REVIEW

Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises

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Einflussfaktoren der Übertragung von Infektionen in der Luft und Kontrolle der Belüftung in Gesundheitseinrichtungen


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Introduction

The experience in 2003 with severe acute respiratory syndrome (SARS) highlighted the issue of aerosol transmission, both short range between healthcare workers and their patients,1−3 and long
Aerosol transmission and ventilation control

range amongst the residents of the Amoy Gardens estate.\textsuperscript{4,5} Aerosol or airborne transmission is already well recognized for many human pathogens. Much work has been performed using air-sampling techniques together with culture and molecular detection methods for viruses\textsuperscript{6–16} [particularly varicella zoster virus (VZV)],\textsuperscript{17–24} bacteria\textsuperscript{25–33} [particularly tuberculosis (Mycobacterium tuberculosis, TB) and other mycobacteria],\textsuperscript{34–42} and fungi (particularly Aspergillus spp.).\textsuperscript{43–56} Beggs reviewed the importance of airborne transmission of infection in hospitals, focusing mainly on bacteria that are well known to cause nosocomial infections, i.e. Staphylococcus aureus and meticillin-resistant S. aureus (MRSA), M. tuberculosis, Acinetobacter spp., Aspergillus spp., Pseudomonas spp. and Legionella spp.\textsuperscript{57} He concluded that, for these infections, although contact spread was still the main route of infection, infections via the airborne route, both direct and indirect (via the settling of airborne pathogens on fomites), were probably underestimated.

The generation of such infectious aerosols of infectious human pathogens can occur in many ways, and in many settings, although some have been studied more extensively than others due to their greater clinical significance. The literature on the risks of aerosol transmission of infection in hospital operating theatres is extensive.\textsuperscript{58–65} Over 40 studies on the relationship between ventilation systems and the transmission of infection in hospitals, offices, aeroplanes and ships were reviewed recently by Li et al.\textsuperscript{66} Studies have also been conducted on how infectious aerosols generated by various procedures in hospital environments can lead to infection in burns care facilities\textsuperscript{67–69} and medical intensive care units.\textsuperscript{70,71} In particular, the use of oxygen masks,\textsuperscript{72,73} and power tools in dental practice\textsuperscript{74–77} and orthopaedic\textsuperscript{77–84} may pose a risk of aerosol infection. Aerosol dispersal of infectious agents has also been demonstrated in wastewater spray sites,\textsuperscript{85} surface waves on the sea,\textsuperscript{86} the flushing of the household toilet,\textsuperscript{87} and even just opening a standard hinged door.\textsuperscript{88}

**Definitions**

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. One set of infection control guidelines for healthcare settings suggested that only TB, measles (rubeola virus) and chickenpox (VZV) should be considered as ‘true’ airborne infectious diseases.\textsuperscript{89} However, it is likely that other infectious agents may also behave as ‘airborne’, given a favourable environment, e.g. whooping cough (Bordetella pertussis), influenza virus, adenovirus, rhinovirus, Mycoplasma pneumoniae, SARS coronavirus (SARS-CoV), group A streptococcus and Neisseria meningitidis. Many more organisms fall into this category, as it probably includes virtually all pathogens where replication and/or colonization occur in the respiratory tract. Table I lists organisms associated with varying degrees of aerosol transmission.\textsuperscript{90} Each organism can also be transmitted through direct contact with infected body fluids.

A recent systematic review demonstrated that adequate or inadequate ventilation has an effect on the risk of infection via infectious aerosols.\textsuperscript{66} This interdisciplinary review, authored by a large group of engineers, microbiologists and epidemiologists, defined the following terms.

- **Airborne transmission** refers to the passage of micro-organisms from a source to a person through aerosols, resulting in infection of the person with or without consequent disease.
- **Aerosols** are a suspension of solid or liquid particles in a gas, with particle size from 0.001 to over 100 µm.\textsuperscript{91} Infectious aerosols contain pathogens.
- **A droplet nucleus** is the airborne residue of a potentially infectious (micro-organism-bearing) aerosol from which most of the liquid has evaporated.\textsuperscript{92}

On the basis of these definitions, the following clinically applicable distinctions are made between short-range airborne infection routes (between individuals, generally less than 1-m apart) and long-range routes (within a room, between rooms or between distant locations, generally greater than 1-m distances):

