Evidence summary for the relative importance of droplet versus contact transmission to the spread of SARS-CoV-2

Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

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Key points

- Understanding the relative importance of different modes of transmission is important for informing infection prevention and control (IPC) measures. This review concentrates on the relative importance of droplet versus contact transmission (in other words, direct versus indirect droplet transmission) to the spread of SARS-CoV-2 and other similar enveloped respiratory viruses (that is, other beta-coronaviruses, influenza and respiratory syncytial virus (RSV)).

- Each mode of transmission, and the degree to which it contributes to the overall spread of SARS-CoV-2, has important implications for public health guidance, particularly with regards to healthcare precautions and personal protective equipment (PPE) use.

- This review included six studies with various designs: systematic reviews (n=2), mathematical modelling studies (n=3), and a cross-sectional survey (n=1).

- The methodological quality of all six studies were low or critically low. Two of the included studies are published as pre-prints and have not yet been formally peer-reviewed.

- Two systematic reviews that included a large number of studies examining the transmission of influenza, SARS-CoV-1 and MERS-CoV were unable to ascertain the relative importance of different modes of transmission, but suggested that the relative importance may be context-specific (that is, it may be dependent on host, viral and environmental factors).

- Although the three mathematical modelling studies suggested that person-to-person transmission (that is, any transmission, contact or droplet, which occurs directly between two close individuals) contributed more to the spread of SARS-CoV-2 than environmental transmission (that is, transmission involving contaminated objects or surfaces), these findings are likely biased by the inappropriate data and unclear assumptions used to populate the key model parameters.

- A cross-sectional survey of healthcare workers infected with SARS-CoV-2 reported that the most commonly self-reported, perceived route of infection was droplet transmission. However, the perceived route of infection may differ substantially from the actual route of infection; therefore, a survey without any supporting data from epidemiological investigations is unlikely to provide robust evidence.

- In conclusion, there is currently insufficient evidence to determine the relative importance of droplet versus contact transmission to the spread of SARS-CoV-2 and other similar enveloped respiratory viruses. However, it is likely that the relative importance of these modes of transmission is context-specific.

Evidence summary for the relative importance of droplet versus contact transmission to the spread of SARS-CoV-2

The Health Information and Quality Authority (HIQA) has developed a series of 'Evidence Summaries' to assist the Clinical Expert Advisory Group (EAG) in supporting the National Public Health Emergency Team (NPHET) in their response to COVID-19. These summaries are based on specific research questions. This review was developed to address the following research question:

> **What is the relative importance of droplet versus contact transmission (in other words, direct versus indirect droplet transmission) to the spread of SARS-CoV-2?**

Background

Direct droplet transmission refers to virus transfer from an infected person to a susceptible individual, through droplets generated during coughing, sneezing, breathing or talking. It is characterised by short range transmission (generally less than one metre), direct inoculation of the susceptible person through coughing/sneezing/breathing from the infected person and deposition mainly on mucous membranes and upper respiratory tract.(1) Indirect droplet transmission refers to virus transfer from an infected person to a susceptible individual via contaminated hands or via intermediate objects or surfaces known as fomites (for example, hand rails, mobile phone or door knobs). It is characterised by self-inoculation of mucous membranes by contaminated hands.(1) There are a range of terms relating to these modes of transmission that are used interchangeably in the literature, which can be confusing.(1-4) Direct droplet transmission can also be called droplet transmission. Indirect droplet transmission can also be called contact transmission. Additionally, contact transmission can also be direct, such as via an infected individual's hands, or indirect through the presence of virus particles on fomites.(1, 5) Transmission exclusively through contaminated intermediate objects or surfaces can be referred to as fomite or environmental transmission.(4, 6) Transmission that occurs between two close individuals but can be either via direct or indirect droplets (for instance, shaking hands), but has no involvement of fomites, can also be called human-to-human or person-to-person transmission.(7, 8) For the purpose of clarity, the terms *direct droplet transmission*, *indirect droplet transmission*, *environmental transmission* and *person-to-person transmission* will be used throughout this report, unless there is a need to use the language of included studies.

Aerosol transmission is distinct from direct droplet transmission as it is based on smaller particle size (generally defined as <5 micrometres in diameter),[1] enabling a greater travel distance and the potential to remain suspended in the air for prolonged periods.[1, 5] The potential for aerosol transmission of SARS-CoV-2 is currently subject to much debate,[9] and HIQA has recently reviewed the evidence in a separate evidence summary.[10]

Understanding the relative contribution of each mode of transmission to the spread of SARS-CoV-2 has important public health implications for both the general population and healthcare workers.[1, 11] This information can inform infection prevention and control (IPC) measures, including the relative importance of certain public health interventions (for example, physical distancing versus hand hygiene or environmental decontamination). For instance, physical distancing measures focus on keeping individuals a certain minimum distance away from one another (usually one to two metres) and aim to reduce the risk of direct droplet transmission.[12] Whereas hand hygiene and environmental decontamination measures focus on the cleaning of hands and surfaces, and aim to reduce the risk of indirect droplet transmission.[13] At present, the WHO recommends both contact and droplet precautions when caring for COVID-19 patients.[5] This stance is also reflected in the guidance provided by the Health Protection Surveillance Centre of Ireland[14] and Public Health England.[15] Hence, understanding the relative contribution of direct versus indirect droplet transmission for the spread of SARS-CoV-2 is important for prioritising public health measures to tackle the most probable mode of transmission. Given the recent emergence of SARS-CoV-2, extrapolating data from other enveloped respiratory viruses that have similar virological properties to SARS-CoV-2 (that is, beta-coronaviruses, influenza and respiratory syncytial virus (RSV)), may provide some indirect evidence for the most important mode of transmission.[1]

Methods

The processes as outlined in HIQA's protocol (available at www.hiqa.ie) were followed. Below is a summary of all relevant evidence for the relative importance of direct versus indirect droplet transmission for the spread of SARS-CoV-2 and other similar enveloped respiratory viruses, identified from 1 January 2020 until 12 June 2020.

