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Abstract

This literature review explores the role that ventilation, assessed by air changes per hour (ACH), plays in infection transmission and disease control. The *American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) Position Document on Airborne Infectious Diseases* (2009) notes the dilution effect that ACH has on infectious disease transmission. The Wells-Riley equation supports the premise that increasing the volume of "clean" air dilutes the room air and thus exposes people in the room to fewer potentially infectious particles. ACH is the only variable in the Wells-Riley equation that can be quantified by direct measurement. Our knowledge of the effect of the many other variables (e.g., infectious dose, relative humidity, temperature, host susceptibility, chain of transmission) on disease transmission is limited.

The majority of studies conducted to assess the role of ventilation in infection transmission and disease control have been either observational or based on animal models that are not particularly applicable to the study of human disease. Case studies on aircraft and other vehicles, schools, and "sick" buildings and hospitals, as well as some animal studies, suggest that regardless of actual ACH, ventilation rate is just one of many factors that affect the transmission of infectious disease.

The ability to precisely predict particulate movement is needed to increase our understanding of how airborne disease organisms move within ventilated facilities. A recently published empirical study (Faulkner et al. 2013) indicates that in some situations there may be limits to the improvements in the environment that can be achieved by increasing ACH in the occupied zones of rooms.

Existing ventilation guidelines that recommend specific ACH rates for some defined spaces are often based on experiential and observational evidence rather than on hard data. Nonetheless, ACH has been shown to be an important environmental control in preventing the transmission of infectious disease in public spaces. Considerably more research is needed—in conjunction with rigorous and sustained space-specific risk assessments—before standard ventilation recommendations are changed in any way.

Room Ventilation and Airborne Disease Transmission

The relationship between air changes per hour (ACH) and infection transmission, in a closed environment or outdoors, is enigmatic. ACH is a measure of how many times the air in a defined space is replaced. Air change rate (ACR) and ACH are often used interchangeably. Examples of technical definitions for ACH include:

- The ratio of the total volume of air passing through the zone to and from the outdoors per unit of time to the volume of the zone
- The ratio of the volumetric flow rate of air into the space to the interior volume of the space
- The ratio of air supply into a zone (i.e., a room or space) to the volume of the zone
- The number of times the air in a defined space is replaced

Several studies have shown a direct relationship between ACH and infectious disease transmission, while others suggest an indirect relationship (Artenstein et al. 1967; Aintablian, Walpita, and Sawyer 1998; Booth et al. 2005; Chen and Li 2008; Sawyer et al. 1994; Suzuki et al. 2002; Mastorides et al. 1999; Huynh et al. 2008). This inconsistency suggests that modes of transmission vary by setting and circumstances and that transmission may result from a combination of factors. Memarzadeh (2011a, 2011b) and Li and colleagues (2007, 2005) recently conducted studies and comprehensive

reviews of the extensive literature on airborne and droplet infectious disease transmission.

Li and colleagues (2007) posed two questions that sum up why more specific investigation is needed to determine the relationship between ACH and infectious disease transmission.

1. Is there sufficient evidence to support the ventilation rate and/or airflow pattern as a contributing cause(s) for the spread of airborne infectious diseases?

2. If so, is there sufficient evidence to support minimum ventilation requirements to minimize transmission of airborne infectious diseases in different settings (nosocomial or otherwise)?

Li and colleagues (2007) came to these conclusions:

1. There is strong and sufficient evidence to demonstrate an association between ventilation and air movements in buildings and the transmission and spread of infectious diseases such as measles, *Mycobacterium* tuberculosis (M. tb), chickenpox (varicella), influenza, smallpox, and severe acute respiratory syndrome (SARS).

2. There are insufficient data to support minimum ventilation requirements for specific public spaces (e.g., hospitals, isolation rooms, schools, offices) in relation to the spread of infectious disease via airborne and droplet routes.

Research has identified many variables that influence disease transmission and the possible interactions that affect a pathogen's ability to be transmitted or to remain viable and virulent (e.g., necessary infecting dose, susceptibility of the host, infectivity of the pathogen, environmental factors) (WHO 2009). Despite this knowledge, no definitive quantitative analysis establishes either a minimum or an optimum ACH in relation to other variables that may affect infection transmission for any specific functional area or protocol. In single-use facilities such as school buildings, laboratories, offices, and airplanes, the ACH is often determined non-scientifically on the basis of factors such as comfort, seasonal changes in temperature and humidity, and reduction of noxious odors or volatile organic compounds (VOCs).

Most researchers agree that a facility housing several different functions should employ an ACH parameter that maximizes comfort and reduces

odors and disease transmission. Depending on the facility, other factors may also influence the determination of an appropriate ACR. For example, Memarzadeh (1998) showed that "controlling the humidity in animal rooms is more significant in managing the production of ammonia (from animal urine) than is the use of high air change rates." This finding allowed for a decrease in the ACR from 15 to as low as 5, while improving the welfare of the animals.

Faulkner and colleagues (2013) performed an empirical study to determine the effects of ACH on particulate concentrations in the occupied zone and ventilation outlet of an empty ventilated chamber given a known particulate density in the incoming ventilation air. The results indicated that in some situations the advantages of increasing ACH may be limited.

These parameters will likely differ depending on the function of the space. Most studies do not account for the amount of time an infected individual spent in the space (Memarzadeh 2011a, 2011b). Most experts now agree that in mechanically ventilated spaces, the ACH should be determined on the basis of a risk assessment of the use and conditions of the space. Memarzadeh (2010) provides a novel methodology to approximate how much air displacement and containment leakage might occur during a momentary positive pressure reversal in a facility that is designed to sustain directional airflow even under failure conditions. This methodology can be used to quantify contaminant migration across a boundary in room types such as airborne-infection isolation (AII) rooms and protective environment (PE) rooms that use sustained differential air pressure to prevent infectious particle transmission.

Memarzadeh and Xu (2012) discuss the importance of applying a scientific analysis to disease transmission and designing a ventilation system based on a site-specific risk analysis. Conditioned ventilation air can cost $4 to $8/cfm/year, which is a substantial cost for large biomedical facilities that use high air-exchange rates to maintain healthy environments. Increasing the air exchange rate of a typical 70-square-meter laboratory from 6 ACH to 14 ACH can increase the annual heating, ventilation, and air conditioning (HVAC) energy cost by around $8,000 (Memarzadeh 2009). Because so many factors affect disease transmission, Memarzadeh and Xu (2012) suggest that a ventilation system based on a thorough risk assessment can reduce infection risk without necessarily increasing ventilation airflow rate.

Chain Model of Disease Transmission

To become infectious, a microorganism must have the following:

1. A portal of entry
2. A host
3. A portal of exit

These are the critical components of the chain of disease transmission represented in Figure 1.

- The agents are disease-causing organisms such as bacteria, fungi, viruses, and protozoa.
- A reservoir is any place an infectious agent can survive, grow, or multiply.
- The portal of exit is the path by which an infectious agent leaves the reservoir.
- The mode of transmission is the means by which an organism is transferred from one carrier to another by either direct transmission (direct contact between infectious host and susceptible host) or indirect transmission (which involves an intermediate carrier such as an environmental surface or a piece of medical equipment).
- The portal of entry is the route through which the pathogen enters its new host.
- A susceptible host is a person who can get sick when exposed to a pathogen.

Furthermore, disease transmission is dependent on factors such as the following (Green 1969):

- Dose (adequate number of pathogenic organisms)
- Virulence of the organism
- Susceptibility of the host (i.e., whether the host is immune-compromised, has lowered immunity, or is unvaccinated)
- Viable mode of transmission (a sufficient number of the organism is transferred from source to host)
- The correct portal of entry into the host