- The short-range airborne infection route depends on the close proximity of the infected source and susceptible host. A study was performed recently (Xie et al., unpublished observations) to define more clearly the size of the droplets originally referred to by Wells.\textsuperscript{92} These terms are also in common current use. This study proposes the following size definitions: ‘large-droplet’ diameter >60 µm, ‘small droplet’ diameter ≤60 µm and ‘droplet nuclei’ diameter <10 µm. Note that small droplets may also participate in short-range transmission, but they are more likely than larger droplets to evaporate to become droplet nuclei and then be considered as having the potential for long-range airborne transmission (see below).\textsuperscript{93}
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Aerosol route of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Inhalation of spores</td>
</tr>
<tr>
<td>Arenaviruses</td>
<td>Inhalation of small particle aerosols from rodent excreta</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>Inhalation of airborne conidia (spores)</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Conidia, inhaled in spore-laden dust</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Inhalation of airborne bacteria</td>
</tr>
<tr>
<td>Chickenpox/shingles (varicella zoster virus)</td>
<td>Droplet or airborne spread of vesicle fluid or respiratory tract secretions</td>
</tr>
<tr>
<td>Coccidioidomycosis (coxsackie virus)</td>
<td>Aerosol droplet spread</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>Presumably by inhalation</td>
</tr>
<tr>
<td>Human parvovirus</td>
<td>Contact with infected respiratory secretions</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Possible respiratory spread</td>
</tr>
<tr>
<td>Norwalk virus</td>
<td>Airborne transmission from fomites</td>
</tr>
<tr>
<td>Hantavirus</td>
<td>Presumed aerosol transmission from rodent excreta</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Inhalation of airborne conidia</td>
</tr>
<tr>
<td>Influenza</td>
<td>Airborne spread predominates</td>
</tr>
<tr>
<td>Lassa virus</td>
<td>Aerosol contact with excreta of infected rodents</td>
</tr>
<tr>
<td>Legionellosis</td>
<td>Epidemiological evidence supports airborne transmission</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis</td>
<td>Oral or respiratory contact with virus-contaminated excreta, food or dust</td>
</tr>
<tr>
<td>Measles</td>
<td>Airborne by droplet spread</td>
</tr>
<tr>
<td>Melioidosis</td>
<td>Inhalation of soil dust</td>
</tr>
<tr>
<td>(Neisseria meningitidis) Meningitis</td>
<td>Respiratory droplets from nose and throat</td>
</tr>
<tr>
<td>(Haemophilus influenzae) Meningitis</td>
<td>Droplet infection and discharges from nose and throat</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Droplet spread and contact with respiratory secretions</td>
</tr>
<tr>
<td>Nocardia</td>
<td>Acquired through inhalation</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td>Presumably through inhalation of contaminated soil or dust</td>
</tr>
<tr>
<td>Whooping cough (Bordetella pertussis)</td>
<td>Direct contact with discharges from respiratory mucous membranes of infected persons by the airborne route</td>
</tr>
<tr>
<td>Plague (Yersinia pestis)</td>
<td>Rarely airborne droplets from human patients. In the case of deliberate use, plague bacilli would possibly be transmitted as an aerosol</td>
</tr>
<tr>
<td>Pneumonia (S. pneumoniae)</td>
<td>Droplet spread</td>
</tr>
<tr>
<td>Pneumonia (Mycoplasma pneumoniae)</td>
<td>Probably droplet inhalation</td>
</tr>
<tr>
<td>Pneumonia (Chlamydia pneumoniae)</td>
<td>Possibilities include airborne spread</td>
</tr>
<tr>
<td>Psittacosis (Chlamydia psittaci)</td>
<td>By inhaling the agent from desiccated droppings, secretions and dust from feathers of infected birds</td>
</tr>
<tr>
<td>Q fever (Coxiella burnetti)</td>
<td>Commonly through airborne dissemination of coxiellae in dust</td>
</tr>
<tr>
<td>Rabies</td>
<td>Airborne spread has been demonstrated in a cave where bats were roosting, and in laboratory settings, but this occurs very rarely</td>
</tr>
<tr>
<td>Rhinitis/common cold (rhinovirus, coronavirus, parainfluenza, respiratory syncytial virus)</td>
<td>Presumably inhalation of airborne droplets</td>
</tr>
<tr>
<td>Rubella</td>
<td>Droplet spread</td>
</tr>
<tr>
<td>Smallpox (Variola major)</td>
<td>Via respiratory tract (droplet spread)</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Pulmonary sporotrichosis presumably arises through inhalation of conidia</td>
</tr>
</tbody>
</table>
Exhaled air from both nose and mouth is able to enter and mix with air in the breathing zone of another person standing nearby (e.g. patients and doctors on a ward round at the bedside). Thus, short-range transmission implies that air flows between individuals may interact to infect one another. In addition, it has been shown that the use of a simple oxygen mask may also generate a short-range (<1 m) infectious aerosol, with a potential risk to nearby healthcare workers and other patients. Together with nebulizers, oxygen masks fall into this classification of potential short-range aerosol transmission sources, but some droplets generated by such masks can evaporate to become droplet nuclei that can also transmit infection over larger distances.