Results

Of 3,770 citations screened, six studies were included in this review.[4, 6-8, 16, 17] A summary of the included studies is provided in Table 1 (systematic reviews), Table 2 (mathematical modelling studies) and Table 3 (the cross-sectional survey). Two systematic reviews were included that narratively synthesised the relative importance of different modes of transmission for influenza,[4] SARS-CoV-1[4] and

MERS-CoV.[4, 16] Three mathematical modelling studies were included that modelled the contribution of environmental transmission to the overall reproductive number (R_0) (that is, the expected number of secondary cases that one primary case will generate in a susceptible population) of SARS-CoV-2.[6-8] One cross-sectional survey was included that explored the self-reported, perceived route of infection in 105 healthcare workers infected with SARS-CoV-2.[17] The results of this review are presented and summarised by study design. Appendix 1 provides the references of 51 studies identified during the course of this review that did not provide any comparative data to address the research question (and hence were excluded), but provide potential evidence for either direct or indirect droplet transmission.

Methodological quality of included studies

Overall, the methodological quality of all six included studies was low or critically low. The overall confidence in the results of both systematic reviews were critically low, given the lack of protocols,[4, 16] the lack of clear inclusion or exclusion criteria,[16] the lack of independent double screening and data extraction,[4, 16] the lack of an excluded studies list,[4, 16] the lack of quality appraisal of included studies,[4, 16] and the limited discussion of the heterogeneity of findings.[16]All three mathematical modelling studies were of low quality, given critical concerns regarding the unreliability of the data informing key parameters,[6-8] the limited uncertainty analysis undertaken,[7, 8] the use of poorly defined epidemiological data[6-8] and the lack of internal[7] or external[7, 8] model validation. The cross-sectional survey was of low quality, given concerns regarding the lack of a focused research question, the potential for selection bias, the potential limited generalisability, and the lack of sample size calculations undertaken.[17]

Two out of the six studies (33%) included in this review are published as pre-prints,[7, 8] so have not yet been formally peer-reviewed raising additional concerns about overall quality and the potential for results to change prior to formal publication.

Systematic reviews

Dawson et al.[16] conducted a systematic review of MERS-CoV literature relating to four key areas: virology; clinical characteristics, outcomes, therapeutic and preventive options; epidemiology and transmission; and the animal interface and the search for natural hosts of MERS-CoV. The searches were conducted on 14 July 2017. Of 208 studies included in the systematic review, 35 were relevant for the topic of epidemiology and transmission. No quality appraisal was conducted by the authors of this review. The authors concluded that based on the evidence, there is no compelling evidence of direct person-to-person transmission of MERS-CoV, such as through droplets, but secondary infection, such as through environmental contamination, has been reported. The authors concluded that direct contact transmission could only be inferred in about 10% of cases, with the suggestion that indirect contact transmission (that is, environmental transmission), particularly in healthcare settings, may be more important for the spread of MERS-CoV. The MERS-CoV virus has been isolated from environmental samples in hospital rooms, suggesting the potential role of environmental transmission. The authors also concluded that nosocomial transmission due to inadequate infection control is well established as a significant driver of MERS-CoV infections. However, the authors acknowledge the limited number of robust studies conducted investigating the mode of transmission of MERS-CoV, hence key knowledge gaps remain.

Otter et al.[4] conducted a systematic review of the importance of contaminated surfaces in the transmission of influenza and human coronaviruses. The searches were conducted on 22 November 2014 (pre-dating the emergence of SARS-CoV-2). Of 254 studies included in this review, 38 examined virus survival on surfaces, 51 examined environmental transmission, 18 examined surface contamination, and 147 examined disinfection and the impact on transmission. The majority of studies focused on influenza (n=198, 78%) with the remainder focused on coronaviruses (n=56, 22%). No quality appraisal was conducted by the authors of this review. The authors concluded that the surface survival of SARS-CoV-1 and MERS-CoV is greater than that of influenza virus, but that in theory all three of these viruses may cause infection via contaminated surfaces. The authors highlighted that mathematical modelling, intervention trials and animal studies suggest that contact transmission is the most important mode of transmission for influenza specifically, but also that this is context-specific. However, the authors concluded that for influenza, SARS-CoV-1 and MERS-CoV, the relative importance of indirect contact transmission (that is, environmental transmission) compared with other transmission routes, principally direct contact transmission (that is, via contaminated hands), droplet and airborne routes, is still uncertain.

