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Original Article

# COVID-19 transmission: a rapid systematic review of current knowledge

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## ABSTRACT

**Objectives:** The objective of this study was to identify the potential and definite sources of transmission of coronavirus disease 2019 (COVID-19).
**Methods:** Due to time constraints and the acute nature of the pandemic, we searched only PubMed/MEDLINE from inception until January 28, 2021. We analyzed the level of evidence and risk of bias in each category and made suggestions accordingly.
**Results:** The virus was traced from its potential origin via possible ways of transmission to the last host. Symptomatic human-to-human transmission remains the driver of the epidemic, but asymptomatic transmission can potentially contribute in a substantial manner. Feces and fomites have both been found to contain viable virus; even though transmission through these routes has not been documented, their contribution cannot be ruled out. Finally, transmission from pregnant women to their children has been found to be low (up to 3%).
**Conclusion:** Even though robust outcomes cannot be easily assessed, medical personnel must maintain awareness of the main routes of transmission (via droplets and aerosols from even asymptomatic patients). This is the first attempt to systematically review the existing knowledge to produce a paper with a potentially significant clinical impact.

**Keywords:** Airborne particulate matter; COVID-19; Pathogen transmission

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## Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic on March 11, 2020 by the World Health Organization; since then, the disease has spread to more than 129 million people and has claimed more than 2,8 milllion lives [1]. This novel coronavirus disease has proven, so far, to be both highly transmittable (unlike severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) and not too fatal (unlike Ebola) [2]. Numerous reports concerning vehicles of transmission have been published, implicating a vast spectrum of possible transmission routes, including fomites [3], asymptomatic transmission (through simple exhalation) [4], and body fluids and secretions. In this systematic review, the first in the current literature according to our knowledge, we analyzed all available data on the possible

transmission routes of COVID-19.

## Materials and Methods

### Objective

This study was performed to identify potential and definite sources of transmission of COVID-19.

### Types of Studies

Due to the acute nature of the pandemic, all types of studies were considered eligible for inclusion; therefore, cohort studies (prospective and retrospective), case reports (including 3 or fewer cases) and case series (more than 3 cases), comments, research letters, laboratory studies, reviews, and meta-analyses were included. We excluded studies that did not focus on transmission routes of the disease. Only studies in English, or studies with an abstract available in English, from which adequate data extraction could be performed, were included.

### Search Methods

Due to time constraints and the acute nature of the pandemic, we decided to search only PubMed/MEDLINE from inception until January 28, 2021. The snowball procedure was performed in order to identify studies from the references of the included studies. The search was conducted using terms "COVID-19," "novel coronavirus," "SARS-CoV-2," "transmission," "transmissibility," and their synonyms using Boolean operators (OR, AND). Two authors (LT, PM) independently searched the database and disagreements were resolved through consensus with a third reviewer.

### Selection of Studies

Two authors (LT, PM) independently assessed the titles and abstracts, and after the initial stage of exclusion of irrelevant studies, they retrieved the full texts for further assessment. A flow diagram (Figure 1) visually depicts the study selection process.

### Data Extraction

Two authors (LT, PM) independently performed data extraction from the included studies based on a prespecified Excel sheet. The data extracted were relevant to the study characteristics (author, journal, year, country, type), the demographic characteristics

