Abstract

In the medical literature, three mutually non-exclusive modes of pathogen transmission associated with respiratory droplets are usually identified: contact, droplet, and airborne (or aerosol) transmission. The demarcation between droplet and airborne transmission is often based on a cut-off droplet diameter, most commonly 5 μm. We argue here that the infectivity of a droplet, and consequently the transmissivity of the virus, as a function of droplet size is a continuum, depending on numerous factors (gravitational settling rate, transport, and dispersion in a turbulent air jet, viral load and viral shedding, virus inactivation) that cannot be adequately characterized by a single droplet diameter. We propose instead that droplet and aerosol transmission should be replaced by a unique airborne transmission mode, to be distinguished from contact transmission.

KEYWORDS
aerosols, airborne, droplets, influenza, respiratory pathogens, SARS-CoV-2, transmission mode

INTRODUCTION

Knowledge of the fundamental biological and physical variables affecting transmission pathways of respiratory viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or influenza viruses is critical for the design of effective intervention strategies. The transmission pathways from the donor to the recipient host are highly complex, they are shaped by social context, and they involve processes across several biological levels of organization, from molecular mechanisms to behavioral patterns, as well as physico-chemical mechanisms. The interplay of physical properties such as the size of pathogen-carrying infectious droplets, within-host and population dynamical properties such as the host’s immune response, pathogen infectivity, contact rates, behavioral features of individuals such as proximity to infectious sources and duration of exposure, and social aspects such as living conditions are all part of a highly complex transmission process. This complexity has been reduced in the medical literature to three modes of pathogen transmission associated with respiratory droplets: they are usually designated as “contact,” “droplet,” and “airborne” (or aerosol) transmission modes. The generation of respiratory droplets and especially their fate after being expelled are the processes fundamental for this classification of transmission modes. Respiratory droplets are produced within the thoracic or extrathoracic human respiratory tract or outside the respiratory tract upon release of mucosalivary fluid by an infected person that breaks up during violent expiratory activities. All mechanisms of human oro-nasal activity such as breathing, speaking, laughing, coughing, sneezing, and singing produce particles within the inhalable range for humans.

According to the traditional view held by the biomedical community, the three transmission modes may be described as follows (see, eg, the isolation precautions guideline and its updates). Direct contact transmission occurs when infectious agents are transferred from one infected person to another person without a contaminated intermediate object or person, whereas indirect contact transmission involves the transfer of an infectious agent through a contaminated
intermediate object (fomite) or person. Droplet transmission refers to transmission by large droplets (diameter \( d_\text{L} > 5 \mu m \)) that are transported by the turbulent air flow generated by a violent expiratory event (coughing or sneezing). They are presumably sprayed and directly deposited upon the conjunctiva or mucus membranes of a susceptible host. Since large droplets deposit on environmental surfaces rather quickly by gravitational settling, droplet transmission is viewed to be important at close range: in still air, a 50 \( \mu m \) water droplet crosses a vertical 1.5 m distance in 20 seconds.\(^6\) Airborne (or aerosol transmission) is defined as pathogen transmission via inhalation of small respiratory droplets (typically \(<5 \mu m\): a 5 \( \mu m \) droplet settles gravitationally in still air within approximately 32 minutes). Given their small size they can deposit deep within the respiratory tract, including the alveolar region (see, eg, Vincent\(^7\) or Drossinos and Housiadas\(^9\)). These droplets, often referred to as “droplet nuclei,” are small enough to remain airborne sufficiently long to transmit the pathogen. Airborne transmission thus does not depend on direct face-to-face interactions.

It is important to stress that droplet diameter is a dynamic quantity. Respiratory droplets are generated in a high relative humidity environment: upon expulsion, their diameter equilibrates by shrinking to the usually lower ambient relative humidity and temperature via water evaporation. Hygroscopic growth may also occur for a recently emitted droplet which, after partial evaporation, may encounter locally higher relative humidity or when the warm and humid exhaled air encounters colder environments. Evaporation and condensation, being molecular processes, are very fast, depending on the instantaneous droplet diameter. The evaporation time to reach the droplet equilibrium diameter varies from milliseconds for small droplets, for example, those of droplet diameters smaller than 10 \( \mu m \), to seconds for larger droplets, for example, those greater than 100 \( \mu m \).\(^8\) Hence, even though the droplet diameter is a sensitive function of ambient conditions the relevant time scales are short (as is the gravitational settling time, see Reference 9 for an analysis of coupled evaporation and settling).

