Chapter

Perspective Chapter: Analysis of SARS-CoV-2 Indirect Spreading Routes and Possible Countermeasures

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Abstract

The research community agrees that the main indirect way the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads among people who do not keep social distance is through the emission of infected respiratory droplets. Infected people exhale droplets of different sizes and emission velocities while breathing, talking, sneezing, or coughing. Complex two-phase flow modeling considering evaporation and condensation phenomena describes droplets' trajectories under the specific thermofluid dynamic boundary conditions, including air temperature, relative humidity, and velocity. However, public health organizations simply suggest a safe distance in the range of 1–2 m regardless of the effect of boundary conditions on droplets' motion. This chapter aims to highlight open research questions to be addressed and clarify how framework conditions can influence safe distance in an indoor environment and which technical countermeasures (such as face masks wearing or heating, ventilation, and air conditioning (HVAC) control) can be adopted to minimize the infection risk.

Keywords: SARS-CoV-2, droplets, airborne, aerosol, face masks, HVAC system, safe distance, contagion prevention

1. Introduction

Regardless of whether vaccination is efficient and effective [1, 2], a good knowledge of the mechanisms underlying infection among people would have helped against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreading by minimizing lockdown measures. The scientific community has largely investigated how an infected person transmits pathogens to a susceptible person [3]. What is known is that an infected person emits a certain number of droplets. Some of these droplets, defined as infected, carry a certain number of virions or viral particles that can potentially infect target host cells if reached. The literature also shows that the emission of droplets can occur in different ways, for example, through speech, breathing, coughing, and sneezing. What is still not commonly agreed upon is related

to the i) number, ii) size distribution, and iii) emission velocity of the potentially infected droplets for each of these emission modes. After the seminal papers of Wells [4] and Duguid [5], many investigators have grappled with the issue showing broad differences in the experimental results [6]. The reasons can be identified in i) a not full understanding of the physics underpinning the formation of respiratory droplets, ii) the absence of a common methodology, being the different experiments performed by using different techniques and under different ambient conditions, iii) the lack of a rigorous presentation of data, which is often not provided, and iv) the natural variability across individuals.

In addition, the conditions of the ambient air in which these droplets move have also to be considered. Knowing this information is essential to studying the mechanisms that govern the motion of potentially infected droplets. Safe distance, defined as the average distance to which, ideally, a negligible infection probability exists, can be identified once the emitted infected droplets' trajectory is known. However, rigorous terminology and definitions are needed to investigate droplets' motion based on the scientific method. To date, instead, a lack of unambiguous and agreed terminology exists. For example, terms commonly used for direct transmissions, such as "*droplets*," "*aerosol*," and "*airborne*," have been often used with various meanings by several authors. Tang et al. [7] highlighted how significant confusion over the definition and application of relevant terms among professionals (i.e., clinicians versus aerosol scientists) and the general public generates problems in mutual understanding. A second example is the lack of a distinction between solid and liquid carriers, i.e., droplets. Without it, the impact of the thermohygrometric conditions of the ambient air, i.e., relative humidity and temperature, is not adequately considered when studying particles' motion and viral load (defined as the number of copies of ribonucleic acid (RNA) detected in a certain volume). Solid particles that carry viral charges on their surface do not change size or shape along their trajectory except in particular environmental conditions, i.e., if they are condensation nuclei. On the other hand, droplets emitted with a certain viral load reduce their volume through evaporation along their trajectory, resulting in the variation of the balance of forces and viral load. Although experimental results demonstrated that a SARS-CoV-2 viral load lower than 100,000 virions per cubic centimeter (cc) corresponds to a negligible risk of infection [8, 9], to date, the infection risk as a function of the infected droplets' viral load along their trajectory has not yet been sufficiently investigated.

This chapter underlines what are the unsolved research questions (RQs) crucial for a full understanding of SARS-CoV-2 spreading routes and relative countermeasures. Nevertheless, this chapter proposes rigorous terminology and reports evidence to minimize the risk of SARS-CoV-2 infection based on the existing knowledge. The study demonstrates why an effective strategy cannot disregard, at least, i) the use of the facial mask, ii) the control of the thermohygrometric conditions of the ambient air, and iii) the maintenance of the safe distance. In particular, the simplified model shows that the facial mask acts as a first physical barrier against the larger droplets, which can reach very high viral loads in the case of incomplete evaporation. On the other hand, the control of the thermohygrometric conditions acts as a second immaterial barrier that guarantees the complete evaporation of the smaller droplets that come out of the mask before reaching any susceptible subject. Once droplets are completely evaporated, the virions are released into the surrounding environment, where the viral load is low enough to be unlikely to infect.

2. Size distribution of the infected droplets and calculation of the number of virions emitted

Many studies are available in the literature focusing on analyzing the dimensional distribution of the droplets emitted for different possible emission mechanisms such as breathing, speech, cough, and sneezing. However, since no universally accepted standard test identifies the instrumentation and the procedure to investigate the topic, the results are difficult to compare with each other. For example, if a single cough event is considered, [10] states that the droplets in the submicron range represent 97% of the exhaled droplets, while [11] reports only less than 4% and [5] measures not even a single droplet within submicron range. Therefore, the first unsolved research question RQ1 is the standardized characterization of the sizes and the distribution of the exhaled droplets for all the expulsion processes.

Since a standard characterization of the initial distribution of droplet sizes is missing, in the following evaluation, the data reported by [12] were used. [12] has been selected as a data source due to the high number of citations, the robust methodology adopted, and the quality of exposure. The following results are affected by the data source selected; nevertheless, the focus of this chapter is more on the suggested methodology to assess SARS-CoV-2 spreading mechanisms and the related comparison. In [12], only droplets with a diameter greater than 20 microns were considered, although a "*16-channel dust monitor*" was available. Furthermore, only speech and cough mechanisms were investigated. In the first case, the involved subjects were asked to count from 1 to 100. Therefore, assuming that about 100 seconds are necessary to complete the count, the emission rate is calculated by dividing the droplets counted by this time interval. Moreover, the individuals were asked to make 20 coughs each to simulate the cough mechanism.

Since the data refer to a group of people, the average number of droplets $N_{\text{droplet},\mu}$ emitted by a subject for each jth-dimensional interval [drops/individual] is calculated as

$$N_{\text{droplet},j,\mu} = \frac{\sum_{i=1}^{N} N_{\text{droplet},j,i}}{N_{\text{sample}}} \tag{1}$$

where $N_{\text{droplet},i}$ is the number of droplets emitted by the ith individual [droplets/person], while N_{sample} is the number of people who participated in the test. The number of droplets emitted by 99% of individuals, assuming a Gaussian distribution with a standard deviation σ_j, for the jth interval is equal to

$$N_{\text{droplet},j,99\%} = N_{\text{droplet},j,\mu} + 2.58 * \sigma_j \tag{2}$$

The total number of droplets emitted $N_{\text{droplet},\mu}$ and $N_{\text{droplet},99\%}$ are, respectively, computed as

$$N_{\text{droplet},\mu} = \sum_{j=1}^{M} N_{\text{droplet},j,\mu} \tag{3}$$

$$N_{\text{droplet},99\%} = \sum_{j=1}^{M} N_{\text{droplet},j,99\%}. \tag{4}$$

where M is the number of dimensional intervals on which the range has been divided.

