# Inflammation in the scar caused by BCG vaccination years previously: a case report, systematic review and critical appraisal

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**Keywords**

BCG Scar, Intravesical Immunotherapy, Case Report, Systematic review, mRNA COVID-19 vaccination, Kawasaki disease, Acute Lymphoblastic Leukaemia.

**Plain language summary**

**Background**. Living "BCG" mycobacterial germs are in most countries injected into the skin of the shoulder of newborn babies as a vaccine to prevent or reduce the severity of TB disease. Also, since 1976, patients with bladder cancer are often treated with BCG infused into their bladder to help cure the bladder cancer.

**Methods**. We report an elderly patient who as an adverse reaction to BCG instillation into their bladder developed inflammation in the scar on their shoulder from childhood BCG vaccination. We then summarised other articles that have been published already describing similar things.

**Findings**. A previously healthy 72-year-old man noticed blood in his urine, which led to the diagnosis of bladder cancer. After removal of the bladder cancer through a telescope inserted into his bladder, he commenced having BCG infused into his bladder. All this treatment was done as an outpatient, without having to sleep in a hospital. A month later, the scar on his shoulder at the site of his childhood BCG vaccination became red and swollen. This local skin reaction varied over time, increasing after each BCG instillation into his bladder, and eventually resolved without treatment. The bladder cancer was cured and the patient has been well for 14-years since. Our review of other articles concerning BCG scar inflammation did not reveal any similar reports, although we were told about other patients who have had similar experiences. Several other diseases, treatments and vaccines have in the past also caused inflammation in old BCG vaccination scars.

**Conclusions.** This shows that some parts of the BCG vaccine must persist for decades in the BCG vaccination scar in people's shoulders, explaining how BCG treatment in the bladder can later cause the scar in the shoulder to become inflamed.

**Abstract**

**Background**. Live *Bacillus Calmette-Guérin* (BCG) mycobacteria are in most countries injected into the skin of the shoulder of newborn babies as a vaccine to prevent or reduce the severity of tuberculosis disease. Also, since 1976, patients with bladder cancer are often treated with BCG instillations into their bladder as intravesical immunotherapy that reduces the risk of bladder cancer recurrence.

**Methods**. We report an elderly patient who as an adverse reaction to BCG instillation into their bladder developed inflammation in the scar on their shoulder from childhood BCG vaccination. The relevant published literature is systematically reviewed and critically appraised.

**Findings**. A previously healthy 72-year-old male noticed blood in his urine, which led to the diagnosis of bladder cancer. After endoscopic removal of the bladder cancer, he commenced immunotherapy with BCG instillations into his bladder, all as outpatient treatment. Approximately one month later, the scar on his shoulder at the site of his childhood BCG vaccination became red and swollen with a serous secretion. This local skin reaction fluctuated, increasing after each BCG instillation into his bladder, and eventually resolved spontaneously without medical intervention. The bladder cancer was cured, without recurrence during 14-years follow-up. Our systematic review of the literature concerning BCG scar inflammation did not reveal any similar reports, although anecdotally, we found that other patients have had similar experiences. We identified diverse evidence that years after BCG vaccination, antigens and/or mycobacteria remain immunologically active in BCG vaccination scars. Furthermore, mRNA COVID-19 vaccination, Kawasaki disease, acute lymphoblastic leukaemia, and immunosuppressive therapy with TNF inhibitors have all caused adults to develop inflammation in their BCG scar years or decades after childhood BCG vaccination.

**Conclusions**. This case report and systematic review demonstrate the persistence of immunologically relevant BCG mycobacteria and/or mycobacterial antigens at the site of BCG vaccination for more than 70 years.

**Clinical case report**

A 72-year-old Caucasian male businessman sought medical care because he had for two days noticed blood discolouring his urine. He was otherwise well and had diet-controlled diabetes. He was an ex-smoker (42 pack-years) and throughout his working life had been heavily exposed to paint solvents from spray painting cars. Examination was normal except for microscopic quantities of blood detected on bedside dipstick testing of his urine. Examination of his bladder through a flexible cystoscope revealed a tumour. Bladder biopsy followed by microscopic examination revealed this to be a transitional-cell carcinoma of the bladder. Blood tests revealed that the patient did not have human immunodeficiency virus antibodies or any other apparent cause of immunosuppression. He was treated with excision of the bladder cancer through a rigid cystoscope. This was followed by intravesical immunotherapy constituting weekly instillations into his bladder of live *Bacillus Calmette-Guérin* (BCG) mycobacteria for six weeks followed by monthly maintenance therapy for six months. The immunotherapy was associated with moderate bladder irritation, BCG prostatitis and systemic flu-like symptoms. The biopsy, surgical excision of the bladder cancer, intravesical immunotherapy and all care were provided as an ambulatory outpatient, without any nights spent in hospital.