A related topic of current research interest is the size of an equilibrated droplet, the final residue size. Respiratory droplets are aqueous droplets containing nonvolatile species like organic and inorganic salts, surfactants and proteins, and microbes.\(^10\) The equilibrium droplet size and the evaporation rate depend on ambient conditions (temperature and humidity) as well as droplet properties, namely its chemical composition (presence of solutes) and droplet curvature (Kelvin effect). The combined effect of solute speciation and concentration (which decreases the droplet vapor pressure) and droplet curvature (which increases the droplet vapor pressure, but only becomes significant for diameters of aqueous droplets of less than approximately 0.5 \( \mu m \)) are collectively described by the Köhler curve.\(^11\) An initial estimate of the equilibrated droplet size was that it shrinks to half its initial size.\(^13\) More recent work considers the effect of droplet chemical composition (pure water with added salt and added glycoprotein [mucin] and surfactant) to find that the equilibrated diameter may be less than half the initial diameter.\(^12\)\(^13\) For pure saliva droplets the final droplet size was estimated to be about 20% of the initial droplet size for a variety of ambient conditions.\(^14\) Given the importance of the droplet size in determining its transport and deposition properties,\(^6\) the effect of respiratory-droplet composition on the final droplet size could become an important direction for future work. Herein, all droplet diameters are taken to be the locally equilibrated diameters, unless otherwise stated.

We contend that the received view of transmission modes becomes increasingly difficult to sustain in light of new experimental, empirical, and theoretical findings. In our view, the demarcation between the three transmission modes is arbitrary, and especially the distinction between droplet and aerosol transmission is not tenable any longer as it is not based on well-defined physical properties of droplets or their dynamics in a complex physical environment. For example, current estimates of large-droplet dispersion suggest that the exhaled buoyant turbulent flow may transport them to considerable distances (larger than 1 or 2 m) where they may be inhaled instead of directly deposited on an individual’s face, that is, large droplets usually associated with what is referred to in the biomedical literature as droplet transmission may behave as what is referred to as aerosols. We argue here for a view that describes modes of transmission as a continuum based on physical properties of exhaled droplets and their interactions with the environment and human behavior. A similar idea was recently proposed by Bahl et al.\(^15\)

We question this sharp dichotomy in that it considers the droplet diameter, through its effect on the droplet airborne lifetime, a good, in fact the only, proxy for the airborne transmissibility of the pathogen. It neglects that the infectious agent is the pathogen within the airborne droplet, not the droplet itself. This realization implies that other physical, biological, even behavioral effects, should be considered in a proper description of the transmission pathways. An early attempt,\(^16\) summarized in Reference,\(^17\) to quantify these processes and to combine them into a single number, the (airborne) basic reproduction number, showed that it depends on the transmission rate (a function of contact time, pathogen load, droplet-susceptible individual interaction, droplet deposition probability on the respiratory tract, infection probability), on the pathogen removal rate (via inhalation, pathogen inactivation, settling), on droplet generation rate (viral shedding), and on pathogen infectivity. A proper description of transmission modes should consider all these effects.

Merging the two non-contact transmission modes, large-droplet and aerosol, into a unique non-contact airborne transmission mode has significant repercussions for disease-spreading prevention and research priorities. Personal protective equipment is traditionally divided into source-control equipment (eg, surgical facemasks that partially block droplet shedding, thereby protecting nearby individuals providing “outward” protection) and susceptible-control (eg, N95 respirators that filter inhaled air, thereby protecting the wearer providing “inward” protection). This largely arbitrary separation is based on the acceptance of the existence of two distinct non-contact transmission modes. Both types of personal protective equipment contribute in different, but overlapping ways to preventing the spreading of a respiratory pathogen. Similarly, the specification of a well-defined spatial separation distance (social distancing) is based on the consideration of
a well-defined large-droplet transmission mode. Lastly, the realization that the non-contact transmission mode is a unique airborne mode would give impetus to developing new experimental and clinical-study designs to answer the many open questions related to respiratory modes of pathogen transmission.

