

Effectiveness of Bacille Calmette-Guerin Vaccination Policies in Reducing Infection and Severity of COVID-19: a Systematic Review Protocol



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ABSTRACT

Introduction: The bacille Calmette-Guerin (BCG) vaccine is used for the prevention of tuberculosis (TB) worldwide. Evidence reports a much lower incidence of COVID-19 in TB-endemic areas implying a possible protective mechanism of BCG in countries with mandated BCG policies. The objective of the study is to synthesize and critically evaluate the effectiveness of national BCG vaccination policies in reducing infection and severity of COVID-19 in their native population.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a comprehensive search using

pre-identified keywords will be done in PubMed, Cochrane, HERDIN Plus, WPRIM, Web of Science and EBSCO databases. After the initial selection of studies based on eligibility criteria, methodological appraisal will be conducted using the Joanna Briggs Institute appraisal instruments and an adapted quality assessment checklist for ecologic studies. Relevant data will be extracted and synthesized including reporting descriptive and inferential statistics to interpret results.

Results: The study will generate a systematic review synthesizing evidence regarding the effects of BCG in curtailing the spread of the COVID-19 pandemic.

Discussion: The battle against the COVID-19 pandemic is far from over, and as such, further studies must be undertaken to verify the evidence behind initial strategies in battling it. This includes the use of BCG in decreasing COVID-19 incidence and mortality. The results of the review can ultimately guide health authorities and policy makers create evidence-based decisions regarding BCG vaccination policies and clinical trials related to COVID-19 control and prevention.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) has caused millions of cases and deaths and a global pandemic.[1] Although physical distancing and aggressive contact tracing has slowed down the spread of the virus, the economic and social life of people has remained slack.[2] Because of this, a race for vaccines effective against COVID-19 has erupted in the past year, with the goal of permanently curbing its spread via herd immunity.

Currently, the World Health Organization has issued Emergency Use Authorization (EUA) on 22 COVID-19 vaccines, though the EUA per country may vary.[3] Despite numerous potential candidates for a COVID-19 vaccine, developers still report that production can only provide sufficient doses for more than one-third of the world's population by the end of 2021. In addition, even in a highly optimistic scenario where 10 billion doses are effectively manufactured, with a two-dose regimen, the recommended dosage for most candidates, existing annual production capacity is too limited to achieve herd immunity on a global scale.[4,5] AstraZeneca chief executive Pascal Soriot stated that with the scale of the pandemic, the total planned number of doses from Moderna, Pfizer and AstraZeneca would still not be enough to vaccinate everyone in the world.[6,7] This presents a problem to low-income countries, as they may have to wait until 2023 or 2024 for adequate vaccination.[8]

As of June 23, 2021, the total vaccines administered globally are 2.8 billion doses and approximately 40.5 million are administered each day.[9] Pfizer-BioNtech, AstraZeneca, Sinopharm, Sinovac and Novavax are few of the vaccines that were granted an EUL or emergency use listing.[3] Though vaccine innovation is very important in ending the pandemic, there are certain more barriers the world has to face before reaching herd immunity, such as certain problems like vaccine hesitancy and vaccine inequity.[10] Due to the

emergence of COVID-19 variants, there are still questions regarding vaccine effectivity and efficacy of the current vaccines has been raised.[10]

Bacille Calmette-Guerin, also known as the BCG vaccine, used for the prevention of pulmonary and extrapulmonary tuberculosis,[11] is a live attenuated vaccine that is derived from *Mycobacterium bovis*. Studies showed that getting vaccinated with BCG makes the immune system more active against multiple forms of infections.[11] It is suggested that the BCG vaccine contributes to the reduction of morbidity and mortality in countries with universal BCG policies because of the lower incidence of COVID-19, implying a protective mechanism.[12] The BCG vaccine is inexpensive and thus, it is easily accessible, especially in low income countries which may not have immediate access to COVID-19 vaccines.[13] The purpose of this systematic review is to synthesize and critically evaluate the effectiveness of national BCG vaccination policies in reducing infection and severity of COVID-19 in their native population.