Long-range aerosol transmission refers to the potential for agents to be carried long distances by air flows to cause infection, and includes the traditional terms 'small-droplet' or 'droplet nuclei' and 'airborne'. Virtually all infectious agents that can cause infection at long range can also cause infection at short range as well as by direct contact. Therefore, use of the term 'long range' refers to the greatest distance from their source at which these agents have the potential to cause infection.

Infectious agents transmissible by aerosols

If the pathogen has some part of its life cycle in the respiratory tract, it is more likely to be present in aerosols generated and projected into the surrounding air by breathing, talking, coughing, sneezing and singing. For truly airborne pathogens (TB, measles and VZV), the routes of acquisition and dissemination of the infectious particles are well recognized to be via the respiratory tract. In the other pathogens listed in Table I, acquisition of the infection is also via the respiratory tract, which is the primary site of infection and replication. Therefore, these other pathogens, such as parvovirus B19, enteroviruses and the organisms of atypical pneumonias (M. pneumoniae, Chlamydophila psittaci and Chlamydophila pneumoniae, previously Chlamydia psittaci), Chlamydophila pneumoniae (previously Chlamydia pneumoniae), Coxiella burnetti and Legionella pneumophila], have the potential to be transmitted via aerosols as their life cycle involves replication at some point in the respiratory tract. Regarding L. pneumophila, replication also occurs in water systems, and human infection can occur via infected water aerosols, such as showerheads and fountains. With SARS-CoV, viral RNA as well as viable (culturable) virus has been found in air samples. Therefore, SARS-CoV can potentially be transmitted by short- and long-range aerosols to cause disease, as has been strongly implicated by several studies.

With influenza, there is ongoing debate about the nature of transmission between people. A recent review suggested that 'aerosol-generating procedures...should be performed with proper infection control precautions’, but the authors do not elaborate on exactly what these precautions should be. Recent guidelines from the UK review the evidence for aerosol transmission of influenza more comprehensively. The report concluded that whilst close contact with infected individuals seems to be responsible for the vast majority of transmission, most reports of influenza transmission

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Aerosol route of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcal diseases</td>
<td>Airborne spread is rare but has been demonstrated in patients with associated viral respiratory disease</td>
</tr>
<tr>
<td>Streptococcal diseases</td>
<td>Large respiratory droplets. Individuals with acute upper respiratory tract (especially nasal) infections are particularly likely to transmit infection with one outbreak</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Inhalation of sporulated oocysts was associated with one outbreak</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Exposure to tubercle bacilli in airborne droplet nuclei</td>
</tr>
<tr>
<td>Tularaemia (Francisella tularensis)</td>
<td>By inhalation of dust from contaminated soil, grain or hay</td>
</tr>
</tbody>
</table>

Virtually all of these pathogens are also transmissible by direct contact. Pathogens in bold are those which are considered to have the potential to be transmitted by the long-range airborne route. The original wording of the reference text concerning aerosol transmission routes has been retained as much as possible. Now known as Chlamydia psittaci and Chlamydia pneumoniae, but the original classification has been retained here as in the original reference text.
do not provide enough temporal-spatial data to determine whether transmission is mainly due to droplet, contact or airborne spread. This is probably the most realistic assessment, and this uncertainty is reflected in the large range of values for the basic reproductive number (R₀), the number of secondary cases arising from a single index case in an otherwise totally susceptible population, ranging from 1—2\(^9\) to 2—7\(^10\) to <21.\(^1\) However, there are reports to suggest that in pandemic or large, explosive outbreak situations, influenza can become truly airborne.\(^2,3\) For comparison, the R₀ values of other commonly encountered infections are shown in Table II.

