



Transmissibility and transmission of respiratory viruses

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Abstract | Human respiratory virus infections lead to a spectrum of respiratory symptoms and disease severity, contributing to substantial morbidity, mortality and economic losses worldwide, as seen in the COVID-19 pandemic. Belonging to diverse families, respiratory viruses differ in how easy they spread (transmissibility) and the mechanism (modes) of transmission. Transmissibility as estimated by the basic reproduction number (R_0) or secondary attack rate is heterogeneous for the same virus. Respiratory viruses can be transmitted via four major modes of transmission: direct (physical) contact, indirect contact (fomite), (large) droplets and (fine) aerosols. We know little about the relative contribution of each mode to the transmission of a particular virus in different settings, and how its variation affects transmissibility and transmission dynamics. Discussion on the particle size threshold between droplets and aerosols and the importance of aerosol transmission for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus is ongoing. Mechanistic evidence supports the efficacies of non-pharmaceutical interventions with regard to virus reduction; however, more data are needed on their effectiveness in reducing transmission. Understanding the relative contribution of different modes to transmission is crucial to inform the effectiveness of non-pharmaceutical interventions in the population. Intervening against multiple modes of transmission should be more effective than acting on a single mode.

Human respiratory viruses include a broad range of viruses that infect cells of the respiratory tract, elicit respiratory and other symptoms, and are transmitted mainly by respiratory secretions of infected persons. Respiratory virus infections often cannot be differentiated clinically. Respiratory viruses belong to diverse virus families that differ in viral and genomic structures, populations susceptible to infection, disease severity, seasonality of circulation, transmissibility and modes of transmission. Together, they contribute to substantial morbidity¹, mortality² and concomitant economic losses³ annually worldwide. In addition, occasional pandemics cause extreme disruption to societies and economies as exemplified by the current COVID-19 pandemic. Until effective treatments or vaccines for COVID-19 are available, we have to rely heavily on population-based and individual-based public health measures to mitigate transmission. The effectiveness and the suitability of a non-pharmaceutical intervention (NPI) to mitigate transmission depends substantially on the ease of transmission (transmissibility) and the mechanism of transmission (modes of transmission) specific to that virus, as these interventions can target some but not all potential modes of transmission. Therefore, understanding how to evaluate the transmissibility and evidence

supporting different modes of transmission will aid in the control of respiratory virus transmission.

Previous reviews and commentaries discussed the transmissibility of influenza virus^{4,5}; methods for studying transmission, including animal models⁴⁻⁷, human models^{6,8} and epidemiological studies⁹; the mechanism and evidence for different modes of transmission^{4,6,7,9-12}; factors affecting transmission^{4,5,11,13}; controversies regarding the relative importance of different modes of transmission^{14,15}; pharmaceutical interventions¹ and NPIs^{11,16-18} for mitigating transmission¹⁶⁻¹⁹; and guidelines from public health agencies on infection prevention and control recommendations for respiratory viruses^{9,15}. These various aspects of transmissibility and transmission have been more comprehensively studied for influenza virus^{1-7,10,14,17,19} than for other respiratory viruses^{9,11,12,15,16,18}. In this Review, I will bring these discussions together to provide a broad overview of the transmissibility and modes of transmission of respiratory viruses, the approaches used to make these assessments, the viral, host and environmental determinants of transmission, and common NPIs for mitigating respiratory virus transmission, in the hope of illustrating the common approaches for studying respiratory virus transmission as well as the interconnection and

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differences between these discussions. I also discuss recent controversies regarding the role of aerosols in transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the difficulties in evaluating the relative contribution of each mode to the transmission of respiratory viruses.

Transmissibility

In the control of a novel pandemic, one of the most important early questions is how easily the disease will spread from an infected person to a susceptible person; that is, how transmissible the disease is. Transmissibility is determined by the infectivity of the pathogen, the contagiousness of the infected individual, the susceptibility of the exposed individual, the contact patterns between the infected individual and the exposed individual, and the environmental stress exerted on the pathogen during transmission. These will determine the scale and intensity of control measures needed to suppress transmission. In animal models, volunteer transmission studies, modelling studies and observational as well as interventional epidemiological studies, although the number of successful transmission events (that is, infection in the exposed individual) is often used as an outcome measure, these study designs answer different research questions when evaluating the transmissibility of a respiratory virus.

Evaluating transmissibility in animals and volunteers

Animal models are often used to compare the transmissibility of respiratory viruses with different naturally occurring or engineered genomic constructs to identify viral molecular determinants of increased transmissibility, or to compare the transmissibility between different modes of transmission (BOX 1). For example, for influenza virus, animal transmission studies have been used

to evaluate the molecular determinants of transmissibility²⁰, the airborne transmission potential of emerging viruses²¹ or drug-resistant viruses²², the relative importance of droplets and aerosols to transmission²³ and the anatomical site that drives the different routes of transmission²⁴. Alternatively, volunteer transmission studies, where transmission is observed in susceptible volunteers who are exposed to other volunteers who are either experimentally or naturally infected⁸, may be used to provide important information on the effectiveness of interventions and the importance of presymptomatic or asymptomatic transmission in a controlled setting²⁵. However, these studies can be challenging and expensive to conduct, and may be criticized as too artificial⁸.

Evaluating transmissibility in the population

Mathematical or statistical models are often used to estimate transmissibility of a respiratory virus in the population, especially during pandemics to assess the extent of transmission. With use of data from surveillance, observational and interventional epidemiological studies, or simulation from modelling studies, transmissibility is usually assessed by the estimation of the basic reproduction number (R_0) or secondary attack rate (SAR) (BOX 2). In addition, by comparing the two simultaneously, one can assess the role of specific populations (for example, households or schools)²⁶ or superspreading events²⁷ in driving community transmission.

Modes of transmission

Respiratory viruses are transmitted between individuals when the virus is released from the respiratory tract of an infected person and is transferred through the environment, leading to infection of the respiratory tract of an exposed and susceptible person. There are a number of different routes (or modes) through which transmission could occur, the chance of which is modified by viral, host and environmental factors. Although there is evidence in support of individual modes of transmission, the relative contribution of different modes to a successful transmission event, and the relative effect of each factor on each mode or multiple modes simultaneously, is often unknown.

Direct contact, indirect contact, droplet and aerosol

Respiratory viruses can be transmitted via respiratory secretions over multiple routes independently and simultaneously. Traditionally, it is believed that respiratory viruses are transmitted directly via physical contact between an infected individual (infecter) and a susceptible individual (infectee), indirectly via contact with contaminated surfaces or objects (fomites) or directly through the air from one respiratory tract to another via large respiratory droplets or via fine respiratory aerosols^{6,7} (FIG. 1). These four major modes of transmission (direct contact, indirect contact/fomite, droplet and aerosol) are often the foci of transmission control; for example, infection prevention and control measures in health-care settings are designed specifically for each mode²⁸. Some respiratory viruses, including influenza viruses, coronaviruses and rhinoviruses, can be recovered from faeces^{29,30} or infect cells in the gastrointestinal

Box 1 | Evaluating transmissibility in animal transmission studies

In the simplest form of animal transmission studies, naive ('infecter' or 'donor') animals are first inoculated with a candidate virus, with infection confirmed by the recovery of virus in respiratory specimens; other naive ('infectee' or 'contact') animals are then co-housed with the infected animals for some period to observe whether the contact animal subsequently acquires infection. The number of donor and contact animals used may vary, or multiple donor–contact pairs of animals are used, and transmissibility is assessed by counting the proportion of contact animals infected²⁰⁴. This basic design can be adjusted to study transmissibility for different modes of transmission: direct contact transmission studies are done by co-housing donor and contact animals in the same cage to allow all major modes of transmission to occur; airborne transmission studies are done by physically separating the donor and contact animals usually by an air-permeable barrier, with some distance between the cages or no distance, so only aerosol route, with or without the droplet route, of transmission can occur²⁰⁵; and fomite transmission studies are done by putting contact animals in the cage that was previously used to house the donor animals¹⁰⁸. Depending on the specific respiratory virus studied, costs, availability of reagents and desired pathogenesis, different animal models are available for transmission studies^{204,206,207}, including mice, guinea pigs, ferrets, Syrian hamsters and non-human primates. Transgenic or transduced mouse models may also be used to better mimic human pathogenesis when access to non-human primates is limited; for example, transgenic mice expressing the human ACE2 receptor as a model for coronavirus infection²⁰⁸. In animal transmission studies, it has been suggested that a minimum of four pairs of donor–contact animals per group is required for sufficient power to detect differences in transmissibility between experimental groups²⁰⁹, and this is usually considered as an accepted number to report in studies of influenza virus²¹⁰.

