# INPLASY

## BCG vaccine for prevention or treatment of viral infections (other than COVID-19) in humans and animals: A protocol for a systematic review

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## INTRODUCTION

**Review question / Objective** This systematic review aims to evaluate the effect of BCG vaccine on mortality and non-mortality outcomes due to viral infections (other than COVID-19) in humans and animals.

**Rationale** Bacillus Calmettee Guerin (BCG) vaccine not only offers protection against certain forms of tuberculosis but has also been shown to reduce mortality from infections from other non-related organisms(1). A meta-analysis of 3 randomised controlled trials in newborns showed that administration of BCG-Denmark reduced all-cause mortality by 38% [Mortality Rate Ratio (MRR), 0.62; 95% CI, 0.46–0.83) and this effect was due to a reduction in infection related deaths (MRR for deaths due to infection, 0.57; 95% CI, 0.35–0.93)(2). This non-specific effect of BCG-Denmark vaccine was mainly to be due to reduction in bacterial infections which cause sepsis and pneumonia in the newborn period.

There is also evidence from human and animal studies that BCG vaccine may reduce the risk of viral infections through its non-specific protective properties(3,4). However, a full systematic review and meta-analysis addressing this role of BCG vaccine on viral infections has not been undertaken yet. This information is of importance, first to show whether the non-specific protection of BCG vaccine extends to cover viral infections. Second, demonstration of BCG vaccine's efficacy in reducing viral infections will be of value in the setting of emerging new pandemics in the future if BCG can be used to vaccinate the population until a new vaccine specific for the causative organism is developed. This systematic review will assess the question whether BCG vaccine gives protection against infections caused by viruses.

**Condition being studied** Viral infection. Viral infection will be determined by one of several possible ways such as clinical features consistent with viral infections, complications caused by viral infections, viral serology/titres diagnostic of viral

infections, and other findings which suggest the development or progression of viral infections.

## METHODS

**Search strategy** A search has been conducted in 3 databases (MEDLINE, Embase and PubMed), and the search terms have now been finalised. Search terms (MEDLINE, PubMed, Embase) finalised, but article selection has not yet commenced. Embase:
1 *BCG vaccine/
2 exp *Mycobacterium bovis/
3 *Mycobacterium tuberculosis/
4 (Bcg or bacile-calmette-guerin or bacille-calmette-guerin or bacilli-calmette-guerin or bacillus-calmette-guerin or bacillus-de-calmette-guerin or bacillus-of-calmette-guerin or calmette-guerin-bacile or calmette-guerin-bacille or calmette-guerin-bacillus or calmette-guerin-bacilli or mycobacterium-bovis or tubercle-bacilli-vaccine).tw,kf,dq.
5 1 or 2 or 3 or 4
6 exp virus infection/
7 exp virus antibody/
8 exp virus/
9 heterologous immunity/
10 vaccinia/
11 sexually transmitted disease/ or exp condyloma acuminatum/ or genital herpes/ or lymphogranuloma venereum/
12 (viral-infection* or viral-disease* or virus-disease* or viral-antibod* or non-specific-effect* or nonspecific-effect* or off-target-effect* or offtarget-effect* or vaccinia or rift-valley-fever or herpes-simplex or wart or warts or verruca).tw,kf,dq.
13 6 or 7 or 8 or 9 or 10 or 11 or 12
14 5 and 13
15 exp coronavirus disease 2019/
16 (2019-novel or 2019nCoV or 2019-nCoV or COVID-19 or COVID19 or COVID-2019 or COVID2019 or CONVID-19 or CONVID19 or CORVID-19 or CORVID19 or CoV2 or CoV-2 or HCoV* or Ncov* or Ncorona* or Ncorono* or NcovChina* or NcovChinese* or NcovHubei* or NcovWuhan* or SARS2 or SARS-2 or SARScoronavirus2 or SARScoronavirus-2 or SARScoronovirus2 or SARScoronovirus-2 or SARSCov19 or SARSCov-19 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or WN-CoV or WNCoV or wuhan-virus).tw,kf,dq,ot.
17 ((pneumonia* or outbreak* or respiratory-illness* or respiratory-disease* or respiratory-symptom* or seafood-market* or food-market* or wildlife) and (Wuhan or China or Chinese or Hubei or Huanan)).tw,kf,dq,ot.
18 ((new or novel or nouveau or "19" or "2019" or Wuhan or Hubei or Huanan or China or Chinese)

adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).tw,kf,dq,ot.
19 (coronavirinae/ or betacoronavirus/ or coronavirus infection/) and (epidemic/ or pandemic/)
20 ((coronavirus* or corona-virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).tw,kf,dq,ot.
21 severe-acute-respiratory-syndrome-coronavirus-2.hw.
22 coronavirus-disease-2019.hw.
23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 14 not 23