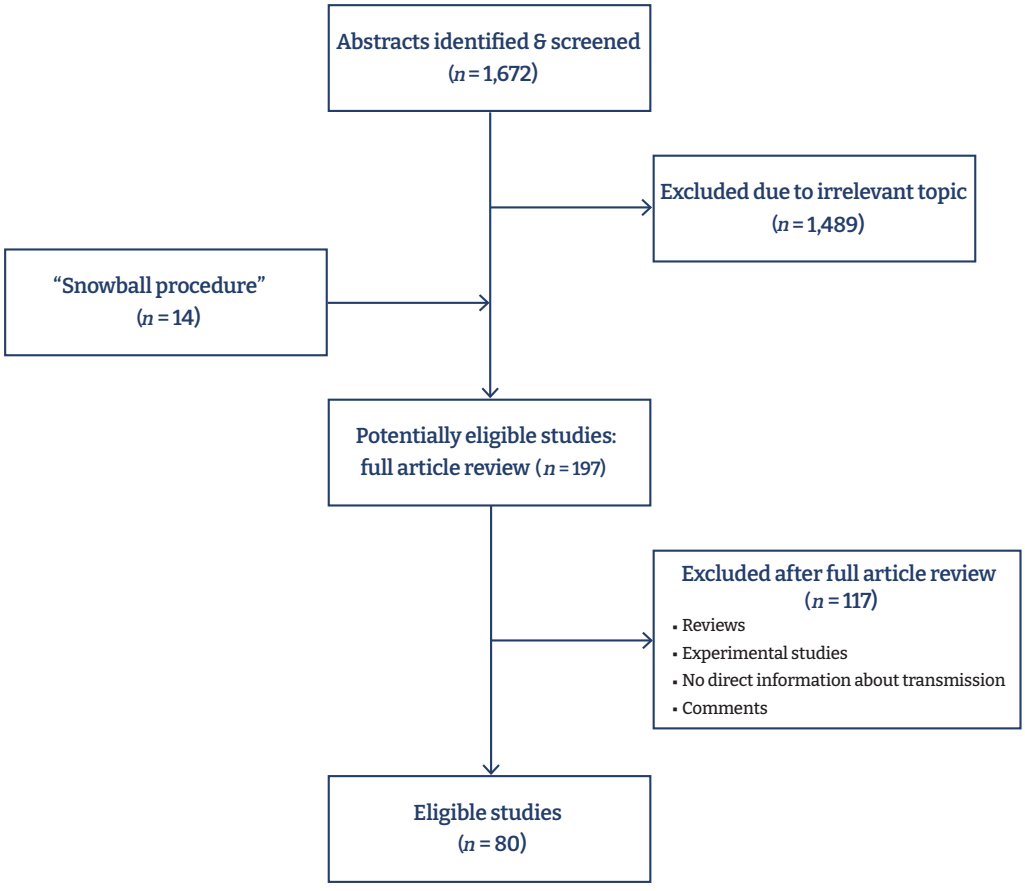


**Figure 1.** Flowchart of the study.

of patients (age, sex ratio, proposed route of transmission, comorbidities) and specific data related to the disease (positive samples, duration of positive samples, antibody titers). The last author (AF) reviewed the 2 Excel sheets and disagreements were resolved through consensus.

### Risk of Bias Assessment

We assessed the risk of bias using the Newcastle-Ottawa scale [5] for cohort studies. Due to the lack of standardized tools for assessing case reports and case series, we used the Joanna Briggs checklist for case series [6] and the criteria established by Pierson [7] to evaluate case reports.

## Results

The initial search yielded 1,672 results. After the exclusion of 1,489 studies due to irrelevant topics or a lack of information about the transmission of COVID-19, 197 studies underwent full-text review. The snowball procedure revealed 14 more references, and after the exclusion of 117 additional studies, 80 were finally included in the review (Figure 1). Thirteen were cohort studies [8–20] and the rest were case series, case reports, or studies with other designs. Table 1 presents the characteristics of the studies [3,4,8–62]. To summarize the findings, symptomatic human-to-human transmission remains the main vehicle that drives the epidemic, but asymptomatic transmission can potentially contribute in a substantial manner. Feces and fomites have both been found to contain viable virus; even though transmission through these routes has not been documented, their contribution cannot be ruled out. Finally, the transmission from pregnant women to their children has been found to be low (up to 3%). The risk of bias assessment revealed that 4 cohort studies were of low quality (<6 of 9 stars) according to the Newcastle-Ottawa scale, while most case series and case reports were of good overall quality (Tables S1–S3).

## Discussion

The most important transmission route of a respiratory virus is the air, but a variety of vehicles are implicated in this mechanism. These vehicles are categorized according to their size: large droplets with a diameter of >20 μm, small particles with a diameter of <5 to 10 μm, and intermediate particles with sizes between 10 and 20 μm [63]. The above-mentioned categorization is of major clinical and epidemiological significance since (a) large droplets cannot follow inhalation streamlines and fall very quickly, following gravity, but can stay on surfaces and produce fomites; and (b) small particles usually evaporate and form residual particulates (aerosols) that can travel in the air, transmit the virus at greater distances, and (if their size is <5 μm) travel deep in the human respiratory tract [64]. Moreover, up-to-date data suggest that exhalations, sneezes, and coughs can produce turbulent gas that not only traps and carries larger droplets, but can significantly decrease their evaporation, thereby extending their lifetime by a factor by up to 1,000 times [65]. The above-mentioned data can—and perhaps should—alter global policies of social distancing and support more aggressive use of face masks among the general population.

