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Transmission routes of respiratory viruses among humans

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Respiratory tract infections can be caused by a wide variety of viruses. Airborne transmission via droplets and aerosols enables some of these viruses to spread efficiently among humans, causing outbreaks that are difficult to control. Many outbreaks have been investigated retrospectively to study the possible routes of inter-human virus transmission. The results of these studies are often inconclusive and at the same time data from controlled experiments is sparse. Therefore, fundamental knowledge on transmission routes that could be used to improve intervention strategies is still missing. We here present an overview of the available data from experimental and observational studies on the transmission routes of respiratory viruses between humans, identify knowledge gaps, and discuss how the available knowledge is currently implemented in isolation guidelines in health care settings.

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Introduction

Viral respiratory tract infections are a leading cause of morbidity and mortality worldwide, representing an enormous economic and disease burden [1]. Respiratory viruses replicate in the respiratory tract from where they are subsequently shed and transmitted via respiratory secretions. They are classified in different virus families and differ in virulence and target groups. Respiratory tract infections may range from asymptomatic to acute live threating disease thereby posing a major health threat to young children, elderly, and immunocompromised people. Respiratory viruses spread via three different transmission routes: contact (direct or indirect), droplet and aerosol transmission (Table 1) [2,3]. Contact transmission refers to direct virus transfer from an infected person to a susceptible individual (e.g. via contaminated hands) or indirect virus transfer via intermediate objects (fomites). Transmission of virus through the air can occur via droplets or aerosols. The commonly accepted cut-off size between the large droplets and small aerosols is 5 μm, although this varies considerably between studies, ranging up to 12 μm [4–8]. Droplets generated during coughing, sneezing or talking do not remain suspended in air and travel less than 1 m before settling on the mucosa of close contacts or environmental surfaces. Aerosols have a slow settling velocity, thus they remain suspended in the air longer and can travel further [5,9,10].

Transmission via each of these three routes is complex and depends on many variables such as environmental factors (e.g. humidity and temperature), crowding of people, but also on host factors such as receptor distribution throughout the respiratory tract. The fact that all these variables affect the different transmission routes of the different respiratory viruses in a dissimilar way, makes it very difficult to investigate them experimentally [9,11]. Here, we summarize the evidence from experimental and observational studies on inter-human transmission routes of important respiratory viruses (summarized in Table 2). A literature search was conducted for each respiratory virus using 'human transmission experiments' and 'transmission (routes)' of the virus of interest as search criteria in PubMed and Google Scholar. Subsequently, the backward snowball method was applied in which additional papers were identified based on the reference list of a paper of interest. As this review focuses on the evidence on inter-human transmission routes, data from animal studies were excluded. In addition, intervention studies, (aircraft) outbreak reports and household studies were excluded if the transmission route was not specifically investigated. The strengths and weaknesses of the different methods employed in transmission studies are summarized in Table 3. Finally, we discuss our findings in the light of several available (inter)national guidelines on infection control. Our observations underscore the urgent need for new knowledge on respiratory virus transmission routes and the implementation of this knowledge in infection control guidelines to advance intervention strategies for currently circulating and newly emerging viruses and to improve public health.

Table 1

Commonly accepted respiratory routes of transmission

Transmission route	Particles involved and particle characteristics	Characteristics/definition of transmission
Contact		Self-inoculation of mucous membranes by contaminated hands.
Direct	Deposited on persons.	Virus transfer from one infected person to another.
Indirect	Deposited on objects.	Virus transfer through contaminated intermediate objects (fomites).
Airborne		
Droplet	Droplets (>5 μm). Remain only shortly in air (<17 min) [116]. Dispersed over short distances (<1 m).	Short range transmission. Direct inoculation of naïve person through coughing/sneezing/ breathing of infected person. Deposition mainly on mucous membranes and upper respiratory tract.
Aerosol	Aerosols, droplet nuclei (<5 μm), Remain in air for an almost infinite amount of time. Dispersed over long distances (>1 m).	Long range transmission. Inhalation of aerosols in respirable size range. Deposition along the respiratory tract, including the lower airways.