In contrast, other pathogens, such as human immunodeficiency virus and hepatitis B and C viruses, replicate mainly outside the respiratory tract and are not naturally transmitted via aerosols. With other organisms that can replicate on many surfaces either inside or outside the body, e.g. S. aureus, the picture is not so clear-cut. Although mainly spread by direct contact, there is a suggestion that patients that carry S. aureus in the respiratory tract can spread the bacteria by short-range aerosols.\(^4,5\) S. aureus on skin epithelial cells on fomites, such as bed sheets, can also be spread during bed making.\(^4,5\) This becomes more important when considering resistant strains such as MRSA.\(^5\)

## Sources of infectious agents

A commonly encountered source is the patient with flu-like symptoms who is coughing, sneezing and dispersing the organism (Figure 1).\(^6,7\) In the diagnostic laboratory, it may be an inoculated culture medium that is dropped or spilt, as has been reported for laboratory-acquired SARS infection.\(^8\) A more worrying possibility is the deliberate release of a biological agent, such as during the US terrorist anthrax attacks of 2001—2002,\(^9,10\) and an accidental release, such as the anthrax incident in the Russian city of Sverdlovsk of 1979.\(^11\)

A sneeze can generate up to 40 000 droplets (Figure 1),\(^6,7\) which can evaporate to produce droplets of 0.5—12 \(\mu\)m in diameter.\(^8\) A cough can generate about 3000 droplet nuclei, the same number as talking for 5 minutes.\(^11\) During normal breathing, exhalation can project droplets up to 1 m in room air, which may be inhaled by another person nearby (Figure 2),\(^4\) whereas sneezing can project droplets several metres (Figure 1).\(^6,7\) In addition, a recent study has shown that some individuals may exhale more particles during quiet breathing than others, suggesting that some people may be more infectious than others when infected with the same organism.\(^12\) The way that an infectious aerosol is generated should be considered when assessing the probable distance of spread. As noted earlier, large droplets can evaporate to become small droplets that can evaporate further to become droplet nuclei and hence become truly airborne if this evaporation process can occur before the

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Basic reproductive number (R₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>15—17</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>15—17</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>10—12</td>
</tr>
<tr>
<td>Mumps</td>
<td>10—12</td>
</tr>
<tr>
<td>Rubella</td>
<td>7—8</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>5—6</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>5—6</td>
</tr>
<tr>
<td>Smallpox</td>
<td>4—7</td>
</tr>
<tr>
<td>Influenza</td>
<td>1.68—20</td>
</tr>
<tr>
<td>SARS</td>
<td>2—3</td>
</tr>
</tbody>
</table>

SARS, severe acute respiratory syndrome.
droplet lands on the ground. The 2003 SARS epidemics also revealed iatrogenic and environmental factors that might contribute to producing virus-laden aerosols, such as those produced by nebulizers, tracheostomies, bronchoscopies, and, in the Amoy Gardens outbreak, a defective sewage system. Mechanics of aerosol transmission of infectious agents

Once infectious droplets are released, the main factors that determine how they move are their size and the airflow patterns that carry them around (Figure 3). The droplet size changes with time, depending on the environmental conditions. Humidity in the air alters the rate of droplet evaporation and therefore its size. Droplets in dry air evaporate quickly, reduce in size and fall to the ground more slowly. The changing size of a droplet affects how it will respond to airflow patterns and how quickly it will settle. Movement in air is determined by Stokes’ settling law, which governs how quickly a sphere falls under the opposing forces of gravity downwards and air friction upwards (Figure 3).

Knight estimated the times taken for particles of various diameters to fall 3 m (corresponding to the height of a room). Partsicles of diameters 1–3 μm remained suspended almost indefinitely, 10 μm took 17 min, 20 μm took 4 min, and 100 μm took 10 s to fall to the floor. ‘Naked’ viruses, bacteria and fungal spores (i.e. without associated water, mucus or pus droplets) range in approximate size from 0.02 to 0.3 μm, from 5 to 100 μm and from 1 to 10 μm, respectively. Infectious agents from patients can be expelled as individual or clusters of ‘naked’ organisms, or disseminated on skin cells, mucus or saliva. The amount of solid matter in a droplet ultimately determines its minimal size limit.

