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Transmission mode associated with coronavirus disease 2019: a review

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Abstract. – **OBJECTIVE:** In late December 2019 in Wuhan (China), Health Commission reported a cluster of pneumonia cases of unknown etiology, subsequently isolated and named Severe Acute Respiratory Syndrome (SARS) Coronavirus 2 (CoV-2). In this review, the main transmission routes and causes of mortality associated with COVID-19 were investigated.

MATERIAL AND METHODS: A review was carried out to recognize relevant research available until 10 April 2020.

RESULTS: The main transmission routes of COVID-19 have been the following: animal to human and human-to-human pathways, namely: respiratory transmission; oro-fecal transmission; air, surface-human transmission. Transmission from asymptomatic persons, healthcare transmission, and interfamily transmission have been well documented.

CONCLUSIONS: SARS-CoV-2 possesses powerful pathogenicity and transmissibility. It is presumed to spread primarily via respiratory droplets and close contact. The most probable transmission pathway is definitely the inter-human one. Asymptomatic patients seem to play a crucial role in spreading the infection. Because of COVID-19 infection pandemic potential, careful surveillance is essential to monitor its future host adaptation, viral evolution, infectivity, transmissibility, and pathogenicity in order to gain an effective vaccine and flock immunity and reduce mortality as soon and as much as it is possible.

Key Words:
SARS-COV-2, Transmission, COVID-19.

Introduction

On December 31, 2019, the Wuhan (China) Municipal Health Commission reported a cluster of pneumonia cases of unknown etiology in the town of Wuhan, in Hubei (China), to the World Health Organization (WHO)[1,2].

On 9th January 2020, the causative agent of this mysterious pneumonia was identified as a novel Coronavirus. This causative virus has been called Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), and the correlated infective disease has been named as COronaVIrus Disease 2019 (COVID-19)[3].

Previously, the same family of Coronavirus had been the cause of epidemics characterized by Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)[4].

This is the third highly infective diffusive human Coronavirus that has happened in the last two decades[5].

On March 11th, 2020, WHO declared the SARS-CoV-2 infection to be a pandemic, with 159 countries involved[6].

However, in the following month (January), thousands of people in China, including many provinces (such as Hubei, Zhejiang, Guangdong, Henan, Hunan, etc.) and cities (Beijing and Shanghai) were attacked by the rampant spreading of the disease[7].

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Furthermore, the disease spread to other countries, such as Thailand, Japan, the Republic of Korea, Vietnam, Germany, the United States, and Singapore.

The SARS-CoV-2 is a β-coronavirus, an enveloped, non-segmented positive-sense RNA virus (subgenus sarbe-covirus, Orthocoronavirinae subfamily)[8].

Coronaviruses (CoVs) are divided into four genera, including α-/β-/γ-/δ-CoV. α-CoV and β-CoV can infect mammals, while γ-CoV and δ-CoV tend to infect birds[9]. Previously, six CoVs have been identified as human-susceptible viruses, among which α-CoVs HCoV-229E and HCoV-NL63 and β-CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, causing mild respiratory symptoms similar to a common cold, respectively. The other two known β-CoVs, SARS-CoV and MERS-CoV, cause severe and potentially fatal respiratory tract infections. It was found that the genome sequence of SARS-CoV-2 is 96.2% identical to a bat CoV, RaTG13, whereas it shares 79.5% identity with SARS-CoV-2[10]. Based on virus genome sequencing results and evolutionary analysis, the bats have been thought to be natural hosts of virus origin, and SARS-CoV-2 might be transmitted from bats *via* unknown intermediate hosts to infect humans[11,12].

Shortly, worldwide, all researchers have been trying to find out the virus transmission pathways to humans, as well as its pathogenicity and evolution, to ascertain death causes in its most serious cases[13].

Recently, it has been clarified that SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV, to infect humans[14].

Person to person transmission has been described both in hospital and family settings, facilitating its spread *via* droplets, contaminated hands or surfaces, and even by feces[5].

Current estimates for the mean or median incubation period range from 4 to 6 days, comparable to SARS-CoV (4.4 days) and MERS-CoV (5.5 days worldwide)[15].

Transmission of Coronavirus from contaminated dry surfaces has been postulated, including self- inoculation of the mucous membrane of the nose, eyes, or mouth, pointing out the importance of a full understanding of CoV persistence on inanimate surfaces[16].

The aim of this review is to analyze the modalities of transmission of SARS-CoV-2 infection.

Materials and Methods

This systematic review was carried out in accordance with the PRISMA statement.

Literature Search

SCOPUS and Medline (using PubMed as the search engine) databases were searched in order to recognize relevant research available until 20 April to examine the modalities of transmission and the causes of mortality associated with SARS-COV-2 infection.

MeSH term was using the entry terms: "SARS-CoV-2" AND "transmission"; "SARS-CoV-2"; "COVID-19".

A search of the research articles that were suitable for inclusion in this narrative review was carried out as well, and the research papers of significance therein were collected and reviewed.

Inclusion and Exclusion Criteria

The following inclusion criteria were adopted: studies that assessed the SARS-CoV-2 in relationship with the transmission. The following exclusion criteria were applied: scientific articles that were not published in the English language and/or conference abstracts and/or review.

For duplicate studies, the only article with further detailed information was included.