Like most people born in the United Kingdom, the patient had a scar in the skin of his shoulder from childhood BCG vaccination, which in his case had been administered on his right side more than 70 years previously. Approximately one month after the first dose of immunotherapy, this BCG vaccination scar became increasingly red, swollen and tender, progressing over approximately one week to ooze a few drops per day of a serous fluid. This skin inflammation fluctuated throughout the duration of his immunotherapy, tending to worsen in the days following each installation of BCG into his bladder. No discrete nodule, abscess nor ulceration occurred. This skin inflammation only caused the patient trivial symptoms but stimulated sufficient curiosity for him to make an infectious disease specialist aware of the phenomenon, leading to this publication. This local reaction resolved spontaneously within two months after the immunotherapy was completed and did not require any medical intervention. Follow-up including regular urinalysis testing and annual screening cystoscopies were normal and the patient has remained well with no cancer recurrence 14 years later.

## Introduction

This clinical case seemed surprising because the inflammation in the patient's BCG scar occurred at a body site far from the bladder immunotherapy and so long after the BCG vaccine had been administered. The sequence of events clearly implied that the recent installation of BCG mycobacteria into the bladder as immunotherapy for bladder cancer caused the inflammation in the BCG scar that had been quiescent for many decades. This implied that immunologically relevant BCG antigens and/or mycobacteria must have persisted at the intradermal site of the BCG vaccination for approximately 70 years. The specialist urologist physician leading the care for this patient reported to us that he recalled other patients who had reported self-limiting BCG scar inflammation developing soon after commencing BCG immunotherapy for bladder cancer. Furthermore, there have been recent reports of vaccination against COVID-19 also causing BCG scar inflammation. We therefore did a systematic review of BCG scar inflammation and critically appraised the implications of this clinical case in relation to the related published literature.

## Methods

### *Consent*

Written informed consent for publication of their clinical details was obtained from the patient.

### *Information sources*

For the current systematic review, four databases were searched: PubMed, Scopus, Web of Science and Embase.

### *Search strategy*

The following search terms were used:

PubMed: ("Bacillus Calmette-Guérin" OR " BCG") AND ("scar" AND ("reactivation" OR "reaction" OR "inflam*"))

Scopus and Embase: ( ALL ( "Bacillus Calmette-Guérin" OR "BCG" ) AND ALL ( "scar reactivation" OR "scar reaction" OR "scar inflammation") )

Web of Science: "Bacillus Calmette-Guérin" OR "BCG" (All Fields) and “scar reactivation” OR “scar reaction” OR “scar inflammation” (All Fields)

The search term syntax was edited slightly between databases in order to maximise the number of relevant publications found by each database.

The date each search was conducted was the 28th of June 2022. This systematic review was not registered with PROSPERO nor any other database.

***Inclusion criteria***

The titles and abstracts were screened and reviewed for eligibility as depicted in Figure 1. Publications of all types (including research studies, case reports, reviews etc.) related to BCG scar reactivation or reaction or inflammation were included. We included human and animal studies involving any age group (i.e. including adults or children) published in any year identified by the above search terms. We additionally searched by hand relevant literature, including reviews and book chapters for any other eligible publications concerning inflammation, reaction or reactivation of an existing BCG vaccination scar for any reason.

***Exclusion criteria***

Studies published in languages other than English or Spanish were excluded from our search for operational reasons.

***Selection process***

The titles and abstracts of studies identified by the database and manual searches were reviewed by the first author VA who prepared a shortlist of potentially eligible publications. This shortlist was then reviewed together with the full text of each publication jointly by VA with the last author CAE to discuss each publication and decide which publications to consider eligible for selection. Discrepancies were to be decided by a third reviewer, but this did not prove to be necessary.

***Data items and extraction***

Data were extracted directly into summary tables by the first author VA, assisted when uncertainties arose by CAE. For all studies, the following data items were retrieved: first author, year of publication, country of origin, the type of study, the number and age of the

subjects included in the study, the type of BCG scar reaction and the time interval between the BCG vaccination and the development of a BCG scar reaction, as shown in Table 1.

***Quality assessment***

The literature identified by our systematic review constituted case series, case reports and literature reviews. These types of publications are not amenable to the quality assessment tools most frequently used in systematic reviews. We therefore studied diverse resources summarising tools that are available for systematic reviews (1,2). This identified quality assessment tools designed to assess case series and case reports and we selected the "JBI critical appraisal tool" as the most appropriate for the publications included in our systematic review, as shown in Table 2 (3–5).

The publications identified by this systematic review were not amenable to formal data synthesis, heterogeneity nor bias evaluation.

