Original articles and reviews

Abstract

Background. Indoor human environments, including homes, offices, schools, workplaces, transport systems and other settings, often harbor potentially unsafe microorganisms. Most previous studies of bioaerosols in indoor environments have addressed contamination with bacteria or fungi. Reports on the presence of viral aerosols in indoor air are scarce, however, despite the fact that viruses are probably the most common cause of infection acquired indoor.

Objective. This review discusses the most common respiratory (influenza viruses, rhinoviruses, coronaviruses, adenoviruses, respiratory syncytial viruses, and enteroviruses) and gastrointestinal (noroviruses) viral pathogens which can be easily transmitted in indoor environments.

Results. The vast majority of studies reviewed here concern hospital and other health facilities where viruses are a well-known cause of occupational and nosocomial infections. Studies on other indoor environments, on the other hand, including homes, non-industrial workplaces and public buildings, are scarce.

Conclusions. The lack of regulations, threshold values and standardized detection methods for viruses in indoor environments, make both research and interpretation of results difficult in this field, hampering infection control efforts. Further research will be needed to achieve a better understanding of virus survival in aerosols and on surfaces, and to elucidate the relationship between viruses and indoor environmental characteristics.

Key words
• viruses
• indoor
• droplet
• droplet nuclei
• fomites

INTRODUCTION

Private and public indoor environments, including homes, offices, schools, workplaces and transport systems contain numerous potentially harmful pollutants. Research on exposures to indoor pollutants has so far focused mainly on chemical compounds. Recently, exposure to biological agents, mostly bacteria and fungi, has aroused growing interest, but reports on the presence of viral aerosols in indoor air remain scarce.

Viruses are small (20-400 nm), obligate intracellular parasites. They represent a common cause of infectious disease acquired indoors, as they are easily transmitted especially in crowded, poorly ventilated environments [1, 2]. During and after illness, viruses are shed in large numbers in body secretions, including blood, feces, urine, saliva, and nasal fluid. Consequently, viral transmission routes are diverse, and include direct contact with infected persons, indirect contact with contaminated surfaces, fecal-oral transmission (through contaminated food and water), droplet and airborne transmission. Droplet transmission occurs when viruses travel on relatively large respiratory droplets (> 10 µm) that people sneeze, cough, or exhale during conversation or breathing (primary aerosolization). A single cough can release hundreds of droplets, a single sneeze thousands (up to 40 000) at speeds of up to 50-200 miles per hour, each droplet containing millions of viral particles (although the number varies greatly in the course of infection). Aerosol droplets travel only short distances (1-2 meters) before settling on surfaces, where viruses can remain infectious for hours or days. Virus survival on fomites is influenced by temperature, humidity, pH and exposure to ultraviolet light. Hands that come into contact with these surfaces become contagious (through later contact with mucous membranes). Secondary aerosolization can occur when air displacements disperse the viruses back into the air from contaminated surfaces. Droplet transmission is not to be confused with airborne transmission. Droplets do not remain suspended in the air. On the other hand, airborne transmission depends on virus-containing droplet nuclei (small-particle residue ≤ 5 µm) of evaporated droplets or dust particles that can remain suspended in the air for long periods. Viruses contained within the droplet nuclei can be transported over considerable distances by air
Viruses in indoor environments

Roy and Milton proposed a classification for pathogen airborne transmission: obligate, preferential, or opportunistic [3].

1) obligate: refers to an infection that, under natural conditions is initiated only through aerosol (droplet nuclei) deposited in the distal lung. The best known obligate airborne microorganism is *Mycobacterium tuberculosis*. No groups of viruses belong to this category;

2) preferential: refers to pathogens that can initiate infection by multiple routes, but are predominantly transmitted by droplet nuclei (e.g. chickenpox and measles);

3) opportunistic/rare: refers to pathogens transmitted mainly via other routes but able to spread via droplet nuclei or dust in certain circumstances.

The vast majority of respiratory and enteric viruses belong to the third group. Viruses able to transmit infection via the airborne route can almost ever transmit infection also over short ranges and through direct contact. The most important source of potentially pathogenic viral aerosol is other humans (ill or in incubation period). Airborne viral particles can also spread by other means. The flushing of a toilet, for example, can aerosolize significant concentrations of airborne viruses [3]. Once released in indoor environments, the movement and fate of viruses in the air is a complex process, involving many factors: the mechanism and speed by which the droplets are ejected from the infected person, the concentration of viruses in respiratory secretions, the presence of particulates/organic matter, environmental factors affecting the infectivity and viability of viruses (e.g. temperature and humidity), and ventilation, heating, or air conditioning. Morawska reviewed the influence of these parameters on airborne viral transmission [4]. The dynamics of survival and dissemination of viruses in aerosols indoors, as well as the role of ventilation and other environmental factors are still poorly understood.

