South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: BACILLE CALMETTE-GUÉRIN (BCG) VACCINE FOR PREVENTING SARS-CoV-2 INFECTION OR IMPROVING COVID-19 OUTCOMES: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

Date: 20 May 2022 *(Update of initial review of 27 May 2020)*

Key findings

- An initial rapid review of available evidence was conducted in May 2020 to evaluate the efficacy and safety of BCG for preventing COVID-19 infection and improving outcomes in confirmed infection. However, there was insufficient evidence to support the inclusion of BCG vaccine in prevention or treatment guidelines for COVID-19.
- An updated search was conducted in May 2022 and 1 RCT of relevance was identified.
- Regarding cumulative incidences of documented COVID-19; 14.2% (102/753) in the BCG vs 15.2% (108/758) in the placebo group (adjusted hazard ratio (aHR) 0.94, 95%CI: 0.72 to 1.24) had documented COVID-19.
- One person in the BCG group vs 2 participants in the placebo group (HR, 95% CI: 0.32, 0.03 to 3.59) were hospitalized for COVID-19.
- There were 31 serious adverse events that occurred; 13 after BCG and 18 after placebo, but none were considered related to study medication.
- There is currently insufficient evidence to support the inclusion of BCG vaccine in prevention or treatment guidelines for COVID-19.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The NEML MAC on COVID-19 Therapeutics suggests that BCG vaccines not be recommended for the prevention of COVID-19 infection.
Rationale: Evidence from a single RCT suggests that there is no difference in COVID infections, hospitalisations or deaths (very low certainty evidence).

Level of Evidence: Low certainty evidence
Review indicator: Additional high-quality evidence

(Refer to appendix 2 for the evidence to decision framework)

NEML MAC ON COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees. Secretariat: Trudy Leong, Milli Reddy.

PROSPERO registration: CRD42021286710

BACKGROUND

Effective options to prevent infection with SARS-CoV-2 and improve outcomes of patients with COVID-19 need to be identified urgently.

The BCG vaccine, a live attenuated strain of *Mycobacterium bovis*, was first used in humans in 1921[1]. BCG vaccination was introduced in South Africa in 1973 and is given intradermally at birth using the Danish BCG strain[2]. There are several strains of the vaccine, which have different microbiological properties[2].

Much remains unknown about the mechanism of action of the BCG vaccine and which conditions it protects against. In 2017 WHO reviewed the use of BCG vaccine for protection against mycobacterial infections including tuberculosis (TB), leprosy and other nontuberculous mycobacteria infections, making a series of recommendations for use of the vaccine in different populations, including for re-vaccination in adolescents and adults[3 4]. WHO noted that BCG vaccination prevents severe forms of TB in children, especially TB meningitis and disseminated TB. This is the primary indication for the vaccine.

There is experimental evidence from both animal[5] and human studies[6] that the BCG vaccine has non-specific effects on the immune system which confers protection against conditions other than TB. Studies have linked BCG to protection against a range of pathogens, including: a decreased childhood mortality from infections unrelated to tuberculosis, *Staphylococcus aureus*, and fungi such as *Candida albicans*[7]. Importantly, the BCG vaccine has possibly reduced the severity of infections by other viruses, such as yellow fever[8] . BCG is also used as an adjuvant immunotherapy for patients with non-muscle-invasive bladder cancer and is postulated to have beneficial impacts on other types of cancer, eczema and other allergic conditions, type-1 diabetes and multiple sclerosis, amongst other conditions[3 8 99]However, these effects have not been well characterized and the clinical relevance is unclear. Mechanisms of protective actions may include molecular similarity between BCG antigens and viral or other antigens, activation of bystander B and T cells (heterologous immunity) and long-term activation and reprogramming of innate immune cells (trained immunity)[10].