***Results***

***Systematic review publication characteristics***

243 publications were identified by our search strategy, 214 of which were unique after removing duplicates. Following further screening, only 7 articles identified by our search strategy were eligible and were therefore selected for inclusion from the systematic review. Eleven additional publications were identified through manual search that also met our selection criteria (Figure 1). Although our search and eligibility criteria included no date limits, all 18 selected articles were published between 2004 and 2022.

***Systematic review publication quality assessment***

Quality assessment was conducted for the 18 eligible studies selected for this report and 16 of them were assessed to be of high-quality using the JBI critical appraisal checklist for case reports (Table 2). The quality of the studies conducted by Rezai et al. (literature review) and Park et al. (retrospective review) could not be meaningfully assessed using the aforementioned checklist.

***Systematic review participant characteristics***

Of the 18 studies included, there were 13 case reports, 2 case series, 1 literature review, 1 retrospective review and 1 clinical trial (Table 1). The studies were conducted in Europe, USA and Asia. The study populations included paediatric and adult patients with ages ranging from 14 days to 53 years of age.

***Systematic review causes of BCG scar inflammation***

All 18 studies were related to BCG scar reaction, reactivation or inflammation following: mRNA COVID-19 vaccination (5 articles) (6–10):

- Multisystem Inflammatory Syndrome in Children (MIS-C) (3 articles) (11–13),
- Kawasaki and incomplete Kawasaki disease (5 articles) (14–18),
- acute lymphoblastic leukaemia (1 article) (19),
- tumour necrosis factor (TNF) inhibitors (1 article) (20),
- measles (1 article) (21),
- scarlet fever (1 article) (22)
- and a delayed BCG granulomatous reaction (1 article) (23) (Table 1).

***Systematic review timing of BCG scar inflammation***

The time between BCG vaccination and BCG scar reaction varied between studies from 14 days to 48 years. However, as shown in Figure 2, this variable interval reflected the interval between childhood BCG vaccination until the age at which specific stimuli were associated with inflammation developing in BCG scars.

***Comparison of systematic review findings to the case we report***

All the studies identified through the systematic review, including the new case we report here, described a local inflammatory response at the BCG scar vaccination site. The types of BCG scar reactions were variable including erythema, induration, pruritus, secretions or bleeding. Moreover, in all adult-population-based studies identified through this systematic review and in the new case we report here, there was a considerable time delay between the BCG vaccination and the development of BCG scar inflammation. Nonetheless, the new case we report here constitutes the first report of a BCG scar inflammation following intravesical

BCG instillations for bladder cancer, and more than 70 years following BCG vaccination appears to be the longest delay reported.

**Discussion**

We report a case of BCG immunotherapy causing inflammation in the scar from BCG vaccination more than 70 years previously. We have also systematically reviewed the literature concerning inflammation in BCG scars, revealing diverse causes of late inflammation in BCG scars. Here we discuss the health implications of this report case and systematic review of related publications.

BCG vaccine is produced from a live attenuated *Mycobacterium bovis (M. bovis)* strain that is widely used to prevent tuberculosis (24). An additional use of BCG is instillation into the bladder as intravesical immunotherapy, which is the mainstay of treatment to prevent bladder cancer progression and recurrence (25). This BCG immunotherapy is primarily employed following transurethral resection for high-risk non-muscle-invasive bladder cancer, and it can also be used in higher-risk patients (25). Non-muscle-invasive bladder cancer includes carcinoma in situ, a superficial, aggressive cancer of urothelial cells with a diffuse pattern that makes complete resection of the tumour difficult, for which recurrence is a significant concern. Intra-vesical BCG instillations have been assessed to have an 87% response rate and reduce the four-year risk of recurrence by 83% (26).

In 1929, autopsy studies suggested that mycobacterial infections could inhibit cancer, but it was not until 1976 that the beneficial effect of BCG immunotherapy in bladder therapy was first reported (25). Now, nearly half a century later, the antitumour effects of BCG infection remain poorly understood (6). However, the induction of a local intravesical immune response and inflammation initially towards the BCG pathogen and subsequently towards the malignant cells is well established (28). BCG binding to the malignant urothelial cells is facilitated by fibronectin (28). Subsequently, BCG becomes internalised and recognised by the first line of innate immune defence (28). The major histocompatibility complex type II is upregulated within the malignant cells, leading to the secretion of interleukins six, eight and the granulocyte-macrophage colony-stimulating factor. Cluster of differentiation type four (CD4)+ and CD8+ T cells, natural killer cells and macrophages recruited to the site result in T-cell mediated cytotoxicity to bladder cancer cells (28). BCG immunotherapy can also result in systemic inflammation with generalized humoral responses, development of lymphadenitis

and positive tuberculin skin test results (29). BCG immunotherapy has been widely used to treat bladder tumours due to its favourable safety profile and apparent superiority to chemotherapy (3). 84% of patients with bladder carcinoma *in situ* have been reported to respond to BCG immunotherapy, after which bladder cancer recurrence occurs in only a small minority of patients (30).

