Sexual transmission of SARS-CoV-2 virus and its role in the spread of COVID-19: A living systematic review protocol

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Abstract

Objective

To provide a review of the literature on the presence of SARS-CoV-2 in the sexual fluids of patients with COVID-19 and to observe its possible sexual transmission in a timely, rigorous, and continuously updated manner.

Data sources

We will conduct searches in PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), grey literature, and a centralized repository in L·OVE (Living OVerview of Evidence). L·OVE is a platform that maps PICO questions to evidence from the 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.

Eligibility criteria for selecting studies and methods

We adapted an already published standard protocol for multiple parallel systematic reviews to the specificities of this question. We will include randomized trials evaluating the sexual transmission of the SARS-CoV-2 virus. Randomized trials evaluating the sexual transmission of other coronaviruses, such as MERS-CoV and SARS-CoV, and non-randomized studies in COVID-19 will be searched if no direct evidence from randomized trials is found or if the direct evidence provides a low to a very low level of certainty for critical outcomes.

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 the review if the conclusions change or if there are substantial updates.

PROSPERO Registration

(CRD42020189368).

Main messages

- SARS-CoV-2 infection is transmitted mainly through respiratory droplets and direct contact; however, there is no consensus on sexual viral transmission.
- Knowing whether SARS-CoV-2 is sexually transmitted is important to decide on additional needs to reduce the spread of the COVID-19 pandemic.

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]; three months later, almost half a million contagion cases were identified across 197 countries[3]. On March 11, 2020, the World Health Organization 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 ranges from about 0.5% to 10%[7]. The case fatality rate for hospitalized patients has been reported to be higher than 10% in some centers[8].

The SARS-CoV-2 infection, which causes the COVID-19 disease, is mainly transmitted through respiratory droplets and direct contact. The virus has been isolated in different body fluids, such as saliva, feces, and urine. However, its presence in semen or vaginal fluid and the role of sexual transmission is unknown.

It is essential to know if the SARS-CoV-2 virus is transmitted sexually since it would allow to implement and reinforce preventive measures to reduce the spread of the COVID-19 pandemic.

With innovative and agile processes and taking advantage of technological tools while also resorting to several research groups' collective effort, this living systematic review aims to provide a timely, rigorous, and continuously updated summary of the evidence available on the sexual transmission of the SARS-CoV-2 virus.

Methods

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 question's specificities assessed in this review and submitted to PROSPERO (CRD42020189368).

Eligibility criteria

Types of studies

We will include all kinds of studies evaluating or analyzing the possibility of transmitting the virus sexually. We will exclude studies evaluating the effects on animal models or in vitro conditions. We will not include studies that have not been approved by an Ethics Committee.

Types of participants

We will include trials evaluating participants older than 15 years diagnosed with COVID-19 according to disease criteria defined by the trial authors. We will not restrict our criteria to any disease stage, whether the participants have active disease or are recovering. If substantial clinical heterogeneity is found in how the condition was defined, we will explore it using a sensitivity analysis.

Type of exposure

The exposure of interest will be the body fluids of people with COVID-19 potentially associated with the sexual transmission of SARS-CoV-2, such as the presence of the virus in semen, vaginal fluid, or other fluids studied.

Based on the review question, we will not consider a comparison group.

Type of outcomes

We will not use the outcomes as an inclusion criterion 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[14], the existing guidelines and reviews, and the judgment 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 to incorporate ongoing efforts to define Core Outcomes Sets (e.g., COVID-19 Core Outcomes[15]).

Primary outcome

- SARS-CoV-2 sexually transmitted infection.

Secondary outcomes

- Detection of the virus in sexual fluids.

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[16].

Search strategies

Electronic searches

Our literature search was devised by the team maintaining the L·OVE platform, using the following approach:

1. Identification of terms relevant to the population and exposure components of the search strategy, using Word2vec

technology[11] to the corpus of documents available in Epistemonikos Database.
2. Discussion of terms with content and methods experts to identify relevant, irrelevant, and missing terms.
3. Creation of a sensitive boolean strategy encompassing all of the relevant terms.
4. Iterative analysis of articles missed by the boolean strategy, and refinement of the strategy accordingly.