Temperature differences can set up large exchange flows between rooms, in a similar way to leaving a front door open on a cold day (Figure 4). Opening a hinged door leads to a sweeping action, which can also move a considerable volume of infectious air across the open doorway (Figure 4). A typical hinged door (about 1 m wide) opening relatively slowly from closed to 45° sweeps out one-eighth of a circle of circumference (C) \(2\pi = 6.3\) m (C = \(2\pi r\)).
Therefore, the door edge travels about 6.3/8 = about 0.8 m in about 2 s, generating an air flow with speed of approximately 0.8/2 = 0.4 m/s. In practice, doors may be opened faster and wider than this. As the door opens, air inside the room is dragged (or ‘entrained’) into the region swept by the door, leading to a large exchange of air across the doorway. At least one case report has described a secondary case of chickenpox arising from infectious air being transported out of an isolation room containing a patient with severe chickenpox via the opening of a hinged door. Closing a door does not seem to lead to any significant air exchange between rooms. Such problems with hinged doors may be reduced by the use of sliding doors.

The effect of movement of people on air flow produces a similar effect to door opening, but is more complex and difficult to calculate. The velocity of the layer of air closest to the body is comparable to a person’s walking speed. As a person moves at speed \( U \), there is a volume flux, \( F \), of air volume of approximately \( F = CAU/2 \), where \( C \) is the drag coefficient for a body (approximately equal to 1 in this example), \( A \) is the cross-sectional area of the body (for a person about 1.7 m tall, 0.3 m wide and 0.15 m deep, \( A = 1.7 \times 0.3 = 0.51 \text{ m}^2 \)) and \( U \) is velocity. In addition, there is a wake bubble of volume \( \varepsilon V \), where \( V \) is the volume of the body. In this example, \( V = 1.7 \times 0.3 \times 0.15 = 0.0765 \text{ m}^3 \) (i.e. a person of 76.5 kg, since 1 m\(^3\) = 100 × 100 × 100 cm\(^3\) = 1000 L water, assuming human body density has an average density equal to that of water) and \( \varepsilon = 1–3 \). For a person walking at speed \( U = 1 \text{ m/s} \), this corresponds to \( F = 1 \times 0.51 \times 1/2 = 0.255 \text{ m}^3 = 255 \text{ L/s} \), with an attached wake of \( \varepsilon V = 0.0765–0.2295 \text{ m}^3 = 76–230 \text{ L/s} \). Thus, movement of people in a room plays a significant part in disturbing the flow and also in transporting infected air from one place to another (Figure 5).

Thus, room air flow is governed by a combination of air movements caused by differences in temperature/humidity and moving bodies/equipment. 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. The infectivity of the droplet nuclei will also change with time, as the infectious organism will also be affected by the air temperature and humidity.

**Environmental survival of infectious agents**

To transmit from the respiratory tract of one person to another, the organisms in such droplets must...
Hence, it is difficult lipid-enveloped such guidelines tend to be-chemical hazards such as exhaust fumes Viruses without similarities with other viruses of ultraviolet (UV) radiation. Influ-
taneous rhagic fevers 1, tularaemia 10, Q fever 100, viral haemor-
phagic fevers 1–10 organisms). M. tuberculosis may need only a single organism to cause disease, and as many as 3000 organisms can be produced by a cough or talking for 5 min, with sneezing producing many more. For many common agents, the

remain airborne for a sufficient amount of time and must remain viable in a sufficient quantity to be inhaled by a susceptible host. Many environmental factors affect the viability of an infectious agent, e.g. temperature, humidity and air flows that might lead to dehydration, ultraviolet (UV) radiation, chemical hazards such as exhaust fumes from road transport or air pollution, and possibly cigarette smoke and air fresheners inside houses. Some organisms resist environmental degradation better than others. M. tuberculosis is a hardy organism with a thick cell wall, and can survive for long periods in the environment.

Measles and VZV are both lipid enveloped and are sensitive to changes in temperature, relative humidity (RH) and UV radiation. Viruses without a lipid envelope generally survive longer at high RH (>50%), e.g. poliovirus, but lipid-enveloped viruses survive longer in low RH (<50%), e.g. influenza. Lassa fever virus and human coronavirus (hCV) 229E. Data on hCV 229E from Ijaz et al. showed that, when airborne, this virus had a survival half-life of about 3 h at an RH of 80%, 67 h at an RH of 50% and 27 h at an RH of 30%, at 20 °C, suggesting that high RH above 80% is most detrimental to survival of this coronavirus. Influenza has been shown to survive for 24–48 h on hard, non-porous surfaces such as stainless steel and plastic, but for less than 8–12 h on cloth, paper and tissues. In addition, influenza virus survived for up to 5 min on hands, and could be transferred to hands from these non-porous surfaces for 24 h and from tissues for 15 min. More recently, it has been shown that SARS-CoV can survive in alkaline diarrhoea stools for up to four days, and remain infectious in respiratory specimens for more than seven days at room temperature. Similarities with other viruses of nosocomial importance, i.e. other RNA, lipid-enveloped, respiratory viruses such as Influenza, suggest that such organisms can survive for long enough in aerosols to cause disease, especially when associated with biological fluids such as mucus, faeces and blood. This sensitivity to environmental conditions may also partially explain the seasonality of some viral infections.

