Public Health Ontario | Santé publique Ontario

SYNTHESIS

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Additional Routes of COVID-19 Transmission – What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence on a specific aspect or emerging issue related to COVID-19.

Updates in Latest Version

This updated version replaces the December 1, 2020 version *COVID-19 Routes of Transmission – What We Know So Far*.[1] The update version focuses on evidence from systematic reviews and meta-analyses, as the body of evidence for each mode of transmission has increased since the last version. This version does not include transmission through respiratory droplets or aerosols, as PHO has recently published *COVID-19 Transmission through Large Respiratory Droplets and Aerosols…What We Know So Far* (May 21, 2021).[2]

Key Findings

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted primarily at short range through respiratory particles that range in size from large droplets to smaller droplets (aerosols);[2] however, other transmission routes are possible:
    - SARS-CoV-2 can survive on a variety of surfaces, potentially leading to transmission via fomites; however, epidemiological evidence supporting fomite transmission is limited.
    - Transmission through the ocular surface is a possible route of transmission of SARS-CoV-2 based on the detection of viral RNA in ocular samples and limited epidemiological evidence that eye protection decreases the risk of infection.
    - There is evidence for vertical intrauterine transmission of SARS-CoV-2 from mother to child; however, intrauterine transmission is uncommon.
- Routes of transmission that are theoretically possible due to the detection of viral RNA, but have not been clearly demonstrated, are: 1) vertical transmission through breast milk; 2) fecal-oral transmission; 3) transmission from transplant of blood, blood products and organs; and 4) sexual transmission via semen and vaginal secretions.

Background

SARS-CoV-2 is transmitted most frequently and easily at short range through exposure to respiratory particles that range in size from large droplets, which fall quickly to the ground, to smaller droplets, known as aerosols, which can remain suspended in the air.[2] Meyerowitz et al. (2021) noted that respiratory droplets and aerosols were the dominant mode of SARS-CoV-2 transmission, with vertical intrauterine transmission and fomite transmission rare and no evidence for sexual, bloodborne or fecal-oral transmisison.[3]

The purpose of this document is to outline the evidence for various SARS-CoV-2 transmission routes, aside from respiratory droplet and aerosol transmission. During the COVID-19 pandemic, evidence on routes of transmission has evolved. In some instances, there remains uncertainty on the relative contribution from certain modes of transmission and it is challenging to determine the precise mode of transmission where there are multiple opportunities for transmission to occur.[4] Within this document, we underpin our findings with systematic reviews and meta-analyses, supported by primary literature where relevant.

Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding SARS-CoV-2 routes of transmission. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted in order to be timely (e.g., quality assessment).[5]

We conducted literature searches in MEDLINE (March 1, 2021), National Institutes of Health COVID-19 Portfolio (Preprints) (March 5, 2021), Embase (March 2, 2021) and Global Health/Scopus (March 4, 2021) (search strategies available upon request). We searched PubMed and Google Scholar on June 14, 2021, for additional articles of interest. English-language peer-reviewed and non-peer-reviewed records that described routes of transmission of COVID-19 were included. We restricted the search to articles published after January 1, 2020. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate. We reviewed citations from included articles to identify additional research. Prior to publishing, PHO subject-matter experts review all What We Know So Far documents. As the scientific evidence expands, the information provided in this document is only current as of the date of respective literature searches.

Fomite Transmission

Main findings: Laboratory-controlled studies indicate that SARS-CoV-2 can survive on a variety of surfaces, potentially leading to transmission via fomites. However, epidemiological evidence supporting fomite transmission of SARS-CoV-2 does not exclude other modes of transmission and are primarily based on reverse transcription polymerase chain reaction (RT-PCR) detection of viral RNA on surfaces without viability testing.

SARS-CoV-2 on surfaces

In two studies on hospital environments around COVID-19 patients, researchers failed to detect viable virus on surfaces or detection of viable virus was inconsistent.[6,7] In a systematic review and meta-analysis of 18 studies, Marzoli et al. (2021) concluded that while SARS-CoV-2 survived for 28 days on glass, steel and polymer/paper banknotes, there was little evidence for SARS-CoV-2 transmission from dry surfaces.[8] Low temperatures and high humidity increased virus survival on surfaces, however,

increased ultraviolet (UV) light or sunlight decreased virus survival.