METHODOLOGY

Design

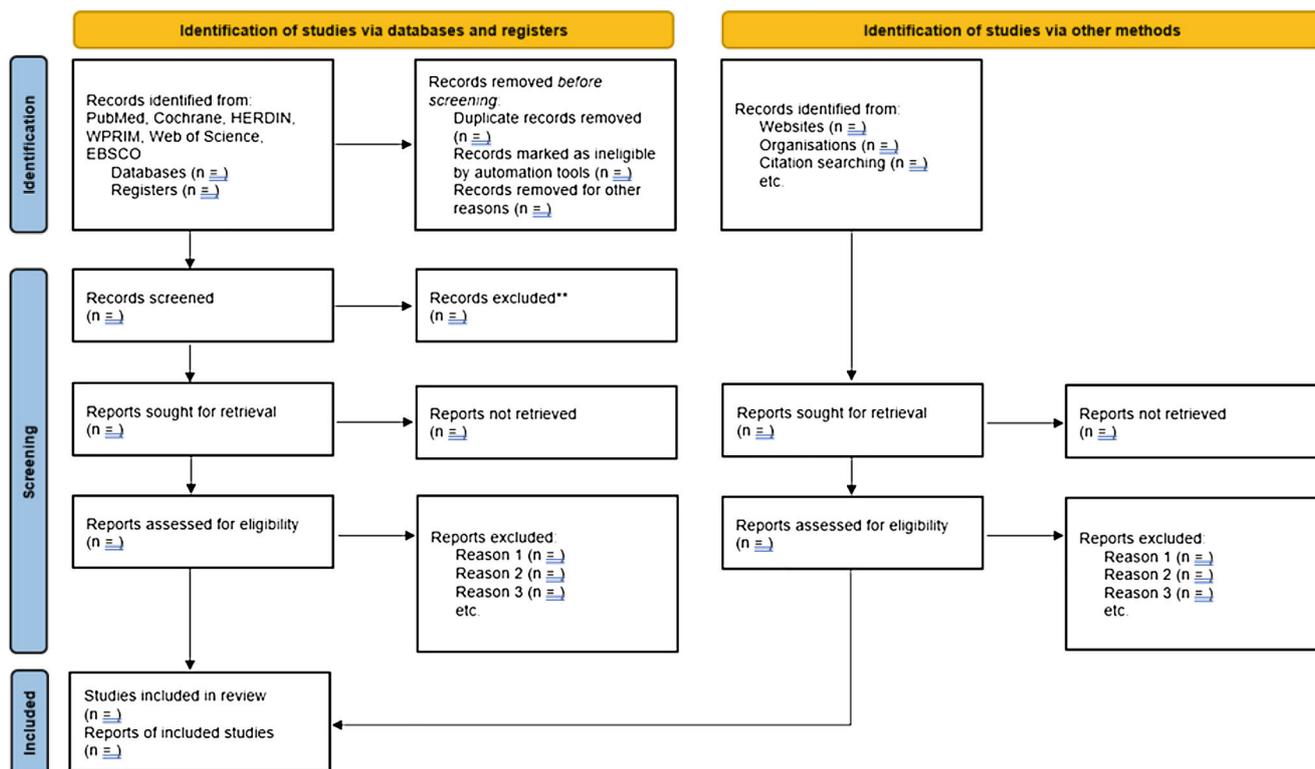
The systematic review will be conducted in April 2021 following the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA-P) methodology as outlined by Shamseer et al.[14] for conducting systematic review and meta-analysis protocols (Figure 1).

Inclusion and Exclusion Criteria

Literature will include studies classified under Level 1A to 2C for therapy/prevention questions using the Oxford Center for Evidence-Based Medicine (2009) Levels of Evidence table.[15] Descriptive studies, commentaries, editorials, ongoing research, unpublished studies and other working papers are excluded from the study. Literature not written in English and/or predates 2020 will not be included in the review.

Search Strategy

Using the Population/Intervention/Comparison/Outcomes (PICO) approach, the researchers



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71.

Figure 1: PRISMA flow diagram for searches of databases, registers and other sources

elaborated the research question of this review to: “Can national BCG vaccination policies aid in reducing infection and severity of COVID-19 in their native population?” The search strategy will be performed following the PRISMA-P guidelines using the search terms and databases in Table 1. Search terms will include “Universal BCG vaccination,” “BCG policy,” “Bacille Calmette-Guérin policy,” “COVID-19,” “SARS-COV-2” and “TB Vaccine policy”. Snowball search will be done by manually checking the reference sections of the studies and cited studies for additional relevant articles.[16] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in April 2021 (registration ID: CRD42021244060).

Study Selection Process

Search results will be input into Google Sheets for duplicate removal. Six researchers will be assigned to individually screen the studies obtained during the formal literature search against the eligibility criteria. Disagreements will be resolved through consensus or discussion.

