Pathogens and Global Health

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ypgh20

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https://doi.org/10.1080/20477724.2023.2228048

A narrative review of alternative transmission routes of COVID 19: what we know so far

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ABSTRACT
The Coronavirus disease 19 (COVID-19) pandemics, caused by severe acute respiratory syndrome coronaviruses, SARS-CoV-2, represent an unprecedented public health challenge. Beside person-to-person contagion via airborne droplets and aerosol, which is the main SARS-CoV-2's route of transmission, alternative modes, including transmission via fomites, food and food packaging, have been investigated for their potential impact on SARS-CoV-2 diffusion. In this context, several studies have demonstrated the persistence of SARS-CoV-2 RNA and, in some cases, of infectious particles on exposed fomites, food and water samples, confirming their possible role as sources of contamination and transmission. Indeed, fomite-to-human transmission has been demonstrated in a few cases where person-to-person transmission had been excluded. In addition, recent studies supported the possibility of acquiring COVID-19 through the fecal-oro route; the occurrence of COVID-19 gastrointestinal infections, in the absence of respiratory symptoms, also opens the intriguing possibility that these cases could be directly related to the ingestion of contaminated food and water. Overall, most of the studies considered these alternative routes of transmission of low epidemiological relevance; however, it should be considered that they could play an important role, or even be prevalent, in settings characterized by different environmental and socio-economic conditions. In this review, we discuss the most recent findings regarding SARS-CoV-2 alternative transmission routes, with the aim to disclose what is known about their impact on COVID-19 spread and to stimulate research in this field, which could potentially have a great impact, especially in low-resource contexts.

KEYWORDS
SARS-CoV-2; COVID-19; alternative routes of transmission; fomites; cold-chain; food

Introduction

Severe acute respiratory syndrome coronaviruses 2 (SARS-CoV-2)

Coronaviruses (CoVs) are single-stranded, positive-sense, enveloped RNA viruses, belonging to the family *Coronaviridae*, subfamily *Orthocoronavirinae*, and are classified into four genera: the alpha- beta-, gamma-, and deltacoronaviruses [1–3]. CoVs display on their surface the spike (S) envelope glycoprotein, which contains the receptor binding domain for the interaction with host cell receptors [4,5].

Members of this large family of viruses can infect both animals and humans causing respiratory, enteric, hepatic, and neurological diseases. Animal species susceptible to CoVs infection include camels, cattle, cats, and bats [6–10]. Up to date, nine Coronaviruses are known to infect humans, of which seven have been isolated in the last 20 years. The majority of human CoVs (HCoV-229E, HCoV-OC43, HCoV-NL63e HCoV-HKU1) cause common colds and self-limiting upper respiratory tract infections in immunocompetent individuals. Other coronavirus strains, such as the severe acute respiratory syndrome coronaviruses (SARS-CoV-1 and 2) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), are instead highly virulent, manifesting with respiratory and extra-respiratory symptoms of variable clinical severity [11] (Table 1), and have been implicated in epidemics in recent years, with mortality rates up to 11% (SARS-CoV-1) and 32.7% (MERS-CoV) [12,13,15,16]. Most infected people develop mild to moderate illness and recover without hospitalization, the main symptoms being fever, cough, tiredness, shortness of breath and gastrointestinal irritation. In some cases, particularly in elderly and immunocompromised individuals, the infection with these coronavirus strains, including SARS-CoV-2 lead to potentially life-threatening outcomes, such as interstitial pneumonia.

SARS-CoV-2 shares a 79% sequence identity with SARS-CoV and 50% with MERS-CoV. SARS-CoV-2 was isolated for the first time in late December 2019 in Wuhan, China, as the etiological agent of a cluster of pneumonia cases, later identified as Coronavirus disease 19, COVID-19. Since then, the virus has been rapidly spreading worldwide with confirmed cases in

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Table 1. Epidemiological data of principal human Coronaviruses.

Virus	Genus	Diffusion	Mortality	Ref
HCoV-229E	α-Coronavirus	Endemic	Rare	[8]
HCoV-NL63	α-Coronavirus	Endemic	Rare	[8]
HCoV-OC43	β- Coronavirus	Endemic	Rare	[8]
HCoV-HKU1	β- Coronavirus	Endemic	Rare	[8]
SARS-CoV	β- Coronavirus	Epidemic	11%	[12]
MERS-CoV	β- Coronavirus	Epidemic	32.7%	[13]
SARS-CoV-2	β- Coronavirus	Pandemic	1%	[14]

223 countries and territories around the world reporting over 550 million infected people and more than 6 million deaths [14,17].

SARS-CoV-2 transmission

Like other coronaviruses, transmission of SARS-CoV-2 occurs predominately from person to person when respiratory droplets or aerosol, emitted by infected individuals [18–21], come into contact with nasal, conjunctival, or oral mucosa [22,23]. Aerosols and droplets are currently distinguished based on their size: according to the World Health Organization (WHO) and Center for Disease Control and Prevention (CDC), particles with a diameter more than 5 µm are considered as droplets while those with diameters less than 5 µm are considered as aerosols [24,25]. Droplet transmission occurs when bacteria or viruses travel on relatively large respiratory droplets that people sneeze, cough, or exhale. These droplets may be loaded with infectious particles and can infect another person if the bacteria/viruses contact their eyes, nose or mouth. They may also fall on surfaces and then be transferred onto someone's hand, who then rubs their eyes, nose or mouth. Due to their larger size, large respiratory droplets are less persistent, falling quickly out of the air and, when inhaled, usually reach only the upper respiratory tract. Respiratory enveloped viruses such as SARS-CoV-2, are usually not viable in small droplet-nuclei; for this reason, short-range droplets are considered the dominant vehicles for transmission and close contact (for 15 min face to face, within 2 m) is considered the highest risk [26].

On the other hand, airborne transmission occurs when bacteria or viruses travel in droplet nuclei that become aerosolized. Aerosol can persist in the air for a longer-lasting period compared to droplets and can reach deeper into the lower respiratory tract [27,28]. Although airborne transmission may not be considered prevalent due to the dilution and inactivation of the viruses during longer periods of travel in the air [29], it has been demonstrated that SARS-CoV-2 can persist in artificially generated aerosols for a period long enough to support its high oral transmissibility [30–32]. van Doremalen et al. studied the stability of SARS-CoV-2 in aerosol under controlled laboratory conditions and demonstrated that during a period of 3 hours SARS-CoV-2 retained infectivity with an 84% reduction of the viral titer [33]. Moreover, Guo et al. [34] found that a mean of 23% of air samples collected in ICU and general COVID-19 wards tested positive for SARS-CoV-2. Recently, Lednicky et al. [35] reported that viable SARS-CoV-2 were isolated from air samples gathered 2–4.8 m away from patients, with concentrations ranging from 6 to 74 TCID50 units/l of air. In addition to respiratory droplets, airborne transmission is another important SARS-CoV-2 transmission route, particularly in indoor settings with poor ventilation or air re-circulation [36–38]. The possibility of alternative indirect routes of transmission, including transmission through water, food and surfaces, have also been considered but the impact of these on the spread of COVID-19 is still under debate. Although international public health authorities and regulatory bodies agree on considering these alternative routes of transmission of low relevance, results from several studies demonstrated possible SARS-CoV-2 transmission through contact with contaminated objects and surfaces, including food or food packaging, and via the contact-oral route through ingestion of contaminated food and water [39–41].

Methods

We are undertaking a narrative review summarizing the scientific evidence and discussing the most recent findings regarding SARS-CoV-2 transmission via fomites, food and food contact materials, with the aim to provide a comprehensive view of this topic, and better understand the dynamics of COVID-19 spread.

SARS-CoV-2 transmission via fomites

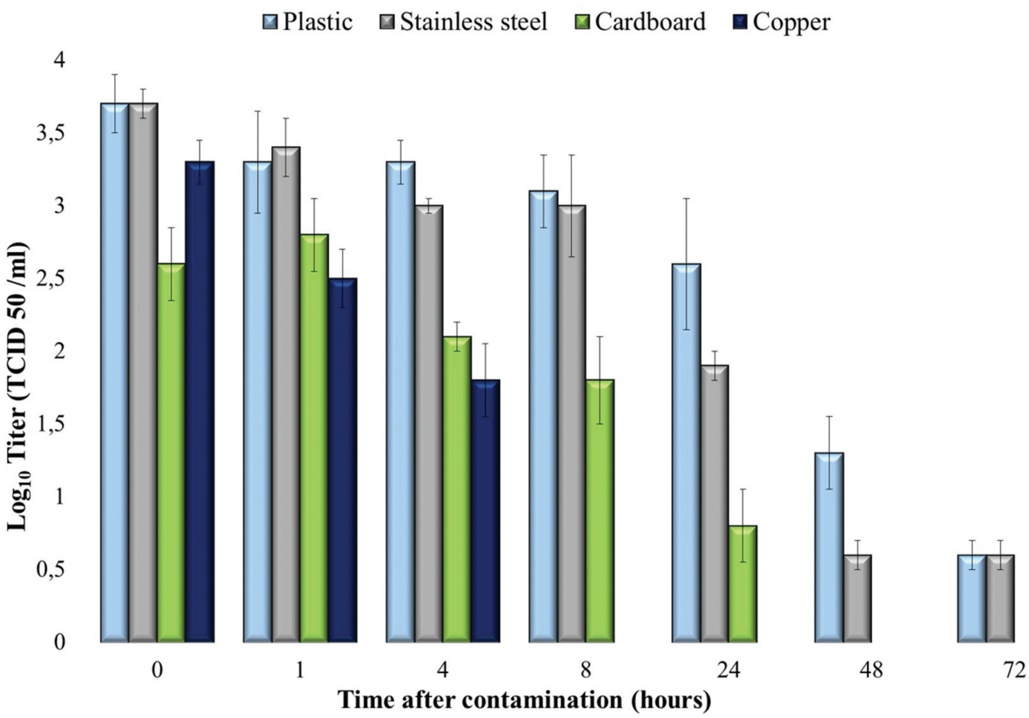
From the beginning of pandemics, fomites have been suggested as possible sources of SARS-CoV-2 transmission [42]. Fomites could be contaminated directly via respiratory droplets or aerosol, and indirectly by cross-contamination. The number of viable viruses initially contaminating a surface depends on the contamination route and the viral load of the infected person [43]. The putative transmission via fomites could occur by contact with contaminated surfaces and subsequently the transfer of viable viruses to nasal, buccal or ocular mucous membranes; thus, the adoption of appropriate disinfection and cleaning strategies has been proposed in order to reduce the contamination of surfaces and, consequently, the risk of infection [44]. To evaluate the risk of virus transmission through fomites, several studies, especially those related to the factors influencing the persistence of infectious virus particles on surfaces, have been made. Most of these studies focused on the detection and persistence of SARS-CoV-2 infectious particles and/or viral RNA on inert surfaces. In this context, it is important to stress that the detection of only viral RNA has different implications compared to the detection of infectious particles, since it is not always indicative of the presence of viral particles; thus, studies focused only on the detection of viral RNA could be subject to important limitations.

