**Clinical Librarian Service Search Results**

**Request:** What literature or evidence available concerning BCG vaccination and COVID-19? Is it beneficial?

**Summary**

A search of good quality resources has retrieved a small amount of literature addressing the BCG vaccine and COVID-19.

The search has retrieved details of two clinical trials, (Australia x 1, The Netherlands x 1), which have recently started investigating BCG vaccination use in COVID-19.1,2

These trials appear to primarily be in response to theories highlighted in the literature concerning BCG vaccination and it’s potential for beneficial use in non-tuberculous respiratory infections.3-8 A recent paper made available via the preprint server, MedRxiv, (Miller et al, 2020)3, specifically reports on an epidemiological study into the correlation between universal BCG vaccination programmes and COVID-19 morbidity and mortality. The authors of this paper, yet to be peer-reviewed, suggest that variations between national experiences of COVID-19 might be correlated with variations in those countries national BCG vaccination programme and policies. The authors suggest that countries without universal national programmes of BCG vaccination may have been more severely affected.

The results listed below are split into three sections: Clinical trials, a small selection of papers and a small selection of online commentary. Should any further literature concerning BCG use in non-tuberculous infections be require, it can easily be supplied.

I hope that I have interpreted your request correctly. Please let me know if you would like me to search further.

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**Accessing Articles**

Links are provided where online access to the full-text is available. An OpenAthens username and password may be required for online access to articles. You can register for one here: <https://openathens.nice.org.uk/>

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If the full-text is not available, you can request an Inter-Library Loan freely and directly via our Inter-Library Loans system: CLIO. Register for CLIO (using your library membership number) at: [https://derbyill.cliohosting.co.uk](https://derbyill.cliohosting.co.uk/). Further information can be found at: <http://www.uhdblibrary.co.uk/ills>.

**Feedback**

Once you have read this report, I would appreciate it if you would complete our online literature search feedback form at:

<https://www.smartsurvey.co.uk/s/LiteratureSearchFeedback20202021/>

This relates to this specific search and will help us to monitor and improve our service.

Many Thanks.

Lisa Lawrence

Clinical Librarian

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**Current at:** 2nd April 2020.

**Time taken for search:** 3.5 hours.

**Please acknowledge this work in any resulting paper or presentation as:**

Evidence Search: LS1 BCG vaccination and COVID-19. Lisa Lawrence. (02/04/2020). Derby, UK: University Hospitals of Derby & Burton NHS Foundation Trust Library and Knowledge Service.

**Disclaimer:** Please note that the information supplied by the Library and Knowledge Service in response to a literature search is for information purposes only. Every reasonable effort will be made to ensure that this information is accurate, up-to-date and complete. However, it is possible that it may not be representative of the whole body of evidence. No responsibility can be accepted by the Library for any action taken on the basis of this information.

Guidance or information relating to specific drug queries or procedures should be referred to Medicines Information on RDH ext. 85379 or Burton ext. 5168 or 5101.

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For local UHDB guidelines and policies please refer to the red button on the Trust intranet, or [**https://derby.koha-ptfs.co.uk/cgi-bin/koha/opac-main.pl**](https://derby.koha-ptfs.co.uk/cgi-bin/koha/opac-main.pl)

**Results: Current trials**

1. **BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE).**

**ClinicalTrials.gov Identifier:** NCT04327206.

**Recruitment Status:** Not yet recruiting.

**First posted:** March 31, 2020.

**Last Update Posted:** March 31, 2020.

**Sponsor & Responsible Party:** Murdoch Childrens Research Institute, Australia.

**Brief Summary:** *“Open label, two group, phase III randomised controlled trial in up to 4170 healthcare workers to determine if BC vaccination reduces the incidence and severity of COVID-19 during the 2020 pandemic”*

**Trial registration page:** <https://clinicaltrials.gov/ct2/show/NCT04327206>

1. **Reducing Health Care Workers Absenteeism in SARS-CoV-2 Pandemic Through Bacillus Calmette-Guérin Vaccination, A Randomized Controlled Trial (BCG Corona).**

**ClinicalTrials.gov Identifier:** NCT04328441.

**Recruitment Status:** Recruiting.

**First posted:** March 31, 2020.

**Last Update Posted:** March 31, 2020.

**Sponsor & Responsible Party:** MJM Bonten, UMC Utrecht, Netherlands.

**Brief Summary:** *“Rationale: SARS-CoV-2 spreads rapidly throughout the world. A large epidemic in the Netherlands would seriously challenge the available hospital capacity, and this would be augmented by absenteeism of healthcare workers (HCW). Strategies to prevent absenteeism of HCW are, therefore, desperately needed to safeguard continuous patient care. Bacille Calmette-Guérin (BCG) is a vaccine against tuberculosis, with protective non-specific effects against other respiratory tract infections in in vitro and in vivo studies, and reported significant reductions in morbidity and mortality. We hypothesize that BCG vaccination can reduce HCW absenteeism during the epidemic phase of SARS-CoV-2.*