Crowded indoor environments, especially when poorly ventilated, represent greater risks for viral transmission. Hospitals in particular, are environments where viral aerosol can be particularly hazardous, since patients tend to be especially prone to infection due to preexisting illness. Elderly patients, children, cancer patients, patients undergoing major surgery, immunocompromised or immunosuppressed patients are most at risk. Nosocomial infections may be transmitted by patients, hospital personnel and visitors. The main routes of transmission in hospitals are airborne, droplet and contact. Establishing how viruses are transmitted under different circumstances, and whether transmission requires close contact, is of great importance as such information will affect the choice of infection control measures in health-care settings. Existing standard precautions apply to all clients and patients attending healthcare facilities. Transmission-based precautions [specific for airborne, droplet or contact transmission], applying only to hospitalized patients, are also available. Both protocols are continuously updated at the international level.

The first reviews on viruses in indoor environments were published in the 1980s [5, 6]. Adenovirus (type 4), the first virus to be isolated from indoor aerosol, was identified in 1966 in aerosol samples from the quarters of military recruits infected with Acute Respiratory Disease [7]. Enterovirus (cossackievirus A-21) was identified in 1970 in aerosol samples from the barracks of soldiers affected by acute respiratory infection [8]. Since then, human infections due to viral aerosol (or contact with contaminated surfaces) have been studied in various environments, including office building, hospitals, restaurants, transport systems and schools [3].

This review discusses the most common respiratory (influenza viruses, rhinoviruses, coronaviruses, adenoviruses, respiratory syncytial viruses, and enteroviruses) and gastrointestinal viruses (noroviruses) for which evidence exists on transmission in indoor environments. We will mainly focus on airborne transmission, a route with the potential for infecting a large number of hosts over long distances from the source of viral contamination.

**INFLUENZA VIRUS**

Influenza virus infection is one of the most common and highly contagious infectious diseases and can occur in people of any age. The virus, belonging to the *Orthomyxoviridae* family, can cause mild to severe acute febrile illness, resulting in variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death. About 50% of all infections may be asymptomatic. Asymptomatic patients however, shed virus and can transmit the disease, thus creating a reservoir for the virus. In most cases, the influenza virus is transmitted by droplets, through the coughing and sneezing of infected persons, but it can also be transmitted by airborne droplet nuclei as well as by contact, either through direct skin-to-skin contact or through indirect contact with contaminated environments. Controversy exists with regard to the importance of the airborne route as compared to droplet or contact transmission. In clinical studies, virus-laden particles within the respirable aerosol fraction have been detected in exhaled breaths of patients with influenza and in the air samples from healthcare settings during seasonal peak [9]. Moreover, the scientific literature presents evidence in support of a contribution of aerosol transmission to the spread of influenza A, including the prolonged persistence of infectious aerosolized influenza virus at low humidity; the transmission of influenza by aerosols, reproducing the full spectrum of disease, at doses much smaller than those required by intranasal drop inoculation (large droplet transmission); and the interruption of transmission of influenza by blocking the aerosol route through UV irradiation of upper room air [9-12]. A paper by Brankston and colleague, however, following a systematic review of the experimental and epidemiological literature on this subject, concluded that, in most clinical settings, transmission occurs preferentially at close range rather than over long distances [13]. Influenza viruses have been detected in different indoor environments (e.g., homes, schools, office buildings). Public places such as hospitals, where the pres-
ence of a susceptible population is often combined with a high population density, may harbor high concentrations of pathogens and therefore pose a considerable risk for the transmission of the virus, with potentially fatal consequences for hospitalized patients [14-16]. Using real-time polymerase chain reaction, Blachere and coworkers measured the amount and size of airborne particles containing influenza virus in an emergency department. The authors confirmed the presence of airborne influenza virus, and found over 50% of detectable influenza virus particles to be within the respirable aerosol fraction [10]. Lindsley and colleagues detected small airborne particles containing influenza RNA in a health care facility during influenza season. They also found a correlation between the number of influenza-positive samples and the number and location of patients with influenza [17]. As for contact transmission through indoor surfaces, results from different studies clearly demonstrate that influenza virus is present on fomites in various indoor environments (homes and day care centers, childcare facilities, and others) during the influenza season [18, 19]. Viruses can be transferred from surfaces to hands, and vice versa. The importance of this mode of transmission for influenza is unclear however, since, while the virus can survive on surfaces for hours or even days, it cannot survive on hands for longer than five minutes [20]. A recent study concluded that influenza A transmission via fomites is possible but unlikely to occur [19]. The overall burden of health care facility-acquired influenza is uncertain. However, influenza outbreaks occur frequently in these environments, and involve almost all types of healthcare facilities [14, 16, 20-24]. Other indoor environments such as the transport vehicles and schools may be susceptible to infection from airborne influenza. Transmission during air travel is documented [25-28]. In this context, the risk of infection is difficult to estimate, and very few control methods are available [28]. Large outbreaks of influenza have been described in schools, involving both students and staff members. Schools are known to have an important role in influenza transmission in a community since children have a higher influenza attack rate than adults (children get the flu twice as often as adults) [29, 30]. This is why school closures can be effective in reducing the impact of influenza on a community [31]. Private and public buildings are also indoor environments which may pose health risks. A recent study by Goyal and colleagues used the ventilation systems of two buildings as a long-term sampling device to determine the presence of a variety of airborne viruses (the presence of human respiratory viruses and viruses with bioterrorism potential), influenza A and B were detected (along with other groups of viruses), meaning that contamination exists in the surrounding environment [32].

