Literature screening report

Quantitative and qualitative role of aerosolized transmission of Sars-CoV-2

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Abstract

There is little doubt that SARS-CoV-2 is transmitted at distances greater than 2 metres. Simulations and retrospective case studies show that transmission is possible both in the extended short range and at long distances and via intermediate (5-100 µm) and small (>5 µm) aerosols. It is difficult to quantify the relative contribution of long-distance transmission versus extended short range, as both ranges are not always distinguished and because there is some confusion about aerosol nomenclature. However, recent studies suggest that for SARS-CoV-2, these modes of transmission are dominant as compared to direct contact and fomites. This probably explains the importance of environmental factors such as air renewal (room ventilation) and duration of exposure in the transmission observed in many outbreaks.
Only indoor spaces appear to be relevant for airborne transmission. The highest risks are observed in spaces with high density and/or low ventilation, such as gyms, bedrooms or enclosed offices. For this reason, it is necessary to adapt prevention measures to the conditions of use of the spaces and the expected immunity rate of the occupants of the room. This may be even more relevant with the appearance of the Delta variant. The increase in transmissibility observed for the Delta variant may be due, among other factors, to a higher viral load in the infected people. This feature could give an advantage to the delta variant in the small, long-range, aerosol transmission.

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Content

Preamble

A large number of scientific publications become available on a daily basis, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Leading authorities should base decisions or policies on this knowledge; hence they need to master the actual state of this knowledge. Due to the large number of publications shared daily, decision makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the authors of this report were mandated by the Swiss School of Public Health plus (SSPH+), on request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature.

Background

The question of the transmission of SARS-CoV-2 by aerosols is a matter of debate in the scientific community. Although this question has been raised since the beginning of the pandemic, it remains topical and takes on a particular dimension with the emergence of new variants (some of which are more transmissible) and the recent reopening of public spaces like restaurants.

Questions addressed

- 1. Preliminary comments - about droplets and aerosols
- 2. Which conditions support the effective transmission by droplet vs. aerosol routes ?
- 3. Is there evidence for long-range transmission of Sars-CoV-2? Is it weak/medium/strong ?
- 4. How significant is the risk of transmission by aerosols over a short-range, vs. "extended short-range" vs. long-range ?
- 5. Is it possible to quantify the three transmission routes (direct, droplet, aerosol) in terms of effectively transmitting Sars-CoV-2 ?
- 6. What is the relative risk of different exposure scenarios, e.g. casual contact (shopping), household, office, school, etc ?
- 7. Did the importance of the three transmission routes change during the course of the pandemic, in particular after the emergence of B1.1.7 ?

Methodology

A literature search was carried out to collect evidence from peer reviewed studies, pre-print papers, government and national sanitary agencies reports (CDC, ANSES). The search focused mainly on the period October 2019 to 15 August 2021. We used Pubmed and Web of Sciences databases and alerts from targeted scientific journals (Journal of infectious diseases, Indoor Air, Emerging infectious diseases, International journal of infectious diseases, Building and Environment, Journal of environmental health, JAMA, Infectious Disease Modelling, Environmental Research, New England Journal of Medicine, Journal of Hospital Infection, Nature, Science and PNAS.

Key words: COVID – transmission – variant- aerosol - route of transmission, evolution, airborne, viability.

Results and Findings

1. Preliminary comments - about droplets and aerosols

Summary:

The distinction between aerosol and droplets is a major source of confusion. The terms used have different meanings in different disciplines and the sizes to which they refer are not always clear. The aerodynamic behavior of liquid particles follows a continuum, and the 5 µm limit is not adequate to distinguish rapidly settling particles from those remaining in suspension. The nomenclature adopted here distinguishes between large aerosols (> 100 µm), intermediate aerosols (5-100 µm), and small aerosols (< 5 µm).

Results:

By definition, an aerosol is a suspension of liquid or solid particles in a gas. However, there is considerable confusion around the use of the terms aerosol and droplet, whose definitions can vary according to the field. This is particularly the case in the medical field on the one hand, which refers to the penetration capacity in the respiratory system, and in the exposure sciences on the other hand, which refers to the aerodynamic behavior of airborne liquid particles. This imprecision is the cause of much confusion and the distinction between the terms droplets and aerosols wrongly suggests that the behavior of the latter is dichotomous (Tang et al. 2021; Randall et al. 2021).

In practice, it is a continuum, in which the force of sedimentation, the effect of entrainment by air displacements and the mechanisms of condensation-evaporation will work concomitantly. The aeraulic behavior of the liquid particles will ultimately be determined by their size, but also by the environmental conditions in which they evolve. Their aeraulic behavior, which has long been known and is not specific to COVID-19, can be illustrated by their sedimentation speed (or terminal velocity) depending on their aerodynamic diameter and moisture content (Vuorinen et al. 2020).

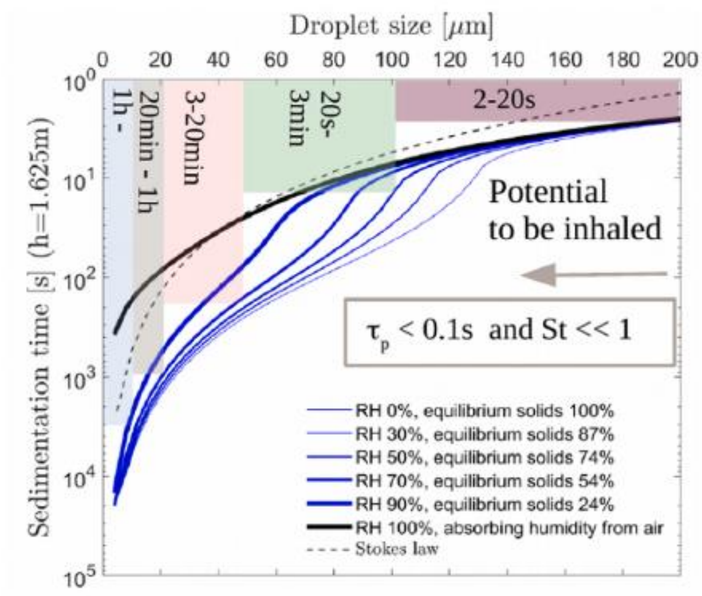

Figure 1. Sedimentation time for water droplets containing non-volatile material (from Vuorinen et al.2020).