Various studies found that SARS-CoV-2 RNA can persist from hours to a few days on different surfaces, such as stainless steel, plastic and cardboard (Table 2). Furthermore, studies concerning the persistence of viable SARS-CoV-2 viral particles on fomites have been performed, showing that infectious particles can also be detected on fomites [33,50–53]. van Doremalen et al. were the first to examine the surface stability of SARS-CoV-2 infectious particles on plastic, stainless steel, copper and cardboard, demonstrating that, under laboratory conditions, infectious viral particles can persist on contaminated surfaces (Figure 1) [33].

In vitro studies demonstrated that SARS-CoV-2 infectious particles can also persist on organic surfaces, such as skin, for approximately 9 h [54], and retain

Table 2. Maximum persistence of SARS-CoV-2 RNA on different surfaces.

Surface	Temperature	Max persistence	References
Stainless steel	22–27°C	7 days	[45,46]
Plastic	25°C	8 days	[47]
Glass	22–27°C	4 days	[47]
Wood	22–27°C	2 days	[45,46]
Money	22°C	4 days	[48,49]
Human skin	25°C	19 hours	[47]



	Initial titer (TCID 50 /ml)	Final titer (TCID 50 ml)	% reduction (at LOD)	Persistence (hours)
Plastic	5012	4	99	72
Stainless steel	2512	5	99	72
Cardboard	316	6	98	24
Copper	1778	63	96	4

Figure 1. Surface stability over time of viable SARS-CoV-2. Figure shows how the viral titer decreasing trend varies in different materials such as plastic, stainless steel, cardboard and copper. The maximum persistence is observed for plastic and stainless steel (72 hours) while the viral titer decreases faster in copper (4 hours) [33].

infectivity longer in the presence of a moderate protein concentration (11.4 g/L), suggesting that a protein-rich medium like airway secretions could protect the virus and may enhance its persistence and transmission on fomites [55]. Other studies investigated the effects of temperature and humidity on virus integrity and persistence on fomites. Biryukov et al. observed that, on non-porous surfaces contaminated with a simulated clinically relevant matrix (i.e. saliva), higher temperatures and humidity caused a more rapid decay of SARS-CoV-2 [56]. Chin et al. demonstrated that the survival time of SARS-CoV-2 in cell culture medium was 14, 7 and 1 day respectively at 4°C, 22°C and 37°C [45]. The same study demonstrated that SARS-CoV-2 retained its infectivity on plastic surfaces at room temperature and 65% relative humidity for 4 days, while it completely decayed after 7 days. More recently, several other studies confirmed the positive effect of low temperatures on virus stability, especially in extremely dry or humid environments, as reported by Morris et al. [57]. Indeed, typical climate-controlled conditions such as those found in indoor environments are also favorable for virus stability. In a study by Liu et al. the persistence of SARS-CoV-2 RNA was evaluated in both an apartment and a department store that were blocked and unoccupied for more than 28 days. Authors found that SARS-CoV-2 RNA can be detected up to 57 days after the last exposure in room-temperature environments. Moreover, they found, in a cold storage container that carried contaminated items, that SARS-CoV-2 RNA was able to persist for at least 60 days on the surface of cold-chain food packages (under 18°C) [46].

Other studies demonstrated that SARS-CoV-2 genetic material can be detected on surfaces of hospital wards [58–60] as well as in indoor environments and objects that come into contact with respiratory droplets emitted by infectious patients long after exposure. SARS-CoV-2 viral RNA has been further detected on surfaces in playgrounds, retail stores and healthcare settings [61–67] proving that viruses emitted by infected individuals persist in the environment for long periods of time.

Although most of these studies demonstrated the high frequency of detection of SARS-CoV-2's genetic material on fomites [68], infectious particles were also detected on fomites but in fewer studies. In these studies, SARS-CoV-2 infectious particles were isolated from: frozen food packaging [69], the nightstands of infected cases [70], isolation rooms of patients undergoing mechanical ventilation [71], and on the windowsill of a patient's quarantine unit [72].

Given that SARS-CoV-2 infectious particles can be found on fomites, the transfer from surfaces to hands and from hands to mucosa has been addressed to support the plausibility of this alternative route of transmission. The still too few studies investigating the risk of transmission of SARS-CoV-2 from surfaces, based on previous studies performed on other members of the *Coronaviridae* family, highlighted that the dynamics of pathogen transfer are very intricate and several variables must be taken into account: the transfer efficiency is dependent on the combination of different parameters such as viral load, viral species, fomite material, skin surface characteristics and environmental conditions such as temperature and humidity [73–75].

The first parameter that has been considered is the amount of virus that can be transferred to the fomites from an infected individual. In a study performed on 92 patients with confirmed COVID-19, Yu et al. demonstrated that the viral load of sputum specimens in the lower respiratory tract correlated to the severity of COVID-19 and with the risk of its progression to a more severe form [76]. Pan et al. have reported a median of 7.5×10^5 (max 10^7) gene copies per mL in the sputum of infected patients [77]. These results are consistent with those obtained by Wang et al., which, using a mathematical model, also demonstrated that the total amount of virions expelled was higher when sneezing compared to coughing and speaking [78]. More recently, Johnson et al., analyzing the droplets and bioaerosols emitted by nasal swab positive patients, captured during the combined expiratory activities of breathing, speaking and coughing, demonstrated that SARS-CoV-2 RNA was present at concentrations up to 4.8×10^5 gene copies/mL and showed a positive correlation between the number of copies detected in naso-pharyngeal swabs and in samples of air emitted by participants, highlighting, however, an average threefold reduction in the latter [79]. Indeed, authors agree that the viral RNA levels recovered on environmental surfaces are lower than those detected in the nasopharynx, indicating that only a part of the viruses reaches fomites. Beside the amount of infectious virus on the fomite, the possibility of virus transmission from surfaces and its efficiency depends on the type of contact with the contaminated surface: different pressures, times of contact and rubbing actions influence the transfer efficiency of virus particles. For example, it is well established that rubbing increases microbial transfer. Behzadinasab et al. measured the percentage of SARS-CoV-2 that was transferred from a solid to an artificial finger considering brief and low-pressure contacts with no rubbing. They found that, on non-porous surfaces, transfer efficiency to skin is greater (13–16%) when the drop is still wet and that a small amount of virus particles (3–9%) can still be transferred even 30 min later when the droplet is dry. Insead, transfer efficiency resulted very low on porous surfaces [80].

Another parameter that has been considered is the stability of SARS-CoV-2 particles on human skin. A study performed by Thomas et al. [81] on influenza

A showed that the virus was readily inactivated on human hands, suggesting a protective anti-viral role of skin. To date, however, no studies report a similar activity for SARS-CoV-2. Harbourt et al. studied the persistence of infectious SARS-CoV-2 on dead porcine (pig) skin, finding that the virus was able to retain infectivity for 4 days at 22 ± 2 °C, and 8 h at 37 ± 2 °C (relative humidity of 40–50%) [49]. In another work, Hirose et al. used dead human skin as a model, showing that infectious viral particles were able to persist up to 9 h at 25 °C (relative humidity of 45–55%); in particular, the SARS-CoV-2 titer was over 1 Log_{10} $TCID_{50}$, in all skin samples tested after 4 h from contamination, suggesting that there is a significant opportunity for transmission from skin in the tested conditions [47].

More recently, Butot et al. measured transfer rates for SARSCoV-2 from food items and packaging materials (cardboard and plastic) to nitrile gloves and from gloves to face [74]. The cumulative transfer rates were approximately 4.0% for food items and were higher under wet conditions compared to dry conditions. Concerning packaging materials, the plastic packaging under wet conditions provided the highest cumulative transfer rate (3.0%) while no transfer from plastic or cardboard was observed with a dry inoculum. Authors conclude that in the tested conditions the obtained results suggest a minor role of foods or food packaging materials in virus transmission, which however cannot be ruled out, also considering that the infectious dose for humans has not yet been precisely established, though it has been assessed as being only five infectious particles in Syrian hamster models [82].

Concerning epidemiological investigations, the first studies advocating possible indirect transmission of SARS-CoV-2 through fomites were performed at the beginning of 2020. Cai et al investigated a cluster of COVID-19 cases associated with a shopping mall in Wenzhou in January 2020, and, being able to exclude person-to-person interaction, suggested that the rapid spread observed in the study could reasonably be ascribed either to transmission via fomites (e.g. elevator buttons or restroom taps) or virus aerosolization in a confined public space (e.g. restrooms or elevators) [83]. Also, Xie et al., monitoring a cluster of patients from January to February 2020 in Guangzhou, China, found an epidemiological association between two cases for which ‘person-to-person’ transmission had been excluded, identifying fomites (elevator buttons) as the most likely contamination source [84]. More recently, on 15 January 2022, in Beijing, a local confirmed case without any contact or travel history, was attributed to international mail delivered from North America [85]. In addition to these studies, mathematical models have been used by Kraay et al. to estimate the impact of fomite transmission in highly at-risk environments such as child daycares, schools, nursing homes and offices. From their findings, authors concluded that fomite transmission could sustain SARS-CoV-2 transmission in many settings [86]. In particular, diverse studies demonstrated that households are subjected to the highest risk of COVID-19 transmission [87–90]. Indeed, in home settings the opportunity and frequency of contact with contaminated surfaces is higher than in other indoor environments, and the risk of COVID-19 transmission via fomites could be reasonably higher in households than in public indoor settings [91,92]. This was very recently supported by a longitudinal cohort study in which authors assessed whether the presence of SARS-CoV-2 on frequently-touched surfaces and residents’ hands was a predictor of SARS-CoV-2, providing the first experimental evidence correlating the presence of SARS-CoV -2 on candidate vectors with risk of infection in due to household contact [93].