Quality Assessment and Data Extraction

Two reviewers (F.V. and P.S.) evaluated articles independently. The title, abstract, and full text of each potentially pertinent study was reviewed. Any divergence on the eligibility of the studies was determined throughout debate or by consulting an additional reviewer (C.L.). The following information was extracted from all qualified papers: authors, year of publication, the nationality of subjects, and study characteristics.

Results

Characteristics of Eligible Studies

After a free search for scientific literature by reviewers, a total of 506 (100%) documents were collected. 78 (15%) were ruled out because reviews, 359 (71%) were only abstracts, and 12 (3%) studies were disqualified after subsequent analysis of the title. 27 (5%) of these records were ruled out because not in English. In conclusion, 30 (6%) studies met the inclusion criteria and were included in

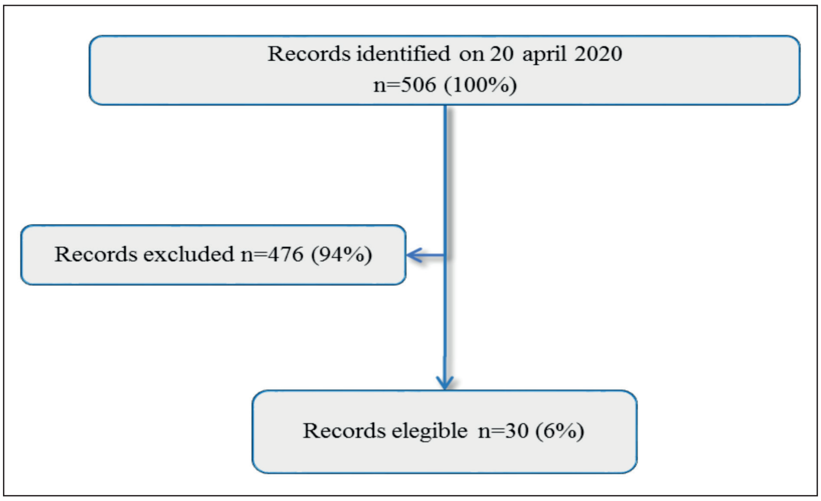

Figure 1. Flow diagram illustrating in/excluded studies in this review.

the systematic review. In flowchart is shown the description of the choice of the articles (Figure 1).

Currently, few studies exist which define the pathophysiological characteristics of COVID-19, and there is considerable uncertainty as to its spread mechanisms.

The main transmission routes were analyzed: a) from animal to human; b) human-to-human and in particular: I) respiratory transmission; II) oral-fecal transmission; III) asymptomatic patients transmission; IV) healthcare worker (HCW)-patients transmission; V) mother-to-child, in the uterus transmission; VI) children-adult transmission; c) air, surface-human transmission. A summary of the details of the included research articles is reported in Table I.

Animal-Human Transmission

The initial outbreak of this pandemic infection was reported to be Huanan Seafood wholesale Market in Wuhan, in December 2019 and involved about 66% of the staff there. The market was shut down on January 1st 2020, after the announcement of an epidemiologic alert by the local health authority on December 31st 2019[13].

Several studies have been examined regarding transmission modalities; however, it remains rather uncertain as to how SARS-CoV-2 spreads. Figure 2 shows a graphic image of what results from this paper concerning how this virus is transmitted to humans through various pathways.

Hussin et al[17] stated that the zoonotic origin should be certain. Based on a big number of infected people that were exposed to the wet animal market in Wuhan City, China, where live animals are routinely sold, it is suggested that this is the likely zoonotic origin of the COVID-19[17].

Efforts have been made to search for a reservoir host or intermediate carriers from which the infection may have spread to humans. Initial reports identified two species of snakes that could be a possible reservoir of COVID-19[17]. Nevertheless, to date, there has been no consistent evidence of CoV reservoirs other than mammals and birds[18,19].

We still do not know the animal involved even though, according to Lu et al[20] and Wan et al[21], genomic sequence analysis of COVID-19 showed 88% identity with two bat-derived SARS-like Coronaviruses indicating that mammals were the most likely link between COVID-19 and humans[20,21].

Person-To-Person Transmission

Doubtlessly, the most probable transmission pathway seems to be the interhuman one[22]. Today's knowledge is largely derived from similar CoVs, which are transmitted from human-to-human through respiratory fomites[23]. SARS-CoV-2 is powerfully pathogenic and transmissible[23-26]. This is supported by proofs of cases that occurred within families and among people who had not visited the live animal market in Wuhan[24-26].

Respiratory viruses are generally most contagious when symptoms are noticeable in patients. Furthermore, there is an increasing body of evidence suggesting that human-to-human transmission may occur during COVID-19 asymptomatic incubation period, which has been estimated to last from 2 through 10 days[23-27]. As a proof of this, symptomatic fever occurs only in 43.8% of patients at the early stages of the SARS-CoV-2 infection[23-28].

Table I. Transmission pathways associated with COVID-19 infection.

