CADTH COVID-19 PANDEMIC

COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

Ongoing Trials for Bacille Calmette-Guérin (BCG) Vaccines in the Prevention of COVID-19

This report is current as of August 10, 2020.
To produce this report, CADTH used a modified approach to the selection of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

Version: 4.0
Publication Date: August 2020
Report Length: 13 pages

Cite As: *Ongoing Trials for Bacille Calmette-Guérin (BCG) Vaccines in the Prevention of COVID-19*. Ottawa: CADTH; August 2020. (CADTH health technology review).

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Version	Date of publication	Summary of revisions
1.0	June 26, 2020	Information current as of June 26, 2020
2.0	July 10, 2020	Two trials added. Information current as of July 9, 2020.
3.0	July 28, 2020	One trial added. Information current as of July 27, 2020.
4.0	August 11, 2020	One trial added. Information current as of August 10, 2020.

About This Document

This report provides information on the ongoing phase II, phase III, and phase IV trials for bacille Calmette-Guérin (BCG) vaccines in the prevention of COVID-19. It is important to note that this report is not a systematic review and does not include a critical appraisal of any trials. It is not intended to provide any recommendations.

In Canada, the National Advisory Committee on Immunization makes recommendations for the use of vaccines that are approved for use in humans and also identifies target groups for vaccination. Statements and publications by the National Advisory Committee on Immunization related to COVID-19 will be available at https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci.html.[1]

The current report excludes novel vaccines, which are discussed in the CADTH report *Ongoing Trials for Novel Vaccines in the Prevention of COVID-19*.[2] The novel vaccine report also includes a background discussion of traditional vaccine platforms such as live attenuated vaccines and more novel vaccine platforms.[2]

Background

Currently, outside of clinical trials, there is no vaccine that has been authorized for use to prevent COVID-19. However, there is a growing number of vaccines being investigated in various stages of development to prevent COVID-19.

Bacille Calmette-Guérin (BCG) is a strain of the bacteria *Mycobacterium bovis* used as a live attenuated vaccine for tuberculosis (TB) — a bacterial infection. It is currently not routinely recommended for use in Canada.[3] This vaccine is commonly administered to infants in many countries worldwide.[3] VPM1002 is a recombinant BCG vaccine that induces a greater immune response and is currently undergoing clinical trials for newborn immunizations to prevent TB and for post-exposure immunization to prevent TB recurrence in adults.[4-6]

It has been proposed that BCG vaccination may be protective against viral pathogens, such as influenza, through non-specific effects and innate immunity.[7] A rapid review conducted by the Centre for Evidence-Based Medicine in April 2020 found evidence that BCG vaccination prevents pneumonia and influenza in children and elderly patients.[8] It has been suggested that the non-specific immune effects induced by BCG vaccination may have a protective effect against COVID-19.[7,9] A systematic review (May 2, 2020)[10] and the Centre for Evidence-Based Medicine rapid review (April 10, 2020)[8] have found a lack of evidence for a protective effect of BCG vaccination on COVID-19. These reviews cite studies that examine the correlation between countries with different BCG vaccination policies and COVID-19 infection and/or mortality; however, they state that the limited and conflicting nature of this data precludes any conclusions about BCG vaccines and COVID-19.[8,10] These correlation studies provide the rationale for ongoing randomized controlled trials for

BCG vaccines in the prevention of COVID-19. On April 12, 2020, WHO published a scientific brief stating that WHO does not recommend BCG vaccination for preventing COVID-19, as there is no evidence that this vaccine is protective.[11]

The purpose of this report is to provide information on the ongoing randomized controlled clinical trials for BCG vaccines in the prevention of COVID-19 that are in phase II, phase III, and phase IV. Ongoing trials for novel vaccines, plasma products, and drugs for COVID-19 are reviewed in separate CADTH reports.

Objective

To describe the trial characteristics and estimated primary completion dates of the ongoing phase II, phase III, and phase IV studies evaluating BCG vaccines for the prevention of COVID-19.

Selection Criteria and Methods

The trials were identified from the ClinicalTrials.gov website,[12] the Health Canada Clinical Trials Database,[13] and the WHO International Clinical Trials Registry Platform[14] using the search criteria described in Table 1. Grey literature relating to BCG vaccine and COVID-19 was identified by searching relevant websites from the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist[15] and CADTH COVID-19 Grey Literature Resources,[16] which include the websites of regulatory agencies, health technology assessment agencies, and clinical guideline repositories. Google was used to search for additional internet-based materials.