Figure 1: Chain Model of Disease Transmission
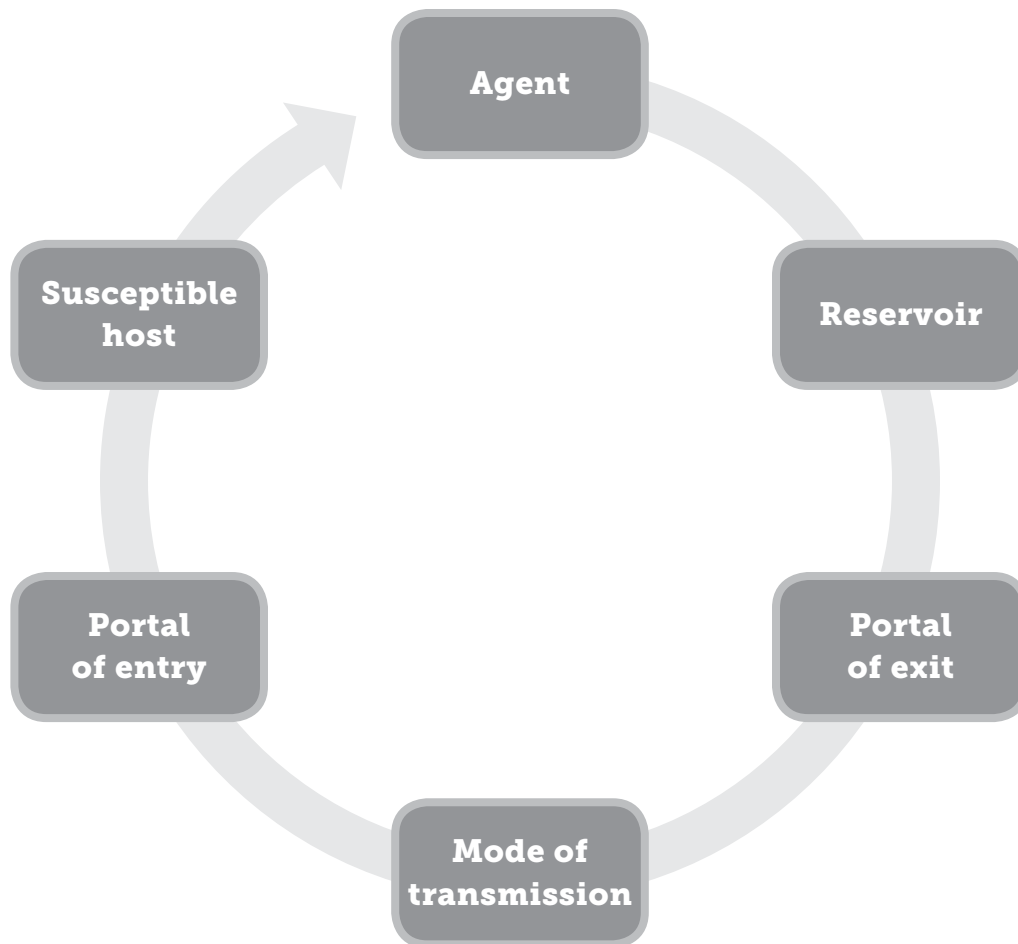
Transmission of a microorganism can occur by more than one route. In an enclosed environment, the chain of transmission is influenced by the ventilation conditions. Numerous variables can affect each factor and the microorganism's ability to move to the next level of infection. In the chain of transmission, a microorganism must leave one host or reservoir to be transmitted to another. This suggests that there is a spatial component to the chain of transmission, whether transmission occurs through direct or indirect contact or via an airborne route. The airborne transport of micro-organisms represents a possible weak link in the infection transmission route. This is where infection control measures (i.e., providing barriers to transmission) may have the greatest chance of breaking the infection cycle (Fletcher et al. 2004).

Environmental infection control strategies must be based on the principles of the chain of disease transmission, regardless of the disease of concern.

The presence of microbes in the environment does not necessarily lead to infection or even cross-transmission. For an infection to develop, the chain of transmission must be intact, and there must be a susceptible recipient.

While evidence and data are sufficient to support an association between ventilation flows and the transmission of airborne pathogens, airborne pathogen transmission is poorly understood. It is extraordinarily difficult, if not impossible, to trace airborne infectious disease transmission routes using standard epidemiological techniques. Not only does airborne evidence rapidly disappear, but the many factors that can affect the spread of disease make it extremely difficult to rule out any single route of infection.

Airborne infectious disease outbreaks are difficult to investigate, primarily because the path of transmission is transient. It is difficult to pinpoint the time of infectious particle release (exhalation or procedural) and to locate the source/index person and infected persons, and the exact states of the HVAC system operating conditions at the time of transmission are often unknown.

Existing Standards and Ventilation Risk Assessment

Risk assessment is essential to determining the most efficient, cost-effective ACH for any particular space or combination of spaces and should be done early in the design process and remain an ongoing process (Memarzadeh and Xu 2012).

ASHRAE (2003) suggests the following steps be part of any risk assessment:

1. Identify the risks.
2. Estimate the level of exposure to the risks.
3. Estimate the probability of risk occurrence.
4. Determine the value of the potential loss.
5. Rank the risks.
6. Identify vulnerabilities.

The Facility Guidelines Institute's *Guidelines for Design and Construction of Health Care Facilities* (FGI 2010) weighs the susceptibility of occupants against the degree of environmental contamination for hospital settings. This consideration can also be applied to other building types.

Disease Transmission Terms

Masago and colleagues (2008) and Jones and colleagues (2009) have clarified the terminology used to describe the complexity of disease transmission (see Table 1). Their definitions not only help us understand Masago and Jones's methodology for risk assessment, which is examined later in this monograph, they also help us evaluate other studies on disease transmission. Masago and Jones make a clear distinction between how the terms are used in models of disease transmission and how they are applied in a real-world situation such as an outbreak. This is important because it is extremely difficult to conduct controlled experiments in this field. Predictive modeling that incorporates numerous variables is more practical and can provide mitigating solutions for real-world scenarios.

Many terms (e.g., *high*, *low*, *adequate*, *inadequate*) used to describe ACH, ventilation rates, HVAC systems, filtration, number of particles, types of spaces, and other variables that are part of or affected by a ventilation system can be misleading as they are subjective and cannot be quantified in relation to airborne disease transmission.

Table 1: Comparison of Some Disease Transmission Terms
(Proposed by Masago et al. [2008] and Jones et al. [2009])

Term	Modeling	Real World
Exposure	The individual actually received some dose.	The individual was exposed to the source of the contaminant but it is not known whether he or she really received a dose. A clinical test can be used to look for evidence of exposure.
Infection	The microorganism has begun its replication in the host. This can be measured by antibody response or identification of the biological agent at the site of replication.	Infection is usually synonymous with disease (impairment of the person's health status or some function), although disease does not always manifest as a clinical condition.
Contagion	It is possible to estimate the probability of transmission from an infected individual to a susceptible individual based on exposure scenarios and the characteristics of the microorganism. Estimates of very low risks can be made.	Very high levels of disease transmission can be evaluated through investigations, but risk of contagion is generally addressed as yes or no without quantification of probability.
Sputum vs. saliva	Sputum is the material that is brought up into the mouth from the lungs with persistent deep coughing and includes some saliva. Saliva is the liquid produced in the mouth that aids in digestion. Saliva is easier to collect and measure. In the mouth, the sputum mixes with saliva. The numbers of bacilli can be 100 times higher in sputum than in saliva.	
High or low Adequate or inadequate Critical or non-critical	These terms can refer to air changes per hour, ventilation rates and HVAC systems, filtration, number of particles, and spaces.	

Risk factors for most infectious agents are difficult to quantify. Many elements must be considered, including the susceptibility of people exposed. For example, measles is highly contagious. However, immunization against this virus virtually eliminates susceptibility even if the exposure involves household contact. Other risk variations among individuals may be due to genetics, health status, or gender. Risk factors may also be related to the local environment, such as age and operational status of the ventilation equipment (Memarzadeh 2011b).

Temperature and relative humidity are important factors to consider when performing a risk assessment and developing control measures. Their role in surface survival of pathogens is well known (Memarzadeh 2011a). Other risk factors related to socio-adaptive behaviors include compliance with use of standard operating procedures involving personal protective equipment (PPE), decontamination of environmental surfaces, adherence to isolation precautions, and use of respiratory hygiene strategies (e.g., covering one's mouth and nose when sneezing or coughing, wiping down surfaces with disinfectant, proper discarding of contaminated disposables such as tissues). Although the presence of a risk factor for a particular pathogen increases the chances an illness will be contracted, it does not always lead to an illness. On the other hand, the absence of any single risk factor or the existence of a protective factor does not necessarily protect against infectious illness (Memarzadeh 2011b). It is crucial to find a balance between reducing infectious disease transmissibility and maintaining occupant comfort.

Existing standards and guidelines suggest that the risk of infectious airborne transmission can, in part, be controlled mechanically. They recommend setting barriers to break the chain of infection (Siegel et al. 2007). However, ACH is not the sole determinant of disease transmission, and the ACH differs among buildings and spaces based on function and natural or mechanical ventilation schemes. The World Health Organization (WHO) guideline on natural ventilation discusses the difficulties in developing ventilation guidelines for infection control due to insufficient data to recommend a minimum ventilation flow rate for infection control against droplet nuclei (WHO 2009).

Role of Ventilation in Disease Transmission

Ventilation can reduce the concentration of airborne pathogens by removing or diluting airborne droplet nuclei. Studies have shown that tuberculin conversion among health care workers was strongly associated with inadequate

ventilation in general patient rooms and with type and duration of work but not with ventilation in respiratory isolation rooms (Menzies et al. 2000).

Menzies and colleagues (2000) found an association between tuberculin conversion of a non-infected individual exposed to an infectious source of tuberculosis (TB) and an ACH of less than 2 in general or non-isolation patient rooms. Conversion was not associated with the ventilation rates in respiratory isolation rooms. However, regardless of the ACH, the time to conversion was the same. This finding may indicate that ACH is relatively unimportant in respiratory isolation rooms (Menzies et al. 2000). It is generally accepted that a higher ventilation rate can dilute the contaminated air inside a space more rapidly than a lower ventilation rate, and presumably also decrease the risk of transmission to individuals in the space. However, studies of TB outbreaks suggest that while ventilation is an important determinant of disease transmission, the identification of other contributing factors makes it difficult to generalize ventilation rate as the cause. These studies were largely based on questionnaires and retrospective observations (Menzies et al. 2000).

