The controversy around airborne vs. droplet transmission of respiratory viruses – implication for infection prevention

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Abstract

Purpose of review: Health agencies recommend Transmission-based Precautions, including Contact, Droplet and Airborne Precautions, to mitigate transmission of respiratory viruses in healthcare settings. There is particular controversy over the importance of aerosol transmission and whether Airborne Precautions should be recommended for some respiratory viruses. Here, we review the current recommendations of Transmission-based Precautions and the latest evidence on the aerosol transmission of respiratory viruses.

Recent findings: Viral nucleic acids, and in some instances viable viruses, have been detected in aerosols in the air in healthcare settings for some respiratory viruses such as seasonal and avian influenza viruses, MERS-CoV and RSV. However, current evidences are yet to demonstrate that these viruses can effectively spread via airborne route between individuals, or whether preventive measures in Airborne Precautions would be effective.

Summary: Studies that use transmission events as outcome to demonstrate human-to-human transmission over the aerosol route or quantitative measurement of infectious respiratory viruses in the air are needed to evaluate the infectiousness of respiratory viruses over the aerosol route. When a respiratory virus in concern only leads to disease with low severity, Airborne Precautions are not likely to be justified.

Keywords: Respiratory viruses; aerosol; droplet; healthcare settings; infection control

Introduction

Acute respiratory tract infections caused by respiratory virus infections are one of the most common acute medical complaints, and also a major cause of hospitalization each year [1]. While the majority of respiratory tract infections are acquired in the community, nosocomial transmission can occur and poses a health risk for vulnerable patients some of whom may have compromised immune systems, as well as an occupational health threat for health care personnel (HCPs). Infection prevention and control guidelines are recommended to reduce the risk of nosocomial transmission of respiratory viruses that may occur from patients to other patients, from patients to HCPs, from HCPs to other HCPs, and from HCPs to patients. While Standard Precautions are recommended at all times, Transmission-based Precautions may be used additionally with the aim to reduce transmission via interventions specific to the putative transmission routes of that pathogen when Standard Precautions alone are deemed insufficient [2, 3]. However, there are gaps in our knowledge on the relative importance of different modes of transmission in the nosocomial transmission of specific respiratory viruses, in particular the importance of aerosol transmission that requires more stringent personal or systemic interventions. Here, we review the current understanding and latest evidence for the aerosol transmission of respiratory viruses that are of significant health consequences and/or shown to have transmitted in healthcare settings, and discuss the evidence needed to evaluate the importance of aerosols in nosocomial transmission of respiratory viruses.

Transmission-based infection control recommendations for respiratory viruses

Respiratory viruses are thought to transmit via multiple modes of transmission, sometimes divided into the three categories contact, large respiratory droplets, and fine respiratory droplets, with the latter sometimes also referred to as aerosol or airborne transmission (Figure 1) [2, 3]. Contact transmission refers to infection transmitted from an infected person to a susceptible individual through the transfer of virus-laden respiratory secretions directly via physical contact (Figure 1A) or indirectly via intermediate surfaces or objects (Figure 1B). Droplet transmission refers to infection transmitted by the deposition of virus-laden respiratory droplets expelled from an infected person onto the mucosal surfaces (e.g. eyes, nose and mouth) of a susceptible individual (Figure 1C). Aerosol transmission refers to the infection of a susceptible individual via inhalation of virus-laden fine respiratory droplets, aerosols, through the air, generated either directly from fine respiratory droplets expelled from an infected person (Figure 1C) or when a medical aerosol-generating procedure (AGP) is performed on the infected person (Figure 1D). Aerosol transmission was classified by Roy and Milton into "obligate", "preferential" or "opportunistic" [4], where transmission only occurs solely through aerosols in obligate aerosol transmission, transmission occurs through multiple routes but predominately through aerosols in preferential aerosol transmission, and transmission occurs predominately through other routes but may also occur in special circumstances through aerosols in the opportunistic aerosol transmission.