Ecological studies have reported an association between BCG and COVID-19[11 12]. Countries which have not had a policy of universal BCG vaccination, such as Italy and the USA, have experienced higher rates of COVID-19 mortality per million population than places with long-standing universal BCG vaccination policies, such as South Korea and Japan. There are many possible explanations for the difference in mortality due to COVID-19 observed, including differences in COVID-19 testing strategies, reporting biases in COVID-19 deaths, variations in the effectiveness of COVID-19 prevention and treatment between countries, differences between countries in demographics and prevalence of co-morbidities, and the various stages of the pandemic in countries. There is also little evidence of whether the association between COVID-19 mortality and BCG vaccination observed in between-country comparisons hold within countries (i.e., whether patterns of COVID-19 mortality at sub-national level are associated with variations in coverage of BCG vaccination in different parts of the country, and with changes in coverage over time). One study in Israel compared the number of cases of COVID-19 in symptomatic adults who were born three years before and after the change in BCG vaccination policy[13]. Rates of SARS-CoV-2 infection were similar in vaccinated and unvaccinated groups. Even though such studies may provide useful information, they remain ecological studies involving analyses at a population and not individual level.

Given the uncertainty in the current evidence base, this review aimed to evaluate the reported benefits and harms of BCG prevention and treatment strategies in patients with COVID-19.

RESEARCH QUESTION: Does Bacille Calmette-guérin (BCG) Vaccine prevent SARS-COV-2 infection and improve COVID-19 Outcomes?

METHODS

In May 2020 a rapid review of the evidence was conducted including a systematic search on the Medline (Pubmed) electronic database and a search of the COVID-19 'Living synthesis of study results' resource maintained by WHO and partners (https://www.who.int/teams/blueprint/covid-19). At that time two electronic databases of clinical trial

registries: Cochrane COVID-19 register (https://covid-19.cochrane.org/) and the Network Meta-analysis website (www.covid-nma.com) was searched.

At that time one systematic review was identified and the review quality assessed using the AMSTAR criteria[14]. As evidence was limited in 2020, a search was also conducted for non-randomised studies (case reports, case series, non-randomised cohorts).

This is the first update of the initial review conducted in 2020. Two electronic databases were systematically searched (Pubmed and www.covid-nma.com) on 9 May 2022. One reviewer (MR) conducted screening of records and data extraction, with results reviewed and checked by another reviewer (JN). Records were screened to identify new systematic reviews, meta- analyses and RCTs evaluating the effect of BCG compared to standard of care or placebo in the prevention and management of COVID-19. The search strategy is shown in Appendix 1.

In addition, the robustness of the selected RCTs will be measured using the fragility index.

Eligibility criteria for review

Population: Patients at risk of COVID-19 infection or with COVID-19 disease. No restriction on age.

Intervention: Bacillus Calmette–Guérin (BCG) vaccination, regardless of BCG strain, either alone or in combination with other medicines. No restriction on previous vaccination, vaccine dose, route of delivery, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (no BCG vaccine, placebo, or other active comparator).

Outcomes: Incidence of SARS-CoV-2 infection, incidence of clinical and laboratory-confirmed COVID-19, mortality, hospitalisation, duration of hospitalisation, time to negative SARS-CoV2 PCR on nasopharyngeal swab, duration of ICU stay, duration of mechanical ventilation, adverse events, adverse reactions.

Study designs: Randomised controlled trials, systematic reviews and meta-analyses of studies.

RESULTS

The initial Medline (PubMed) search was done on 2 May 2020. Six titles/abstracts were identified, none of which were eligible. The Cochrane register search located seven items, none of which were eligible. One systematic review report was identified, published on 12 April 2020 by WHO[15]. The review was a product of WHO's ongoing evidence review of the major scientific databases and clinical trial repositories, using English, French and Chinese search terms for COVID-19, coronavirus, SARS-CoV-2 and BCG. No eligible studies were identified in that review. The review was considered high-quality, based on the review report and review protocol[16].

Ten randomised controlled trial protocols were identified, one of which was in South Africa, which is testing the efficacy of BCG revaccination among health workers[17]. The other studies were in Australia[18] , Brazil[19] , Columbia[20] , Denmark[21], Egypt[22] , France[23], the Netherlands[24] [25] and the Unites States[26] . All trials were being conducted among health care workers, aside from the trial in Brazil, which is among patients with laboratory or clinical-epidemiological confirmed cases of COVID-19, and one of the trials in the Netherlands which was among elderly people[25].