Some studies have demonstrated that air dilution or replacement does not protect personnel from exposure to concentrated bursts of aerosols in biological laboratories. In fact, Crane (1994) notes an observation by Chatigny and West (1976) that increasing ventilation rates from 6 to 30 ACH has a minimal effect on aerosol concentration of microorganisms in the first few minutes after release.

The maximum ventilation rate (above which there is no further reduction of infection risk) is not known. Although the minimum ventilation flow rate may be used in an effort to reduce energy consumption (Masago et al. 2008), it is unclear what the optimal level is.

Since most ventilated rooms have incomplete mixing under steady state operating conditions, contaminant concentrations will vary considerably throughout the room. This is especially true for particulates because, depending on their size and other properties, they may be less likely to follow air flow patterns. A complex interaction of the particulate inertia, drag forces from airflow, and gravity dictates movement and deposition of particulates in confined spaces. Under steady state conditions, one could conduct a mass balance analysis to determine the mass of particulates entering the chamber through the air inlet and the mass of particulates exiting the chamber through the exhaust air, then assume that the remainder of the particulate mass is removed from the air by deposition onto the floor via gravity or by colliding with and adhering to walls and other surfaces. Some of the particu-

late mass would remain suspended in the air within the room to maintain a certain room concentration. A recent empirical study by Faulkner and colleagues (2013) showed that the advantages of increasing ACH in terms of improving environments in the occupied zone of rooms may have limits, a finding that warrants further investigation.

There has never been a major infectious disease outbreak in a hospital that could be directly attributed to ventilation. Thus, the status quo seems to be effective in controlling the spread of some diseases. We should be cautious in making blanket changes to the existing ventilation standards without conducting more targeted research.

Since more than 1 billion passengers travel by air annually, many studies have looked at ventilation and infection rates in aircraft cabins. Some have indicated that the risk of catching an infectious illness on commercial aircraft may be reduced if the cabin ventilation rates are increased and/or the cabin air is refreshed more frequently. The studies suggest that risk of disease transmission within the aircraft cabin seems to be affected by cabin ventilation and efforts to increase ventilation will reduce risk (Aviation Health Working Group 2001b; WHO 1998; Withers and Christopher 2000). It is interesting to note that no peer-reviewed scientific work has compared the relationship between cabin air quality and aircraft ventilation rates and heightened health risks with other modes of transport or with office buildings (Mangili and Gendreau 2005; National Research Council 2002; GAO 2004; U.S. House of Representatives 2003; Aerospace Medical Association 1997; Rayman 1997).

In addition to air exchange, negative pressurization is often used in spaces such as AII room and biocontainment laboratories to prevent contaminants from flowing out of the room. However, aerosol transmission can occur between persons within or between these rooms for several reasons. The individuals may not be aware that they are infectious (such as in an emergency room or a school); they may be asymptomatic carriers; or a mechanical failure may occur in a building that is not equipped to deal with a total air handling system shutdown.

ASHRAE (2001) Standard 62-2001 notes that study results can be inconsistent because the ventilation rate and CO_2 concentrations used to measure contaminants are only surrogates for the actual agents that might be causing the symptoms. Seppänen, Fisk, and Mendell (1999) conducted a comprehensive review of 20 studies done in work settings to examine the relationship between ventilation rates and occupant health. This review found a consistent

relationship between ventilation rates below 10 l/s per person and increased symptoms among occupants. In some studies, ventilation rates greater than 10 l/s per person, even up to 20 or 30 l/s per person, were associated with further significant reductions in occupant symptoms.

Apte, Fisk, and Daisey (2000) corroborated these findings in an analysis of a large data set of adults in office buildings. This study found statistically significant, dose-dependent increases of up to a factor of six in the risk of building-related lower respiratory and mucous membrane irritation symptoms when average workday indoor CO_2 concentrations increased by 420 ppm above outdoor levels, which was still below the ASHRAE 62-2001 [133] standard of 1,000 ppm.

Mechanics of Disease Transmission

Prior to the 2003 worldwide severe acute respiratory syndrome (SARS) epidemic, there was strong evidence that ventilation and indoor environmental surfaces are an important determinant of nosocomial disease transmission (Bean et al. 1982). In the early 20th century, the work of Wells (1934), Wells and Stone (1934), and Duguid (1945) demonstrated that airborne particles can remain airborne for as long as one week after initial aerosolization. This early work was the basis for the airborne droplet nuclei theory for infectious disease transmission used to date (Wells 1934; Wells and Stone 1934).

According to the Centers for Disease Control and Prevention's (CDC) *Guidelines for Environmental Infection Control in Health-Care Facilities* (CDC and HICPAC 2003), only TB, measles (rubeola virus), and chickenpox should be considered true airborne infectious diseases. However, other infectious agents, such as SARS-CoV, are sometimes considered opportunistic because they could be transmissible over short distances (e.g., 1 to 2 meters) in favorable environmental conditions.

The 2003 SARS epidemic began in China when SARS-CoV emerged, likely in circulation among animals, and was spread person to person. The epidemic drew attention to the potential contribution of mechanical ventilation as one outbreak involved a combination of insufficient ACH, environmental survival of the virus, and ambient conditions that led to airborne dispersal over a large area (Li et al. 2005). When patients infected with the virus were admitted to health care facilities, transmission occurred where there were lapses in use of PPE and/or close contact in enclosed environments.

When someone with SARS coughs or sneezes, others may become infected by inhaling droplets in the air or touching surfaces where droplets may have been deposited. This indicates that SARS-CoV can be transmitted via both airborne and contact mechanisms. The SARS virus may live on hands, tissues, and other surfaces for up to six hours in these droplets and up to three hours after the droplets have dried. Live virus has been found in the stool of people with SARS, where it has been shown to live for up to four days. The virus may be able to live for months or years when the temperature is below freezing. Booth and colleagues (2005) reported that SARS-CoV RNA can be detected in the air, and in some cases the airborne virus can be grown in culture, demonstrating extended viability outside the infected host (Xiao et al. 2004). The SARS outbreak was initially thought to be spread through contaminated droplets. Most transmission in health care facilities appeared to be related to contact and droplet spread over distances of 1 to 2 meters.

Hanley and Borup (2010) provide examples of disease transmission in buses and taxis in which air conditioning and/or natural ventilation are available (Daisey, Angell, and Apte 2003; Daisey and Angell 1998; Olsen et al. 2003; Olsen and Dossing 1982; Ko, Thompson, and Nardell 2004; McFarland et al. 1993). Passengers shedding virus in these spaces are a probable source of aerosol transmission. The studies showed via contour maps that movement in or out of a vehicle, time spent in the vehicle, temperature and humidity of the vehicle, and physical contact with contaminated objects (e.g., money) are all factors in transmitting infection.

A study by Han and colleagues (2009) is significant in the study of airborne transmission of viral disease. An outbreak of influenza A pandemic (H1N1) occurred in June 2009 among members of a tour group in China who had traveled in the same bus for seven hours. Apparently, the index case-patient noticed flu-like symptoms prior to arriving in China. Secondary cases developed in 30 percent of the tour group members who had talked with the index case-patient and in one other passenger who had sat within two rows of the index case-patient. Tour group members who had not talked with the index case-patient did not become ill. Other kinds of contact, such as dining at the same table and receiving chewing gum from the index case-patient, played no role during this outbreak. Per this investigation, H1N1 pandemic virus infection was found to be caused by transmission during coughing or vocalization by an index case-patient, which indicates droplet transmission.

Wells's Quantum Theory of Disease Transmission

In 1955, Wells introduced the quantum theory of disease transmission. He proposed a hypothetical infectious dose unit, the quantum of infection, which is defined as the number of infectious airborne particles (one or more) required to infect a susceptible person (Wells 1934; Wells and Stone 1934; Wells 1955). Wells suggested that the number of people infected may follow a discrete probability distribution. Using a Poisson distribution line to calculate the frequency of infection in a population, he indicates that 63.2 percent of a population may become infected if a susceptible person breathes in one quanta of contagion (Beggs et al. 2003).

Beggs and colleagues (2003) indicate that because the overall infectivity of any airborne pathogen depends as much on the immunological state of the susceptible individuals as on the physical and biological characteristics of the agent, it is impossible to directly measure the quanta present in any outbreak. It is, however, possible to indirectly determine the quanta if the physical parameters associated with the outbreak are known. The epidemiological models discussed in the sidebar have been used to determine the quanta of infection associated with outbreaks of TB, measles, and other airborne infections.