The intravesical installation of this mycobacterial pathogen can lead to various adverse effects; thus local and systemic adverse events cause approximately three per cent of patients to discontinue the treatment (31). Gonzales et al. were the first to report the timeline of BCG immunotherapy infectious complications (26). Generally, the manifestation of systemic symptoms occurs early in the therapy course, while delayed-onset complications remain localised in the bladder (26). Localised symptoms including cystitis, increased urinary frequency, and haematuria frequently occur due to the local inflammatory process. However, these are usually self-limiting and without severe complications.

Early-onset systemic complications usually manifest within the first few weeks following initial BCG instillation, presumably once the patient's immune system has become sensitised to *M. bovis*. For example, BCG-osis refers to the dissemination of the mycobacterial pathogen resulting in sepsis, multiorgan failure, liver and pulmonary infections (29). These adverse events that occur in three to seven per cent of patients are usually mild but can become life-threatening (32). Although the mechanism of BCG-osis remains unclear, there are two main theories: that BCG-osis arises from the systemic dissemination of the mycobacterial pathogen; or results from a delayed-type (i.e. type IV) hypersensitivity reaction to the attenuated *M. bovis* (33).

We propose that in the present case, the local reaction at the BCG vaccination site was the result of a delayed-type hypersensitivity immune reaction. The BCG vaccination scar comprises of various delayed-type hypersensitivity cells, including fibroblasts, macrophages and cytotoxic $CD8^+$ T cells. Therefore, we hypothesise that quiescent $CD8^+$ T cells from the childhood vaccine scar were reactivated after exposure to the attenuated mycobacterium strain following systemic dissemination.

Dermatological reactions at BCG vaccination sites have been extensively reported among infants with Kawasaki disease (34,35). The pathophysiology of this reaction is the focus of ongoing research, but cross-reactivity between the human heat shock protein (HSP) 63 and the HSP 65 from mycobacterium BCG is a possible mechanism (34). Moreover, BCG scar

swelling has been reported many years after vaccination during infection with measles, human herpesvirus and after influenza and severe acute respiratory syndrome coronavirus two (SARS-CoV-2) vaccinations (35). Similarly to Kawasaki disease, the BCG scar reaction was likely the result of cross-reactivity between T-cells stimulated by *M. bovis* with components of the SARS-CoV-2 vaccine (36). This finding is relevant to our case, as it further supports the idea of a delayed hypersensitivity reaction mediated by T-cells remaining at the BCG vaccination site.

Murine models suggest that live BCG pathogens remained viable for five months following BCG vaccination (35). In humans, it is postulated that live BCG persist at the BCG vaccination site for up to one month. However, there have been reports of longer viability, especially among HIV-positive individuals (24). Nonetheless, for the present case, it seems more likely that the presence of BCG antigens in the scar, rather than persistently viable BCG bacilli, led to the inflammation at the site of the BCG vaccination approximately 70 years later. Hypersensitivity reactions do not require viable mycobacterial pathogens but can happen even in the presence of fragments of bacteria (26).

This local reaction at the BCG vaccination site raises the question of whether a history of tuberculosis infection would increase the risk of adverse events following BCG immunotherapy. Currently, BCG immunotherapy is solely contraindicated during active infections and in immunosuppressed individuals (30). A population-based retrospective study provided evidence that the efficacy and safety of the BCG immunotherapy were independent of a previous diagnosis of tuberculosis (37).

The effect of pre-existing immunity to BCG in bladder cancer immunotherapy does not appear to have yet been fully explored. Among patients treated with intravesical BCG, better oncological response and survival rates following intravesical BCG treatment were reported in those who had previously been vaccinated with BCG versus those who had not been vaccinated (37,38). This was supported in an orthotopic model of bladder cancer in which administration of BCG prior to intravesical instillation triggered enhanced T cell-mediated immune responses and achieved better tumour control (38). Most notably, patients with positive tuberculin skin test results, which usually indicates prior immunity to BCG, had significantly higher survival rates following intravesical BCG immunotherapy (38). In the current clinical case, the local reaction at the vaccination site implies that BCG antigens were

still present there, which may have caused ongoing sensitisation to *M. bovis* that may have contributed to the efficacy of BCG immunotherapy in this patient.

Flores and colleagues presented evidence that a decrease in BCG intravesical dose did not affect bladder cancer recurrence compared to standard regimens, while this decreased dose was associated with reduced adverse events (39). Interestingly, the reduced dose regimens were more effective in European patients compared to North American cohorts. Therefore, it was suggested that the BCG vaccination programme within Europe might have played a role. As better treatment response to BCG immunotherapy is predicted by prior immunity to BCG, we hypothesise that the presence of a BCG scar, a positive tuberculin skin test result or history of past tuberculosis disease may justify a reduced dose of intravesical BCG.