Table 1: Selection Criteria

Population	People at risk of Sars-CoV2 infection (COVID-19)
Intervention	Prophylactic vaccine with BCG vaccine strains, recombinant BCG (VPM1002)
Comparator	No restriction
Outcomes	No restriction
Study designs	Randomized controlled trials — phase II, phase III, or phase IV

BCG = bacille Calmette-Guérin; SARS-CoV2 = severe acute respiratory syndrome coronavirus 2.

Exclusion Criteria

Trials investigating novel vaccines and other repurposed vaccines are excluded. Therapeutic vaccines are excluded. Phase I trials and pre-clinical studies are excluded.

The trials are organized according to the phase of clinical development, and in order of estimated primary completion dates (earlier first).

Results

As of August 10, 2020, a total of 20 trials met the selection criteria as follows: 16 phase III trials, three phase IV trials, and one trial where the phase was not stated (Table 2). The estimated enrolment for these trials ranges from 500 patients to 10,778 patients. Most of the trials (n = 15) are being conducted in healthy adult health care workers, and no trials are evaluating children. Five phase III trials are expected to have reached their primary completion dates by the end of 2020. One trial is being conducted in Canada, as highlighted in Table 1.

Other resources from the grey literature search are presented in Appendix 1. These resources did not meet the inclusion criteria.

Limitations

There may be reporting errors in the study records posted on the clinical trial registries.[17] Not all ongoing trials are posted to the websites and, as such, clinical trial registries may provide an incomplete picture of the ongoing clinical trials related to COVID-19.

We have chosen to show the earliest trial completion date; that is, the "estimated primary trial completion date" (the date on which the data collection is completed for all the primary outcome measures) and not the "estimated trial completion date" (the date on which the last patient was examined or received a treatment) to be able to quickly identify trials that may have results available ahead of the completion of a trial. For some trials not listed with clinicaltrials.gov, the meaning of the dates are less clear. All dates reported on trial registries may be subject to change as trials proceed.

Additionally, given the rapid changes occurring with the scientific evidence related to COVID-19, reporting amendments to the included trial protocols may be delayed.

Summary

As of August 10, 2020, there were 20 ongoing randomized controlled trials for BCG vaccines in the prevention of COVID-19 that met the inclusion criteria.

Table 2: Ongoing Randomized Controlled Trials of BCG Vaccines for COVID-19 (August 10, 2020)

Vaccine (strain, where stated) Sponsor	Trial name or study title	Study design, locations	Estimated primary completion date[a]	Population	Trial registry number	Study status
Phase III						
BCG vaccine (Danish strain) Ain Shams University	Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19	Participant blinded, PC, MC, adaptive N = 900 Egypt	October 1, 2020	Healthy adult health care workers	NCT04350931	Not yet recruiting
BCG vaccine UMC Utrecht	Reducing Health Care Workers Absenteeism in COVID-19 Pandemic by Enhanced Trained Immune Responses Through Bacillus Calmette-Guérin Vaccination, a Randomized Controlled Trial (BCG CORONA)	DB, PC, MC, adaptive N = 1,500 Netherlands	October 25, 2020	Healthy adult health care workers	NCT04328441 EudraCT Number: 2020-000919-69-NL	Recruiting
BCG vaccine (Danish strain 1331) Murdoch Children's Research Institute	BCG Vaccination to Reduce the Impact of COVID-19 in Healthcare Workers Following Coronavirus Exposure (BRACE) Trial	DB, PC, MC (multi-country) N = 10,078 Australia and Europe	October 30, 2020	Healthy adult health care workers	NCT04327206	Recruiting
BCG vaccine (Danish strain 1331) National Korányi Institute of Pulmonology	Reducing Absences from Work of Healthcare Workers due to COVID-19 Infection by BCG Vaccination	Open label, PC, MC N = 1,000 Hungary	November 2020 (estimate of trial duration)	Healthy adult health care workers	EudraCT Number: 2020-001783-28/HU	Ongoing