For liquid particles >100 µm (aerodynamic diameter), sedimentation will generally dominate and these will settle to the ground after a few seconds or ten seconds. For liquid particles < 5 µm, the effect of sedimentation is marginal and the time before deposition can reach several hours. As their terminal velocity (the sedimentation speed in still air) is much lower than the natural air currents, these particles will behave essentially like a gas, following the air currents in the room. However, some of these particles may be deposited on nearby surfaces (e.g. floor, but also walls and furniture) due to Brownian motion and interception mechanisms. For particles of intermediate size (5 -100 µm) the propagation distance will depend on the sedimentation rate, but also largely on the environmental conditions (humidity, temperature) and the presence of air movements (e.g. ventilation, blast effect during a sneeze...). In this document, similar to the size ranges proposed by Milton (Milton 2020), we will use wherever possible the following simplified nomenclature to designate the different ranges of liquid particles.

Liquid particles

- **large aerosols** (> 100 µm): can marginally penetrate the upper airways and sediment rapidly
- **Intermediate aerosols** (5-100 µm): with mixed behavior (sedimentation/suspension)
- **small aerosols** (< 5 µm): likely to penetrate the deep lung and remain suspended for long periods.

2. Which conditions support the effective transmission by droplet vs. aerosol routes ?

Summary:

*Existing theoretical and experimental knowledge indicates that in the near field (typically <2m), transmission will depend largely on the **conditions of emission** of liquid particles, the viral load of the liquid, and their **carrying capacity**. Beyond the near field, intermediate and small aerosols will dominate, and the risk of transmission will also depends on the conditions of **propagation**, the **air renewal** in the room, relative humidity and the **duration** of exposure. Different emission events result in significantly different transmission distances, which can be ordered as breathing < speaking < coughing < sneezing (e.g. ten times greater distance compared to coughing).*

Results:

Any agitation of liquid is likely to generate the **emission** of aerosols. The droplets and aerosols produced during human activity, come from the lungs and the upper respiratory tract. The upper respiratory tract is more involved in the formation of aerosols > 10 µm, while the lungs emit mostly smaller aerosols. Breathing and speech, are likely to produce a majority of small aerosol emissions < 5 µm (Johnson and Morawska 2009). This mode of emission is of particular interest, as it is more frequent than coughing and sneezing, especially in asymptomatic individuals. In addition, higher viral loads are observed in the lungs compared to the upper respiratory tract (Tang et al. 2020).

Experimental data show that a healthy individual emits 10 to 10^4 particles per liter of exhaled air, 95% of which are particles <1 µm (Fabian et al. 2008). During speech, emission can reach 5000 particles per minute. Coughing generates 10^3-10^4 particles between 0.5 and 30 µm in size, with a majority of particles <2 µm. A sneeze produces approximately 10^6 particles between 0.5 and 16 µm (Zhu, Kato, and Yang 2006; Tang et al. 2006). Particles emitted during exhalation, speech, or coughing are polydisperse in nature. Johnson observed three different median particles sizes during speech and voluntary coughing of 1.6, 2.5, and 145 µm, and 1.6, 1.7, and 123 µm, respectively (Johnson et al. 2011). The literature is consistent that the order of increasing emissivity is: breathing < speaking < coughing. A high variability is however observed between the tested subjects.

Analysis of oral fluid from COVID infected patients, shows a mean viral RNA **load** of $7 \cdot 10^6$ copies/mL with a maximum up to $2 \cdot 10^9$ copies/mL (Wölfel et al. 2020). For these viral load levels, there is a 37% probability that a 50 µm droplet before dehydration contains at least one virus, and this probability is reduced to 0.37% for a 10 µm droplet (Stadnytskyi et al. 2020).

For a spherical particle, the viral load **carrying capacity** varies with its volume, and thus the cube of its radius. It is therefore possible to estimate, for a given viral load scenario, the probability of finding the virus in an aerosol. For a viral concentration of $7 \cdot 10^6$ copies/ml, the chances of finding a virus in a 5 µm liquid particle are 0.05%, whereas for a 50 µm particle, they are 50%. However, the number of aerosols emitted far exceeds the number of larger droplets.

Zhao et al have conducted simulations of the propagation of aerosol generated by speech over a wide range of temperatures (0-40 ° C) and relative humidity (0-92%). These show that a distance of 1.4 m is required to block the propagation of 95% of the large aerosols and that this percentage changes little as a function of environmental conditions. However, some particles can reach greater distances and simulations show that in a low temperature, high humidity environment, some particles can travel up to 6 m (Zhao et al. 2020). The drier and warmer the ambient air is, the higher the evaporation rate.
Evaporation reduces the size of aerosols, which slows sedimentation and increases the residence time in the air (Xie et al. 2007). Water particles of 1 µm will evaporate completely in a few tenths or hundredths of a second, while water particles of 100 µm will evaporate completely in tens of seconds. For human saliva, which is not integrally composed of nonvolatile material, this mechanism is more limited. An experimental study shows that saliva particles shrink to about half their original diameter (Vejerano and Marr 2018).

The initial velocity of the particles also plays an important role in the propagation, especially for large and intermediate aerosols due to their inertia. For intermediate and small aerosols, dragging by the ambient air flow, for example during a sneeze, can occur. The horizontal distance travelled by aerosols varies greatly depending on their size, but also on the initial air speed. Simulations show that this distance can be less than 1 m for an air displacement of 1 m/s (normal speech), while it can increase to 6 m, in the case of an air displacement of 50 m/s (sneeze)(Xie et al. 2007). These results are consistent with those of Wei et al. who conducted a simulation of the path of 10 µm, 50 µm, and 100 µm particles under different ejection conditions (Wei and Li 2015), as well as with experimental tests, which show that aerosols produced by coughing and sneezing can reach distances of 7-8 m (Bourouiba 2020).