Box 2 | Basic reproduction number and secondary attack rate

Basic reproduction number

The reproduction number (denoted as R) is defined as the average number of successful transmissions per infectious individual in a population and can be estimated from mathematical models that describe the natural history of disease. The effective reproduction number (R_t) represents R at any time (t) during an epidemic. The basic reproduction number (R_0) is R at the start of an epidemic and represents the average number of secondary infections caused by a primary infection after its introduction to a completely susceptible population²¹¹. Therefore, R_0 is an important quantity that reflects the capacity of a virus to be transmitted (that is, transmissibility) and will inform the potential ease or difficulty in controlling transmission of the disease. Reported estimates of R_0 were heterogeneous between viruses and even for the same virus: R_0 for rhinovirus^{212,213}, parainfluenza virus²¹² and adenovirus^{212,214} was usually slightly above 1 to 5, R_0 for coronaviruses^{213,215} could be up to 8 (also based on a recent preprint²¹³), whereas R_0 for respiratory syncytial virus^{212,213}, influenza viruses²¹⁶, varicella zoster virus²¹⁷ and measles virus²¹⁸ may be as low as around 1 but could go up to above 5 or even above 10 (TABLE 1). Advanced model structures (for example, ‘susceptible–exposed–infectious–recovered’) or further compartmentation (for example, age, contact patterns or vaccination status) allow a more complex description of disease or transmission dynamics (for example, presymptomatic transmission⁹⁵, asymptomatic infection, waning immunity²¹⁹ or seasonality or contact patterns²²⁰), the prediction of impacts of interventions, or identifying the key factors required for such predictions²²¹. Incorporation of phylogenetic data into epidemiological models has identified important factors that drive influenza virus transmission at the population level^{222,223} and evaluated the transmissibility of emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants²²⁴. Furthermore, the effect of superspreading events on transmission may be described by a dispersion parameter (k), where for a disease with low dispersion most secondary infections are from only a small number of the most infectious individuals^{225,226}, and estimating ‘individual-based’ R instead of ‘population-based (mean)’ R could account for individual variations in contagiousness²²⁵. Therefore, R_0 takes on different values for different populations and scenarios^{216–218} and whether superspreading events are considered²²⁷, and comparing transmissibility between respiratory viruses directly on the basis of R_0 estimated from different studies will be challenging. An important application of R_0 is determining the herd immunity threshold needed for an epidemic to end²²⁸. During an epidemic when $R_t < 1$, which occurs when the proportion of immune individuals in the population reaches the herd immunity threshold, transmission decreases over time and the epidemic eventually ends. The modes of transmission and their virus, host and environmental determinants²¹¹ influence transmissibility by modulating how effective the contact allows transmission, once contact between susceptible and infectious individuals is established.

Secondary attack rate

The secondary attack rate (SAR) is defined as the proportion infected among those susceptible in contact with the primary case²²⁹. Some suggested calling it ‘secondary infection risk’, as the quantity refers to a proportion and not a rate²³⁰, because infection may not necessarily lead to symptomatic illness, and ‘symptomatic secondary infection risk’ could be used instead when one is referring to the risk of symptomatic infection²³¹. SAR is most frequently used to estimate the transmission risk in households^{232,233}, and sometimes in outbreaks if the index (primary) cases introducing the infection are known and supplemented with contact tracing^{27,234}; that is, case-ascertained studies where exposed individuals are followed up to observe them for infection once a primary case is ascertained²³⁵, either by identifying symptomatic illness or by systematic collection of a respiratory or serum specimen regardless of symptoms for laboratory-confirmed infection. The proportion of exposed household contacts with infection (that is, the household SAR) is then used to describe the transmission risk from the index member to household members. Similarly to R_0 , reported estimates of household SAR were heterogeneous, ranging between 1% and 38% for influenza virus²³⁰, and estimates were lower if infections were ascertained only in contacts with symptomatic illness excluding asymptomatic infections^{231,236,237}, or if only laboratory-confirmed illnesses were included²³⁸. For other respiratory viruses, household SARs for respiratory syncytial virus^{237,239} and coronaviruses²⁴⁰ generally fall in a similar range as for influenza virus, and are higher for rhinovirus²³⁸, parainfluenza virus^{237,241}, varicella zoster virus^{232,242} and measles virus^{232,243} (TABLE 1), but direct comparison between viruses is again challenging. Case-ascertained studies can be used to evaluate factors affecting transmission — for example, virus type/subtype, age, types of contact²⁴⁴, asymptomatic or presymptomatic transmission^{244,245} and pre-infection immunity^{237,238,242,245} — or the effectiveness of interventions, such as the postexposure prophylaxis use of antivirals²⁴⁶ and non-pharmaceutical interventions¹²⁵, and vaccine efficacy²⁴⁷. Individual-based hazard models and Bayesian Markov chain Monte Carlo techniques can account for multiple index cases, unobserved transmission or multiple covariates, for example, incorporating symptom onset data to estimate transmission risk within households versus outside households²⁴⁸, or viral shedding data to estimate the effectiveness of face masks and hand hygiene in reducing transmission²⁴⁹.

tract²⁹, suggesting infection may spread via faeces; for example, via aerosolization during toilet flushing³¹. Studies have shown SARS-CoV-2 in ocular secretions³² and influenza virus infection by ocular exposure³³, suggesting respiratory viruses might also be transmitted via exposure to the eyes.

Terminology and defining features of each mode of transmission. The lack of standardization of terminology and the defining features of each major mode of respiratory virus transmission, in particular the difficulty

to differentiate between ‘droplets’ and ‘aerosols’, has caused much confusion³⁴. Although the direct contact route traditionally refers to transmission via direct physical contact between infectors and infectees^{6,7,9}, some consider exposure to infectious (large) droplets as an additional form of contact transmission^{28,35,36}, sometimes using the term ‘droplet contact’ to describe transmission via droplets³⁷ and ‘direct contact’³⁵ or ‘close contact’³⁶ to describe transmission via both physical contact and exposure to droplets. The WHO uses ‘direct, indirect, or close contact’ to describe ‘contact and droplet

transmission, although it is unclear whether 'close contact' refers to transmission via droplets alone, direct (physical) contact alone or both^{38,39}. Some attempted to define 'close contact transmission' by proposing three subroutes as 'short-range airborne', 'large droplets' and 'immediate body-surface contact' to describe transmission in close proximity, where the last refers to an infectee in contact with the infector's immediate contaminated bodily surfaces (for example, skin and clothes), and is to be distinguished from the (distant) fomite route, which involves delayed and less frequent touching from a greater distance⁴⁰. Some use 'airborne' to describe transmission via droplets and aerosols as both can travel through the air⁹, whereas others use it to describe transmission via aerosols only^{6,12,28,39,41}.

In the 1930s, William F. Wells, who studied air bacteriology and the transmission of respiratory tuberculosis, proposed that the particle size of exhaled respiratory droplets influences how they are transported in the air, and could be classified as 'aerosols' or 'droplets', with

different implications to disease transmission⁴² (BOX 3). Subsequently, animal studies, experimental volunteer studies and observational epidemiological studies were conducted to study the transmission of respiratory syncytial virus (RSV), rhinovirus and influenza virus in homes and health-care settings^{43,44}. In recent years, on the basis of different aspects of particle behaviours⁴⁵, various particle size cut-offs, often in the range between 5 and 20 μm , have been used to differentiate particles as 'aerosols' or 'droplets'. For example, the cut-off at 5 μm used by many regulatory bodies^{35,38} is based on early studies of pulmonary tuberculosis that believed particles smaller than 5 μm would deposit in the pulmonary/alveolar region of the lung by settlement and initiate infection, whereas particles larger than 5 μm deposit in the nasal cavity by centrifugal force^{28,46,47}. Other studies put similar emphasis on the region of particle deposition in the human respiratory tract, and suggested that particles smaller than 10 μm reach and deposit in the pulmonary region^{12,45,48,49}, and particles of size between

Short-range transmission

- Droplet
- Aerosol
- Direct (physical) contact
- Indirect contact (fomite)

