COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

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

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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. The goal is to provide an evergreen document that is regularly updated. Updates will occur for only a limited period of time after which this document will become dormant. 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.

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

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. This vaccine is commonly administered to infants in many countries worldwide. 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.

It has been proposed that BCG vaccination may be protective against viral pathogens, such as influenza, through non-specific effects and innate immunity. 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. It has been suggested that the non-specific immune effects induced by BCG vaccination may have a protective effect against COVID-19. A systematic review (May 2, 2020) and the Centre for Evidence-Based Medicine rapid review (April 10, 2020) 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. 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.
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, the Health Canada Clinical Trials Database, and the WHO International Clinical Trials Registry Platform 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 and CADTH COVID-19 Grey Literature Resources, 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. Results from the grey literature search will be updated every three months.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>People at risk of Sars-CoV2 infection (COVID-19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Prophylactic vaccine with BCG vaccine strains, recombinant BCG (VPM1002)</td>
</tr>
<tr>
<td>Comparator</td>
<td>No restriction</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No restriction</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Randomized controlled trials — phase II, phase III, or phase IV</td>
</tr>
</tbody>
</table>

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). The tables of ongoing trials will be updated every two weeks or when key trial data or results become available. The table will be updated with links to trial results as peer-reviewed publications become available.

Results

As of June 24, 2020, a total of 16 trials met the selection criteria as follows: 12 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 = 11) 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.
Limitations

There may be reporting errors in the study records posted on the clinical trial registries. 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 June 24, 2020, there were 16 ongoing randomized controlled trials for BCG vaccines in the prevention of COVID-19 that met the inclusion criteria. Ongoing trials will be updated every two weeks.
Table 2: Ongoing Randomized Controlled Trials of BCG Vaccines for COVID-19 (June 24, 2020)