2 | AIRBORNE TRANSMISSION: A UNIQUE NON-CONTACT TRANSMISSION MODE

Wells,19 expanding on Flügge,20 proposed the distinction between airborne and large-droplet transmission based on the airborne lifetime of respiratory droplets. Accordingly, airborne transmission, also referred to as aerosol transmission or transmission by droplet nuclei, is transmission attributed to the small emitted droplets that have rapidly dried out by evaporation in the transition from the respiratory-tract high relative humidity to the ambient relative humidity.17 In his classic study of airborne transmission, Wells19 investigated the relationship between droplet size, evaporation, and settling rate by studying the evaporation of falling droplets, referred to as the Wells evaporation-falling curve of droplets.21 The proposed classification was based solely on a single droplet removal process, gravitational settling in still ambient air, coupled to simultaneous water evaporation. A water droplet of 1 μm diameter settles (ie, crosses a typical vertical distance of approximately 1.5 m from the mouth of an infectious person to the ground) in approximately 12 hours, a 10 μm droplet in 9 minutes, and a 50 μm droplet in 20 seconds. The rapid decrease of the droplet airborne lifetime (for Stokesian particles of diameter \(d_p\), the gravitational settling time decreases as \(d_p^{-2}\) with increasing diameter) led to the rough demarcation between airborne and large-droplet transmission at the diameter value of 5 μm. This estimate has been universally accepted by health organizations and it still constitutes the basis for recommendations on non-pharmaceutical interventions. It is worth noting that Well’s original demarcation, based on his evaporation-falling curve, was at 100 μm,21 a droplet-diameter demarcation that is recently reconsidered.22 Since then, respiratory droplet evaporation has been extensively studied.\(^{12,21,23,24}\)

2.1 | Physico-chemical processes

The gravitational settling time, calculated in still air assuming well-mixed conditions and neglecting any spatial heterogeneity in the population distribution, does not exhibit a drastic change at the demarcation diameter, nor does the evaporation time. More importantly, this classification neglects the considerable recent efforts invested in understanding droplet transport and dispersion in a buoyant turbulent jet emitted in a spatially heterogeneous environment. Work by Bourouiba et al.\(^{25}\) and Bourouiba\(^{26}\) argues that momentum transfer from the expelled, high speed turbulent air jet during violent expiratory events (air velocities may vary from 12 m/s for a cough to 30 m/s for a sneeze) may extend particle airborne lifetimes from seconds to minutes. In addition, the coupling of flow entrainment of the droplet and buoyancy effects (coupled cloud-emitted droplet dynamics) may propel droplets (full spectrum of droplet sizes) to 7 to 8 m. Similar work was reported by Zhu et al.\(^{27}\) who noted that motion of particles larger than 300 μm is dominated by inertial effects and not by gravitation, 500 μm particles traversing 1.5 m ballistically. More recently, Feng et al.\(^{28}\) argued that microdroplets follow the airflow streamlines and can deposit on the head region of a person facing the infectious individual even at 3.0 m separation. This distance can be further extended by ambient air flow (light air, light, and moderate breeze). A similar observation was reported by Dbouk and Drikakis,\(^{23}\) who calculate that saliva droplets generated by coughing did not travel further than 2 m in still air, but could travel up to 6 m at wind speeds of 1.11 and 4.16 m/s. In short, the currently accepted demarcation does not respect basic aerosol-particle transport and dispersion properties in a turbulent jet. For a recent review of evidence for the horizontal distance crossed by an expelled respiratory droplet cf. Bahl et al.\(^{15}\)

Another significant droplet-dependent parameter is droplet shedding (emitted droplet number per expiratory event as a function of droplet diameter, an indication of the emitted viral load). Early work on droplet emission rates considered violent expiratory events,\(^{29,30}\) typical of infected individuals with symptoms, and to a lesser degree speaking. More recent work\(^{31–34}\) has concentrated on speaking, typical of asymptomatic individuals, and on the importance of super-emitters,\(^{31}\) that is, individuals who emit considerably more droplets than average. Whereas a critical analysis of experimental results on droplet generation is beyond the scope of this work, it suffices to mention that measured emitted-droplet diameters may vary from approximately 500 nm, or even smaller, to more than 500 μm, their diameter and emitted number per diameter varying with expiration mode and experimental technique. The original Duguid\(^\text{29}\) coughing data are unimodal, the droplet size distribution peaking at approximately 10 μm, the Loudon and Roberts\(^\text{20}\) coughing size-distribution is bimodal with peaks at 1.3 μm and 40-50 μm, whereas the speaking data (under different respiratory activities including breathing) reported by Morawska et al.\(^\text{34}\) are almost trimalodal, peaking at 0.80, 1.80, and 3.5 μm (speaking) with a smaller peak at 5.5 μm (speaking). Johnson et al.\(^\text{33}\) fitted their speaking and coughing data to three log-normal distributions peaking at (count mean diameters, approximately) 1.6, 2.5, and 145 μm. Their experimental droplet size distributions were mostly lower than those of Duguid\(^\text{29}\) and Loudon and Roberts,\(^\text{20}\) except at small diameters, at approximately 3 μm (coughing) or 7 to 8 μm (speaking). Asadi et al.\(^\text{31}\) noted increased droplet shedding due to speaking with increasing loudness, and increased emissions for speech compared to breathing. Average droplet shedding of approximately four particles per second was measured (the range being 1-14 particles/s, the larger rates attributable to speech super-emitters), the geometric mean diameter being 1.0-1.25 μm (depending on expiratory activity). The wide variation of measured droplet size distributions, and their dependence on an individual’s physiological characteristics, leads to a wide range of estimated viral shedding.