Reference	Geographic area	Transmission mode reported	Population of study/ materials examined	RNA-CoV-2 research
Yeo et al[51]	Wuhan (China)	Faecal-oral	2–10% of patients with COVID-19	SARS-CoV-2 RNA in the stool
Holshue et al[47]	USA	Faecal-oral	First patient in USA	SARS-CoV-2 RNA in the stool - qRT-PCR
Wang et al[48]	Wuhan (China)	Faecal-oral; Animal-human; Healthcare-patients	138 patients hospitalized	qRT-PCR and sequencing in the nasopharyngeal and oropharyngeal sample
Chen et al[49]	Wuhan (China)	Faecal-oral	99 patient with 2019-nCoV pneumonia	RT-PCR in the throat-swab specimens
Xiao et al[55]	Wuhan (China)	Faecal-oral	73 patients	qRT-PCR in the serum, nasopharyngeal and oropharyngeal swabs, urine, stool and tissues
Lu et al[20]	Wuhan (China)	Animal-human; Person-to-person	9 patients	Sanger sequencing from bronchoalveolar lavage fluid and cultured isolates
Hussin et al[17]	Wuhan (China)	Animal-human	large number of infected people that were exposed to the wet animal market	Genomic sequence analysis and RT-PCR in the sputum
Bassetti et al[18]	Italy	Animal-human	41 patients	RT-PCR in the lower respiratory tract
Li et al[23]	Wuhan (China)	Person-to-person	First 425 confirmed cases	isolation of 2019-nCoV,RT-PCR, a genetic sequence in the respiratory specimens
Deng et al[43]	China	Respiratory	3 macaques	RT-PCR in conjunctival swabs samples
Cai et al[22]	Wenzhou (China)	Respiratory	Cases associated with a shopping mall in Wenzhou	RT-PCR in the throat-swab specimens
Cohen et al[56]	Thailand	Asymptomatic patients	Asymptomatic patients	n.r.
Rothe et al[60]	Germany	Asymptomatic patients	4 patients	qRT-PCR in the sputum
He et al[58]	China	Person-to-person	77 infector-infected transmission pairs	RT-PCR in throat swabs

Continued

Table I (continued). Transmission pathways associated with COVID-19 infection.

Reference	Geographic area	Transmission mode reported	Population of study/ materials examined	RNA-CoV-2 research
Zou et al[33]	Zhuhai (China)	Asymptomatic patients	18 patients in Zhuhai	Viral load in upper respiratory specimens
Li et al[27]	Wuhan (China)	Asymptomatic patients	Dynamic metapopulation model among 375 Chinese cities	n.r.
Chen et al[63]	China	Asymptomatic patients	A 46-year-old woman	RT-PCR in the oropharyngeal swab
Chan et al[5]	Shenzhen (China)	Person-to-person; Respiratory; Healthcare-patients; Children-adult	6 patients	RT-PCR and sequencing in the nasopharyngeal or throat swabs
Li et al[69]	Wuhan (China)	Healthcare-patients	80 healthcare workers and patients	n.r.
To et al[67]	UK	Healthcare-patients	451 staff members	RT-PCR in the nasopharyngeal swabs
Wei et al[77]	China (China)	From mother to child	9 hospitalized infants	n.r.
Hong et al[76]	Wuhan (China)	From mother to child	10 neonates (including 2 twins) born to 9 mothers with SARS-CoV2	RT-PCR in the throat swabs
Zeng et al[79]	Wuhan (China)	From mother to child	6 pregnants and their newborns	RT-PCR in the throatswabs, test for IgG and IgM antibodies
Dong et al[81]	Wuhan (China)	From mother to child	A 29-year-old primiparous woman and her newborn	RT-PCR in the nasopharyngeal swabs an tests for IgG and IgM antibodies
Zeng et al[82]	Shanghai (China)	Children-adult	First pediatric case	Positive for SARS-CoV-2 by nasal and throat swabs
Cao et al[86]	Shanghai (China)	Children-adult	Afamilial cluster (3 patients)	Positive for SARS-CoV-2 by nasal and throat swabs
Ong et al[89]	Singapore	Air, Surface-human	3 patients	RT-PCR in the respiratory sample and in the stool
Otter et al[16]	UK	Air, Surface-human; Healthcare-patients	Healthcare settings	PCR or fluorescence or haemagglutinin assays
Dowell et al[90]	USA	Air, Surface-human; Healthcare-patients	Hospital Surfaces, Healthcare of two Hospital (A and B)	RT-PCR in swab samples of respiratory secretions
van Doremalen et al[45]	USA	Air, Surface-human	SARS-CoV-2 and SARS-CoV-1 aerosols, plastic, stainless steel, copper, and cardboard.	n.r.