This appears to be the first publication reporting a local inflammatory reaction at a BCG vaccination site following intravesical BCG immunotherapy for bladder cancer. Based upon the evidence reviewed above, we hypothesise the pathophysiology of the case we describe, of BCG bladder immunotherapy causing inflammation in a BCG scar that had been quiescent for more than 70 years. The pathophysiology that we propose is summarised in the schematic in Figure 3. This demonstrates that immunologically relevant BCG antigens must remain in the skin at the site of BCG vaccination for decades following BCG vaccination. We have systematically reviewed publications concerning BCG scar inflammation and discussed the implications of this observation for BCG vaccination, BCG immunotherapy and human health in general.

## Data availability

*Underlying data*

All data underlying the results are available as part of the article and no additional source data are required.

*Reporting guidelines*

The article presented here complies with PRISMA guidelines for systematic reviews and can be found in the following repository.

Harvard Dataverse: PRISMA checklist for 'Inflammation in the scar caused by BCG vaccination years previously: a case report, systematic review and critical appraisal'. https://doi.org/10.7910/DVN/NB2KFW (40).



## Acknowledgments

We thank the patient for making us aware of the focus of this publication.

## Grant information

This work was supported by Wellcome [105788, a Research Training Fellowship award to SD; 099951, a Global Health Trials Award to CAE]; the CONCYTEC/ FONDECYT [E067-2020-02-01 number 083-2020; to SD & CAE]; The United Kingdom Research and Innovation Medical Research Council Skills Development Fellowship [MR/T040165/1; to SD]; The United Kingdom Research and Innovation Quality-Related Strategic Priorities Fund [to Imperial College London for a grant to CAE]; Research and fellowship funding from the charity IFHAD: Innovation For Health And Development.

The funders had no role in study design, conduct, analysis, decision to publish, or preparation of the manuscript. All authors had full access to the data and took the decision to submit for publication.

**Competing interests**

All authors declare that they meet the criteria for authorship and have no competing interests related to this research or publication.

**Ethics and consent**

Written informed consent for publication of their clinical details was obtained from the patient.

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**Table 1. Summary of study characteristics.**

*Abbreviations: N/A = not applicable, BCG = Bacillus Calmette-Guérin, MIS-C = Multisystem Inflammatory Syndrome in Children*

Note concerning Rezai et al. 2014: *the 15,955 participants were categorised into two groups and BCG scar inflammation was reported in 39.4% (5,196/13,186) of participants who met the criteria for Kawasaki disease (fever lasting >5 days in addition to >4 of the 5 classical symptoms) and in 100% (2769/2769) of participants meeting the criteria for incomplete Kawasaki disease (fever lasting >5 days in addition to 2 or 3 of the 5 classical symptoms).