In 2022, through weekly surveillance of living maps and publications we identified an RCT[27] on BCG vaccination to reduce healthcare worker absenteeism in the COVID-19 pandemic. This triggered an update of the initial BCG review (27 May 2020). In May 2022 a search on Pubmed resulted in 11 articles and a search on COVID-NMA resulted in 1 article. The 11 studies from Pubmed were considered 'not relevant'. The reasons for exclusion included : not specific to COVID-19 infection (n=3), reviewed experimental vaccines for COVID-19 (n=1), summary of a protocol (n=1), not a meta-analysis of RCTs (n=2), revaccination versus placebo to prevent tuberculosis and leprosy (n=1), case reports of

reactivation of BCG vaccine scars (n=1), not specific to BCG vaccine (n=1), and revaccination in a phase II trial (n=1). The RCT from the Covid-nma.com was also excluded because it was a Phase II trial. Therefore, in total 12 studies were excluded.

Table 1 describes the main characteristics and outcomes of the 1 included RCT. Table 2 summarises the results. Table 3 lists the excluded studies and table 4 describes planned and ongoing registered studies.

Effects of intervention(s)

The outcomes for the data from 1 RCT conducted in health care workers, comparing BCG to placebo is summarised here.

Adult (≥18 years of age), health care workers with expected exposure to COVID-19 patients as part of their clinical duties from nine Dutch Hospitals were included in this partially blinded RCT. Participants were randomized (1:1) to BCG 0.1 mL of the Danish strain 1331, SSI, Denmark, equivalent to 0.075 mg
attenuated Mycobacterium bovis, or 0.1 mL of normal saline solution as an intradermal injection and followed up for 1 year through a mobile phone application.

Primary Outcomes:

None reported relevant to review eligibility criteria

Secondary Outcomes of relevance to PICO:

Cumulative incidences of documented COVID-19: 14.2% (102/753) in the BCG vs 15.2% (108/758) in the placebo group (adjusted hazard ratio (aHR) 0.94, 95%CI: 0.72 to 1.24).

COVID-19 Hospitalizations: 1 in the BCG group vs 2 in the placebo group (HR, 95% CI: 0.32, 0.03 to 3.59)

Adverse Events: 31 serious adverse events (13 after BCG vs 18 after placebo), n=0 considered related to study medication

Fragility index: The fragility index for the index trial, by both exact and chi^2, was calculated as zero (emphasising the fragility of the trial data).

CONCLUSION

The one RCT reviewed found no effect of BCG vaccination on documented COVID-19 disease among health care workers in the Netherlands. There is currently insufficient evidence to support the inclusion of BCG vaccine in prevention or treatment guidelines for COVID-19.

Reviewers: Milli Reddy, Jeremy Nel, Helen Rees

Declaration of interests: MR (Better Health Program, South Africa), JN (Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand and HR (Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand), MR (Better Health Program, South Africa) have no interests to declare in respect of BCG vaccination.

Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias assessment
Doesschate et al. BCG vaccine to reduce healthcare worker absenteeism in COVID-19 pandemic, a randomized controlled trial. Clin Microbiol Infect. 2022 Apr 28:S1198-743X(22)00214-2. doi: 10.1016/j.cmi.2022.04.009. Epub ahead of print. PMID: 35489606; PMCID: PMC9046133.	BCG-CORONA: parallel, partially blinded, placebo-controlled RCT Randomization from 24 March 2020 to 23 April 2020. Database locked on 18 April 2021. Subjects followed for 1 year using a mobile phone application ClinicalTrials.gov (NCT03987919, NCT04328441)	1511 participants were randomized n=9 hospitals in the Netherlands **Exclusion criteria:** allergy to BCG, active /latent Mycobacterium tuberculosis infection, any other active infection, immunocompromised state, current/ planned pregnancy	BCG: 0.1 mL of the Danish strain 1331, SSI, Denmark, equivalent to 0.075mg attenuated Mycobacterium bovis vs 0.1 mL of normal saline solution as an intradermal injection (placebo)	**Median duration of follow-up:** BCG vs Placebo 358 person-days (inter quartile range 351-361) vs 355 (IQR 351-361) **Primary Outcomes:** None relevant to review eligibility criteria **Secondary Outcomes:** ***Cumulative incidences of documented COVID-19:*** 14.2% (102/753) in the BCG vs 15.2% (108/758) in the placebo group (adjusted hazard ratio (aHR) 0.94, 95%CI: 0.72 to 1.24). ***COVID-19 Hospitalizations***: 1 in the BCG group vs 2 in the placebo group (HR, 95% CI: 0.32, 0.03 to 3.59) ***Adverse Events:*** 31 serious adverse events (13 after BCG vs 18 after placebo), n=0 considered related to study medication.	Overall risk of bias: **HIGH RISK** • *Randomisation:* Participants and study personal conducting follow up were blinded but blinding was only partially possible due to the local reaction that occurs with a BCG vaccination: **HIGH RISK** • *Deviations from intervention:* **LOW RISK** • *Missing outcome data*: No noticeable differential loss to follow-up between groups: **LOW RISK** • *Measurement of the outcome*: Self-reporting of symptoms and COVID-19 test results by participants carried a risk of under-detection and/or misclassifications of endpoints. Adjustment to the weekly instead of daily self-reporting of symptoms, provided a risk of recall bias: **HIGH RISK** • *Selection of the reported results:* **LOW RISK**

Table 2: Summary of findings

Question: Does Bacille Calmette-guérin (BCG) Vaccine prevent SARS-COV-2 infection and improve COVID-19 Outcomes?

Certainty assessment				No of patients		Effect	Certainty
№ of studies	Study design	Risk of bias	Other considerations	BCG	placebo	Relative (95% CI)	
Cumulative incidences of documented COVID-19							
1	RCT	serious[a]	none	102/753 (14.2%)	108/758 (15.2%)	aHR 0.94 (0.72 to 1.24).	⊕◯◯◯ Very low
COVID-19 Hospitalizations							
1	RCT	serious[a]	none	1	2	aHR 0.32 (0.03 to 3.59)	⊕◯◯◯ Very low
Adverse Events							
1	RCT	serious[a]	none	0	0	Not reported	⊕◯◯◯ Very low

CI: confidence interval; RCT: randomised control trial; RR: risk ratio

Explanations

a. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention and selection of reported results

b. Due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants and events

c. Inconsistency downgraded by 1 level: I^2=:60.5%.