For infection control and prevention in healthcare settings, Standard Precautions such as hand hygiene, respiratory hygiene and the use of PPE e.g. gloves, masks and gowns are universally recommended to all patients. In contrast, Transmission-based Precautions are sometimes recommended in specific populations or healthcare settings, in addition to the Standard Precautions, to decrease the risk of transmission of particular diseases by targeting their putative predominant transmission route(s) (Table 1). For example, infections that may be spread through the airborne route follow the strictest precaution guidelines, with the use of airborne isolation infection room (AIIR) and respirators as one of the major components. Infected patients requiring Airborne Precautions are required to stay in a negative-pressure AIIR, and all HCPs and visitors who enter the same room with the patient should wear a fit-tested N95 filtering facepiece respirator which has an enhanced filtration efficiency on aerosols [3, 5, 6]. Droplet Precautions, on the other hand, are less stringent. Ideally infected patients should be placed in single rooms, but it is also acceptable to accommodate patients infected by the same pathogen together. Surgical masks are required when working within close distance with the infected patients requiring Droplet Precautions. However, special air handling and ventilation in patient room is not required based on the principle that the risk of droplet transmission is very low beyond 1-2 meters. Contact Precautions focus on the disruption of physical contact between the infectious patient and susceptible individual, therefore the use of gloves and gowns and practice of hand hygiene are recommended for HCPs. Transmission-based Precautions can be applied in combination for diseases that are believed to have multiple transmission routes.

The assignment of specific Transmission-based Precautions for patients with acute respiratory illnesses (ARI) in specific healthcare settings and scenarios depends on 1) strong evidences of person-to-person transmission via that specific route in healthcare or non-healthcare settings if an etiology is identified; 2) epidemiological or clinical information suggests the etiologic agent is a pathogen of potential concern if an etiology is yet to be identified; and 3) the types of contact and procedures to be taken [2, 3]. In other words, the assignment of Transmission-based Precautions depends on the believed predominant route(s) of transmission, severity of the disease, the prevalence of the disease in the community i.e. whether it is a widely circulating or a (re-)emerging infectious disease, and the probability of increased nosocomial transmission via a specific route during contact and medical procedures. Transmission-based Precautions are often at first used empirically based on clinical symptoms and the likely etiology, and revised to pathogen-specific recommendations once the etiologic agent is identified.

While some respiratory viruses may spread through multiple modes of transmission (Table 2), respiratory droplets are traditionally considered to be a more important mode of transmission than aerosols for many such viruses [7], either based on observed evidence in support of the droplet route, or lack of evidence for the aerosol route [8], so that Droplet Precautions are usually recommended when an etiology is not yet identified. However, evidence supporting potential transmission via the aerosol route for some respiratory viruses have been increasingly published over the past decade [9], leading to reviews of existing infection control guidelines.

Differentiating droplet and aerosol transmission

Respiratory particles can be classified as being droplets or aerosols based on particle size and specifically in terms of the aerodynamic diameter, where a particle of any shape with an aerodynamic diameter 1μm follows the same behavior as a spherical particle with a diameter of 1μm [10]. Both droplets and aerosols can be generated during coughing, sneezing, talking or exhaling, but large droplets settle quickly whereas small aerosols can remain airborne and may transport over longer distances by airflow [11, 12]. Therefore unlike larger droplets, aerosols can pose an infection risk over a greater distance, although it should be noted that most aerosol transmission is likely to occur at close range because of dilution and inactivation of viruses over longer periods of time and greater distances. Small aerosols are also more likely to be inhaled deep into the lung and cause infection in the alveolar tissues of the lower respiratory tract, whereas large droplets are trapped in the upper airways [13]. Infection via aerosols may therefore lead to more severe disease [14, 15]. There has not been complete agreement on the exact particle size threshold used to differentiate between droplets and aerosols. The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) consider disease transmission with particles >5μm as droplets transmission and with particles ≤5μm as aerosol transmission [2, 3], while some researchers have suggested particles ≤20μm or ≤10μm should be considered aerosols either based on their potential to remain in the air for a prolonged period of time, or because they can reach the respirable fraction of the lung (i.e. the alveolar region) [16-18].