The definition of the initial viral load of emitted droplets and the relationship with the viral load present in oronasopharyngeal (ONP) swabs represents the second RQ2. To calculate the number of virions emitted, it was assumed that all the infected droplets had the same initial viral load λ_0 [RNA copies/mL]. This simplifying hypothesis is necessary since the topic is still under investigation and without clear results [13]. There is evidence that viral load in emitted droplets should be lower than in ONP swabs: for example, [14] detected RNA copies of SARS-CoV-2 in exhaled breaths (EBs), which was three to four orders of magnitude lower than the RNA detected in the same participants' ONP swabs and with no correlation among EB and ONP. Nevertheless, since the results may vary based on the methodology applied, in the following assessment, it is conservatively assumed that the initial viral load λ_0 is equal to the one present in ONP swab.

Defined V_j as the average volume of a droplet emitted in the jth dimensional interval [mL], the released virions are calculated as in Eq. (5), while in Eq. (6), the worst case is defined

$$N_{\text{virions},\mu} = \sum_{j=1}^{M} N_{\text{droplet},j,\mu} \times \left(V_j || \times \lambda_0\right) \tag{5}$$

$$N_{\text{virions},99\%} = \sum_{j=1}^{M} N_{\text{droplet},j,99\%} \times \left(V_j || \times \lambda_{\text{viral}}\right). \tag{6}$$

To calculate the emission rate in the case of speech, the values are multiplied by 0.6 to have [virions/min]. In the cough case, the values are divided by 20 to have an emission rate in [virions/cough].

3. Calculation of the infected droplets' trajectory and viral load

To calculate droplets' trajectory and viral load variation, the model proposed by [15] was considered. However, a premise must be highlighted. Only part of the volume of the infected droplets is occupied by saliva, as virions occupy the remaining part. For example, considering the voidage ratio (i.e., the difference between the droplet's volume and the sum of the virions' volumes, divided by the volume of the infected droplets) in analogy with similar physical problems, only a part of the infected droplets' volume consists of a liquid that can evaporate. However, to date, the literature has no answer to RQ3: What effect the virions can induce on the droplet evaporation process? Therefore, it cannot be excluded that an infected droplet evaporates faster than a pure water droplet and that the evaporation time is proportional to the voidage ratio. On the other hand, it is not known, for example, if the virions hinder the mass transfer phenomenon by retaining water in the droplet. Similarly, virions' heat capacity is unknown, i.e., how long the virions take to reach thermal equilibrium with the water surrounding them. Therefore, due to the existing research gaps, the following assumption was made: the reduction of the infected droplet's evaporation time due to the lower volume of aqueous solution contained is counterbalanced by the potential obstacle the virions could cause during the evaporation mechanism. Therefore, the mass variation due to evaporation is calculated as

$$\frac{dm_G}{dt} = \frac{2\pi p D_G M_V D_\infty C}{R_0 T_\infty} ln\left(\frac{p - p_{va}}{p - p_{v,\infty}}\right). \tag{7}$$

where m_G is the mass of the droplet [kg], D_G is the diameter of the droplet [m], D_∞ is the vapor diffusion coefficient in the air surrounding the droplet [m^2/s], M_v is the molar mass of the vapor in [kg/kmol], R_0 is the universal gas constant in [J/kmolK], p_{va} and $p_{v,\infty}$ are, respectively, the partial pressure of the vapor on the surface of the droplet and far away in [Pa], and p and T_∞ are the air pressure [Pa] and temperature [K], respectively. C is a corrective coefficient that takes into account the presence of other constituents in human saliva different from pure water. The temperature variation T_G on droplet surface [K] due to the evaporation phenomenon is calculated as

$$m_G c_L \frac{dT_G}{dt} = 2\pi D_G^2 K_g \frac{T_\infty - T_G}{D_G} + r\frac{dm_G}{dt} - \pi\Gamma\left(T_G^4 - T_\infty^4\right). \tag{8}$$

where c_L is the specific heat in [kJ/kg·K], K_g is the thermal conductivity of the gas in [kJ/s·m·K], r is the latent heat of vaporization in [kJ/kg], Γ is the Stefan-Boltzmann constant in [$kW/m^2 \cdot K^4$]. In the second-member heat balance, therefore, there are three contributions, namely, heat conduction (first term), heat convection (second term), and heat radiation (third term). To calculate droplets' trajectory, the following equation was solved:

$$m_G \overrightarrow{a_G} = m_G \vec{g}\left(1 - \frac{\rho_a}{\rho_G}\right) - C_w A_G \rho_g \frac{{v_{\text{rel}}}^2}{2} \times \frac{\overrightarrow{v_{\text{rel}}}}{|v_{\text{rel}}|} \tag{9}$$

where a_G is the droplet's acceleration [m/s^2], g is the gravity acceleration [m/s^2], ρ_a and ρ_G are, respectively, the air and the droplet's densities [kg/m^3], C_w is the Stokes coefficient [−], A_G is the cross-sectional area of the droplet, and v_{rel} is the relative velocity between the drop and the surrounding air. Since the droplets' diameter along the horizontal distance is known, the droplet viral load [RNA copies/mL] is calculated as

$$\begin{cases} \lambda(x) = \dfrac{\lambda_0 D_{G,0}^3}{{D_G}^3(x)}. \\ \lambda(x) = \lambda_{\max} \end{cases} \tag{10}$$

In Eq. (10), $\lambda_{\max}$ is calculated as the ratio between the number of virions and the volume of the minimum droplet in which they can be contained. Therefore, since virion volume is assumed to not change during droplets' evaporation, the voidage ratio decreases to a minimum, which corresponds to the maximum allowable concentration $\lambda_{\max}$. To date, no data about this maximum concentration exist. To cover the gap, the most conservative assumption is made. Specifically, the minimum voidage ratio of a bed of sphere, i.e., 39%, from [16] is considered. Therefore, the maximum viral load is equal to

$$\lambda_{\max} = \frac{\sum N_{\text{virions}}}{V_G} = \frac{(1-\varphi) \times \frac{V_G}{V_{\text{virions}}}}{V_G} = \frac{(1-\varphi)}{V_{\text{virions}}} = 1.165 \times 10^{15}\left[\frac{\text{RNAcopies}}{\text{mL}}\right]. \tag{11}$$

where N_{virions} is the number of virions contained in the droplet [#], V_G is the droplet's volume [mL], φ is the minimum void ratio (assumed equal to 39%), and V_{virion} is the mean virions' volume [mL]. For the analysis, an average virion diameter of 100 nm is assumed [17].

4. The proposed terminology for infectious droplets' transmission mode classification

The terminology suggested in [18] is adopted in this chapter, and it is the following:

- "Airborne transmission" is defined as the transport of solid particles in a fluid suspension in the examined environment, in whatever way they are carried, regardless of the carrying speed of the fluid current and, therefore, also including the transport of ultrafine particles (and, as such, virions as well) subject to Brownian motions;

- "Droplet transmission" is defined as the transport of droplets in the environment, regardless of how they are carried, including when they contain insoluble solid particles inside them (such as virions).