*Objective: Primary objective: To reduce absenteeism among HCW with direct patient contacts during the epidemic phase of COVID19. Secondary objective: To reduce hospital admission, ICU admission or death in HCW with direct patient contacts during the epidemic phase of COVID19.*

*Study design: A placebo-controlled adaptive multi-centre randomized controlled trial.*

*Study population: HCW with direct patient contacts, defined as nurses and physicians working at emergency rooms and wards where COVID-infected patietns are treated.*

*Intervention: Participants will be randomized between intracutaneous administration of BCG vaccine or placebo in a 1:1 ratio.*

*Main Study parameters/endpoints: Primary endpoint: number of days (unplanned) absenteeism for any reason. Secondary endpoints: number of days of (unplanned) absenteeism because of documented SARS-CoV-2 infection, and the cumulative incidence of hospital admission, Intensive Care Admission, and death.*

*Nature and extent of the burden and risks associated with participation, benefit and group-relatedness: Based on previous experience and randomized controlled trials in adult and elderly individuals, the risks of BCG vaccination are considered low. The objective of this trial is to evaluate the beneficial effects of BCG vaccination through a lower work absenteeism rate of HCW and/or a mitigated clinical course of SARS-CoV-2 infection. The primary endpoint and the adaptive design with frequent interim analyses facilitate maximum efficiency of the trial, so that results can inform policy making during the ongoing epidemic”.*

**Trial registration page:** <https://clinicaltrials.gov/ct2/show/NCT04328441>

**Results: Papers / Letters**

1. **Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study.**

**Author(s):** Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH.

**Citation:** medRxiv 2020.03.24.20042937;

doi:https://doi.org/10.1101/2020.03.24.2004293

Please note the disclaimer from the medRxiv website: *“This article is a preprint and has not been peer reviewed … It reports new medical research that has yet to be evaluated and should not be use dot guide clinical practice”.*

**Abstract:** COVID-19 has spread to most countries in the world. Puzzlingly, the impact of the disease is different in different countries. These differences are attributed to differences in cultural norms, mitigation efforts, and health infrastructure. Here we propose that national differences in COVID-19 impact could be partially explained by the different national policies respect to Bacillus Calmette-Guerin (BCG) childhood vaccination. BCG vaccination has been reported to offer broad protection to respiratory infections. We compared large number of countries BCG vaccination policies with the morbidity and mortality for COVID-19. We found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies. Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population. We also found that BCG vaccination also reduced the number of reported COVID-19 cases in a country. The combination of reduced morbidity and mortality makes BCG vaccination a potential new tool in the fight against COVID-19.

**Source:** medRxiv

**Full Text/URL:** <https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v1>

1. **Rapid Response: Does BCG bolster one’s immunity against COVID-19?** Rapid response to: COVID-19: what treatments are being investigated?

**Author(s):** Athikarisamy SE, Jacob JR.

**Citation:** BMJ 2020;368:m1252/rr-4.

**Publication Type:** Letter to the editor.

**Source:** BMJ.

**Full Text/URL:** <https://www.bmj.com/content/368/bmj.m1252/rr-4>

1. **SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics.**

**Author(s):** Cao, Q, Chen, Y-C, Chen C-L, Chiu C-H.

**Citation:** Journal of the Formosan Medical Association. March 2020; 119(3): 670-673.

**Extract:** *“Adults with COVID-19 usually showed a significant or progressive decrease in the absolute number of peripheral blood lymphocytes at the early stage of the disease. T lymphocyte subsets showed a decrease in both CD4+ and CD8+ T cell subsets, and neutrophil-to-lymphocyte ratio is an early and reliable indicator for the development of severe COVID-19, suggesting that SARS-CoV-2 can consume lymphocytes, which may also be an important reason for the virus to proliferate and spread in the early stage of the disease.* *Severe cases in adults usually progress 7–10 days after the onset of disease, likely due to rapid virus replication, inflammatory cell infiltration, and an increased proinflammatory cytokine and chemokine response, leading to acute respiratory distress syndrome (ARDS), a fatal acute lung injury. In children, however, white blood cell count and absolute lymphocyte count were mostly normal, and no lymphocyte depletion occurred, suggesting less immune dysfunction after the SARS-CoV-2 infection. On the other hand, the mild disease in children may be related to trained immunity. Trained immunity, as a new immune model, refers to the use of certain vaccines such as Bacille Calmette-Guérin (BCG) to train innate immunity to generate immune memory.* *BCG has been proved to provide nonspecific protection of mice against influenza virus infection probably by the induction of trained immunity. Most, if not all, of the infants received regular immunizations, including BCG, in China and other Asian countries, and it is well known that influenza can cause more ARDS in the adults, yet very less in children”.*