| Study | Year | Origin | Topic | Type of study | Study population | Number of subjects | Age of subjects | Type of BCG scar reaction | Time following BCG vaccination |
|---|---|---|---|---|---|---|---|---|---|
| **COVID-19 related** | | | | | | | | | |
| Tao et al. | 2022 | USA | mRNA COVID-19 vaccine | Case report | Adult | 1 | 48 years | Erythema, induration & mild pruritus | 43 years |
| Mohamed et al. | 2021 | Denmark | mRNA COVID-19 vaccine | Case series | Adults | 2 | 53 & 49 years | Clear, yellowish serous secretion & clear yellowish secretion, itching and bleeding | 48 & unknown years |
| Lopatynsky-Reyes et al. | 2021 | Costa Rica & USA | mRNA COVID-19 vaccine | Case series | Adults | 2 | 31 & 28 years | Erythema, induration & erythematous reaction with pain, induration and mild oedema | 31 & 28 years |
| Hung et al. | 2022 | China | mRNA COVID-19 vaccine | Clinical trial | Children | 2 | 11 & 14 years | Erythema, increased induration of the BCG scar | 11 & 14 years |
| Lim et al. | 2021 | Singapore | mRNA COVID-19 vaccine | Case report | Adults | 2 | 34 & 45 years | Swelling & erythema | 34 & 45 years |
| Zaki et al. | 2022 | Abu-Dhabi | MIS-C | Case report | Infant | 1 | 6 months | Redness & crusting | 6 months |
| Patil et al. | 2022 | Dubai | MIS-C | Case report | Infant | 1 | 55 days | Erythema & ulceration | 55 days |
| Tsuboya et al. | 2022 | Japan | MIS-C | Case report | Child | 2 | 3 years | Erythema & induration | 3 years |
| **Non-COVID-19 Infections** | | | | | | | | | |
| Muthuvelu et al. | 2019 | Malaysia | Measles infection | Case report | Infant | 1 | 7 months | 2.5 cm area of erythema, induration & widespread maculopapular rash | 7 months |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Villavicencio et al. | 2022 | US | Scarlet fever | Case report | Child | 1 | 2 years | Enlarging, nonhealing ulceration | 2 years |
| **Kawasaki & incomplete Kawasaki disease** | | | | | | | | | |
| Lim et al. | 2020 | Singapore | Kawasaki disease | Case report | Child | 1 | 11 months | Erythema & induration | 11 months |
| Pavon et al. | 2006 | Mexico | Kawasaki disease | Case report | Child | 1 | 13 months | Erythema and induration in the area surrounding the BCG application with flakes on the surrounding skin | <=13 months |
| Rezai et al. | 2014 | N/A | Kawasaki & incomplete Kawasaki disease | Literature review | Children | 15,955* | 0-120 months | Erythema | N/A |
| Novais et al. | 2016 | Portugal | Incomplete Kawasaki disease | Case report | Infant | 1 | 4 months | Marked erythema & induration | 4 months |
| Park et al. | 2018 | Republic of Korea | Kawasaki disease | Retrospective review | Children | 1,058 | 0-18 months | Redness or crust formation | 0-18 months |
| **Other studies** | | | | | | | | | |
| Swinson et al. | 2004 | UK | Acute lymphoblastic leukemia | Case report | Infant | 1 | 14 days | Erythematous papules | 14 days |
| Gosse et al. | 2022 | France | TNF inhibitors | Case report | Adult | 1 | Scar inflammation occurred at age 21 years (currently 41 years) | Epithelioid granuloma that was culture positive for BCG | 21 years following childhood vaccination and 5 years following a second vaccination |
| Abraham A Ayantund | 2012 | UK | Delayed BCG granulomatous reaction | Case report | Adult | 1 | 29 years | Cutaneous granuloma | 29 years |

**Table 2. Quality assessment.**
*Abbreviations: N/A = not applicable.*

| Study | Year | Patient's demographics were clearly described | Patient's history was clearly described and presented as a timeline | The current clinical condition of the patient on presentation was clearly described | Diagnostic tests or assessment methods and the results were clearly described | The intervention (s) or treatment procedure (s) were clearly described | The post-intervention clinical condition was clearly described | Adverse events (harms) or unanticipated events were identified and described | The case report provides takeaway lessons |
|---|---|---|---|---|---|---|---|---|---|
| COVID-19 related | | | | | | | | | |
| Tao et al. | 2022 | YES | YES | YES | YES | YES | YES | YES | YES |
| Mohamed et al. | 2021 | YES | YES | YES | YES | YES | YES | YES | YES |
| Lopatynsky-Reyes et al. | 2021 | YES | YES | YES | YES | YES | YES | YES | YES |
| Hung et al. | 2022 | YES | YES | YES | YES | YES | YES | YES | YES |
| Lim et al. | 2021 | YES | YES | YES | YES | YES | YES | YES | YES |
| Zaki et al. | 2022 | YES | YES | YES | YES | YES | YES | YES | YES |
| Patil et al. | 2022 | YES | YES | YES | YES | YES | YES | YES | YES |
| Tsuboya et al. | 2022 | YES | YES | YES | YES | YES | YES | YES | YES |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Non-COVID-19 Infections** | | | | | | | | | |
| Muthuvelu et al. | 2019 | YES | YES | YES | YES | YES | YES | YES | YES |
| Villavicencio et al. | 2022 | YES | YES | YES | YES | YES | YES | YES | YES |
| **Kawasaki & Incomplete Kawasaki disease** | | | | | | | | | |
| Lim et al. | 2020 | YES | YES | YES | YES | YES | YES | YES | YES |
| Pavon et al. | 2006 | YES | YES | YES | YES | YES | YES | YES | YES |
| Rezai et al. | 2014 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Novais et al. | 2016 | YES | YES | YES | YES | YES | YES | YES | YES |
| Park et al. | 2018 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **Other studies** | | | | | | | | | |
| Swinson et al. | 2004 | YES | YES | YES | YES | YES | YES | YES | YES |
| Gosse et al. | 2022 | YES | YES | YES | YES | YES | YES | YES | YES |
| Abraham A Ayantund | 2012 | YES | YES | YES | YES | YES | YES | YES | YES |