Mathematical modelling studies

Elmojtaba et al.[7] conducted a mathematical modelling study to investigate the contribution of environmental transmission (that is, environment-to-human transmission) compared with person-to-person transmission to the spread of SARS-CoV-2. The data informing epidemiological parameters of the model were based on datasets from the United Kingdom and China, which were both also mathematical modelling studies.[18, 19] Neither of these two studies specifically examined the role of environmental transmission. The data informing the parameters relating to environmental transmission were obtained indirectly from studies modelling cholera transmission.[20, 21] The data relating to the persistence of the virus on surfaces was obtained indirectly from a review of other coronaviruses.[22] Other key parameters (contact rate from contaminated environment, the relative shedding rate of asymptomatic humans to the environment, the minimum concentration of virus in the environment capable of ensuring 50% chance of contracting the disease) were based on assumptions by the authors, which were not explained. The authors estimated that environmental transmission contributed 46% and 28% to the overall reproductive number (R_0) in the Chinese (R_0=6.02) and UK (R_0=5.11) datasets respectively.

Ferretti et al.[(6)] conducted a mathematical modelling study to estimate the contribution of different transmission routes to the spread of SARS-CoV-2. The data informing the epidemiological parameters were obtained from 40 transmission pairs with known dates of symptom onset identified from public sources and based in eight countries (Vietnam, South Korea, Germany, Taiwan, China, Hong Kong, Singapore and Italy). The data informing doubling time and incubation period were obtained from published sources based on the early stages of the epidemic in China and hence the overall R_0 was assumed to be 2.0. The data informing the parameters relating to the environmental transmission were anecdotally-based or obtained indirectly from a review of other coronaviruses.[(22)] The authors considered the single transmission route (environmental) and the three clinical status categories (pre-symptomatic, symptomatic and asymptomatic) to be mutually exclusive. On this basis, the authors estimated that environmental transmission contributed 10% to the overall R_0, although there was a substantial degree of uncertainty around this estimate (95% confidence interval (CI), 2-56%). This was in comparison with 47% (95% CI, 11-58%) contribution from pre-symptomatic transmission, 38% (95% CI, 9-49%) contribution from symptomatic transmission and 6% (95% CI, 0-57%) contribution from asymptomatic transmission. The authors acknowledge that the estimates pertaining to both environmental and asymptomatic transmission are largely speculative, due to the predominantly anecdotal and indirect data informing the parameters for these models.

Ogbunugafor et al.[(8)] conducted a mathematical modelling study to investigate whether variability in environmental transmission could explain differences in SARS-CoV-2 outbreak intensity. The data informing the epidemiological parameters were obtained from publicly available sources for 17 countries that had the largest reported number of COVID-19 cases as of 30 March 2020 (Table 1). The authors found that for 10 of the 17 included countries, the model incorporating elements of environmental transmission provided a better fit for the observed number of cases in the country data, than the model which did not incorporate elements of environmental transmission. The data informing viral decay parameters were obtained directly from a laboratory-based study that examined the stability of SARS-CoV-2 on a variety of materials (copper, plastic, cardboard and stainless steel) and in aerosol.[(23)] The authors acknowledge the limited data to inform many of the parameters and therefore undertook model fitting against the epidemiological data to ascertain certain missing parameters (including, contact rate of a person with the environment, transmission probability of environment to people, probability of shedding by an asymptomatic or symptomatic person to the environment). The proportion of viruses in the environment was assumed to be 1% by the authors, however, it is not clear what data informed this assumption. The overall R_0 was estimated to be 2.82. The R_0 corresponding to person-to-person transmission (R_p) was estimated to 2.33 while the R_0 corresponding to environmental transmission (incorporating two dual transmission stages person-environment and environment-person) (R_e^2) was estimated to be 1.38. Therefore, person-to-person transmission was estimated to infect 1.69 times more people than environmental transmission. Unlike the other two mathematical modelling studies discussed above,(6, 7) Ogbunugafor et al.(8) did not consider person-to-person transmission (R_p) plus environmental transmission (R_e^2) to sum to the overall reproductive number (R_0) (that is, they were not considered mutually exclusive).

The authors also estimated the effect on the overall R_0 by simulating hypothetical scenarios where environments were composed entirely of certain materials or aerosols, using data from a laboratory-based study that tested the stability of SARS-CoV-2 on these surfaces and in aerosols.(23) Of note, the authors considered aerosol as an environmental surface for the purpose of this model. The authors commented that the extent to which transmission can be attributed to the environmental route can differ substantially depending on the environmental reservoir. Based on these hypothetical scenarios, the authors estimated that the proportion of all transmission events (both environmental and person-to-person) occurring through the environmental route were 4.6% for aerosol, 6% for copper, 28% for cardboard, 43% for stainless steel and 52% for plastic (noting that each surface was simulated separately).

Cross-sectional survey

Jin et al.(17) conducted a cross-sectional survey of all 105 confirmed SARS-CoV-2 infected healthcare workers in one hospital in China (Table 2). The survey aimed to explore participants perceived infection routes, influencing factors, psychosocial changes, and management procedures. The questionnaire was electronic, self-administered and was provided to eligible healthcare workers at least two weeks after initial infection. Of 105 eligible participants, 103 completed the questionnaire (98.1% response rate).