**Source:** Elsevier Science Direct.

**Full Text/URL:**

<https://www.sciencedirect.com/science/article/pii/S092966462030067X>

1. **COVID-19 vaccination clinical trials should consider multiple doses of BCG.**

**Author(s):** Ayoub B.

**Citation:** OSF Preprints, 26 March. 2020. Web.

**Source:** OSF Preprints – Sourced from WHO database of publications on coronavirus disease (COVID-19).

**Full Text/URL:** <https://osf.io/h24bj>

1. **BCG-Induced Cross-Protection and Development of Trained Immunity: Implication for Vaccine Design.**

**Author(s):** Covián, Camila; Fernández-Fierro, Ayleen; Retamal-Díaz, Angello; Díaz, Fabián E; Vasquez, Abel E; Lay, Margarita K; Riedel, Claudia A; González, Pablo A; Bueno, Susan M; Kalergis, Alexis M

**Source:** Frontiers in immunology; 2019; vol. 10 ; p. 2806

**Publication Type(s):** Journal Article Review

**PubMedID:** 31849980

Available at [Frontiers in immunology](http://europepmc.org/search?query=(DOI:10.3389/fimmu.2019.02806)) - from Europe PubMed Central - Open Access

Available at [Frontiers in immunology](https://www.frontiersin.org/articles/10.3389/fimmu.2019.02806/pdf) - from Unpaywall

**Abstract:** The Bacillus Calmette-Guérin (BCG) is a live attenuated tuberculosis vaccine that has the ability to induce non-specific cross-protection against pathogens that might be unrelated to the target disease. Vaccination with BCG reduces mortality in newborns and induces an improved innate immune response against microorganisms other than Mycobacterium tuberculosis, such as Candida albicans and Staphylococcus aureus. Innate immune cells, including monocytes and natural killer (NK) cells, contribute to this non-specific immune protection in a way that is independent of memory T or B cells. This phenomenon associated with a memory-like response in innate immune cells is known as "trained immunity." Epigenetic reprogramming through histone modification in the regulatory elements of particular genes has been reported as one of the mechanisms associated with the induction of trained immunity in both, humans and mice. Indeed, it has been shown that BCG vaccination induces changes in the methylation pattern of histones associated with specific genes in circulating monocytes leading to a "trained" state. Importantly, these modifications can lead to the expression and/or repression of genes that are related to increased protection against secondary infections after vaccination, with improved pathogen recognition and faster inflammatory responses. In this review, we discuss BCG-induced cross-protection and acquisition of trained immunity and potential heterologous effects of recombinant BCG vaccines.

**Database:** Medline

1. **Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis.**

**Author(s):** de Castro, María José; Pardo-Seco, Jacobo; Martinón-Torres, Federico

**Source:** Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; Jun 2015; vol. 60 (no. 11); p. 1611-1619

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article Observational Study

**PubMedID:** 25725054

Available at [Clinical infectious diseases : an official publication of the Infectious Diseases Society of America](https://academic.oup.com/cid/article-pdf/60/11/1611/17853364/civ144.pdf) - from Unpaywall