n.r.=not reported

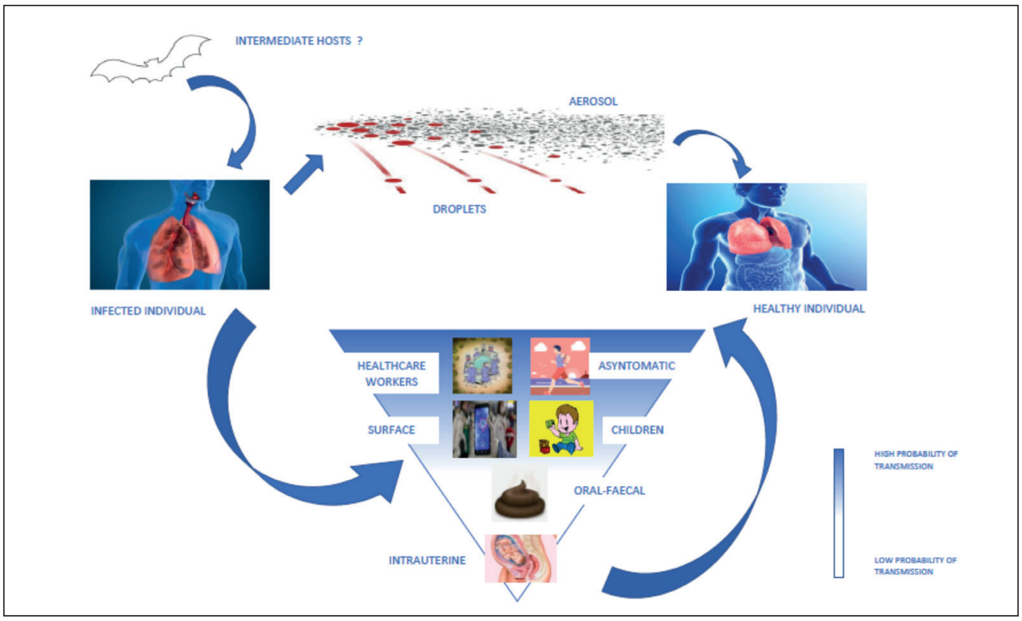

Figure 2. Transmission pathways of COVID-19 infection.

SARS-CoV-2 has a strong pathogenicity and transmissibility, being more infectious than SARS-CoV and MERS-CoV[29].

Close contact of a possible or confirmed case is classified as: a person living in the same household as a COVID-19 patient; a person having had direct physical contact with a COVID-19 patient (e.g., shaking hands); a person having unprotected direct contact with infectious secretions of a COVID-19 patient (e.g., being coughed on, touching used paper tissues with a bare hand); a person having had face-to-face contact with a COVID-19 patient within 2 meters and > 15 minutes; a person who has been in closed places (e.g., classroom, meeting room, hospital waiting room, etc.) with a COVID-19 patient for 15 minutes or more and at a distance of less than 2 meters; a healthcare worker (HCW) or other person providing direct care to a COVID-19 patient, or laboratory workers handling specimens from a COVID-19 patient without recommended personal protective equipment (PPE) or with a possible breach of their PPE; a contact in an aircraft sitting within two seats (in any direction) from a COVID-19 patient, travel companions or persons providing care, and crew members serving in the section of the aircraft where the index case was seated (if severity of symptoms or movement of the patient signal more extensive exposure, passengers seated in the entire section or all passengers on the aircraft may be considered close contacts)[30].

Encountering a COVID-19 case and being near for 15 or 50 seconds is not the only cause of infection, though it is the most likely route in the two cases above. Moreover, being infected after a very short exposure is possible if no mask is worn[31]. The powerful infectivity of SARS-CoV-2 may be inferred by the latest conclusions reported by Wrapp et al[32] who showed that the SARS-CoV-2 binds to ACE2 receptors with a higher affinity than SARS-CoV[32]. Another underlying reason was reported by Zou et al[33], in that the shedding pattern of viral nucleic acid in COVD-19 patients was similar to that of patients with influenza and seemed different than that of SARS-CoV infected patients[33,34].

The level and duration of virus replication are important factors in evaluating transmission risks and helping decision-making in treatment and quarantine[35]. According to Zhou et al[14], the median duration of viral shedding was 20 days from illness onset, but the SARS-CoV-s was always detectable until death in non-survivors. The shortest detected duration of viral shedding in survivors was 8 days, whereas the longest was 37 days[14]. Longer viral shedding also means longer treatment and quarantine times[14].

SARS-CoV-2 frequently causes cluster transmission, i.e., family and workplace. In some cities, the cases involving cluster transmission accounted for 50% to 80% of all COVID-19 confirmed cases[36,37].

Human-to-human transmission of SARS-CoV and MERS-CoV occurred mainly through hospital transmission, while among family members only in 13% to 21% of MERS cases and 22% to 39% of SARS cases[11].

As stated by Riou et al[38], early human-to-human transmission of 2019-nCoV was characterized by R0 values around 2.2 (median value, with 90% high density interval: 1.4-3.8)[38].

Lauer et al[39] observed that COVID-19 average incubation period is 5.1 days and it is expected that nearly all infected people who have symptoms will do so within 12 days of infection. The present period of active monitoring (14 days) is well supported by evidence.

Respiratory Transmission

Novel Coronavirus pneumonia broke out from Wuhan and has spread to the whole nation and worldwide since December 2019. The fight to the virus has come to its critical stage. Previous epidemiological investigations and animal experiments suggested that aerosol could act as a virus transmitter[40]. According to Cai et al[22], SARS-CoV-2 is presumed to spread primarily *via* respiratory droplets and close contact[22]. Contagion can occur through droplets, especially if they are located in the so-called "expiratory cone", i.e., in front of or in the immediate vicinity of the patient. The estimated spreading distance appears to be about one meter. It seems possible that an aerosol-mediated transmission exists (particles <5 nm) since the particles would remain in the air longer than the droplets[41,42].

Touching the mouth, nose, and eyes after contact with virus-contaminated materials and other infectious items may lead to COVID-19 transmission[43].

However, aerosol transmission cannot be ruled out tout-court either, although the information available to date is still somewhat unreliable[24,43,44].