Droplet size is of paramount importance in determining the deposition location within the respiratory tract.\(^\text{6,7,11,35}\) The transmission of
some respiratory pathogens, for example mycobacterium tuberculosis, occurs via infection in the lower respiratory tract, and hence on inhalation of small droplets (<1 μm droplets) that can reach the alveolar region. For such diseases, the distinction between aerosol and large droplet transmission may be helpful. For other diseases, however, where infection may also start in the upper respiratory tract, the distinction is probably not useful. Corona Virus Disease 2019 (COVID-19) and influenza belong to the second category. For these, there are other factors related to successful transmission of the pathogen, such as viral load and whether the expired pathogen originates at the lower or upper respiratory tract, a factor that may be associated with the disease stage of the infected person. The resulting viral dose is of relevance for the inhaling susceptible together with proximity and duration of exposure. In addition, there might be a correlation between region of droplet generation within the respiratory tract and emitted size, as generated droplets may deposit in the respiratory tract during exhalation. However, the relation between viral dose and the probability of developing clinical symptoms is difficult to establish. It depends on viral density, viability, and viral contamination but also on other prognostic factors modifying the immune response and clinical outcome.

The per-droplet emitted viral load depends on the pathogen concentration in the oral fluid and the volume of the droplet. We consider that the average viral load (herein, the number of viruses) varies linearly with droplet volume, even though smaller droplet might be virus-enriched. The strong dependence of viral load on the droplet diameter (it varies as $d^{3}$) and the Stokesian settling time dependence on $d^{-2}$ may be construed as supporting evidence for the importance of contact transmission: large emitted droplets do not remain airborne for long times and they contain many pathogens. Once again, this argument lumps together numerous processes that determine pathogen transmissivity in a single number, the droplet diameter. It is worth noting that for an average oral-fluid virus RNA load of $7 \times 10^6$ copies per cm$^3$ a 5 μm droplet (arising from a droplet of 10 μm pre-evaporation diameter) contains on average $3.7 \times 10^{-3}$ RNA copies (the probability of a droplet containing a viral RNA copy being 0.37% assuming that the number of viruses in a droplet is Poisson distributed), whereas a 50 μm droplet (arising from an emitted 100 μm droplet) contains on average 3.67 RNA copies (the probability of a droplet containing a virus being 97.4%). For larger droplets, we may neglect evaporation to calculate that a non-evaporated 250 μm droplet would contain approximately 58 copies. This simple calculation suggests that droplet diameter is not sufficient to determine the infectivity of a droplet, and that at least viral shedding should be incorporated in the estimate, that is, the total emitted viral load per, for example, minute of speaking or per cough or sneeze should be considered.

### 2.2 Biological processes

Several biological processes affect the infectious airborne lifetime and infection probability. Droplet shedding, through the mechanism that induces an expiratory event, viral load (through the viral concentration in the respiratory-tract regions), minimum infectious dose, and virus inactivation contribute to the infectivity of a droplet. The 5 μm demarcation neglects these significant contributions to the infectivity of a droplet.

Higher viral load was associated with symptomatic infected patients compared to asymptomatic. Patients with lower respiratory tract clinical symptoms had higher viral loads than those with upper respiratory tract infection. Viral shedding lasts longer in hospitalized patients. This pattern may differ among respiratory infections and shows some variability between asymptomatic and symptomatic persons with the symptomatic being predominantly those with higher viral loads and viral shedding. Higher viral dose has been associated with the development of symptoms. Virus inactivation is another major determinant of airborne infectious lifetime. Since the review of Weber and Stilianakis research has continued to address the roles of temperature and humidity (relative or absolute) in the inactivation of aerosolized influenza A viruses and, more recently, of SARS-CoV-2 (eg, while environmental UV-radiation has received less attention. The resulting overall picture remains complex, in particular with regard to the interaction of temperature and humidity, but these studies confirm that both influenza A viruses and SARS-CoV-2 can remain viable in the aerosolized state for up to several hours and support the view that crowded, open-plan, poorly ventilated indoor environments offer suitable conditions for airborne transmission. Recent outbreaks of COVID-19 related to, in particular, meatpacking plants illustrate this risk connected to certain dry and cold indoor environments.