Figure 1 is an elaboration of the results calculated by [15]. The ordinate shows the vertical distance traveled by a droplet with an initial diameter of 20 microns (solid line) and by one of 40 microns (dashed line) falling from a height of 2 m. On the abscissa, the horizontal distance is shown. An air temperature equal to 20°C and an emission droplet velocity equal to 10 m/s are the boundary conditions. As shown, the time required for the complete evaporation (extreme points of the trajectories symbolized with a star), or the distance traveled, also depends on air relative humidity.

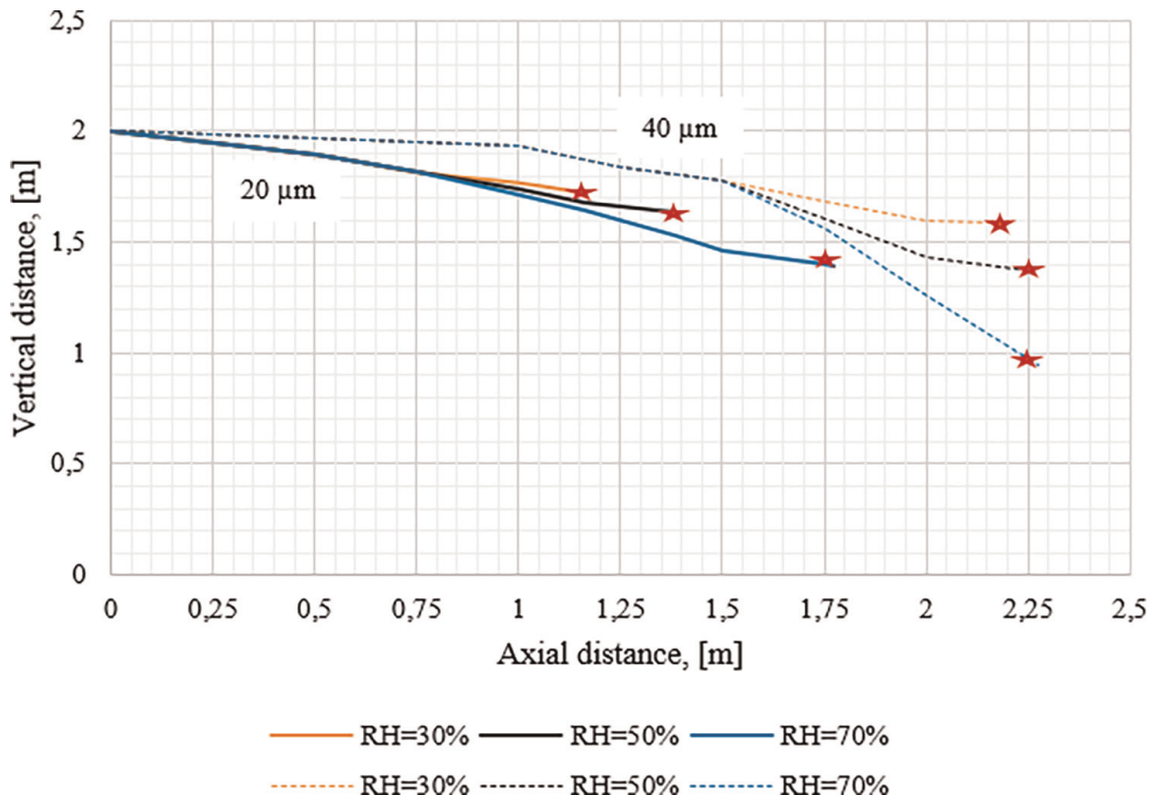

Figure 1.
Vertical and horizontal distance traveled by droplets with an initial diameter equal to 20 microns (continuous line) and 40 microns (dashed line) for three air relative humidity (RH) of 30%, 50%, and 70%. Air temperature and droplets' emission velocity equal to 20°C and 10 m/s (cough case) are considered boundary conditions. Figure elaborated from the results of [15].

Therefore, it is crucial to separate the two different transmission routes, since the evaporation of the infected droplet marks the boundary between two different modes of transport of the virions, i.e., through liquid or a solid carrier.

5. Methodology to compare droplet and airborne transmission modes

The data reported by [9], which identified and reported the link between ONP viral load and cell culture probability, were interpolated through the Matlab "curve fitting tool" by an interpolating equation of the fourth degree:

$$P(\lambda) = \alpha\lambda^4 + \beta\lambda^3 + \gamma\lambda^2 + \delta\lambda + \tau \tag{12}$$

where α, β, γ, δ, and τ are coefficients calculated equal to −0.3314, 9.34, −91.98, 385.2, and − 586.4, respectively. Based on these data, an R_2 equal to 0.9994 was calculated.

To compare airborne and droplet transmission modes, another relevant and open research question RQ4 is: What happens to viruses after complete droplet evaporation and if they retain their full potential for infection? The droplets produced from body secretions such as sneezing and coughing are not constituted of pure water and have a significant amount of residue or dissolved substances, including virions. While pure droplets evaporate completely, the real droplet evaporates to form a solid droplet residue or droplet nucleus. The final size of the droplet nucleus, once the droplet has evaporated to its crystallization diameter, will depend on the amount of the material dissolved [19]. Those residues potentially give a means for the virus to be further transported, provided that it survives the drying process. There is evidence supporting that viruses coated by a lipid membrane tend to retain their infectivity longer at low relative humidity [20]. However, the opposite is true in relevant counterexamples as discussed by [21]. There are many literature examples, in which virions' spreading after droplet evaporation is modeled by considering the virions i) entrapped in the droplet nuclei and ii) preserving their infectivity [22, 23]. Nevertheless, since there is no empirical evidence that i) virions are entrapped in the droplet nucleus, ii) multiple droplet nuclei can be generated by one droplet, and iii) dissolved substances (including virions) can be expelled by the droplet during evaporation, in this chapter, a different approach is suggested to compare droplet and airborne transmission modes. The idea is to compute the number of total droplets that an infected subject should emit to have the same number of airborne virions that touch the host surface in Brownian motion as those that impact the same surface being carried on a droplet of diameter D_G characterized by a medium concentration λ_0. Virions must traverse the distance to the target cell to infect it [24]. The same authors, to support the hypothesis of diffusion-limited infection, declared that it is not the amount of virus in a medium overlay in a culture well that determines the infectivity but the viral load.

Although several complex models exist to investigate the results of the impact of a droplet against a surface [25], it is assumed, for simplicity, that the impact area on which the virions are deposited is equal to the cross-sectional area of the droplet. Therefore, in the proposed model, the impact area is expressed as

$$S = \frac{\pi}{4} {D_G}^2. \tag{13}$$

The number of virions deposited by the droplet $N_{\text{virions,droplet}}$ [RNA copies] on the surface S is calculated as

$$N_{\text{virions,droplet}} = \frac{\pi}{6} {D_{G,0}}^6 \times \lambda_0. \tag{14}$$

Since the average SARS-CoV-2 virion diameter is 100 nm, the virions motion follows the Brownian mechanism once released from the droplet in the surrounding air. For the comparison, it is assumed that virions are dispersed in the volume of inhaled air: the underlying hypothesis is that all the virions can infect but are released in the air as single particles after droplet drying. Virions that can come into contact with the surface S are contained in a control volume V_c [m^3], defined as

$$V_c = S \times dz \tag{15}$$

where dz is the average diameter of the virion in [m]. The airborne viral load $\lambda_{\text{airborne}}$ [RNA copies/mL] required to deposit the same number of virions as those contained by a droplet of diameter D_G can be found as

$$\lambda_{\text{airborne}} = \frac{N_{\text{virions,droplet}}}{V_c}. \tag{16}$$

It is assumed that the droplet's diameter distribution remains the same over time. Therefore, the time required to achieve the airborne viral load $\lambda_{\text{airborne}}$ is calculated as

$$t = \frac{\lambda_{\text{airborne}} \times V}{\sum_{j=1}^{M} N_{\text{droplet},j,\mu} \times \left(V_j || \times \lambda_0\right) \times 0.6}. \tag{17}$$

where 0.6 is the correction factor used to convert the values in [droplets/(person × minute)] in the case of speech. The volume V, conservatively, can be assumed to equal the volume that a person emits during a conversation, which is 11.7 L/min, or 11,700 mL/min [26].