RHINOVIRUS

Rhinovirus [RV] is a small RNA virus belonging to the Picornaviridae family. More than 100 immunologically distinct serotypes have been identified and new serotypes are continuously emerging. These viruses are the most frequent causative agents of both upper (common colds) and lower respiratory tract infections in infants and young children, and are associated with a broad variety of clinical outcomes, ranging from asymptomatic infections to severe respiratory disease requiring hospitalization (pneumonia and bronchiolitis). They have also been implicated in acute exacerbations of asthma and chronic obstructive pulmonary disease [33], and are, as a result, a major cause of pediatric hospitalization. Household transmission of infection from children to adults has been described; the introduction of RV into a household by one family member will cause the disease in about 70% of other family members [34]. Although the method of transmission of RVs is disputed, they are thought to be mainly transmitted via large droplets, but indirect contact with contaminated fomites has also been shown to transmit infection [35, 36]. Rhinoviruses can survive on environmental surfaces for several hours. Infectious viruses have been recovered from naturally contaminated objects in the surroundings of persons with RV colds [2].

Several studies have demonstrated that aerosol transmission is a possible method of transmission among adults, in both natural and experimental conditions, even if this kind of transmission is not frequent [37-39]. Huynh and coworkers demonstrated that RV aerosols are generated by coughing, talking, sneezing and even simply breathing [40]. In one study, the authors detected an identical RVs in a nasal mucous sample from a patient with an upper respiratory tract infection and from an air sample collected in that same person’s office during his illness. Moreover, they showed a significant positive relationship between the frequency of virus detection in air filters and the degree of building ventilation with outdoor air, suggesting that lower ventilation rates are associated with increased risk of exposure to potentially infectious droplet nuclei [39]. Rhinovirus outbreaks in health care facilities, capable of determining severe infections and also death have been documented [41-45]. RVs have also been detected in transport vehicles [46].

CORONAVIRUS

Coronaviruses are RNA viruses of the family Coronaviridae, known to cause respiratory and enteric disease in humans and animals. Coronaviruses are second to RV as a cause for the common cold. They may also cause other respiratory tract infections, such as pneumonia and pharyngitis. Severe acute respiratory syndrome [SARS] is a serious, potentially life-threatening viral infection caused by a previously unrecognized virus from the Coronaviridae family. The earliest symptom is a sudden onset of high fever. Some patients may also have chills and headaches. After 3 to 7 days, patients experience cough and breathing difficulties, followed by pneumonia. In late 2002, the syndrome was observed for the first time in southern China. The disease has now been reported in Asia, North America and Europe.

The most common mode of transmission is through water droplets generated when an infected person coughs or sneezes. Transmission is thus most likely to occur in close proximity to someone who is infected or by touching a contaminated surface [47]. Current studies in different indoor environments, however, indicate that SARS may be transmitted through the airborne route as well [48]. Several clusters of infection have been reported, which point to a likely transmission by this route, including transmission in an aircraft from an infected person to passengers located...
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Recent AdVs have been detected in the air of hospital pediatric departments using real-time qPCR coupled with air-sampling filter methods [57, 58]. Adenovirus outbreaks have been documented in different indoor environments, including health care facilities [59-63], schools [64, 65], military hospitals and barracks [66, 67]. However, data on the presence of AdV in the aerosol (or on fomites) of these indoor environments are scarce. Adenovirus-containing airborne particles were also detected in the public areas of different health care facilities [including the emergency room and outpatient department] throughout the year.