<1 μm
Aerosol

>100 μm
Droplet

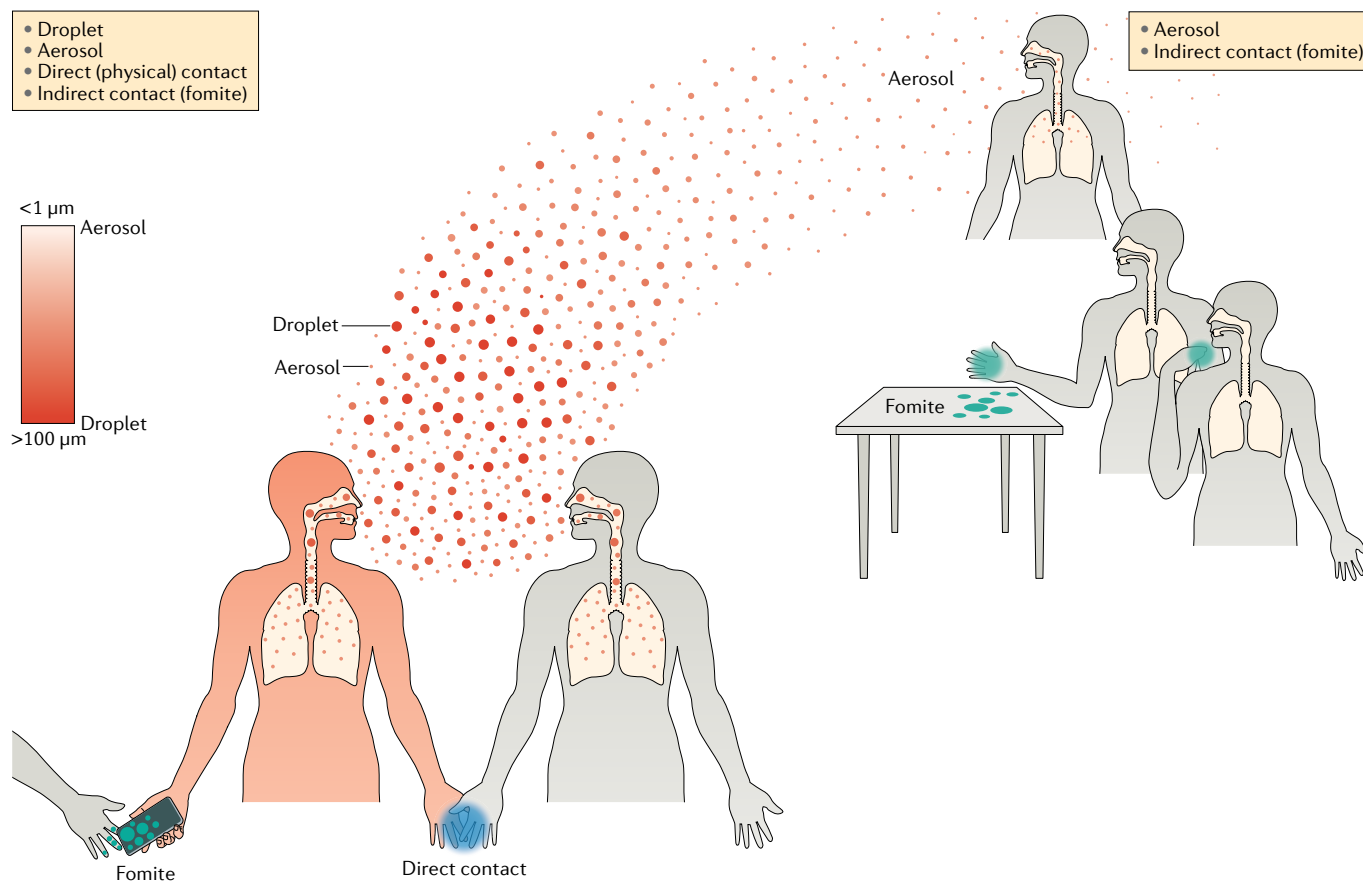


Fig. 1 | Major modes of transmission of respiratory viruses during short-range and long-range transmission. During an acute respiratory virus infection, an infected individual (infector; red) may shed virus in exhaled breath droplets and aerosols, and may also contaminate their immediate bodily surfaces (for example, skin and clothes) or surrounding objects and surfaces (for example, tables) with their respiratory secretions. In general, if a susceptible individual (infectee; grey) is close to the infector, short-range transmission may occur when the infectee breathes in the virus-laden droplets or aerosols released by the infector, during direct (physical)

contact with the infector or during physical contact with objects or surfaces contaminated (fomite) by the infector. If the infectee is at a distance from the infector, long-range transmission may occur when the infectee breathes in the virus-laden aerosols released by the infector or during physical contact with a fomite. However, the terminology and the defining features of each mode of respiratory virus transmission, especially regarding redefining the particle size threshold between droplets and aerosols, is under active discussion (see the section Terminology and defining features of modes of transmission).

Box 3 | Initial recognition of the importance of aerosols in disease transmission

Engineers coined the term ‘aerosol’ in the 1920s and defined it as a two-phase system consisting of a collection of solid or liquid particles and the gas in which they are suspended, exemplified by a wide range of products from combustion processes or meteorological phenomena such as dust, fume, mist and clouds, with particle size ranges from about 0.002 μm to more than 100 μm (in aerodynamic diameter)⁴⁸. A related term, ‘bioaerosol’, describes aerosols of biological origin such as viruses, bacteria, fungi, fungal spores and pollen⁴⁹. The term ‘aerosol’ is commonly used when ‘bioaerosol’ is actually meant; for example, the transmission of virus-laden aerosol particles is referred to as ‘aerosol transmission’. In the 1930s William F. Wells, who studied air bacteriology and the transmission of respiratory tuberculosis, proposed the differences between droplets and aerosols and their implications for transmission⁴². Wells suggested respiratory droplets expelled from the nose or mouth undergo evaporation, with smaller droplets evaporating almost immediately, while larger droplets (which may also be referred to as ‘drops’³⁴) settle to the ground rapidly without much evaporation⁴². He therefore hypothesized that “Transmission of infection through the air may therefore take one of two forms, depending on the size of the infected droplet. The more obvious form, recognized by Flügge, is droplet infection proper. It applies to droplets larger than 0.1 mm in diameter, which are rapidly removed from the air by gravity before they can dry and within a short distance from the source. The second form may be called air-borne infection and deals with the dried residues of infected droplets, or droplet nuclei, derived directly from droplets less than 0.1 mm in diameter, depending primarily on air for the buoyancy that keeps them suspended for longer times and carries them longer distances”²⁵⁰. In the 1940s he subsequently demonstrated the use of ultraviolet germicidal irradiation to prevent airborne transmission of measles in schools¹⁹⁶, and in the 1950s together with Richard L. Riley demonstrated the airborne transmission of tuberculosis¹⁶⁸.

10 and 100 μm are inspired but deposit in the head airways or tracheobronchial regions^{49,50}. Some consider particles smaller than 20 μm important for aerosol transmission as particles of 20 μm were estimated to take 4 minutes to settle on the ground from a height of 3 m, whereas particles smaller than 3 μm practically do not settle due to regular resuspension by air currents⁵¹.

A recent workshop on the airborne transmission of SARS-CoV-2 suggested referring to ‘aerosols’ as a stable suspension of solid and/or liquid particles in air, with a particle size cut-off set to an order of magnitude larger than previously thought (that is, ~30–100 μm), and ‘droplets’ as liquid particles that are larger than aerosols⁵². Some argued such dichotomization based on particle size alone has not accounted for the influence of expiratory activities on particle behaviour and proposed a turbulent gas cloud model to describe exhaled particle behaviour⁵³. The model describes exhaled air as primarily a multiphase turbulent gas cloud (‘puff’) that consists of clusters of exhaled particles mixed with ambient air, where the particles have sizes on a continuous scale and are carried forwards by the momentum of expiratory activities⁵³. The behaviour of exhaled particles is then influenced by conditions of both the ambient and the exhaled air, such as composition, temperature, humidity and airflow, highlighting the chance of larger droplets to be propelled further away than would be expected on the basis of particle size alone^{53,54}.

Increased concern for aerosol transmission. To many, bioaerosols (BOX 3) pose particular concerns in transmission control. As bioaerosols can remain airborne for a prolonged period and travel through the air over long distances^{55–60}, this potentiates disease transmission over long distances and therefore requires additional

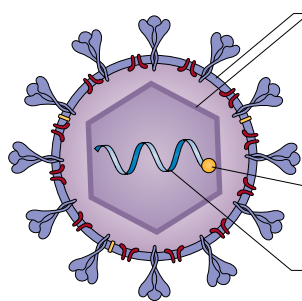
measures (for example, larger spatial separation between hospital beds²⁸). Individuals with higher bioaerosol production might contribute to superspreading events^{61,62}. Some hypothesize that the propensity of aerosol deposition in the lower respiratory tract⁴⁵ might require a lower infectious dose and lead to severer disease. Volunteer challenge studies showed that influenza virus and adenovirus infection initiated by the inhalation of infectious bioaerosols required a lower infectious dose^{51,63,64}, whereas rhinovirus might require a similar or a higher infectious dose⁵¹. Infection initiated by inhaling infectious influenza virus bioaerosols led to higher risk of fever compared with intranasal inoculation⁶⁵, although some studies alternatively suggested that infection initiated by droplets leads to severer disease due to a higher infectious dose⁶⁶. Alternatively, a narrower bottleneck of the minimum infectious virions required for transmission via aerosols may reduce virus diversity in the population and therefore the chance of a pandemic strain emerging⁶⁷, whereas a wider bottleneck via the contact route may allow the propagation of minor variants, such as drug-resistant viruses⁶⁸.

Determinants of transmission

Virus, host and environmental factors influence whether a successful transmission occurs by governing the infectivity of the respiratory virus, the contagiousness of the infector, the susceptibility of the exposed individual and the environmental stress on the virus (FIG. 2). These determinants may have different relative effects on each mode of transmission⁶⁹.

Viral determinants. The propensity for respiratory viruses to be transmitted is affected by virus stability under environmental stress^{70,71}, which in turn is influenced by the composition and structure of the virus envelope^{72,73}, capsid⁷⁴, internal proteins and genomes⁷⁵ as well as the formation of viral aggregates⁷⁶. For instance, DNA viruses such as herpesviruses (for example, varicella zoster virus (VZV)) with a more densely packaged genome have a stronger capsid structure that may prevent premature release of the viral genome before infection⁷⁷. RNA virus genomes such as those of influenza virus have higher mutation rates, giving rise to diverse viral genomic variants (quasispecies) in infected individuals⁷⁸, which may allow faster host adaptation of a virus strain that is efficiently transmitted via respiratory droplets⁷⁹. In addition to virus stability, other viral factors, such as viral protein expression and modification, also influence transmission. Viral surface and internal proteins can affect transmissibility by determining the site of infection and interacting with specific host receptors with differing binding specificity and affinity. In studies of the pandemic potential of avian influenza viruses, human adapted haemagglutinin (HA) and polymerase subunit PB2, which exhibit a preferential binding to α 2,6-linked sialic acids and support viral genome replication in the lower-temperature environment of the mammalian airway, respectively, conferred efficient transmission over the respiratory droplet route in ferrets⁸⁰. Similarly, an optimal ratio of HA to neuraminidase (NA) was essential for efficient transmission over