### Transmission from Animals to Humans: the Start of the Nightmare

A laboratory genomic analysis revealed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is 96% identical on the whole-genome level to a bat coronavirus CoVZXC21 (RaTG13), and there is a very high similarity (80% sequence identity) between this novel coronavirus and the SARS coronavirus (SARS-CoV-1) that was responsible for the earlier SARS pandemic in the recent past [21]. The study of Xu et al. [22] provides some insights into these issues. The authors found that the human angiotensin converting enzyme 2 (ACE-2) receptor is the gate of viral entry into the human body, while a simple nucleotide replacement (Arg426 with Asn426) increased the binding ability of the novel virus, which may explain its high transmissibility. Although the available data clearly suggest that bats are the reservoir of SARS-CoV-2 and that patient zero was linked to the Wuhan market, the fact that bats are not sold in this market suggests that there may be a possible intermediate host such as snakes, pangolins, or even turtles [66]. The quest to elucidate this major aspect of the pandemic is still ongoing.

### Direct Contact as the Main Vehicle and Airborne Transmission as a Possible Alternative Symptomatic Transmission

SARS-CoV-2 is, mainly, a respiratory virus. Therefore, its main route of transmission is contact with droplets produced by a symptomatic patient by coughing, sneezing, or exhaling. We identified 35 studies published in the literature, most of them being case reports or case series, that provide enough evidence for human-to-human transmission through droplets or direct contact with symptomatic patients [3,4,12,13,17,19,23–48,67–70]. All these case series reported either familial clusters, clusters from common indoor places (meetings, buses, temples, hospitals, spas, restaurants), or crowded outdoor facilities (markets). These studies all suggest that transmission of SARS-CoV-2 between humans is relatively easy, as expected.



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**Table 1.** Study characteristics

| Study | Type of study | Country | Type of transmission | Vehicle of transmission |
|---|---|---|---|---|
| Xu et al. [22] | Experimental | China | Bat to human | |
| Zhou et al. [21] | Experimental | China | Bat to human | |
| Zhang et al. [48] | Experimental | China, Wuhan | Multiple routes | Droplets, aerosol, feces, blood, serum |
| Dong et al. [55] | Case report | China, Wuhan, Renmin Hospital | Vertical | Amniotic fluid, placenta |
| Yu et al. [58] | Case series | China | Vertical | Amniotic fluid, placenta, close contact |
| Fan et al. [56] | Case report | China | Vertical | Amniotic fluid, placenta, close contact |
| Chen et al. [8] | Retrospective | China, Wuhan Zhongnan Hospital of Wuhan University | Vertical | Amniotic fluid, placenta |
| Li et al. [57] | Case report | China, Zhejiang Province | Vertical | Amniotic fluid, placenta |
| Chen et al. [9] | Retrospective | China, Hubei | Vertical | Amniotic fluid, placenta, close contact |
| Zeng et al. [18] | Retrospective | China, Wuhan Zhongnan Hospital of Wuhan University | Vertical | Amniotic fluid, placenta, close contact |
| Wang et al. [16] | Case report | China, The Affiliated Infectious Hospital of Soochow University | Vertical | Amniotic fluid, placenta |
| Zhu et al. [20] | Retrospective | China, Maternal and Child Health Hospital of Hubei Province | Vertical | Amniotic fluid, placenta |
| Xiao et al. [52] | Case series | China, Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, Guangdong Province | Fecal-oral | Feces |
| Ling et al. [14] | Retrospective | China, Shanghai Public Health Clinical Center | Fecal-oral | Feces |
| Zhang et al. [53] | Case series | China, Tianjiin | Fecal-oral | Feces |
| Xie et al. [60] | Case series | China, Union Hospital, Tongji Medical College, Wuhan | Ocular | Tears |
| Xia et al. [59] | Case series | China, Zhejiang, University School of Medicine First Affiliated Hospital, Hangzhou | Ocular | Tears |
| Sun et al. [62] | Case report | China, Eighth People's Hospital of Guangzhou Medical University | Urine | Urine |
| Cai et al. [23] | Case series | China, Wenzhou | Respiratory contact | Droplets, aerosol, fomites |
| Chan et al. [24] | Case series | China | Respiratory contact | Droplets, aerosol, fomites |
| Ghinai et al. [25] | Case report | USA, Illinois | Respiratory contact | Droplets, aerosol, fomites |
| He et al. [26] | Case series | China, Guangzhou Eighth People's Hospital | Respiratory contact | Droplets, aerosol, fomites |
| Holshue et al. [27] | Case report | USA, Washington | Unknown | Unknown |
| Huang et al. [28] | Case series | China | Respiratory contact | Droplets, aerosol, fomites |
| Kakimoto et al. [29] | Case series | Japan, Yokohama | Respiratory contact | Droplets, aerosol, fomites |
| Kimball et al. [30] | Case series | USA, Washington | Respiratory contact | Droplets, aerosol, fomites |
| Le et al. [31] | Case report | Vietnam | Respiratory contact | Droplets, aerosol, fomites |
| Li et al. [32] | Case series | China, Zhoushan | Respiratory contact | Droplets, aerosol, fomites |
| Li et al. [12] | Prospective | China, Wuhan | Respiratory contact | Droplets, aerosol, fomites |
| Li et al. [13] | Retrospective | China, Department of Thoracic Surgery Tongji Hospital | Respiratory contact | Droplets, aerosol, fomites |
| Lillie et al. [33] | Case series | UK | Respiratory contact | Droplets, aerosol, fomites |
| Liu et al. [34] | Case report | Taiwan | Respiratory contact | Droplets, aerosol, fomites |
| Luo et al. [35] | Case series | China, Huai'an No. 4 Hospital of Jiangsu Province | Respiratory contact | Droplets, aerosol, fomites |
| Phan et al. [36] | Case report | Vietnam | Respiratory contact | Droplets, aerosol, fomites |
| Pongpirul et al. [37] | Case report | Thailand | Respiratory contact | Droplets, aerosol, fomites |
| Qian et al. [38] | Case series | China, Zhejiang | Respiratory contact | Droplets, aerosol, fomites |
| Rothe et al. [39] | Case series | Germany | Respiratory contact | Droplets, aerosol, fomites |
| Shim et al. [40] | Case series | South Korea | Respiratory contact | Droplets, aerosol, fomites |