Current state of knowledge on healthcare-associated transmission of respiratory viruses with aerosol transmission potential

Measles virus is one of the few respiratory viruses with strong evidence supporting human-to-human transmission preferentially through the airborne route with Airborne Precautions recommended [19]. For example, an airborne outbreak of measles was reported in the 1980s where transmission occurred without face-to-face interaction, as some secondary cases reported to arrive at the clinic after the index case had left, and measles are believed to not survive long on surfaces [20, 21]. Despite the availability of an effective 2-dose measles-mumps-rubella (MMR) vaccine and high vaccination coverage in many countries, HCPs continue to be at risk to occupational exposure of measles, with measles outbreaks in HCPs reported in countries with either high or low vaccination coverage [22, 23], in countries with measles eliminated previously [24], and in HCPs who have been vaccinated previously [25]. A very recent study showed healthcare-associated measles infections in hospitalized infants who were too young to receive vaccination [26].

Seasonal influenza virus transmission is traditionally thought to be droplet-borne predominately with Droplet Precautions recommended, but there has been considerable debate on its airborne transmissibility over the past decade [18]. Recent studies in ferret models demonstrated transmission of human influenza A virus in the absence of droplets and physical contact [27, 28]. The detection of airborne influenza virus in the environment [29-33], and the detection of infectious influenza virus in aerosols from human exhaled breath [34] and coughs [35] further support the potential for transmission to occur via aerosols. Of note, however, environmental studies mostly demonstrated the detection of viral genome copies and thus airborne virus infectivity remains unclear [29-31].

For zoonotic influenza viruses associated with severe disease such as avian influenza A(H5N1) and A(H7N9) virus infections in humans, the US CDC recommends Contact and Airborne Precautions in light of the lack of a widely available safe and effective vaccine, suspected high morbidity and mortality and few confirmed cases in the community [36]. On the other hand, for H5N1 the WHO recommends Droplet Precautions only, based on the lack of evidence of sustained human-to-human or airborne transmission, but recommends both Contact and Airborne Precautions for novel ARIs based on precautionary principle as the modes of transmission for the novel ARIs are unlikely to be known when they are first identified [2]. One study reported about 8% recovery of influenza A(H5N6) virus RNA, another avian influenza virus that shown to infect humans, from about 250 air samples collected in live poultry markets in Guangdong, China, including the isolation of viable influenza A(H5N6) virus in one air sample [37]. Coupled with evidences of recovery of avian influenza viruses such as H5N2 and H9N2 from the air in poultry housing facilities [38-40] and the experimental demonstration of airborne transmission of human- and avian-origin H5N1 viruses from infected chickens to naïve chickens or ferrets [41], these may suggest the potential risk of airborne transmission of avian influenza viruses.

The recent outbreaks of Middle East respiratory syndrome (MERS) created considerable attention and concern [42]. While most outbreaks have occurred in the Middle East [43], a large outbreak in South Korea in 2015 highlighted the importance of infection control in emerging infectious diseases even in developed locations [44]. The major modes of transmission of MERS coronavirus (MERS-CoV) either from animals (e.g. camels) to humans or between humans have not been clearly identified. Direct contact with animals was documented in the first case of MERS [45]. Environmental detection of infectious MERS-CoV in air and on surfaces like ventilator exit suggests that MERS-CoV might be transmitted via contact and airborne routes [46]. The WHO considers most MERS-CoV transmission occurred in the absence of basic infection control measures or before a case was suspected or confirmed [47], and in their latest risk assessment published in 2018 concluded that so far there was no evidence in support of sustained human-to-human transmission in the community nor airborne transmission as the major route of transmission [48], supporting the recommendation of Contact and Droplet Precautions. On the other hand, although the above findings are insufficient to clarify the contribution of each transmission route, considering the severity of MERS-CoV infections, out of an abundance of caution US CDC suggests Contact and Airborne Precautions when caring for patients with probable or confirmed MERS-CoV infection [49].

Respiratory syncytial virus (RSV) is an important disease in children and sometimes in immunocompromised adults. A systematic review reported substantial risks of nosocomial RSV transmission in neonatal/pediatric settings and adult haematology and transplant units [50]. It is believed that RSV is transmitted by the direct or indirect contact and droplet route [51], and the WHO currently recommends Droplet and Contact Precautions [2] while the US CDC recommends Contact Precautions [3]. The US CDC recognizes that RSV may be transmitted by the droplet route as well, but they conclude high compliance to Standard plus Contact Precautions only were shown to be successful in preventing nosocomial transmission, suggesting direct contact is the predominant route of RSV transmission in healthcare settings [3]. RSV viral RNA was recovered in the air in pediatric or adult ambulatory care clinics; however, only a small percentage of them were in particles <5um [12, 31]. In contrast, another study recovered infectious RSV virus from the air collected over 1m away, presumably aerosols, from RSV-positive hospitalized infants, and were still present 2 hours after the infected cases have been discharged [52].