In health care settings, studies documented the presence of viral RNA in the environment of symptomatic and asymptomatic patients with COVID-19 (especially medical equipment, phones, bed rails, door handles, toilets, cadavers).[7,9-17] In a systematic review and meta-analysis of 10 studies, Vicente et al. (2021) reported that the there was a decreased probability of RT-PCR-positives from aerosol samples compared to surface samples (odds ratio [OR]: 0.67; 95% confidence interval [CI]: 0.09–1.24; p=0.023).[18] In a hospital in Wuhan, China, Ye et al. (2020) reported that the most commonly contaminated surfaces were self-service printers for patient use, keyboards and doorknobs.[19] In Italy, Colaneri et al. (2020) detected viral RNA on the external surface of continuous positive airway pressure helmets worn by patients; however, samples did not grow in viral culture.[20] A study reported viral RNA on the surfaces of keyboards, telephones and scanners in a microbiology laboratory testing COVID-19-patient respiratory samples (Bloise et al. 2020).[21] In a multicenter study in South Korea, Kim et al. (2020) reported contamination of surfaces was common, especially in places not adequately sanitized.[22] Cheng et al. (2020) reported that the median load of viral RNA on environmental surfaces around hospitalized COVID-19 patients was 9.2×10^2 copies/mL (range: 1.1×10^2 to 9.4×10^4 copies/mL) and positivity rates of environmental samples increased with increasing viral loads in clinical samples from patients.[14]

In addition, viral RNA has been detected on surfaces in non-health care settings.[23-25] In a study of six playgrounds in an area of high SARS-CoV-2 transmission in Israel, Kozer et al. (2021) reported that 4.6% (2/43) of playground surfaces were positive for viral RNA, while 4.0% (1/25) of drinking water fountains were positive.[26] In a study of 39 patients and 259 environmental samples from their homes (Guangzhou, China), Luo et al. (2020) reported surfaces most commonly contaminated with viral RNA were in the bathroom on high touch surfaces (i.e., toilets, door knobs, faucets).[27]

SARS-CoV-2 in food

To date, there is no evidence for food-borne transmission of SARS-CoV-2.[28] There is likely a risk of transmission from respiratory droplets or aerosols during close contact during eating; in addition, there is a possibility of indirect transmission with fomites on utensils during eating. Several studies have identified viral RNA on food preparation surfaces and utensils, which could potentially be a source of infection through the oral mucosa; however, the contribution of this mode of transmission is unknown. Several narrative reviews concluded that SARS-CoV-2 was not a food-borne illness, with transmission via food considered only a theoretical possibility.[28,29] In a study of surfaces in health care settings, Mouchtouri et al. (2020) detected viral RNA on food preparation areas.[30] Liu et al. (2020) reported on the detection of viral RNA on wooden chopsticks handled by asymptomatic and presymptomatic patients with COVID-19.[31]

Epidemiological evidence of fomite transmission

There were few studies documenting fomite transmission, and where documented, other modes of transmission were not ruled out. In a case-control study of hemodialysis patients, Thadhani et al. (2021) (preprint) examined 170,234 adult patients from 2,600 outpatient facilities in the USA.[32] In 2,379 SARS-CoV-2-positive cases and 2,379 non-SARS-CoV-2 controls, 1.3% (95% CI: 0.90–1.87) of cases and 1.4% (95% CI: 0.97–1.97) of controls were exposed to a chair previously sat in by a patient with COVID-19. The risk of transmission among cases was not different from controls (OR: 0.94; 95% CI: 0.57–1.54; p=0.80). From a detailed investigation by Lessells et al. (2020), including whole genome sequencing, into an inter-facility outbreak of up to 135 nosocomial COVID-19 cases (including 88 staff and 47 patients) in South Africa, a patient in the emergency department likely spread the infection to at least five hospital units, a local nursing home and an outpatient dialysis unit on campus.[33] Based on the pattern of transmissions, the authors concluded that indirect contact and fomite transmission were the predominant modes of

transmission, facilitated by frequent patient movement between wards. However, given the volume of cases in the outbreak areas, and the potential for additional unidentified cases who were never tested, other modes of transmission cannot be ruled out. In an epidemiological and environmental study of two family clusters (n=five patients) of COVID-19 in Guangzhou, China, Xie et al. (2020) reported potential transmission via contaminated surfaces.[34] In this case, the proposed link between the two families was through nasal secretions, in which a patient had touched a contaminated elevator button. In this study, other modes of transmission cannot be ruled out and viability testing was not conducted (only viral RNA detection by PCR).