One of the survey questions asked participants to rate what they perceived to be the most likely route of their own infection. The survey permitted multiple answers. The following options were provided to participants to choose from: droplet transmission, contact transmission, aerosol transmission, digestive tract transmission, other, or not sure.

The most likely perceived route of transmission was droplet (n=81, 78.6%), followed by contact (n=56, 54.3%), aerosol (n=25, 24.3%), digestive tract (n=8, 7.8%), and not sure (n=14, 13.6%).

Other relevant findings from this survey were that 87 participants (84.5%) believed that they acquired the infection in the hospital environment. The majority of participants (n=71, 68.9%) worked in departments considered at low risk of nosocomial infection. Eighty respondents (77.7%) reported always following hand hygiene, and 68 participants (66%) reported always wearing a mask during their routine clinical work, prior to becoming infected with COVID-19. Notably, previous experience in dealing with epidemics such as SARS was very low, with only five participants reporting any such experience (4.9%).

Discussion

In summary, the methodological quality of all six included studies was low or critically low. Two systematic reviews that included a large number of studies examining the transmission of influenza, SARS-CoV-1 and MERS-CoV were unable to ascertain the relative importance of different modes of transmission. No relevant systematic review was found for RSV. Although the synthesised evidence would appear to suggest an important role for environmental transmission, particularly in healthcare settings in the case of MERS-CoV,(16) the overall contribution to the spread may be context-specific (that is, it may be dependent on host, viral and environmental factors)(2) and difficult to quantify. Three mathematical modelling studies suggest that person-to-person transmission contributes more to the spread of SARS-CoV-2 than environmental transmission,(6-8) however, these findings are likely biased by the inappropriate data and unclear assumptions that were used to populate the key model parameters. In particular, the assumptions that environmental transmission and the clinical status of patients (that is, pre-symptomatic, asymptomatic or symptomatic) are mutually exclusive,(6) or that the various routes of transmission are mutually exclusive,(7) do not appear plausible. One of these studies suggested that the importance of environmental transmission can vary from setting to setting.(8) Although this finding involved entirely hypothetical simulations, it is plausible that, in reality, the importance of environmental transmission to the overall spread of the virus, can depend on the context. None of the mathematical modelling studies differentiated between direct droplet transmission and indirect droplet transmission that occurs between two people (that is, the spread of the virus through contaminated hands). These modelling studies should be viewed as tests of hypothetical plausibility rather than hypothesis confirming, and hence their findings should be interpreted with caution. Finally, a cross-sectional survey of healthcare workers infected with SARS-CoV-2 in a hospital in China reported that the most commonly self-reported, perceived route of transmission was via droplets. However, the responses may be biased by participants knowledge regarding the most common routes of transmission (that is, healthcare workers are likely to have some baseline understanding of how the virus spreads, and may assume that this is how they got infected), by recall bias (that is, respondents may have forgotten the circumstances surrounding exposure to the virus) and by social desirability (that is, respondents may not be likely to admit infection through contaminated hands or environments). Furthermore, peoples' perceptions of how they became infected may differ substantially from how they actually became infected. As no supporting data from epidemiological investigations were provided to verify these findings, it is important that these findings are interpreted with caution.

Based on the totality of the evidence, it is currently not possible to determine with any degree of certainty, the relative importance of direct versus indirect droplet transmission to the spread of SARS-CoV-2. Given the recent emergence of SARS-CoV-2, systematic reviews examining modes of transmission for similar enveloped respiratory viruses (influenza, SARS-CoV-1 and MERS-CoV), were also included as inferences may possibly be extrapolated to the transmission of SARS-CoV-2. However, despite years of research, dating back to the 1940s for influenza,(24) there is still substantial uncertainty regarding the relative importance of different modes of transmission to the spread of these viruses.(4, 16) The World Health Organization (WHO) updated their scientific brief on 9 July 2020 regarding the transmission of SARS-CoV-2, and similarly concluded that the relative importance of different modes of transmission of SARS-CoV-2 remains to be elucidated.(5) Understanding the relative importance of different modes of transmission is important for informing IPC measures. Though this review did not explicitly examine the relative effectiveness of public health interventions targeting different modes of transmission (for instance, physical distancing versus hand hygiene), these studies would likely be confounded by the fact that public health interventions are rarely conducted in isolation, particularly in the context of a pandemic.(25) Given the interaction between transmission modes and the effectiveness of public health interventions, it is possible that the findings of this review would also be applicable to a review of public health interventions.

One of the key challenges in ascertaining the relative importance of direct and indirect droplet transmission is understanding the predominant mode of transmission when people are in continuous close contact, as commonly occurs in family clusters. In these situations, the possibility of multiple modes of transmission cannot be ruled out, as evident in many epidemiological investigation studies, where a common conclusion is transmission via close or physical contact.(26-28) Though some epidemiological investigations have deduced that certain infections were likely caused by direct droplet (in a singing class)(28) or indirect droplet transmission (via a contaminated church pew),[28] these conclusions are largely speculative due to the inability to rule out infection from other sources, particularly asymptomatic carriers. A rapid review conducted by the Norwegian Institute of Public Health similarly concluded that 'people in close relations and people staying in close proximity to each other are exposed to multiple ways of transmission', and hence, 'it is very challenging to acquire strong evidence regarding the relative importance of different routes of transmission'.[29]