The concerns with increased aerosol transmission during AGPs were highlighted in the SARS outbreaks in 2003 [53], and Airborne Precautions are usually recommended when AGPs are performed. However, there has been very limited research on which care activities or medical procedures should be considered as aerosol-generating, nor the roles of AGPs in nosocomial transmission of respiratory viruses. A recent study reported that among 7 patient care activities evaluated, including bathing, changing linens, pouring, flushing, bronchoscopy with nebulized medication administration (NMA), bronchoscopy without NMA and NMA alone, significant aerosol generation was only observed during NMA (either alone or during bronchoscopy) [54]. A systematic review found that tracheal intubation was consistently associated with the increased risk of SARS transmission among HCPs [55], but it is unclear whether the transmission was exclusively via airborne route or whether the droplet and close-contact transmission took place when the HCPs were performing the AGPs. Therefore although it is likely that AGPs would be associated with an increased production of aerosols, more evidences in evaluating whether there is an increased risk of transmission associated with AGPs are needed [56].

Other respiratory viruses including adenovirus, parainfluenza virus and rhinovirus have very limited data investigating their transmission routes, but studies have recovered respiratory viruses in airborne particles collected from the environment [57] or human exhaled breath [58].

Other considerations for the implementation of Airborne Precautions

In addition to needing more evidence on the relative importance of each transmission mode to inform the assignment of Transmission-based Precautions, other considerations such as the effectiveness and feasibility of the implementation of the preventive measures should also be taken into account. In terms of effectiveness, theoretically wearing a respirator should provide better protection than surgical mask. Studies under controlled settings have confirmed the enhanced filtration capacity of respirators [59, 60], but respirators have not been shown to provide significantly better protection against respiratory infections than surgical masks [61, 62]. A recent meta-analysis reported no significant difference in the overall risk of laboratory-confirmed respiratory infection among HCPs wearing respirator to those wearing surgical masks, albeit with a low statistical power in majority of the studies [63]. Compliance of wearing a respirator could be an issue as wearing respirators are often considered as uncomfortable, which could lead to improper wearing and negate any potential protective effect, although we could not identify any study of clinical effectiveness between respirators being worn with high versus low compliance. Apart from personal protection, the effectiveness of systemic interventions in reducing airborne transmission is also not clear. Ventilation may be able to control aerosol transmission [64], and a previous modelling study suggested that increasing ventilation may able to achieve similar effects on reducing transmission to those of personal interventions [65]. In terms of feasibility, the allocation of single-patient room will be difficult when there is large number of admissions simultaneously for example during influenza seasons, so that one may opt for increasing bed spacing in multi-bed rooms, and leaving negative-pressure AIIRs available for the respiratory diseases with very strong evidence of transmission over the aerosol route, or those believed to have severe health consequences.

Conclusions

It remains challenging to understand the relative contributions of each transmission route to transmission for many respiratory viruses. Health agencies may base their recommendations for Transmission-based Precautions on whether there is evidence that an intervention specific to a particular route has been effective in mitigating transmission, or reason out of an abundance of caution and recommend base on a presence of evidence in support of a particular route of transmission. As more evidence suggests the importance of airborne route for respiratory diseases, concerns have raised on the necessity to revise the current infection control recommendations for the addition of Airborne Precautions for some respiratory viruses.

Current evidences on the potential airborne transmission are yet to demonstrate for most respiratory viruses that they can effectively spread via airborne route, or whether preventive measures in Airborne Precautions would be effective and justified. A number of airborne transmission studies have been conducted in animal settings or through environmental samplings. Animal studies can be used to demonstrate transmission events via the aerosol route, but differences in physiology between animals and humans limit the interpretations of the findings. Most environmental sampling studies reported the detection of viral RNA in the air, but limited studies demonstrated a recovery of viable virus which limits the interpretation for the risk of airborne transmission. Using human challenge models to demonstrate transmission via the airborne route will be challenging due to ethical considerations as it is expected disease established from airborne infection will be more severe [6]. Studies that use transmission events as outcomes to demonstrate the importance of the aerosol route in human-to-human transmission, or quantitative measurement of infectious respiratory viruses in the air, are much needed to help delineate these uncertainties by evaluating the infectiousness of respiratory viruses in the aerosol route. When a respiratory virus in concern only lead to disease with low severity, Airborne Precautions are not likely to be justified.