Transmission via the Conjunctiva

Main findings: Transmission through the ocular surface is a possible route of transmission of SARS-CoV-2 based on the detection of viral RNA in ocular samples of patients with COVID-19 and epidemiological evidence that eye protection decreases the risk of infection. In addition, several-meta-analyses demonstrate that ocular symptoms are the first manifestation of COVID-19 in a small proportion of patients (approximately 0.5–2.5% of all patients), potentially indicative of the eye acting as the location of initial infection. The risk of tears or ocular secretions acting as a source of infection is low.

SARS-CoV-2 can infect the eye, acting as a potential site of initial infection that can spread to other organs. Several studies have demonstrated the expression of angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptors in the eye's surface epithelium (i.e., conjunctiva, limbus and cornea) and corneal endothelium, indicating a potential entry point for SARS-CoV-2.[35-39] In addition, other proteases (e.g., furin) and glycoproteins (e.g., CD1437) on the ocular surface can aid in viral attachment and cell entry.[40] While ACE2 and TMPRSS2 receptors are present in ocular tissues, their expression is relatively low compared to other tissues such as in the nose and lungs.[41] Deng et al. (2020) demonstrated that rhesus macaques (*Macaca mulatta*) developed mild disease after inoculation of the conjunctiva, providing further animal-study evidence of conjunctival transmission.[42] Petronio Petronio et al. (2021), along with other authors, propose several mechanisms for ocular involvement in SARS-CoV-2 infection and transmission: 1) direct inoculation in the conjunctiva by infectious droplets [or aerosols]; 2) the nasolacrimal duct acts as a conduit for SARS-CoV-2 migration to the upper respiratory tract; or 3) haematogenic infection of the tear gland.[39,43] In addition, infection of the eye could arise from hand-to-eye contact, where a person touches a contaminated surface then rubs their eye(s) (i.e., fomites).[39]

Ocular symptoms as first manifestations of SARS-CoV-2 infection

In a systematic review and meta-analysis of 38 studies and 8,219 patients, Nasiri et al. (2021) reported the pooled prevalence of ocular symptoms in patients with COVID-19 was 11.0% (95% CI: 5.71–17.72); the most common ocular symptoms were dry eyes, itchy eyes, redness, tearing, eye pain and discharge.[44] Several researchers have suggested that if ocular symptoms appear before other symptoms, then the likely route of transmission was through the ocular surface.[39] We included five systematic reviews and meta-analyses in which the pooled prevalence of ocular symptoms as the first symptoms of COVID-19 ranged from approximately 0.5% to 2.5%.[44-48] The number of primary studies included in the systematic reviews and meta-analyses ranged from two to six, with 181 to 1,074 patients.

SARS-CoV-2 in ocular samples

While SARS-CoV-2 RNA has been detected in ocular samples from patients, with or without ocular symptoms, there was little evidence for tears or conjunctiva secretions being a source of infection. We are only aware of one study reporting the detection of live virus from ocular samples; Colavita et al.

(2020) demonstrated positive viral cultures (using Vero E6 cells) from ocular fluid in one patient.[49] Further work is needed to determine if SARS-CoV-2 can remain infectious in tears.

In seven systematic reviews and meta-analyses, the pooled prevalence of SARS-CoV-2-positive tears/conjunctiva swabs ranged from 1.0% to 16.7%.[45-47,50-53] In the systematic reviews and meta-analyses we found, five to 12 primary studies were included and the samples size in the primary studies ranged from 60 to 667 patients. None of the reviews examined the risk of infection via tears or transmission through the conjunctiva.

Epidemiological evidence of conjunctival transmission

In three primary studies of SARS-CoV-2, researchers demonstrated that wearing protective eyewear was associated with a reduced risk of infection in health care settings. In a single hospital case-control study of 32 infected staff and 552 uninfected but exposed staff (Boston, Massachusetts), Klompas et al. (2021) reported that infected staff members were less likely to wear eye protection (prevalence ratio: 0.44; 95% CI: 0.18–1.08); this result was not significant but trended toward a wearing eye protection trended toward a protective effect.[54] Khalil et al. (2020) performed a multicenter cross-sectional comparative study in Bangladesh (98 SARS-CoV-2-positive physicians, 92 SARS-CoV-2-negative or no symptom physicians), in which the use of face shields and/or goggles reduced the risk of infection (OR: 0.44; 95% CI: 0.23–0.84).[55] In a case report, Lu et al. (2021) reported a health care worker self-reporting eye redness followed by pneumonia following care of a patient with COVID-19; the health care worker was wearing a respirator, but no eye protection.[56]