There are some data to cautiously suggest that environmental transmission may not be a driver for the spread of SARS-CoV-2. An animal model study involving golden hamsters reported that SARS-CoV-2 transmitted efficiently from inoculated hamsters to naïve hamsters by direct contact and via aerosols, but environmental transmission in soiled cages was less efficient.[30] However, obvious differences exist physiologically and behaviourally between hamsters and humans and hence direct extrapolation to humans may not be appropriate. A review published by Wiersinga et al.[31] on 10 July 2020, concluded that SARS-CoV-2 transmission occurs 'primarily via respiratory droplets from face-to-face contact, and to a lesser degree, via contaminated surfaces'. However, this conclusion appears to be based solely on the systematic review and meta-analysis by Chu et al.[25] which did not examine different modes of transmission per se, but rather the effectiveness of different public health interventions (including physical distancing) in preventing person-to-person transmission of SARS-CoV-1, SARS-CoV-2 and MERS-CoV. Chu et al.[25] found that for these viruses, being at least one metre apart was associated with a large reduction in infection rates compared with being in direct physical contact with an infected individual. This underlines the importance of close physical contact to the spread of these viruses. However, as discussed above, showing that close physical contact is important for the transmission of the virus is not the same as showing that transmission occurs predominantly through direct droplets, as these types of close interactions allow for multiple modes of virus transmission. A commentary by Goldman et al.[32] also concluded that the risk of SARS-CoV-2 environmental transmission may not be overly important, as the author argues that survival of the virus on inanimate surfaces in real-life situations is likely to be substantially less than in any of the laboratory-based studies, where larger viral loads than produced naturally were used.[23] However, surface sampling studies in real-world health care[33, 34] and non-health care[35, 36] settings have found evidence of SARS-CoV-2 RNA on inanimate surfaces and in some situations have successfully isolated the virus.[34] Hence the importance of environmental transmission to the spread of SARS-CoV-2 remains unclear.

It is also important to consider other plausible modes of transmission for SARS-CoV-2, in particular aerosol transmission, and how this may influence the relative importance of direct versus indirect droplet transmission. A separate evidence summary conducted by HIQA has concluded that there is some limited, low certainty evidence that SARS-CoV-2 may transmit via aerosols, however, it is not known if this is restricted to specific contexts, for example, enclosed or poorly ventilated environments. It is also uncertain what contribution aerosol transmission makes, if it occurs, to the COVID-19 pandemic relative to other transmission modes.[10] Kutter et al.[1] and Gralton et al.[11] highlight that modes of transmission of respiratory viruses are unlikely to be mutually exclusive, with the three main forms (that is, direct droplet, indirect droplet and aerosol) likely contributing in varying degrees, depending on the virus in question

A finding from one of the included mathematical modelling studies,[8] was the simulated impact on the overall reproductive number in different hypothetical settings composed of different materials and in aerosols. Although the simulations were entirely theoretical, they did illustrate the important role of context in determining the relative contribution of environmental transmission to the spread of SARS-CoV-2. Similarly, other evidence suggests that temperature and relative humidity impact on the propagation of droplets; therefore, the dominant mode of transmission (droplet or aerosol) may depend on the ambient conditions.[37] It is reported that the majority of outbreaks of COVID-19 to date have taken place indoors;[38] this suggests that environmental factors such as heating, ventilation and air-conditioning (HVAC) may have a role in the spread of SARS-CoV-2.[39] Applying the precautionary principle, both the WHO and the European Centre for Disease Prevention and Control (ECDC) acknowledge the possibility of SARS-CoV-2 aerosols spreading through HVAC systems within a building, vehicle or stand-alone air-conditioning units if air is recirculated, and recommend adequate ventilation in enclosed spaces.[5, 39] Proximity and duration of exposure between individuals is also likely influential, as larger droplets may not travel beyond one to two metres before falling to the ground,[5, 11] and hence in the context of widespread physical distancing, direct droplet transmission may be contributing less to the spread of the virus.[12] Therefore, it is likely that the relative importance of any mode of transmission is very much dependent on the context of the interaction, including the location (indoors or outdoors), the proximity to others, the duration of exposure, the composition of surfaces, the control measures in place, and the temperature and humidity.

One of the main reasons why the relative importance of various modes of transmission is still largely uncertain, even for viruses that have been around for a long time, is related to the fact that this is a particularly challenging area of research.[1, 2] Study designs involving direct human transmission (where human volunteers are experimentally infected with the virus) are naturally ethically flawed for SARS-CoV-2; in their absence, a myriad of experimental and observational designs are employed, each with clear advantages and disadvantages in their ability to definitively answer such a research question.[1] Therefore, conclusions about the likely forms of transmission, and their relative contribution, are typically made with consideration of a broad and multidimensional evidence-base. The form of evidence-base typically takes a considerable degree of time to mature, and often draws conclusions of mixed transmission routes, with different routes predominating depending on specific contexts such as environmental setting or exposure time.[2] Such an evidence-base is currently lacking in terms of the relative importance of direct versus indirect droplet transmission to the spread of SARS-CoV-2, but more robust conclusions may be drawn as additional studies are published in this rapidly emerging area. In order to accurately quantify the relative importance of different modes of transmission for SARS-CoV-2, a potential study design may be a large prospective cohort study following non-infected individuals in a particular setting (for instance in a work environment) over a long period of time. Regular participant and environmental testing for SARS-CoV-2, combined with in-depth epidemiological investigations (including detailed journal reports of daily interactions by participants and movement history through phone applications) and phylogenetic analysis (to provide further evidence of infector-infectee linkage) of confirmed cases would be important components of any such study.