The situation is more complex in airborne bacteria. Gram-negative bacteria such as Escherichia coli and Klebsiella pneumoniae tend to behave like enveloped viruses, i.e. are less stable at high RH. In contrast, a study on another airborne Gram-negative bacterium, Salmonella seftenberg, found the opposite, i.e. that survival or ‘tenacity’ was highest at high RH. Cox suggested that a temperature of 10 °C offers optimal survival to most infectious pathogens. Hence, it is difficult to predict the survivability of infectious organisms from their structural characteristics alone.

**Infectious doses of aerosol-transmitted agents**

The infectious dose of a pathogen is the number of organisms required to cause infection. Theoretically, a single organism in a favourable environment may replicate sufficiently to cause disease. Guidelines for commissioning operating theatres recommend that the bioload in an empty theatre should not exceed 35 bacteria-carrying particles (e.g. skin scales)/m³, where 1 CFU represents the progeny from one viable bacterium. During an operation, the bioload in the same theatre should not exceed 180 colony-forming units per cubic metre (CFU/m³), which 1 CFU represents the progeny from one viable bacterium. Such guidelines are developed in an attempt to minimize the risks of surgical nosocomial transmission.

Data from research performed on biological warfare agents suggest that both bacteria and viruses can produce disease with as few as 1–100 organisms (e.g. brucellosis 10–100, Q fever 1–10, tularemia 10–50, smallpox 10–100, viral haemorrhagic fevers 1–10 organisms). M. tuberculosis may need only a single organism to cause disease, and as many as 3000 organisms can be produced by a cough or talking for 5 min, with sneezing producing many more. For many common agents, the
infectious dose almost certainly varies between individual pathogens and their hosts, e.g. immunocompromised hosts may not only be more susceptible to infection with a lower infectious dose, but may also be a more infectious source, as the pathogen is poorly controlled by the defective immune system. This may allow higher pathogen loads to be disseminated into the surrounding environment in some cases, possibly leading to super-spreading events, such as described in some SARS outbreaks.\(^1\)\(^-\)\(^5\) Knowledge of the infectious dose of airborne pathogens may allow an estimate of the number of air changes required in an indoor environment to reduce the concentration of such pathogens below the level that can cause disease.

**Methods of control of infectious aerosols**

Li et al. reviewed the evidence for the effects of ventilation on the transmission of infectious diseases.\(^6\)\(^6\) They concluded that there was good evidence (as demonstrated by the contemporary technology available at the time of the studies) for aerosol transmission influenced by ventilation factors in outbreaks involving measles,\(^13\)\(^3\) chickenpox,\(^14\)\(^3\) the pneumococcus (\*Streptococcus pneumoniae*),\(^13\)\(^5\) SARS-CoV,\(^1\)\(^-\)\(^5\) tuberculosis,\(^13\)\(^6\),\(^13\)\(^7\) influenza,\(^13\)\(^8\),\(^13\)\(^9\) and smallpox.\(^14\)\(^0\) Therefore, from this and other studies reviewed here, it should be possible to reduce the risk of aerosol transmission by altering ventilation parameters in healthcare environments.

For short-range aerosol transmission exposures, personal protective equipment (PPE; i.e. gowns, gloves and facemasks) is recommended in addition to the usual contact-transmission prevention precautions (i.e. handwashing, avoiding touching mucous membranes of the eyes, nose and mouth) to protect susceptible healthcare workers. Seto et al. performed a study on the effectiveness of masks in reducing infection during the SARS outbreak, and found that surgical masks were effective in reducing infection from SARS to a certain extent.\(^1\)\(^4\)\(^1\) However, with more infectious diseases such as TB, measles or chickenpox, a surgical mask alone may be insufficient aerosol protection, and masks with built-in filters, i.e. filtered face piece masks, may be required. Droplet nuclei produced during respiration, talking, coughing and sneezing from such patients are very small, less than 5 \(\mu\)m in diameter, and behave similarly to smoke particles in air.\(^1\)\(^4\)\(^2\) Where susceptible hosts are widely separated in an indoor space, the potential for airborne transmission depends partially on the ventilation system present. In the community, some studies during the SARS outbreak in Hong Kong suggested that the use of facemasks and covering the mouth when sneezing may have contributed to an overall reduction in the incidence of viral respiratory infections at this time.\(^1\)\(^4\)\(^3\),\(^1\)\(^4\)\(^4\)