Vertical Transmission

Main findings: There is evidence for the vertical transmission of SARS-CoV-2, specifically intrauterine transmission from mother to child; however, this does not appear to be common. There is no evidence for mother-to-child transmission of SARS-CoV-2 through breast milk; however, an infected mother can transmit the virus to a newborn through respiratory droplets and aerosols during close contact. Researchers inconsistently detect SARS-CoV-2 RNA by PCR in breast milk, with no evidence for the detection of live virus by culture.

Intrauterine or transplacental transmission

Schwartz et al. (2020) and Schwartz (2020) proposed that confirming vertical, intrauterine transmission requires detection of SARS-CoV-2 in chorionic villous cells using immunohistochemistry or *in situ* hybridization, specifically, testing the placenta, amniotic fluid and umbilical cord tissue.[57,58] Early onset of COVID-19 or detection of viral RNA soon after birth in newborns, along with immunological response in newborns are not sufficient to confirm intrauterine transmission.

For the purposes of this section, we will concentrate on the evidence supporting intrauterine transmission of SARS-CoV-2, excluding evidence of intrapartum or post-partum transmission. Tests used to determine intrauterine transmission (maternal umbilical cord blood, placenta or amniotic fluid; newborn immunoglobulin M [IgM]) were performed on a small proportion of births examined in the included studies; therefore there is limited evidence available to assess the overall risk of intrauterine transmission.

In an umbrella review, Ciapponi et al. (2021) (preprint) reported that the pooled prevalence of SARS-CoV-2-RNA-positive cord blood (from confirmed positive mothers) by PCR ranged from 0–14.3% (12 studies; sample size range: 4–81), 0–12.7% (15 studies; 1–63) for placenta samples, and 0–11.1% (15 studies; 3–81) for amniotic fluid.[59] The proportion of newborns with a positive SARS-CoV-2 RNA PCR test

at birth (specimens tested were not reported, but included NP swabs) ranged from 0–27.3% (44 studies; 4–1,116 newborns). Based on the systematic review and meta-analysis of Juan et al. (2020), Ciapponi et al. concluded that the risk of intrauterine or transplacental transmission through the umbilical cord blood, placenta and amniotic fluid was very low; however, the certainty of the evidence was very low.[60]

Ten systematic reviews and meta-analyses reported on SARS-CoV-2-PCR-positive newborns, in addition to testing of intrauterine tissues for viral RNA by PCR or newborn serology for IgG and IgM antibodies.[61-71] The prevalence of SARS-CoV-2-PCR-positive (includes oral swabs, anal swabs, blood samples, nasopharyngeal [NP] swabs) newborns ranged from approximately 2.5% to 6.5%. A small proportion of the RT-PCR-positive newborns had evidence of vertical transmission; the pooled prevalence of positive samples ranged from 0–12% for placental samples (n=6–67 samples), 0–3.0% for umbilical cord tissue/blood (n=30–108), 0–2.0% for amniotic fluid (n=24–111), and 4.0–33% for IgM antibodies (n=9–82). The number of primary studies in the included systematic reviews and meta-analyses ranged from 16 to 69, with 183 to 1,035 newborns.

Transmission through breast milk

In six systematic reviews and meta-analyses, the pooled prevalence of SARS-CoV-2-positive breast milk samples ranged from approximately 2% to 13% and no studies reported the detection of live virus after culturing attempts.[61,72-76] The number of primary studies in systematic reviews and meta-analyses ranged from 10 to 37, with 62 to 789 lactating women per systematic review. We are not aware of any studies documenting SARS-CoV-2 transmission through breast milk.