Conclusion

In conclusion, it is currently not possible to determine with any degree of certainty, the relative importance of direct versus indirect droplet transmission to the spread of SARS-CoV-2. Furthermore, there is still substantial uncertainty surrounding the relative importance of different modes of transmission for other similar respiratory viruses. However, it is likely that the relative importance of these modes of transmission is context-specific; with factors such as the location (indoors or outdoors), the proximity to others, the duration of exposure, the composition of surfaces, the control measures in place, and the temperature and humidity, likely influential. Large observational studies that incorporate in-depth epidemiological, environmental and virological investigations are required to address this important research question.

Table 1. Summary of systematic reviews

Author Country Study design Study URL	Population setting	Primary outcome results	Quality appraisal
Dawson et al. 2019 **Systematic review** **https://www.liebertpub.com/doi/10.1089/vbz.2017.2191** **DOI:** 10.1089/vbz.2017.2191	**Virus(es):** MERS-CoV **Relevant outcome of interest:** Epidemiology and transmission **Study types:** Peer-reviewed primary research articles about MERS-CoV **Population of interest:** Human and animal studies included	**Main review findings** *No. of studies providing evidence:* 208 studies included in review ▪ 35 relevant to epidemiology and transmission *Quality of relevant studies:* No quality appraisal conducted by authors of review *Authors interpretation:* ▪ There is no compelling evidence of direct human-to-human transmission, such as through droplets, but secondary infection has been reported. ▪ There is possible evidence of environmental contamination (fomites) in health care settings (nosocomial transmission) and close contact with an active MERS case. ▪ Nosocomial transmission due to inadequate infection control is well established as a significant driver of MERS-CoV infections in humans. ▪ Direct contact could be inferred in only about 10% of the cases, and some authors suggested that environmental transmission could be important.	**Tool used** AMSTAR-II **Overall assessment:** Critically low
Otter et al. 2016 **Systematic Review** **https://pubmed.ncbi.nlm.nih.gov/26597631/** **DOI:** 10.1016/j.jhin.2015.08.027	**Virus(es):** ▪ Influenza ▪ SARS-CoV-1 ▪ MERS-CoV **Relevant outcome of interest:** Transmission of viruses **Study types:** Studies evaluating	**Main review findings** *No. of studies providing evidence:* ▪ coronavirus survival surfaces (9 studies) ▪ influenza survival surfaces (29 studies) ▪ coronavirus environmental transmission (8 studies) ▪ influenza virus environmental transmission (43 studies) ▪ coronavirus surface contamination (4 studies) ▪ influenza virus surface contamination (14 studies) ▪ disinfection influenza transmission (112 studies) ▪ disinfection SARS transmission (35 studies)	**Tool used** AMSTAR-II **Overall assessment:** Critically low

	contamination of any surface were included (experimental, animal, modelling) **Population of interest:** Laboratory- and field- based environmental	*Quality of relevant studies:* No quality appraisal conducted by authors of review *Authors interpretation:* ▪ It seems that surface survival of SARS-CoV-1/MERS-CoV is greater than that of influenza virus ▪ The importance of indirect contact transmission (involving contamination of inanimate surfaces) is uncertain compared with other transmission routes, principally direct contact transmission (independent of surface contamination), droplet and airborne routes. ▪ Influenza virus, SARS-CoV-1 and probably MERS-CoV are shed into the environment at concentrations far in excess of the infective dose, they can survive for extended periods on surfaces, and sampling has identified contamination of hospital surfaces Mathematical and animal models, and intervention studies suggest that contact transmission is the most important route but is context specific.	

Table 2. Summary of mathematical modelling studies

Author Study design Study URL	Population setting	Primary outcome results			Quality appraisal
Elmojtaba et al. 2020 **Mathematical modelling study** https://www.researchsquare.com/article/rs-32476/v1	**Transmission Details** Not reported **Population details** Based on data from the UK and China (these studies were also mathematical modelling studies) **Patient demographics (age/sex, travel history)** Not reported **Clinical characteristics** Not reported	**Study design** **Type of Model** Deterministic **Parameters (Source, date)** *Parameters directly extracted from published sources:* ▪ Doubling time, incubation period. (Published data based on early epidemic data in China, Jan 2020). *Parameters obtained from indirect evidence* ▪ Environmental transmission (Published data relating to cholera transmission, 2001 and 2019) ▪ Persistence of virus on surfaces (Published data based on other coronaviruses, Mar 2020) ▪ Epidemiological parameters (obtained from another mathematical modelling study which used UK data, which in itself made assumptions and estimations on certain key parameters, Mar 2020) ▪ Reproductive rate corresponding to human-to-human transmission and environment-to-human transmission (obtained from 2	**Main findings** Reproduction number/component thereof (Ro) -the average number of infections caused by an infectious individual in the absence of widespread immunity – (uncertainty, % contribution to overall Ro,) Overall Ro using 2 different data sources = 6.02 (China) and 5.11 (UK) Ro corresponding to human-to-human transmission (R_{hh}) = 3.25 (54%) (China) and 3.67 (72%) (UK) Ro corresponding to environment-to-human transmission (R_{he}) = 2.77 (46%) (China) and 1.44 (28%) (UK).	**Other relevant findings** Authors deduce that the major contribution is coming from human-to-human transmission. The authors suggest that reducing environmental transmission has the effect of reducing the maximum infection and delaying the time to reach this maximum, up to a certain limit.	**De-novo modelling tool** Low quality (based primarily on the unreliability of the key parameters and the associated assumptions. Also limited uncertainty analysis undertaken).