Despite this evidence, there is still debate over whether infectious viruses may persist in a natural environment in sufficient concentrations to cause infection. Indeed, some studies assessed as low or insignificant the risk of transmission via fomites. A scoping review by Mohamadi et al. that analyzed results from 25 primary studies, highlights a noticeable variability in the findings of articles assessing the risk of transmission via fomites, showing however that, in the majority of cases, the risk of SARS-CoV -2 infection via contaminated surfaces was assessed as low [94]. In a study performed in Barreiras city, Brazil, Rocha et al. investigated the presence of SARS-CoV-2 genetic material in objects of high frequent contact and were not able to find traces of the virus on the analyzed surfaces, suggesting that fomites and the environment did not result as important transmission routes for COVID-19 in this mid-sized city [95]. This result is consistent with what was observed by Harvey et al., who conducted longitudinal swab sampling of high-contact, non-porous surfaces in a Massachusetts town during a COVID-19 outbreak and found that the risk of acquiring COVID-19 by touching contaminated surfaces is less than 0,05% [96]. However, this low risk should also be considered in view of its implications on public health, which could be, instead, rather significant. In this context, it is important to consider the significance a low percentage of risk of transmission via fomites could assume when referred to large populations, such as large countries, and depending on the socio-economic context.

SARS-CoV-2 transmission via contaminated food packaging

Although the aforesaid studies highlight as low the risk of fomites transmission of SARS-CoV-2 for most of the common environmental conditions, the role of food packaging of cold chain products in SAR-CoV-2 transmission is of particular interest. Indeed, several *in vitro* studies demonstrated that SARS-CoV-2 persists longer at low temperatures. Cold-chain products are kept at low temperatures, around −18°C, throughout the entire process, from processing, storage, transportation, distribution and retailing, and for this reason contaminated cold-storage foods and packaging may be more at risk for SARS-CoV-2 transmission, also between countries and regions, and may cause human infection, in particular to high-risk people (such as dockworkers or stevedores).

From 2020 on, detection of SARS-CoV-2 on the packaging materials of frozen fish and meat, imported from countries with significant COVID-19 epidemics such as Ecuador, Brazil, Indonesia, India, Germany and Norway, has been reported [97]. By the end of the year, SARS-CoV-2 RNA was detected in food or food packaging samples collected in China, with an overall positive rate of 0.048% [96]. The detection of SARS-CoV-2 on the packaging surface of cold-chain products that arrived from very distant countries and took at least 20 days to be delivered, indicates that SARS-CoV-2 RNA persists for almost 1 month in this environment [98].

The possibility that cold-chain products' packaging could indeed act as vectors for the spread of COVID-19 was postulated for the first time by Liu et al. [99] during the outbreak that occurred in Qingdao City, in September 2020. On this occasion, two stevedores working at Qingdao Port were found to be SARS-CoV-2 positive having no COVID-19 case contact history and no foreign personnel contact history; both, however, carried out loading and unloading of the same batch of frozen cod. Surface swab samples of the frozen cod outer packages were collected and resulted positive for SARS-CoV-2 nucleic acid. Subsequently, the whole viral genome sequence of surface swab samples and nasopharyngeal swab samples of the stevedores were analyzed and resulted highly homologous. Interestingly, further phylogenetic analysis revealed that the SARS-CoV-2 isolated from the patient's nasopharyngeal swab and the imported frozen cod outer packages' surfaces belonged to a European Branch that was not circulating locally at the time [100]. Together with the epidemiological data, authors concluded that the COVID-19 outbreak of Qingdao was probably caused by SARS-CoV-2 contamination of outer cod packaging during production or cold-chain transportation [101].

The outbreak that occurred in Qingdao port on September 2020 has been the most studied since it was the first time the possibility of 'fomite-to-human' transmission of COVID-19 was demonstrated, meaning that SARS-CoV-2 was transmitted from cold chain food packaging materials to humans, and from human to human during cold chain transportation [102].

Following this event, on October 2020, China Center for Disease Control and Prevention issued an official release, confirming that novel coronavirus could persist for a long period, also not under laboratory conditions, on the outer packaging of items under special conditions of cold chain transport, suggesting that these items could act as carriers of SARS-CoV-2 [103].

Indeed, during 2020 China reported several infection clusters in different cities, such as Qingdao, Dalian, Tianjin, Beijing and Shanghai, which supposedly did not originate from interpersonal transmission. Several studies investigated these outbreaks and concluded that all of them could reasonably have originated from workers at port cold storage, seafood processing facilities, and market sites related to imported cold-chain food. Since on all these occasions person-to-person transmission was excluded, contact with contaminated cold-chain food packaging was considered as the most probable route of infection [104–108].

Several authors have reviewed the occurrence of transmission via contaminated food packages [109]: to date, a total of nine cases imputable to cold chain food contamination (Table 3).

Consistent with these findings, in January 2022, China's State Council updated two technical guidelines for cold-chain operators to prevent and control COVID-19. The document, officially titled 'Technical Guidelines for the Prevention and Control of Novel Coronavirus in Cold-Chain Food Production and Operation and the Cold-Chain Food Production and Operation Process Covid Control and Disinfection,' set guidelines for seafood suppliers, logistics operators, and seafood vendors, suggesting particular attention by the Chinese government to this issue [112].

Outside China, similar events have been reported in New Zealand and among workers at frozen food

Table 3. Coronavirus disease 2019 outbreaks related with cold chain food packaging.

Date	City	Place	Zero patient	SARS-CoV-2 source	Ref
June 11	Beijing	Wholesale market	Employee	Food packaging (frozen fish)	[108]
July 22	Dalian, Lioling	Seafood processing enterprise	Dockworker	Food packaging (frozen fish)	[109]
September 24	Qingdao	Port, Dock	Stevedores, Dockworker	Food packaging (frozen fish)	[101]
October 11	Qingdao	Dagang company	Stevedores, Dockworker	Food packaging (frozen fish)	[107]
October 25	Xinjiang	Kashgar airport	Stevedore	Container frozen products	[107]
November 8	Tianjin	Hailian Frozen Food Co	Stevedores, Dockworker	Food packaging (frozen meat)	[110]
November 9	Shanghai	Pudong Airport	Stevedore	Container frozen products	[107]
November (end)	Jiaozhou (Qingdao)	Fishery company	Stevedore	Food packaging aquatic products	[106]
December 15	Dalian	Port	Stevedore	Frozen food packaging	[111]

processing facilities in other countries, including Japan, Australia, Germany, England and Wales, and the United States, and have been recently discussed by Chen et al. [92].

SARS-CoV-2 transmission via contaminated food and water

As with fomite transmission, the possibility for transmission of SARS-CoV-2 via contaminated food and water has also been investigated in several studies.

The novel coronavirus RNA was detected for the first time on actual food samples in June 2020, on frozen seafood [113] and from there on, in several cases SARS-CoV-2 genetic material was detected on the surface of frozen food products [114,115], with frozen fish and meat products being the most likely to retain viral RNA [116,117].

Several authors have attempted to investigate the persistence of infectious SARS-CoV-2 particles on different categories of foods, including deli foods, meat, seafood and fresh produce. Jia et al demonstrated that infectious SARS-CoV-2 remained detectable on pork chops, pork mince and deli turkey for at least 3 weeks at 4°C [118], and similar results have been reported in other studies. Feng et al detected infectious SARS-CoV -2 on salmon, beef and pork after 9 days following storage at 4°C, and after 20 days following storage at −20°C [119]. Infectious SARS-CoV-2 was detected up to 9 days from artificially inoculated salmon incubated at 4°C also by Dai et al [120], while Norouzbeigi et al assessed infectious SARS-CoV-2 particles up to 8 weeks following inoculation in ice cream stored at −20°C and −80°C [121]. Overall, in high-protein unprocessed and minimally processed foods and foods high in both protein and fats, SARS-CoV-2 retains infectivity for at least 14 days at refrigeration temperature, although infectivity has been demonstrated to decline depending on the storage temperature [121]. High temperatures, instead, rapidly inactivate the virus: exposure to 56°C for 30 min can significantly reduce the vial titer [122]. Concerning pH, SARS-CoV-2 is most stable at slightly acidic pH (6–6,5), starts destabilizing at pH 5 and is completely inactivated at pH < 2,7 [123].

Considering the environmental resistance characteristics of SARS-CoV-2, thermally treated food products and acidic foods can be generally considered at low risk [124]. Greater attention has instead been givento products that can be consumed raw, such as plant-based products. Literature on this topic is scarce for SARS-CoV-2, but studies have been done on other coronavirus family members. Mullis et al. [125] demonstrated that a bovine coronavirus can persist on lettuce under household refrigeration conditions for 14 days. Similar results were obtained by Blondin-Brosseau et al [126], who examined the persistence of the human coronavirus HCoV-229E on fresh produce. Authors studied different types of fruit and vegetables and demonstrated that the virus can retain its infectivity for 24 h on tomatoes and apples and 96 h on cucumbers and lettuce, while it was not able to persist on strawberries. These results are consistent with the environmental resistance characteristics of the virus: tomatoes and apples display a more acidic pH (4,2 e 3,9 respectively) compared to cucumbers and lettuce (5,7 and 5,8) while strawberries are highly acidic (pH 3) and determine viral inactivation [127]. Based on these results it is possible to hypothesize that SARS-CoV-2 could show similar resistance characteristics.