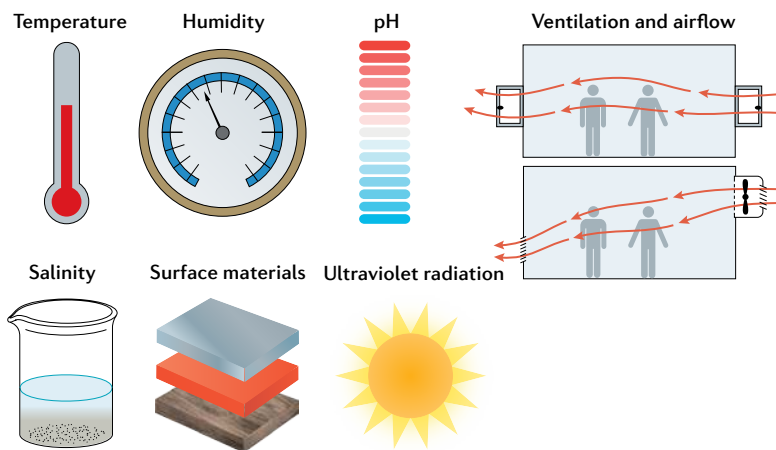
Viral determinants of virus survival and transmission



- Viral envelope (if present) and capsid**
 - **Surface protein expression and modification**
 - site of infection
 - host receptor binding specificity and affinity
 - formation of viral aggregates
 - **Capsid structure** → virus stability
- Internal proteins and viral genomes**
 - **Densely packaged** → virus stability
 - **Polymerase** → host-adapted virus replication
- Viral genomes**
 - **Mutations** → host adaptation

Environmental determinants of virus survival and transmission

The following environmental factors could influence virus survival, host susceptibility and human behaviour:



Host determinants of contagiousness, susceptibility and transmission

Factors affecting host contagiousness at the individual level

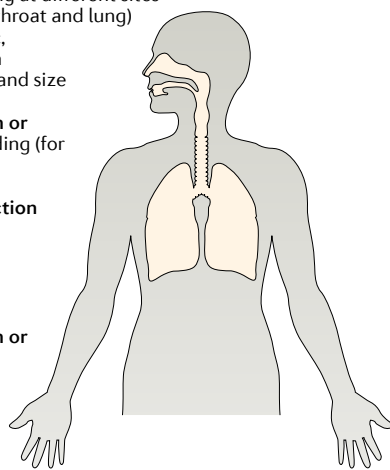
- **Tissue and cellular tropism** → viral shedding at different sites of the respiratory tract (for example, nose, throat and lung)
- **Symptom presentation** → presymptomatic, asymptomatic or symptomatic transmission
- **Lung function** → exhaled particle number and size distribution
- **Pre-existing immunity from prior infection or vaccination** → heterogeneity in viral shedding (for example, supershedder)

Factors affecting host susceptibility to infection at the individual level

- **Tissue-specific receptor expression, glycosylation and glycan expression**
 - site of infection
 - risk of infection
- **Pre-existing immunity from prior infection or vaccination** → risk of infection
- **Lung anatomy** → site of virus-laden particle deposition

Factors affecting transmission at the population level

- **Social contact patterns** → mode of transmission
- **Age-related mixing patterns** → age-specific risk of transmission



the respiratory droplet route²⁰, which is hypothesized to be associated with the release of single viral particles instead of aggregates with increased NA activity⁸¹. The loss of glycosylation sites at specific HA amino acid positions also conferred transmissibility to an avian influenza virus in a mammalian model⁸², thereby increasing its pandemic potential.

Fig. 2 | Viral, environmental and host determinants of respiratory virus transmission.

Virus, environmental and host factors influence whether a successful transmission occurs by governing the infectivity of the respiratory virus, the contagiousness of the infected person, the environmental stress on the virus, which affects its persistence and survival during transmission, and the susceptibility of the exposed person.

Environmental determinants. Environmental determinants could, on one hand, affect transmissibility by influencing the survival and persistence of respiratory viruses in respiratory droplets or fomites after their release to the environment, or on the other hand, modulate transmission by modulating host factors such as viral shedding and human behaviour. These effects could differ across different transmission modes and settings, and may favour one mode over another. As demonstrated mostly for influenza virus, environmental factors that may affect virus survival include temperature, humidity, salinity, pH, the medium or materials of the contaminated objects or surfaces, ventilation, airflow and ultraviolet radiation^{83,84}. Their effects on survival may differ between viruses⁸⁵, and their effects on transmission may be assessed in animal, epidemiological or modelling studies⁸⁶. Interestingly, although a higher temperature is usually associated with lower influenza virus survival, different studies have suggested that the association between influenza virus survival and relative humidity may follow a monotonic inverse or a U-shaped relationship¹³. For transmission, transmission risk assessment suggested non-fabric surface materials, compared with fabric surfaces, favour fomite transmission for RSV and rhinovirus but not for influenza virus in hospital rooms and aircraft cabins⁸⁷. In guinea pig models, a cold and dry environment was shown to favour influenza virus transmission, with the contact route dominating at higher temperatures⁸⁸. Alternatively, to explain the difference in seasonality of influenza virus circulation across regions with temperate, subtropical and tropical climates, ecological studies suggested that influenza virus transmission was favoured in a cold-and-dry climate if a lower threshold of humidity and temperature was reached; otherwise transmission was favoured in a humid-and-rainy climate when precipitation was greatest⁸⁹. However, it was unclear how much was due to changes in virus survival, host susceptibility, indoor crowding or the dominant route of transmission^{89,90}.

Host determinants. Host determinants in both infectors and infectees could affect the propensity of transmission or the preferential routes of transmission. For infectors, tissue and cellular tropism for productive virus replication in the respiratory tract determines the site of release of virus progeny. Compared with SARS-CoV, which replicates mainly in alveolar epithelium, SARS-CoV-2 replicates extensively in both bronchial and alveolar epithelia, which, together with other factors, might explain its more efficient transmission⁹¹. Host viral shedding could determine the contagiousness of the infector. However, nasal or throat viral shedding alone was inadequate to explain influenza A virus transmission in households⁹²,

suggesting the importance of other host factors (for example, variability in symptom presentation⁹³ or lung function⁹⁴) that may lead to heterogeneity in contagiousness and partially explain the presence of superspreaders and superspreading events. For SARS-CoV-2, some studies showed presymptomatic viral shedding and transmission⁹⁵, and similar levels of viral shedding⁹⁶ in asymptomatic and symptomatic infected individuals, demonstrating substantial 'silent' presymptomatic transmission or transmission from a substantial fraction of infected individuals who are asymptomatic⁹⁷ is possible. Pre-existing immunity⁹⁸ and vaccination history^{93,99} may also modulate virus shedding in infectors. For infectees, tissue-specific expression of viral receptors¹⁰⁰ or glycosylation and glycan expression¹⁰¹ along the respiratory tract determines the site of infection and may affect the preferential route of infection. Interestingly, despite the aerodynamic tendency of aerosols to deposit in the lower respiratory tract¹⁰², a preferential expression of ACE2 and the observation that virus-laden aerosols deposited mostly in the nose may indicate that virus-laden aerosols may initiate SARS-CoV-2 infection in the nasal cavity¹⁰⁰. Although host genetics is suggested to modulate infection severity upon virus exposure, less evidence is available for its role in the transmissibility and modes of transmission of respiratory viruses¹⁰³. At the population level, heterogeneous social contacts and age-related mixing patterns between infected and susceptible individuals drives transmission in specific groups or favours a particular route of transmission in different settings¹⁰⁴.

Evidence and relative importance of modes of transmission

Various approaches, including environmental sampling, experimental animal and volunteer transmission studies, and epidemiological observations (mostly from outbreak investigations), have been used to provide evidence in support of each individual mode of transmission for different respiratory viruses, although for each, some may criticize their relevance^{6,7}. Furthermore, although attempts have been made to classify each mode as 'obligate', 'preferential' or 'opportunistic'^{15,50}, limited research was done to quantify the relative importance of each mode to transmission⁹.

Evidence supporting individual modes of transmission.

There are different types of evidence in support of individual modes of transmission of common respiratory viruses in humans (TABLE 1). For the direct (physical) contact and the fomite routes, experimental studies demonstrated the survival of respiratory viruses on surfaces, although higher viral doses than would usually be identified in natural settings are usually used^{105,106}. Virus genetic material, and much less often infectious viruses, were recovered from patients' hands or naturally contaminated objects in homes, workplaces, day-care centres, nursing homes and hospitals^{105–107}. Experimental animal studies^{68,108} and limited experimental human^{109–111} or epidemiological¹¹² studies were able to demonstrate disease transmission via fomites in the absence of direct disease contact, droplets and aerosols. For the droplet and aerosol routes, collection of exhaled

breath from healthy individuals suggested human expiratory activities release respiratory droplet particles in a continuum of particle size, covering droplets or aerosols, via the mouth and nose. The particle sizes and their respective concentrations depend on the expiratory activities involved and the original sites of particle generation in the respiratory tract¹¹³. Although many recognize the generation of respiratory droplets and aerosols via talking, coughing and sneezing, additionally studies have demonstrated the exhalation of aerosols during normal breathing; such generation varies considerably between individuals^{94,113,114}. Furthermore, studies showed that exhaled particles could contain respiratory viruses¹¹⁵. Viral RNA (for example, influenza virus, rhinovirus and coronavirus RNA) was recovered from both exhaled breath droplets and aerosols of symptomatic infected individuals^{93,99,115}, but infectious virus has so far been only found in aerosols and not in droplets for influenza virus^{93,99,116}. Experimental animal studies of influenza virus¹⁰⁸, experimental human studies of rhinovirus¹¹⁷ and epidemiological studies of SARS-CoV¹¹⁸ have demonstrated transmission via respiratory droplets (including both droplets and aerosols); however, experimental animal studies of influenza virus^{23,119} and SARS-CoV-2 (REF.¹²⁰), experimental human studies of Coxsackie virus⁶³ (which belongs to the same family as rhinovirus) and epidemiological studies of influenza virus¹²¹ and rhinovirus¹²² have demonstrated that transmission likely occurs via aerosols. Epidemiological studies observed reduced SARS-CoV transmission associated with the use of masks and respirators in health-care settings¹²³ and reduced influenza virus transmission after disinfection of room air by ultraviolet light¹²⁴, suggestive of the role of aerosols and/or droplets in the transmission. Notably, few studies have demonstrated transmission via droplets only in the absence of aerosols, direct physical contact and fomites^{7,62}.