Beggs and colleagues (2003) compared quanta production rate data for TB and measles outbreaks from a variety of sources and noted that a vast range of quanta production rates are associated with TB outbreaks. It appears that for normal pulmonary TB patients the quanta production rate is quite low (1.25 quanta/h) (Riley et al. 1962). The much higher TB quanta production rates (> 2,000 quanta/h) appear to be associated with outbreaks that involve large amounts of aerosolised infectious agent (Kantor, Pobletem, and Pusateri 1998; WHO 2001) such as occurred in an Arkansas hospital in 1985 during the irrigation of a hip abscess teeming with M. tb bacilli (Hutton et al. 1990). The high quanta value attributed to the school measles outbreak (Riley, Murphy, and Riley 1978) indicates the highly infectious nature of this disease (Wells 1995; Beggs et al. 2003).

Wells (1934) and Wells and Stone (1934) established that the primary mode of airborne infection was via droplet nuclei, while a host of other investigations showed that particles are generated when an infected person coughs, sneezes, talks, vomits, defecates, or undergoes medical procedures such as suctioning, endotracheal intubation, or cough induction by chest physiotherapy (Yu et al. 2004; Yu et al. 2005; Morawska 2006). Most of the studies rely on the Wells-Riley equation (Wells 1955; Riley, Murphy, and Riley

Mathematical Models of Infectious Disease Transmission

Mathematical models of infectious disease transmission are used to better understand the dynamics of a real-world situation and to test hypotheses about the variables involved. Models make assumptions that quantify certain features of the scenario while at the same time limiting their applicability to all scenarios. However, the most common disease-transmission models have been successfully used to plan control and mitigation measures against future epidemics of an infectious disease.

All of the accepted models assume that (1) all susceptible individuals have an identical pulmonary ventilation rate, (2) the air in the room space is completely mixed and the infectious agent is evenly distributed throughout the room space, and (3) all susceptible individuals are equally vulnerable to the infectious agent (Beggs et al. 2003). However, in reality, complete air mixing and even distribution of the airborne infectious agent is never completely achieved.

Although all of the models can be used to predict the number of new cases of a disease over time for a given number of susceptible individuals and infectors and specified ventilation conditions, they are not universally applicable (Beggs et al. 2003).

Susceptible-Infected-Recovered Model

One of the first and simplest transmission models was the Susceptible-Infected-Recovered (SIR) model formulated in the 1920s. The basic theory for the dynamics of transmission describes a population divided into three classes or states: susceptible (S), infectious (I), and recovered (R). The model assumes that the population is closed (i.e., no one enters or leaves the population and there is a permanent immunity).

Over time and with better understanding of the epidemiology of infectious disease, many extensions of the SIR model have been created to account for factors such as contact rates among different age groups, speed of the disease's outbreak, demographic effects (crude birth rates and crude death rates in many developing countries are large enough to affect the population dynamics of infection), spatial effects (how populations are geographically dispersed), and stochastic effects. Other models, such as agent-based and spatial-transmission models, provide a means to assess location of hosts and their typical movement as well as a quantitative description of the infection process.

The Wells-Riley Model

Most of the published studies performed to quantify the risk of airborne transmission in enclosed spaces stem from the work of Wells (1955) and Riley and colleagues (1978), referred to as the Wells-Riley equation. This model includes Wells's quantum theory of disease transmission and addresses the probability of a susceptible person becoming infected by inhaling a quanta of infection.

The Wells-Riley equation predicts the infection rates of persons who shed infectious particles within a building. When an infected person coughs or sneezes, a percentage of the expelled microbes become droplet nuclei that have the potential to cause disease if they gain access to mucosal membranes of a susceptible person, either directly or indirectly (CDC 2010).

The probability of infection through infectious droplet nuclei is inversely correlated to the ventilation rate. The parameters used in the Wells-Riley equation include ventilation rate, generation of droplet nuclei from the source (quanta/minute), and duration of exposure.

The Wells-Riley analysis has been applied to numerous risk analysis studies for disease transmission, but the model has limitations (Wells 1955). For example, the analysis assumes air is well mixed and concentration of bioaerosols is uniform. Thus, it does not account for other influences, such as distance between infected and susceptible people or the stochastic effects inherent in a small population. The result is the quantification of the average risk only rather than including the expected range (Noakes and Sleigh 2008). Perhaps the biggest limitation of the Wells-Riley model is the representation

of the infectious dose. This parameter cannot fully capture the complex interaction between infectors, pathogens, and potential hosts (Noakes and Sleigh 2009).

The Mass Action Model

The Mass Action (MA) model (Riley 1974) has been used to determine the dynamics of diseases with short incubation periods, such as measles. In the MA equation, the number of infectious transmissions per infected case is a function of the number of susceptible individuals in the population. This scenario is characterized by an increased number of infected cases in successive time periods. Simultaneously, the number of susceptible individuals in the population decreases, leading to a slow reduction of susceptible individuals.

Gammaitoni and Nucci's Model

The Gammaitoni and Nucci (GN) epidemiological model (Gammaitoni and Nucci 1997a, 1997b) is based on Wells's experiments and includes the change of quanta level in a room space over time. Gammaitoni and Nucci took into consideration that the previous models neglect differences in susceptibility and assume

that the rate at which quanta of infection are added to the air by infectious persons is constant; the latent period of the disease is longer than the time scale of the model, the number of infective persons in the room is constant; droplet nuclei are instantaneously and evenly distributed in the room; droplet nuclei are removed by fresh-air ventilation of the room; ultraviolet irradiation is at a constant rate; fresh air is at the same temperature and pressure as the air already present in the room; the number of infected persons is proportional to the number of encounters between susceptible persons and quanta of infection; and the encounter rate is proportional to both the number of susceptible persons and quanta of infection in the room (law of mass action). The GN model indicates that a certain number of persons exposed to a source of TB infection will be infected in spite of all precautions, but if the infection rate is known this number can be kept low by increasing the disinfection rate and decreasing the time of exposure.

Beggs and colleagues (2003) compared the applicability of the various models. He noted that although any of the models can be used to make reasonable predictions under different circumstances, their limitiations can lead to inadequate protection measures when performing a risk assessment (Beggs et al. 2003).

1978) that predicts the infection rates of persons who shed infectious particles within a building (see sidebar on page 14). While the technology and the proposed causative factors for disease transmission have progressed considerably, almost every peer-reviewed scientific publication on infection control and HVAC recommends further study to quantify the most appropriate ACH standard.

The work of Menzies and colleagues (2000), Schulman and Kilbourne (1962), and Hoge and colleagues (1994) provided direct, strong evidence in support of the Wells-Riley equation. The rate of increase for new cases of airborne contagion in a group breathing the same atmosphere expresses the contagion potential as inversely proportional to the sanitary ventilation per susceptible occupant (Wells 1955). This means that the subsequent analysis using the Wells-Riley equation is justified.

Knibbs and colleagues (2011) used the GN model to estimate airborne transmission risk. The GN model is capable of incorporating non–steady-state quanta levels. Sze To and Chao (2010) conducted a comprehensive review and comparison of the Wells-Riley and dose-response models. While the Wells-Riley model is quick and does not require interspecies extrapolation of infectivity, dose-response models can consider disease transmission routes besides airborne. These models can also calculate the infectious source strength of an outbreak in terms of the quantity of the pathogen rather than a hypothetical unit. Sze To and Chao point out that current risk models do not account for spatial distribution of airborne pathogens, which is a critical factor in infection risk assessment of respiratory disease. Infection risk assessment models of respiratory diseases must be further developed to make them more universal in their application.

There are many well-documented observational studies in the literature for airplanes, taxis, schools, and so on (Hanley and Borup 2010; Daisey, Angell, and Apte 2003; Daisey and Angell 1998; Olsen et al. 2003; Olsen and Dossing 1982; Ko, Thompson, and Nardell 2004; McFarland et al. 1993), but none quantitatively shows the effects of any single or combined variable other than ACH for airborne transmission via a ventilation system. It is widely conjectured that, more often than not, infections occur via a combination of airborne and contact transmission. Although there is little evidence that ventilation directly reduces the risk of disease transmission, many studies suggest that insufficient ventilation increases the risk.

There is clear and undisputed evidence that using higher ventilation rates in conjunction with other preventive measures reduces the risk of disease transmission. A WHO (2009) report on the use of natural ventilation notes that where droplet nuclei are an important mode of disease transmission, average quanta production rates in subjects are usually < 1 quanta/minute. With a quanta production rate of 10 quanta/minute, the estimated risk of infection with 15 minutes of exposure in a room with 12 ACH is 4 percent, and with 24 ACH it is 2 percent. This illustrates the importance of adequate ventilation.

Evidence of Relationship Between ACH and Disease Transmission

Unfortunately, most studies showing a relationship between ventilation and infection transmission are not current (i.e., most were published between 1945 and 2009). A few significant studies published between 2009 and 2012

expand our knowledge of disease transmission, but these are still not conclusive in a quantitative sense.