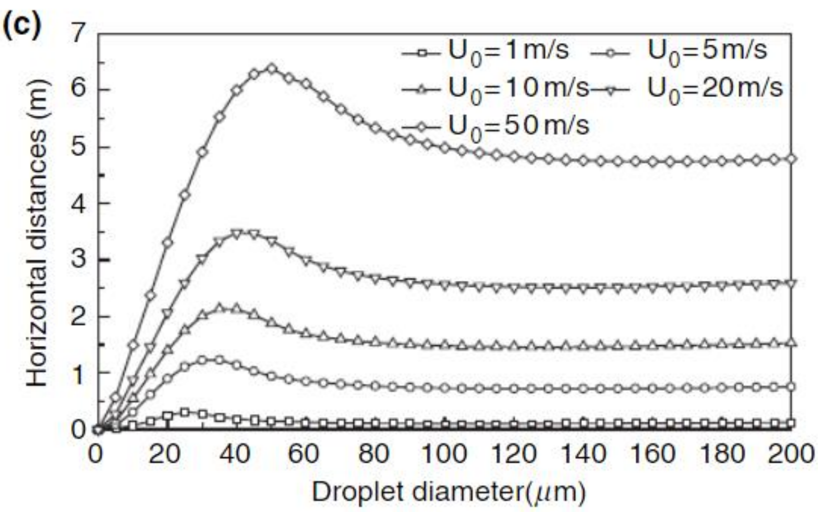

Figure 2. Horizontal distance travelled as a function of initial velocity and droplet size, with an ambient Temperature of 20°C and relative humidity of 50% (from Xie et al.2020).

In the near-field of the emitter (1-2 m from the infected person), the concentration of aerosols depends essentially on the emission conditions (initial ejection speed in particular) and sedimentation. In the so-called "far field", this concentration is largely influenced by the air movements and the **air renewal** of the room, which reduces the presence of the pollutant through dilution. An efficient ventilation allows to lower the concentration of small and intermediate aerosols, which are relatively little affected by the sedimentation effect.

The concentration of virus-loaded aerosol near the exposed individuals, is however not the sole determinant of transmission. Since the carrying capacity of intermediate and small aerosols is severely limited by their size, a certain dose must be inhaled to reach the infectious threshold. Although the minimum viral load is not well known at this time, it is generally considered that a few hundred SARS-CoV-2 viruses would be sufficient to cause disease in susceptible individuals. To achieve this infectious dose with small aerosols, it is therefore necessary to be exposed for a certain **duration** time. The importance of exposure duration has also been highlighted in the retrospective analysis of several case situations (Miller et al. 2021) and is corroborated by field observations.

A modelling simulation (Chen et al. 2020) was conducted for exhaled droplets for talking and coughing in close contact (<2m). While for talking (Figure 3), the exposure is negligible for distances longer than 0.2, for coughing (Figure 4) the droplets travel further, i.e. 0.7m. However, this study did not consider sneezing, for which was found (Han, Weng, and Huang 2013) to generate at least ten times more particles than cough.

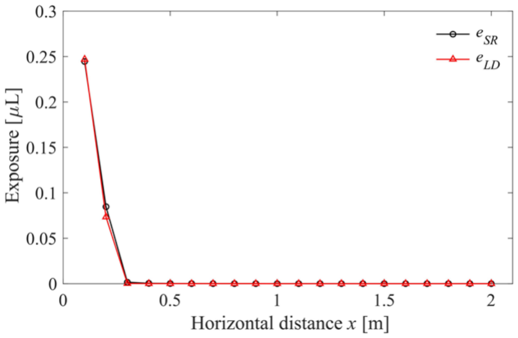

Figure 3. Potential exposure when talking, expressed in total droplet volume (μL), as a function of distance.

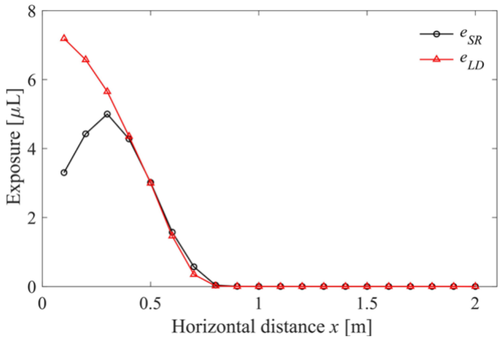

Figure 4. Potential exposure when coughing (once), expressed in total droplet volume (μL), as a function of distance.

3. Is there evidence for long-range transmission of Sars-CoV-2? Is it weak/medium/strong ?

Summary:

The evidence for the presence of the virus in intermediate and small aerosols is strong, both experimentally and in real-life situations. The viability of the virus in aerosols is however only moderately documented, probably due to the complexity of these measurements.
There is growing evidence of transmission to humans by the airborne route, although it is often difficult to distinguish between modes of transmission in real-life situations. There is, however, a strong indirect bundle of evidence, through cluster studies, experimental data and simulation to support this mode of transmission. Moreover an airborne transmission of SARS-CoV-2 is consistent with observations previously made with other viruses and recent observations in animal transmission. For these reasons, ***the transmission of the virus to humans beyond a distance of 2 meters must be considered as a given****.*

Results:

There is no doubt about the presence of SARS-CoV-2 in intermediate and small aerosols in settings where positive cases are present. In situ, there are numerous studies, which show the presence of SARS-CoV-2 or similar viruses in air for liquid particles in the micrometer range. These studies have mostly been performed in hospital setting where COVID patients are concentrated (Chia et al. 2020; Liu et al. 2020; Ong et al. 2020; Fears et al. 2020; Guo et al. 2020; Santarpia et al. 2020; Lednicky et al. 2020). Other areas have also been investigated and aerosols-containing viruses have been found in public places such as entrances of department stores (Liu et al. 2020) or in industrial areas near urban centre (Setti et al. 2020). Some authors however, such as Faridi who investigated patient rooms, reported negative results (Faridi et al. 2020), which could be explained by differences in sampling and analysis methodology.

As the detection of airborne virus is mostly done by PCR, a positive test does not constitute a per se demonstration of the presence of viable virus. If the knowledge acquired with other viruses and the data on the survival of SARS-CoV-2 outside the environment suggest this viability, the experimental evidence is currently quite limited. Its construction is very progressive, probably due to the difficulty of the technical realization of these tests. A limited number of studies have examined the viral viability of SARS-CoV-2 or similar viruses (SARS-COV-1, MERS-CoV) in air. Of the 11 such studies identified by da Silva (da Silva et al. 2020), 7 found positive viability, 1 had negative viability, and 2 had uncertain results. Only 5 of these studies were specific to SARS-CoV-2: 2 positive, 2 uncertain, 1 negative (note that the negative study was conducted in a patient room that had been empty for 4 days). Half-lives of 1.1 to 1.2 hours were observed in small aerosols for SARS-CoV-2 and SARS-CoV-1, respectively were observed experimentally (van Doremalen et al. 2020). Similar results were obtained by Smither, who observed half-lives for SARS-CoV-2 in artificial saliva aerosols of 30 to 177 minutes, depending on the experimental conditions (Smither et al. 2020). Noteworthy, comparative experiments between nebulized liquids containing three viruses showed that with SARS-CoV-2 is more resistant in aerosols than SARS-CoV And (MERS-CoV), maintaining infectiousness after up to 16h (Fears et al. 2020).