6. Strategies against SARS-CoV-2 direct transmission within confined spaces

The strategy to minimize the risk of virus spreading must avoid the viral load reaching the susceptible subject. Alternatively, any viral load that comes into contact with the host surface should be responsible for a negligible risk of infection, i.e., equal to or less than 10^5 virions/mL [9]. As for industrial practice where filtration processes are carried out in two stages, in an enclosed space where at least one infected subject and other susceptible occupants are present, the infection risk is minimized by adopting two filters. The first filter is the mask or any other barrier that physically blocks with sufficient effectiveness the larger droplets that are the droplets that, statistically, contain the greatest number of virions. **Figures 2** and **3** schematically represent, respectively, two subjects with and without the facial mask. Once emitted, droplets' trajectory toward the susceptible subjects depends on ambient air fluid dynamic and thermohygrometric conditions. Assuming the experimental data of [12], an infected subject who does not wear a mask emits during a conversation, on

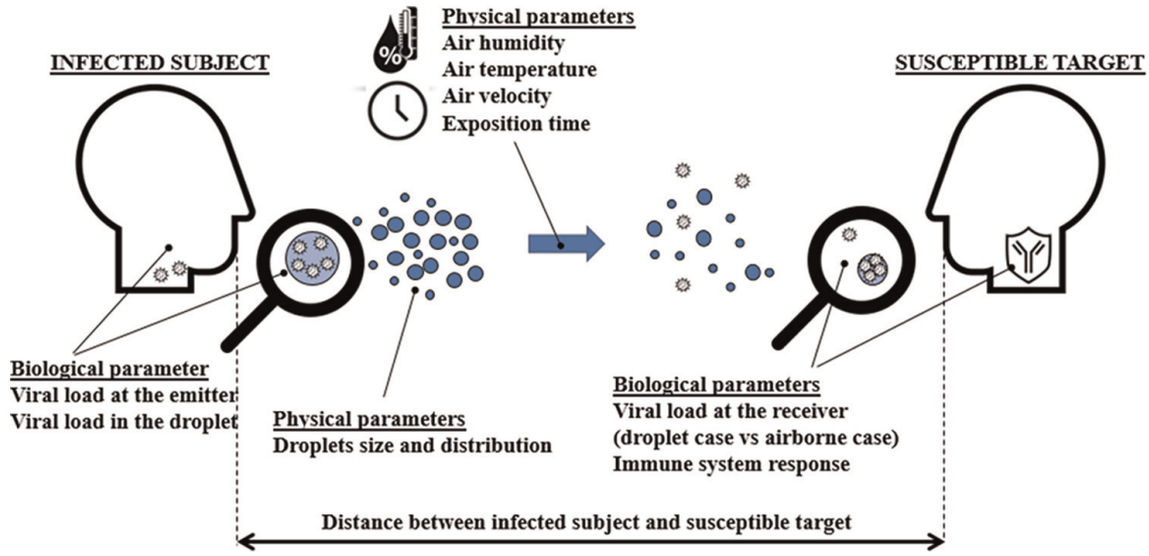

Figure 2.
Direct transmission occurring between infected and susceptible subjects that do not wear a mask or other physical barrier.

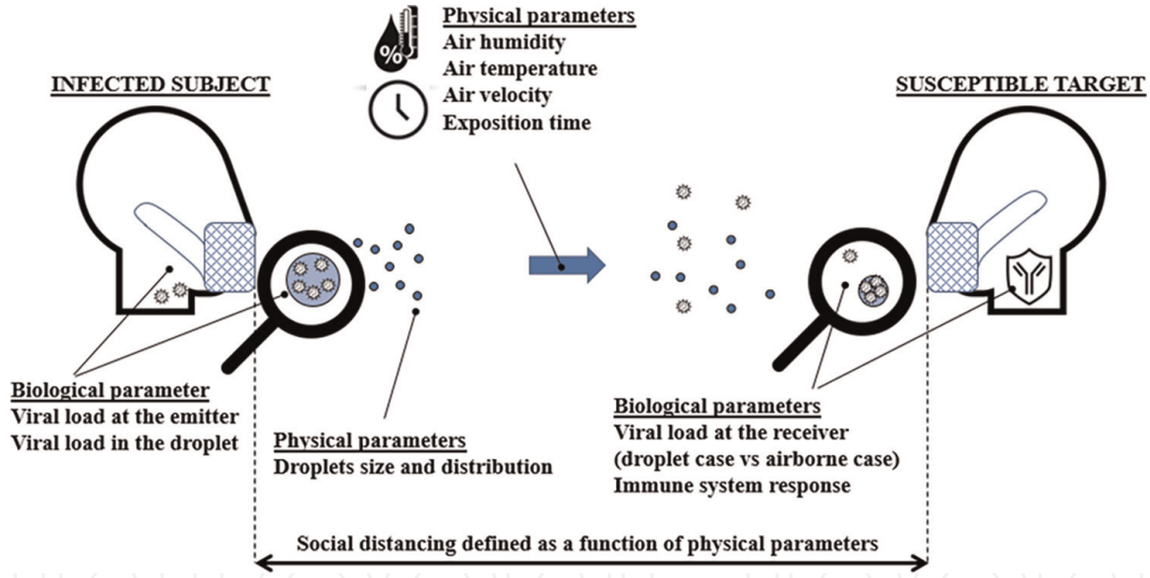

Figure 3.
Direct transmission occurring between infected and susceptible subjects that wear a mask or other physical barrier.

average, 460 droplets per minute whose size distribution is reported in **Figure 4**. In the worst case, the number of emitted droplets can be up to approximately 1850 per minute. On the other hand, conservatively, wearing a mask not all the droplets are captured, and vice versa, some of them escape due to the imperfect seal on the face [27]. Since no confirmation about the size of escaping particles is currently available, conservatively assuming a diameter less than or equal to 30 microns, for example, the rate of emitted droplets is about 10 times lower than the previous case. If higher tightness is achieved, a lower emission rate would be possible. For example, if the mask would block all the droplets with a diameter greater than 20 microns, the emission rate would be reduced by a factor of 30.