Methodological Appraisal

Studies meeting the eligibility criteria will be assessed by two authors as to their methodological quality using the Joanna Briggs Institute (JBI) critical appraisal instruments appropriate for the study design. JBI does not have a critical appraisal tool for ecologic studies, and as such, these will be assessed using the quality assessment checklist adapted from Betran et al.[17] (Table 2). The researchers pre-established the minimum standard or passing score of 70% of the total items in the checklists to be included in the review.[18] Studies below 70% on the appropriate appraisal tool will be deemed of low methodological quality and would therefore be excluded.

During instances when scores resulted in disagreement between the two reviewers, a third researcher will be tasked in assessing the study. Any further disagreements between their ratings will be resolved through discussion and consensus.

Data Extraction

Six researchers will then extract data from selected studies including: population details (including demographics and baseline characteristics),

Table 1: Detailed search and selection strategy

PICO Component	
Population:	Native population of countries with national BCG vaccination policies
Intervention:	National Bacille Calmette-Guérin (BCG) policy Vaccine for tuberculosis (TB) disease. ^[1]
Outcome:	Decreased infection incidence and reduced severity
Search Terms	#1 Universal BCG vaccination #2 BCG policy #3 Bacille Calmette-Guérin #4 policy #5 COVID 19 #6 SARS COV 2 #7 TB vaccine policy
Databases	PubMed, Cochrane, HERDIN Plus, WPRIM, Web of Science, EBSCO

intervention details, study design and methodology, and outcomes relevant to the research question. Two researchers will check the accuracy of recorded data. Missing data will be sought out by contacting the original investigators of the study via email. All data extracted will be recorded through Google and Excel spreadsheets.

Study Synthesis

All relevant data related with the outcomes of the review will be extracted and synthesized from the studies. Researchers will compare and contrast the measures of effects (eg, effect size, odds ratio, risk ratio, confidence intervals, etc.) that will be reported by studies from different countries. Descriptive and inferential statistics, if applicable, will be used to interpret the result while considering the sample, setting, methodology and data quality. Any discrepancies will be discussed and clarified by all authors.

Ethics and Dissemination

No ethics approval will be sought for the conduct of the study following local and international ethical guidelines. This systematic review will be disseminated through peer-reviewed publication as well as scientific symposia and conferences related to this field.

DISCUSSION

This protocol included comprehensive details of the search strategy, study selection process,

methodological appraisal, data extraction and synthesis following the available guidelines for systematic review to reduce possible risk of bias in implementation and analyses. This ensures transparency of methods in conducting this study and can also serve as a model for future systematic reviews.

Prevention strategies are very important in battling current and future diseases that may lead to more disastrous situations, with the COVID-19 pandemic being the chief among them. However, because of the influx of evidence, data syntheses such as this planned systematic review can segregate which efforts are best focused on versus those that may only deplete already scarce resources. Clinical trials and vaccination protocols are crucial in providing a solution to this pandemic and this review aims to provide much needed information as to the usefulness in providing resources, specifically to BCG vaccination strategies against COVID-19. This study is not merely limited to the effect of BCG vaccination policies on COVID but will include other factors perceived to have had a hand in producing this trend, such as the economic status of countries. Assessing these possible confounding factors will better demonstrate if the trend is due to the BCG policies and can therefore better advise future planned clinical trials.

The results of the review are expected to provide evidence as well as raise awareness to the public, health workers and policy makers in terms of national BCG vaccination policies related with COVID-19 control and prevention. As there is currently a number of available researches related to COVID-19 and vaccination policies, appraisal and synthesis of these

Table 2: Quality assessment checklist for ecological studies adapted from Betran et al. (2015)