The impact of cross contamination by infected food handlers has been studied by Haddow et al., who evaluated the stability of SARS-CoV-2 on apples, tomatoes and peppers, following a low-dose aerosol exposure. The authors concluded that, under the tested experimental conditions, the risk of transmission was extremely low; however, their conclusions did not completely exclude the possibility [128].

Other studies focused on the presence and persistence of SARS-CoV-2 in water, since it could represent a source of food contamination, especially of fresh products such as vegetables. Several studies have reported the detection of SARS-CoV-2 RNA in wastewater in The Netherlands [129], France [130], U.S.A [131], Australia [132] and Italy [133]. SARS-CoV-2 was also detected in surface water [134] but no cases are known of detection or isolation from potable water. In addition, human coronaviruses are readily inactivated by oxidizing agents and chlorine and, compared to other intestinal non-enveloped viruses, they decline faster in water [135–137].

These data indicate that the risk of SARS-CoV-2 transmission through the ingestion of contaminated food or water is epidemiologically of low significance; however, considering the scarcity of epidemiologic studies on this topic, these results could be underestimated, and further investigation is required to assess the impact of this route of transmission.

SARS-CoV-2 fecal-oro transmission

Many of the mammal-associated coronaviruses such as canine coronavirus [138], equine coronavirus [139] and other human coronaviruses are well known to cause gastroenteritis in their host species and have been demonstrated to be transmitted via the fecal-oro route [140,141].

Due to the high expression levels on enterocytes of the angiotensin-converting enzyme 2 (ACE2), which is the primary receptor that mediates SARS-CoV-2 entry, enterocytes can be susceptible to SARS-CoV-2 infection and it has been suggested that the ingestion of infectious virus particles could result in an enteric infection [142,143]. Other coronaviruses, that similarly use the ACE2 receptor for entry, such as the alpha coronavirus NL63 that causes the common cold, also have been reported to induce gastrointestinal symptoms [144]. Moreover, several studies confirm the co-expression in human enterocytes of two mucosa-specific membrane-associated serine proteases, TMPRSS2 and TMPRSS4, that are known to facilitate the membrane fusion and allow the release of the viral genome into the host cell cytosol, increasing the cells' susceptibility to the virus [145]. Zang et al. [146] also reported that these enzymes are highly expressed in human small intestinal enterocytes and demonstrated productive infection of SARS-CoV-2 in ACE2+ TMPRSS2 + mature enterocytes.

In vitro studies further investigated the possibility of the intestines being one of the viral target organs. Lamers et al. [147] demonstrated that SARS-CoV-2 productively infected human small intestinal organoids established from primary human gut epithelial stem cells, while Lee et al. confirmed the co-expression of SARS-CoV-2 entry genes in a subset of epithelial cells in the GI tract [148]. Moreover, Chan et al. demonstrated that SARS-CoV produced a persistent infection in colonic cells [149]. Current research is providing growing evidence for intestinal infection caused by SARS-CoV-2. The enteric reservoir of endemic human coronaviruses is supported by symptoms of enteritis or abdominal complaint in some patients, also in the absence of respiratory symptoms [150,151].

SARS-CoV-2 gastrointestinal symptoms, including diarrhea, abdominal pain and vomiting, have been reported in approximately 60% of patients and are considered a common symptom of COVID-19 [152,153]. Endoscopic and histological examination of patients with COVID-19 showed intestinal infection with SARS-CoV-2, which caused inflammatory infiltration, and SARS-CoV-2 infection was also correlated to alterations in gut microbiota composition, consistent with elevated expression of inflammatory cytokines such as IL-2, IL-4, IL-6, IL-10 and IL-18 [149,154]. Therefore, the fecal-oro route transmission of SARS-CoV-2 cannot be excluded.

In addition, several researchers attempted to isolate infectious particles in feces. To date, there are numerous cases of detection of viral RNA in stool samples [155–159]. In a recent meta-analysis of 60 studies comprising 4,243 patients, 48.1% of stool samples was positive for virus RNA, 70% of which remained positive also after respiratory clearance [160].

Indeed, infectious SARS-CoV-2 particles have been detected in the feces of four different patients [156,161,162] as in Dergham et al. [163] where gastrointestinal infection occurred without respiratory symptoms. Active replication in the gastrointestinal tract has been suggested by Wölfel et al. and the evidence for gastrointestinal infection is supported by the fact that RNA-positive stool samples have been found in patients that tested negative to the oro- or nasopharyngeal swab [164].

Epidemiological studies suggested fecal-oro transmission in cases such as the Diamond Princess cruise ship, where at least 20% of passengers were confirmed to be infected with SARSCoV-2, plausibly as the result of a superspreading event not implying person-to-person transmission [165].

Altogether, these findings enable us speculate on the possibility that, in these cases, SARS-CoV-2 might have been transmitted by oral acquisition. Results from some studies suggested that SASR-CoV-2 is susceptible to fecal-oro transmission [166] and other studies demonstrated the fecal-oro transmission route in Syrian hamster models, which detected subclinical respiratory infection after oral acquisition of SARS-CoV-2, although with less efficiency, and showed how orally infected hamsters had a level of detectable viral shedding from oral swabs and feces like that of intranasally infected hamsters [148]. However, full evidence for fecal-oro transmission is still lacking and further studies are needed to assess this route as a novel transmission mode of COVID-19.

The fecal-oro transmission and its significance in developing countries

Statistical studies performed by Rothschild elicited the hypothesis that fecal-oro transmission is prevalent, compared to respiratory transmission, in developing countries. The hypothesis is also correlated with low mortality rates from COVID-19 in developing countries, since gastrointestinal infection usually causes minor or no symptoms [167]. Indeed, diverse factors account for the major vulnerability to the potential fecal-oro transmission of developing countries and low-income communities, including low levels of sanitation, sharing of water sources, transmission from fecal sources to foods mediated by insects and other vectors, over-crowding, poor hygiene and food handling practices [168,169]. The poor socio-economic resources do not allow an effective implementation and management of socio-sanitary prevention and containment strategies. One of the most impacting of these limitations is that several developing countries, including Pakistan, Brazil, Ecuador, Nigeria and other States of Africa, Asia and South America have nonfunctional or no wastewater treatment facilities, and untreated sewage is directly discharged into surface water and soil [170,171]. In addition, developing countries suffer from poor policies and regulations.

Altogether these factors offer a plausible scenario of the strong impact which fecal-oro transmission of COVID-19 could have in low resource settings.

Conclusions

Coronavirus disease 2019 (COVID-19) is a rapidly growing infectious disease that has become one of the leading causes of death. Given the unprecedented public health challenge due to the high virus contagiousness, several authors have investigated its transmission pathways and dynamics, with the aim to develop and implement control measures to control and restrict spread. Infection via respiratory droplets has indeed been established as the main SARS-CoV-2 transmission route; however, the use of personal protective equipment and social distancing has not resulted in a drastic reduction of COVID-19 spread, and several studies are currently discussing the role of alternative transmission pathways, especially via fomites, including food packaging, food and water. Indeed, diverse types of environmental contamination that can lead to SARS-CoV-2 transmission have been reported. SARS-CoV-2 can persist for long periods in climate-controlled environments on different surfaces. Genetic material has been retrieved frequently on exposed fomites and, in some cases, infectious viral particles have also been detected. Various factors can impact on the persistence of infectious viral particles on fomites, including environmental humidity and temperature. In particular, low temperature plays a key role in increasing the persistence of SARS-CoV-2 and, for this reason, cold chain products have been suggested as possible vehicles for COVID-19. Indeed, in several cases SARS-CoV-2 was transmitted from cold chain food packaging materials to human and from human to human during cold chain transportation, confirming the possibility of 'fomite-to-human' transmission. In addition, frozen food intended to be consumed without heating treatment could also be considered at risk. The finding of SARS-CoV-2 genetic material on food and wastewater has opened a discussion about the possibility to acquire COVID-19 through the ingestion of contaminated food and water. Considering its environmental resistance characteristics, SARS-CoV-2 cannot persist in thermally treated food products and acidic foods but could represent a risk for vegetables and plant-based products, also considering the impact of irrigational water. This topic is of utmost interest given that current research is providing growing evidence for the intestinal infection of SARS-CoV-2. To date, there have been numerous cases of detection of viral genetic material in feces of infected patients, and gastrointestinal infections have been reported also in the absence of respiratory symptoms. The fecal-oro transmission route has been considered plausible and could be of great impact in countries where sanitation levels are low. It is in fact important to stress that the results discussed in this review must be interpreted taking into consideration the framework in which they took place, including the already existing strategies for infection and prevention control. Indeed, the findings reported in this review bring one to the conclusion that alternative transmission pathways can be considered of low epidemiological relevance. However, it is important to consider what significance the low percentage of risk of transmission via these alternative routes and its impact on public health could assume if related to large populations and/or to other environmental factors. Indeed, the impact of alternative transmission routes could vary greatly according to environmental factors and socio-economic status. These pathways could be important or even prevalent in those settings where the opportunity to implement adequate hygiene measures is difficult. In this context, investigating all SARS-CoV-2 possible transmission pathways can be important for the effective management of current and future possible pandemics. Furthermore, the recent findings that suggest that alternative routes of transmission, especially fecal-oro, might be prevalent in specific settings, could provide a relevant basis for deeper investigations of the gastrointestinal form of the disease, which could lead to an increased knowledge of COVID-19 pathophysiology.

In conclusion, in the light of the above considerations, the alternative routes of transmission of COVID-9 should be considered as potentially greatly impacting public health and should not be underestimated. The research in this field is scarce and needs to be increased. In this context, even if the fecal-oro route currently remains a hypothesis, assessing its relevance can be of crucial importance for public health especially in low-resource contexts. Indeed, a major comprehension of the possible novel mechanisms of COVID-19 transmission can be exploited not only to extend our knowledge of COVID-19 physiopathology and spread dynamics, but importantly to allow the implementation of more effective prevention and control strategies and to reinforce policies and regulations, especially in developing countries.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was funded by the National Funding for Centers of Excellence (Science Department 2023-2027, Roma Tre University, MIUR, Articolo 1, Commi 314–337, Legge 232/2016), by Next Generation EU PNRR Rome Technopole (ECS_00000024), MUR, PNRR, Missione 4 Componente 2, "Dalla ricerca all'impresa, Investimento 1.4" and by "ETICO": Lazio Innova, POR FESR Lazio 2014 2020, Bando Gruppi di Ricerca 2020 (CUP E85F21000870002).Institutional Review Board StatementNot applicable.