Table 2

Overview of the evidence on transmission routes of respiratory viruses based on experimental data and the transmission route according to infection prevention guidelines

Virus	Virus family[a]	Transmission route	
		Experimental and observational data	Guidelines[b]
Measles virus	*Paramyxoviridae*	Aerosol [75–77,78•,79•].	Contact [3,110], droplet [3,109–111], aerosol [3,109–111].
Parainfluenza virus	*Paramyxoviridae*	Limited data, contact (by fomite) [83,84] [e].	Contact [3,109–111], droplet [3,109–111], aerosol [3,109].
HMPV	*Pneumoviridae*	Limited data, contact (by fomite)[e] [30]	Contact [3,110,111], droplet [3,110,111].
RSV	*Pneumoviridae*	Contact [89,88], droplet [88], aerosol [90,91••].	Contact [3,109–111], droplet [3,109,110], aerosol [109,111].
HCoV	*Coronaviridae*	Limited data, contact (by fomite) [65–67] [e].	Contact [3,110,111], droplet [3,110,111].
MERS-CoV	*Coronaviridae*	Contact [84] [e] [89] [c] [91••], droplet [89] [c], aerosol [91••].	Contact [111], droplet [3,111]
SARS-CoV	*Coronaviridae*	Contact [70] [e] [73,79,101], droplet [73,78•,79•,117], aerosol [76,118] [c] [82] [c,d].	Contact [3,110,111], droplet [3,110,111], aerosol [3,110,111].
Rhinovirus	*Picornaviridae*	Contact [35,36,42], aerosol [37,40,119].	Contact [109–111], droplet [109,111], aerosol [109–111].
Adenovirus	*Adenoviridae*	Contact [100] [e] [100,101], droplet [103•], aerosol [102,103•].	Contact [3,109–111], droplet [3,109,110], aerosol [110,111].
Influenza virus	*Orthomyxoviridae*	Droplet/aerosol [55,56,57•,59]	Contact [109–111], droplet [3,109–111], aerosol [3,109–111].

[a] Taxonomy was based on [62], airborne transmission is seemingly linked to:
[b] WIP [108], 'Blue Book' [109], 'Red Book' [110], CDC [3] and Up-To-Date [111]. The conclusions on experimental data as presented in this table reflect the conclusions from the authors.
[c] Superspreader events.
[d] Aerosol-generating procedures (in a nosocomial situation).
[e] Conclusions were drawn based on stability experiments.

Measles virus (MV)

Measles is one of the most contagious viral diseases in humans that has been associated with aerosol transmission for a long time [12,13,14••,15–17,18••]. However, it should be noted that MV also replicates systemically, and that there is a role for dead cell debris-associated virus spread via fomites. In the late 1970s and early 1980s, data from retrospective observational studies obtained during outbreaks in pediatric practices, a school, and a sporting event suggested transmission through aerosols [14••,15–17,18••]. Indeed, those studies showed that most secondary cases never came in direct contact with the index patient and some were never even simultaneously present in the same area as the index case [14••,18••]. Examination of airflow in the pediatricians' offices showed that aerosols were not only dispersed over the entire examination room but also accumulated in the hallway and other areas [14••,18••]. Furthermore, based on the investigation of air circulation in a sport stadium, in which a MV outbreak occurred, authors suggested that MV had been dispersed through the ventilation system [16]. Thus it was concluded that MV can be transmitted via aerosols. Although coughing is a common symptom associated with measles disease, index patients were described to cough

Table 3

Overview of the methods to study human-to-human transmission and their respective pro's and con's