Table 3. List of Excluded Studies

#	Citation	Reason for exclusion
1.	Giamarellos-Bourboulis EJ, et al. Activate: Randomized Clinical Trial of BCG Vaccination against Infection in the Elderly. Cell. 2020 Oct 15;183(2):315-323.e9. doi: 10.1016/j.cell.2020.08.051. Epub 2020 Sep 1. PMID: 32941801; PMCID: PMC7462457.	Not specific to COVID-19
2.	Checcucci E, et al. The vaccine journey for COVID-19: a comprehensive systematic review of current clinical trials in humans. Panminerva Med. 2022 Mar;64(1):72-79. doi: 10.23736/S0031-0808.20.03958-0. Epub 2020 May 26. PMID: 32456404.	Experimental vaccines for COVID-19
3.	Junqueira-Kipnis AP, et al. BCG revaccination of health workers in Brazil to improve innate immune responses against COVID-19: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020 Oct 26;21(1):881. doi: 10.1186/s13063-020-04822-0. Erratum in: Trials. 2020 Nov 24;21(1):967. PMID: 33106170; PMCID: PMC7586662.	Summary of a protocol
4.	Singh S, et al. BCG vaccination impact on mortality and recovery rates in COVID-19: A meta-analysis. Monaldi Arch Chest Dis. 2021 Aug 9;91(4). doi: 10.4081/monaldi.2021.1875. PMID: 34461704.	Not a meta-analysis of RCTs
5.	Glynn JR, et al. The effect of BCG revaccination on all-cause mortality beyond infancy: 30-year follow-up of a population-based, double-blind, randomised placebo-controlled trial in Malawi. Lancet Infect Dis. 2021 Nov;21(11):1590-1597. doi: 10.1016/S1473-3099(20)30994-4. Epub 2021 Jul 5. PMID: 34237262; PMCID: PMC8550897.	Revaccination versus placebo to prevent tuberculosis and leprosy
6.	Irfani TH, et al Tuberculosis and Coronavirus Disease 2019 (COVID-19) from A Clinical Perspective: A Systematic Review. Medeni Med J. 2020;35(4):338-343. doi: 10.5222/MMJ.2020.36775. Epub 2020 Dec 25. PMID: 33717627; PMCID: PMC7945727.	Examining the effects of COVID-19 on Tuberculosis (TB) management and to highlight evidence of the extent of TB and COVID-19 co-infection
7.	Khera D, et al . Does Bacille Calmette-Guérin Vaccination Provides Protection against COVID-19: A Systematic Review and Meta-analysis. Indian J Community Med. 2021 Oct-Dec;46(4):592-599. doi: 10.4103/ijcm.IJCM_952_20. Epub 2021 Dec 8. PMID: 35068716; PMCID: PMC8729290.	Only observational studies included in the review
8.	Mohamed L, et al,. Reactivation of BCG vaccination scars after vaccination with mRNA-Covid-vaccines: two case reports. BMC Infect Dis. 2021 Dec 20;21(1):1264. doi: 10.1186/s12879-021-06949-0. PMID: 34930152; PMCID: PMC8685493.	Case reports of reactivation of BCG vaccine scars
9.	Bhagavathula AS, et al. Vaccines and Drug Therapeutics to Lock Down Novel Coronavirus Disease 2019 (COVID-19): A Systematic Review of Clinical Trials. Cureus. 2020 May 28;12(5):e8342. doi: 10.7759/cureus.8342. PMID: 32494546; PMCID: PMC7263008.	Not specific to BCG
10.	Leeson CE et al. Systematic Review: Safety of Intravesical Therapy for Bladder Cancer in the Era of COVID-19. SN Compr Clin Med. 2020;2(9):1444-1448. doi: 10.1007/s42399-020-00461-3. Epub 2020 Aug 18. PMID: 32838196; PMCID: PMC7433676.	Indication is bladder cancer
11.	Dos Anjos et al. Efficacy and Safety of BCG Revaccination With M. bovis BCG Moscow to Prevent COVID-19 Infection in Health Care Workers: A Randomized Phase II Clinical Trial. Front Immunol. 2022 Mar 22;13:841868. doi: 10.3389/fimmu.2022.841868. PMID: 35392074; PMCID: PMC8981724.	Revaccination in a phase II trial
12.	Usha Padmanabhan, Sanjay Mukherjee, Rohidas Borse, Sameer Joshi, Rajesh Deshmukh. 2020. Phase II Clinical trial for Evaluation of BCG as potential therapy for COVID-19	Preprint of a Phase II trial