Our main search source will be the Epistemonikos database, a comprehensive database of systematic reviews and other evidence types[12]. We supplemented the database 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, and only articles fulfilling Epistemonikos criteria are visible by users. The remaining articles are only accessible for members of the 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 ((sex* OR intercourse* OR semen* OR vagin*) AND (transmi* OR route* OR source* OR acquisition* OR spread*))

Other sources

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

1. Screen the reference lists of other systematic reviews and evaluate all the articles they include in full text.
2. Scan the reference lists of selected guidelines, narrative reviews, and other documents.
3. Conduct cross-citation search in Google Scholar and Microsoft Academic, using each included study as the index reference.
4. 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.
5. Email the contact authors of all of the included studies to ask for additional publications or data on their studies and other studies on the topic.
6. Review the reference list of each included study.

Selection of studies

The results of the literature search in the 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 (i.e., author names, journal, year of publication, volume, number, pages, article title, and article abstract).

In the L·OVE platform, 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 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 this project.

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 (including disease severity and age), and study eligibility criteria; details about the administered intervention and comparison, including the type of sexual relationship, type of fluid, and phase of the disease (active or recovered); 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.

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 the risk of bias in randomized trials)[17]. We will consider the effect of the assignment on 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 (1) the randomization process, (2) deviations from intended interventions (effects of assignment to interventions at baseline), (3) missing outcome data, (4) measurement of the outcome, and (5) selection of reported results. Answers to signaling questions and supporting information collectively will lead to a domain-level judgment in the form of 'Low risk of bias', 'Some concerns', or 'High risk of bias'. These domain-level judgments will inform an overall 'risk of bias' judgment 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 Non-randomized Studies of Interventions (ROBINS-I), a tool for assessing the risk of bias in non-randomized studies of interventions[18]. We will assess the following domains: bias due to

confounding, bias in the 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 the 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 according to ROBINS-I guidance. We will not consider time-varying confounding, as these confounders are not relevant in this setting[18]. As we are studying the general population, we will not consider potential baseline confounders.

Measures of treatment effect

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

We will use mean difference and standard deviation for continuous outcomes 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 with 95% CI. When possible, we will multiply the standardized mean difference by a standard deviation that is representative from the pooled studies, for example, the standard deviation 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 is known, we will also present continuous outcomes as minimally important difference units or inform the results as the difference in patients' proportion achieving a minimal important effect between intervention and control[19].

These results will then be displayed on the 'Summary of Findings Table' as a mean difference[19].

Strategy for data synthesis

If we include more than one trial, we will conduct a meta-analysis for clinically homogeneous studies using RevMan 5[20], using the inverse variance method with a random-effects model. A narrative synthesis will be presented for any outcomes where data was insufficient to calculate an effect estimate.

Subgroup and sensitivity analysis

If relevant heterogeneity is detected, we will perform subgroup analysis according to sex, type of sexual relationship, type of fluid, and outcomes. 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 studies with a high risk of bias, and if non-randomized 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.

Assessment of certainty of the 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)[21], 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 tables[19,22], and also interactive Summary of Findings tables. A Summary of Findings table with all the comparisons and outcomes will be presented as an appendix.

Living evidence synthesis

An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform will provide instant notification of articles with a high likelihood to be eligible. The authors will review these and decide upon inclusion and 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.

Notes

Authorship contributions

AS, GR conceived the standard protocol for all the reviews being conducted by the COVID-19 L·OVE Working Group. GD drafted the manuscript, and all other authors contributed to it. The corresponding author is the guarantor and declares that all authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

Epistemonikos and several expert teams created the COVID-19 L·OVE Working Group to provide decision-makers with the best evidence related to COVID-19. Up-to-date information about the group and its member organizations is available here.

Acknowledgments

The members of the COVID-19 L·OVE Working Group and Epistemonikos Foundation have made it possible to build the systems and compile the information needed by this project. Epistemonikos is a collaborative effort based on the ongoing volunteer work of over a thousand contributors since 2012.

Competing 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.

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This project was not commissioned by any organization and did not receive external funding.

Epistemonikos Foundation provides training, support, and tools at no cost for all the members of the COVID-19 L·OVE Working Group.

Ethics

As researchers will not access information that could lead to identifying an individual participant, obtaining ethical approval was waived.

Data sharing

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

PROSPERO registration

(CRD42020189368).

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