### 2.3 Epidemiological processes

The above considerations establish, in our view, the mechanistic basis for a unique non-contact airborne transmission mode. Building on this mechanistic foundation, a number of epidemiological models have attempted to shed further light onto the spatio-temporal transmission dynamics of pathogen-loaded respiratory droplets and non-pharmaceutical interventions such as the use of personal protective equipment. These models provide insights into the transmission dynamics of respiratory infections, such as influenza, by looking at the three currently defined transmission modes and their relative importance. They point to the potential of aerosol transmission to be a substantial route of transmission as well as the non-mutual exclusiveness of the modes. Models are sensitive to unmeasured or difficult to measure parameters such as viral load and droplet shedding. However, valuable epidemiological evidence to assess better the relative importance of these modes and to uncover the potentially important, and currently underestimated, airborne transmission mode is increasing. For example, the previously mentioned works on droplet transport and dispersion emphasize the importance of an external air flow, as provided for example by indoor ventilation, in estimating droplet-susceptible interactions. Robinson et al. explored spatial disease
dynamics by coupling droplet transport and population dynamics, to evaluate ventilation (ambient air flow), specifically uni-directional flow, as an efficient infection control measure. It concluded that in indoor ventilated environments, a threshold uni-directional ventilation velocity exists, such that at higher ambient-air velocities infection probability decreases since droplets are rapidly removed. It argued that the efficiency of ventilation as a control measure depends on the ambient air velocity and the spatial distribution of susceptible and infectious individuals.

Other measures address behavioral and social aspects affecting viral transmissivity, through their effect on person-to-person contacts and their duration. Using data from randomized control trials for personal protective equipment in households to reduce influenza transmission, Cowling et al.59 investigated the modes of transmission. The model estimated that aerosol transmission accounts for approximately half of all transmission events, indicating that measures to reduce transmission by contact or large droplets may not be sufficient for infection control.

Despite the lack of reliable estimates for model parameters, models provide, based on first principles, useful and robust insights into the fundamental underlying outbreak dynamics. Most models attribute to aerosol transmission a higher weight in contrast to the current credo in the biomedical community. New epidemiological findings on outbreak events65,66 provide support for this conclusion on the role of aerosol transmission. Both model results and the recent epidemiological findings also support the call for adaptations of the current classification, which would have implications for the design of control measures to contain transmission of respiratory pathogens.

3 | CONCLUSIONS

We suggest that the traditional distinction between droplet-nuclei (or aerosol or airborne) and large-droplet transmission is no longer tenable in view of the extensive theoretical and experimental work on respiratory droplets. It is our view that it should be replaced by a unique non-contact airborne transmission mode, a transmission mode distinct from contact transmission. This suggestion would also help to quell the sometimes vehement arguments over “aerosolization,” that is whether small droplet ($d_p < 5 \mu m$) transmission is a significant mode of transmission of SARS-CoV-2 (see, eg, the recent arguments in Peters et al.67 and the reply in Dancer et al.37).

One of the distinguishing features of SARS-CoV-2 is its long incubation period that consists of a latent period and the subsequent appearance of asymptomatic infections from which transmission can arise. Some of them recover without ever developing identifiable symptoms, while others will develop clinical symptoms. Violent expiratory events (coughing and sneezing) are associated with infected individuals with clinical symptoms. Asymptomatic individuals, however, contribute to viral spreading via normal respiratory activities: breathing, speaking, laughing, singing, and light coughs. In addition, their behavior remains unchanged, retaining the same average daily contacts and contact times with other individuals. It is, therefore, of great importance to understand the droplet shedding (and the associated viral load and airborne lifetimes of the emitted infectious droplets), and behavioral/social characteristics of these two groups, especially since it is currently believed that asymptomatic infectious individuals, whether on the way to develop symptoms or not, might make a substantial contribution to the transmission of SARS-CoV-2.

The work reviewed here suggests that the range and duration in which airborne droplets pose a significant infection risk for influenza A and SARS-CoV-2 may have been significantly underestimated. As a consequence, recommendations on the use of N95 or surgical masks or on spatial separation should be continuously reviewed in light of the emerging findings on the biophysics of airborne droplets. Given that, as argued here, the infectivity of a droplet, and consequently, the transmissivity of the virus, as a function of droplet size is a continuum, recommendations to always wear facemasks in indoor public areas, even if a spatial separation of at least 1 to 2 m can be observed, are, in our view, justified.

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CONFLICT OF INTEREST
The authors declare there is no conflict of interest.

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Nikolaos I. Stilianakis affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

DISCLOSURE
The views expressed in this article are purely those of the authors and may not, under any circumstances, be regarded as an official position of the European Commission.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.
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