Authors' contributions

Conceptualization, G.A, A.A and V.G.; writing – original draft preparation, A.A. and V.G; writing – review and editing with input from all other authors (M.P., N.P. and F.T.), G.A., A.A and V.G; figures conceptualization and design M.P., V.G. and A.A; supervision, G.A. All authors provided critical feedback. All authors have read and agreed to the final version of the manuscript.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

[1] Triggle CR, Bansal D, Ding H, et al. A comprehensive review of viral characteristics, transmission, pathophysiology, immune response, and management of SARS-CoV-2 and COVID-19 as a basis for controlling the pandemic. Front Immunol. 2021 Feb 26;12:631139.
[2] Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health. 2020 Mar;25(3):278–280. doi: 10.1111/tmi.13383
[3] Zheng J. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci. 2020;16:1678–1685. doi: 10.7150/ijbs.45053
[4] Lam TT, Shum MH, Zhu HC, et al. Identifying SARS-CoV-2 related coronaviruses in malayan pangolins. Nature. 2020;583:282–285. doi: 10.1038/s41586-020-2169-0
[5] Chams N, Chams S, Badran R, et al. COVID-19: a multidisciplinary review. Front Public Health. 2020 Jul 29;8:383. doi: 10.3389/fpubh.2020.00383
[6] de Wit E, van Doremalen N, Falzarano D, et al. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016 Aug;14(8):523–534. doi: 10.1038/nrmicro.2016.81.
[7] Gong SR, Bao LL. The battle against SARS and MERS coronaviruses: reservoirs and animal models. Animal Model Exp Med. 2018 Jul 28;1(2):125–133. doi: 10.1002/ame2.12017
[8] Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23. doi: 10.1007/978-1-4939-2438-7_1
[9] Wilder-Smith A, Teleman MD, Heng BH, et al. Asymptomatic SARS coronavirus infection among healthcare workers, singapore. Emerg Infect Dis. 2005 Jul;11(7):1142–1145.
[10] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507–513. doi: 10.1016/S0140-6736(20)30211-7
[11] Wang C, Horby PW, Hayden FG, et al. A novel coronavirus outbreak of global health concern. Lancet. 2020 Feb 15;395(10223):470–473. doi: 10.1016/S0140-6736(20)30185-9
[12] Chan-Yeung M, Xu RH. SARS: epidemiology. Respirology. 2003 Nov;8(Suppl 1):S9–14. doi: 10.1046/j.1440-1843.2003.00518.x
[13] Zhang AR, Shi WQ, Liu K, et al. Epidemiology and evolution of middle east respiratory syndrome coronavirus, 2012–2020. Infect Dis Poverty. 2021;10:66. doi: 10.1186/s40249-021-00853-0
[14] Alimohamadi Y, Tola HH, Abbasi-Ghahramanloo A, et al. Case fatality rate of COVID-19: a systematic review and meta-analysis. J Prev Med Hyg. 2021 Jul 30;62(2):E311–E320. doi: 10.15167/2421-4248/jpmh2021.62.2.1627.
[15] Vijayanand P, Wilkins E, Woodhead M. Severe acute respiratory syndrome (SARS): a review. Clin Med (Lond). 2004 Mar-Apr;4(2):152–160. doi: 10.7861/clinmedicine.4-2-152
[16] World Health Organization. Middle east respiratory syndrome coronavirus (MERS-CoV). Available from: http://www.who.int/emergencies/mers-cov/en/.
[17] Sharma A, Ahmad Farouk I, Lal SK. COVID-19: a review on the novel coronavirus disease evolution, transmission, detection, control and prevention. Viruses. 2021 Jan 29;13(2):202. doi: 10.3390/v13020202
[18] Cevik M, Kuppalli K, Kindrachuk J, et al. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ. 2020 Oct 23;371:m3862. doi: 10.1136/bmj.m3862.
[19] Meyerowitz EA, Richterman A, Gandhi RT, et al. Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. Ann Intern Med. 2021 Jan;174(1):69–79. doi: 10.7326/M20-5008.
[20] Siegel JD, Rhinehart E, Jackson M, et al. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. 2007. Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html
[21] Rabaan AA, Al-Ahmed SH, Al-Malkey M, et al. Airborne transmission of SARS-CoV-2 is the dominant route of transmission: droplets and aerosols. Infez Med. 2021 Mar 1;29(1):10–19.
[22] Zhou L, Ayeh SK, Chidambaram V, et al. Modes of transmission of SARS-CoV-2 and evidence for preventive behavioral interventions. BMC Infect Dis. 2021 Dec;21(1):496.
[23] Cevik M, Marcus JL, Buckee C, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission dynamics should inform policy. Clin Infect Dis. 2021 Jul 30;73(Suppl 2):S170–S176. doi: 10.1093/cid/ciaa1442
[24] European Centre for Disease Prevention and Control. Surveillance definitions for COVID-19. 2020. Available from: https://www.ecdc.europa.eu/en/covid-19/surveillance/surveillance-definitions.
[25] World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. 2020. https://apps.who.int/iris/handle/10665/333114.
[26] Gralton J, Tovey E, McLaws ML, et al. The role of particle size in aerosolised pathogen transmission: a review. J Infect. 2011 Jan;62(1):1–13.
[27] Thomas RJ. Particle size and pathogenicity in the respiratory tract. Virulence. 2013 Nov 15;4(8):847–858. doi: 10.4161/viru.27172
[28] Klompas M, Baker MA, Rhee C. Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. JAMA. 2020 Aug 4;324(5):441–442. doi: 10.1001/jama.2020.12458
[29] Shiu EYC, Leung NHL, Cowling BJ. Controversy around airborne versus droplet transmission of respiratory viruses: implication for infection prevention. Curr Opin Infect Dis. 2019 Aug;32(4):372–379. doi: 10.1097/QCO.0000000000000563
[30] Leclerc QJ, Fuller NM, Knight LE, et al. What settings have been linked to SARS-CoV-2 transmission clusters?

Wellcome Open Res. 2020 Jun 5;5:83. doi: 10.12688/wellcomeopenres.15889.2
[31] Yu IT, Li Y, Wong TW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med. 2004 Apr 22;350(17):1731–1739. doi: 10.1056/NEJMoa032867
[32] Smither SJ, Eastaugh LS, Findlay JS, et al. Experimental aerosol survival of SARS-CoV-2 in artificial saliva and tissue culture media at medium and high humidity. Emerg Microbes Infect. 2020 Dec;9(1):1415–1417.
[33] van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020 Apr 16;382(16):1564–1567. doi: 10.1056/NEJMc2004973.
[34] Guo ZD, Wang ZY, Zhang SF, et al. Aerosol and surface distribution of severe acute respiratory syndrome coronavirus 2 in hospital wards, Wuhan, China, 2020. Emerg Infect Dis. 2020 Jul;26(7):1583–1591. doi: 10.3201/eid2607.200885
[35] Lednicky JA, Lauzardo M, Fan ZH, et al. Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients. medRxiv. Int J Infect Dis. 2020 Sep 16;100:476–482. Update in. doi: 10.1101/2020.08.03.20167395
[36] Hamner L, Dubbel P, Capron I, et al. High SARS-CoV-2 attack rate following exposure at a choir practice - Skagit County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020 May 15;69(19):606–610. doi: 10.15585/mmwr.mm6919e6
[37] Lu J, Gu J, Li K, et al. COVID-19 outbreak associated with air conditioning in restaurant, Guangzhou, China, 2020. Emerg Infect Dis. 2020 Jul;26(7):1628–1631. doi: 10.3201/eid2607.200764
[38] Jang S, Han SH, Rhee JY. Cluster of coronavirus disease associated with fitness dance classes, South Korea. Emerg Infect Dis. 2020 Aug;26(8):1917–1920. doi: 10.3201/eid2608.200633
[39] Mehraeen E, Salehi MA, Behnezhad F, et al. Transmission modes of COVID-19: a systematic review. Infect Disord Drug Targets. 2021;21(6):e170721187995. doi: 10.2174/1871526520666201116095934
[40] Mourmouris P, Tzelves L, Roidi C, et al. COVID-19 transmission: a rapid systematic review of current knowledge. Osong Public Health Res Perspect. 2021;12(2):54–63. doi: 10.24171/j.phrp.2021.12.2.02
[41] Escandón K, Rasmussen AL, Bogoch II, et al. COVID-19 false dichotomies and a comprehensive review of the evidence regarding public health, COVID-19 symptomatology, SARS-CoV-2 transmission, mask wearing, and reinfection. BMC Infect Dis. 2021 Jul 27;21(1):710. doi: 10.1186/s12879-021-06357-4.
[42] HO Transmission of SARS. WHO transmission of SARS-CoV-2: implications for infection prevention precautions; 2020. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions.
[43] Julian TR, Leckie JO, Boehm AB. Virus transfer between fingerpads and fomites. J Appl Microbiol. 2010 Dec;109(6):1868–1874. doi: 10.1111/j.1365-2672.2010.04814.x
[44] Choi H, Chatterjee P, Lichtfouse E, et al. Classical and alternative disinfection strategies to control the COVID-19 virus in healthcare facilities: a review. Environ Chem Lett. 2021;19(3):1945–1951. doi: 10.1007/s10311-021-01180-4
[45] Chin AWH, Chu JTS, Perera MRA, et al. Stability of SARS-CoV-2 in different environmental conditions. Lancet Microbe. 2020 May;1(1):e10.
[46] Liu H, Fei C, Chen Y, et al. Investigating SARS-CoV-2 persistent contamination in different indoor environments. Environ Res. 2021 Nov;202:111763.
[47] Hirose R, Ikegaya H, Naito Y, et al. Survival of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus on human skin: importance of hand hygiene in coronavirus disease 2019 (COVID-19). Clin Infect Dis. 2021 Dec 6;73(11):e4329–e4335. doi: 10.1093/cid/ciaa1517
[48] Newey CR, Olausson AT, Applegate A, et al. Presence and stability of SARS-CoV-2 on environmental currency and money cards in Utah reveals a lack of live virus. PLoS One. 2022 Jan 25;17(1):e0263025. doi: 10.1371/journal.pone.0263025
[49] Harbourt DE, Haddow AD, Piper AE, et al. Modeling the stability of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on skin, currency, and clothing. PLoS Negl Trop Dis. 2020 Nov 9;14(11):e0008831. doi: 10.1371/journal.pntd.0008831
[50] Carraturo F, Del Giudice C, Morelli M, et al. Persistence of SARS-CoV-2 in the environment and COVID-19 transmission risk from environmental matrices and surfaces. Environ Pollut. 2020 Oct;265(Pt B):115010.
[51] Wei L, Lin J, Duan X, et al. Asymptomatic COVID-19 patients can contaminate their surroundings: an environment sampling study. mSphere. 2020 Jun 24;5(3):e00442–20. doi: 10.1128/mSphere.00442-20
[52] Colaneri M, Seminari E, Novati S, et al. COVID19 IRCCS San Matteo Pavia Task Force. Severe acute respiratory syndrome coronavirus 2 RNA contamination of inanimate surfaces and virus viability in a health care emergency unit. Clin Microbiol Infect. 2020 Aug;26(8):e1094.1–e1094.5.
[53] Marquès M, Domingo JL. Contamination of inert surfaces by SARS-CoV-2: persistence, stability and infectivity. A review. Environ Res. 2021;193:110559. doi: 10.1016/j.envres.2020.110559
[54] Hirose R, Itoh Y, Ikegaya H, et al. Takaaki Nakaya Differences in environmental stability among SARS-CoV-2 variants of concern: omicron has higher stability (pre-print). bioRxiv. 2022. doi: 10.1101/2022.01.18.476607
[55] Pastorino B, Touret F, Gilles M, et al. Prolonged Infectivity of SARS-CoV-2 in Fomites. Emerg Infect Dis. 2020 Sep;26(9):2256–2257.
[56] Biryukov J, Boydston JA, Dunning RA, et al. Increasing temperature and relative humidity accelerates inactivation of sars-cov-2 on surfaces. mSphere. 2020;5(4):4. doi: 10.1128/mSphere.00441-20
[57] Morris DH, Yinda KC, Gamble A, et al. Mechanistic theory predicts the effects of temperature and humidity on inactivation of SARS-CoV-2 and other enveloped viruses. Elife. 2021 Jul 13;10:e65902. doi: 10.7554/eLife.65902.
[58] Li YH, Fan YZ, Jiang L, et al. Aerosol and environmental surface monitoring for SARS-CoV-2 RNA in a designated hospital for severe COVID-19 patients. Epidemiol Infect. 2020 [Published 2020 Jul 14];148:e154.
[59] Razzini K, Castrica M, Menchetti L, et al. SARS-CoV-2 RNA detection in the air and on surfaces in the COVID-19 ward of a hospital in Milan, Italy. Sci Total Environ. 2020 Nov 10;742:140540. doi: 10.1016/j.scitotenv.2020.140540

