Bacille calmette#guerin (BCG) vaccine for preventing SARS#CoV#2 infection or improving COVID# 19 outcome: evidence review of clinical benefits and harms.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

South African National Department of Health
Brief Report of Rapid Review
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: 27 May 2020

Key findings

- We conducted a rapid review of available published clinical evidence regarding use of Bacille Calmette-Guérin (BCG) vaccine with or without other medicines for preventing COVID-19 or improving outcomes in those with COVID-19 disease.
- We found one high-quality systematic review (12 April 2020), which identified no randomised controlled trials, but six registered protocols for planned or ongoing clinical trials.
- It is unclear whether the use of BCG vaccine prevents infection with SARS-CoV-2 or has any effect on outcomes of COVID-19 disease.
- The safety of BCG vaccine when administered to prevent or treat COVID-19 is unclear.

THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

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.

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available

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[1].

Much still remains unknown about 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 the 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 7 9]. 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.

METHODS

We conducted a rapid review of the evidence 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). Additionally, we searched 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).

One reviewer summarised the included systematic review and assessed the review quality using the AMSTAR criteria (MFC)[14]. One reviewer checked the results (TK). HR reviewed the overall report. The search strategy is shown in Appendix 1.

We sought systematic reviews of clinical trials in people with and without COVID-19 and randomised controlled trials and, as evidence was limited, we also searched for non-randomised studies.

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, 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: *Eligible study designs:* case reports, case series, non-randomised cohorts as well as randomised controlled trials, and systematic reviews of studies.

RESULTS

Results of search:

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 recent systematic review report was identified, published on 12 April 2020 by WHO[15]. The review is 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 is in South Africa, which is testing the efficacy of BCG revaccination among health workers[17]. The other studies are in Australia[18] , Brazil[19] , Columbia[20] , Denmark[21], Egypt[22] , France[23], the Netherlands[24 25] and the Unites States[26] . All trials are 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 is among elderly people[25].

CONCLUSION

There is currently insufficient evidence to support the inclusion of BCG vaccine in prevention or treatment guidelines for COVID-19.

There are at least ten registered RCTs on this topic, some of which are already recruiting patients. The findings of trials of BCG in other settings may only provide indirect evidence of the efficacy of BCG vaccination for COVID-19 protection in South Africa. Firstly, studies in settings with a low TB prevalence may provide only indirect evidence of the efficacy and safety of the vaccine in settings such as South Africa with its high TB burden. The data from studies among health workers may not be generalisable to the general population outside of healthcare settings. Further, findings from countries with different BCG policies may not be generalisable to South Africa. Brazil, Columbia and Egypt currently have a national BCG vaccination policy for neonates, as in South Africa. But, policies elsewhere differ: Australia discontinued 'vaccination for all' in the 1980s, and Netherlands and the United States have never had a national BCG vaccination programme[2]. A trial of the efficacy of revaccination of BCG in adolescents and adults in the general

population in South Africa might provide actionable information. BCG revaccination is considered by WHO, on the basis of low-quality evidence, to be safe[3].

Reviewers: Matthew F. Chersich (Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand), Tamara Kredo (Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Stellenbosch University), Helen Rees (Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand).

Declaration of interests: MFC, HR and TK have no interests to declare in respect of BCG vaccination.

Appendix 1: Search strategy

Medline (PubMed)

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: 6 publications were identified in the search, none of which satisfied the eligibility criteria

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
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