In situ evidence of transmission via small and intermediate aerosols in humans is limited but growing. The press reports numerous cases of super-contamination, which can hardly be explained by surface transmission or by transmission via large aerosols (so called droplets) alone. However, there are far few scientific publications reporting and analyzing such events. In practice, it is very difficult to differentiate between the transmission routes and the argument for transmission via aerosols is often based on indirect evidence (e.g. a particularly high reproduction or attack rate) (Correia et al. 2020). This evidence is growing and some authors suggested recently that the aerosol route is the dominant transmission route of SARS-CoV-2 (Wang et al. 2021).Published case studies identified so far are presented in Table 1. High occupancy, inadequate ventilation, and the presence of long exposure periods are frequently observed in these cases.

Location	Situation	Reference
Skagit Valley (USA)	53 of 61 members of a choir tested positive after a 2½-hour rehearsal. The distance between rows was 1.4 m. The inferred mean emission rate was E = 970 (± 390 SD) quanta per hour.	(Miller et al. 2021)
Diamond Princess" cruise ship	621 out of 3711 passengers were infected on the cruise ship "Diamond Princess". The estimated reproduction rate for this confined case is 11 (number of infected persons per case), whereas estimates given by other studies were 1.1-7.	(Mizumoto and Chowell 2020)
Zhejiang province (China)	Contamination of bus passengers during a 100-minute trip with an index case. The attack rate was compared to a second bus making the same trip without positive cases. The chance of infection in bus 1 was 34% higher. No significant difference in attack rate according to position on the bus, suggesting airborne contamination.	(Shen et al. 2020)
Wuhan (China)	A retrospective analysis of cases in healthcare personnel showed that none of the 278 personnel using N95 masks were infected with SARS-CoV-2, while 10 of 213 physicians or nurses were infected, regardless of their low risk of exposure	(Wang, Pan, and Cheng 2020)
Guangzhou (China)	10 persons (68 present in the same room), members of three separate families were infected after eating in a restaurant where an index case was present. The restaurant was poorly ventilated: 0.77 ACH.	(Li, Qian, et al. 2021)
Seoul (South Korea)	97 of the 1143 employees of a call center were infected. 94 of them worked on the same floor of the building. The attack rate on this floor was 43%.	(Park et al. 2020)

Seoul (South Korea)	Cluster of infections (n=10) in an apartment building. All cases were found in apartments connected by a single air duct.	(Hwang et al. 2021)
China	Analysis of 318 outbreaks involving 1245 infected persons in different settings suggests that long-range aerosol transmission occurred in cluttered, poorly ventilated spaces	(Qian et al. 2020)
Switzerland	5 of the 10 participants tested positive within days of a court hearing. The building's ventilation was down. The inferred mean emission rate was of about E = 100 quanta per hour.	(Vernez et al. 2021)
New Zealand	2 patients infected while in a quarantine hotel without contact or proximity with the index-case. A aerosol transmission was hypothesized.	(Eichler et al. 2021)
Netherlands	17 (81%) residents and 17 (50%) healthcare workers from the same ward in a nursing home were tested positive. The energy-efficient ventilation system was limiting the supply of outside air, possibly favouring aerosol transmission.	(de Man et al. 2020)
Israel	9 individuals were tested positive (6 healthcare personal) after treatment of an asymptomatic patient in a paediatric ward. 3 HCWs had no direct contact with the patient.	(Goldberg et al. 2021)

Table 1. Cases of contamination with strong suspicion of aerosol transmission reported in the literature.

The Sars-CoV-2 epidemic is characterized by the important role of cluster transmission or “superspreading events” in which one individual can infect numerous other individuals. An analysis of WHO transmission data in several countries has estimated that only 10% of index cases are responsible for 80% of secondary cases (Endo et al. 2020). The reasons that favor this mode of transmission are not elucidated, but several leads, such as donor-derived modification of the virion, altered infectivity due to host microbiome or physical/environmental conditions, have been considered (Lakdawala and Menachery 2021). A number of these superspreading events occurred in crowded indoor spaces with poor ventilation, suggesting that airborne transmission could have played an important role in the transmission (Lewis 2021).

For obvious ethical reasons, there is no human experimentation in humans and direct evidence on the transmission of SARS-CoV-2 remains limited. However, long-range transmission in humans is known for other infectious agents, including coronaviruses. Contamination situations have been shown for example: (1) via aerosols produced by the wastewater system (McKinney, Gong, and Lewis 2006), (2) between occupants of the same building; hotel, hospital (Tsang et al. 2003; Li et al. 2007; Yu et al. 2004) and, (3) in poorly ventilated or restricted spaces such as airplanes (Moser et al. 1979; Olsen et al. 2003). In animals, several experimental studies have reported non-contact transmission. The absence of other modes of transmission (fomites, droplets), however, is not always established. A recent study in ferrets, whose cages are at an air distance of about one meter, is probably the most conclusive to date (Kutter et al. 2021). Airborne transmission was observed for SARS-CoV-2, SARS-CoV, as well as A/H1N1 influenza virus

4. How significant is the risk of transmission by aerosols over a short-range, vs. "extended short-range" vs. long-range ?

5. Is it possible to quantify the three transmission routes (direct, droplet, aerosol) in terms of effectively transmitting Sars-CoV-2 ?

Summary:

The propagation of aerosols beyond the near field of the emitter (>1-2 m) is known since a long time and has been demonstrated experimentally. This mode of propagation occurs mainly in the "extended short range" (the same room), for which there is a growing, evidence of transmission of SARS-CoV-2. The hypothesis of long-distance (e.g. to another room) transmission is mainly supported by mathematical modelling studies and in situ measurements. Some studies suggest that long range transmission could be marginal as compared to "extended short range" transmission. This evidence is however limited since only a few studies tried to quantify these two routes. The significance of the three transmission routes can be ordered as fomite < droplet < aerosol.

