STUDY PROTOCOL

Use of gloves for the prevention of COVID-19 in healthy population: A living systematic review protocol

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Abstract

Background and aims: The efficacy of using gloves by the general population to prevent COVID-19 is unknown. We aim to determine the efficacy of routine glove use by the general healthy population in preventing COVID-19. This is the protocol of a living systematic review.

Methods: We adapted an already published common protocol for multiple parallel systematic reviews to the specificities of this question. We will conduct searches in PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), grey literature, and in a centralized repository in L·OVE (Living OVerview of Evidence). L·OVE is a platform that maps PICO questions to evidence from Epistemonikos database. In response to the COVID-19 emergency, L·OVE was adapted to expand the range of evidence it covers and customized to group all COVID-19 evidence in one place. The search will cover the period until the day before submission to a journal. We will include randomized trials evaluating the effect of use of gloves in healthy population to prevent COVID-19 disease. Randomized trials evaluating the effect of use of gloves during outbreaks caused by MERS-CoV and SARS-CoV, and nonrandomized studies in COVID-19 will be searched in case no direct evidence from randomized trials is found.

Two reviewers will independently screen each study for eligibility, extract data, and assess the risk of bias. We will perform random-effects meta-analyses and use GRADE to assess the certainty of the evidence for each outcome.

A living, web-based version of this review will be openly available during the COVID-19 pandemic. We will resubmit it if the conclusions change or there are substantial updates.

KEYWORDS
coronavirus infections, COVID-19, double-glove, glove, severe acute respiratory syndrome coronavirus 2, systematic review

1 | INTRODUCTION

COVID-19 is an infection caused by the SARS-CoV-2 coronavirus.[1] It was first identified in Wuhan, China, on December 31, 2019[2]; 3 months later, almost half a million cases of contagion had been identified across 197 countries.[3] On 11 March, 2020, WHO characterized the COVID-19 outbreak as a pandemic.[1]

While the majority of cases result in mild symptoms, some might progress to pneumonia, acute respiratory distress syndrome and death.[4-6] The case fatality rate reported across countries, settings and age groups is highly variable, but it would range from about 0.5% to 10%.[7] In hospitalized patients, it has been reported to be higher than 10% in some centres.[8]

Gloves are part of personal protective equipment (PPE). For healthcare workers, they reduce the risk of infection and contamination, taking care of both healthcare workers and patients. During the current COVID-19 pandemic, healthcare workers are in the front-line, at greater risk of becoming infected than the general population. Gloves, along with face masks and other elements, allow to reduce that risk.

However, people have also used gloves in ordinary activities like going to the supermarket, drugstores, or in public transport. This may create a false sense of security, making people more susceptible to contamination due to an inadequate use or when taking them out without the appropriate technique. The incorrect use of gloves by the general population could increase the risk of infection and contamination of surfaces. Additionally, the use of gloves by the general population could threaten the supply of PPE for healthcare workers.

The efficacy of using gloves by the general population to prevent COVID-19 is unknown. Despite not having evidence to support its use, a large number of people have decided to use them, and governments and media do not have a clear message about using gloves by the general population. If we also consider the shortage of medical supplies, it is crucial to determine the efficacy of routine glove use by the general population in preventing COVID-19.

Using innovative and agile processes, taking advantage of technological tools, and resorting to the collective effort of several research groups, this living systematic review aims to provide a timely, rigorous, and continuously updated summary of the evidence available on the efficacy of the use of gloves in the prevention of COVID-19 disease in healthy population.

2 | METHODS

2.1 | Protocol and registration

This manuscript complies with the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA) guidelines for reporting systematic reviews and meta-analyses.[9]

A protocol stating the shared objectives and methodology of multiple evidence syntheses (systematic reviews and overviews of systematic reviews) to be conducted in parallel for different questions relevant to COVID-19 was published elsewhere.[10] This protocol was adapted to the specificities of the question assessed in this review and submitted to PROSPERO (CRD42020188674).