During breastfeeding, an infected mother can transmit SARS-CoV-2 to the child through respiratory droplets and aerosols during close contact. In a systematic review and meta-analysis, Raschetti et al. (2020) reported that close contact of mother and child in the first 72 hours of life increased the risk of infection in the child (adjusted odds ratio [aOR]: 6.6; 95% CI: 2.6–16.0; p<0.0001), while use of expressed breast milk did not (aOR: 2.2; 95% CI: 0.7–6.5; p=0.15).[77] In experiments that inoculated breast milk with live SARS-CoV-2, Holder pasteurization inactivated the virus; therefore, donated breast milk that is pasteurized may be safe for recipient children and care providers.[78]

Fecal-oral Transmission

Main findings: While fecal-oral transmission of SARS-CoV-2 is possible, it is unclear the extent to which this transmission route plays in the epidemiology of COVID-19. The risk of transmission via feces or urine is considered very low, as researchers do not routinely detect live SARS-CoV-2 in these samples.

Researchers have documented ACE2 receptor expression in gastrointestinal epithelial cells; SARS-CoV-2 infects these glandular cells, as evidenced by RNA detection and intracellular staining (marker of viral replication) of viral nucleocapsid protein in gastric, duodenal and rectal epithelia.[79] Given detection of infectious virus in stool and that virus can infect via the oral mucosa, fecal-oral transmission is possible.[80]

SARS-CoV-2 in feces and urine

Live virus has been cultured in stool samples of patients with COVID-19.[81,82] In a systematic review, viable virus was detected in the stool of six out of 17 patients, where culturing of virus was attempted.[83] It is important to note that the authors did not define positive and negative controls in these studies. While researchers have detected live virus in feces, the role of fecal-oral transmission in COVID-19 epidemiology is unclear. In six systematic reviews and meta-analyses, the pooled prevalence of SARS-CoV-2-RNA-positive stool in patients with COVID-19 ranged from approximately 41% to 54% and viral RNA shedding in stool lasted longer than in NP swabs.[83-88] The number of primary studies included in

reviews ranged from eight to 44, with 138 to 1,989 patients.

We are only aware of one instance where infectious virus was isolated from the urine of a patient with COVID-19 (Sun et al. 2020).[89] In five systematic reviews and meta-analyses, the pooled prevalence of SARS-CoV-2 RNA in urine ranged from approximately 0.5% to 16.4%.[84,90-93] The number of primary studies included in reviews ranged from seven to 27, with 155 to 569 patients.

Viral RNA can be detected in wastewater systems in areas experiencing outbreaks; however, the risk of transmission through contaminated wastewater is low.[94,95] In a study of treated and raw sewage in Germany, the authors detected viral RNA, but not viable virus.[96] Where wastewater contaminates recreational or drinking water (especially in resource-limited countries), there is a theoretical risk of transmission; however, there is no documented transmission in these settings.[97]

Environmental sampling in health care and non-health care settings detected viral RNA on toilets and other bathroom surfaces.[14,22,23,27,98,99] While readily detected, it is not clear if the source of viral RNA in bathrooms was the result of contamination from respiratory droplets or feces.

Epidemiological evidence of fecal-oral transmission

There are few epidemiological studies examining or reporting fecal-oral transmission. In addition, there were no instances of documented SARS-CoV-2 transmission via urine. Kang et al. (2020) reported on an outbreak of COVID-19 in a high-rise apartment building in Guangzhou, China, where the proposed mode of transmission was through fecal aerosols via the pipes in the building.[24] However, the authors did not demonstrate the exact mode of transmission, specifically whether it was direct contact or indirectly through inhalation of aerosolized virus or touching contaminated surfaces. In a retrospective cohort study in a densely populated area of Guangzhou, China, Yuan et al. (2020) postulated the mode of transmission was through the fecal-oral route, initiated from contaminated sewage in street puddles (viral RNA-positive).[100] In this study, there was an increased risk of infection when patients worked as cleaners/waste pickers (RR: 13; 95% CI: 2.3–180; n=33), wore outdoor shoes inside their homes (RR: 7.4; 95% CI: 1.8–34; n=33) and handling dirty shoes at home (RR: 6.3; 95% CI: 1.4–30; n=33). The authors did not confirm transmission via sewage in this study, as the authors did not detect viable virus from samples and they did not rule out other modes of transmission.

Transmission via Blood, Blood Products and Organs

Main findings: While SARS-CoV-2 RNA is detected in the blood of patients with COVID-19, all systematic reviews and primary studies indicate the risk of blood-borne or organ-transplant transmission is low. Compared to respiratory samples, viral RNA detection in blood and blood products is relatively uncommon and, to our knowledge, there has been no detection of viable virus from these sources.