Key points

1. Many respiratory viruses are believed to transmit over multiple routes, and the relative significance between droplet and aerosol transmission remains unclear.
2. Implementation of pathogen-specific Transmission-based Precautions becomes difficult with uncertainty on the contributions of each transmission mode for particular respiratory viruses.
3. There is lack of available evidence demonstrating the aerosol transmissibility of many respiratory viruses such as influenza and RSV in natural setting.
4. Studies that use transmission events as outcome to demonstrate human-to-human aerosol transmission, or quantitative measurement of infectious respiratory viruses in the air, are much needed to evaluate the infectiousness of respiratory viruses in the aerosol route.
5. When a respiratory virus in concern only lead to disease with low severity, Airborne Precautions are less likely to be justified.

Table 1. Transmission-based Precautions and the specific infection preventive and control measures as recommended by the WHO [2] and US CDC [3]. Contact, Droplet and Airborne Precautions are considered as Transmission-based Precautions that should be implemented in addition to Standard Precautions.

Types of Precautions	Rationale	Measures
Standard	To minimize the spread of infection within healthcare facilities from direct contact of contaminations	1. Practice of hand hygiene 2. Use of personal protective equipment (PPE) 3. Practice of respiratory etiquette 4. Environmental cleaning and disinfection 5. Proper handling of patient-care equipment and waste management 6. Proper handling of needles and other sharps
Contact	To minimize the spread of infections particularly by hand-to-hand contact and self-inoculation of nasal and/or conjunctival mucosa	1. Proper use of PPE including disposable gloves and gowns 2. Appropriate patient placement in a single room or with patient infected by same pathogen 3. Limit patient movement and minimize patient contact 4. Environmental cleaning and disinfection of the patient room
Droplet	To minimize the spread of respiratory infections that are transmitted predominantly via large droplets (>5μm) in short distance	1. Proper use of PPE including surgical mask when entering the patient's room 2. Appropriate patient placement in a single room or with patient infected by same pathogen 3. Limit patient movement and ensure that patients wear surgical mask when outside their rooms

Airborne	To minimize the spread of respiratory infections that are transmitted through inhalation of infectious aerosols (≤5μm) over a long distance	1. Proper use of PPE including NIOSH-certified N95 or equivalent particulate respirator 2. Isolation of patient in single, airborne isolation infection room (AIIR) 3. Limit patient movement and ensure that patients wear surgical mask when outside their rooms

Table 2. Recommendation on Transmission-based Precautions for selected respiratory viruses by the WHO [2] and the US CDC [3]. References to additional guidelines are also provided whenever available. The rationale for any discrepancies in the recommendation by the two health agencies are discussed in the text. Note that additional Airborne Precautions are recommended when performing aerosol-generating procedures (AGPs) regardless of the pathogen.

Respiratory viruses	**Transmission-based Precautions**	
	WHO	**US CDC**
Measles	Airborne	Airborne
Seasonal influenza	Droplet	Droplet [66]
Avian influenza	Contact + Droplet	Contact + Airborne [36]
MERS-CoV	Contact + Droplet [47, 67]	Contact + Airborne [49]
RSV	Contact + Droplet	Contact

Figure Legend

Figure 1. Different transmission routes of respiratory viruses in a healthcare setting. **A. Direct contact transmission**: The HCP is exposed to infectious viruses by direct physical contact with the infected patient. **B. Indirect contact transmission**: The HCP is exposed to infectious viruses by physical contact with objects contaminated with infectious viruses (fomites) released from the infected patients. **C. Droplet and Aerosol transmission**: The infected patient is releasing infectious agents via droplets and aerosols to the healthcare personnel (HCP) in close proximity, and via aerosols to other patients and HCP in further distances. **D. Aerosol transmission during aerosol-generating procedures (AGPs):** During AGPs, increased amount of infectious virus-laden aerosols is released to the nearby HCP and other patients and HCPs.

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Conflicts of interest

The authors report no potential conflicts of interest.

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