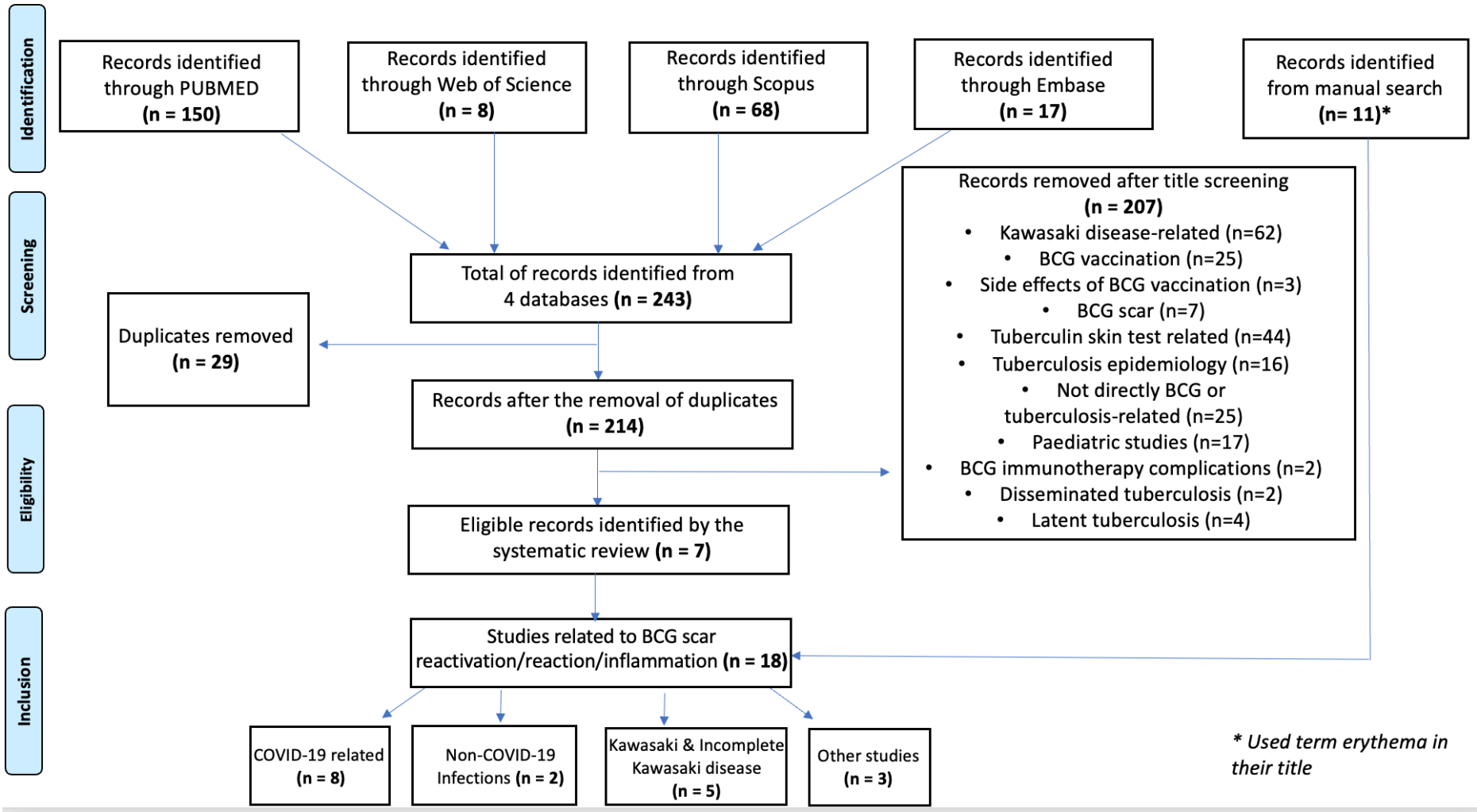


**Figure 1. Flowchart for the systematic review study selection process.**
Seven studies identified by bibliographic searches met the eligibility criteria, supplemented by 11 other publications identified by manual searches, so a total of 18 publications were selected for the current systematic review. *Abbreviation: BCG = Bacillus Calmette-Guérin.*