Vaccine (strain, where stated) Sponsor	Trial name or study title	Study design, locations	Estimated primary completion date[a]	Population	Trial registry number	Study status
BCG vaccine (Danish strain 1331) Bandim Health Project University of Southern Denmark	Using BCG Vaccine to Enhance Non-specific Protection of Health Care Workers During the COVID-19 Pandemic. A Randomized Controlled Multi-center Trial	DB, PC, MC N = 1,500 Denmark	December 2020	Healthy adult health care workers	NCT04373291 EudraCT Number: 2020-001888-90	Not yet recruiting
BCG vaccine (Tokio 172 strain) Hospital Universitario Dr. Jose E. Gonzalez	Prevention, Efficacy and Safety of BCG Vaccine in COVID-19-Randomized Clinical Trial	DB, PC, number of centres not stated) N = 908 Mexico	January 1, 2021	Healthy adult health care workers	NCT04461379	Not yet recruiting
BCG vaccine Assistance Publique – Hôpitaux de Paris	Randomized Controlled Trial Evaluating the Efficacy of Vaccination with Bacillus Calmette and Guérin (BCG) in the Prevention of COVID-19 Via the Strengthening of Innate Immunity in Health Care Workers	Participant blinded, PC, MC N = 1,120 France	February 11, 2021	Healthy adult health care workers	NCT04384549 EudraCT Number: 2020-001678-31/FR	Not yet recruiting
Recombinant BCG vaccine (VPM1002) Accelagen Pty Ltd	A Multicenter, Phase III, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy of the recombinant BCG VPM1002 on the Incidence or Disease Severity of SARS-COV-2/COVID-19 Among High-Risk Participants in Australia	DB, PC, MC N = 3,468 Australia	March 30, 2021	Healthy adult health care workers, adults over the age of 65 or over the age of 18 with comorbidity (who have not received BCG vaccine in the past year)	ACTRN12620000707965	Not yet recruiting

Vaccine (strain, where stated) Sponsor	Trial name or study title	Study design, locations	Estimated primary completion date[a]	Population	Trial registry number	Study status
Recombinant BCG vaccine (VPM1002) University Health Network, Toronto	A Randomized, Double-blind, Placebo-controlled Phase 3 Study: Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 Infection Rate and COVID-19 Severity (COBRA)	DB, PC (number of centres not stated) N = 3,626 Canada	April 1, 2021	Adult front-line employees of provincial or municipal police force	NCT04439045 CTA Control # 238868	Not yet recruiting
Recombinant BCG vaccine (VPM1002) Serum Institute of India Pvt. Ltd.	A Multicenter, Phase III, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy of Recombinant BCG VPM1002 in Reducing Infection Incidence and Disease Severity of SARS-COV-2/COVID-19 Among High-Risk Subjects	DB, PC, MC, adaptive N = 5,946 India	April 2021 (estimated trial duration)	Healthy adults at high-risk of SARS-CoV-2/ COVID-19 infection (who have not received BCG vaccine in the past year)	CTRI42972	Closed to Recruitment of Participants
BCG vaccine (Danish Strain 1331) TASK Applied Science	Reducing Morbidity and Mortality in Health Care Workers Exposed to SARS-CoV-2 by Enhancing Non-specific Immune Responses Through Bacillus Calmette-Guérin Vaccination,a Randomized Controlled Trial	DB, PC, (number of centres not stated) N = 500 South Africa	April 28, 2021	Healthy adult health care workers	NCT04379336	Recruiting
Recombinant BCG vaccine (VPM 1002) Vakzine Projekt Management GmbH	A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicentre, Clinical Trial to Assess the Efficacy and Safety of VPM1002 in Reducing Hospital Admissions and/or Severe Respiratory Infectious Diseases in Elderly in the SARS-CoV-2 Pandemic by Modulating the Immune System	DB, PC, MC N = 2,038 Germany	May 31, 2021	Healthy adults age 60 and older	NCT04435379 EudraCT Number: 2020-001675-33	Recruiting

Vaccine (strain, where stated) Sponsor	Trial name or study title	Study design, locations	Estimated primary completion date[a]	Population	Trial registry number	Study status
BCG vaccine Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences	Investigating the Effect of BCG Vaccine on Preventing COVID-19 Infection in Healthcare Staff Exposed to SARS-CoV-2	DB, PC, MC, adaptive N = 500 Iran	June 5, 2021	Healthy adult health care workers	IRCT47279	Recruiting
BCG vaccine Universidad de Antioquia	Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection in Medellín, Colombia, 2020	DB, PC, MC N = 1,000 Colombia	June 2021	Healthy adult health care workers aged 16 to 65	NCT04362124	Not yet recruiting
Recombinant BCG vaccine (VPM 1002) Vakzine Projekt Management GmbH	A Phase III, Double-blind, Randomized, Placebo-controlled Multicentre Clinical Trial to Assess the Efficacy and Safety of VPM1002 in Reducing Healthcare Professionals' Absenteeism in the SARS-CoV-2 Pandemic by Modulating the Immune System	DB, PC, MC N = 1,200 Germany	June 30, 2021	Healthy adult health care workers	NCT04387409 EudraCT Number: 2020-001376-15	Recruiting
BCG-10 (Anti-Tuberculosis Vaccine BCG 10) University of Rzeszów	A multi-centre, randomised, double-blind, placebo-controlled phase III study assessing the impact of BCG vaccination on the incidence and course of SARS-CoV-2 infection among healthcare workers in Poland during the COVID-19 pandemic	DB, PC, MC N = 1,000 Poland	December 2021	Healthy adult (> 25 years) health care workers	EudraCT Number: 2020-002111-22/PL	Ongoing
Phase IV						
BCG vaccine (Danish strain 1331) Radboud University	Reducing Hospital Admission of Elderly in SARS-CoV-2 Pandemic Via the Induction of Trained Immunity by Bacillus Calmette-Guérin Vaccination, a Randomized Controlled Trial	Single-blind, PC, adaptive, MC N = 2,014 Netherlands	May 2021	Adults older than 60 years of age	NCT04417335 EudraCT Number: 2020-001591-15/NL	Active, not recruiting