There is a possibility of airborne transmission when exposed to high concentrations of aerosolized virus in a relatively closed environment for an extended time[45].

The virus aerosol, the Wuhan scientists concluded, is a potential transmission pathway. Since aerosols can come directly from patients as well as from stirring up droplets that landed on surfaces, effective sanitization is critical in minimizing aerosol transmission of SARS-CoV-2. The continuous use of appropriate personal protective equipment (PPE) guarantees its availability and healthcare provider safety[46].

Oral-Fecal Transmission

Holshue et al[47] detected SARS-CoV-2 RNA has been detected in the stool of a patient in the USA. This could be extremely dangerous, especially in areas with poor sanitation[47].

In early reports from Wuhan, 2-10% of COVID-19 patients had gastrointestinal symptoms, such as diarrhea, abdominal pain, and vomiting[48,49].

Abdominal pain was recognized more frequently in patients admitted to the intensive care unit (ICU) than in individuals who did not require ICU care, and 10% of patients presented diarrhea and nausea 1-2 days before the fever and respiratory illness[48].

The mechanisms by which SARS-CoV-2 interacts with the gastrointestinal tract is unknown. SARS-CoV-2 is thought to use ACE2 as a viral receptor, and ACE2 mRNA is highly expressed in the digestive system[50].

These findings support a possible role of fecal-oral transmission and suggest the need for increased control measures in particular during the convalescence period of infected patients[51].

Xiao et al[52] showed that SARS-CoV-2 can be found in feces, thus stool samples can contain the virus even when it is no detectable in the respiratory tract; therefore, the fecal-oral route of transmission is possible. Furthermore, the occurrence of gastrointestinal symptoms, in particular diarrhea, in COVID-19 positive subjects can contribute to spreading the virus[52].

Additionally, Wu et al[53] have shown that SARS-CoV-2 viral RNA may be present in fecal samples for nearly 5 weeks after the patients' respiratory samples tested negative for this virus[53].

The possibility of fecal-oral transmission of SARS-CoV-2 has implications, especially in areas with poor sanitation. CoVs are susceptible to antiseptics containing ethanol and disinfectants containing chlorine or bleach[54]. Severe precautions must be detected when handling the stools of patients infected with CoVs, and sewage from hospitals should also be accurately disinfected. The significance of frequent and appropriate hand hygiene should be emphasized[51,55].

Asymptomatic Patients Transmission

Among CoV's most worrying aspects, as emerged from several studies[27,28,33,34,56,57], the virus is also transmitted by asymptomatic patients.

The estimate of the prevalence and contagiousness of undocumented new SARS-CoV-2 infections is serious for understanding the general prevalence and pandemic probable of this disease.

He et al[58] revealed that the proportion of transmission before symptom onset was 44%, and the infectiousness declined moderately rapidly within 7 days of illness beginning. Viral load data were not used in the valuation but showed comparable monotonic decreasing patterns, subsequently symptom onset[58]. However, He et al[58] also demonstrated that viral shedding might begin 2-3 days before showing first symptoms. These results showed asymptomatic and pre-symptomatic transmission[58].

Asymptomatic infections may happen due to weakened immune responses and subclinical indicators, or since the virus is waiting for opportunities to reproduce and spread[34]. Understanding its mechanism necessitates additional investigation of asymptomatic patients, as well as blood tests pointing to signs of an immune response, which can help identify asymptomatic or pre-symptomatic cases[56]. This phenomenon suggests whether asymptomatic patients were really infected without showing symptoms. Whether asymptomatic people can transmit SARS-CoV-2 to others is unclear[34]. Guan et al[28] indicate that 56.2 % of patients have not fevered at the early stages of the SARS-CoV-2 infection.

The 6th Guide for COVID-19[59] reported that asymptomatic patients might serve as a source of infection[59]. Rothe et al[60] in "The New England Journal of Medicine" (NEJM) first reported a German to be confirmed with COVID-19 after contact with an asymptomatic Chinese patient. Nevertheless, it evicted that the Chinese patient had a fever in Germany and took antipyretics.

Zhou et al[33] in NEJM described that a viral load revealed in an asymptomatic patient was like that detected in symptomatic patients, indicating the potential for transmission in asymptomatic patients.

Li et al[27] reported that 86% of all infections were undocumented prior to travel restrictions starting from January 23rd, 2020[27]. Furthermore, this study stated that undocumented infections were the infection source for 79% of documented cases. These findings explained the rapid geographic spread of SARS-CoV-2 and indicating that to contain this virus will be particularly challenging[27]. Another uncertainty was whether those who are asymptomatic could cause large-scale infections. Consistent with epidemiological data in mainland China, only 1.2% of patients with COVID-19 were asymptomatic[29]. Because of the above causes, such patients will usually not cause large-scale transmissions of SARS-CoV-2[34,61].

Besides patients and asymptomatic carriers, those in convalescence may also be infectious. According to the guideline in China, patients should be isolated until two consecutive SARS-CoV-2 RNA tests of respiratory tract specimens are both negative, with an interval of at least 24 h[62].

Chen et al[63] have studied the case of a patient who, after two weeks, became positive again after two consecutively negative results. The result of the SARS-CoV-2 RNA test likely depends on the viral load of the specimen[63]. Therefore, there could be false negatives on occasion for oropharyngeal or nasopharyngeal swabs tests affected by the place from which the sample was taken, the experience of the operator, and the actual quantity of virus[63].