Results:

The factors favoring transmission beyond the near field of the emitter (>1-2 m) have already been discussed in question 2. It is essentially the intermediate and small aerosols that are concerned by these mechanisms. Their dissemination in the same room is primarily conditioned by the aeraulic of the room. The presence of local air currents, especially those generated by pulsed air movements, can contribute to maintain high aerosol concentrations over large distances (e.g. 6-7m) and favor the propagation. These aeraulic behaviors have been known for a long time (SARS-CoV-2 did not revolutionize the laws of physics). In particular, it has been shown that air movements produced by coughing or sneezing promotes this phenomenon (Xie et al. 2007; Bourouiba 2020; Wei and Li 2015). Computational Fluid Dynamics (CFD) simulations, performed after contamination situations or as a preventive measure, highlight the role of ventilation-induced directional airflows. These can be related to the geometry of the space, as for example in vehicles (Zhang, Han, et al. 2021) or to an inhomogeneous distribution of ventilation (Li, Qian, et al. 2021; Abuhegazy et al. 2020). However, the aeraulic conditions of the spaces are situation-dependent and it is difficult to transpose the simulations performed to another context or to generalize them.

Qian, who analyzed 318 outbreaks in China, found that the short- (<2m) and extended-short range (>2 m, in the same room) were more probable by several factors, as compared to the long-range transmission (Qian et al. 2021). The study reported that for about 80% of the data, the outbreak occurred in a home or on transport (~30%). Only for a small fraction, i.e. 2%, the outbreak took place in restaurants, entertainment venue or at a shopping center. These numbers could be used to indicate roughly the contribution of different zones of transmission in the total count; i.e. the outbreaks that occurred at home or on transport indicate that the transmission in (extended) short range is responsible for >95% of the cases.

Within the short-range (i.e. distance of < 1.5m), the direct and the droplet transmission routes are more likely than for long-range transmission. The long distance dissemination of aerosols (another room) is however possible. In this case, the question of local air currents near the source of emission becomes secondary and it is the aeraulic conditions of the building (exchanges between spaces, typology of the ventilation) which will be determining. Several mitigating effects must be considered: (1) the decrease of the aerosol concentration due to the increase of the dilution volume, (2) the dilution due to a fresh air supply in the ventilation system (if the circulation is generated by the ventilation system), and (3) the loss of aerosols by deposition on surfaces (e.g. ducts) or in the particle filters of the ventilation system. A simulation with a relatively simple dilution model in a multi-room space using the same ventilation plenum was performed by Pease (Pease et al. 2021). The results obtained show, on the one hand, a strong dilution of the aerosol concentration between the room where the source is present and the related rooms and, on the other hand, the importance of air filtration and the supply of fresh outside air. In absence of adequate filtration, the probability of infection in the source and connected rooms differ by factors 2 to 3, while with air filtration (i.e. MERV) this likelihood substantially decreases in the connected rooms. The filtration, however, does not affect the source room when recirculating the indoor air. A greater impact on the decrease of the virus' concentration in the source room is obtained with higher air change rates per hour (ACH). For example, by increasing ACH from 1.8 to 12 ACH, the probability of the infections drops from 8% to 2%.

It is difficult to find clear cases of long-range transmission in real situations. In published studies, the long-range transmission is often linked with ventilation system. For example, Nissen et al. (Nissen et al. 2020) detected viral RNA below ventilation openings that were 50 meters far from the COVID wards. The authors also found that the relatively low humidity in hospitals were favoring of the long-term transmission of the virus. This was explained by the fact that the larger particles (released through cough) dry faster in low humidity conditions, traveling further as smaller aerosol.

A modeling of the contamination situation on board the Diamond Princess, taking into account different transmission situations (short-range / long-range / fomite), has been performed. For 132 iterations (corresponding to 132 different parameters settings), a good correlation with the field data was observed. The mean contribution of the different transmission modes for the short-range / long-range/ fomite was 35%, 35%, and 30%, respectively. The mean contribution of droplet vs. aerosol transmission cases was 41%/59% (the author considers a cut-off of 10 μm) (Azimi et al. 2021). A high variability was observed between these iterations, however.

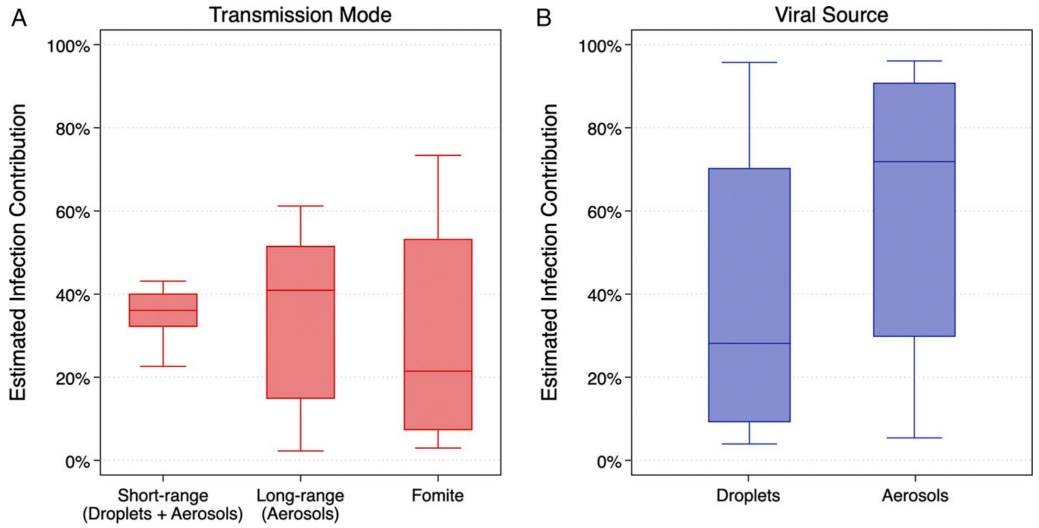

Figure 5. Relative contributions estimated for various transmission modes in the Diamond Princess case (from Azimi et al. 2021)

A retrospective analysis of the restaurant outbreak case in Guangzhou, showed no correlation between the number of surface touches and close contacts events and the infection risk, supporting further the small contribution of surface and contact in the virus transmission (Zhang, Chen, et al. 2021). Lei established a mathematical model to compare transmission routes for three viruses, i.e. influenza, norovirus and COVID-19, during transport by air in similar flight conditions. Different pathogen-specific parameters (e.g. inactivation rate and surface transfer efficiency) were modelled for the three pathogens. Unlike the studies previously mentioned Lei found that for COVID-19the number of infected passengers was of the same order for all three routes (Lei et al. 2018). Airborne, close contact and fomite routes contributed 21, 29 and 50%, respectively. Another study (Li, Zhang, et al. 2021) measured the aerosol's distribution also in the aircraft. The study conducted the measurements using manikins. It was found that the particles were distributed across at least four rows of seats. Considering the ventilation rate that exists in the aircraft, it should be noted that in other settings the particles' spread could reach further distances.