Study design	Pro	Con	Reference
Virus stability	• Can provide indirect evidence for transmission route. • Easy to perform.	• Not conclusive as transmission itself is not investigated.	[42,43,65,70]
Outbreak (household or hospital) reports	• Study natural infections. • Includes the most susceptible patients who are difficult to include in experimental studies.	• Retrospective. • Usually not conclusive on transmission route or relative importance of transmission routes.	[120–123]
Outbreak report — aircraft	• Relatively easy to perform • Outbreak in closed setting	• Retrospective which can result in recall-bias and hard to trace back passenger movements. • Inconclusive. • Only reported in case of secondary infections and in these cases infections may also occur before or after the flight.	[118,124–127]
Non-pharmaceutical Intervention	• Can help to discriminate between transmission routes if performed properly.	• Usually no controlled environment. • Difficult to determine ideal time-point of the intervention. • Risk of drop-out or perseverance.	[35,128–131]
Pharmaceutical intervention	• Can help to identify relative importance of transmission routes • Controlled environment	• Difficult to include enough patients to obtain statistically significant results	[132]
Experimental infection	• Controlled environment. • Donor selection and control. • Real-time data collection. • Repeatable. • Various parameters can be studied at the same time. • Possibility to study different inoculation routes.	• Ethical obstacles. • Infectivity and disease can differ from that in a natural infection (attenuated strains). • Difficult to create ideal and comparable circumstances. • Many factors have to be taken into account: duration, influence of superspreaders, sampling methods. • Difficult to get naïve or risk group participants who are interesting to study.	[42,44,102]
Miniature field trial	• Can discriminate between contact and airborne transmission.	• Ethical obstacles. • Exposure time may not be sufficient. • Difficult to create ideal and comparable circumstances.	[38••,39••,40]
Air sampling	• Noninvasive for patients. • Quantification of viable virus in the air. • Characterization of droplet/ aerosol size. • Can be used in parallel with human studies or outbreaks. • Can gain information on possible aerosol spread. [34••,37,57•,91••,103•,133]	• In a nosocomial setting aerosol-generating procedures can play a major role. • Frequently only detection by PCR. • Direct human-to-human transmission is not studied (circumstantial). • Technical issues (procedure may affect virus viability) or false interpretation.	
Air tracer studies	• Monitoring airflow pattern can indicate possible airborne transmission (if not done retrospectively). • Visualize airstream	• Usually performed retrospectively and not during outbreaks	[134,135]
Computational Modeling/Simulation	• Describes transmission in a greater context. • Can account for heterogeneity of transmission within a population. • Human mannequins can be used as replacement for humans	• Theoretical (for mathematical modeling). • Artificial setting.	[82,136–141]

frequently and vigorously in the outbreak reports of pediatric practices. Remington *et al.* calculated the infectious dose of MV produced by the index case through coughing, using a mathematical model based on airborne transmission. They found that the index case produced a very high infectious dose compared to cases from other outbreaks and mentioned a phenomenon called superspreading [18••]. Superspreaders are individuals who are able to infect a disproportionally large number of susceptible contacts when compared to a typical individual [19–22], which may contribute to the efficient transmission of MV.

Parainfluenza (PIV) and human metapneumovirus (HMPV)

There is a substantial lack of (experimental) evidence on the transmission routes of PIV (types 1–4) and HMPV. For both viruses, contact and droplet transmission are commonly accepted transmission routes [23–25]. However, only virus stability on various surfaces has been investigated so far and it has been shown that PIV and HMPV are stable on non-absorptive surfaces and can barely be recovered from absorptive surfaces [26–30].

Respiratory syncytial virus (RSV)