One of the limitations of this category of test, however, is that it cannot tell whether the virus is dead or alive. It amplifies the genetic material of dead virus fragments and living ones, leading to false positives[64]. Moreover, the respiratory epithelial cell has a half-life of up to three months, and RNA virus in the cell can be detached with PCR testing one to two months after the elimination of the cell[64].

The Bronchoalveolar lavage fluid (BALF) specimen test is considered more accurate but with a higher exposure risk. Combination with the SARS-CoV-2 RNA test and other detective methods, such as a specific antigen, IgM antibody, or the next-generation sequencing, is also conducive to diagnosis[63].

HCW-Patients Transmission

Similar to SARS and MERS and according to Chan et al[65] another critical route of spreading SARS-CoV-2 is hospital-associated transmission and, in particular, through HCWs.

As of February 11th 2020, 3019 HCWs might have been infected with 2019-nCov in China, 1716 HCW cases were confirmed by nucleic acid testing[12], and at least 6 HCWs died, including the famous whistleblower Dr. Li Wenliang[12].

Transmission among HCW staff occurred in 3.8% of COVID-19 patients, issued by the National Health Commission of China on February 14th 2020. Hospital-associated transmission is a critical route of spreading of 2019 novel CoV infection and pneumonia[5].

In Italy, the number of infected HCWs amounts now to 10% of the total; up to April 9th, the overall number of deceased white-coats was 105[66].

The nature of work performed by healthcare professionals means that they are at increased risk of COVID-19 infection, especially those working in the frontline, and can also transmit the infection to vulnerable patients[67].

HCWs are at high risk while reducing COVID-19 on the very frontline, and nosocomial outbreaks among HCWs are not unusual in similar settings. In view of this difficult situation, the central institutional health bodies in the various countries are recommending urgent interventions to help protect HCWs[12].

A few reasons led to a more severe situation than expected among HCWs[12]. Firstly, many infected individuals showed atypical symptoms, such as gastrointestinal symptoms and fatigue, or were asymptomatic[68]. This situation may have led to a lack of recognition of the infection, while patients were highly contagious[68].

Furthermore, HCWs were not well-prepared for this sudden CoV outbreak, especially in infectious diseases' departments[69]. It was noticed that for HCWs there was no awareness of taking precautions and inadequate training incorrectly wearing personal protective equipment (PPE)[12]. Also, pressure of treatment, work intensity, and lack of rest indirectly increased the probability of infection for HCWs[70,71].

Especially in the early stages, this emergency condition has been much underestimated by many, including HCWs. Hospitals in Europe (i.e., Italy and Spain) were not ready for it: in the same waiting room, infected as well as healthy patients were gathered. This made hospitals the most favorable milieus for the spreading of the virus[5]. Incidentally, the centralized climatization system contributed a lot negatively, as it had no High-Efficiency Particulate Air (HEPA) filters, which might have worked as barriers to the infection[72].

It seems to be of great importance to set up intense education programs, spread information about contagion pathways and use general and PPEs by adopting safety procedures in accordance with internationally recognized organizations' guidelines, preventing accidents and/or inconveniences to patients[73]. In order for these education programs to effectively reach the HCWs, they should be put among hospitals' strategic objectives by their management[73].

From March 24th 2020, Italy's High Health Institute (ISS), in cooperation with the National Guarantor of Rights of convicts or people deprived of freedom, started up a "National Survey on COVID-19 contagion in residential and socio-sanitary facilities" in order to monitor the situation and adopt all reinforcement strategies of programs, as well as of prevention and control fundamentals of healthcare-related infections (ICA). This survey consisted of filling in a questionnaire to acquire information on how to handle any suspect/confirmed novel CoV infection cases[30]. This study revealed that 17.3% of HCWs were positive to SARS-CoV-2 and mortality rate among residents, taking into account deaths of patients resulting positive to COVID-19 or with pseudo-influenza symptoms, was 3.1% but went up to 6.8 in the Region of Lombardy[30].

Transplacental Transmission

An important fact is that there is no evidence of transplacental transmission from mother to child. According to Han et al[34], Chen et al[74], Qiao et al[75], all pregnant mothers underwent cesarean sections, so it remains unclear whether transmission can occur during vaginal birth[34,74,75].

Controversy exists regarding whether SARS-CoV-2 can be transmitted in utero from an infected mother to her infant before birth. In a small study conducted on women in their third trimester who were confirmed to be infected with the CoV, there was no evidence that there is the transmission from mother to child; also, in this case, all pregnant mothers underwent cesarean sections[34-76]. However, pregnant mothers were relatively more susceptible to infection by respiratory pathogens and severe pneumonia; therefore, infants might be infected by COVID-19[77].

Wei et al[77] reported nine infants under 1 year of age suffering from COVID-19, the youngest of which was only 56 days old[77].

Recently, Chen et al[74] reported 9 pregnant women confirmed with COVID-19 who all delivered by cesarean section. Neonatal throat swabs, amniotic fluid, cord blood, and breast-milk samples from 6 of these patients were collected, and all samples tested negative for SARS-CoV-2[74]. This suggests that the risk of vertical transmission of SARS-CoV-2 is reduced as no presence of virus particles in the products of conception or in the infants occurred[34,76,78].