6. What is the relative risk of different exposure scenarios, e.g. casual contact (shopping), household, office, school, etc ?

Summary:

Only indoor spaces appear to be relevant for airborne transmission of SARS. Highly variable transmission risks have been observed or estimated in different settings. The highest risks are observed in spaces with high occupancy and/or low ventilation, such as gyms, bedrooms or enclosed offices. However, it is more the conditions of use and ventilation of the room (and in particular the supply of fresh air), than the type of activity that seems to determine the risk. Recent studies suggest on the one hand that to keep transmission rates low and reproduction rates <1, it is necessary to adapt prevention measures (e.g. wearing a mask, social distancing) to the conditions of use of the spaces and, on the other hand, that these measures can be modulated by the expected immunity rate of the occupants of the room.

Results:

Regarding airborne transmission, studies are concomitant on the fact that it is essentially a problem related to indoor spaces, where the risk of transmission is much higher than outdoors (Bhagat et al. 2020). In most cases, the outdoor risk is several orders of magnitude lower than the indoor risk of transmission and may only become comparable for highly specific meteorological and topographical situations (Rowe et al. 2021). It also appears that well-characterized transmission clusters and episodes are overwhelmingly identified in indoor spaces (Weed and Foad 2020; Bulfone et al. 2021).

Several studies have sought to estimate the risks of transmission in buildings and indoor facilities. Buonano simulated aerosol transmission in different typical indoor spaces using a compartment model and considering high emission and transmissibility conditions (with ci = 0.02, cv = 109 viruses/ml). The estimated reproduction rates found for a pharmacy, a supermarket, a post office and a bank were 0.49, 0.17, 0.41, 0.81, respectively (Buonanno, Morawska, and Stabile 2020). Lelieveld performed an estimation of the transmission risk in some typical indoor spaces (Lelieveld et al. 2020). Although the results of these simulations are largely dependent on the emission scenario, this example illustrates the importance of the environmental conditions and the effect of ventilation and prevention measures.

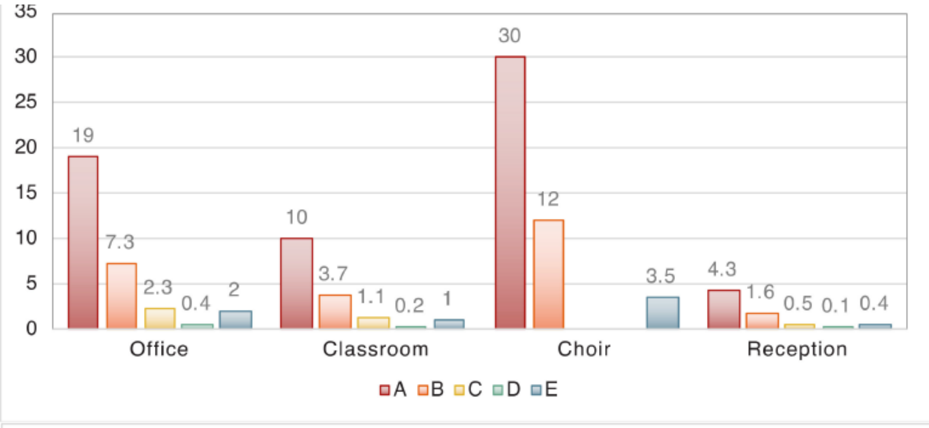

Figure 6. Individual risk of a particular person being infected in four indoor environments and five scenarios. Scenario A: passive ventilation, no masks. Scenario B: active ventilation with outside air, no masks. Scenario C: active ventilation, facial masks (not for choir). Scenario D: active ventilation, high-quality masks (not for choir). Scenario E: high-volume filtration with HEPA (from Lelieveld et al. 2020).

In his analysis of the effectiveness of different control strategies, Shen made a comparison of the transmission probabilities in different indoor spaces taking into account their typical volumes, their occupancy density and the residence time of the occupants. He observed a large variability in infection and reproduction rates between these spaces. The highest probability of infection (> 30%) were found for spaces such as gyms, bedrooms, enclosed offices and premises in long-term care facilities (Shen et al. 2021). High transmission rates in gym facilities were further pointed out by Stephenson, who reports low use of face masks during physical efforts, extended close contact, and high emissions due to loud speaking (Stephenson 2021).

Published estimates of transmission rates for different indoor spaces can vary considerably, as they depend largely on the scenario and parameters considered. It should be kept in mind that it is the emission factors, physical environment and transmission control measures, rather than the nature of the activity, that will actually determine the transmission rate. In particular, the density of people (and thus the possible increase in the number of emitters and targets), factors affecting room air exchange (volume, ventilation rate, mixing efficiency), and the presence of directional air movement in the room should be considered.

In the case of airborne transmission the role of the ventilation conditions seems particularly important. This is illustrated both in retrospective case studies and in prospective studies. Some examples, among many studies, are given below. These illustrate the importance of the role of air movements induced by ventilation but also, more widely, of the importance of the ventilation strategy used.