Relative importance of modes of transmission. Very few experimental human transmission or epidemiological studies have evaluated the relative importance of different modes of transmission in the same study^{25,117,125}. In a human challenge transmission study of rhinovirus, the authors observed that droplet and aerosol routes alone were sufficient to allow rhinovirus transmission to occur, whereas transmission via fomites was not observed (in the article 'aerosols' probably refers to both droplets and aerosols)¹¹⁷. In a recent similar study of influenza virus²⁵, by attributing its failure to achieve the targeted SAR to a higher ventilation rate when compared with an earlier proof-of-concept study¹²⁶, the authors suggested aerosol transmission was more important than transmission via the large droplet and contact routes.

Alternatively, the relative importance of different modes of transmission in different circumstances may be evaluated using mathematical mechanistic models, simulations and risk analyses; for example, outbreaks in aircraft³⁶, on cruise ships¹²⁷ and in health-care settings⁶¹ or during patient care¹²⁸ (for example, in households^{49,129}). By describing the efficiency of virus transfer at each step of a transmission route and coupled with a dose–response model with reference to

Table 1 | Transmissibility of, modes of transmission of and transmission-based precautions for common respiratory viruses in humans

Transmissibility and transmission	HCoV	IV	MeV	PIV	RSV	HMPV	VZV	RhV	HAdV ^a
Transmissibility^b									
Basic reproduction number (R_0)	0.5–8.0	1.0–21.0	1.4–770	2.3–2.7	0.9–21.9	–	1.2–16.9	1.2–2.7	2.3–5.1
Household SAR (%)	0–38.2	1.4–38.0	52.0–84.6	36.0–67.0	11.6–39.3	–	61.0–78.1	28.0–58.0	–
Evidence for direct contact transmission^c									
Infectious virus survival on experimentally contaminated hands ^d	✓	✓	–	✓	✓	–	✓	✓	–
Virus genetic material recovered on naturally contaminated hands	–	–	–	–	–	–	✓	✓	–
Infectious virus recovered on naturally contaminated hands	–	–	–	–	–	–	–	✓	–
Transfer of virus genetic material between hands experimentally	–	✓	–	–	–	–	–	–	–
Transfer of infectious virus between hands experimentally	–	–	–	–	✓	–	–	✓	–
Infection initiated via exposure to infectious virus on hands demonstrated in volunteer studies	–	–	–	–	–	–	–	✓	–
Transmission of laboratory-confirmed infection via hands demonstrated in observational studies	✓	✓	✓	–	✓	–	–	–	✓
Transmission of laboratory-confirmed infection via hands demonstrated in volunteer studies	–	✓	–	–	–	–	–	✓	–
Evidence for indirect contact (fomite) transmission^c									
Infectious virus survival on experimentally contaminated surfaces ^d	✓	✓	–	✓	✓	✓	✓	✓	✓
Virus genetic material recovered on naturally contaminated surfaces	✓	✓	✓	✓	–	–	✓	✓	✓
Infectious virus recovered on naturally contaminated surfaces	✓	✓	–	–	–	–	–	✓	✓
Transfer of virus genetic material between hands and surfaces experimentally	–	✓	–	–	–	–	–	✓	–
Transfer of infectious virus between hands and surfaces experimentally	–	✓	–	✓	✓	–	–	✓	✓
Infection initiated via exposure to infectious virus on surfaces demonstrated in volunteer studies	–	–	–	–	–	–	–	–	–
Transmission of laboratory-confirmed infection via surfaces demonstrated in observational studies	✓	–	–	–	–	–	✓	–	–
Transmission of laboratory-confirmed infection via surfaces demonstrated in volunteer studies	–	–	–	–	✓	–	–	✓	–
Evidence for droplet transmission^{c,e}									
Infectious virus survival in experimentally generated droplets	–	✓	–	(✓)	–	–	–	–	–
Virus genetic material recovered in droplets in human exhaled breath ^f	(✓)	(✓)	–	(✓)	(✓)	(✓)	–	(✓)	–
Infectious virus recovered in droplets in human exhaled breath	–	(✓)	–	–	–	–	–	–	–
Virus genetic material recovered in droplets in the air	(✓)	(✓)	(✓)	–	(✓)	–	–	(✓)	(✓)
Infectious virus recovered in droplets in the air	–	–	–	–	(✓)	–	–	–	–
Infection initiated via exposure to infectious virus in droplets demonstrated in volunteer studies	✓	✓	–	–	✓	✓	–	✓	(✓)
Transmission of laboratory-confirmed infection via droplets demonstrated in observational studies	–	–	–	–	–	–	–	–	–
Transmission of laboratory-confirmed infection via droplets demonstrated in volunteer studies	–	–	–	–	–	–	–	–	–

Table 1 (cont.) | Transmissibility of, modes of transmission of and transmission-based precautions for common respiratory viruses in humans

Transmissibility and transmission	HCoV	IV	MeV	PIV	RSV	HMPV	VZV	RhV	HAdV ^a
Evidence for aerosol transmission^{c,e}									
Infectious virus survival in experimentally generated aerosols	✓	✓	✓	✓	✓	–	–	–	✓
Virus genetic material recovered in aerosols in human exhaled breath ^f	✓	✓	–	✓	✓	✓	–	✓	–
Infectious virus recovered in aerosols in human exhaled breath	–	✓	–	–	–	–	–	–	–
Virus genetic material recovered in aerosols in the air	✓	✓	✓	✓	✓	–	✓	✓	✓
Infectious virus recovered in aerosols in the air	✓	✓	–	–	✓	–	–	–	–
Infection initiated via exposure to infectious virus in aerosols demonstrated in volunteer studies	–	✓	–	–	–	–	–	✓	✓
Transmission of laboratory-confirmed infection via aerosols demonstrated in observational studies	✓	✓	✓	–	–	–	✓	–	–
Transmission of laboratory-confirmed infection via aerosols demonstrated in volunteer studies	–	–	✓	–	–	–	✓	✓	–
Transmission-based precautions in health-care settings^g									
Contact precautions ^h	Y	Y	N	Y	Y	Y	N	Y	Y
Droplet precautions	Y	Y	N	Y	Y	Y	N	Y	Y
Airborne precautions	N	N	Y	N	N	N	Y	N	N

See Supplementary Table 1 for supporting references as well as evidence stratified by coronavirus types or influenza virus (IV) types/subtypes. Human bocavirus is not shown due to a lack of evidence regarding all modes of transmission. HAdV, human adenovirus; HCoV, human coronavirus; HMPV, human metapneumovirus; MeV, measles virus; N, not recommended; PIV, parainfluenza virus; RhV, rhinovirus; RSV, respiratory syncytial virus; SAR, secondary attack rate; VZV, varicella zoster virus; Y, recommended; ✓, evidence identified; (✓), evidence identified only in particles with aerodynamic diameter between 5 and 100 µm (applicable to droplet transmission only); –, evidence not found. ^aHAdV types that are considered mainly respiratory (but not enteric) are included. ^bThe range of reported estimates of the mean or median is provided. Estimates of household SAR in the absence of interventions were extracted where possible. ^cObservational studies include epidemiological or outbreak investigations, whereas volunteer studies include challenge studies or randomized (controlled) trials. ^dData include contamination by direct virus inoculation or contamination by volunteers who were experimentally infected. ^eParticles with aerodynamic diameter larger than 5 µm are traditionally defined as droplets, whereas those with a smaller aerodynamic diameter are defined as aerosols. However, there is ongoing discussion on redefining the particle size threshold between droplets and aerosols (see the section Terminology and defining features of modes of transmission). Therefore, for evidence on droplet transmission, evidence is provided in parentheses if evidence of virus recovery is identified only in particles with aerodynamic diameter between 5 and 100 µm. Air samples collected without size fractionation but that were collected more than 2 m from a known source (for example, an infected individual) are considered as evidence suggestive of aerosols. ^fEvidence for virus genetic material recovered in droplets or aerosols in human exhaled breath for PIV, RSV and HMPV is based on the author's own additional data of the published study⁹³. ^gEach precaution represents a set of infection prevention and control practices and personal protective equipment recommended by the WHO for health-care workers during routine patient care (excluding aerosol-generating procedures) within health-care facilities, with consideration of the current understanding on the modes of transmission of the respective pathogen. ^hFor IV, contact precautions are recommended for zoonotic IV only but not for endemic or pandemic IV.

the minimal infectious virus dose needed to initiate infection, one may estimate the relative infection risk between routes, thereby identifying the major transmission route in a particular circumstance. Furthermore, these approaches can also inform the likely values of the impact of individual determinants¹³⁰ on each route, and the potential effectiveness of route-specific interventions such as face coverings¹²⁸, and allow comparison of the major transmission modes between viruses³⁶. However, a particular challenge for this approach is to identify the minimal infectious dose required for the virus to establish infection via a specific transmission mode.