(Continued to the next page)

**Table 1.** Continued

| Study | Type of study | Country | Type of transmission | Vehicle of transmission |
|---|---|---|---|---|
| Tong et al. [41] | Case series | China, Zhoushan in Zhejiang Province | Respiratory contact | Droplets, aerosol, fomites |
| van Doremalen et al. [42] | Experimental | USA | Respiratory contact | Droplets, aerosol, fomites |
| Wang et al. [43] | Retrospective | China, Wuhan Zhongnan Hospital of Wuhan University | Respiratory contact | Droplets, aerosol, fomites |
| Wei et al. [17] | Retrospective | China | Respiratory contact | Droplets, aerosol, fomites |
| Xu et al. [44] | Case series | China, Guangzhou Women and Children's Medical Center | Respiratory contact | Droplets, aerosol, fomites |
| Yu et al. [45] | Case series | China, Wuhan | Respiratory contact | Droplets, aerosol, fomites |
| Yu et al. [46] | Case series | China, Shangai, Wuhan | Respiratory contact | Droplets, aerosol, fomites |
| Zhang et al. [47] | Case series | China | Respiratory contact | Droplets, aerosol, fomites |
| Zhong et al. [19] | Retrospective | China, Zhongnan Hospital, Wuhan | Respiratory contact | Droplets, aerosol, fomites |
| Bai et al. [4] | Case series | China, Anyang | Respiratory contact | Droplets, aerosol, fomites |
| Ong et al. [3] | Case series | Singapore | Respiratory contact | Droplets, aerosol, fomites |
| Li et al. [11] | Prospective | China | Sexual intercourse | Semen |
| Zhao et al. [49] | Case series | China | Respiratory contact | Droplets, aerosol, fomites |
| Sayampanathan et al. [15] | Retrospective | Singapore | Respiratory contact | Droplets, aerosol, fomites |
| Kawasuji et al. [10] | Retrospective | Japan | Respiratory contact | Droplets, aerosol, fomites |
| Lin et al. [54] | Case series | China | Respiratory contact | Droplets, aerosol, fomites |
| Chia et al. [50] | Case series | Singapore | Respiratory contact | Droplets, aerosol, fomites |
| Kasloff et al. [51] | Experimental | Canada | Respiratory contact | Droplets, aerosol, fomites |
| Kaya et al. [61] | Case series | Turkey | Ocular | Tears, conjunctival secretions |

The real problem originates from disturbing data reported in experimental studies suggesting that the virus could remain vital for hours in the air and potentially spread through aerosols. For instance, a study reported that some viable virus particles were present for at least 3 hours in the air and in the form of aerosols [42]. Although conflicting data have been reported on virus transmissibility via aerosols, as well as virus longevity and infectibility in aerosols in real-world settings, these findings are alarming and may have important implications for measures taken by the general public. If this is the case, then a mask should always be used when entering a closed-door room.