2.2 | Search strategies

2.2.1 | Electronic searches

Our literature search was devised by the team maintaining the L·OVE platform (https://app.iloveevidence.com), using the following approach:

- Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology[11] to the corpus of documents available in Epistemonikos Database.
- Discussion of terms with content and methods experts to identify relevant, irrelevant, and missing terms.
- Creation of a sensitive boolean strategy encompassing all of the relevant terms.
- Iterative analysis of articles missed by the boolean strategy, and refinement of the strategy accordingly.

Our main search source will be Epistemonikos database (https://www.epistemonikos.org), a comprehensive database of systematic reviews and other types of evidence.[12] We supplemented it with articles from multiple sources relevant to COVID-19 (without any study design, publication status, or language restriction).[13]

In sum, Epistemonikos Database acts as a central repository. Only articles fulfilling Epistemonikos criteria are visible by users. The remaining articles are only accessible for members of COVID-19 L·OVE Working Group.

Additional searches will be conducted using highly sensitive searches in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and the WHO International Clinical Trials Registry Platform, without any language or publication status restriction. The searches will cover from the inception date of each database until the day before submission.

The following strategy will be used to search in Epistemonikos Database. We will adapt it to the syntax of other databases.

(coronavir*OR coronovirus*OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov*OR "covid-19" OR covid19*OR "covid 19" OR "2019-nCoV" OR cv19*OR "cv-19" OR "cv 19" OR "n-cov" OR ncov*OR "sars-cov-2" OR "sars-cov2" OR (wuhan*AND [virus OR viruses OR viral] OR coronav*) OR (covid*AND [virus OR viruses OR viral]) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome" OR "covid-19-related" OR "SARS-CoV-2-related" OR "SARS-CoV2-related" OR "2019-nCoV-related" OR "cv-19-related" OR "n-cov-related") AND (coronavir*OR coronovirus*OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov*OR "covid-19" OR covid19*OR "covid 19" OR 2019-nCoV

OR cv19*OR "cv-19" OR "cv 19" OR "n-cov" OR ncov*OR "sars-cov-2" OR (wuhan*:ti,ab AND [virus OR viruses OR viral OR coronav*]) OR (covid*AND [virus OR viruses OR viral]) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome") AND (glov*OR "double-gloving" OR "double-glove" OR "double-gloves")

2.2.2 | Other sources

In order to identify articles that might have been missed in the electronic searches, we will do the following:

- Screen the reference lists of other systematic reviews and evaluate in full text all the articles they include.
- Scan the reference lists of selected guidelines, narrative reviews, and other documents.
- Conduct cross-citation search in Google Scholar and Microsoft Academic, using each included study as the index reference.
- Review websites from pharmaceutical companies producing drugs claimed as effective for COVID-19, websites or databases of major regulatory agencies, and other websites specialized in COVID-19.
- Email the contact authors of all of the included studies to ask for additional publications or data on their studies, and for other studies in the topic.
- Review the reference list of each included study.

2.3 | Eligibility criteria

2.3.1 | Types of studies

We will preferently include randomized trials. However, information from nonrandomized studies will be used if there is no direct evidence from randomized trials or the certainty of evidence for the critical outcomes resulting from the randomized trials is graded as low- or very low, and the certainty provided by the nonrandomized evidence grades higher than the one provided by the randomized evidence.[14]

We will exclude studies evaluating the effects on animal models or in vitro conditions.

2.3.2 | Types of participants

We will include trials assessing participants at risk of COVID-19 as defined by the authors of the trials. We will exclude trials evaluating healthcare workers, since they have been considered to be at a higher risk of contagion. If substantial clinical heterogeneity on how the condition was defined is found, we will explore it using a sensitivity analysis.

In case no direct evidence from randomized trials is found, or if the evidence from randomized trials provides low- or very low-certainty evidence for critical outcomes, we will include information from randomized trials evaluating use of gloves in other coronavirus infections, such as MERS-CoV or SARS-CoV infections.[14]

2.3.3 | Type of interventions

The intervention of interest is use of gloves. We will not restrict our criteria to a specific type, brand, or single or double gloves.