Tests for IgG and IgM antibodies for SARS-CoV-2 became available in February 2020. An important study conducted by Zeng et al[79] introduced this new method on 6 pregnant women with established COVID-19 and their infants because serologic standards would tolerate more detailed research of infection in newborns. Blood samples were collected from the mothers at the carriage, and neonatal blood and throat swab samples were collected at birth. Quantitative RT-PCR for SARS-CoV-2 nucleic acid was conducted on newborn serum and throat swabs[79]. All had cesarean deliveries in their third trimester in negative pressure isolation rooms. SARS-CoV-2 was not detected in the serum or throat swab by

RT-PCR in any of their newborns, but the IgG concentrations were raised in 5 infants. IgG is inertly moved across the placenta from mother to fetus, beginning at the end of the second trimester and spreads high concentrations at the time of birth[80]. Nevertheless, IgM, which was noticed in 2 infants, is not usually transferred from mother to fetus because of its more massive macromolecular structure. Whether the placentas of women in this study were damaged and abnormal is indefinite. Otherwise, IgM could have been formed by the infant if the virus crossed the placenta[79].

Dong et al[81] showed that a neonate born to a mother with COVID-19 had higher antibody levels and abnormal cytokine test results 2 h after birth. The higher IgM antibody level recommends that the neonate was infected in utero because IgM antibodies frequently do not appear until 3 to 7 days after infection. Furthermore, the mother's vaginal secretions were negative for SARS-CoV-2[81].

These studies are limited by the small sample size, and controversy remains whether it exists or not a mother to child in the uterus transmission.

Children-Adult Transmission

During the emerging stage of the SARS-CoV-2 outbreak, the infection was disseminated by person-to-person transmission in the community almost exclusively among adults.

Newborn babies, particularly at an early stage, seemed to be spared by the infection. Later, the first cases began to appear[5,82,83].

After this stage, likely after mid-January, 2020, the virus further spread to the family *via* infected adults to cause intrafamilial transmission, especially transmission to the elderly and children, who are vulnerable to the infection. With the progression of the outbreak, the first infant case was reported from Xiaogan, Hubei province[5,84,85].

The first pediatric case outside the Hubei province was reported from Shanghai, China[83], a 7-year-old boy who complained fever for one day. The boy and his father were coming from Wuhan on January 11. His father also developed fever since January 14. The father was admitted to a hospital because of fever and progressive cough and soon was diagnosed as COVID-19 on January 19. Nasal and throat swabs taken were positive for SARS-CoV-2[82-84].

Follow-up testing for SARSCoV-2 on January 24 (day 5) and January 28 (day 9) were still positive but turned negative on January 31 (day 12) and February 1 (day 13). He recovered gradually after supportive treatment. The child's mother, who did not go to Wuhan but came to the hospital to take care of him was tested positive for SARS-CoV-2 by nasal and throat swabs. The mother remained symptomless throughout his admission. The case reported by Cai et al[83] probably was the first evidence indicating children as a source of adult infection. Infected children may be asymptomatic or have fever, dry cough, and fatigue; some patients involvement gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea[83]. Most infected children have insignificant clinical manifestations and typically have a good prognosis. Frequently, they recover within 1-2 weeks after the beginning of the disease[82,84,85].

If the disease should go further extension without being efficiently contained, the outbreak might go into an explosion stage, when the school transmission mixed with a broader community spread could occur[86]. Children at that stage can further become the main spreader of SARS-CoV-2 because their infection is usually mild. At this stage, temporary school closure was considered necessary to contain the spread of the disease. The situation is similar to what we have seen in influenza outbreaks, where school children are vectors for the dissemination of influenza virus either in the household or in the community[86,87].

This is just the reason why one of the first moves the Italian Government made was to shut down schools in order to prevent the infection from spreading.

Though the incidence of critical illness in children is short, the current incidence is adequate to alert pediatricians[88]. It is essential to recognize children with COVID-19, particularly those with underlying/comorbid disease(s), and to treat them early. In summary, special consideration should be dedicated to children because they are a particular group of patients[88]. Through analysis of the epidemiological history of a lesser number of child cases of COVID-19 and a fuller grasp of the epidemiological features of SARS-CoV-2, it will be possible to provide more effective preventive measures and treatment procedures and lay a solid foundation for winning the battle against this epidemic. Serological reports will be helpful to estimate the cumulative incidence of infections[88].

Air, Surface-Human Transmission

A crucial point remains, though: how long does the CoV survive in the environment or on objects? And, most of all, how long is it able to infect?

CoVs have been implicated in nosocomial outbreaks with environmental contamination as a route of transmission. Similarly, the nosocomial transmission of SARS-CoV-2 has been reported[89]. However, the transmission modality and extent of environmental contamination are unknown[89].

Transmission of CoVs from contaminated dry surfaces has been postulated, including self-inoculation of mucous membranes of the nose, eyes, or mouth[16,90], emphasizing the importance of a full understanding of coronavirus persistence on inert surfaces[54].

A study[45] conducted in Wuhan predicted 10 experimental conditions involving two viruses (SARS-CoV-2 and SARS-CoV-1) in 5 environmental conditions (aerosols, plastic, stainless steel, copper and cardboard).