Transmission of RSV among humans is thought to occur via droplets and fomites [1,7]. In the 1980s three potential transmission routes of RSV were studied in humans by dividing infected infants and healthy volunteers into three groups, representing: Firstly, all transmission routes, secondly, transmission via fomites and finally, airborne transmission by allowing the volunteers to have either, firstly, direct contact with infants (cuddlers), secondly, touching potential fomites (touchers) or finally, sitting next to the infant (sitters). Volunteers in the group of the cuddlers and touchers but not the sitters became infected, suggesting that direct contact and droplet transmission were the probable routes for efficient infection of the volunteers and that transmission via aerosols was less likely [31]. Another study on the transmission via fomites showed that RSV could be recovered from countertops for several hours, but only for several minutes from absorptive surfaces such as paper tissue and skin [32••]. Later on, in the late 1990s, Aintablian *et al.* detected RSV RNA in the air up to 7 m away from a patient's head [33]. In spite of that, since virus infectivity could not be demonstrated, potential airborne transmission of RSV has been considered negligible and transmission of RSV was thought to occur mainly through contact and droplet transmission. However, in a recent study authors were able to collect aerosols that contained viable virus from the air around RSV infected children [34••]. Although the detection of viable virus in the air is by itself not enough to confirm aerosol transmission, the general presumption that RSV exclusively transmits via droplets should be reconsidered and explored further.

Rhinovirus

Extensive human rhinovirus transmission experiments have not led to a widely-accepted view on the transmission route [35–37,38••,39••,40]. Inhalation of aerosols (0.2–3 μm) resulted in efficient rhinovirus infection [41], but little to no infectious rhinovirus could be demonstrated in sneezes and coughs as detected by virus titration [42]. Rhinovirus can survive on stainless steel, plastic and skin for a couple of hours [42,43]. Additionally, virus was detected in saliva, occasionally on hands and could be recovered from the skin of recipients after rubbing either a contaminated fomite or hand [42,44]. When rubbing of fomites was followed by auto-inoculation this resulted in infection of the volunteers [35]. In a three-day rhinovirus experiment with healthy volunteers different exposure modes were used to investigate the rhinovirus transmission route: Firsrtly, small-particle exposure (separating donor and recipients by wire mesh), secondly, large particle exposure (encouraging contact, coughing and sneezing while wearing gloves) and finally, direct contact exposure (hand contact followed by self-inoculation). From the results it was concluded that direct contact was the main transmission route [36]. Furthermore, rhinovirus RNA was detected in offices by air sampling studies and subsequent sequencing resulted in a matched air-mucus pair [37]. In a miniature field trail, experimentally infected donors with severe colds participated in a card game with susceptible recipients for ~12 hours [38••,39••,40]. A restraining device, preventing touching of the head and face, was used in the aerosol condition and heavily contaminated cards and exaggerated hand-to-face movements in the fomite condition. In these experiments aerosol transmission was suggested [40].

In general, transmission rates and exposure time varied between studies, which may contribute to the different routes of transmission that were observed. Therefore, the donor-hours of exposure was determined using donors with severe rhinovirus infections. At 200 hours of exposure to donors, transmission had occurred to 50% of the susceptible recipients, though the transmission route itself was not investigated [38••].

Influenza A virus

Due to the severity of the yearly influenza epidemics and the potential of zoonotic influenza A viruses to cause severe outbreaks, there have been many studies on influenza A virus transmission among humans. Different kinds of studies, such as air sampling and intervention studies, as well as human challenge studies have been conducted. In addition, transmission events have been described extensively after outbreaks in aircrafts, households and hospital settings. However, until today, results on the relative importance of droplet and aerosol transmission of influenza viruses stay inconclusive and hence, there are many reviews intensively discussing this issue [10,45–50].

Already in the mid-1900s human challenge models were used to assess the transmission route of influenza virus [51•,52–54]. It was shown that illness outcome is dependent on the inoculation route and tends to be milder in intranasally infected volunteers in comparison to inoculation through inhalation [52,53]. Furthermore, illness seemed to be milder in experimentally infected volunteers than in naturally infected individuals [51•]. Increasing numbers of studies focused on the detection and quantification of influenza viruses contained in droplets and aerosols expelled into the air through breathing, sneezing and coughing of infected individuals

[9,55–56,57•,58–61]. Influenza virus RNA was detected in the air up to 3.7 m away from patients with the majority of viral RNA contained in aerosols (<5 μm) [59]. The presence of virus in aerosols could indicate potential airborne transmission, although many studies only quantified the amount of viral RNA [55,57•,61]. A few studies quantified viable virus, although this was only recovered from a minority of samples [9,58,59].