SARS-CoV-2 in blood, blood products and organs

Two systematic reviews and meta-analyses reported the prevalence of SARS-CoV-2-RNA-positivity in blood samples from patients with acute post-acute COVID-19 was less than 18%.[96,102] In a systematic review and meta-analysis of five studies and 71 patients with acute COVID-19, Johnson et al. (2021) reported that the prevalence of SARS-CoV-2 RNA in whole blood was 17% (95% CI: 0–45); in five studies and 159 patients the prevalence of SARS-CoV-2 RNA in serum was 8% (95% CI: 0–35).[84] In a meta-analysis including 456 patients with post-acute COVID-19 (timing of blood collection was not reported), Morone et al. (2020) reported 17.5% of blood samples were positive for viral RNA by RT-PCR; however, no viable virus was cultured.[90]

Epidemiological evidence of transmission via blood, blood products and organs

While SARS-CoV-2 RNA is present in blood and blood products, the risk of blood-borne transmission is low. In a review, Kiely et al. (2020) noted that bloodborne transmission was only a theoretical possibility and that a blood phase for COVID-19 infection was brief, uncommon and usually associated with severe disease.[101] In an adult with severe aplastic anemia, Cho et al. (2020) reported that a patient did not develop COVID-19 after receiving apheresis platelet transfusion from a donor who tested positive for SARS-CoV-2 after donation.[102] In an immunocompromised child, COVID-19 did not develop after platelet transfusion from an asymptomatic donor with COVID-19 (Essa et al. 2020).[103] In two patients with acute myeloid leukemia receiving allogeneic haematopoietic stem cell transplantation, Leclerc et al. (2021) reported that the two patients did not contract SARS-CoV-2 from two asymptomatic donors that tested positive on the day of donation.[104] In France, low levels of viral RNA were detected in pathogen-reduced platelet concentrate, plasma and red blood cell units from asymptomatic, SARS-CoV-2-positive donors; none of the four recipients developed disease even though they all had immune system compromise.[105] In the French study, positive plasma samples did not grow virus in culture attempts. Dres et al. (2020) reported no transmission of SARS-CoV-2 through extracorporeal membrane oxygenation and dialysis membranes.[106]

No studies have confirmed transmission of SARS-CoV-2 through organ transplantation. Hong et al. (2020) reported a possible infection in a liver recipient, in which the donor was infected at time of donation; however, transmission may have been through direct close contact with a patient with COVID-19.[107] Puodziukaite et al. (2021) reported that two recipients of kidneys from a patient with acute COVID-19 did not result in SARS-CoV-2 infection.[108]

Sexual Transmission

Main findings: The risk of transmission via semen or vaginal secretions is low; however, transmission may occur via other routes during sexual activity (e.g., fecal-oral, respiratory droplets or aerosols during close contact). Currently there is no evidence for sexual transmission, and there is no evidence for the detection of live virus in semen or vaginal secretions.

Based on viral detection in feces, some have proposed possible transmission of SARS-CoV-2 through certain sexual behaviours involving oral-anal contact.[109] In addition, the detection of viral RNA and live virus detected in the saliva of COVID-19 patients represents a potential mode of transmission during sex or intimate contact.[110,111] Jing et al. (2020) reviewed the literature on ACE2 receptor expression in the female reproductive system and noted expression of ACE2 receptors in the vagina.[112] ACE2 receptors are also present in testes (i.e., spermatogonia, Leydig and Sertoli cells).[113]

SARS-CoV-2 in semen and vaginal secretions

To date, most studies have failed to detect viral RNA in semen or vaginal secretions in patients with COVID-19.[114-118] In a systematic review and meta-analysis of 23 studies, Tur-Kaspa et al. (2021) reported that SARS-CoV-2 RNA was not detected in 98.0% (293/299) of seminal fluids, 94.1% (16/17) of testicular biopsies, 100% (89/89) of prostatic fluids, 98.3% (57/58) of vaginal fluids, and 100% (16/16) of oocytes.[119] Massarotti et al. (2020) hypothesized that viral RNA detections in semen are due to viral RNA-contamination by patient urine.[120]

Zoonotic and Zooanthroponotic Transmission

Main findings: Animal-to-human (zoonosis) transmission is uncommon compared to human-to-animal (zooanthroponosis) transmission.