According to the shown data, coughing without a mask, almost 110 droplets per cough are emitted. Wearing a facial mask, the emission rate is reduced at least by a

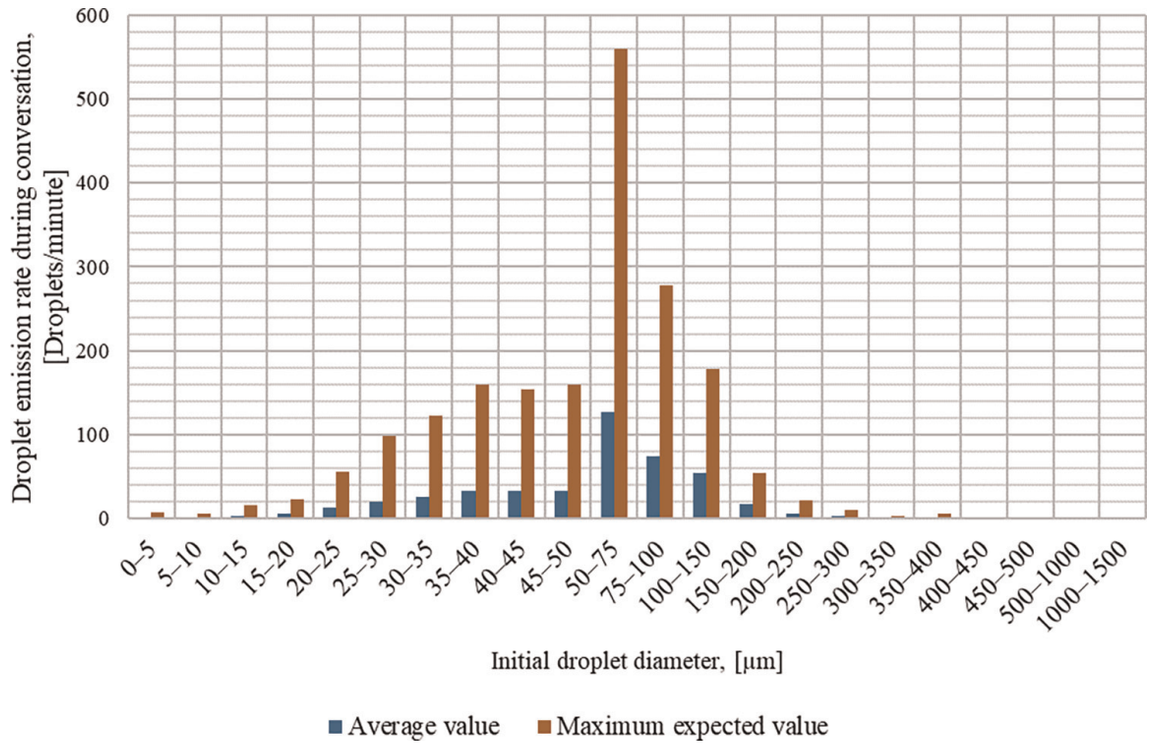

Figure 4.
Droplet rate emission during a conversation.

factor of 10. The role of the mask is even more evident considering the number of virions emitted in the environment. **Figure 5** shows that more than 87% of virions are emitted during speech within droplets having a diameter greater than 450 microns, i.e., 5% of the total emitted droplets. Therefore, assuming conservatively a threshold value of 30 microns (9% of the total emitted droplets), the droplets that can escape the facial mask during a speech carry, on average, about 0.0024% of the total virions. The same is for coughing. Better results would be achieved by tight facial masks. For example, let us assume a viral load at the emission equal to $10^{10.42}$ virions/mL. This value is the upper limit found in SARS-CoV-2 positive samples, and it refers to SARS-CoV-2 infection in the early stages of the COVID-19 pandemic [28]. If the same viral load characterizes all the droplets at the emission, the average virions emission rate is approximately 10 million virions per minute when no mask is worn. This value can achieve up to 45 million virions per minute for those infected subjects that emit more than the average, such as superemitters. Coughing without a mask, up to 58 million virions can be emitted per cough. Wearing a mask able to block droplets larger than 30 microns, the virions' emission rate can be reduced by a factor of 1000 or 50,000, respectively in the case of speech and cough.

Although the mask acts as the first element for reducing the risk of transmission of the infection, the infected droplets that escape are still a potential risk for susceptible individuals in the vicinity of an infected subject. Therefore, the second stage of filtration aims to minimize the infection risk occurring if the virion reaches the target negligible. The second barrier is immaterial and consists of the control of the air relative humidity and keeping a safe distance.

The safe distance is defined as the distance beyond which all the droplets have completely evaporated. The hypothesis is that all the carried virions are released into the surrounding ambient air and maintain their infectious potential. Therefore, droplet transmission is switched to airborne transmission. On the other hand, in the case of

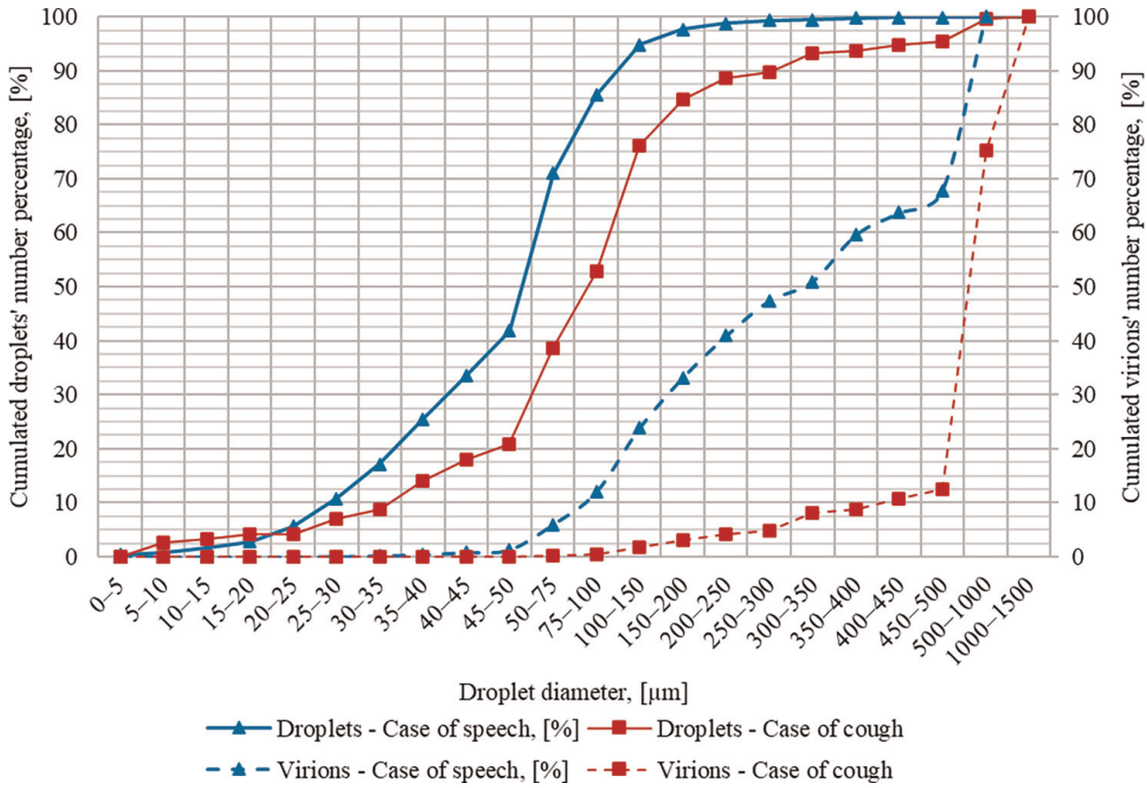

Figure 5.
Cumulative curves of the number of droplets (solid curve) and virions (dashed curve) during speech (blue) and cough (red).