Vaccine (strain, where stated) Sponsor	Trial name or study title	Study design, locations	Estimated primary completion date[a]	Population	Trial registry number	Study status
BCG vaccine (Moscow strain 361-1) Hellenic Institute for the Study of Sepsis	A Randomized Clinical Trial for enhanced Trained Immune Responses Through Bacillus Calmette-Guérin Vaccination to prevent infections by COVID-19: THE ACTIVATE II TRIAL	DB, PC, MC N = 900 Greece	May 25, 2021	Adults aged 50 years or older with a history of at least one of the following: • coronary heart disease • chronic obstructive pulmonary disease • Charlson Comorbidity Index, more than 3	NCT04414267 EudraCT Number: 2020-002448-21/GR	Recruiting
BCG vaccine (Tice strain) Texas A&M University	Bacillus Calmette-Guerin Vaccination as Defense Against SARS-CoV-2: A Randomized Controlled Trial to Protect Health Care Workers by Enhanced Trained Immune Responses	DB, PC, MC N = 1,800 US	May 2021	Healthy adult health care workers	NCT04348370	Recruiting
Phase not stated						
BCG vaccine (Danish strain) Dr. Narayanan Parameswaran, Jawaharlal Institute of Post Graduate Medical Education and Research	Effect of BCG-Denmark (Green Signal) on Prevention of COVID 19 Infection in Health Care Workers – a Double Blind Randomized Controlled Trial	DB, PC, single centre N = 1,826 India	May 2021 (estimated trial duration)	Healthy adult health care and laboratory workers; exclude those who have received BCG vaccine in the past one year	CTRI43105	Not yet recruiting

BCG = bacille Calmette-Guérin; DB = double blind; MC = multi-centre; PC = placebo controlled; SARS-CoV2 = acute respiratory syndrome coronavirus 2.

[a] The date on which the data collection is completed for all the primary outcome measures.