**Abstract:** BACKGROUND Bacille Calmette-Guerin (BCG) vaccination has been suggested to have nonspecific beneficial effects in children from developing countries, reducing morbidity and mortality caused by unrelated pathogens. OBJECTIVE We aimed to assess the heterologous protective effects of BCG vaccination against respiratory infection (RI) and sepsis not attributable to tuberculosis in children born in Spain. METHODS We conducted a retrospective epidemiological study using data from the Official Spanish Registry of Hospitalizations (CMBD-HA) to identify differences in hospitalization rates (HR) in BCG-vaccinated children (Basque Country, where neonatal BCG is part of the immunization schedule and has a 100% coverage) as compared to non-BCG-vaccinated children (from the rest of Spain, where BCG is not used). RESULTS A total of 464 611 hospitalization episodes from 1992 to 2011 were analyzed. The HR due to RI not attributable to tuberculosis in BCG-vaccinated children was significant lower compared to non-BCG-vaccinated children for all age groups, with a total preventive fraction (PF) of 41.4% (95% confidence interval: 40.3-42.5; P-value <.001). According to age group, PF was 32.4% (30.9-33.9; P-value <.001) for children under 1 year old, 60.1% (58.5-61.7; P-value <.001) for children between 1 and 4 years old, 66.6% (62.8-70.2; P-value <.001) for children between 5 and 9 years old, and 69.6% (63.3-75.0; P-value <.001) for children between 10 and 14 years old. The HR due to sepsis not attributable to tuberculosis in BCG-vaccinated children under 1 year of age was also significantly lower, with a PF of 52.8% (43.8-60.7; P-value <.001). CONCLUSIONS BCG vaccination at birth may decrease hospitalization due to RI and sepsis not related to tuberculosis through heterologous protection.

**Database:** Medline

**Results: Example Commentary/Media Reports**

1. **COVID-19: Could TB vaccine offer protection?**

**Author(s):** Newman, T.

**Date:** 2 April 2020.

**Source:** Medical News Today – Sourced via Google.

**Full Text/URL:**

<https://www.medicalnewstoday.com/articles/covid-19-could-tb-vaccine-offer-protection>

1. **Can a century-old TB vaccine steel the immune system against the new coronavirus?**

**Author(s):** de Vrieze, Jop.

**Date:** 23 March 2020.

**Source:** Sciencemag.org – Sourced from WHO database of publications on coronavirus disease (COVID-19).

**Full Text/URL:**

<https://www.sciencemag.org/news/2020/03/can-century-old-tb-vaccine-steel-immune-system-against-new-coronavirus>

1. **A Vaccine From The 1920s Is Now Being Tested For Use Against The Coronavirus Pandemic.**

**Author(s):** Mack, E.

**Date:** 31 March 2020.

**Source:** Forbes – Sourced via Google.

**Full Text/URL:**

<https://www.forbes.com/sites/ericmack/2020/03/31/a-vaccine-from-the-1920s-could-help-fight-the-coronavirus-pandemic/#1287502f1220>

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**Databases searched:**

* + **Evidence-Based Reviews/Point-of-Care:** Cochrane Library, UpToDate, DynaMed, BMJ Best Practice.
  + **Guidance:** NICE Guidance, selected International Guidelines.
  + **Healthcare Databases:** MEDLINE, EMBASE, PubMed, NICE Evidence.
  + **Other:** Google, Google Scholar, World Health Organization Database of publications on coronavirus disease (COVID-19), COVID-19 collections: BMJ/Lancet/Elsevier/LitCOVID, MedRxiv.

**Local Guidance:** Local guidance has not been searched as part of this literature search. However, local guidelines, policies and procedures are available via the red button on the intranet.

**Search Terms:**

|  |  |
| --- | --- |
| ***Subject Headings*** | ***Free Text Words*** |
| BCG Vaccine | 2019nCoV |
| Coronaviridae Infections | “Bacill\* Calmette-Guerin vaccine\*” |
| Coronavirus Infections | Bacillus Calmette-Guerin |
|  | BCG |
|  | BCG vaccin\* |
|  | nCoV |
|  | “novel CoV” |
|  | “novel coronavirus” |
|  | SARS-CoV-2 |
|  | sarscov2 |

**Search Limits:** English language.

**Search History:**

**Search Example:**

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Database** | **Search term** | **Results** |
| 1 | Medline | (BCG vaccin\* OR "Bacill\* Calmette-Guerin vaccin\*").ti,ab | 11392 |
| 2 | Medline | exp "BCG VACCINE"/ | 18957 |
| 3 | Medline | exp "CORONAVIRIDAE INFECTIONS"/ | 10749 |
| 4 | Medline | exp "CORONAVIRUS INFECTIONS"/ | 9850 |
| 5 | Medline | (covid-19 OR "covid 19" OR SARS-CoV-2 OR "novel coronavirus" OR "corona virus" OR nCoV OR "CoV 2" OR Cov2 OR sarscov2 OR 2019nCoV OR "novel CoV").ti,ab | 2683 |
| 6 | Medline | (1 OR 2) | 22770 |
| 7 | Medline | (3 OR 5) | 12721 |
| 8 | Medline | (4 OR 5) | 11837 |
| 9 | Medline | (6 AND 7) | 0 |
| 10 | Medline | (6 AND 8) | 0 |

**Search Date: 02/04/2020**

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