Coronavirus

In humans, alpha (229E and NL63) and beta coronaviruses (OC43, HKU1, SARS and MERS) are associated with respiratory disease [62,63]. Alpha coronaviruses have a high attack rate early in life and spread rapidly during outbreaks, indicating efficient human to human transmission [63]. Furthermore, samples obtained from staff and patients of a neonatal and pediatric intensive care unit showed a high incidence of human coronaviruses HCoV-229E and HCoV-OC43, suggesting staff-to-patient and patient-to-staff transmission [64]. Unfortunately, there is very little data to corroborate on the HCoV-229E, HCoV-NL63 and HCoV-OC43 transmission routes. HCoV-OC43, HCoV-229E and HCoV-NL63 infectivity was lost between 0 and 72 hours on non-absorptive surfaces, although it can survive several days in medium or PBS [65–67]. Aerosolized HCoV-229E had a half-life of 67 hours in a rotating steel drum (at 20 °C and 50% relative humidity) [68]. SARS-CoV and MERS-CoV appeared to have an unusual capacity to survive on dry surfaces as compared to HCoV-229E, HCoV-OC43, and HCoV-NL63 [69,70].

The SARS outbreak was primarily linked to healthcare settings, with ≥49% of the cases linked to hospitals [71], most probably caused by aerosol-generating procedures on severely ill patients [72,73]. Aerosol-generating procedures like intubation, the use of continuous positive-pressure ventilation and drug delivery via nebulizers are likely to produce 'fine infectious droplets', which travel further than droplets from coughs [74]. Additionally, superspreading events contributed to the dispersion of the SARS outbreak [73,75–77], particularly in the Hotel Metropole and the Prince of Wales Hospital in Hong Kong [76]. Moreover, a link with transmission to healthcare workers was observed when they were in close proximity (<1 m) to an index patient, suggesting direct contact or droplet transmission [73,78•,79•]. Air samples and swabs from frequently touched surfaces in a room occupied by a SARS patient tested positive by PCR, although no virus could be cultured from these samples [80]. In the Amoy gardens outbreak fecal droplet transmission was suggested [81,82].

To date, there is little data on the human-to-human MERS-CoV transmission route [83]. MERS-CoV remained stable on non-absorptive for 8 up to 48 hours and for 10 min at 20 °C and 40% relative humidity in aerosols [84]. MERS-CoV outbreaks in humans are, like those with SARS-CoV, primarily linked to healthcare settings, with a link to hospitals in ≥31% of the cases [71,85,86] and healthcare associated human-to-human transmission was observed [87,88]. Superspreader events were shown to play an important role in nosocomial outbreaks [71,89]. Virus was isolated from environmental samples in hospital rooms, suggesting direct contact or fomite transmission. Moreover, the airborne potential of MERS was investigated by air sample analysis [90,91••]. Viral RNA was detected on the inlet of air ventilation equipment [90] and virus was isolated from air samples and surfaces from inaccessible areas like the ventilator exit, implicating potential aerosol transmission [91••].

Adenovirus

Human adenoviruses can cause respiratory disease (mainly type 1–5, 7, 14 and 21) [92,93], conjunctivitis or infantile gastroenteritis (type 40 and 41) [94]. They are a common cause of respiratory illness and pneumonia in children [95,96], whereas infections are generally asymptomatic in adults [92]. Adenoviruses cause nosocomial outbreaks, especially in pediatric care facilities, where they spread rapidly [95,97,98]. Moreover, adenovirus type 4 and 7 are responsible for large outbreaks of acute respiratory disease, especially in crowded conditions. This is illustrated by, for example, outbreaks among military recruits for which airborne spread was suggested [92,94,99]. It is difficult to eliminate adenovirus from skin, fomites and environmental surfaces [100]. An outbreak in a mental care facility was probably enhanced by spending the day mainly in a crowded room while sharing cigarettes and soda cans, suggesting indirect fomite spread [101]. In a study published in 1966, experimental infections with adenovirus administered as aerosols (0.3–2.5 μm) or droplets (15 μm) to healthy, male inmates, resulted in infection of all volunteers, although the resulting illness resembled a natural infection only in the aerosol group [102]. During a military training period, increased numbers of adenovirus infections occurred over time, which correlated with an increased detection of PCR-positive air filters. Additionally, a correlation between disease and the extent of ventilation was observed, with more ventilation resulting in fewer disease cases [103•]. In a more recent study in military recruits, positive viral DNA samples were mainly obtained from pillows, lockers and rifles, although adenovirus DNA was also detected in air samples. No consistent correlation between increased positive environmental samples and disease was observed [104].