Aerosol transmission of SARS-CoV-2 and influenza virus

Historically, national and international agencies commonly consider respiratory viruses to be transmitted over the contact and/or droplet route, and exercise caution when one is considering the possibility of aerosol transmission^{28,131}. However in recent years, more researchers have advocated the recognition of the importance of aerosol transmission^{12,132}. The recent controversy regarding aerosol transmission of SARS-CoV-2

reflects the perspectives and long-standing challenges in evaluating the relative importance of each mode of transmission for respiratory viruses.

The report by the WHO–China Joint Mission on Coronavirus Disease 2019 (REF.¹³³) published on 28 February 2020 stated that “airborne spread has not been reported for COVID-19 and it is not believed to be a major driver of transmission based on available evidence; however, it can be envisaged if certain aerosol-generating procedures are conducted in health-care facilities”. The initial perception was that droplets and fomites were the major routes of transmission for SARS-CoV-2. However, as more data on SARS-CoV-2 transmission became available, on 27 March, the WHO published another scientific brief specifically on the modes of SARS-CoV-2 transmission³⁸. It described droplet transmission as transmission that occurs through infective respiratory droplets of diameter larger than 5 µm to 10 µm or fomites in the immediate environment around the infected person, and airborne transmission through infective droplet nuclei smaller than 5 µm (REF.³⁸). Addressing the findings of SARS-CoV-2 remaining infectious in artificially generated aerosols for 3 hours or more¹³⁴ and the absence of

SARS-CoV-2 in a small number of air samples collected near symptomatic individuals with COVID-19 (REFS^{135,136}), the WHO continued to recommend droplet and contact precautions in the absence of aerosol-generating procedures (that is, airborne transmission was not considered to be a major route).

On 6 July 2020, a group of 239 multidisciplinary scientists published an open letter advocating the recognition of potential airborne transmission of SARS-CoV-2 (REF¹³²), citing the latest studies of SARS-CoV-2 as well as previous studies of influenza virus, coronaviruses and other respiratory viruses. These studies included mechanistic evidence showing generation of (non-virus-containing) aerosols from human expiratory activities^{113,137}, infectious influenza virus in cough aerosols^{99,138}, that exhaled droplets of 60–100 µm can be carried less than 1 m away by breathing and more than 2 m by coughing¹³⁹, and survival of SARS-CoV-2 in artificially generated aerosols (the same study referenced by the WHO)¹³⁴. Furthermore, these studies provided evidence of SARS-CoV-2 viral RNA¹⁴⁰, or infectious RSV¹⁴¹, Middle East respiratory syndrome-related coronavirus¹⁴² and SARS-CoV-2 (REF¹⁴³) in aerosols from the air near infected individuals. They also cited epidemiological observations of outbreaks or infection clusters of SARS and COVID-19, sometimes supported by additional modelling studies, which suggested transmission occurs mainly via aerosols. These studies included the large community outbreak of SARS in Amoy Gardens in Hong Kong⁵⁹; clusters of SARS-CoV-2 infections in a restaurant in Guangzhou^{54,144} and a shopping mall in Wenzhou¹⁴⁵, China, and a choir in Skagit County, Washington, United States^{144,146,147}; and a modelling study with tracer gas measurement to simulate the spread of exhaled respiratory droplets from the suspected index patient for the SARS-CoV-2 restaurant outbreak in Guangzhou¹⁴⁸. Some argued^{149,150} that the current epidemiological data and clinical observations for COVID-19 do not support the letter's claim of the importance of aerosols in SARS-CoV-2 transmission; for example, the lack of observed long-range transmission or observed increased risk of infection among health-care workers in the absence of airborne precautions¹⁵⁰, which the authors of the open letter responded to¹⁵¹. On 9 July, the WHO issued an updated scientific brief³⁹, citing some of the evidence described in the open letter¹³² and extensive subsequent evidence on SARS-CoV-2 transmission. Addressing studies that identified low quantities of SARS-CoV-2 RNA in the exhaled breath of infected individuals¹⁵² or in air samples collected from health-care facilities in the absence of aerosol-generating procedures^{140,153–156}, the WHO commented these do not necessarily indicate a sufficient dose of infectious virus for transmission to occur¹⁵⁷. Addressing outbreak reports^{54,147,158,159}, the WHO acknowledged possible SARS-CoV-2 transmission through aerosols in indoor crowded spaces in the absence of aerosol-generating procedures, although transmission through droplets or fomites cannot be ruled out. Therefore, the WHO concluded that SARS-CoV-2 is transmitted primarily through direct, indirect or close contact with infected persons or their respiratory droplets that are expelled

during coughing, sneezing, talking or singing, that transmission via fomites is likely and that transmission via aerosols is possible in indoor crowded spaces³⁹.

This is not the first time that the same evidence base has led different scientists or regulatory bodies to different conclusions on the importance of the aerosol route of transmission, with a similar discussion for influenza virus^{6,10,14,160}, where there is evidence both for and against the importance of aerosol transmission. In support, infectious influenza virus was detected in aerosols in exhaled breath and coughs^{93,99} and in the air¹⁶¹, infectious aerosols could initiate infection in volunteers^{51,64}, long-range transmission followed airflow¹⁶² and epidemiological studies showed increased transmission with less ventilation¹²¹ or decreased transmission with upper air disinfection by ultraviolet light¹²⁴. Additional evidence includes influenza virus survival in artificially generated aerosols¹⁶³, suggestive of infectiousness in aerosols in nature; however, this work has been criticized as being too artificial⁶, and influenza virus RNA recovery in the air in both community settings¹⁶⁴ and health-care settings^{55,56,165} (even beyond 1.5 m from the source^{55,56}) has been criticized because infectious virus was not identified. Some argued that there is insufficient evidence of influenza virus aerosol transmission⁶, such as evidence for infectious virus recovery far from the source, infection initiated by inhaling air from patient rooms, transmission over long distances, association between airflow and disease spread after removal of the source patient, and effectiveness of ultraviolet irradiation in reducing transmission; moreover, aerosol transmission is argued against as outbreaks in aircraft still occur despite their being well ventilated. Some researchers have explicitly considered that transmission via the aerosol route is essentially a long-range transmission⁶ and have argued that influenza virus transmission is mostly observed at close range and particularly with prolonged close contact. Importantly, some researchers have argued that since the goal of recognizing the importance of aerosol transmission is to minimize the risk of transmission in health-care settings by airborne precautions¹⁵, such recognition may be counterproductive due to resource limitations, logistics challenges and low compliance⁶.

In summary, some researchers argued that the ability to be transmitted over long distances is a prerequisite for aerosol transmission⁶, as was shown for measles virus^{57,58}, VZV^{166,167} and *Mycobacterium tuberculosis*¹⁶⁸, the three respiratory pathogens that are widely accepted to be transmitted mainly via aerosols¹². They also require evidence of transmission via aerosols in the absence of all other routes⁶. The latest WHO scientific brief on modes of transmission of SARS-CoV-2 also reflects the emphasis of identifying infectious virus, and not viral RNA alone, in air samples³⁹. However, although transmission over longer distances through the air is possible for some respiratory viruses^{57,166}, this would require large numbers of viruses to be produced at the source and could be prevented by air dilution via ventilation or virus inactivation by environmental determinants. A failure to observe long-range transmission is therefore not evidence against aerosol transmission⁷, as it could also be explained by low rates of virus emission at the source

or by effective dilution or inactivation. The observation that influenza virus viral load in aerosols decreased substantially with increasing distance from the source, possibly because of dilution of virus concentration further from the source^{56,169}, suggests that if aerosol transmission does occur, it will occur mostly at close range and rarely at long range¹⁷⁰. Furthermore, transmission via the droplet route in the absence of all other routes has yet to be observed (TABLE 1), raising the concern of the available evidence that supports placing relatively more emphasis on droplets over aerosols.

Non-pharmaceutical interventions

At the early stage of pandemics, virus-specific pharmaceutical interventions such as vaccines and therapeutics are not available, and in resource-limited settings, such interventions are rarely readily available. Furthermore, owing to constant viral evolution, new viral strains emerge or resistance is gained such that pharmaceutical interventions can soon become outdated. Therefore, at the early stages of a pandemic, NPIs become the most important public health measures that individuals or communities can adopt to reduce respiratory virus transmission. Common NPIs include the use of personal protective equipment (PPE) or hygiene practices at the individual level, environmental disinfection or dilution at a systemic level, and social distancing measures at the community level, which reduce transmission by interfering with a single mode or multiple modes of transmission. In particular, in health-care settings, different NPIs constitute part of standard precautions or transmission-based precautions (that is, contact, droplet or airborne precautions) (TABLE 1), which represent different sets of practices and PPE that health-care workers adopt to lower the risk of nosocomial transmission. Although many NPIs have demonstrated mechanistically the ability to inactivate or reduce the amount of respiratory viruses in experimental or natural settings, the effectiveness of these NPIs in preventing infection at the individual level or mitigating transmission at the population level depends on a number of factors: the overall risk of transmission in a specific setting (for example, dining in restaurants versus playing sports outdoor) or population group (for example, health-care workers versus institutionalized individuals); the risk of transmission through the specific modes which the NPIs act on, and whether the virus could be transmitted via alternative modes after intervention; and individual adherence or population-wide adoption of the NPIs (TABLE 2).

