14-year-old girl post-BNT162b2 vaccination. *Pediatr Int*. 2022;64(1):e15090. doi:10.1111/ped.15090
18. Mohamed L, Madsen AMR, Schaltz-Buchholzer F, et al. Reactivation of BCG vaccination scars after vaccination with mRNA-Covid-vaccines: two case reports. *BMC Infect Dis*. 2021;21(1):1264. doi:10.1186/s12879-021-06949-0

19. Barros Rodrigues J, Pacheco M, Antunes I, Sousa R. Inflammation of BCG inoculation site scar after the first dose of an anti-SARS-CoV-2 mRNA vaccine. *Acta Med Port*. 2022. doi:10.20344/amp.16971
20. Tao J, Rosenfeld D, Hsu J, Bhatia A. Reactivation of a BCG vaccination scar following the first dose of the Moderna COVID-19 vaccine. *Cutis*. 2022;109(3):148-149. doi:10.12788/cutis.0470
21. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999;20(2):109-117. doi:10.2165/00002018-199920020-00002
22. Zimmermann P, Finn A, Curtis N. Does BCG vaccination protect against nontuberculous mycobacterial infection? A systematic review and meta-analysis. *J Infect Dis*. 2018;218(5):679-687. doi:10.1093/infdis/jiy207
23. Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert Rev Vaccines*. 2010;9(2):209-222. doi:10.1586/erv.09.161
24. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *Int J Epidemiol*. 1993;22(6):1154-1158. doi:10.1093/ije/22.6.1154
25. Mouhoub E, Domenech P, Ndao M, Reed MB. The diverse applications of recombinant BCG-based vaccines to target infectious diseases other than tuberculosis: an overview. *Front Microbiol*. 2021;12:757858. doi:10.3389/fmicb.2021.757858
26. Netea MG, Dominguez-Andres J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020;20(6):375-388. doi:10.1038/s41577-020-0285-6
27. Zimmermann P, Curtis N. The influence of BCG on vaccine responses—a systematic review. *Expert Rev Vaccines*. 2018;17(6):547-554. doi:10.1080/14760584.2018.1483727
28. Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer—a current perspective. *Nat Rev Urol*. 2014;11(3):153-162. doi:10.1038/nrurol.2014.15
29. Novais C, Fortunato F, Bicho A, Preto L. Bacillus Calmette-Guerin reactivation as a sign of incomplete Kawasaki disease. *BMJ Case Rep*. 2016;2016:bcr2015213875. doi:10.1136/bcr-2015-213875
30. Finotti P. Sequence similarity of HSP65 of *Mycobacterium bovis* BCG with SARS-CoV-2 spike and nuclear proteins: may it predict an antigen-dependent immune protection of BCG against COVID-19? *Cell Stress Chaperones*. 2022;27(1):37-43. doi:10.1007/s12192-021-01244-y
31. Peetermans WE, Raats CJ, Langermans JA, van Furth R. Mycobacterial heat-shock protein 65 induces proinflammatory cytokines but does not activate human mononuclear phagocytes. *Scand J Immunol*. 1994;39(6):613-617. doi:10.1111/j.1365-3083.1994.tb03421.x
32. Eggenhuizen PJ, Ng BH, Chang J, et al. BCG vaccine derived peptides induce SARS-CoV-2 T cell cross-reactivity. *Front Immunol*. 2021;12:692729. doi:10.3389/fimmu.2021.692729
33. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature*. 2020;586(7830):589-593. doi:10.1038/s41586-020-2639-4
34. Khattou ILO, Rada N, Draiss G, Bouskraoui M. Loco-regional BCGitis revealing a HIV infection in an infant: a case report. *Open Infect Dis J*. 2019;11(1):13-16. doi:10.2174/1874279301911010013
35. Eregie CO. Ulceration of a previously healed BCG scar in suspected disseminated BCG infection. *Ann Trop Paediatr*. 1997;17(2):135-139. doi:10.1080/02724936.1997.11747876

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