SARS-CoV-2 remained viable in aerosols throughout the duration of this experiment (3 hours), with a reduction in infectious titer from 103.5 to 102.7 TCID50 (Median Tissue Culture Infectious Dose)/liter of air. SARS-CoV-2 was more stable on plastic, and stainless steel than on copper and cardboard and viable virus were detected up to 72 hours after application to these surfaces. However, the virus titer was significantly reduced (from 103.7 to 100.6 TCID50/ml of the medium after 72 hours on plastic and from 103.7 to 100.6 TCID50/ml after 48 hours on stainless steel)[45].

Copper and cardboard turned out as the least hospitable materials, whereas for a total neutralization of infectiveness, 72 hours are necessary unfortunately. The estimated median half-life of SARS-CoV-2 was approximately 5.6 hours on stainless steel and 6.8 hours on plastic[45]. At a temperature of 30°C or more, the length of persistence is shorter[91].

Contamination of recurrent touch surfaces in healthcare settings is, therefore, a potential source of viral transmission[91].

Contamination with respiratory droplets or fecal material of the various surfaces make the environment a potential means for spreading the virus[92].

If we touch contaminated surfaces and, without noticing, bring a hand to the mouth, nose, or eyes, we get infected. Hence the importance of suggestions by the WHO regarding frequent hand and surfaces' washing[30].

The WHO recommends *"to ensure that environmental cleaning and disinfection procedures are followed consistently and correctly. Thoroughly cleaning environmental surfaces with water and detergent and applying commonly used hospital-level disinfectants (such as sodium hypochlorite) are effective and sufficient procedures"*[1].

On different types of materials, COVID-19 can remain infectious from 2 hours up to 9 days, such as on inanimate surfaces like metal, glass or plastic but can be efficiently neutralized through surface disinfection procedures with 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute[91]. The typical use of bleach is at a dilution of 1:100 of 5% sodium hypochlorite resulting in a final concentration of 0.05%[1]. A concentration of 70% ethanol is also recommended by the WHO for disinfecting small surfaces[1].

A higher temperature, such as 30°C or 40°C reduced the duration of persistence[91].

Significant environmental contamination by patients with SARS-CoV-2 through respiratory droplets and fecal shedding suggests the environment as a potential medium of transmission and supports the need for strict adherence to environmental and hand hygiene[89].

Conclusions

The Italian Healthcare System is one of the most well-developed systems globally[35-93]. Despite this, the recent COVID-19 outbreak found the country unprepared to cope with the impact of the COVID-19 pandemic. There have been early responses from institutions, declaring a state of national emergency on January 31st 2020, applying restrictions on public congregations, affecting schools, meetings and sports events, and healthcare limitations in public places[30].

Although WHO issues regular updates about disease transmission and the proper use of PPE, the reality, as noted in the same WHO report, is that such a large-scale outbreak has resulted in a shortage of PPE for healthcare providers[93,94].

Severe measures have already been accepted, including the closure of hospital districts, restricting visitor access to hospitals, identification of external triage areas, dedicated patient transport, and isolation pathways; conclusively, cessation of elective surgery, with the only emergency, trauma and selected oncological surgery measures. In terms of public health, several actions have been implemented, including: the use of telemedicine consultations; domestic isolation of COVID-19 patients who are not severely poorly; production and distribution of instructive videos and television segments, firm restrictions *vs.* public gatherings, school closures, and university closures[95].

Because of the pandemic potential of COVID-19 infection, utmost surveillance is essential to monitor its future host adaptation, viral evolution, infectivity, transmissibility, and pathogenicity, so as to obtain an effective vaccine and flock immunity to drastically reduce its mortality.

The strengths of this study are due to a systematic and rigorous search strategy to retrieve relevant articles according to the research objective.

Despite the little time elapsed from COVID-19 pandemic's beginning up to now, the number of scientific papers has been remarkable, and plenty of real-time information is coming from the most notable world and national health organizations. This made allowed us to give an accurate description of transmission modalities known so far.

The weaknesses of the present study derive from it being only focused on the articles published either in English during the early outbreak period, considering that the pandemic started in China. Although it cannot reflect the entire body of research on COVID-19 worldwide, it will provide some evidence for future study and control.

Current evidence on the transmissibility of COVID-19 has been focused on China mainly; little attention has been paid to European countries. Given the rapid increase of COVID-19 in Europe, it is urgent to understand the mode transmission of COVID-19 to guide the implementation of prioritized prevention and control measures.

If prevention is still a better strategy compared to treatment, probably, we should focus on new strategic approaches to outbreak management[96,97].

Currently, COVID-19 is representing an important challenge for public health, also in consideration of recent Italian spread; however, existing source containment strategy, contact investigation, infection control at health care facilities, as well as in community settings coupled to new approaches based on new mathematical tools to forecast disease spread, could be useful and helpful to activate and improve the strategic plan to control outbreak[96-98].

The outbreak of COVID-19 in Italy is a unique historical event that will need to be investigated more extensively and with more refined methodologies. What is certain is that it is essential to study workers' stigma in the face of pandemics and the training and information provided for HCWs, to ensure adequate levels of satisfaction can be maintained and prevent phenomena such as fatigue and burnout[99].

Conflict of Interests

The authors declared there is no conflict of interest.

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