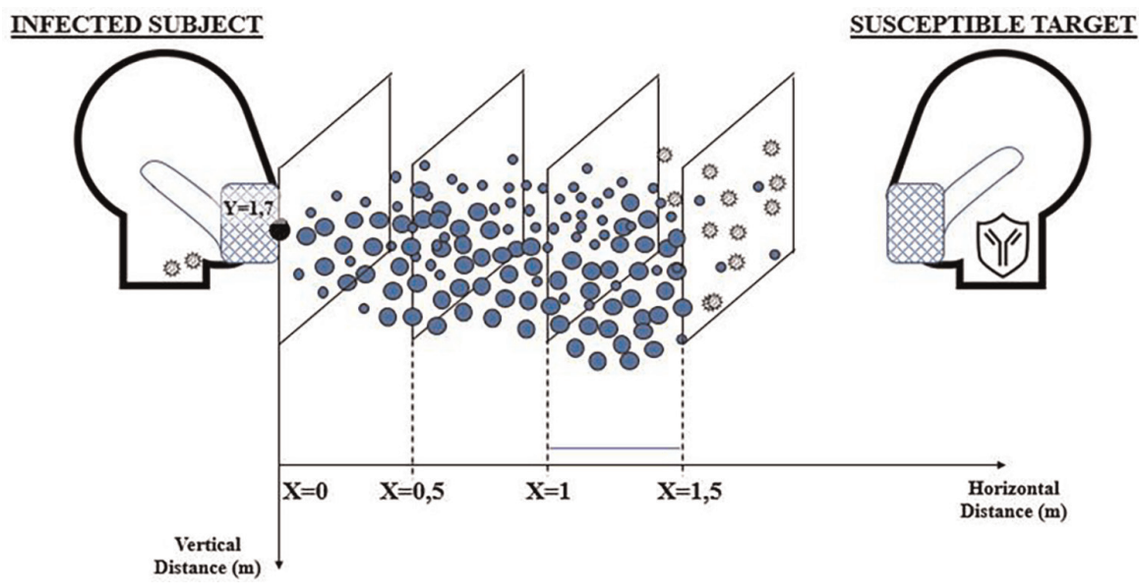

Figure 6.
Simplified scheme to investigate droplets' motion toward a susceptible target.

incomplete evaporation, the droplets reach the host surface at a viral load higher than the one they had at the emission. **Figure 6** shows infected and susceptible subjects, both equipped with masks. As the horizontal distance from the point of emission increases, the viral load of the infected droplets increases up to a maximum value calculated in Eq. (11). Regarding the scheme proposed in **Figures 6** and 7 shows the viral load of the droplets that come out of the mask with an initial diameter of 10

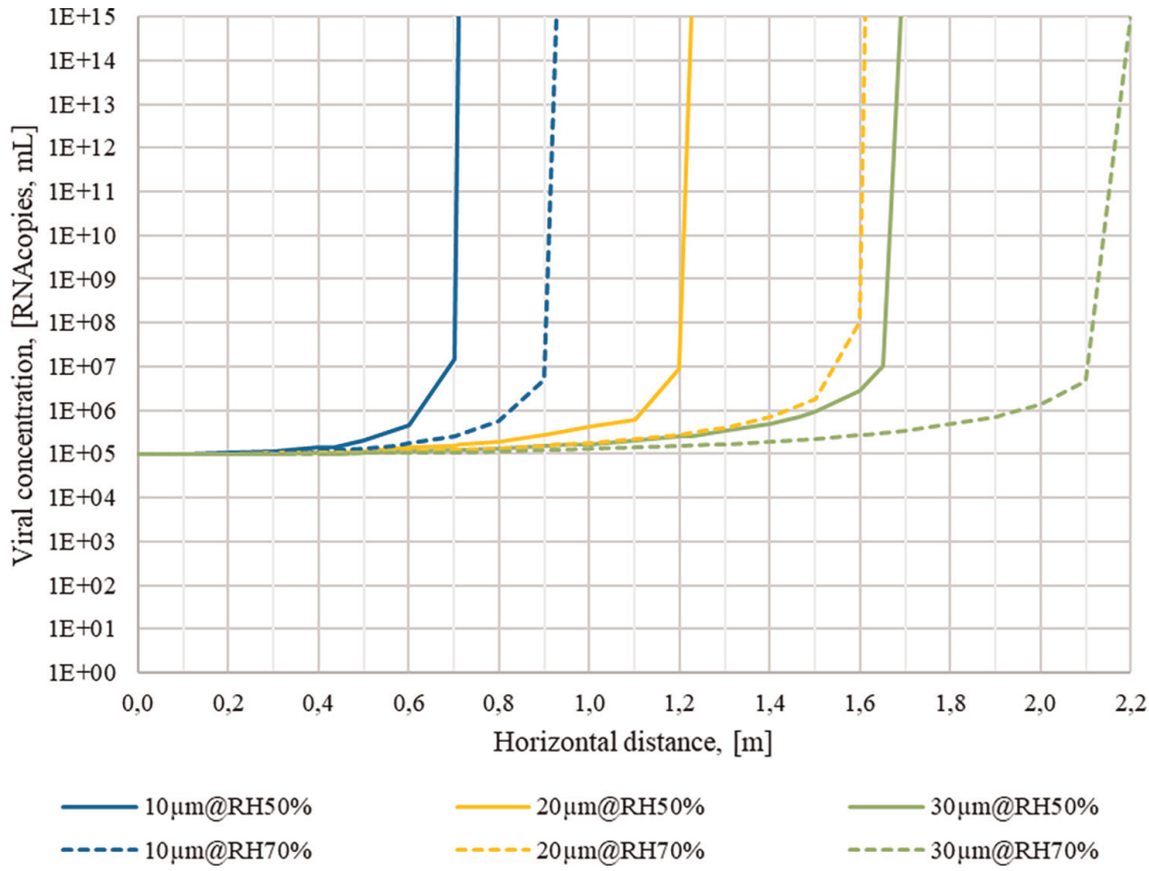

Figure 7.
The trend of the viral load through the horizontal distance from the infected subject. The continuous and dashed curves were calculated for 50% and 70% relative humidity, respectively.

microns, 20 microns, and 30 microns. The continuous curves refer to an air relative humidity equal to 50%, while the dashed ones refer to 70%. As the relative humidity increases, the front of the potential infection moves toward the susceptible subject. For example, the 30-micron droplets completely evaporate at 1.7 m for a relative humidity of 50%, while 2.2 m are necessary for a relative humidity of 70%. Therefore, at a distance of 1.8 m, an infected 30-micron droplet still conveys infecting particles with an air relative humidity of 70%.