Table 4. Characteristics of planned and ongoing studies

Treatment (per arm)	n	Sponsor/Funder	Reg. number	Full text link;
BCG vaccine Intracutaneously 0.1ml BCG vaccine, which accounts for 0.075mg of attenuated Mycobacterium bovis.vs Placebo	1500	UMC Utrecht	NCT04328441	https://clinicaltrials.gov/ct2/show/NCT04328441
Biological: Ad26 COVID-19 Spike plus TICE® BCG Mix for Intradermal Injection	20	Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair	NCT02403505	https://clinicaltrials.gov/ct2/show/NCT02403505
BCG vaccine vs 0.9% sodium chloride (NaCl) saline solution	725	Universidade Federal do Rio de Janeiro	NCT04659941	https://clinicaltrials.gov/ct2/show/NCT04659941
CoronaVac® plus TICE® BCG Mix for Intradermal Injection	20	Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chair	NCT03348670	https://clinicaltrials.gov/ct2/show/NCT03348670
BCG-Denmark vs Saline	668	University of Southern Denmark	NCT04641858	https://clinicaltrials.gov/ct2/show/NCT04641858
BCG vs Saline	400	University of Campinas, Brazil	NCT04369794	https://clinicaltrials.gov/ct2/show/NCT04369794
BCG Vaccine vs 0.9%NaCl	10078	Murdoch Childrens Research Institute	NCT04327206	https://clinicaltrials.gov/ct2/show/NCT04327206
BCG Vaccine vs placebo	908	Hospital Universitario Dr. Jose E. Gonzalez	NCT0446137	https://clinicaltrials.gov/ct2/show/NCT0446137
Bacille Calmette-Guérin (BCG) vs placebo	5200	UMC Utrecht	NCT04537663	https://clinicaltrials.gov/ct2/show/NCT04537663
Biological: BCG vaccine (Freeze-dried)	2175	Tuberculosis Research Centre, India	NCT04475302	https://clinicaltrials.gov/ct2/show/NCT04475302?
BCG vs placebo	1120	Assistance Publique - Hôpitaux de Paris	NCT04384549	https://clinicaltrials.gov/ct2/show/NCT04384549
BCG-Denmark vs Saline	1700	Bandim Health Project	NCT04542330	https://clinicaltrials.gov/ct2/show/NCT04542330
BCG Vaccine vs Placebo	1800	Texas A&M University	NCT04348370	https://clinicaltrials.gov/ct2/show/NCT04348370
Biological: Bacillus Calmette-GuérinBiological: Saline injection	150	Massachusetts General Hospital	NCT02081326	https://clinicaltrials.gov/ct2/show/NCT02081326
VPM1002 vs Placebo	59	Vakzine Projekt Management GmbH	NCT04387409	https://clinicaltrials.gov/ct2/show/NCT04387409
0.10 mL intradermal injection of BCG Vaccine over the distal insertion of the deltoid muscle onto the humerus. Vs Placebo intradermal injection of 0.1ml of 0.9% NaCl solution	500	Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Mdical Sciences	IRCT20200411047019N1	https://en.irct.ir/trial/47279
BCG vs Placebo	1120	Assistance Publique Hopitaux de Paris	2020-001678-31	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001678-31/FR
Bacille Calmette-Guerin Plus Mitomycin-C	500	UMC Utrecht	2020-002503-19	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000235-51/GB
BCG vaccine (Danish strain 1331, SSI, Denmark) VS Placebo	1000	Hungary - National Institute of Pharmacy	2020-001783-28	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001783-28/HU
BCG Vaccine Vs Measles, mumps, and rubella vaccine (live)	100	Netherlands - Competent Authority	2020-002456-21	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002456-21/NL
Bacillus Calmette-Guerin vs Solution for injection	1900	University of Southern Denmark & Independent Research Fund Denmark	2020-003904-15	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-003904-15/DK
Bacillus Calmette-Guerin Vaccine vs Placebo	900	ACTIVATEII	2020-002448-21	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002448-21/GR
Anti-Tuberculosis Vaccine BCG 10 vs Solution for injection	1000	University of Rzeszów & Medical Research Agency (Agencja Badań Medycznych)	2020-002111-22	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002111-22/PL
BCG Vaccine vs Solution for injection	1500	University of Southern Denmark and AJ Vaccines	2020-001888-90	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001888-90/DK
BCG vs Solution for injection	5200	UMCU Utrecht and ZonMW	2020-003470-47	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-003470-47/NL
BCG vaccine vs Concentrate and solvent for solution for injection	1000	University Medical Center Utrecht	2020-000919-69	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000919-69/NL#B

Appendix 1: Search strategy

Database A

Search strategy: ((COVID-19[Supplementary Concept]) OR severe acute respiratory syndrome coronavirus 2[Supplementary Concept]) OR ("2019 nCoV"[tiab] OR 2019nCoV[tiab] OR "2019 novel coronavirus"[tiab] OR "COVID 19"[tiab] OR COVID19[tiab] OR "new coronavirus"[tiab] OR "novel coronavirus"[tiab] OR "SARS CoV-2"[tiab] OR (Wuhan[tiab] AND coronavirus[tiab])) AND (("BCG Vaccine"[MeSH]) OR BCG)