[60] Zhou J, Otter JA, Price JR, et al. Investigating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surface and air contamination in an acute healthcare setting during the peak of the coronavirus disease 2019 (COVID-19) pandemic in London. Clin Infect Dis. 2021 Oct 5;73(7):e1870–e1877. doi: 10.1093/cid/ciaa905
[61] Abrahão JS, Sacchetto L, Rezende IM, et al. Detection of SARS-CoV-2 RNA on public surfaces in a densely populated urban area of Brazil: a potential tool for monitoring the circulation of infected patients. Sci Total Environ. 2021 Apr 20;766:142645. doi: 10.1016/j.scitotenv.2020.142645
[62] Dargahi A, Jeddi F, Vosoughi M, et al. Investigation of SARS CoV-2 virus in environmental surface. Environ Res. 2021 Apr;195:110765.
[63] Kozer E, Rinott E, Kozer G, et al. Presence of SARS-CoV-2 RNA on playground surfaces and water fountains. Epidemiol Infect. 2021;149:e67. doi: 10.1017/S0950268821000546
[64] Singh M, Sadat A, Abdi R, et al. Detection of SAR-CoV-2 on surfaces in food retailers in Ontario. Curr Res Food Sci. 2021;4:598–602. doi: 10.1016/j.crfs.2021.08.009
[65] Jiang FC, Jiang XL, Wang ZG, et al. Detection of severe acute respiratory syndrome coronavirus 2 RNA on surfaces in quarantine rooms. Emerg Infect Dis. 2020;26(9):2162–2164. doi: 10.3201/eid2609.201435
[66] Ong SWX, Tan YK, Chia PY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA. 2020;323(16):1610–1612. doi: 10.1001/jama.2020.3227
[67] Guadalupe JJ, Rojas MI, Pozo G, et al. Presence of SARS-CoV-2 RNA on surfaces of public places and a transportation system located in a densely populated urban area in South America. Viruses. 2021 Dec 23;14(1):19. doi: 10.3390/v14010019
[68] Onakpoya IJ, Heneghan CJ, Spencer EA, et al. SARS-CoV-2 and the role of fomite transmission: a systematic review. F1000Res. 2021 Mar 24;10:233. doi: 10.12688/f1000research.51590.3.
[69] Wang J, Fengqin L, Zhaoping L, et al. COVID-19 outbreaks linked to imported frozen food in China: status and challege. Chin CDC Weekly. 2022;4:483–487. doi: 10.46234/ccdcw2022.072
[70] Marcenac P, Park GW, Duca LM, et al. Detection of SARS-CoV-2 on surfaces in households of persons with COVID-19. Int J Environ Res Public Health. 2021 Aug 2;18(15):8184. doi: 10.3390/ijerph18158184
[71] Ahn JY, An S, Sohn Y, et al. Environmental contamination in the isolation rooms of COVID-19 patients with severe pneumonia requiring mechanical ventilation or high-flow oxygen therapy. J Hosp Infect. 2020 Nov;106(3):570–576.
[72] Santarpia JL, Rivera DN, Herrera VL, et al. Aerosol and surface contamination of SARS-CoV-2 observed in quarantine and isolation care. Sci Rep. 2020 Jul 29;10(1):12732. Erratum in: Sci Rep. 2020 Aug 12;10(1):13892. doi: 10.1038/s41598-020-69286-3
[73] Todt D, Meister TL, Tamele B, et al. A realistic transfer method reveals low risk of SARS-CoV-2 transmission via contaminated euro coins and banknotes. iScience. 2021 Aug 20;24(8):102908. doi: 10.1016/j.isci.2021.102908
[74] Butot S, Zuber S, Moser M, et al. Data on transfer of human coronavirus SARS-CoV-2 from foods and packaging materials to gloves indicate that fomite transmission is of minor importance. Appl Environ Microbiol. 2022 Mar 14;88(7):e0233821. doi: 10.1128/aem.02338-21
[75] Castaño N, Cordts SC, Kurosu Jalil M, et al. Fomite transmission, physicochemical origin of virus-surface interactions, and disinfection strategies for enveloped viruses with applications to SARS-CoV-2. ACS Omega. 2021 Mar 5;6(10):6509–6527. doi: 10.1021/acsomega.0c06335
[76] Yu X, Sun S, Shi Y, et al. SARS-CoV-2 viral load in sputum correlates with risk of COVID-19 progression. Crit Care. 2020 Apr 23;24(1):170. doi: 10.1186/s13054-020-02893-8.
[77] Pan Y, Zhang D, Yang P, et al. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis. 2020;20(4):411–412. doi: 10.1016/S1473-3099(20)30113-4
[78] Wang Y, Xu G, Huang YW, et al. Modeling the load of SARS-CoV-2 virus in human expelled particles during coughing and speaking. PLoS One. 2020;15(10):e0241539. doi: 10.1371/journal.pone.0241539
[79] Johnson TJ, Nishida RT, Sonpar AP, et al. Viral load of SARS-CoV-2 in droplets and bioaerosols directly captured during breathing, speaking and coughing. Sci Rep. 2022 Mar 3;12(1):3484. doi: 10.1038/s41598-022-07301-5
[80] Behzadinasab S, Chin AWH, Hosseini M, et al. SARS-CoV-2 virus transfers to skin through contact with contaminated solids. Sci Rep. 2021;22868. doi: 10.1038/s41598-021-00843-0.
[81] Thomas Y, Boquete-Suter P, Koch D, et al. Survival of influenza virus on human fingers. Clin Microbiol Infect. 2014 Jan;20(1):O58–64.
[82] Rosenke K, Meade-White K, Letko M, et al. Defining the Syrian hamster as a highly susceptible preclinical model for SARS-CoV-2 infection. Emerg Microbes Infect. 2020 Dec;9(1):2673–2684.
[83] Cai J, Sun W, Huang J, et al. Indirect virus transmission in cluster of COVID-19 cases, Wenzhou, China, 2020. Emerg Infect Dis. 2020 Jun;26(6):1343–1345. doi: 10.3201/eid2606.200412
[84] Xie C, Zhao H, Li K, et al. The evidence of indirect transmission of SARS-CoV-2 reported in Guangzhou, China. BMC Public Health. 2020 Aug 5;20(1):1202. doi: 10.1186/s12889-020-09296-y.
[85] Chen W, Chen CL, Cao Q, et al. Time course and epidemiological features of COVID-19 resurgence due to cold-chain food or packaging contamination. Biomed J. 2022 Jun;45(3):432–438. doi: 10.1016/j.bj.2022.03.002
[86] Kraay ANM, Hayashi MAL, Berendes DM, et al. Risk for fomite-mediated transmission of SARS-CoV-2 in child daycares, schools, nursing homes, and offices. Emerg Infect Dis. 2021;27(4):1229–1231. DOI:10.3201/eid2704.203631
[87] Bernal JL, Panagiotopoulos N, Byers C, et al. Transmission dynamics of COVID-19 in household and community settings in the United Kingdom. Eurosurveillance. 2022. doi: 10.2807/1560-7917.es.2022.27.15.2001551
[88] Madewell ZJ, Yang Y, Longini IM Jr, et al. Household transmission of SARS-CoV-2: a systematic review and meta-analysis. JAMA Netw Open. 2020 Dec 1;3(12):e2031756. doi: 10.1001/jamanetworkopen.2020.31756
[89] Signorelli C, Odone A, Stirparo G, et al. SARS-CoV-2 transmission in the Lombardy Region: the increase of household contagion and its implication for