		other mathematical modelling studies, and assuming that transmission from the reservoir (that is, the Huanan seafood market) equates purely to environmental transmission, and based on other unclear assumptions, Dec 2019 – Jan 2020 and Jan-Feb, 2020). *Parameters based on assumptions by the authors* ▪ Contact rate from contaminated environment, the relative shedding rate of asymptomatic humans to the environment, the minimum concentration of virus in the environment capable of ensuring 50% chance of contracting the disease.			
Ferretti et al. 2020 **Mathematical modelling study** https://science.sciencemag.org/content/368/6491/eabb6936	**Transmission Details** Not reported **Population details** 40 transmission pairs with known dates of onset of symptoms identified from the public sources. Transmission data from 8 countries (Vietnam, South Korea, Germany, Taiwan, China, Hong Kong, Singapore, Italy). **Patient demographics (age/sex, travel history)**	**Study design** **Type of Model** Deterministic and Probabilistic **Parameters (Source, date)** *Parameters directly extracted from published sources:* ▪ Doubling time, incubation period. (Published data based on early epidemic data in China, Jan 2020). *Parameters calculated by the authors based on publicly available data* ▪ Generation time. (Estimated from publicly available data on transmission pairs from Vietnam, South Korea, Germany, Taiwan,	**Main findings** **Ro (uncertainty, % contribution to overall Ro)** Overall Ro = 2.0 Pre-symptomatic (direct transmission from an individual that occurs before the source individual experiences noticeable symptoms): 0.9 (Uncertainty median, 0.7. 95% CI, 0.2-1.1) (Point estimate 47%, uncertainty median 35%, 95% CI, 11-58%) Symptomatic (direct transmission from a symptomatic individual, through a contact that can be	**Other relevant findings** N/A	**De-novo modelling tool** Low quality (based primarily on the unreliability of the key parameters and the associated assumptions)

	Not reported **Clinical characteristics** Not reported	China, Hong Kong, Singapore and Italy, Mar 2020). *Parameters with Bayesian priors informed by anecdotal reports or indirect evidence.* ▪ Proportion asymptomatic (Media reports of Diamond Princess off the coast of Japan, Feb 2020) ▪ Relative infectiousness of asymptomatic (Indirect evidence relating to observations of missing links in Singapore outbreak, Mar 2020) ▪ Fraction of all transmission that is environmentally mediated (Anecdotal) ▪ Environmental infectiousness (Inferred from a previously published systematic review, Mar 2020).	readily recalled by the recipient): 0.8 (Uncertainty median, 0.6. 95% CI, 0.2-1.1) (Point estimate 38%, uncertainty median 28%, 95% CI, 9-49%) Environmental transmission (transmission via contamination, and specifically in a way that would not typically be attributable to contact with the source in a contact survey): 0.2 (Uncertainty median, 0.4, 95% CI, 0.0-1.3) (Point estimate 10%, uncertainty median 19%, 95% CI, 2-56%)† Asymptomatic (direct transmission from individuals who never experience noticeable symptoms): 0.1 (Uncertainty median, 0.2. 95% CI, 0.0-1.2) (Point estimate 6%, uncertainty median 9%, 95% CI, 0-57%)†.		
Ogbunugafor et al. 2020 **Mathematical modelling study** https://www.medrxiv.org/content/10.1101/2020.05.04.20090092v4	**Transmission Details** Not reported **Population details** Data from the 17 countries with the most COVID-19 cases as of 30 Mar 2020 (Australia, Austria, Canada, China, Denmark, France, Germany, Iran, Italy, Netherlands, Norway, South Korea, Spain, Sweden, Switzerland,	**Study design** **Type of Model** Deterministic **Parameters (Source, date)** *Parameters directly extracted from published sources:* ▪ Incubation period. (Published data from China, Jan- Feb 2020). ▪ Average life expectancies. (Published data from the 17 countries of interest, weighted by	**Main findings** **Ro (% contribution to overall Ro)** Overall Ro = 2.82‡ R_p – the expected number of people infected by a single infected person via person-to-person transmission exclusively = 2.33‡ ◊ R_e[2] - the expected number of people infected by a single infected person by way of the	**Other relevant findings** The authors found that for 10 of the 17 included countries, the model incorporating elements of environmental transmission (SEIR-W model) provided a better fit for the observed number of cases in the country	**De-novo modelling tool** Low quality (based primarily on the unclear comparability of the epidemiological data used and the lack of uncertainty analysis).