Respiratory Syncytial Virus

Human respiratory syncytial virus (RSV) is a single-stranded RNA virus of the family Paramyxoviridae, and is the leading cause of lower respiratory tract infection in infants and young children worldwide. In adults and healthy children, the symptoms are usually mild and typically mimic the common cold. In some cases, especially in premature babies and infants with additional, underlying disease, RSV infection can be severe (bronchiolitis and/or viral pneumonia) and require hospitalization. Respiratory syncytial virus can also become serious in older adults, adults with heart and lung diseases, or with weakened immune systems. In mild climates, RSV infections usually occur during late fall, winter, or early spring. The virus is highly contagious. Transmission rates up to 100%, have been shown to occur in day care centers and neonatal units of hospitals when RSV is introduced by an infected individual. Infants secrete enormous concentrations of RSV, often more than 10^7/mL of nasal discharge. Transmission can occur when infectious material comes into contact with mucous membranes of the eyes, mouth or nose, and possibly through the inhalation of droplets generated by a sneeze or cough. Infection can also result from contact with contaminated environmental surfaces, the commonest mode of transmission in school classrooms and daycare centers. Hall, et al. demonstrated that contact transmission with fomites predominates over droplet contact [68]. Considerable controversy exists with regard to whether RSV is acquired by the inhalation of infectious airborne particles and with respect to the relative importance of this route, as compared to droplet or contact transmission. Recent data support the possibility that RSV could be transmitted by the airborne route. Aintablian detected RSV RNA in air samples from the hospital rooms of infected patients at large distances from the patient's bedside (as far as 7 m from the patient's bedside and for up to 7 days of hospitalization) [69]. A recent study reported the detection of airborne particles containing RSV RNA throughout a health care facility, particles small enough to remain in the air for an extended period and to be inhaled deeply into the respiratory tract [70]. Nosocomial RSV infection outbreaks were recognized shortly after the discovery of the virus in 1956 [71, 72]. Later on, different authors described infections, mostly linked to neonatal intensive care units and pediatric wards [73-76]. Strategies for the prevention of nosocomial RSV infection have been reviewed by Grootveld, et al [77]. Outbreaks have also been documented in other indoor environments. A study aimed at investigating infectious outbreaks in care facilities for the elderly found RSV to
be the second respiratory infection in terms of its median attack rate – 40% (following Chlamydia pneumoniae, 46%) [78]. Outbreaks of RSV, clinically indistinguishable from influenza, were also described in nursing homes [79].

ENTEROVIRUS

Enteroviruses (EVs) are members of the Picornaviridae family, a large and diverse group of small RNA viruses present worldwide. In humans, EVs target a variety of different organs causing gastrointestinal, respiratory, myocardial and central nervous system diseases. In temperate climates, entervoiral infection occurs primarily in the summer and early fall. Although the majority of infections are asymptomatic or result in a self-limited illness, fatalities do occur, especially in neonates or individuals with B-cell immunodeficiencies. Enterovirus outbreaks in neonatal units and school nurseries have been reported from many countries [80-86], reflecting the susceptibility of infants to EV infection and leading to extensive discussion on control measures and interventions.

Gastrointestinal shedding of the virus is prolonged, and faecal-oral transmission is the major mode of transmission. Other important routes of EV transmission are person-to-person contact and the inhalation of airborne viruses in respiratory droplets. As early as the 1960s, Couch, et al. found infectious coxsackievirus, a member of the EV genus, in large droplets and droplet nuclei generated by coughs and sneezes as well as in the air of rooms contaminated by such discharges. They also demonstrated the transmission of this respiratory viral infection to volunteers by the airborne route [8, 53]. Aerosol transmission is suspected of having contributed significantly to the EV 71 epidemic which infected up to 300 000 children and caused 78 deaths in Taiwan in 1998 [87]. Until now, qualitative and quantitative data on EV in aerosols and surfaces in indoor environments have been limited. Tseng, et al. found EVs in concentrations similar to those of influenza and AdV in the pediatrics department air of a medical center in Taipei, Taiwan, with the peak reaching 30 000 copies/m3 [57]. Pappas, et al. found about 20% of the objects in a pediatric office to be contaminated with respiratory viral RNA (either RV or EV), objects which may thus represent fomites for the transmission of viruses [88].