Figure 8 shows in the ordinate axis the infection probability of the host surface when a 30-micron droplet deposits its viral load on it. The distance is shown on the abscissa axis. Two initial viral loads are examined: 10^5 virions/mL and 10^8 virions/mL, i.e., one thousand times greater. The second case simulates a variant of the original SARS-CoV-2 virus that causes a greater average viral load at emission [29]. Although an initial viral load equal to 10^5 virions/mL is responsible for a negligible viral replication probability, when air relative humidity is equal to 70%, the evaporation causes the increase of the viral load and so the infection probability. In the case of a higher viral load at the emission, the role of relative humidity concerning the risk of viral infection is even more evident. To control the relative humidity at 50% would guarantee the blockage of the infection front at a distance of almost 1.8 m from the infected subject. On the other hand, with increasing air relative humidity up to 70%, the 30-micron droplet completely evaporates at a distance of 2.2 m; furthermore, a viral load able to infect still exists between 1.8 and 2.2 m. Therefore, without the air relative humidity control, the infection front moves toward or away from the susceptible subject based on the existing environmental thermohygrometric conditions.

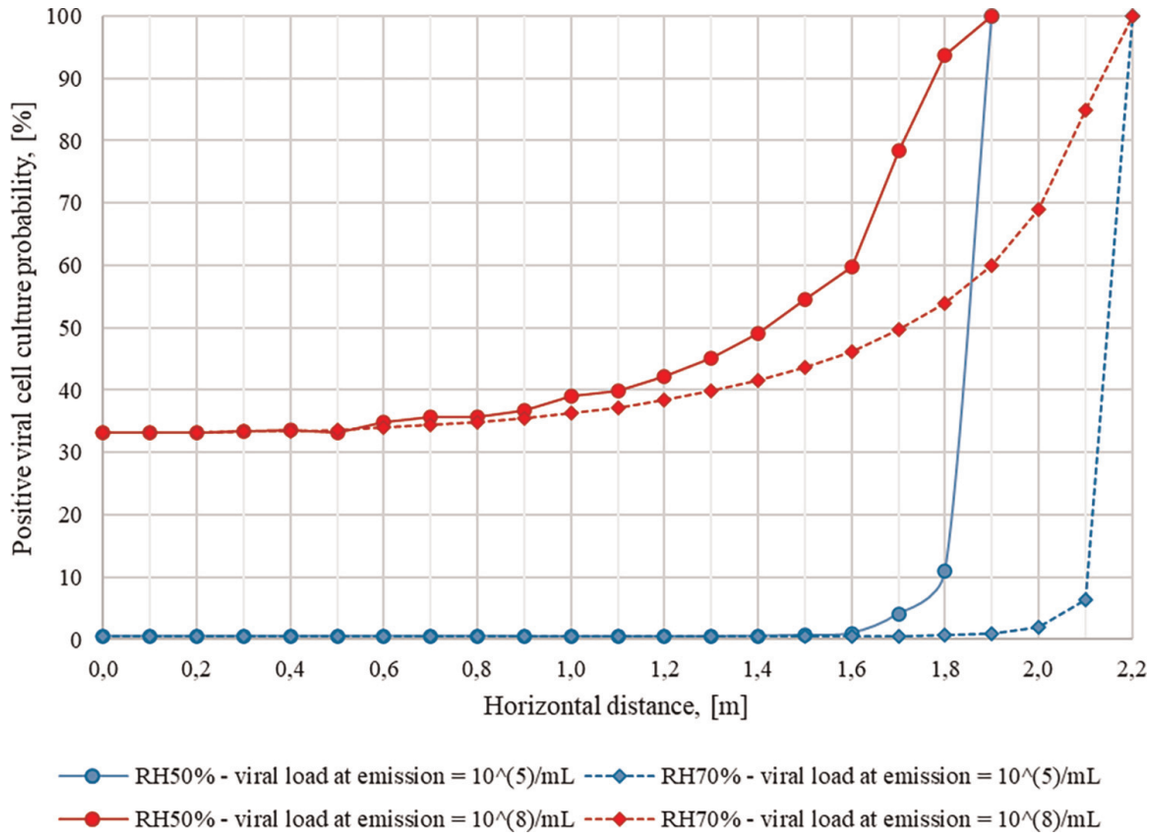

Figure 8.
Estimation of cell culture replication probability through horizontal distance. Initial viral load equal 10^8 virions/mL and 10^5 virions/mL are shown in red and blue, respectively. The continuous and dashed curves are calculated for 50% and 70% relative humidity, respectively.

Virions are released into the air when droplets completely evaporate. Since the virion's average size is 100 nm, Brownian motion occurs. Once released, the virions are wetted particles. However, the liquid film evaporates quickly since the ratio between the evaporating surface and the mass of water is high. In the specific case, since the mass of water does not fill the entire volume but only the external layer of the virions, airborne transmission occurs after the evaporation of the aqueous film. The authors conservatively assume that the minimum volume of air where the virions are released is equal to the volume of exhaled air. In the case of speech, it is 11.7 L/min [26]. Assuming two subjects, one of which is infected, who speak together, if all the droplets that escape the mask evaporate before reaching the host surfaces, the viral load in the volume is, on average, equal to 2.6×10^{-6} and 2.9×10^{-3} virions/mL, respectively, for an initial viral load of 10^5 and 10^8 virions/mL.

Based on these viral loads and the Brownian motion of the virions, airborne transmission causes a negligible infection risk. **Figure 9** shows that the virions that can reach the host surface are those inside the control volume highlighted in red, whose height is equal to the diameter of the virion (indicated as dz). Therefore, the probability of infection with the airborne transmission is much lower than for droplet one. In droplet transmission, infected droplets are blocked by the target surface through interception or impact mechanisms, thus determining a significant deposition of virions in terms of both number and load. For simplicity, it can be assumed that the target surface has a size equivalent to the cross section of the droplets, as shown schematically in **Figure 10**.

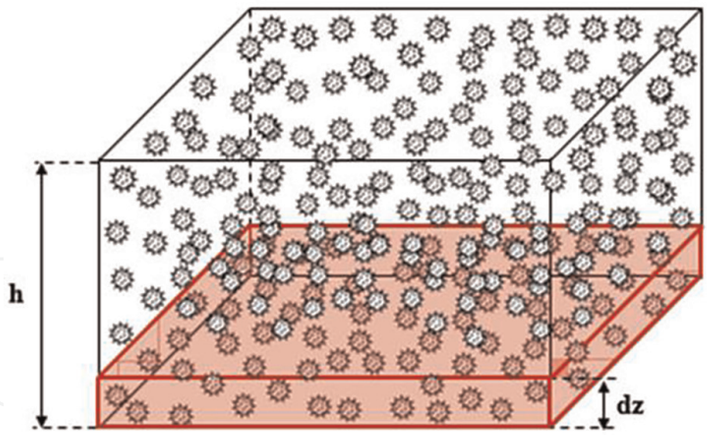

Figure 9.
The control volume where are located the virions that can touch the host surface is colored in red.