References

1. Government of Canada. National Advisory Committee on Immunization (NACI): statements and publications. 2020; https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci.html. Accessed 2020 Jun 10.
2. CADTH. CADTH COVID-19 evidence portal. 2020; https://covid.cadth.ca/. Accessed 2020 Jun 9.
3. Government of Canada. Bacille Calmette-Guérin (BCG) vaccine: Canadian immunization guide. 2014; https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-2-bacille-calmette-guerin-vaccine.html#a3 Accessed 2020 Jun 16.
4. Kaufmann SHE. Vaccination against Tuberculosis: revamping BCG by molecular genetics guided by immunology. *Front Immunol.* 2020;11:316.
5. Loxton AG, Knaul JK, Grode L, et al. Safety and immunogenicity of the recombinant mycobacterium bovis BCG vaccine VPM1002 in HIV-unexposed newborn infants in South Africa. *Clin Vaccine Immunol.* 2017;24(2).
6. Nieuwenhuizen NE, Kulkarni PS, Shaligram U, et al. The recombinant Bacille Calmette-Guérin vaccine VPM1002: ready for clinical efficacy testing. *Front Immunol.* 2017;8:1147.
7. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? *Nature Reviews Immunology.* 2020;20(6):335-337.
8. Soliman R BJ, Plüddemann A, Heneghan C. Does BCG vaccination protect against acute respiratory infections and COVID-19? A rapid review of current evidence. Oxford (UK): Centre for Evidence-Based Medicine; 2020: https://www.cebm.net/covid-19/does-bcg-vaccination-protect-against-acute-respiratory-infections-and-covid-19-a-rapid-review-of-current-evidence/. Accessed 2020 Jun 18.
9. Gursel M, Gursel I. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic? *Allergy.* 2020.
10. Riccò M, Gualerzi G, Ranzieri S, Bragazzi NL. Stop playing with data: there is no sound evidence that Bacille Calmette-Guérin may avoid SARS-CoV-2 infection (for now). *Acta Biomed.* 2020;91(2):207-213.
11. World Health Organization. Bacille Calmette-Guérin (BCG) vaccination and COVID-19. 2020; https://www.who.int/news-room/commentaries/detail/bacille-calmette-gu%C3%A9rin-(bcg)-vaccination-and-covid-19 Accessed 2020 Jun 18.
12. U.S. National Library of Medicine. ClinicalTrials.gov. https://www.clinicaltrials.gov/ Accessed 2020 Aug 10.
13. Government of Canada. Clinical trial search. https://health-products.canada.ca/ctdb-bdec/index-eng.jsp Accessed 2020 Aug 10.
14. World Health Organization. International clinical trials registry platform. https://apps.who.int/trialsearch/. Accessed 2020 Aug 10.
15. Grey Matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Jun 8.
16. CADTH COVID-19 grey literature resources: a curated list of evidence-based sources for health professionals, librarians, and researchers. Ottawa (ON): CADTH; 2020: https://covid.cadth.ca/literature-searching-tools/cadth-covid-19-grey-literature-resources/. Accessed 2020 Jun 8.
17. Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. *BMJ.* 2018;361:k1452.

Appendix 1: Other Resources of Interest

Canadian

Institut National de Santé Publique du Québec. Le vaccin Bacille Calmette-Guérin (BCG) pourrait-il apporter une protection contre la COVID-19? 2020: https://www.inspq.qc.ca/sites/default/files/covid/2993-vaccin-bcg-protection-contre-infections-covid19.pdf. Accessed 2020 Jun 24.

International

World Health Organization. Bacille Calmette-Guérin (BCG) vaccination and COVID-19. 2020: https://www.who.int/publications/i/item/bacille-calmette-gu%C3%A9rin-(bcg)-vaccination-and-covid-19. Accessed 2020 Jun 24.

Other Tools for Tracking COVID-19 Vaccine Trials

World Health Organization. DRAFT landscape of COVID-19 candidate vaccines. 2020: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed 2020 Aug 10.

Danish Medicines Agency. Follow worldwide studies and research on medicines for COVID-19. 2020: https://laegemiddelstyrelsen.dk/en/news/2020/follow-worldwide-studies-and-research-on-medicines-for-covid-19/. Accessed 2020 Aug 10.

Thorlund K, Mills E, Mehta C. Global Coronavirus COVID-19 clinical trial tracker. https://www.covid-trials.org/. Accessed 2020 Aug 10.

Vaccine Centre at the London School of Hygiene & Tropical Medicine. COVID-19 vaccine development pipeline. 2020: https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/. Accessed 2020 Aug 10.

Regulatory Affairs Professional Society. COVID-19 vaccine tracker. 2020: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker. Accessed 2020 Aug 10.

Corum J, Grady D, Zimmer C. Coronavirus vaccine tracker. *The New York Times*; 2020: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html. Accessed 2020 Aug 10.

CADTH Reports

Bacille Calmette-Guérin vaccination: a review of clinical effectiveness and guidelines. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2020: https://cadth.ca/bacille-calmette-guerin-vaccination-review-clinical-effectiveness-and-guidelines. Accessed 2020 Aug 10.

Prevention of Tuberculosis: a review of guidelines. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2020: https://cadth.ca/prevention-tuberculosis-review-guidelines. Accessed 2020 Aug 10.

Bacille Calmette-Guerin vaccination for newborns with severe combined immunodeficiency: safety and guidelines. *(CADTH Rapid response report: summary of abstracts)*. Ottawa (ON): CADTH; 2019: https://cadth.ca/bacille-calmette-guerin-vaccination-newborns-severe-combined-immunodeficiency-safety-and-0. Accessed 2020 Aug 10.

Bacillus Calmette–Guérin vaccine dosage timing for neonates in the NICU: safety and guidelines. *(CADTH Rapid response report: reference list)*. Ottawa (ON): CADTH; 2019: https://cadth.ca/bacillus-calmette-guerin-vaccine-dosage-timing-neonates-nicu-safety-and-guidelines. Accessed 2020 Aug 10.