Discussion

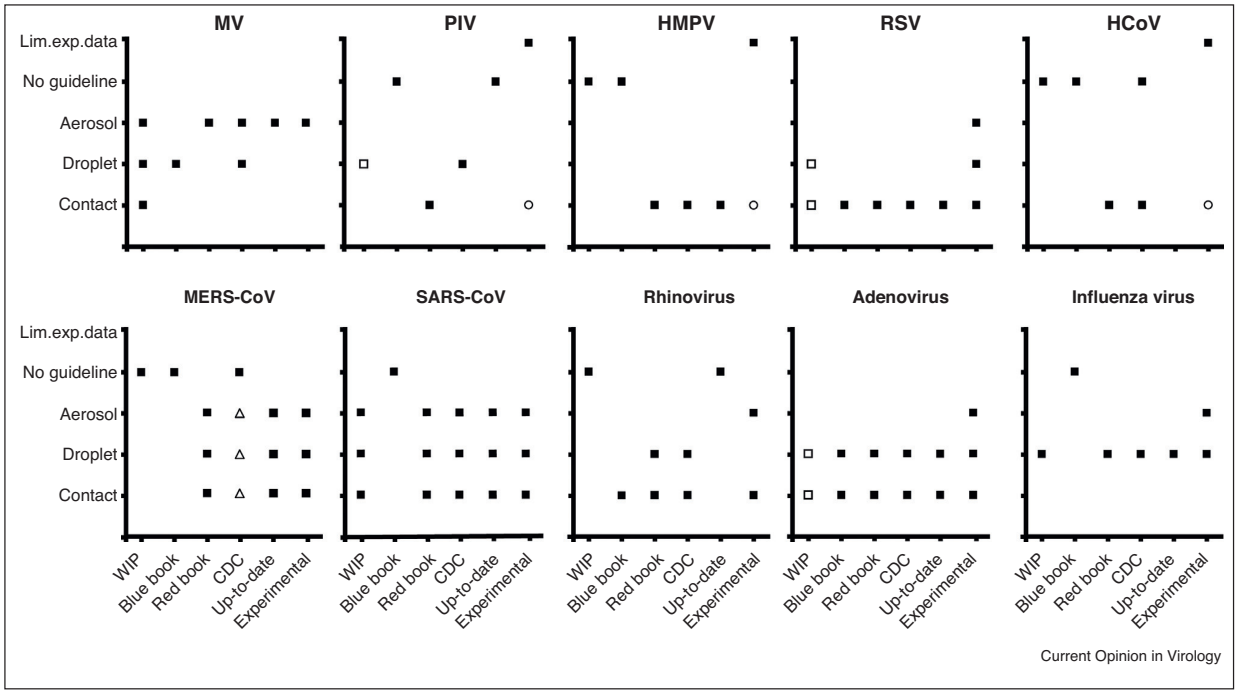
Studies on the transmission routes of respiratory viruses have been performed since the beginning of the 20th century [105]. Despite this, the relative importance of transmission routes of respiratory viruses is still unclear, depending on the heterogeneity of many factors like the

environment (e.g. temperature and humidity), pathogen and host [5,19]. Differences in virus shedding between individuals can contribute to the transmissibility rate, especially in the case of superspreaders [75,106]. In addition, the SARS-CoV outbreak highlighted the impact of aerosol-generating procedures on the increased risk of human-to-human transmission [74,107], demonstrating that for these procedures additional containment measures are necessary.