## Asymptomatic Transmission

Unlike SARS-CoV-1 [71], the novel SARS-CoV-2 has an important but likely devastating characteristic: the viral load of asymptomatic or presymptomatic patients is the same as that of symptomatic patients [49,72], although the former may not seem to be as contagious as the latter [15]. It is not known exactly when a presymptomatic patient becomes contagious, but an interval of 2 to 3 days before symptom onset has been suggested [10,26]. Sufficient reports in the literature have suggested asymptomatic transmission from patients who eventually developed symptoms (presymptomatic, with viral shedding during the incubation period) [46] or from patients who were totally asymptomatic, at rates even as high as 50% [4,73], even though most of authors could not definitively prove this assumption [74]. With an estimation that 20% of cases are totally asymptomatic and that the risk ratio of secondary attack from an asymptomatic versus symptomatic patient is 0.35 (95% confidence interval, 0.1–1.27), asymptomatic transmission is an important aspect of the current epidemic [75]. Some research has also reported a link between different mutations of the virus with the infectivity of asymptomatic patients [76].

## Fomites

It is common knowledge that many contagious diseases can be transmitted through fomites, which are produced by droplets that settle on surfaces after following their trajectory through the air [22]. Some experimental studies have illustrated the presence of the virus on different surfaces after hours or even days in some cases: up to 72 hours for plastic and stainless steel, 8 hours for copper, no more than 24 hours for cardboard [42], and interestingly up to 24 hours on human skin (which makes hand hygiene extremely important) and nearly 8 hours on banknotes [77]. Of course, experimental data provide some insight, but not the same level of evidence as a clinical trial. Guo et al. [78] found that more than 50% of the objects situated in intensive care units and general wards were contaminated



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by the virus (computer mouse, 75%; bed rails, 43%), whereas the virus was present in other rooms where no patients had been transferred, possibly through staff shoes (half of which were found to be positive). Researchers have found extensive environmental contamination in clinical settings, from patients with only mild upper respiratory tract disease or even without any symptoms (87% of room sites including air outlet fans, table, chairs and bed rails) [3,50]. However, the finding of the utmost clinical significance is the viability of the virus in personal protective equipment, especially due to the global shortage that dictated the need for its reuse. The study by Kasloff et al. [51] provides insights on this important issue: the virus (even at low levels) remained viable for 7 days on nitrile gloves and for almost 21 days in N95 and N100 masks (titers decreased from 24 to 48 hours, stabilized from 48 hours to 4 days and then declined from day 7 to day 21). This clearly demonstrates the need for careful attention in the possible reuse of this equipment to avoid secondary transmission to medical staff. These studies present data from hospital wards and intensive care units (with high loads of virus) and probably do not reflect the transmission dynamics in other settings, and they do not provide any data about possible transmission from surfaces; nevertheless, they demonstrate the relatively high circulation of the virus in our surroundings and therefore the need for surface disinfecting policies [79]. According to a recent systematic review, in household settings, contamination of patients' surroundings was as high as 14%, with patients' utensils, electronic high-touch surfaces, beds, and floors representing the most frequently contaminated surfaces [80]. Finally, since fomite transmission is difficult to prove, some publications used mathematical models to demonstrate the contribution of fomites to the growth of the epidemic via transmission, underscoring the need for awareness of this important aspect of transmission [81].

## Fecal Transmission

ACE-2 receptors are highly expressed in the small intestine [82] and clearly play a role in modulating intestinal inflammation [83]. SARS-CoV-2 utilizes the ACE-2 receptor as the main gate for entering the human body and recent data have suggested that the intestine could serve as a target organ for SARS-CoV-2 [52]. This may explain the gastrointestinal manifestations that are present in a small proportion of patients. There are sufficient data to prove the presence of viral genetic material in patients' stool [84], making the fecal-oral route a serious candidate for viral shedding. Moreover, viral clearance in stool seems to be even more prolonged than its clearance in nasopharyngeal swabs [14,84], and this fact suggests that patients (especially children) potentially transmit the virus via contaminated feces even after they have been discharged and recovered [48,53,54]. Virus shedding via stool is present even in patients without gastrointestinal symptoms, a fact with significant implications for pandemic control [85]. Despite the above-mentioned data, there are currently no reports of fecal-oral transmission of COVID-19, even though some researchers have reported recovering infectious virus from stool samples [86]. Nevertheless, sharing toilets with an infected person must be discouraged.