For the control of long-range aerosol transmission, the architecture of the healthcare facilities requires consideration. Hospital rooms are connected by doorways, corridors, stairwells and lift shafts. Small pressure differences, induced by natural forces such as thermal buoyancy due to air temperature differences, the wind or mechanical fans, can generate air flows that move air from one room to another. These air flows are very sensitive to doors or windows being kept open, e.g. although opening a window can enhance natural ventilation, this can change the air pressure in neighbouring rooms and corridors, reducing, or even reversing, airflow directions (Figure 4). This highlights the importance of keeping isolation room windows and doors closed.

The use of air filtration aims to reduce airborne concentrations to well below their infectious dose. Besides simply increasing the number of air changes per hour, there are other ways in which manipulation of air flows can be used to reduce the spread of airborne infection in an indoor environment such as a hospital. One main difficulty in designing ventilation systems for removing airborne pathogens is due to the fact that air flow is generally turbulent. In a hospital environment, if a ventilation system can ensure that the inhaled air for each individual mainly consists of fresh outdoor air, the system would be considered effective as the purpose of ventilation is to protect individuals from inhaling hazardous, infectious air.\(^1\)\(^4\)\(^5\) This principle can be broken down into three approaches, as follows:

- Mixing of the contaminated air with uncontaminated air in the room, reducing the peak concentrations of droplet nuclei in the contaminated air. Over time, the average concentration of the droplet nuclei in the room will increase, unless the air is filtered.
- Diluting contaminated air using ‘fresh’ (uninfected) air. Current recommendations of ventilation flow rate in various different guidelines for hospital ventilation and isolation room designs are based on the principle of dilution.\(^1\)\(^4\)\(^6\) A ventilation flow rate of at least 12 air changes (of a room)/h is suggested for new isolation rooms (constructed since 2001). Existing isolation rooms (constructed before 2001) may still use six air changes/h.\(^8\)\(^9\),\(^1\)\(^4\)\(^7\)
- Controlling the air flow so that it moves from healthcare workers to patient. This requires
putting patients and exhaust vents in close proximity.

Practically, there are at least two commonly used air distribution systems in general hospital wards. These are the mixing ventilation and displacement ventilation systems (Figure 6).

**Mixing ventilation**

The idea is to create a uniform low concentration of infected air in the room air that is subsequently extracted. The air is supplied along the ceiling or directed upwards along the window or wall surface, as shown in Figure 6(a).

**Displacement ventilation**

This refers to ‘fresh’ air sweeping in one direction across a room, carrying the pollutants with it and exhausting the polluted air. The flow is driven by large temperature differences in the room. The vertical downward displacement ventilation system would be the ideal ventilation system for operating theatres, but there is a need for further study in the effectiveness of removing large particles with the upward vertical displacement system shown in Figure 6(b). However, a recent study demonstrated that the exhaled air plumes from a patient lying on his/her side on a bed could be spread over long distances, assisted by differences in air temperature and density, on a ward using displacement ventilation. This suggests that displacement ventilation should be used with caution in hospital wards, where such a risk of aerosol transmission is present.

In practice, ventilation usually consists of a combination of mixing and displacement ventilation. The fresh air stream mixes with convection currents, such as the heat plumes that arise above people and equipment. To remove infectious particles, existing guidelines recommend that the air flow should follow a path from the ceiling supply vents to the healthcare workers, then to the patients, then finally to the exhaust vents that are generally located at a lower level, near the floor.

Ventilation and air flows also affect the thermal comfort of both healthcare workers and patients. The air speed in the occupied zone of a room is designed to be below 0.2 m/s for reasons of comfort. Due to differences in metabolic rate and clothing, the cooling or heating requirements of healthcare workers and patients can be different. Thermal discomfort such as sweating may also discourage the proper use of PPE by HCWs and thus limit its effectiveness.