Intermediate hosts, zoonoses, and enzootic transmission

There is still limited information regarding potential zoonotic reservoirs of SARS-CoV-2 and what risk they pose to humans and other animals. Current research indicates that SARS-CoV-2 is a close relative of SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), which are Beta coronaviruses (βCoVs) that originated from bats (*Rhinolophus* species).[121-123]

Malayan pangolins (*Manis javanica*) have been postulated as the intermediate host based on the presence of viruses closely related to SARS-CoV-2; however, this hypothesis has not been confirmed.[124-126] Shahhosseini et al. (2021) reported that SARS-CoV-2 is the result of a recombination event between Bat-SL-CoV-2 and Pangolin-CoV.[127] Freuling et al. (2020) reported that raccoon dogs (*Nyctereutes procyonoides*) are susceptible to SARS-CoV-2 infection and may represent an important intermediate and reservoir host.[128] Authors in this study infected raccoon dogs through the intranasal route, which led to animal-to-animal transmission through direct contact, with high-level viral shedding with mild disease. Raccoon dogs are widespread in China and raised for their fur. It is important to note that there are no reports of SARS-CoV-2 natural infection in raccoon dogs.

Zoonoses and enzootic transmisison have been demonstrated for several domestic and companion animals. In the Netherlands, there was evidence that COVID-19 transmission occurred from an infectious American mink (*Neovison vison*) to human.[129] However, in most circumstances, transmission of SARS-CoV-2 involving animals is human-to-animal or animal-to-animal, and not animal-human.[130] In laboratory experiments, ferrets (*Mustela putorius*) transmitted virus to other ferrets through respiratory droplets and direct contact,[131] and potentially via aerosols.[132] In laboratory experiments, cats (*Felis catus*) and dogs (*Canis lupus*) were susceptible to COVID-19; however, neither developed clinical disease.[130,133] Cats transmitted the virus to other cats through close contact and can shed virus for 5 days post infection; however, there was no viral shedding in dogs. Authors noted oral and nasal viral shedding 7 days after exposure in two in-contact cats. Therefore, there is a possibility that transmission could occur from cats to humans. In addition, Shi et al. (2020) reported that experimental exposure in cats resulted in subclinical and symptomatic infections, and juvenile cats were at a higher risk of severe infection or death.[134] Recently, Gaudreault et al. (2021) demonstrated that while cats could be re-infected with SARS-CoV-2, they could not transmit the virus to susceptible, co-housed cats.[135] Bao et al. (2021) reported attenuation of SARS-CoV-2 over time, limiting cat-to-cat transmission.[136]

Susceptible non-human hosts and zooanthroponosis

Zooanthroponosis is the transmission of a disease agent from humans to animals (reverse zoonosis). Zooanthroponosis not only poses a risk to non-human animals, but to humans as well, as the virus could potentially become adapted to a new reservoir with potential spillover back into humans.

Most of the evidence to date indicates that non-human animals are more at risk of SARS-CoV-2 infection from humans, especially companion and domestic animals.[137] The first documented instances of zooanthroponosis of SARS-CoV-2 occurred between an infected person in Hong Kong and their companion dog; later human-to-dog transmission was reported in Italy with whole genome sequencing of canine and human samples showing identical strains.[125,138] Currently, cats (domestic, captive) and ferrets appear most susceptible to SARS-CoV-2 infection. Human-to-dog transmission may be limited due to cross-reaction of SARS-CoV-2 and canine respiratory coronavirus (CRCoV), providing some

immunological cross-protection.[139]

The most commonly reported human-to-animal transmission pair has involved domestic cats, where most cats had close contact with a confirmed human case of COVID-19.[130,140,141] In the Netherlands from April through May 2020, Zhao et al. (2021) reported that seroprevalence in cats was 0.4% (95% CI: 0.01–1.55; n=500) and in dogs was 0.2% (95% CI: <0.01–1.24; n=500).[142] In Italy, Patterson et al. (2020) (preprint) reported on PCR and serological testing of in 603 dogs and 316 cats early in the pandemic (March to May, 2020).[143] No animals were PCR-positive; however, 3.4% of dogs and 3.9% of cats had measurable SARS-CoV-2 neutralizing antibodies. In a cross-sectional serosurvey of companion animals in Italy, Colitti et al. (2021) reported that seroprevalence in cats (16.2%; 11/68) was higher than in dogs (2.3%; 3/130).[144] All seropositive companion animals were from homes with a COVID-19 case (n=147); however, 49 owners were not tested. In Wuhan, China, Zhang et al. (2020) reported that 14.7% (15/102) of house cats (from shelters, patient homes and veterinary clinics) seroconverted to SARS-CoV-2 early during the pandemic (January to May, 2020).[145] In a study of 50 cats quarantined with owners or close contacts with COVID-19, Barrs et al. (2020) reported that 12% (6/50) were positive for SARS-CoV-2 and authors determined transmission was from human-to-cat.[146]