Evaluation criterion	Categories	Definition	Points (max=21)
STUDY DESIGN (max=12)			
Design	Cross-sectional	If it is a multi-level design (eg, ecologic + individual), the study is upgraded one point (eg, cross-sectional + multi-level receives 2 points)	1
	Longitudinal		2
Sample size	<80% units	Number of ecologic units included in the analysis as a proportion of the total number of units, eg, 119 countries of a total of 180 worldwide would be 66%.	0
	≥80% units		1
Unbiased inclusion of units	No	Were the units included representative of the group for which inferences are being drawn? For example, for worldwide inferences, inclusion of only developed countries would be biased.	0
	Yes		1
Level of data aggregation	Other than below (City, Municipal)	Population to which the units refer to. "Other" may be: city, race groups.	1
	Regional, State		2
	National		3
Level of inference	Individual or unclear	Use of results of the analysis of the study's sample data to draw inferences for individuals or groups (ecologic).	0
	Ecologic (Group)		1
Prespecification of ecologic units	No	Were the ecologic units selected to suit the hypothesis/objective/s? (as opposed to selection motivated by convenience or necessity)	0
	Yes		1
Outcomes of interest included	Some	Inclusion of all relevant outcomes (ie, infection incidence and infection severity) or only of some outcomes.	1
	All		2
Source of data	Inadequate	Validity of data sources to represent the level that it refers to (eg, the incidence rate in one city would be an inadequate source of data to represent the national incidence rate).	0
	Adequate		1
STATISTICAL METHODOLOGY (max=6)			
Analytic methodology	Spearman's rank correlation, Linear least square regression models, Quadratic model, Exponential model, LOWESS, Fractional polynomial regression, Piecewise regression	All statistical methods are acceptable as long as they are used appropriately. We assign a score based on the sophistication and flexibility of the method.	1
		1 = Spearman's rank correlation, Linear least square regression models, Quadratic model, Exponential model 2 = LOWESS, Fractional polynomial regression, Piecewise regression	2
Validity of regression	No	Did the adjustment have at least 10 units per covariate?	0
	Yes		1
Use of covariates	None	Authors adjusted the analysis for desirable variables or not. Example of socio-economic covariates: GDP or HDI. Example of clinical covariates: proportion of other related conditions	0
	Socio-economic		1
	Socio-economic + clinical		2
Proper adjustment for covariates (yes)	No	Are the outcomes standardized or adjusted for certain factors before model adjustment? For standardized or adjusted outcomes, the standardized or adjusted factors should be included in the adjustment model. If standardized/adjusted outcomes are not used, this criterion is considered to have been met.	0
	Yes		1
QUALITY OF REPORTING (max=3)			
Statement of study design (yes)	No	Did the authors present key elements of study design in the paper?	0
	Yes		1

Table 2: Quality assessment checklist for ecological studies adapted from Betran et al. (2015)(Continued)

Evaluation criterion	Categories	Definition	Points (max=21)
Justification of study design (yes)	No	Did the authors justify the ecologic analysis, the rational and specific objectives, including any prespecified hypotheses?	0
	Yes		1
Discussion of cross-level bias and limitations (yes)	No	Did the authors caution readers about the limitations of ecologic design, ecologic fallacy, impossibility of extrapolating to a different level?	0
	Yes		1

evidences are relevant for a more evidence-based decision-making of different relevant stakeholders. This will better inform future policy makers and funding organizations in sponsoring future clinical trials. This would therefore discuss both the effect of BCG and possible effects of economic status of countries.

Despite the current availability of numerous vaccines against COVID-19, the world is still a long way to herd immunity. Further studies are still needed to ascertain long-term immunity and the need for booster immunization. The emergence of variants also poses a threat to the efficacy of available vaccines. As such, previous strategies, such as the usefulness of BCG vaccination, may be revisited in the future. It is therefore imperative to be informed of the actual effects of such strategies to be able to know its feasibility and guide future research and policy.

Strengths and Limitations

The novelty of the study and methodological quality of the protocol has been validated via cross-checking with existing studies and eventual registration to PROSPERO. In addition, previous studies in the topic were focused on initial studies at the start of the pandemic. This protocol will not only include earlier studies based on ecological studies, but may also include other studies, such as longitudinal studies or randomized controlled trials, should there be any. In addition, ecological studies will undergo the risk of bias assessment with the adapted critical appraisal tool, which is lacking in previous studies regarding the matter. This ensures that the studies included are of good methodological quality. Numerous studies have been produced quickly at the start, with different methods and analyses. The use of quality

assessment narrows down the papers that are of good research methodology.

The study is not without its limitations. Literature available only in English is included, and as such, other papers of good quality may be overlooked. In addition, meta-analysis may be limited depending on whether there are adequate randomized controlled trials and longitudinal studies with outcomes to pool together. Ecological studies that may be included have the risk of using the same datasets. This would therefore prevent meta-analysis of their outcomes because of the use of similar population shared by multiple studies.

Author Contributions

JCO and JTA conceived the idea. JCO, MS, JTA, MJMP, NES, TL and CJE wrote the draft of the manuscript, with joint equal contribution by MRGB and EC. JCO and CJE conducted the protocol registration. MRGB and EC assisted with article interpretation and language edit. All the authors read and approved the final manuscript.

Competing Interests

The authors declare no competing interests.

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Data Availability Statement

The data that supports this study are available in the article and accompanying online supplementary material.

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