A comprehensive literature review by Li and colleagues (2007) of 40 studies found 10 studies that were conclusive and 12 studies that were partly conclusive in favor of the relationship between ACH and airborne transmission. Among the 10 conclusive studies, several showed an association between airflow patterns and the spread of diseases (Bloch et al. 1985; Gustafson et al. 1982; Hutton et al. 1990; Wehrle et al. 1970), including several that examined clusters of SARS-CoV (Li et al. 2005; Yu et al. 2005; Wong et al. 2004). Infectious agents included in this review also involved the measles, M. tb, chickenpox, influenza, smallpox, and cold viruses.

In these studies, a few secondary cases or even a large number of cases at a considerable distance from the index patient were shown to be transmitted via an airborne route. All the outbreaks investigated in the five studies occurred in hospitals or pediatric offices, highlighting the importance of air environments in health care settings. As the first conclusive study, Wehrle and colleagues (1970) used smoke tests to show the airflow pattern and dispersion of virus-laden aerosols from the index patient's room in a three-story hospital. The heat emitted from the radiators used for space heating introduced the upward flows through the stairwell as well as above the semi-open windows (for ventilation). Such air currents carried virus-laden aerosols into other rooms in the upper floors and subsequently caused infection and disease (Langmuir 1980).

These 10 studies demonstrated the role of building ventilation and airflows in relation to the spread or control of airborne infectious diseases. However, data were insufficient to specify or quantify the minimum ventilation requirements in hospital and non-hospital environments in relation to the spread of airborne infection. One exception is the work of Menzies and colleagues (2000), which showed an association between tuberculin conversion and ventilation of general or non-isolation patient rooms of less than 2 ACH. In light of this study and the ambiguous results of the many other studies related to ventilation and disease transmission, it is not surprising that the current design requirements for isolation rooms, operating theaters, and general hospital areas are not based on solid evidence (CDC 1994). Further studies are necessary to determine the ventilation requirements in non-hospital environments such as offices, homes, and schools. It may be beneficial for schools, residential homes for the elderly, institutions for the mentally ill, or prisons to have a higher ventilation rate during influenza peak seasons. Further work is also required to develop practical,

robust, and valid methods for measuring indoor bioaerosols due to their low concentration and mobility.

Of the 12 studies that were partly conclusive, three were outbreaks of M tb. (Calder et al. 1991; Edlin et al. 1992; Ehrenkranz and Kicklighter 1972), three studied SARS-CoV (Li et al. 2005; Olsen et al. 2003; Yu et al. 2004), two were measles outbreaks (Riley, Murphy, and Riley 1978; Remington et al. 1985), and four were on chickenpox, anthrax, and rhinovirus (Hoge et al. 1994; Riley et al. 1962; Moser et al. 1979). In addition, Leclair and colleagues (1980) provided incomplete ventilation data but strong epidemiological evidence for airborne transmission.

Knibbs and colleagues (2011) found that current outdoor air-exchange rates of 4.9 ACH in the lung function laboratory and 23.8 ACH in an emergency department isolation room limited infection risks of influenza, tuberculosis, and rhinovirus to 0.1 to 3.6 percent. For all scenarios, risk decreased rapidly as air exchange increased.

These studies imply that room ventilation is a key determinant of airborne disease transmission if no other factors are taken into account. Despite this, ventilation guidelines in hospitals do not take into account robust scientific evidence related to the prevention of airborne transmission.

Variables Involved in Disease Transmission

It is well documented that no single factor is responsible for the spread of infectious disease, regardless of the offending microorganism. Viruses that can be transmitted by the airborne and/or droplet route include SARS-CoV (FGI 2010), enteric viruses of intestinal origin (e.g., norovirus), chickenpox, measles, mumps and rubella viruses, and M. tb. There has been occasional spread of rabies virus due to aerosolization of laboratory viral strains (Aitken and Jeffries 2001).

Brundage and colleagues (1988) and Fisk (2001) cite evidence that low ventilation rates and other building characteristics (i.e., closed ventilation systems, tight buildings) can lead to increased rates of respiratory-transmitted diseases caused by viruses.

The involvement of numerous interacting and interrelated factors in the spread of infectious disease is also well documented. Among these factors are the effects of aerosol droplet and contact transmission dynamics; the nature of the dust levels; the health and condition of individuals' naso-pharyngeal

mucosal linings; patient susceptibility; the population density in a particular location; the ventilation of the location; temperature; humidity; geographic location; length of exposure; number of infected people producing contaminated aerosols; ventilation rate; infectious particle settling rate; nature of the infectious agent (e.g., enveloped or non-enveloped virus); presence of surrounding organic material; exposure to UV light or antiviral/microbial or fungal chemicals; microorganism resistance to antibiotic, antiviral, or antifungal therapy; type and degree of invasive procedures; spatial considerations such as seating or sleeping arrangements; contact with a carrier; persistence of pathogens within hosts; immuno-epidemiology; evolution; spread of resistance; and the role of host genetic factors. Regardless of the route or interaction of any of these factors, not every exposure to an infectious microbe will necessarily result in a symptomatic infection or an asymptomatic infection that creates a carrier situation leading to further infections of susceptible hosts (Memarzadeh 2001b). See also Figure 1 on page 5.

Spatial Considerations and Dispersion Factors

The puzzle of disease transmission is further complicated by the modes of transmission, the physical mechanisms of transmission, individual behaviors, and the lack of evidence for the effect of spatial and particle dispersion factors. Building ventilation systems help prevent building-associated illness by diluting and removing unknown airborne microbial contaminants.

Data on disease transmission and dilution factors have primarily come from populations that are relatively dense or in a poorly ventilated space. Incidents and data have been extrapolated from a variety of locations and circumstances to derive hypotheses for disease transmission.

It has been noted that in most studies of disease transmission, the duration of exposure is not taken into account (Memarzadeh 2011a, 2001b). However, some observational studies in overcrowded situations indicate that duration of exposure is important. A study of an overcrowded Russian prison, in which susceptible prisoners share enclosed spaces with infectious prisoners for very long periods, found that this arrangement appears to ensure the spread of TB (WHO 2001). From a 1950 study of nurses working in a TB ward, Riley and colleagues (1959) concluded that airborne M. tb bacilli were not very numerous in the ward and that it would take the better part of a year for a tuberculin-negative nurse working on a TB ward to convert to positive.

Beggs and colleagues (2003) conclude from this and other evidence that if a susceptible person remains in the presence of persons with open pulmonary

TB for long enough they will inevitably become infected, even when the quanta production rate is relatively low. Beggs and colleagues (2003) also suggest that ventilation rate expressed as ACH can be very misleading. Absolute ventilation rate, measured in m^3/s or m^3/min, more accurately predicts the potential to transmit disease to susceptible individuals in a more crowded enclosed space.

Chen and Zhao (2010) believe that a systemic and general analysis of factors that influence dispersion in a ventilated room, such as ventilation rate, indoor air humidity, indoor air temperature, ventilation pattern, droplet nuclei size, and exhaled initial velocity, may be helpful to understand the dispersion characteristic of exhaled droplets in an indoor environment.

The dilution effect of the ventilation system has been examined in depth (Cole and Cook 1998; Nardell et al. 1991; Rudnick and Milton 2003). The results of these studies have been used to develop guidelines and standards that specify minimum ventilation dilution recommendations to reduce the risk of airborne transmission of infectious diseases in different indoor environments (CDC 1994; FGI 2010). Air dilution, along with pressure differentials, air filtration, and other mechanical options can keep the risk of M. tb transmission low by reducing exposure to high concentrations of infectious airborne particles. CITC (2007) notes that the more effective the mixing of air, the better the dilution of infectious particles.

Beggs (2003) identified many epidemiologic studies that incorporated the ventilation dilution effect and developed different risk assessment models based on the perfectly mixed assumption inherent in the dilution concept. But most experts agree that evidence is insufficient to suggest a minimum ACH in most situations. There is evidence that low ventilation rates and other building characteristics can lead to increased incidence of respiratory diseases caused by viruses (Brundage et al. 1988; Fisk 2001).

The importance of spatial considerations dilution, and dispersion as evidenced in a Center for Advancing Microbial Assessment (CAMRA) report (Rayman 1997; Jones et al. 2009) has also been shown in a study by Chao and Wan (2006). Richmond-Bryant (2009) studied the characteristics of the spatial velocity and particle concentration profiles that might result in health care workers' exposure to a pathogenic agent in an AII room. Chen and Zhao (2010) note that this and other studies neglected to consider droplet evaporation when doing the simulations. Design of the ventilation system appears to play a significant role in particle transmission as well.