## Pregnancy

The previous pandemic viruses, SARS and MERS, had high fatality rates in pregnant women, which raised theoretical concern regarding their possible risk in the COVID-19 pandemic [87]. We identified 10 studies that dealt with COVID-19 transmission during pregnancy or delivery [8,9,16,18,20,55–58,88]. Vertical transmission (through the placenta) and breastfeeding were investigated. All studies, except for 1, reported negative findings for COVID-19 in neonatal nasopharyngeal swabs, amniotic fluid, and placenta; however, some studies reported positive immunoglobulin M (IgM) and immunoglobulin G antibodies in neonates within hours of birth [18,55], suggesting either a damaged placenta (since IgM antibodies cannot pass through the normal placenta) or virus passage and secondary development of antibodies. It is also important to emphasize that since IgM antibodies develop 3 to 7 days after infection and blood was drawn 2 hours after birth, these antibodies could not have developed due to infection after birth. The infant with a positive throat swab may have acquired the virus due to close contact with the mother, since the authors did not report when the swab was taken and whether the neonate had contact with the mother [58]. Nevertheless, some data have been reported regarding newborns who, despite negative swabs and being separated from the mother without any contact immediately after delivery, developed symptoms suggesting COVID-19 after birth, but the level of evidence is very low for proving vertical transmission [56]. Kotlyar et al. [89] conducted a meta-analysis of 936 SARS-COV-2–tested neonates with COVID-19–positive mothers from 39 studies and identified maternal-to-fetal transmission of the virus in 3.2% of neonates in the third trimester. Regarding breast milk, a recent systematic review found that among 92 newborns whose mothers' milk was tested, only 4 tested positive for SARS-CoV-2 and 5 were reactive for IgM antibodies. Based on these results and taking into account the benefits of breastfeeding, the Centers for Disease Control and Prevention recommend that women with a suspected or confirmed infection with

COVID-19 have no indication to stop breastfeeding [90].

### Other Potential Routes of Transmission

There are sparse data in the literature about possible transmission routes that cannot contribute to widespread infection, but nevertheless may have implications for everyday life, clinical practice, and the personal protective equipment required for several activities. A confirmed case had positive polymerase chain reaction (PCR) results for SARS-CoV-2 in tears and conjunctival secretions; this patient had conjunctivitis, and the results were negative for patients who did not have conjunctivitis [59]. Xie et al. [60] managed to find traces of SARS-CoV-2 on the ocular surface of patients who did not have any eye symptoms, suggesting that the virus could even spread from the normal conjunctiva, whereas other authors demonstrated that patients with oral swabs negative for SARS-CoV-2 could have positive swabs for the conjunctiva and tears [61]. Similarly, a case report described SARS-CoV-2 isolation in urine samples [62]. The presence of the virus in the blood was proven in 15% of patients in 1 study; although the median PCR cycle value was 35.1, suggesting a very low RNA concentration, this finding suggests the possibility of transmission through blood products [28]. Finally, recent reports reported isolating SARS-CoV-2 in the semen of patients in the acute phase, as well as in 8.7% of patients in the recovery phase [11]. A recent systematic review seems to agree with the above-mentioned results, finding a low but significant rate of patients with SARS-CoV-2–positive semen [91]. Medical personnel and the general population should be aware of these findings to minimize the already low probability of transmission through these routes.

## Supplementary Materials

Table S1. Risk of bias for cohort studies; Table S2. Risk of bias for case series; Table S3. Risk of bias for case reports. Supplementary data is available at https://doi.org/10.24171/j.phrp.2021.12.2.02.

## Notes

### Ethics Approval

Not applicable.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

### Availability of Data

All data come from the studies included in references.

### Authors' Contributions

Conceptualization: PM, LT; Data curation: PM, LT; Formal analysis: LT; Investigation: all authors; Methodology: LT, PM; Project administration: PM; Resources: all authors, Software: all authors; Supervision: PM; Validation: all authors; Visualization: all authors; Writing–original draft: PM; Writing–review & editing: all authors.

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