- The role of local air currents in SARS-CoV-2 transmission was illustrated in a cluster retrospective analysis in a poorly ventilated restaurant (Li, Qian, et al. 2021)

- The importance of the role of the in-house ventilation system in dispersing the aerosols was shown experimentally in a concert hall (Schade et al. 2021). It was also illustrated by an outbreak in a Korean call center, in which the transmission zone appeared to be essentially delimited by the configuration of the ventilation system. (Park et al. 2020)
- Infection likelihood estimates, derived from CO_2 measurements, in UK schools were found to be much higher in winter than in summer. The number of airborne secondary infections in winter (January) was about two times those of summer (July), despite similar room occupancy (Vouriot et al. 2021). This has been attributed to the decrease in fresh outside air in winter (closed windows, more recirculation).
- Higher transmission risks among students and teachers were also observed in New York City public schools in winter than in summer (Pavilonis et al. 2021). Counter-intuitively, it was also found that transmission rates were higher during in schools in higher income neighborhoods and newer buildings and lower in schools with mechanical ventilation. Modern ventilation systems are more energy efficient and tend to have a lower fresh air renewal rate.
- Probabilities of infection estimated, using a well-mixed model in a multiroom building, evidenced further the importance of fresh air renewal as well as the role of the filtration efficiency. Increasing the outdoor air to 33% or the filter to MERV-13 (relative to a MERV-8) decreased the infectivity in the connected rooms by 19% or 93% respectively (Pease et al. 2021).

It should be noted that, apart from the question of transmission rate which is specific to SARS-CoV-2, the observations made on the role of ventilation systems in aerosol transmission are not different from data already known for other indoor pollutants, such as particulate matter or chemical pollutants.

However, recent studies have brought new elements, more specific to the SARS-CoV-2 issue. Miksweski calculated the airborne infection risk in three settings, a classroom, prison cellblock, and restaurant, at varying levels of occupant susceptibility to infection. He estimated a vaccination threshold for control of SARS-CoV-2 ranging from 40% for a mechanically ventilation classroom to a 85% for a naturally ventilated restaurant (Mikszewski et al. 2021).

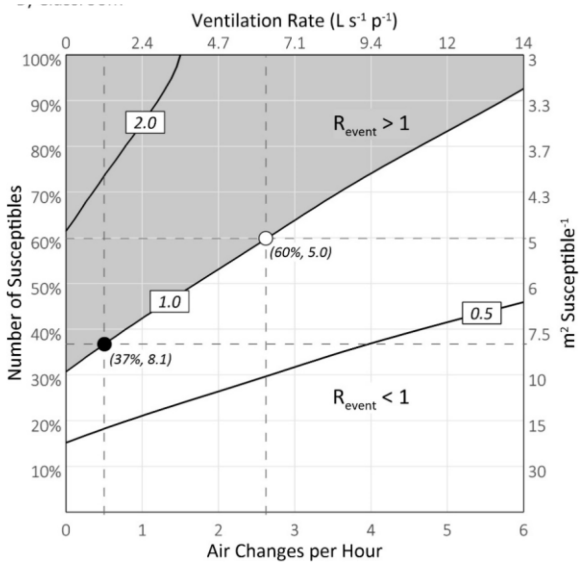

Figure 7. Surface graphs of R_{event} for SARS-CoV-2 as a function of the number of susceptibles and air exchange rate for a classroom. (from Mikszewski et al. 2021).

The role of vaccination, considering also several variants) was further investigated by Giardina. The simulation of three viral infectiousness levels (reflecting wild-type virus, alpha variant, and delta variant) and two student vaccination levels (0% and 50%) in a elementary school showed that transmission remain high when the delta variant predominates and students are unvaccinated. Mitigation measures or vaccinations for students when available were found to substantially reduce these risks (Giardina et al. 2021).

7. Did the importance of the three transmission routes change during the course of the pandemic, in particular after the emergence of B1.1.7 etc ?

Summary:

The information collected so far suggests that Alpha variants have similar viability to other SARS-CoV-2 variants in aerosols and comparable environmental stability and disinfection profiles of Alpha and Delta variants were observed.

There is evidence that the Delta variant is highly contagious, more than 2x as contagious as previous variants. This increase in transmissibility may be due, among other factors**,** to **a higher viral load in the infected people** and consequently **a higher emission rate during the contagious period**. Therefore, we can assume that patients with higher viral loads can be considered as "super or medium" spreaders. Consequently, we can hypothesize that **the transmission route via small aerosols (long-range) is relatively more predominant for Delta variant than it was with other variants.**

There is also evidence that **a non-negligible number of vaccinated individuals may be a source of transmission of Delta variant** while being asymptomatic since they carry a similar viral load than non-vaccinated patients.

Implementation of measures to mitigate the pandemic are expected to exert selection pressure and favour new variants able to escape these measures, including evolution regarding the routes of transmission.

Results:

a) **Transmissibility of the VOCs :** *The Delta variant is highly contagious, more than 2x as contagious as previous variants. We can hypothesize that the transmission route via small aerosols (long-range) is relatively more predominant for Delta variant than there was with other variants.*

Definition of the VOCs: According to CDC, variants of concern (VOC) are : "variants for which there is evidence of either an increase in transmissibility and/or more severe disease (e.g., increased hospitalizations or deaths), and/or significant reduction in neutralization by antibodies generated during previous infection or vaccination, and/or reduced effectiveness of treatments or vaccines, or diagnostic detection failures". Currently, 4 VOCs were identified since the apparition of the wild type in 2019. These 4 VOCs are : B.1.1.7 (Alpha variant), B.1.351 (Beta variant), B1.617.2 (Delta variant) and P.1 (Gamma variant).

Transmissibility: Among these VOCs, Alpha and Delta variants show an increased transmissibility compared to the wild type. In particular, a study from the Public Health England (Allen et al 2021), found a 64% increase in the odds of household transmission associated with infection with Delta variant compared to Alpha, while other studies from England (Davies et al 2021; Volz et al 2021) estimated that the Delta variant has a 43 to 90% and 50 to 100%, respectively, higher reproduction number than preexisting variants. In Japan, it has been demonstrated, that Delta possesses almost 1.4 times higher transmissibility than Alpha (Ito, Piantham, and Nishiura 2021). In France, Alpha itself has been estimated to be 52-69% more transmissible than the previously circulating lineages (Gaymard et al. 2021)) and a very recent study (Alizon et al. 2021) estimated that transmission advantage of Delta in the Ile-de-France is higher than that estimated in the UK (Allen et al 2021). Roughly, that means that **Delta is more than twice as transmissible as the initial wild type** (Kupferschmidt and Wadman 2021).