Output: In the updated search on 9 May 2022 11 studies were identified, all excluded as not relevant to PICO question

Database B

Search strategy: BACILLE CALMETTE-GUÉRIN (BCG)

Output: In the updated search on 9 May 2022 1 study was identified, but excluded as not relevant to PICO question

Appendix 2: Evidence to decision framework

Desirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies **X Don't know**	• **Cumulative incidences of documented COVID-19:** 14.2% (102/753) in the BCG vs 15.2% (108/758) in the placebo group - aHR 0.94, 95%CI: 0.72 to 1.24. • **COVID-19 Hospitalizations:** 1 in the BCG group vs 2 in the placebo group - HR, 95% CI: 0.32, 0.03 to 3.59.	
Undesirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies **X** Don't know	31 serious adverse events (13 after BCG vs 18 after placebo), n=0 considered related to study medication.	
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Very low ○ Low ○ Moderate ○ High ○ No included studies		Overall risk of bias is high
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X** Probably no important uncertainty or variability ○ No important uncertainty or variability		
Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies **X** Don't know		
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings		Would be additional costs if all are revaccinated - BCG vaccination is part of the childhood Expanded Programme on Immunization (EPI).

X Varies o Don't know		
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies		
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know x		All South Africans have access to BCG vaccination
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no X Probably yes o Yes o Varies o Don't know		Majority of South Africans are vaccinated with BCG
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no X Probably yes o Yes o Varies o Don't know		BCG vaccine is administered to all South African Citizens as part of the immunization program

Appendix 3: Updating of a rapid report

Date	Signal	Rationale
6 May 2022	Prophylaxis RCT published.	Previous review was not based on an RCT, review to be updated with RCT information.

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
1	27 May 2002	MFC, TK, HR	There is currently insufficient evidence to recommend BCG vaccines for the prevention of COVID-19 infection. Further evidence from randomised clinical trials is required to determine the safety and efficacy of BCG vaccination as a preventive therapy.
2	20 May 2022	MR, JN, HR	BCG vaccines not be recommended for the prevention of COVID-19 infection as RCT evidence suggests that there is no difference in COVID infections, hospitalisations or death.

For internal NDoH use:
WHO INN: BCG vaccine
ATC: L03AX03
ICD10: U07.1/U07.2

REFERENCES

[1] Luca S, Mihaescu T. History of BCG Vaccine. Maedica (Buchar) 2013;8(1):53-8. https://pubmed.ncbi.nlm.nih.gov/24023600/

[2] Dittrich S, Lamy M, Acharya S, et al. Diagnosing malaria and other febrile illnesses during the COVID-19 pandemic. The Lancet Global health 2020 doi: 10.1016/S2214-109X(20)30210-2 https://pubmed.ncbi.nlm.nih.gov/32339472/

[3] WHO. Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections. 2017. https://www.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf

[4] World Health O. BCG vaccine: WHO position paper, February 2018 - Recommendations. Vaccine 2018;36(24):3408-10. doi: 10.1016/j.vaccine.2018.03.009 https://pubmed.ncbi.nlm.nih.gov/29609965/

[5] de Bree LCJ, Marijnissen RJ, Kel JM, et al. Bacillus Calmette-Guerin-Induced Trained Immunity Is Not Protective for Experimental Influenza A/Anhui/1/2013 (H7N9) Infection in Mice. Front Immunol 2018;9:869. doi: 10.3389/fimmu.2018.00869 https://pubmed.ncbi.nlm.nih.gov/29760700/

[6] Arts RJW, Moorlag S, Novakovic B, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe 2018;23(1):89-100 e5. doi: 10.1016/j.chom.2017.12.010 https://pubmed.ncbi.nlm.nih.gov/29324233/