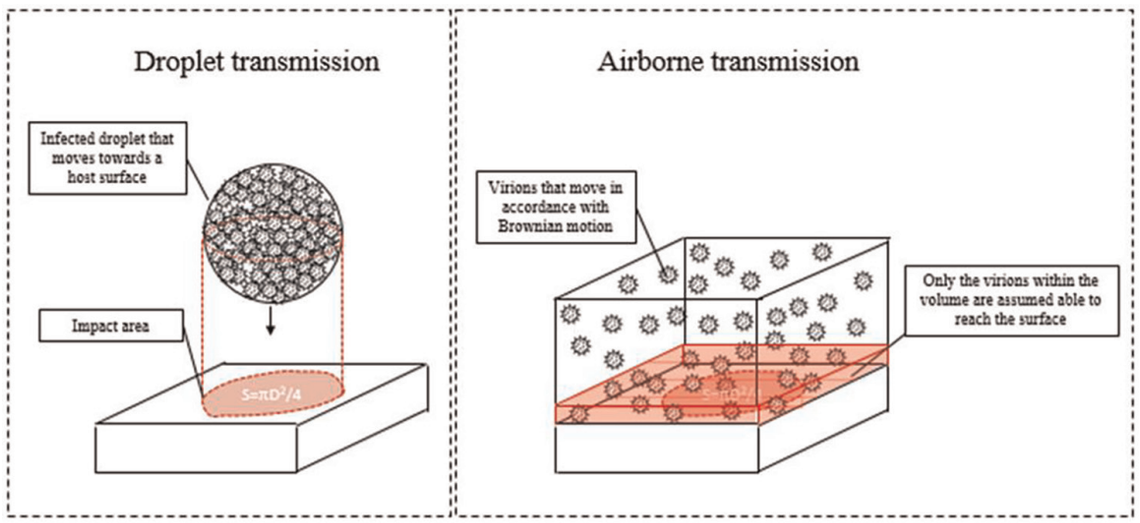

Figure 10.
Comparison between droplet transmission and airborne transmission.

To compare the airborne and droplet transmissions, the number of the infected droplets that have to evaporate to be equivalent to a single infected droplet that reaches the host surface before evaporating is calculated. **Figure 11** shows the results for a 10-micron droplet. The infected subject should emit 1.2×10^{14} droplets so that the number of virions that reach the host through airborne transmission is equivalent to the number released on the same surface by a 10-micron droplet. Assuming the worst case for the speech, i.e., an emission rate equal to 1850 drops per minute, it would take 6.5×10^{10} min for the infected subject to emit that number of drops, or a time interval several orders of magnitude longer than what, reasonably, two individuals employed to speech.

7. Conclusions

This chapter demonstrates that available knowledge is largely inadequate to make predictions on the reach of infectious droplets emitted during an emission

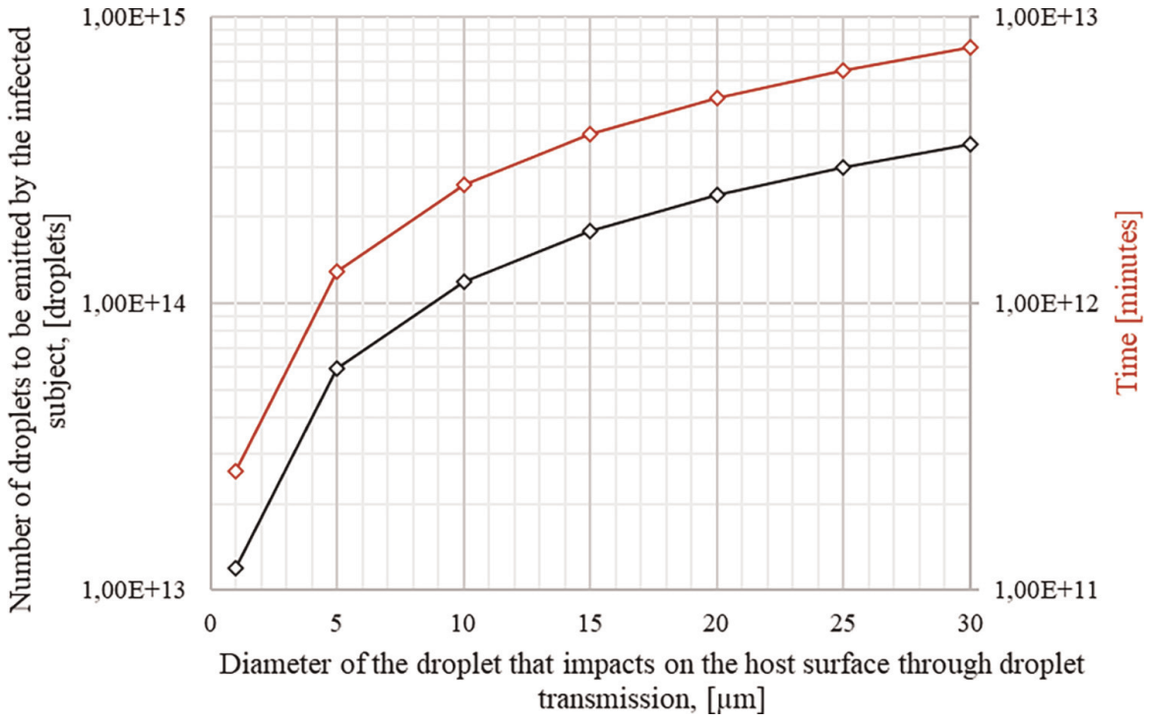

Figure 11.
Number of droplets that the infected subject must emit since the airborne transmission is equivalent to the droplet transmission of an infected droplet with a diameter between 1 and 30 microns.

phenomenon since several research questions still need to be properly addressed: i) standardized characterization of the sizes and distribution of the exhaled droplets for all the human expulsion processes; ii) definition of the initial viral load of emitted droplets and the relationship with the viral load present in oronasopharyngeal swabs; iii) the effect the virions can induce on the droplet evaporation process; and iv) what happens to viruses after complete droplet evaporation and if they retain their full potential for infection.

Nevertheless, in this chapter, some hypotheses have been described to model and compare different SARS-CoV-2 spreading routes. The results show that an effective preventive strategy against SARS-CoV-2 spread cannot neglect three elements: using the facial mask, controlling the relative humidity, and keeping social distance. Particularly, the control of air relative humidity in confined spaces is an essential element. The time an infected droplet takes to evaporate completely depends on the relative humidity of the ambient air. The droplet can move in suspension or settle on a surface, but it remains a potential danger until it completely evaporates. In this case, droplet transmission is substituted by airborne transmission, which should be associated with a modest risk of contagion. The use of the mask allows for blocking of the larger droplets; the control of the air relative humidity guarantees, as suggested in this chapter, that the escaping droplets evaporate until a defined time before reaching the susceptible target. On the other hand, the social distance concept loses its effectiveness. If there is high humidity in the environment, the droplets that escape the mask and that do not settle on the ground would remain in suspension without evaporating and for a relatively long time, significantly increasing the probability of infection [30]. In the worst case, i.e., in saturation conditions (relative humidity equal to 100%), evaporation time tends to infinity, making the concept of safe distance meaningless: at no point in the confined environment, it would be possible to guarantee the absence of virion-carrying droplets. Particular attention must be paid to avoid a susceptible

individual coming into contact with droplets that have not completely evaporated. In such a case, cells' infection risk increases as the droplets' viral load is greater than the initial one. The contact with not completely evaporated droplets could explain, in the case of variants such as, for example, the delta variant, characterized by an average emission load higher by a factor of 10^3 than those of the original virus [29], the greater transmissibility. As the results show, the higher load at the emission determines an increase in the probability of infection of the susceptible targets' cells, especially in the case of high relative humidity conditions when the infection front moves forward. Although there are still many points to be clarified about virus transmission, only through the combined control of the air relative humidity, the social distance, and the wearing of the facial mask, it will be possible to ensure safe conditions in confined places and to minimize infection cases.

Conflict of interest

The authors declare no conflict of interest.

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