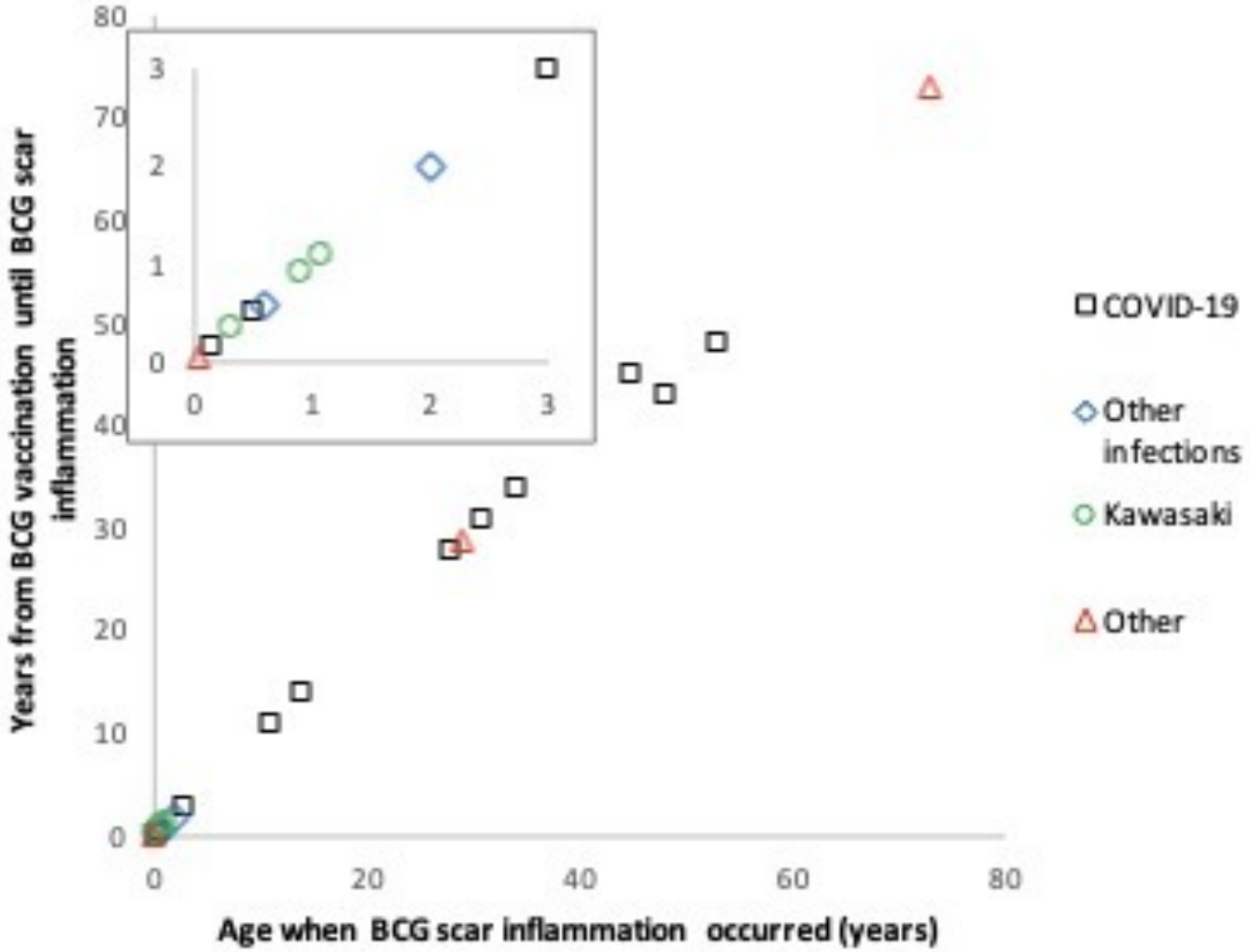


**Figure 2. Graph of BCG scar inflammation timing.** Data are shown for each of the cases identified in the systematic review, plus the case report described in this manuscript. Note that the inset panel enlarges the data for 0-3 years so that each data point is visible.

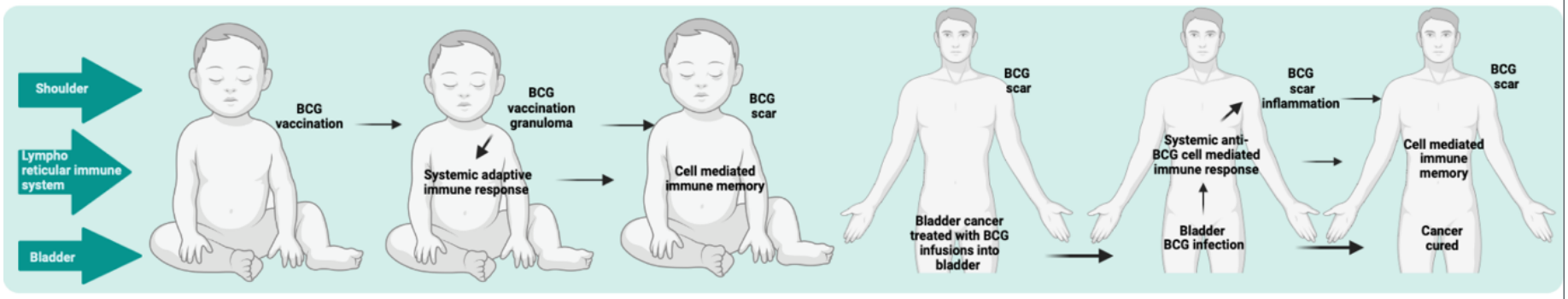


**Figure 3. Schematic.** The schematic shows the pathophysiology that we propose links bladder immunotherapy with BCG scar inflammation.