Inter-human transmission has been studied under many different (experimental) conditions. A summary of the advantages and disadvantages of the different study designs (Table 3) highlights the difficulty of human transmission experiments. As a consequence, contrasting results have been obtained for many viruses. This is also reflected in Table 2, summarizing the experimental data on inter-human transmission. Besides the difficulty of performing studies under well-controlled conditions, another key issue is that often (attenuated) laboratory strains are studied in healthy adults, which does not reflect the natural circumstances and target group and hence influence the outcome of the studies.

Respiratory viruses are an important cause of nosocomial infections, especially in children. Therefore, we consulted the guidelines on infection prevention from National [108], European [109], American [3,110] and International [111]) organizations for their information on transmission routes (Table 2) and associated isolation guidelines (Figure 1). Unfortunately, terms and definitions of respiratory transmission routes and isolation guidelines are not always used in a uniform way, leaving room for personal interpretation. But more importantly, information on the transmission route does not always reflect the isolation guidelines (e.g. for PIV and rhinovirus, Figure 1). As a proxy for transmission route, virus stability is often referred to in the guidelines, however, this can only imply a role for indirect contact transmission but is by no means conclusive on the transmission route. In hospital settings, prevention of contact transmission is generally implemented in standard infection prevention

Fig. 1



Isolation guidelines for respiratory virus infections in comparison to experimental evidence on transmission routes. Isolation guidelines for all respiratory viruses discussed in this review from National (Working Group Infection Prevention (WIP) [108], from the Netherlands National Institute for Public Health and the Environment (RIVM)), European ('The Blue Book' [109]), American ('The Red Book' [110] and the Centers for Disease Control (CDC) [3]) and International (UpToDate [111]) organizations are shown on the *X*-axis, together with the experimental evidence on transmission routes (Table 2). The categories on the *Y*-axis are the different transmission routes (contact, droplet or aerosol), the absence of guidelines for infection prevention ('No guideline'), or the limited availability of experimental data ('Lim. exp. data'). The information shown for influenza virus reflects the guidelines on seasonal influenza virus. Closed squares (■): isolation guidelines for the respective respiratory virus. Open squares (□): guidelines are only for children ≤6 years old. Open circles (○): data from stability experiments only. Open triangles (△): specific CDC guidelines for Healthcare Professionals [115] (not the isolation guideline [3] used in this review).

precautions such as strict hand hygiene and cough etiquette. It is important to note differences in isolation guidelines between different organizations and the lack of correlation to scientific data. The variation in described transmission routes and associated isolation guidelines among the different organizations underscores the lack of convincing data.

Well-designed human infection studies could be employed to investigate the role of transmission routes of respiratory viruses among humans [112••]. However, since human transmission experiments are very challenging, animal transmission models can provide an attractive alternative and should be explored and developed for all respiratory viruses. In such experiments, the influence of environmental factors on transmission routes can also be investigated [113]. However, before extrapolating experimentally generated data to humans, it is important to understand the limitations of these models, and appreciate the heterogeneity of experimental setups employed in laboratories [114]. Furthermore, quantitative data such as viral load in the air can be obtained by air sampling methods in various environments, such as hospital settings. Air sampling of viruses is an increasingly used technology in animal and human experiments. However, whereas most studies rely on the detection of viral genome copies, viability assays such as plaque assays or virus titration should be included to gain information on virus infectivity.

Ultimately, the knowledge gap on inter-human transmission should be filled by developing and performing state-of-the art experiments in a natural setting. Combined with animal transmission models and air sampling in different (health care and experimental) settings, these data should result in a thorough scientific understanding of the inter-human transmission routes of respiratory viruses. Eventually, this knowledge will help with an evidence-based risk assessment of the different transmission routes to improve existing infection prevention strategies.

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