Factors that may explain the acceleration of the transmission of VOCs:

Several parameters can influence the transmission rate of the VOCs (Davies et al. 2021).

- A higher viral load in the infected people and consequently a higher emission rate during the contagious period.
- A longer period of viral shedding and consequently an extension of the period of infectious viral excretion during the symptomatic phase of illness.
- An ability to better escape the immune system in immunocompromised patient (Kemp et al. 2021).
- An increased children susceptibility to infection with VOC than with preexisting variants
- A shorter generation time.

Moreover, Li et al (Li, Deng, et al. 2021) suggested that for the Delta variant, the time window from exposure to the detection of virus with a PCR test was 4 days, instead of 6 days observed previously with the other lineages.

Finally, Pascarella et al. (2021) hypothesized that the surface electrostatic potential changes due to the effect of the mutations characterizing the Delta lineage, can favor the interaction between the B.1.617+ RBD and the negatively charged ACE2 (Angiotensin-Converting Enzyme 2), thus conferring a potential increase in the virus transmission.

Among these different parameters, only the first one could have consequences on **the relative importance of the three transmission routes**. Indeed, we can assume that a patient carrying a higher viral load than another patient will emit more viral particles increasing the short and long-range concentration of airborne virus as well as the rate of fomite deposition on surfaces. However, we can assume **that if patients have higher viral loads, they can be considered as "super or medium" spreaders.** Consequently we can hypothesize that **the transmission route via small aerosols (long-range) is relatively more predominant for Delta variant** than there was with other variants. (see paragraph 2 for evidence of higher viral load with infection with Delta variant).

Concerning the viability of the different variants, a comparable environmental stability and disinfection profiles of Alpha and Delta variants were observed (Meister et al. 2021). Moreover, aerosolization tests were performed in the laboratory with several variants of SARS-CoV-2. No difference in stability was observed for B.1.1.7 in the absence of simulated sunlight for different temperature and humidity conditions. A small but significant difference was observed in the presence of light at 20°C and 20% humidity for two lines, but not B.1.1.7 (Schuit et al. 2021). These results suggest that the transmissibility of B.1.1.7 is not related to differences in aerosol stability.

b) **Viral loads detected by PCR in patients infected with the Alpha or Delta variants:** *Viral loads of Delta infections are on average up to 1000 times greater compared to Alpha and Beta infections.*

First, a study from England (Kidd et al. 2021) showed that the Alpha variant was associated with significantly higher viral load in samples tested by PCR tests. The authors estimated that this increase could be up to 10'000-fold higher than the non-Alpha variants. Then, another study from Germany (Jones et al. 2021) observed that relative to non-Alpha variant cases, patients with Alpha variants had viral loads, estimated with PCR tests that were higher by a factor of 10 and estimated cell-culture infectivity that was higher by a factor of 2.6. Then, Li et al (2021) reported a local transmission of the Delta variant (167 cases) in mainland China and revealed that the viral loads, when patients first become PCR +, were on average 1000 times greater compared to Alpha/Beta lineage infections during initial epidemic wave in China in early 2020.

c) **Healthy carriers of Delta variants among vaccinated people:** *a non-negligible number of vaccinated individuals may be a source of transmission while being asymptomatic*

In Wisconsin, USA, a study (Riemersma et al. 2021) used viral loads data to compare the amount of SARS-CoV-2 RNA, in respiratory specimens from people who self-reported their vaccine status and date of final immunization, during a period in which the delta variant became the predominant circulating variant. Results highlighted that no difference in viral loads was observed when comparing unvaccinated individuals to those who have vaccine "breakthrough" infections. This suggest that if vaccinated patients become infected with the Delta variant, they may be sources of SARS-CoV-2 transmission to others. Moreover, according to CDC (report 25 of May, 2021), about 30% of the cases of "breakthrough" infections, among vaccinated people are asymptomatic. This mean that a non-negligible number of vaccinated individuals may be a source of transmission while being asymptomatic. However, vaccinated people appear to be infectious for a shorter period**.** This cryptic transmission of Delta variants with high viral load between vaccinated patients was also observed in a medical-surgical ward in USA (Linsenmeyer et al. 2021).

d) **Impacts of non-pharmaceutical measures on the transmission of new variants according evolutionary theory:** *Implementation of measures to mitigate the pandemic are expected to exert selection pressure and favour new variants able to escape these measures*.

According to the theory of natural selection, a virus bearing a mutation given a competitive advantage against the pre-existing lineages, will invade the population and became predominant (but see also other scenario*). Vaccines represent a well known selection pressure for evolution of vaccine-resistant variants particularly if the vaccination campaign is too slow (Luo et al. 2021). However, other measures, such as non-pharmaceutical measures, dedicated to limit the propagation of viral diseases, can also exert selection pressure and favour new variants able to escape these measures. Therefore, it is important to have knowledge about the evolutionary possibilities of the virus to predict the type of variants that are likely to appear following the current measures taken in most countries.

Impact of nasopharyngeal mass testing : Among the scenarios for the future, Alizon and Sofonea (Alizon and Sofonea)(2021) mentioned the possibility for a new variant to acquire a pronounced tropism for lower respiratory tracts. Indeed, they explained that specializing in colonizing the epithelium of the upper airways is expected to yield a transmission gain for the virus but it also increases the probability of detection using nasopharyngeal swabs. If case isolation measures are strong, such a tropism can greatly affect further virus transmission. Therefore, if the selection pressure exerted by nasopharyngaeal mass testing measures is significantly enough, the evolution of a virus tropism towards the lower respiratoty tract could be favoured if the decrease in detection probability compensates the decrease in transmission rate.

Impact of lockdown: During the COVID-19 pandemic, evidence that around 10% of infected individuals are responsible for 80% of new cases was shown. Thus, the overdispersion in transmission is an important parameter to take into account when assessing the transmissibility of new variants. By using simulation to estimate the survival chance of different variants (varying in infectiousness and overdispersion ability) in the absence and presence of mitigation, Nielsen et al (Nielsen et al. 2021), found that lockdowns favour the emergence of homogeneously spreading variants over time.

*A favourable mutation within one quasispecies (one virus variant) triggers evolutionary responses in the second one, forcing it to evolve. Consequently, competing virus variants could maintain nearly equal fitness by constant running to stay in the same place relative to their competitor (Red queen's hypothesis, Van Valen 1993).

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