Computational fluid dynamics (CFD) in conjunction with optical measurement methods has incorporated factors such as evaporation features of aerosols to examine dispersion characteristics of expiratory aerosols within an enclosure with a ceiling-return and a unidirectional downward flow. One study showed that small aerosols had settling times of less than 20 seconds in downward flow, but the time increased to 32 to 80 seconds in ceiling-return flow. Lateral dispersion was increased to more than 2 minutes in ceiling-return flow, where there was a combination of turbulent dispersion and bulk-flow transport mechanisms. The significance of aerosol transport by bulk flow was about an order of magnitude stronger than that by turbulent dispersion. However, results also show that aerosols could be dispersed for considerable distances solely by turbulence if they were suspended longer. Large aerosols settled within a very short time due to heavy gravitational effects. The results demonstrated that the dispersion of expiratory aerosol in indoor environments could be controlled by manipulating the ventilation airflow patterns and provided new insights in designing proper bed spacing in hospital ward environments (Chao and Wan 2006).

Memarzadeh and Xu (2012) and Memarzadeh, Olmsted, and Bartley (2010) note that although the respiratory flows of infected individuals are one of the main sources of infectious airborne pathogens in hospitals, there are few studies on how exhalation flows interact with the room ventilation system. All previous studies focused on the contaminants exhaled or released from a standing or seated person. They note that small pressure differences induced by natural forces such as thermal buoyancy due to air temperature differences, the wind, or mechanical fans can move air from one room to another. Air filtration aims to reduce airborne concentrations to well below infectious doses. The spatial position of the patient in relation to others in the room appears to affect risk of transmission. In a hospital setting, patients lie in bed much of the time. The direction of an exhalation jet from a standing or seated person and that from a lying person can be different (e.g., the latter may be lying face up). The upward thermal plume generated by a standing or seated person is much stronger than that generated by a lying person. Thus, some differences between the behaviors of breathing flows in hospital and other indoor environments are expected. The exhalation jet from a lying patient can behave differently in different ventilation systems and can be affected by other factors, such as the mode of contaminant release and the thermal plume generated by the human body or other heat sources. Understanding how different ventilation systems affect breathing flows from a patient lying supine is useful for developing an effective ventilation method to minimize

the risk of cross-infection via airborne transmission. Droplet nuclei 5 μm in diameter exhibit a settling velocity of 1 meter/hour (88 feet per minute) in still air and can follow the exhalation flows as well as the ambient air flows in a hospital ward.

Small droplets may also participate in short-range transmission, but they are more likely than larger droplets to evaporate to become droplet nuclei, at which point they have the potential for long-range airborne transmission. True long-range aerosol transmission becomes possible when the droplets of infectious material are small enough to remain airborne almost indefinitely and to be transmitted over long distances. Pathogens that are not routinely transmitted via the droplet route can be dispersed into the air over short distances. For example, although Staphylococcus aureus is most commonly transmitted via the contact route, viral upper respiratory tract infection has been associated with increased dispersal from the nose into the air over a distance of 4 feet under both outbreak and experimental conditions. This is known as the *cloud baby* and *cloud adult* phenomena (Bassetti et al. 2005).

It is generally accepted that the respiratory flows of infected individuals contribute to the dissemination of infectious airborne pathogens. Memarzadeh and Xu (2012) examined the transport mechanism, the particle path, and a suggested control strategy for reducing airborne infectious disease agents. Most studies on the transmission of infectious disease particles have focused primarily on ACH and how this measure provides a dilution factor for possible infectious agents. The results of this study suggest that in an enclosed and mechanically ventilated room (e.g., an isolation room), the dominant factor in the transmission and control of contaminants is the path between the contaminant source and exhaust. Contaminants are better controlled when this path is uninterrupted by an air stream. This study illustrates that the ventilation system design (when it conforms to the hypothesized path principle) may be a more important factor than flow rate (i.e., ACH). A secondary factor is the distance from the contaminant source. This study provides evidence and support for previous findings that moving away from the patient generally reduces the infection risk in a transient (coughing) situation, although the effect is more pronounced under higher flow rate.

Airborne Particle Transmission

Airborne particles can contain disease-causing microorganisms. Typically, particle sizes for biologic aerosol particles are 0.02 to 0.3 μm for viruses, 0.5

to 10 μm for bacteria, and 0.5 to 30 μm for fungi. Pathogen-laden droplets expelled by an infected person dry out in the room air and produce fine particles and droplet nuclei that can suspend in the air.

Although the liquid evaporates, the residual droplet nuclei may remain in the air for long periods of time depending on particle size, velocity, and density; force of expulsion; humidity; and rate of air flow. Air currents, aided by the ventilation system, help to spread them over a wide area. The disease-causing organisms are inhaled by or come to rest near a susceptible person, who is subsequently infected through mucous membrane contact with contaminated hands or materials. Droplet nuclei are so small that they bypass the innate host defense mechanisms of the human upper respiratory tract and are deposited in the alveoli in the lungs (Fletcher et al. 2004).

Experimental studies with smallpox conducted by Downie and colleagues (1965) and investigations by Yu and colleagues (2004) during the 2003 global SARS outbreaks suggest that droplets from patients could reach persons located 1.83 meters [6 feet] or more from their source.

Particle movement in air is determined by Stokes's settling law, which governs how quickly a sphere falls under the opposing forces of gravity downward and air friction upward. The result is microbes contained in fluids that rapidly fall out of the air. Larger droplets with more mass are more strongly influenced by gravity and less so by air flows and move more ballistically, falling more quickly. Smaller droplets with less mass are less influenced by gravity and can be transported as a cloud over greater distances by air flows. These complex air movements make the route and suspension time of an infectious particle very difficult to determine once it has left the infectious host.

There is essential agreement that particles with an aerodynamic diameter of 5 μm or less are aerosols, whereas particles of 20 μm are large droplets. Studies show that 80 to 90 percent of particles from human expiratory activities are smaller than l μm (Papineni and Rosenthal 1997). When reviewing the literature, it is important to verify the size of the particles being studied and the investigators' definitions.

Sneezing can introduce as many as 40,000 droplets, which can evaporate to produce droplets of 0.5 to 12 μm (Olsen et al. 2003; Riley et al. 1962), while in a patient with active M. tb coughing naturally, the infectious particle size was 2.1 to 3.3 μm (Fennelly et al. 2004). These particles can be expelled at a velocity of 100 m/s (≈20,000 FPM) and reach distances of several meters. A cough can generate about 3,000 droplet nuclei (Fitzgerald and Haas 2005), the same number as talking for five minutes; a single sneeze can generate

100,000 floating bioaerosol particles, many containing viable microorganisms (Duguid 1945). Although a single cough typically produces a small percent of this amount, coughs occur about 10 times more frequently than sneezes. Some studies have shown that an M. tb–infected patient can produce 1 to 249 bacilli an hour, while a person in the infectious stage of a cold may produce 6 to 200 droplet nuclei per hour containing viable viruses that remain airborne longer than 10 minutes (Fitzgerald and Haas 2005).

Infectious bioaerosols may exist as single or aggregate cells, spores, viruses, or infectious material carried by an inanimate disseminating agent. When viable infectious droplets or droplet nuclei are present, any aerosol-generating activity—such as making a bed or walking around—exacerbates the movement of these particles. True long-range aerosol transmission becomes possible when the droplets of infectious material are sufficiently small to remain almost indefinitely airborne and to be transmitted over long distances.

Droplet transmission is a form of contact transmission, and some infectious agents transmitted via the droplet route also may be transmitted via the direct and indirect contact routes. However, in contrast to contact transmission, respiratory droplets carrying infectious pathogens transmit infection when they travel directly from the respiratory tract of the infectious individual to susceptible mucosal surfaces of the recipient, generally over short distances, necessitating mucous membrane protection.

Most pathogens have the potential for being transmitted by large droplets. Examples of pathogens that can be transmitted by large droplets but are not considered true airborne infections include SARS-CoV, whooping cough (Bordetella pertussis), influenza virus, adenovirus, rhinovirus, Mycoplasma pneumoniae, group A streptococcus, and bacterial meningitis (Neisseria meningitidis). Evidence exists that Chlamydia psittaci and Chlamydia pneumonia are transmitted by airborne droplet nuclei (Riley et al. 1962).

Microorganisms are also hygroscopic. A 1.5 µm hygroscopic particle, which is an average size in coughs and sneezes, may increase to 2.0 µm in diameter when passing through the nose and to 4.0 µm in the saturated air of the nasopharynx and the lung (Knight 1993). The larger size may affect retention in the lung. Thus, the relative humidity can have a profound effect on the transport of the particles as a result of change in size, viability, and airborne duration. Gravitational, thermal, and electrostatic fields profoundly affect their aerodynamic behavior (Riley et al. 1962).

Dust has been implicated as a vector in airborne transmission of infectious disease as well as an irritant and allergen. A variety of studies indicate that

most exposures to airborne dust in nonindustrial indoor environments range from 15 to 200 lg/m3. The dust can be described as consisting of a relatively inert base with the addition of biologically active compounds such as allergens or toxic chemicals (Knight 1993; Armstrong, Sherertz, and Llewellyn 1990; Gyntelberg et al. 1993, 1994; Hauschildt, Mølhave, Kjærgaard 1999; Hedge et al. 1989; Hodgson and Collopy 1990; Kjærgaard and Brandt 1993; Lebowitz, Quackenboss, and Kryzanowski 1990; Skov, Valbjørn, and Gyntelberg 1989; Wallace 1996; Mølhave et al. 2000).