containment measures. Acta Biomed. 2020 Nov 20;91 (4):e2020195. doi: 10.23750/abm.v91i4.10994
[90] Li F, Li YY, Liu MJ, et al. Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. Lancet Infect Dis. 2021 May;21(5):617–628.
[91] The International Scientific Forum on Home Hygiene (IFH). White paper: what can we learn from the COVID-19 pandemic? 2021. Available from: https://www.ifh-homehygiene.org/review/developing-and-promoting-home-and-everyday-life-hygiene-meet-21st-century-needs.
[92] Wilson AM, Weir MH, Bloomfield SF, et al. Modeling COVID-19 infection risks for a single hand-to-fomite scenario and potential risk reductions offered by surface disinfection. Am J Infect Control. 2021 Jun;49 (6):846–848. doi: 10.1016/j.ajic.2020.11.013.
[93] Derqui N, Koycheva A, Zhou J, et al. Risk factors and vectors for SARS-CoV-2 household transmission: a prospective, longitudinal cohort study. Lancet Microbe. 2023 Apr;4(6):Se397–e408.
[94] Mohamadi M, Babington-Ashaye A, Lefort A, et al. Risks of infection with SARS-CoV-2 due to contaminated surfaces: a scoping review. Int J Environ Res Public Health. 2021 Oct 20;18(21):11019. doi: 10.3390/ijerph182111019
[95] Rocha ALS, Pinheiro JR, Nakamura TC, et al. Fomites and the environment did not have an important role in COVID-19 transmission in a Brazilian mid-sized city. Sci Rep. 2021 Aug 5;11(1):15960. doi: 10.1038/s41598-021-95479-5.
[96] Harvey AP, Fuhrmeister ER, Cantrell M, et al. Longitudinal monitoring of SARS-CoV-2 RNA on high-touch surfaces in a community setting. medRxiv. Environ Sci Technol Lett. 2020 Nov 1;8 (2):168–175. Updated in: 2021 Feb 9. doi: 10.1021/acs.estlett.0c00875
[97] Lu LC, Quintela I, Lin CH, et al. A review of epidemic investigation on cold-chain food-mediated SARS-CoV-2 transmission and food safety consideration during COVID-19 pandemic. J Food Saf. 2021 Dec;41(6): e12932. doi: 10.1111/jfs.12932.
[98] Bai L, Wang Y, Wang Y, et al. Controlling COVID-19 transmission due to contaminated imported frozen food and food packaging. Chin CDC Weekly. 2021 Jan 8;3(2):30–33. doi: 10.46234/ccdcw2021.008.
[99] Liu P, Yang M, Zhao X, et al. Cold-chain transportation in the frozen food industry may have caused a recurrence of COVID-19 cases in destination: successful isolation of SARS-CoV-2 virus from the imported frozen cod package surface. Biosaf Health. 2020 Dec;2 (4):199–201. doi: 10.1016/j.bsheal.2020.11.003.
[100] Yuan Q, Kou Z, Jiang F, et al. A nosocomial COVID-19 outbreak initiated by an infected dockworker at Qingdao City Port - Shandong Province, China, October, 2020. Chin CDC Weekly. 2020 Oct 23;2 (43):838–840. doi: 10.46234/ccdcw2020.224
[101] National Health Commission of the People's Republic of China. Introduction of cold-chain food and food safety in autumn and winter at the press conference of the joint prevention and control mechanism of the state council of the People's Republic of China. [cited November 25, 2020]. Available from: http://www.nhc.gov.cn/xwzb/webcontroller.do?titleSeq=11351&gecstype=1. [2020-12-31]. (In Chinese)
[102] Chen GS, Hu S, Zheng SL, et al. How to deal with the transmission of SARS-COV-2 on the surface of Cold-chain foods to people: a review. Eur Rev Med Pharmacol Sci. 2021 Oct;25(20):6378–6385. doi: 10.26355/eurrev_202110_27011.
[103] Ma H, Wang Z, Zhao X, et al. Long distance transmission of SARS-CoV-2 from contaminated cold chain products to humans - Qingdao City, Shandong Province, China, September 2020. Chin CDC Weekly. 2021 Jul 23;3(30):637–644. doi: 10.46234/ccdcw2021.164
[104] Ma H, Zhang J, Wang J, et al. COVID-19 outbreak caused by contaminated packaging of imported cold-chain products - Liaoning Province, China, July 2020. Chin CDC Weekly. 2021 May 21;3(21):441–447. doi: 10.46234/ccdcw2021.114
[105] Chi Y, Zheng S, Liu C, et al. Transmission of SARS-CoV-2 on cold-chain food overpacks: a new challenge. J Glob Health. 2021;11:03071. doi: 10.7189/jogh.11.03071
[106] Liu J, Zheng T, Xia W, et al. Cold chain and severe acute respiratory syndrome coronavirus 2 transmission: a review for challenges and coping strategies. Med Rev (Berl). 2022 Mar 1;2(1):50–65. doi: 10.1515/mr-2021-0019
[107] Han S, Liu X. Can imported cold food cause COVID-19 recurrent outbreaks? A review. Environ Chem Lett. 2021 Sep;7:1–11. doi: 10.1007/s10311-021-01312-w
[108] Pang XH, Ren LL, Wu SS, et al. Cold-chain food contamination as the possible origin of COVID-19 resurgence in Beijing. Natl Sci Rev. 2020;7(12):1861–1864. doi: 10.1093/nsr/nwaa264
[109] Zhao X, Mao LL, Zhang JQ, et al. Notes from the field: reemergent cases of COVID-19 — Dalian City, Liaoning Province, China, July 22, 2020. Chin CDC Weekly. 2020;2(34):658–660. doi: 10.46234/ccdcw2020.182
[110] Tianjin Municipal Health Commission. 2020. [cited 2020 Nov 11]. Available from: http://wsjk.tj.gov.cn/ZTZL1/ZTZL750/YQFKZL9424/FKDT1207/202011/t20201111_4067631.html.
[111] Health Commission. Health commission of Liaoning Province. [cited Dec 17] Available from: http://wsjk.ln.gov.cn/wst_zdzt/xxgzbd/yqtb/202012/t20201218_4051961.html.
[112] USDA. Updated Technical Guidelines for Cold Chain Foods CH2022-0022
[113] Nakat Z, Bou-Mitri C. COVID-19 and the food industry: readiness assessment. Food Control. 2021 Mar;121:107661. doi: 10.1016/j.foodcont.2020.107661.
[114] Han J, Zhang X, He S, et al. Can the coronavirus disease be transmitted from food? A review of evidence, risks, policies and knowledge gaps. Environ Chem Lett. 2021;19(1):5–16. doi: 10.1007/s10311-020-01101-x
[115] Yekta R, Vahid-Dastjerdi L, Norouzbeigi S, et al. Food products as potential carriers of SARS-CoV-2. Food Control. 2021 May;123:107754. doi: 10.1016/j.foodcont.2020.107754.
[116] Zhan J. Frozen South American white shrimp products from Pingxiang, Jiangxi, tested positive for nucleic acid in their outer packaging; 2020, July 15. Available from: http://www.xinhuanet.com/politics/2020-07/15/c_1126239771.htm
[117] Economou V, Sakkas H, Bezirtzoglou E, et al. SARS–CoV–2 and food—how confident are we about them? Hygiene. 2021; 1(3):80–98. doi: 10.3390/hygiene1030008
[118] Jia M, Taylor TM, Senger SM, et al. SARS-CoV-2 remains infectious on refrigerated deli food, meats, and fresh produce for up to 21 days. Foods. 2022; 11(3):286. doi: 10.3390/foods11030286