The comparison of interest will be no intervention. Trials assessing gloves plus other personal protective equipment (PPE) will be eligible if the cointerventions are identical in both intervention and comparison groups.

2.3.4 | Type of outcomes

We will not use the outcomes as an inclusion criteria during the selection process. Any article meeting all the criteria except for the outcome criterion will be preliminarily included and evaluated in full text. We used the core outcome set COS-COVID,[15] the existing guidelines and reviews and the judgement of the authors of this review as an input to select the primary and secondary outcomes, as well as to decide upon inclusion. The review team will revise this list of outcomes, in order to incorporate ongoing efforts to define Core Outcomes Sets (e.g., COVID-19 Core Outcomes[16]).

Primary outcome

- COVID-19 cases

Secondary outcomes

- Sick-leave days
- Hospitalizations for COVID-19
- Respiratory failure
- All-cause mortality

Other outcomes

- Gloves adverse events

Primary and secondary outcomes will be presented in the GRADE "Summary of Findings" tables, and a table with all the outcomes will be presented as an appendix.[17]

2.4 | Selection of studies

The results of the literature search in Epistemonikos database will be automatically incorporated into the L·OVE platform (automated retrieval), where they will be de-duplicated by an algorithm comparing unique identifiers (database ID, DOI, trial registry ID), and citation details (ie, author names, journal, year of publication, volume, number, pages, article title, and article abstract).

The additional searches will be uploaded to the screening software Collaboratron.[18]

In both L·OVE platform and Collaboratron, two researchers will independently screen the titles and abstracts yielded by the search against the inclusion criteria. We will obtain the full reports for all titles that appear to meet the inclusion criteria or require further analysis to decide on their inclusion.

We will record the reasons for excluding trials in any stage of the search and outline the study selection process in a PRISMA flow diagram adapted for the purpose of this project.

2.5 | Extraction and management of data

Using standardized forms, two reviewers will extract data independently from each included study. We will collect the following information: study design, setting, participant characteristics, and study eligibility criteria; details about the administered intervention and comparison, including type, preventive scheme, and duration; the outcomes assessed and the time they were measured; the source of funding of the study and the conflicts of interest disclosed by the investigators; the risk of bias assessment for each individual study.

We will resolve disagreements by discussion, and one arbiter will adjudicate unresolved disagreements.

2.6 | Risk of bias assessment

The risk of bias for each randomized trial will be assessed using a 'risk of bias' tool (RoB 2.0: a revised tool to assess risk of bias in randomized trials).[19] We will consider the effect of assignment to the intervention for this review. Two reviewers will independently assess five domains of bias for each outcome result of all reported outcomes and time points. These five domains are: bias due to (a) the randomization process, (b) deviations from intended interventions (effects of assignment to interventions at baseline), (c) missing outcome data, (d) measurement of the outcome, and (e) selection of reported results. Answers to signalling questions and supporting information collectively will lead to a domain-level judgement in the form of "Low risk of bias", "Some concerns," or "High risk of bias." These domain-level judgements will inform an overall 'risk of bias' judgement for each result. Discrepancies between review authors will be resolved by discussion to reach consensus. If necessary, a third review author will be consulted to achieve a decision.

We will assess their risks of bias with the Risk Of Bias In Nonrandomised Studies of Interventions (ROBINS-I), a tool for assessing risk of bias in nonrandomized studies of interventions.[20] We will assess the following domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions (effect of assignment to intervention), bias due to missing data, bias in measurement of outcomes and bias in the selection of the reported result. We

will judge each domain as low risk, moderate risk, serious risk, critical risk, or no information, and evaluate individual bias items as described in ROBINS-I guidance. We will not consider time-varying confounding, as these confounders are not relevant in this setting.[20] As we are studying the general population, we will not consider baseline potential confounders.