MEDLINE:
1 BCG Vaccine/
2 Mycobacterium bovis/ or Mycobacterium tuberculosis/im
3 (Bcg or bacile-calmette-guerin or bacille-calmette-guerin or bacilli-calmette-guerin or bacillus-calmette-guerin or bacillus-de-calmette-guerin or bacillus-of-calmette-guerin or calmette-guerin-bacile or calmette-guerin-bacille or calmette-guerin-bacillus or calmette-guerin-bacilli or mycobacterium-bovis).tw,kf.
4 1 or 2 or 3
5 exp Virus Diseases/ or exp Antibodies, Viral/ or exp *Viruses/im, py or *Immunity, Heterologous/ or *vaccinia/ or sexually transmitted diseases/im or exp sexually transmitted diseases, viral/im or *sexually transmitted diseases/
6 (viral-infection* or viral-disease* or virus-disease* or viral-antibod* or non-specific-effect* or nonspecific-effect* or off-target-effect* or offtarget-effect* or vaccinia or rift-valley-fever or herpes-simplex or wart or warts or verruca).tw,kf.
7 5 or 6
8 4 and 7
9 COVID-19/ or SARS-CoV-2/
10 (2019-novel or 2019nCoV or 2019-nCoV or COVID-19 or COVID19 or COVID-2019 or COVID2019 or CONVID-19 or CONVID19 or CORVID-19 or CORVID19 or CoV2 or CoV-2 or HCoV* or Ncov* or Ncorona* or Ncorono* or NcovChina* or NcovChinese* or NcovHubei* or NcovWuhan* or SARS2 or SARS-2 or SARScoronavirus2 or SARScoronavirus-2 or SARScoronovirus2 or SARScoronovirus-2 or SARSCov19 or SARSCov-19 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or WN-CoV or WNCoV or wuhan-virus).tw,kf,ot.
11 ((pneumonia* or outbreak* or respiratory-illness* or respiratory-disease* or respiratory-symptom* or seafood-market* or food-market* or wildlife) and (Wuhan or China or Chinese or Hubei or Huanan)).tw,kf,ot.
12 ((new or novel or nouveau or "19" or "2019" or Wuhan or Hubei or Huanan or China or Chinese)

adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).tw,kf,ot.

13 (coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)

14 ((coronavirus* or corona-virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).tw,kf,ot.

15 9 or 10 or 11 or 12 or 13 or 14

16 8 not 15

PubMed:

#1 title/abstract

"Bcg" OR "bacile-calmette-guerin" OR "bacille-calmette-guerin" OR "bacilli-calmette-guerin" OR "bacillus-calmette-guerin" OR "bacillus-de-calmette-guerin" OR "bacillus-of-calmette-guerin" OR "calmette-guerin-bacile" OR "calmette-guerin-bacille" OR "calmette-guerin-bacillus" OR "calmette-guerin-bacilli" OR "mycobacterium-bovis" OR "tubercle-bacilli-vaccine" OR "Mycobacterium-tuberculosis"

#2 title/abstract

"viral-infection*" OR "virus-infection*" OR "viral-disease*" OR "virus-disease*" OR "viral-antibod*" OR "virus-antibod*" OR "non-specific-effect*" OR "nonspecific-effect*" OR "off-target-effect*" OR "offtarget-effect*" OR "vaccinia" OR "rift-valley-fever" OR "herpes" OR "wart" OR "warts" OR "verruca" OR "sexually-transmitted-disease*" OR "condyloma-acuminatum" OR "lymphogranuloma-venereum" OR "Heterologous-immunit*"

#3 #1 AND #2

#4 All fields

"2019-novel" OR "2019nCoV" OR "2019-nCoV" OR "COVID-19" OR "COVID19" OR "COVID-2019" OR "COVID2019" OR "CONVID-19" OR "CONVID19" OR "CORVID-19" OR "CORVID19" OR "CoV2" OR "CoV-2" OR "HCoV*" OR "Ncov*" OR "Ncorona*" OR "Ncorono*" OR "NcovChina*" OR "NcovChinese*" OR "NcovHubei*" OR "NcovWuhan*" OR "SARS2" OR "SARS-2" OR "SARScoronavirus2" OR "SARScoronavirus-2" OR "SARScoronovirus2" OR "SARScoronovirus-2" OR "SARSCov19" OR "SARSCov-19" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "WN-CoV" OR "WNCoV" OR "wuhan-virus"

#5 All fields

("pneumonia*" OR "outbreak*" OR "respiratory-illness*" OR "respiratory-disease*" OR "respiratory-symptom*" OR "seafood-market*" OR "food-market*" OR "wildlife") AND ("Wuhan" OR "China" OR "Chinese" OR "Hubei" OR "Huanan")