<table>
<thead>
<tr>
<th>Vaccine (strain, where stated) Sponsor</th>
<th>Trial name or study title</th>
<th>Study design, locations</th>
<th>Estimated primary completion date</th>
<th>Population</th>
<th>Trial registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG vaccine (Danish strain) Ain Shams University</td>
<td>Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19</td>
<td>Participant blinded, PC, MC, adaptive N = 900 Egypt</td>
<td>October 1, 2020</td>
<td>Healthy adult healthcare workers</td>
<td>NCT04350931</td>
</tr>
<tr>
<td>BCG vaccine UMC Utrecht</td>
<td>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)</td>
<td>DB, PC, MC, adaptive N = 1,500 Netherlands</td>
<td>October 25, 2020</td>
<td>Healthy adult healthcare workers</td>
<td>NCT04328441 EudraCT Number: 2020-000919-69-NL</td>
</tr>
<tr>
<td>BCG vaccine (Danish strain 1331) Murdoch Children’s Research Institute</td>
<td>BCG Vaccination to Reduce the Impact of COVID-19 in Healthcare Workers Following Coronavirus Exposure (BRACE) Trial</td>
<td>DB, PC, MC (multi-country) N = 10,778 Australia and Europe</td>
<td>October 30, 2020</td>
<td>Healthy adult healthcare workers</td>
<td>NCT04327206</td>
</tr>
<tr>
<td>BCG vaccine (Danish strain 1331) National Korányi Institute of Pulmonology</td>
<td>Reducing Absences from Work of Healthcare Workers due to COVID-19 Infection by BCG Vaccination</td>
<td>Open label, PC, MC N = 1,000 Hungary</td>
<td>November 2020 (estimate of trial duration)</td>
<td>Healthy adult healthcare workers</td>
<td>EudraCT Number: 2020-001783-28/HU</td>
</tr>
<tr>
<td>BCG vaccine (Danish strain 1331) Bandim Health Project University of Southern Denmark</td>
<td>Using BCG Vaccine to Enhance Non-specific Protection of Health Care Workers During the COVID-19 Pandemic. A Randomized Controlled Multi-center Trial</td>
<td>DB, PC, MC N = 1,500 Denmark</td>
<td>December 2020</td>
<td>Healthy adult healthcare workers</td>
<td>NCT04373291 EudraCT Number: 2020-001888-90</td>
</tr>
<tr>
<td>Vaccine (strain, where stated) Sponsor</td>
<td>Trial name or study title</td>
<td>Study design, locations</td>
<td>Estimated primary completion date</td>
<td>Population</td>
<td>Trial registry number</td>
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<tr>
<td>BCG vaccine</td>
<td>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</td>
<td>Participant blinded, PC, MC N = 1,120 France</td>
<td>February 11, 2021</td>
<td>Healthy adult health care workers</td>
<td>NCT04384549</td>
</tr>
<tr>
<td>assistance publique – hôpitaux de Paris</td>
<td>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</td>
<td>DB, PC (number of centres not stated) N = 3,626 Canada</td>
<td>April 1, 2021</td>
<td>Adult front-line employees of provincial or municipal police force</td>
<td>NCT04439045 CTA Control # 238868</td>
</tr>
<tr>
<td>Recombinant BCG vaccine (VPM1002)</td>
<td>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</td>
<td>DB, PC, MC, adaptive N = 5,946 India</td>
<td>April 2021 (estimated trial duration)</td>
<td>Healthy adults at high-risk of SARS-CoV-2/COVID-19 infection (who have not received BCG vaccine in the past year)</td>
<td>CTRI42972</td>
</tr>
<tr>
<td>Serum Institute of India Pvt. Ltd.</td>
<td>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</td>
<td>DB, PC, (number of centres not stated) N = 500 South Africa</td>
<td>April 28, 2021</td>
<td>Healthy adult health care workers</td>
<td>NCT04379336</td>
</tr>
<tr>
<td>University Health Network, Toronto</td>
<td>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</td>
<td>DB, PC, MC N = 2,038 Germany</td>
<td>May 31, 2021</td>
<td>Healthy adults age 60 and older</td>
<td>NCT04435379 EudraCT Number: 2020-001675-33</td>
</tr>
<tr>
<td>Recombinant BCG vaccine (VPM1002)</td>
<td>Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection in Medellin, Colombia, 2020</td>
<td>DB, PC, MC N = 1,000 Colombia</td>
<td>June 2021</td>
<td>Healthy adult health care workers aged 16 to 65</td>
<td>NCT04362124</td>
</tr>
<tr>
<td>Vaccine (strain, where stated) Sponsor</td>
<td>Trial name or study title</td>
<td>Study design, locations</td>
<td>Estimated primary completion date</td>
<td>Population</td>
<td>Trial registry number</td>
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<tr>
<td>Recombinant BCG vaccine (VPM 1002) Vakzine Projekt Management GmbH</td>
<td>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</td>
<td>DB, PC, MC N = 1,200 Germany</td>
<td>June 30, 2021</td>
<td>Healthy adult health care workers</td>
<td>NCT04387409 EudraCT Number: 2020-001376-15</td>
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<tr>
<td>Phase IV</td>
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<tr>
<td>BCG vaccine (Danish strain 1331) Radboud University</td>
<td>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</td>
<td>Single-blind, PC, adaptive, MC N = 2,014 Netherlands</td>
<td>May 2021</td>
<td>Adults older than 60 years of age</td>
<td>NCT04417335 EudraCT Number: 2020-001591-15/NL</td>
</tr>
<tr>
<td>BCG vaccine (Moscow strain 361-1) Hellenic Institute for the Study of Sepsis</td>
<td>A Randomized Clinical Trial for enhanced Trained Immune Responses Through Bacillus Calmette-Guérin Vaccination to prevent infections by COVID-19: THE ACTIVATE II TRIAL</td>
<td>DB, PC, MC N = 900 Greece</td>
<td>May 25, 2021</td>
<td>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</td>
<td>NCT04414267 EudraCT Number: 2020-002448-21/GR</td>
</tr>
<tr>
<td>BCG vaccine (Tice strain) Texas A&amp;M University</td>
<td>Bacillus Calmette-Guerin Vaccination as Defense Against SARS-CoV-2: A Randomized Controlled Trial to Protect Health Care Workers by Enhanced Trained Immune Responses</td>
<td>DB, PC, MC N = 1,800 US</td>
<td>May 2021</td>
<td>Healthy adult health care workers</td>
<td>NCT04348370</td>
</tr>
<tr>
<td>Vaccine (strain, where stated) Sponsor</td>
<td>Trial name or study title</td>
<td>Study design, locations</td>
<td>Estimated primary completion date(^a)</td>
<td>Population</td>
<td>Trial registry number</td>
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<tr>
<td>Phase not stated</td>
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<tr>
<td>BCG vaccine (Danish strain)</td>
<td>Effect of BCG-Denmark (Green Signal) on Prevention of COVID 19 Infection in Health Care Workers – a Double Blind Randomized Controlled Trial</td>
<td>DB, PC, single centre N = 1,826 India</td>
<td>May 2021 (estimated trial duration)</td>
<td>Healthy adult health care and laboratory workers; exclude those who have received BCG vaccine in the past one year</td>
<td>CTRI43105</td>
</tr>
</tbody>
</table>

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


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


International


Other Tools for Tracking COVID-19 Vaccine Trials


CADTH Reports