2.7 | Measures of treatment effect

For dichotomous outcomes, we will express the estimate of treatment effect of an intervention as risk ratios (RR) or odds ratios (OR) along with 95% confidence intervals (CI).

For continuous outcomes, we will use mean difference and SD (SD) to summarize the data using a 95% CI. Whenever continuous outcomes are measured using different scales, the treatment effect will be expressed as a standardized mean difference (SMD) with 95% CI. When possible, we will multiply the SMD by a SD that is representative from the pooled studies, for example, the SD from a well-known scale used by several of the studies included in the analysis on which the result is based. In cases where the minimally important difference (MID) is known, we will also present continuous outcomes as MID units or inform the results as the difference in the proportion of patients achieving a minimal important effect between intervention and control.[21]

Then, these results will be displayed on the "Summary of Findings Table" as mean difference.[21]

2.8 | Strategy for data synthesis

If we include more than one trial, we will conduct meta-analysis for studies clinically homogeneous using RevMan 5,[22] using the inverse variance method with random effects model. For any outcomes where data was insufficient to calculate an effect estimate, a narrative synthesis will be presented.

2.9 | Subgroup and sensitivity analysis

We will perform subgroup analysis according to the definition of severe COVID-19 infection (ie, respiratory failure vs respiratory distress syndrome vs ICU requirement). In case we identify significant differences between subgroups (test for interaction <0.05), we will report the results of individual subgroups separately.

We will perform sensitivity analysis excluding high risk of bias studies, and if nonrandomized studies are used, excluding studies that did not report adjusted estimates. In cases where the primary analysis effect estimates and the sensitivity analysis effect estimates significantly differ, we will either present the low risk of bias—adjusted sensitivity analysis estimates—or present the primary analysis estimates but downgrading the certainty of the evidence because of risk of bias.

2.10 | Assessment of certainty of evidence

The certainty of the evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development, and Evaluation working group methodology (GRADE Working Group),[23] across the domains of risk of bias, consistency, directness, precision, and reporting bias. Certainty will be adjudicated as high, moderate, low, or very low. For the main comparisons and outcomes, we will prepare Summary of Findings (SoF) tables[17,21] and also interactive Summary of Findings (http://isof.epistemonikos.org/) Tables. A SoF table with all the comparisons and outcomes will be presented as an appendix.

2.11 | Living evidence synthesis

An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d) will provide instant notification of articles with a high likelihood to be eligible. The authors will review these and will decide upon inclusion and will update the living web version of the review accordingly. We will consider resubmission to a journal if there is a change in the direction of the effect on the critical outcomes or a substantial modification to the certainty of the evidence.

This review is part of a larger project set up to produce multiple parallel systematic reviews relevant to COVID-19.[10]

CONFLICT OF INTEREST
All authors declare no financial relationships with any organization that might have a real or perceived interest in this work. There are no other relationships or activities that could have influenced the submitted work.

AUTHOR CONTRIBUTIONS
Conceptualization: María Belén Morales, Luis Ortiz-Muñoz, Giuliano Duarte, Gabriel Rada.
Methodology: Luis Ortiz-Muñoz, Gabriel Rada.
Data Curation: María Belén Morales, Luis Ortiz-Muñoz, Giuliano Duarte.
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Writing-Review and Editing: María Belén Morales, Luis Ortiz-Muñoz.

All authors have read and approved the final version of the manuscript. Giuliano Duarte had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

All data related to the project will be available. Epistemonikos Foundation will grant access to data.

TRANSPARENCY STATEMENT
María Belén Morales affirms that this manuscript is an honest, accurate, and transparent account of the living systematic review being reported; that no important aspects of the review have been omitted; and that any discrepancies from the review as planned (and, if relevant, registered) have been explained.

ETHICAL APPROVAL
As researchers will not access information that could lead to the identification of an individual participant, obtaining ethical approval was waived.

PROSPERO REGISTRATION
This protocol has been submitted (CRD42020188674).

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