#6 All fields

("new" OR "novel" OR "nouveau" OR "19" OR "2019" OR "Wuhan" OR "Hubei" OR "Huanan" OR "China" OR "Chinese") AND ("coronavirus*" OR "corona virus*" OR "betacoronavirus*" OR "CoV" OR "HCoV")

#7 All fields

("coronavirus*" OR "corona-virus*" OR "betacoronavirus*") AND ("pandemic*" OR "epidemic*" OR "outbreak*" OR "crisis")

#8 #4 OR #5 OR #6 OR #7

#9 #3 NOT #8

#10 NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint

#11 #9 AND #10.

**Participant or population** Human subjects and animals of all ages will be included and the results of human and animal studies will be presented separately.

**Intervention** Administration of BCG vaccine.

**Comparator** No BCG vaccine administration.

**Study designs to be included** Randomised controlled trials, cohort studies, case-control studies, case series, experimental studies.

**Eligibility criteria** Pre-specified eligibility criteria as stated in this protocol will be followed.

**Information sources** MEDLINE, Embase, PubMed. The search was performed in these databases since their inception up to 31st October 2023. The search did not include any language restrictions and included all article types. Searches will be additionally supplemented by articles obtained from secondary searches from references of published articles, conference proceedings, thesis documents and other scholarly works recommended by content experts. A search will also be conducted in the WHO International Clinical Trials Registry Platform.

**Main outcome(s)** Viral infections.

**Additional outcome(s)** None.

**Data management** Two reviewers will independently select studies, assess applicability and the risk of bias, and extract data. Disagreements between the reviewers will be resolved by discussion between them and, if needed, a third reviewer will be included to resolve any disagreement.

Data to be collected: Type of study, species studied (humans or if animal the species), location of study, virus studied, study type (clinical trial, cohort, case series, etcetera), blinded or not, randomised or not, concealed randomisation or

not, years of study, entry criteria, BCG type, BCG number of subjects, BCG dose, BCG site, BCG frequency, control group treatment, control number of subjects, follow-up, BCG side effect, outcome in BCG group, outcome in control, effect estimate and additional comments.

Collection of articles and their organisation will be done in EndNote reference management software. Stata statistical software (StataCorp LP, College Station, TX) version 16 or higher will be used for statistical analysis.

## Quality assessment / Risk of bias analysis

Results will be reported using PRISMA (Preferred Reporting Items for Systematic reviews and meta-Analysis) guidelines(5). For observational studies, the risk of bias in non-randomised studies of interventions (ROBINS-I) tool will be used to assess the risk of bias. ROBINS-I classifies risk of bias as low, moderate, serious or critical. Studies assessed as being in critical level of risk of bias will not be included in the meta-analysis(6). For randomised trials, the Cochrane collaboration's tool for assessing risk of bias in randomised trials(7) will be used.

## Strategy of data synthesis

The outcome will be reported as a binary variable [but also sometimes survival time (HR), viral titres, virus LD50]. Study estimates in reported studies are likely to have used crude rates, risk ratios, odds ratios, hazard ratios or rate ratios in their reporting. Random-effects meta-analysis with DerSimonian and Laird approach for estimation of between study variances will be used to combine study estimates separately for randomised trials and for observational studies. The combined estimates will be reported as risk ratio (95% confidence interval). The estimates will be reported separately for humans and animals. Heterogeneity between studies will be estimated and reported using the I2 statistic and 95% prediction interval(8). Funnel plots and other tests to test for publication bias will be performed if there are enough studies (at least 10) included for each of the meta-analysis performed(9)

## Subgroup analysis

Where feasible, subgroup analyses and meta-regression will be performed to explore causes of heterogeneity. The main subgroups of interest are BCG strain, dose(s) of BCG, previous receipt of BCG, and sex.

## Sensitivity analysis

An alternate statistical model using the Hartung-Knapp approach(10) to estimate confidence intervals will be performed for each of the meta-analysis estimates as a sensitivity analysis.

**Language restriction** No language restrictions.

**Country(ies) involved** Australia (Royal Children's Hospital).

**Other relevant information** None

**Keywords** BCG vaccine, viral infection, heterologous immunity, non-specific effects, mycobacteria, humans and animals.

**Dissemination plans** The results of the study will be submitted for publication in a peer-reviewed journal and may be presented at conferences.

## Contributions of each author

Author 1 - Siva Namachivayam - Designing, coordinating, data collection, data management, analysis of data, interpretation, writing the protocol & review.
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Author 2 - Frank Shann - Conceiving the review; designing, coordinating, data collection, data management, analysis of data, interpretation, writing the protocol & review.
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