[7] Redelman-Sidi G. Could BCG be used to protect against COVID-19? Nat Rev Urol 2020 doi: 10.1038/s41585-020-0325-9 https://pubmed.ncbi.nlm.nih.gov/32341531/

[8] Curtis N, Sparrow A, Ghebreyesus TA, et al. Considering BCG vaccination to reduce the impact of COVID-19. Lancet 2020;395(10236):1545-46. doi: 10.1016/S0140-6736(20)31025-4 https://pubmed.ncbi.nlm.nih.gov/32359402/

[9] Ayoub BM. COVID-19 vaccination clinical trials should consider multiple doses of BCG. Pharmazie 2020;75(4):159. doi: 10.1691/ph.2020.0444 https://pubmed.ncbi.nlm.nih.gov/32295694/

[10] Kumar J, Meena J. Demystifying BCG Vaccine and COVID-19 Relationship [published online ahead of print, 2020 Apr 30]. Indian Pediatr. 2020;S097475591600168. https://pubmed.ncbi.nlm.nih.gov/32358227/

[11] Ozdemir C, Kucuksezer UC, Tamay ZU. Is BCG vaccination effecting the spread and severity of COVID-19? Allergy 2020 doi: 10.1111/all.14344 https://onlinelibrary.wiley.com/doi/full/10.1111/all.14344

[12] Miller A, Reandelar MJ, Fasciglione K, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv (preprint) 2020 doi: doi: 10.1101/2020.03.24.20042937 https://wwwmedrxivorg/content/101101/2020032420042937v1

[13] Hamiel U, Kozer E, Youngster I. SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. JAMA 2020 doi: 10.1001/jama.2020.8189 https://pubmed.ncbi.nlm.nih.gov/32401274/

[14] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008. doi: 10.1136/bmj.j4008 https://www.bmj.com/content/358/bmj.j4008

[15] WHO. Bacille Calmette-Guérin (BCG) vaccination and COVID-19. Scientific Brief. 2020;https://www.who.int/news-room/commentaries/detail/bacille-calmette-gu%C3%A9rin-(bcg)-vaccination-and-covid-19

[16] Boutron I, Chaimani A, Devane D, et al. Interventions for preventing and treating COVID-19: protocol for a living mapping of research and a living systematic review, version 2. 11 May 2020. doi10.5281/zenodo.3744599.

[17] BCG Vaccination for Healthcare Workers in COVID-19 Pandemic, 2020. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT04379336

[18] BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE), 2020. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04327206

[19] COVID-19: BCG As Therapeutic Vaccine, Transmission Limitation, and Immunoglobulin Enhancement, 2020 ClinicalTrials.gov https://clinicaltrials.gov/show/NCT04369794

[20] Performance Evaluation of BCG vs COVID-19, 2020. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT04362124

[21] Using BCG Vaccine to Protect Health Care Workers in the COVID-19 Pandemic, 2020. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT04373291

[22] Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19, 2020. ClinicalTrialsgov https://clinicaltrialsgov/show/NCT04350931
in the COVID-19 Pandemic, 2020. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT04373291

[23] Randomized Controlled Trial Evaluating the Efficacy of Vaccination With Bacillus Calmette and Guerin (BCG) in the Prevention of COVID-19 Via the Strengthening of Innate Immunity in Health Care Workers, 2020. ClinicalTrialsgov https://clinicaltrials.gov/show/NCT04384549.

[24] Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine, 2020. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT04328441

[25] Reducing hospital admission of elderly in Coronavirus pandemic by boosting the immune system through vaccination with bacillus Calmette-Gurin (BCG), 2020. EU Clinical trials register https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001591-15

[26] BCG Vaccine for Health Care Workers as Defense Against SARS-COV2, 2020. ClinicalTrials.gov https://clinicaltrials.gov/show/NCT04348370

[27] Doesschate et al. BCG vaccine to reduce healthcare worker absenteeism in COVID-19 pandemic, a randomized controlled trial. Clin Microbiol Infect. 2022 Apr 28:S1198-743X(22)00214-2. https://pubmed.ncbi.nlm.nih.gov/35489606/