A relatively transient condition known as *organic dust toxic syndrome*, which can result in chronic obstructive pulmonary disease in long-duration exposures (Vogelzang et al. 1998), occurs within hours of a high-dose inhalation of endotoxin, fungal spores, and mycotoxins (Von Essen et al. 1990). Mølhave and colleagues (2000) conducted an exploratory study on the effects of dust on the eyes. The results imply that even relatively low concentrations of office dust may have an effect. It is possible that the effects accumulate over repeated daily exposures, resulting in a sensitization of the exposed individuals. The authors suggest that among healthy nonsensitized subjects, a continuum of risk factors may exist. They believe that although it isn't possible to draw final conclusions on the effects of dust, the dust interacts with other variables to cause a reaction. Bacterial endotoxins, present in house dust and airborne particulate matter, are thought to cause a range of flu-like symptoms (Rylander et al. 1989, 1992). The most commonly measured microbiological contaminants measured in schools were allergens in deposited dust (e.g., house dust mite allergen, fungi, bacteria). The levels of these allergens were high enough to cause allergy symptoms in allergic occupants. Evidence of a dose–response relationship was reported (Smedje, Norback, and Edling 1997).

Effects of Ventilation System Design

A ventilation system design study by Memarzadeh, Wilson, and Ramesh (2011) shows how ventilation system design affects particle movement in an AII room. The study indicated that low exhaust and high ventilation flow removed the most particles. With a lying patient, 12 ACH removed more particles than did 16 ACH with high exhaust. This can be explained by the flow pattern above the patient, which is determined by the downward forced convection from the ceiling diffusers above the bed and the upward flow of the cough from the mouth of the lying patient. With greater downward flow (16 ACH rather than 12 ACH) from the ceiling diffuser, the upward movement of droplets carried by the cough of a lying patient could be suppressed

and thus have difficulty reaching high exhausts. The authors concluded that low exhaust removes more particles and decreases the number of particles remaining around a bed than other exhaust locations do. Increasing ventilation flow from 12 to 16 ACH generally helps to remove particles from an isolation room (except in cases of high exhaust and a lying patient coughing), but not necessarily a breathing zone. The number of particles in a bathroom resulting from a cough in a main room is dependent on air-current particle distribution and bathroom location.

Numerous aircraft studies indicate that ventilation is one of the most critical factors in airborne disease transmission (Moser et al. 1979; Aviation Health Working Group 2001a; National Research Council 1986; WHO 1998; Select Committee on Science and Technology 2000; Kenyon et al. 1996). Fernstrom and Goldblatt (2013) reviewed many of the aerobiological variables (e.g., particle size, particle type, duration that particles can remain airborne, distance that particles can travel, meteorological and environmental factors), as well as the common origins of infectious particles. They state that "practitioners of all kinds agree that the airborne transmission of infectious disease is a problem. Just how big or urgent a problem, however, continues to be debated" (Fernstrom and Goldblatt 2013). Studies also have stated that one air change per hour of well-mixed air in any space is thought to remove 63 percent of the airborne organisms in that space (Nardell et al. 1991; Riley and Nardell 1989). The recirculation of cabin air is known not to be a risk factor for contracting upper respiratory tract infections (Zitter et al. 2002), but airborne transmission becomes widespread in passenger cabins with no ventilation (Moser et al. 1979; National Research Council 1986; WHO 1998).

While a 2003 study by Olsen and colleagues showed a spatial component to a SARS transmission aboard an aircraft, another aircraft incident led the CDC to perform an aggressive investigation on M. tb transmission aboard an aircraft in 2007. From this investigation, they developed a risk analysis methodology (the first study of its kind, to our knowledge) that provides a tool to calculate the risk of infection in the real world. The incident resulting in this study occurred when a multidrug-resistant tuberculosis (MDR) infected traveler flew from Atlanta to Paris and then from Prague to Montreal. Each of the transatlantic flights lasted approximately eight hours. The traveler was hospitalized upon his return to Atlanta. The CDC developed a quantitative microbial risk assessment tool to determine the risk of infection to the 80 people within five rows surrounding the infected person during the flights. In this CAMRA study, the investigators (Rayman 1997; Jones et al. 2009)

used computational fluid dynamics to show that the seating pattern in different sizes of aircraft (Boeing 747, Boeing 767, Airbus 310), the location of the air inlets, the overhead baggage compartments, and the air flow pattern all affect the magnitude of the exposures and risk to passengers as a result of the stable eddies within each row and the advective velocity toward the cabin rear. Passengers seated next to the source case had the highest doses.

The CAMRA study showed that the range of bacilli emission from the patient is one of the components that drive the risk. In the human respiratory tract, about 20 percent of particles in the 1 to 4 μm range that are inhaled via the nose deposit in the alveolar region and may be expelled via the sputum and saliva from coughing and sneezing. In the CAMRA risk analysis methodology, concentration in the saliva and the amount and size distribution of particles emitted by coughing were used to determine the concentration of M. tb in the aircraft. The analysis predicted the removal of M. tb from the breathing zones of seated passengers within five minutes of emission, resulting in the conclusion that the concentration of M. tb. would not build up in the aircraft cabin for cough frequencies of 10 to 12 per hour. The doses due to a series of coughs are additive. The study examined two parameters derived from data of symptomatic patients: M. tb concentration in sputum and saliva and number of coughs per hour (Yeager et al. 1967). Using 20 ACH based on the Ko, Thompson, and Nardell (2004) estimate, and assuming that the particles are well mixed, the study determined that the particles are emitted at the air-exchange rate of 4.2 m^3/hour or 2.4 cfm. Decay rate of the M. tb in air or aerosol was not considered. Air inhalation rate for each passenger was set at 0.54 m^3/hour. This model assumes passengers are exposed to equal amounts of M. tb cells. The model provides a useful tool for estimating the probability of risk of exposure to an individual based on their location and distance from the source or index case. The risk of infection on average ranged from 1/1000 to 4/10,000, with detectable average ranges of bacilli in the saliva. However, with nondetectable bacilli, the risk was seen as ranging from less than 2/100 million to approximately 6/billion. The concentrations were assumed on the basis of data from symptomatic patients. This study supported the hypothesis that ventilation may be an important determinant of airborne infection risk on airplanes (Zitter et al. 2002).

Natural vs. Mechanical Ventilation Systems

Escombe and colleagues (2007) examined the effect of natural ventilation in hospitals. Comparisons were made between older hospital buildings that used open windows for ventilation versus newer hospitals that used

mechanical ventilation. A carbon dioxide tracer gas was used to establish the number of air changes in various sizes of rooms, with and without open windows and doors. Infection risk for M. tb was predicted using the Wells-Riley equation (see sidebar on page 14). The risk of airborne spread was far lower in rooms with open windows than in the expensive mechanically ventilated rooms. Low-cost natural ventilation seems to be a better option than negative pressure ventilation in tropical countries. The main drawback is possible contamination of adjacent areas when airflow is inward. In addition, the epidemiology of transmission of TB in the facilities studied by Escombe and colleagues is unknown as this investigation did not include contacts of patients with active TB to discern if there was less occupational transmission of M. tb with high ACH.

Levin (1989, 2007) also suggests that the tuberculosis infection rate was not actually reduced by opening windows as suggested in Escombe and colleagues' investigation because infection rates were merely calculated using the Wells-Riley equation. While it is important to consider the ventilation rate provided by mechanical ventilation systems, the rate through open windows must take into account window size, number of windows, and location in a room as modified by indoor–outdoor temperature differences and wind direction and velocity.

Modes of Transmission

Many people assume that infectious diseases are spread via airborne transmission and they associate that process with natural or mechanically created air currents. This assumption is inherently flawed because in addition to the complexity of airborne transmission, strong evidence suggests that infection transmission may occur via other routes. Transmission of infectious particles may occur through a ventilation system, but there are clear incidents of transmission from water reservoirs or particle settling on surfaces and being acted upon by the surrounding atmosphere via hydro- and hygroscopic factors—temperature and relative humidity and dust, for example. The infectious agent may also undergo a physical change caused by evaporation, dehydration, rehydration, effects of UV light, or any number of other physical parameters.

From a biological perspective, infectious diseases are caused by microbial, viral, or fungal pathogens, each of which has unique attributes that affect transmission (Tang et al. 2011). The pathogens are dependent on physical factors such as cell or particle size, route of entry into the body, physical

state of the infectious agent, virulence, and individual recipient susceptibility. Each of these factors, in turn, may be affected by a multitude of other variables.