	United Kingdom, United States). **Patient demographics (age/sex, travel history)** Not reported **Clinical characteristics** Not reported	population size, extracted from centralised websites with international comparative data, date of extraction unclear) ▪ Death rate due to COVID-19 (Published data from China, Feb 2020) ▪ Recovery rate from COVID-19 (Published data from China, Jan-Feb 2020) ▪ Doubling time (Published data from a review, Mar 2020) ▪ Proportion of asymptomatic cases (Published data from Diamond Princess cruise ship, Feb 2020) ▪ Rate of viral decay in the environment on a variety of materials (aerosol, copper, plastic, cardboard, stainless steel) (Published data from a laboratory-based study, Mar 2020). *Parameters obtained from indirect evidence* ▪ Proportion of asymptomatic individuals who recover without progressing to severe symptoms (Extracted from another mathematical modelling study, Mar 2020) ▪ Reproductive rate (Extracted from 2 other mathematical modelling studies, Jan and Mar 2020. *Parameters estimated through model fitting*	environmental route exclusively = 1.38‡◊. **Hypothetical Ro values based on simulations in different environmental settings**: Environment composed entirely of: ▪ Aerosol = 2.38 ▪ Copper = 2.4 ▪ Cardboard = 2.67 ▪ Stainless steel = 2.94 ▪ Plastic = 3.18. **Hypothetical transmission contribution based on simulations in different environmental settings**: Environment composed entirely of: ▪ Aerosol = 4.6% ▪ Copper = 6% ▪ Cardboard 28%‡ ▪ Stainless steel = 43%‡ ▪ Plastic = 52%.	data. The authors propose that the role of environmental SARS-CoV-2 transmission can vary from setting to setting. The authors deduce that the total number of individuals infected after 30 days of the outbreak, and the total number dead after 30 days are both significantly lower in the "aerosol world" and "copper world" settings .Whereas the "plastic world" scenario has more than 30 times the number of deaths as the "copper world scenario (1,814 vs 55 deaths). However, the authors note that the peak number of deaths will be similar, the survivability of the different surfaces acts to delay infection rather than decrease or increase the number of cases.	

		▪ Expected time in asymptomatic state (fitted and dependant on the incubation period) ▪ Contact rate of people with people, transmission probability of people to people by an asymptomatic/symptomatic person, contact rate of person with the environment, transmission probability of environment to people, probability of shedding by asymptomatic/symptomatic person to the environment, average number of days before infectious. *Parameters based on assumptions by the authors* ▪ % of viruses in the environment			

Table 3. Summary of the cross-sectional survey

Author Country Study design Study URL	Population setting	Primary outcome results		Quality appraisal
Jin et al. 2020 **China** **Cross-sectional survey** **https://doi.org/10.1186/s40779-020-00254-8**	**Setting:** Healthcare workers in a tertiary acute care hospital in Wuhan, China. **Demographics:** 103 Adult healthcare workers ▪ 41 (39.8%) doctors ▪ 55 (53.4%) nurses ▪ 7 (6.8%) lab tech Gender: 39 (37.9%) male, 64 (62.1%) female Age: Median 35 years (Interquartile range= 28-42 years). **Severity of disease:** Presentation: 98 mild/moderate, 5 severe. **Presenting symptoms (before diagnosis):** Fever (48.5%), lethargy (42.7%), muscle aches (35.9%), dry cough (34%). **First symptoms experienced:** Fever (41.8%), lethargy (33%) muscle aches (30.1%).	**Study Design** **Sampling:** Cross Sectional **Location:** Single centre **Distribution:** Electronic **Administration:** Self-completion **Timing of sampling:** >2 weeks post infection Feb 15 –Feb 29 2020 **Relevant Survey Question:** **2. Do you think the most likely route of your infection is: (Multiple choices)** A. Droplet transmission B. Contact transmission C. Aerosol transmission D. Digestive tract transmission E. Other F. Not sure	**Results** **Perceived most likely route of transmission (self-reported)*:** ▪ 81 (78.6%) droplet ▪ 56 (54.3%) contact ▪ 25 (24.3%) aerosol ▪ 8 (7.8%) digestive tract ▪ 14 (13.6%) not sure. **Contextual results:** ▪ 87 (84.5%) felt acquired infection in hospital environment. ▪ Majority 71 (68.9%) worked in departments considered at low risk of nosocomial infection ▪ 80 (77.7%) reported always following hand hygiene before infection ▪ 68 (66%) always wore masks before infection ▪ Previous experience in dealing with epidemics e.g. SARS was low 5 (4.9%).	**Tool used** CEBMa Critical Appraisal Questions for a Survey **Overall assessment:** Low quality

Key: AMSTAR-II - a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both; CEBMa – Center for Evidence Based Management; MERS-CoV - Middle East respiratory syndrome coronavirus; Ro – Reproductive number (the average number of infections caused by an infectious individual in the absence of widespread immunity); SARS-CoV (1/2) - severe acute respiratory syndrome coronavirus (1/2)
* Respondents were permitted to select multiple choices
†Results are speculative according to the study authors
‡Data extracted using webplot digitizer https://apps.automeris.io/
◊Person-to-person transmission (R_p) plus environmental transmission (R_e^2) does not sum to the overall reproductive number (R_0)

Appendix 1. List of 51 studies providing potential evidence for either direct or indirect droplet transmission

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