[119] Feng XL, Li B, Lin HF, et al. Stability of SARS-CoV-2 on the surfaces of three meats in the setting that simulates the cold chain transportation. Virol Sin. 2021 Oct;36 (5):1069–1072. doi: 10.1007/s12250-021-00367-x
[120] Dai M, Li H, Yan N, et al. Long-term survival of SARS-CoV-2 on salmon as a source for international transmission. J Infect Dis. 2021 Feb 13;223(3):537–539. doi: 10.1093/infdis/jiaa712
[121] Norouzbeigi S, Yekta R, Vahid-Dastjerdi L, et al. Stability of severe acute respiratory syndrome coronavirus 2 in dairy products. J Food Saf. 2021 Oct;41(5): e12917. doi: 10.1111/jfs.12917.
[122] Abraham JP, Plourde BD, Cheng L. Using heat to kill SARS-CoV-2. Rev Med Virol. 2020 Sep;30(5):e2115. doi: 10.1002/rmv.2115
[123] Kampf G, Todt D, Pfaender S, et al. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020 Mar;104(3):246–251. Epub 2020 Feb 6. Erratum in: J Hosp Infect. 2020 Jun 17. doi: 10.1016/j.jhin.2020.01.022
[124] Miranda RC, Schaffner DW. Virus risk in the food supply chain. Curr Opin Food Sci. 2019;30:43–48. doi: 10.1016/j.cofs.2018.12.002
[125] Mullis L, Saif LJ, Zhang Y, et al. Stability of bovine coronavirus on lettuce surfaces under household refrigeration conditions. Food Microb. 2012;30 (1):180–186. doi: 10.1016/j.fm.2011.12.009
[126] Blondin-Brosseau M, Harlow J, Doctor T, et al. Examining the persistence of human Coronavirus 229E on fresh produce. Food Microbiol. 2021 Sep;98:103780. doi: 10.1016/j.fm.2021.103780
[127] Anelich LECM, Lues R, Farber JM, et al. SARS-CoV-2 and risk to food safety. Front Nutr. 2020 Nov 2;7:580551. doi: 10.3389/fnut.2020.580551
[128] Haddow AD, Watt TR, Bloomfield HA, et al. Stability of SARS-CoV-2 on produce following a low-dose aerosol exposure. Am J Trop Med Hyg. 2020 Nov;103 (5):2024–2025.
[129] Medema G, Heijnen L, Elsinga G, et al. Presence of SARS-Coronavirus-2 RNA in sewage and correlation with reported COVID-19 prevalence in the early stage of the epidemic in the Netherlands. Environ Sci Technol Lett. 2020;7(7):511–516. doi: 10.1021/acs.estlett.0c00357
[130] Wurtzer S, Marechal V, Mouchel JM, et al. Evaluation of lockdown effect on SARS-CoV-2 dynamics through viral genome quantification in waste water, Greater Paris, France, 5 March to 23 April 2020. Euro Surveill. 2020 Dec;25(50):2000776.
[131] Nemudryi A, Nemudraia A, Wiegand T, et al. Temporal detection and phylogenetic assessment of SARS-CoV-2 in municipal wastewater. Cell Rep Med. 2020 Sep 22;1(6):100098. doi: 10.1016/j.xcrm.2020.100098
[132] Ahmed W, Angel N, Edson J, et al. First confirmed detection of SARS-CoV-2 in untreated wastewater in Australia: a proof of concept for the wastewater surveillance of COVID-19 in the community. Sci Total Environ. 2020 Aug 1;728:138764. doi: 10.1016/j.scitotenv.2020.138764
[133] La Rosa G, Iaconelli M, Mancini P, et al. First detection of SARS-CoV-2 in untreated wastewaters in Italy. Sci Total Environ. 2020;20(736):139652. doi: 10.1016/j.scitotenv.2020.139652
[134] Girón-Navarro R, Linares-Hernández I, Castillo-Suárez LA. The impact of coronavirus SARS-CoV-2 (COVID-19) in water: potential risks. Environ Sci Pollut Res Int. 2021 Oct;28(38):52651–52674. doi: 10.1007/s11356-021-16024-5
[135] Buonerba A, Corpuz MVA, Ballesteros F, et al. Coronavirus in water media: analysis, fate, disinfection and epidemiological applications. J Hazard Mater. 2021 Aug 5;415:125580. doi: 10.1016/j.jhazmat.2021.125580
[136] García-Ávila F, Valdiviezo-Gonzales L, Cadme-Galabay M, et al. Considerations on water quality and the use of chlorine in times of SARS-CoV-2 (COVID-19) pandemic in the community. Case Stud Chem Environ Eng. 2020;2:100049. doi: 10.1016/j.cscee.2020.100049
[137] Hatanaka N, Xu B, Yasugi M, et al. Chlorine dioxide is a more potent antiviral agent against SARS-CoV-2 than sodium hypochlorite. J Hosp Infect. 2021 Dec;118:20–26.
[138] He HJ, Zhang W, Liang J, et al. Etiology and genetic evolution of canine coronavirus circulating in five provinces of China, during 2018-2019. Microb Pathog. 2020;145:104209. doi: 10.1016/j.micpath.2020.104209
[139] Nemoto M, Schofield W, Cullinane A. The first detection of equine coronavirus in adult horses and foals in Ireland. Viruses. 2019 Oct 14;11(10):946. doi: 10.3390/v11100946
[140] Cimolai N. Features of enteric disease from human coronaviruses: implications for COVID-19. J Med Virol. 2020 Oct;92(10):1834–1844. doi: 10.1002/jmv.26066
[141] Guo M, Tao W, Flavell RA, et al. Potential intestinal infection and faecal-oral transmission of SARS-CoV-2. Nat Rev Gastroenterol Hepatol. 2021 Apr;18 (4):269–283. doi: 10.1038/s41575-021-00416-6
[142] Gallagher TM, Buchmeier MJ. Coronavirus spike proteins in viral entry and pathogenesis. Virology. 2001 Jan 20;279(2):371–374. doi: 10.1006/viro.2000.0757
[143] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020 Apr 16;181(2):271–280.e8. doi: 10.1016/j.cell.2020.02.052
[144] Bein A, Kim S, Goyal G, et al. Enteric coronavirus infection and treatment modeled with an immunocompetent human intestine-on-A-Chip. Front Pharmacol. 2021 Oct 25;12:718484. doi: 10.3389/fphar.2021.718484
[145] Matsuyama S, Nao N, Shirato K, et al. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Acad Sci U S A. 2020 Mar 31;117(13):7001–7003. doi: 10.1073/pnas.2002589117
[146] Zang R, Gomez Castro MF, McCune BT, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol. 2020 May 13;5(47):eabc3582. doi: 10.1126/sciimmunol.abc3582
[147] Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science. 2020 Jul 3;369(6499):50–54. doi: 10.1126/science.abc1669
[148] Lee JJ, Kopetz S, Vilar E, et al. Relative abundance of SARS-CoV-2 entry genes in the enterocytes of the lower gastrointestinal tract. Genes (Basel). 2020;11 (6):645. doi: 10.3390/genes11060645
[149] Chan PK, To KF, Lo AW, et al. Persistent infection of SARS coronavirus in colonic cells in vitro. J Med Virol. 2004 Sep;74(1):1–7. doi: 10.1002/jmv.20138
[150] Zhang J, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. J Med Virol. 2020 Jun;92(6):680–682. doi: 10.1002/jmv.25742

[151] Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Lancet Gastroenterol Hepatol. 2020 Apr;5(4):335–337. doi: 10.1016/S2468-1253(20)30048-0
[152] Lan FY, Filler R, Mathew S, et al. COVID-19 symptoms predictive of healthcare workers' SARS-CoV-2 PCR results. PLoS One. 2020;15:e0235460. doi: 10.1371/journal.pone.0235460
[153] Villapol S. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res. 2020 Dec;226:57–69. doi: 10.1016/j.trsl.2020.08.004
[154] Yantiss RK, Qin L, He B, et al. Intestinal abnormalities in patients with SARS-CoV-2 infection: histopathologic changes reflect mechanisms of disease. Am J Surg Pathol. 2022 Jan 1;46(1):89–96. doi: 10.1097/PAS.0000000000001755
[155] Sencio V, Machelart A, Robil C, et al. Alteration of the gut microbiota following SARS-CoV-2 infection correlates with disease severity in hamsters. Gut Microbes. 2022;14(1):2018900. doi: 10.1080/19490976.2021.2018900
[156] Xiao F, Sun J, Xu Y, et al. Infectious SARS-CoV-2 in feces of patient with severe COVID-19. Emerg Infect Dis. 2020 Aug;26(8):1920–1922.
[157] Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020 Jul;5(7):667–678. Epub 2020 May 12. Erratum in: Lancet Gastroenterol Hepatol. 2020 Jul;5(7):e6. doi: 10.1016/S2468-1253(20)30126-6
[158] Lei HY, Ding YH, Nie K, et al. Potential effects of SARS-CoV-2 on the gastrointestinal tract and liver. Biomed Pharmacother. 2021 Jan;133:111064.
[159] Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology. 2020 Jul;159(1):81–95. doi: 10.1053/j.gastro.2020.03.065
[160] Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;323:1843–1844. doi: 10.1001/jama.2020.3786
[161] Zhang Y, Chen C, Zhu S, et al. Isolation of 2019-nCov from a stool specimen of a laboratory-confirmed case of the Coronavirus Disease 2019 (COVID-19). Chin CDC Weekly. 2020 Feb 21;2(8):123–124. doi: 10.46234/ccdcw2020.033
[162] Zhou J, Li C, Liu X, et al. Infection of bat and human intestinal organoids by SARS-CoV-2. Nat Med. 2020;26:1077–1083. doi: 10.1038/s41591-020-0912-6
[163] Dergham J, Delerce J, Bedotto M, et al. Isolation of viable SARS-CoV-2 virus from feces of an immunocompromised patient suggesting a possible fecal mode of transmission. J Clin Med. 2021;10(12):2696. doi: 10.3390/jcm10122696
[164] Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020 May;581(7809):465–469. Epub 2020 Apr 1. Erratum in: Nature. 2020 Dec;588(7839):E35. doi: 10.1038/s41586-020-2196-x.
[165] Rothschild N. Does fecal-oral transmission of SARS-CoV-2 due to low sanitation conditions contribute to low mortality rates from COVID-19. Cureus. 2021 Oct 7;13(10):e18557. doi: 10.7759/cureus.18557
[166] Goh GK, Dunker AK, Foster JA, et al. Shell disorder analysis predicts greater resilience of the SARS-CoV-2 (COVID-19) outside the body and in body fluids. Microb Pathog. 2020 Jul;144:104177. doi: 10.1016/j.micpath.2020.104177
[167] Gwenzi W. Leaving no stone unturned in light of the COVID-19 faecal-oral hypothesis? A water, sanitation and hygiene (WASH) perspective targeting low-income countries. Sci Total Environ. 2021 Jan 20;753:141751.
[168] Street R, Malema S, Mahlangeni N, et al. Wastewater surveillance for covid-19: an African perspective. Sci Total Environ. 2020 Nov 15;743:140719. doi: 10.1016/j.scitotenv.2020.140719
[169] da Silva MG, Carniel ADS. Study of the correlation between Covid-19 cases and deaths and basic sanitation in Brazil: is this a possible secondary route of virus transmission? J Hazard Mater Adv. 2022 Nov;8:100149. doi: 10.1016/j.hazadv.2022.100149.
[170] Arslan M, Xu B, Gamal El-Din M. Transmission of SARS-CoV-2 via fecal-oral and aerosols-borne routes: environmental dynamics and implications for wastewater management in underprivileged societies. Sci Total Environ. 2020 Nov 15;743:140709.
[171] Guerrero-Latorre L, Ballesteros I, Villacrés-Granda I, et al. SARS-CoV-2 in river water: implications in low sanitation countries. Sci Total Environ. 2020;743. doi: 10.1016/j.scitotenv.2020.140832