PPE and personal hygiene practices

Hand hygiene: soaps and alcohol-based hand sanitizers. Since Semmelweis first demonstrated in the 1840s that health-care workers, by adopting hand hygiene practices, reduced mortality in parturient women, hand hygiene has probably been the most widely adopted NPI for mitigating disease transmission (targeting the physical contact route) and is recommended as part of standard precautions for all patient care in health-care facilities¹⁷¹. Common hand hygiene practices used in health-care and community settings include handwashing with

plain (non-antimicrobial) soaps or hand rub using alcohol-based hand sanitizers¹⁷² (TABLE 2). Alcohol-based hand sanitizers are useful in situations where sinks are not readily available, but are not recommended when hands are visibly dirty¹⁷¹. There is mechanistic evidence demonstrating bacterium or virus inactivation by hand hygiene¹⁷³, and a number of systematic reviews of observational studies or randomized trials together suggest that hand hygiene alone is significantly associated with reducing respiratory illnesses; however, it is unclear whether hand hygiene is effective against laboratory-confirmed influenza virus infections^{17–19}, possibly due to insufficiently large study sample size or weak adherence to the intervention^{125,174}.

Face coverings: cloth masks, surgical masks, respirators, face shields and eye protection. Surgical face masks, face shields and eye protection are commonly used by health-care workers during routine patient care or when they are performing high-risk procedures as protection against splashes of bodily fluids or respiratory secretions, and respirators are commonly used as protection against aerosols^{15,131,175}. In the community, the COVID-19 pandemic has not only led to community-wide adoption of surgical face masks; the extremely high demand has also resulted in (reusable) cloth masks being advocated as an alternative to surgical masks¹⁷⁶. Apart from mitigating droplet and aerosol transmission, these face coverings might also reduce contact transmission by reducing the frequency of hands touching respiratory mucosa¹⁷⁷. Mechanistically, face coverings can act either as protection against infection by reducing exposure to a virus when worn by a healthy individual or as source control by filtration⁹³ and deflection when worn by an infected person^{178,179} (TABLE 2). On the basis of systematic reviews of observational studies^{123,180} and randomized trials^{16,18,123}, many believe there is sufficient evidence supporting the effectiveness of the use of face coverings alone, or in combination with other NPIs, in reducing the risk of respiratory illness or virus transmission in health-care settings^{123,180} and high-risk community settings¹⁶, whereas some do not¹⁸. Mechanistic data from one study preliminarily suggest the effectiveness of surgical face masks may differ between viruses⁹³. The relatively lower infection risk in the community compared with health-care settings, the requirement for fit testing and lower adherence argue against the use of respirators in the community¹⁸¹. Although surgical face masks as source control are likely applicable to most settings, as protection against infection they may have more utility in close encounters¹⁷⁸ and crowded indoor settings; however, more research is needed. More research on the use of reusable masks, including cloth masks, in community settings either as source control or as protection is also urgently needed, including key parameters for assessment and standardization to address the diversity of materials available.

Environmental disinfection and dilution

Surface cleaning. Surface cleaning by disinfectants used in health-care settings¹⁸² or household cleaning agents¹⁸³ (TABLE 2) mitigates transmission via the fomite route and

Table 2 | Mechanistic evidence and effectiveness of common non-pharmaceutical interventions

Non-pharmaceutical intervention		Targeted mode of transmission ^a	Mechanism of action	Mechanistic evidence ^b	Effectiveness ^c
PPE and hygiene practice	Hand hygiene	Contact	Soaps remove organic substances by detergent properties Alcohol denatures proteins in the presence of water	Alcohol had higher viricidal activity on enveloped viruses than on non-enveloped viruses Alcohol-based hand sanitizers are more efficacious than soaps with regard to pathogen inactivation in vivo	Multiple systematic reviews suggested hand hygiene alone is significantly associated with reduced respiratory illness but not influenza virus infection in community settings Studies on the effectiveness of hand hygiene in reducing respiratory virus transmission in health-care settings were not identified Insufficient studies to compare the efficacies of soaps versus alcohol-based hand sanitizers against respiratory infections
	Face coverings	Droplet and aerosol (contact)	As source control: when worn by an infected individual, reduce virus release to the environment by filtration and immediate virus exposure of nearby healthy individuals by deflection As protection: when worn by a healthy individual, reduce exposure to virus-laden droplets and aerosols in the air Might also reduce contact transmission by reducing the frequency of hands touching respiratory mucosa	As source control: surgical masks efficaciously reduced influenza virus and coronavirus release from infected individuals by filtration (efficacies on exhaled droplets and aerosols may differ between viruses) Studies using mannequins suggested deflection is also important in reducing virus release As protection against close-range transmission: cloth masks, surgical masks and respirators were efficacious against artificial bacteriophage or influenza virus aerosol challenge by filtration As protection against long-range transmission: in the absence of environmental airflow only 1% of radiolabeled saline aerosols generated from the source mannequin reached the exposed mannequin 3 feet apart, where only fitted respirators but not surgical masks reduced exposure to aerosols	Multiple systematic reviews of observational studies or randomized trials mostly suggested the use of face coverings alone, or in combination with other non-pharmaceutical interventions, is effective in reducing the risk of respiratory illness or respiratory virus transmission in health-care and high-risk community settings Low adherence to use of a face shield during high-risk procedures associated with higher risk of respiratory illnesses in health-care workers Preliminary evidence suggested face mask use by household members before the person with the primary case developed symptoms is significantly associated with reduced SARS-CoV-2 household transmission
Environmental disinfection and dilution	Surface cleaning	Contact (droplet and aerosol)	Common disinfectants in health-care settings: 0.1 M sodium hydroxide, 70% ethanol, 70% 1-propanol, ethylene oxide and sodium hypochlorite Common household cleaning agents: liquid soap, 1% bleach and antimicrobial or antiviral wipes Both disinfect contaminated surfaces by virus inactivation Might also reduce droplet or aerosol transmission by reducing fomites available for resuspension	Common disinfectants in health-care settings effectively inactivated influenza virus and coronaviruses on surfaces in experimental settings Common household cleaning agents effectively inactivated (enveloped) influenza virus, but were less effective for (non-enveloped) adenovirus in experimental settings Biweekly disinfection of toys significantly reduced the presence of virus genetic material in the environment for adenovirus, rhinovirus and RSV, but not coronaviruses, parainfluenza virus and bocavirus, in nurseries in a randomized trial	A systematic review found limited epidemiological studies on the effectiveness of surface and object cleaning in reducing community respiratory virus transmission during pandemics Biweekly disinfection of toys did not reduce respiratory illness in nurseries in a randomized trial The combined use of an alcohol-based hand sanitizer and chloride wipes, compared with hand washing, did not reduce respiratory illness in elementary school students in a randomized trial. Daily household cleaning was significantly associated with reduced household transmission of SARS-CoV-2

Table 2 (cont.) | Mechanistic evidence and effectiveness of common non-pharmaceutical interventions

Non-pharmaceutical intervention	Targeted mode of transmission ^a	Mechanism of action	Mechanistic evidence ^b	Effectiveness ^c
Environmental disinfection and dilution (cont.)	Air dilution by ventilation and directional airflow	Droplet and aerosol Ventilation is the intentional introduction of outdoor air into a building by mechanical ventilation (for example, fans, ductwork or air conditioning) or natural ventilation (for example, windows) Directional airflow provides clean air from the cleanest area to less clean areas	Lower ventilation associated with rhinovirus RNA detection in the air in an office environment in an observational study	Multiple systematic reviews suggested strong and sufficient evidence supporting the association between indoor ventilation and airflow patterns with transmission of SARS-CoV, influenza virus, measles virus and varicella zoster virus Directional airflow may reduce the risk of airborne infection in vulnerable individuals or transmission in health-care and community settings
	Air and surface disinfection by UVGI	Aerosol and contact Use of UV light in the germicidal range (200–320 nm), especially UV-C (200–280 nm), to crosslink nucleic acids Air disinfection: in upper-room UVGI, irradiation is confined to the area above the occupants' heads to minimize direct exposure, but requires good vertical air movement in the room; in in-duct UVGI, air passes through ventilation systems and is irradiated inside before recirculation or exhaustion Surface disinfection: UVGI is used on internal surfaces of ventilation systems, or surfaces and equipment	UV-C efficiently inactivated experimentally generated aerosols containing influenza virus or coronaviruses, but was less effective for adenovirus At higher relative humidity, increased susceptibility to UV-C was observed for experimentally generated aerosols containing adenovirus, but decreased susceptibility to UV-C was observed for influenza virus and vaccinia virus UV-C efficiently inactivated experimentally generated MERS-CoV on glass slides Upper-room UVGI efficiently reduced infectious vaccinia virus aerosols in a simulated hospital room UVGI significantly inactivated experimentally inoculated influenza virus on respirators	Upper-room UVGI was shown to prevent airborne transmission of measles virus in schools Upper-room UVGI was associated with reduced influenza virus infections among individuals with tuberculosis Randomized trials evaluating the effectiveness of UVGI for air or surface disinfection in reducing respiratory virus transmission were not identified.