Infectious disease is transmitted between animals and humans or in a person-to-person pattern, though acquisition typically requires prolonged or repeated contact in an indoor environment, as opposed to casual contact. Diseases can be spread from a single source (index source) such as an individual. The relationship between the incubation period and the pattern of onset of illness determines whether the disease arose from a single source or represents ongoing or propagated transmission (Sartwell 1995).

There are three primary routes of transfer: (1) direct contact and fomites, which are inanimate objects that transport infectious organisms from one individual to another (Boone and Gerba 2007); (2) large droplets (generally with a mass median aerodynamic diameter [MMAD] of > 10 μm); and (3) particles with MMAD < 10 μm, sometimes termed *droplet nuclei*. Clinically applicable distinctions are made between short-range droplet transmission (i.e., between individuals, generally 1 meter apart) and long-range routes (i.e., within a room, between rooms, or between distant locations, generally distances greater than 1 meter). Recent work by Xie and colleagues (2007) identifies large droplets as those larger than 5 to 100 μm at the original time of release. Nicas, Nazaroff, and Hubbard (2005) show by modeling that emitted large droplets will evaporate to 50 percent of their initial value and that if the initial diameter is < 20 μm, this process will happen instantaneously. However, large droplets released in short-range aerosols (e.g., sneezing) are sometimes confused with airborne transmission, but such released particles do not typically transmit over long distances. Clinically applicable distinctions are also made between short-range airborne infection routes (between individuals, generally less than 1 meter [3.28 feet] apart) and long-range routes (within a room, between rooms, or between distant locations, generally greater distances than 1 meter [3.28 feet]). Some infectious agents (e.g., SARS) may transmit primarily by large droplets, but under some situations they may be transmitted through air in various modes (FGI 2010). Roy and Milton (2004) classified aerosol transmission of diseases on the basis of the agent's capacity to be transmitted and to induce disease through fine-particle aerosols and other routes.

A particle's size is a consequence of the process that led to its generation, and thus it is dependent on the source. The content of an infectious agent expelled by an infected person depends, among other factors, on the location within the respiratory tract from where the droplets originate.

Pathogenic organisms usually reside in the tonsil, larynx, and lung and seldom at the front of the mouth. To assess the potential for infection via airborne or droplet route, an understanding of the localities from which droplets originate during various expiratory activities and the numbers of droplets arising from each site is needed (Daisey and Angell 1998). Breathing, coughing, singing, and sneezing by an infected person can generate pathogen-containing particles of saliva and mucus with diameters < 10 μm (Daisey and Angell 1998; Gold and Nankervis 1989). Studies have suggested that droplets larger than 20 μm rapidly settle onto surfaces (Gold and Nankervis 1989), while droplets between 0.5 and 20μm remain in the air for long periods and are more likely to be captured in the respiratory tract and produce infection (McCluskey, Sandin, and Greene 1996). If particles carrying pathogens are inhaled by a susceptible individual and deposited in a suitable location in the respiratory tract, infectious disease may occur (Remington et al. 1985).

WHO's 2009 ventilation guidelines (Atkinson et al. 2009) determined minimum ventilation rate requirements based on the effect of air-change rate on decay of droplet nuclei concentration and estimation of the effect of ventilation rate on infection risk for known airborne diseases using the Wells–Riley equation. These underlying principles indicate that the higher the ventilation rate, the more rapid the decay of particles (e.g., droplet nuclei) in the room air.

Chen and Zhao (2010) recommend that when reviewing the literature and designing CFD analysis to study droplet dispersion as related to indoor disease transmission, the transient process whereby a droplet becomes a droplet nucleus due to evaporation should not be ignored.

Influenza is transmitted primarily through close contact, such as during exposure to large respiratory droplets, direct contact, short-range exposure to infectious aerosols, or a combination of these routes (Brankston et al. 2007). However, the relative contribution and clinical importance of each of these modes of transmission have not been established.

Klontz and colleagues (1989) performed a highly cited study that looked at an influenza outbreak in aircraft. They looked at two military aircraft with fully functioning ventilation systems that had 15 ACH in the passenger cabin and directional airflow from ceiling to floor with minimum horizontal airflow. Within 72 hours of deplaning, 56 percent of the passengers on both planes became ill. A significant difference in risk of acquiring influenza was observed between the two aircraft and appeared to be related

to the number of symptomatic persons on board. The epidemiologic data show that secondary transmission of influenza to family members and roommates occurred in the days following the initial cases. Movement on the plane was not mentioned as a possible factor in transmission. It is difficult to draw conclusions regarding the mode of transmission in this study due to the lack of controlled scientific evidence to support any single or combined factor(s).

One of the major studies to define influenza as an airborne pathogen was a classic observation by Moser and colleagues (1979). The authors investigated an opportunistic outbreak of influenza due to a lack of outdoor air coming into the enclosed space of a grounded aircraft. The ventilation system was inoperative for more than three hours, and 72 percent of passengers were infected with influenza. This outbreak was attributed to poor ventilation but could also have been caused by close contact with the index case. The occurrence of infection increased with time spent on the aircraft. In addition, the aircraft was unique in that half of it was used for cargo and half for passengers. In short, this case study provides no clear evidence for a single mode of transmission or that ventilation was the primary factor. The passengers were moving around and probably touching surfaces that contaminated their hands, and there was no air circulation. Thus, those who became ill may have been infected via any of the common modes of transmission.

Another cluster of disease on an airplane involved (MDR-TB, as reported by Kenyon and colleagues (1996), in which highly infectious TB transmission was limited to proximity of the index patient when the ventilation system was effective. The CDC conducted epidemiological studies of M. tb transmission in airplanes and found that although the airplane environment contributes to the risk of infection transmission, other indoor factors are also involved, although the relative importance of any factor is unknown (Bassetti et al. 2005; Memarzadeh, Wilson, and Ramesh 2011). The results from numerous studies related to modes of transmission suggest that the mode probably differs according to the setting and environmental conditions. This hypothesis has led to the belief that implementing engineering control methods in health care facilities could reduce hospital-acquired infections (Tellier 2006). However, a review of the same evidence by Brankston and colleagues (2007) reinforced that a hierarchy of administrative, environmental, and PPE controls are effective in mitigating cross-transmission of influenza. This review also concluded that "the airborne route of transmission [is] unlikely to be of significance in most clinical settings."

Additional Research Is Needed

A great deal of additional research is needed to make valid conclusions regarding the number of air changes per hour needed to reduce disease transmission. More accurate and comprehensive models that account for mixing, room volume, occupant density, proximity, host susceptibility, and the pathogenicity of infectious agents need to be developed (Beggs et al. 2003). Further measurement is also required of bioaerosols at different concentrations and different airflow rates. A broader variety of mechanical and natural ventilation, HEPA filtration, and UV germicidal irradiation strategies in offices, homes, schools, prisons, long-term health care facilities (e.g., nursing homes), laboratories, and acute health care facilities need to be evaluated under controlled experimental conditions rather than in observational and retrospective studies to determine the best approaches for reducing infectious disease transmission. Strategies may differ according to the disease and the particular set of circumstances, thus giving rise to improved risk assessment methodologies.

Future research should integrate the role of the ventilation system, the health status of the occupants, spatial relationships among them, and duration of exposure, thus requiring a multidisciplinary approach.

Conclusion

In summary, there are insufficient data to specify or quantify the minimum ventilation requirements in public spaces, including hospitals, office buildings, aircraft, and schools in relation to the spread of airborne infection. Further studies are needed to determine ventilation requirements in hospital and non-hospital settings. Practical, robust, and valid methods must be developed for measuring indoor bioaerosols, due to their low concentration and mobility. These studies may be applicable to the ventilation design of future buildings and renovations. The 2013 study by Faulkner and colleagues indicated that in some situations the advantages of increasing ACH may be limited in terms of providing better environments in the occupied zones of rooms.

Although the presence of a risk factor for a particular pathogen increases the chances of contracting an illness, it does not always lead to an illness. On the other hand, the absence of any single risk factor or the existence of a protective factor does not necessarily guard against getting an infection (Memarzadeh and Xu 2012). It is crucial to find a balance between reducing

infectious disease transmissibility and maintaining occupant comfort and ventilation rates.

The variables affecting the relationship between ACH and infection transmission are so many and the evidence for the causative or associated role of ACH in disease transmission is so incomplete that it is not easily possible to determine the direct effect of ventilation on disease transmission. As yet, no single prescribed ACH rate for any particular set of circumstances—or as a function of any other variable—is known to fully prevent disease transmission. However, there is sufficient evidence from studies of natural ventilation and controlled indoor ventilation to suggest that ACH plays a role in controlling disease transmission. Therefore, the most prudent course of action is to carefully consider a risk assessment and look at evidence-based factors to determine the best ACH for a space.

To provide a sound basis for setting standards, more studies are needed in which the relationship between symptoms and measured exposures to multiple specific pathogens/pollutants is investigated. Furthermore, quantitative information is needed on the relationship between exposure and health response for specific pollutants suspected to cause health symptoms.

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