NOROVIRUS

Noroviruses (NoVs) are RNA viruses belonging to the family Caliciviridae, currently subdivided into five genogroups (GI - GV), comprising at least 40 genetic clusters. Genotypes infecting humans are those belonging to GI, GII and GIV. Human NoV is emerging as the leading cause of epidemic gastroenteritis (GE) and as an important cause of sporadic GE in both children and adults. It is responsible for nearly half of all GE cases and for more than 90% of non-bacterial GE epidemics worldwide. Norovirus infection induces vomiting, diarrhea, mild fever, abdominal cramping and nausea. Although typically a self-limiting disease of short duration, new evidence suggests that the illness can be severe and sometimes fatal, especially among vulnerable populations – young children, the elderly and the immunocompromised – and is a common cause of hospitalization. Numerous reports have associated NoV with clinical outcomes other than GE, such as encephalopathy, disseminated intravascular coagulation, convulsions, necrotizing enterocolitis, post-infectious irritable bowel syndrome, and infantile seizures.

Noroviruses are highly contagious with a low infectious dose (< 100 virus particles) [89]. These viruses are present in large numbers in the stools (at least 10⁷ copies/g) and vomit (10⁶ – 10⁷ copies/g) of infected patients. Intense outbreaks occur in institutional settings (e.g., nursing homes, hospitals, and day care) where a considerable proportion of occupants of a particular indoor environment become ill during a relatively short period, typically days to weeks.

Fecal-oral spread is the primary transmission mode and the foodborne and waterborne transmission for NoV is well established. The airborne transmission or the transmissions through contaminated surfaces however, have not been significantly discussed in the NoV outbreak literature. Morawska in 2006 reviewed the state of knowledge on indoor transmission of viral infections highlighting that the spread of viral infections through atomized vomit is a significant route of transmission in diseases which cause frequent vomiting, such as NoVs [4]. A recent editorial published in the Indoor Air journal by Nazaroff, summarizes the evidence concerning airborne transmission of NoV as a cause of acute viral gastroenteritis, and discusses the significance of this issue for indoor environmental quality, concluding that airborne transmission is indeed an important exposure pathway for acute gastroenteritis caused by NoV [90]. Other published studies present and discuss evidence of airborne transmission and the role of indoor environmental contamination for NoV outbreaks across a broad range of indoor environments such as hospitals, schools, kindergartens, restaurants, care facilities, hotels and concert halls [91-98], as well as airplanes, buses and cruise ships [99-101].

Sources of contaminated aerosol are diverse. Vomiting is the main symptom of NoV infections; when sudden projectile vomiting occurs, a fine mist of virus particles passes into the air, which can be inhaled by anyone in the immediate vicinity. Droplets being inhaled can be deposited in the upper respiratory tract, and subsequently be swallowed along with respiratory mucus. Alternatively, aerosol droplets produced during vomiting could settle onto indoor surfaces that might then be transferred to hands of exposed individuals through physical contact, or deposited on the floor from which they can be resuspended by human movement and turbulence. Aerosol droplets can also be generated from toilet flushing [102]. During the illness, up to a trillion genomic copies per gram of feces of NoV can be excreted [90]. Droplet generation from toilets may therefore pose significant risks of viral dissemination both directly (especially in public toilet rooms) and indirectly via surface contamination [90]. Despite the documented role of aerosol in NoV transmission, no reports have been published on efforts to detect NoV in indoor air. Norovirus has, on the other hand, been detected on indoor environmental surfaces and transmission via fomites has been documented [103-105].

CONCLUSIONS

Viruses are a common cause of infectious disease acquired indoors, since they can be easily transmitted, especially in crowded, poorly ventilated environments.
The vast majority of studies reviewed here concern hospital and other health facilities where viruses are a well-known cause of occupational and nosocomial infections. These environments have been studied more extensively than others due to their greater clinical significance (for the number of individuals potentially involved and for the possible consequences for hospitalized patients, already suffering from other morbidities). Studies on other indoor environments, on the other hand, including homes, non-industrial workplaces and public buildings, are scarce. Therefore, more work is still needed to provide a clearer picture regarding the rates of viral diseases transmission [airborne transmission in particular] in these closed environments, and potential ways for reducing the levels of indoor viral pollution and transmission. Further research will also be needed to achieve a better understanding of virus survival in aerosols and on surfaces, and to elucidate the relationship between viruses and indoor environmental characteristics (including temperature, relative humidity and CO$_2$ concentration). The establishment of standardized methods for the detection of specific viral aerosol particles in air and on surfaces is likely to favour the attainment of the above objectives.

**Conflict of interest statement**

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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