Natural SARS-CoV-2 infection of animals has been reported, including 1) companion animals (domestic cats, domestic dogs), 2) wild animals (American mink), and 3) captive animals (ferrets [*Mustela putorius*], gorillas [*Gorilla gorilla*], lions [*Panthera leo*], pumas [*Panthera concolor*], snow leopards [*Panthera uncia*], and tigers [Panthera tigris]).[130,147-149] There is evidence for SARS-CoV-2 infection from human-to-mink; in addition, there is emerging evidence of mink-to-human and mink-to-wildlife/domestic animal transmission. Once transmission of SARS-CoV-2 from humans to mink occurs on a farm, transmission between mink becomes rapid, as reported from Canada, Denmark, France, Greece, Italy, Lithuania, Poland, Spain, Sweden, the Netherlands and USA.[149-151] In a study of ten mink farms after culling (the Netherlands), Van Aart et al. (2021) reported evidence of SARS-CoV-2 was found in 11.9% (12/101) of cats (feral=89; domestic=12; all positive cats were feral) and 15.4% (2/13) of dogs.[152] Assuming no cat-to-cat transmission, the average chance of cat infection from mink-to-cat transmission was 12% (95% CI: 10–18). Since only feral cats were infected, transmission was presumed to be from the mink. In Spain, Aguiló-Gisbert et al. (2021) reported that 15.4% (2/13) of wild American mink (20 km away from nearest mink farm) were positive for viral RNA, indicating sustained mink-to-mink transmission in the wild.[153] Similarly in Utah, USA, Shriner et al. (2021) reported serological evidence for SARS-CoV-2 infection in all 11 free-ranging mink (presumed escapees from a farm) tested; however, no serological evidence of infection was found in wild mink (n=2) or other wild animals (n=89).[154] In North Denmark Region, Larsen et al. (2021) reported that 30% (324/1,092) of people connected to mink farms were SARS-CoV-2-RNA positive on NP swabs; 27% (95% CI: 25–30) of these positive human cases had mink-associated strains of SARS-CoV-2.[155]

Several researchers have highlighted the need to monitor wild animals, to ensure that zooanthroponosis does not occur and to prevent creation of SARS-CoV-2 reservoirs.[156] Other susceptible animals used in experimental models included African green monkeys (*Chlorocebus sabaeus*), ferrets, fruit bats (*Rousettus aegyptiacus*), Chinese hamsters (*Cricetulus griseus*), Cynomolgus macaques (*Macaca fascicularis*), rhesus macaques, mice (*Mus musculus*), and Syrian hamsters (*Mesocricetus auratus*).[130,134,157,158] In North America, several studies have investigated potential reservoir species. Olival et al. (2020) reported that there is a risk of immunologically naïve North American bats acquiring SARS-CoV-2.[159] Fagre et al. (2020) (Preprint) demonstrated that deer mice (*Peromyscus maniculatus*) are susceptible to infection and are potential reservoirs of SARS-CoV-2 in North America.[160] Laboratory studies indicated that domestic ducks (*Anas platyrhynchos domesticus*), chickens (*Gallus gallus domesticus*), Northern treeshrews (*Tupaia belangeris*), Japanese quail (*Coturnix japonica*), turkeys (*Meleagris gallopavo*), Chinese domestic geese (*Anser cygnoides*), and pigs (*Sus scrofa*) were not susceptible to SARS-CoV-2.[130,134,161]

Conclusions

Modes of transmission other than droplets and aerosols can occur, such as fomite, conjunctival and intrauterine transmission; however, current evidence suggests that these routes of transmission occur less frequently. Theoretical, but unlikely, routes of transmission include vertical transmission through breast milk; fecal-oral transmission; transmission from transplant of blood, blood products and organs; and sexual transmission via semen and vaginal secretions. Further experimental and epidemiological studies are required to further characterize the relative contribution of various transmission routes to the epidemiology of COVID-19.

PHO will continue to monitor the scientific evidence on transmission routes of COVID-19, updating this document as necessary.

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