See Supplementary Table 2 for supporting references. MERS-CoV, Middle East respiratory syndrome-related coronavirus; PPE, personal protective equipment; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UV, ultraviolet; UVGI, ultraviolet germicidal irradiation. ^aThe mode or modes of transmission listed in parentheses indicate possible but presumably less important transmission via that mode. ^bMechanistic evidence with regard to virus reduction or inactivation. ^cEffectiveness with regard to prevention of respiratory illness or respiratory virus transmission.

might also block the droplet or aerosol route by reducing fomites available for resuspension due to various activities (for example, walking or door opening)¹⁸⁴. Although supported by mechanistic evidence on virus inactivation, limited epidemiological studies have evaluated its effectiveness in reducing respiratory virus transmission¹⁷. One randomized trial in day-care nurseries suggested biweekly disinfection of toys significantly reduced the detection of adenovirus, rhinovirus and RSV, but not common cold coronaviruses, parainfluenza virus and bocavirus, in the environment; however, surface cleaning did not reduce the incidence of respiratory illness¹⁸⁵, suggesting transmission may have occurred via routes other than the fomite route.

Air dilution by ventilation and directional airflow. Ventilation and directional airflow, although usually used to provide thermal comfort and clean air, could also help in mitigating droplet and aerosol transmission by dilution, especially indoors. Ventilation is an intentional

mechanical or natural introduction of outdoor air into a building (TABLE 2). Natural ventilation, if properly designed, is valuable especially in resource-limited settings, but can be used only in locations where climatic conditions are favourable¹⁸⁶. The ventilation rate is usually described as either per building or per room as the number of air changes per hour, or per occupant in the space as outdoor air rate per person. The minimal ventilation required differs depending on the level of infection risk expected or protection needed; for example, six air changes per hour in patient rooms and 12 air changes per hour in airborne-infection isolation rooms¹⁸⁷. Separately, directional airflow provides clean air from the cleanest patient care areas to less clean patient care areas. Although limited data demonstrate reduced virus recovery in the air with increased ventilation or the presence of directional airflow¹²², it has been suggested there is 'strong and sufficient' evidence supporting the association between ventilation and airflow patterns in buildings and transmission of respiratory viruses, including

SARS-CoV, influenza virus, measles virus and VZV^{41,188}, although this may require further validation by intervention studies or randomized trials⁸⁶. Furthermore, directional airflow may reduce the risk of airborne infection in vulnerable individuals or nosocomial transmission in health-care settings^{187,189}, and also in community settings (for example, aircraft cabins¹⁹⁰). Some suggested that for high levels of virus exposure in crowded indoor areas, increasing indoor mechanical ventilation may be less effective or less cost-effective to achieve sufficient risk reduction¹⁹¹, and that it might increase aerosol dispersion and infection risk for individuals further away from the source¹⁹⁰; an uninterrupted air stream from the source to the exhaust may then have a more important role in reducing transmission¹⁹².

Air and surface disinfection by ultraviolet germicidal irradiation. Concern over aerosol and fomite transmission of SARS-CoV-2 has renewed interest in the use of ultraviolet germicidal irradiation (UVGI)¹⁹³ — that is, the use of ultraviolet light in the germicidal range of wavelengths (200–320 nm) — for the disinfection of air and surfaces¹⁹⁴. For air disinfection, upper-room UVGI and in-duct UVGI are usually used¹⁹⁵ (TABLE 2). The use of UVGI to prevent airborne transmission was pioneered by Wells for the control of tuberculosis; Wells also demonstrated its use to prevent measles virus transmission in schools¹⁹⁶. Upper-room UVGI was associated with reduced influenza virus infections among individuals with tuberculosis¹²⁴. Surface disinfection with UVGI was initially used for bacterial decontamination¹⁹⁷. Studies evaluating the inactivation of respiratory viruses on surfaces using UVGI in experimental settings¹⁹⁸ are scarce and would be strengthened by studies using infectious virus recovery from naturally contaminated surfaces as the outcome measure. Randomized trials evaluating the effectiveness of UVGI for air or surface disinfection in reducing respiratory virus transmission are also lacking. Some proposed disinfecting surgical masks and respirators¹⁹⁹ with UVGI to allow their reuse in resource-limited settings²⁰⁰. Although UVGI is not considered carcinogenic, its domestic use (for example, consumer products advertised for control of COVID-19) is cautioned against as it requires expert knowledge of the dosage required, and the efficacies of these consumer products are in doubt²⁰¹.

Conclusions

The complexity of the control of respiratory virus transmission is reflected by the cross-disciplinary efforts to estimate the transmissibility of a respiratory virus, to evaluate the relative importance of modes of transmission and factors affecting transmission, to evaluate the efficacy and effectiveness of NPIs in different settings, and in turn how these translate to reduced transmissibility in the general and specific populations. Although population-based estimates of transmissibility (R_0) could inform the combined effectiveness of multiple interventions in reducing transmission, the household-based estimates (SAR) in randomized trials could inform the effectiveness of individual interventions. As shown, relative transmissibility between respiratory viruses may

be different depending on whether R_0 or SAR is used to describe transmissibility, amid heterogeneities in estimates of the same virus (TABLE 1). Studies comparing the transmissibility of different respiratory viruses in parallel in the same study, perhaps in case-ascertained household studies, where study settings are more controlled, would be useful to identify which respiratory viruses are more transmissible than others.

The controversies regarding the role of aerosols in the transmission of SARS-CoV-2 and influenza virus highlight our very limited understanding on the relative importance of different modes of transmission. This includes the lack of consensus on the defining features of each mode of transmission, especially the difficulty in differentiating between droplets and aerosols; the different levels of scrutiny when evidence supporting each mode is being evaluated; the technical challenges in recovering infectious virus from the environment; the challenges in identifying the minimal infectious dose required to establish infection in susceptible or immunized individuals; and the lack of quantitative risk assessment for different modes of transmission. Given the different types of qualitative evidence available in support of individual modes of transmission (TABLE 1), discussion may be warranted in assigning priority or strength of evidence to these different types of evidence in support of each mode; for example, whether the demonstration of transmission via aerosols alone in the absence of other routes is essential to support the importance of the aerosol route, as suggested for measles virus⁵⁷ and VZV¹⁶⁶, but which was not done in support of the importance of the droplet route for RSV. These study designs may be possible for aerosols and fomites, but it will be more challenging to demonstrate transmission via direct contact and droplets in the absence of (close-range) aerosols. For rhinovirus, airborne precautions are not required despite the evidence of aerosol transmission in the absence of other routes^{63,117}; in addition, as rhinovirus transmission has been demonstrated independently via direct contact²⁰², fomite¹⁰⁹ and aerosols^{63,117}, efforts should be made to quantitatively evaluate the relative contribution of each mode to transmission and their determinants in different settings¹³⁰. However, the relative contribution of different modes at the population level likely varies between different settings, populations and interventions in place, and at the individual level varies between individuals due to heterogeneity in contagiousness and susceptibility, which also changes over time. There is also minimal research on the modes of transmission of bocavirus and metapneumovirus (Supplementary Table 1). In general, there is a lack of studies demonstrating droplet transmission alone in the absence of other routes for all respiratory viruses (TABLE 1), and such studies are urgently needed to support the importance of droplets over aerosols and will have important implications for the choice of NPIs for mitigating transmission. Alternatively, aerosol transmission does not necessarily indicate a higher intrinsic transmissibility of the virus (TABLE 1) nor long-range transmission, as transmissibility depends on multiple factors, including the degree of presymptomatic transmission, the contagiousness of the infector, the susceptibility

of the infectee, the contact patterns between them and the environmental determinants of transmission in the shared space; and long-range transmission depends on rates of virus emission at the source or effective dilution or inactivation by environmental determinants. Moving beyond deciding on the adoption of an NPI mostly on the basis of the perceived importance of a particular mode of transmission would provide an incentive for public health practitioners to recognize the importance of aerosol transmission.

For common NPIs, although we have mechanistic evidence supporting their efficacy with regard to virus reduction or inactivation, we have limited knowledge of their effectiveness in reducing transmission in the population both in health-care settings and in community settings. This may be because we do not yet know the relative contribution of different modes of transmission in a particular setting and whether the different modes can partially compensate for each other if a mode is absent¹⁷⁴. If the latter is true, studies evaluating the effectiveness of one intervention alone, which targets a specific mode, may underestimate its potential effectiveness because a reduction in transmission via a specific mode by the NPI might be compensated by transmission via another mode¹⁷⁴. Given effectiveness is demonstrated,

the eventual adoption of NPIs would also depend on the perceived severity of the disease¹⁵, the infection risk in a particular setting^{175,180}, the accessibility of the resources, the purpose of interventions⁶ and the economic or societal costs of implementing the intervention. In particular, the choice of which transmission-based precautions to adopt for a particular respiratory virus in health-care settings depends on the perceived major modes of transmission for the pathogen¹⁵, the level of caution and the resources likely available if the recommendation is made¹⁵, and therefore could differ between countries. Intervening against multiple modes of transmission would be more effective than acting against a single mode. For example, although effectiveness of the use of face masks or hand hygiene alone in mitigating community transmission of laboratory-confirmed respiratory virus infection was not demonstrated, possibly due to various experimental challenges, their combined use has been shown to be effective in reducing influenza virus transmission and should be considered²⁰³. A clear public health message accounting for these uncertainties will help to gain public confidence and support public health efforts.

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