To reduce the spread of airborne contamination between rooms, it is common to fit ventilation systems with the capability to produce negative pressures, so that the direction of flow around closed leaky windows and doors can be controlled. For instance, in a negative pressure room, the supply flow rate to the room is less than the exhaust flow rate. Such ‘negative pressure’ isolation rooms are generally separately air-conditioned and temperature controlled, but there is likely to be a temperature difference between adjacent rooms. Current guidelines recommend a minimum negative pressure of 2.5 Pa (0.01 inch water gauge) in

![Fig 6](image)

*Figure 6* Illustration of the two commonly used air distribution methods in rooms. (a) Mixing ventilation: the cool air is supplied at ceiling level at high velocity and returned at either ceiling or floor level. The air in the room is generally fully mixed due to the strong mixing created by the overall air recirculation in the room, governed by the strong supply momentum. (b) Displacement ventilation: the cool air is supplied at floor level at low velocity and returned at ceiling level. The air in the room is divided into two parts: the upper part with ‘polluted’ air and the lower part with ‘clean’ air. Both parts of figure reproduced with the kind permission of CSIRO Australia. © CSIRO.
relation to corridors, although other guidelines recommend a negative pressure of 5–10 Pa.\textsuperscript{147,151–154} In practice, however, the negative pressure will fluctuate with time, depending on the control method and environmental factors. These systems need to be regularly maintained because it is commonly found that some air-supply vents do not supply the air at their specified rate, vents may be blocked and fail to deliver any air, and/or negative pressure rooms are being operated in a positive pressure mode.

Most recently, a study using computational fluid dynamical modelling confirmed that the air exchange rate and airflow patterns are important factors in the control of airborne virus diffusion.\textsuperscript{155} Also, despite the recommendations for ceiling to floor level ventilation air flows, this study suggested that this arrangement results in an ‘up-draft effect and poor infection control efficiency’.\textsuperscript{147,155} There is an obvious need for further work to determine the optimal methods of ventilation control to reduce the risk of aerosol transmission in healthcare premises.

**Conclusions**

- **Droplets generated by talking, laughing, coughing and sneezing potentially lead to the generation of an infectious aerosol.**
- **The survival of such aerosolized pathogens depends upon environmental conditions, such as temperature and RH, both of which can vary with the season and the indoor building environment.**
- **Such aerosols can be transmitted over short and long distances. Short-range transmission occurs over a distance of <1 m between individuals and is mediated mainly by the interaction of breathing zones of individuals. Long-range transmission occurs between distant locations and is primarily governed by air flows driven by pressure differences generated by ventilation systems, open windows and doors, movement of people or temperature differences.**
- **Agents able to transmit infection over long distances can almost always transmit infection over short ranges and through direct contact. In addition, large droplets may become small droplets then droplet nuclei via the process of evaporation. This may explain why some infectious agents, normally only associated with short-range transmission, may occasionally cause outbreaks over greater distances.**
- **Whether an individual acquires an infection depends on the final inhaled pathogen dose and the host’s immune response.**
- **The airborne transmission of diseases may be restricted in three ways:**
  - control the source of infection by quarantine and the use of isolation facilities;
  - control airborne transmission routes by the use of negative pressure ventilation systems, sliding doors instead of hinged doors, and improving seals around doors and windows; and
  - protect exposed susceptible individuals from both aerosol and contact transmission of infection by the use of PPE.

**Search strategy and selection criteria**


**Acknowledgements**

The authors wish to thank Prof. Andrew Davidhazy (School of Photographic Arts and Sciences, Rochester Institute of Technology Rochester, NY, USA) and Blackwell Publishing for their kind permission to reproduce the photographs in Figures 1 and 2, respectively, and CSIRO Australia for the use of the figures in Figure 6(a) and 6(b).

**References**

Aerosol transmission and ventilation control


48. Lutz BD, Jin J, Rinaldi MG, et al. Outbreak of invasive aspergillosis infection in surgical patients, associated with


Aerosol transmission and ventilation control


Nosocomial aspergillosis in outbreak settings

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Auszüge von nosokomialer Aspergillose


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Introduction

Aspergillus spores are ubiquitous in their distribution, and inhalation of spores is believed to be the usual route of transmission. In most healthy individuals, spores are removed by functional innate defence mechanisms such as monocyte-derived and resident macrophages. Unfortunately, in severely immunocompromised hosts, such as patients suffering from haematological malignancies or solid organ transplant patients, invasive aspergillosis (IA) may represent a serious complication in the course of disease. The incidence of IA is increased in these high-risk patients with an overall case-fatality rate of one-half to two-thirds. IA is difficult to treat and multi-variate analysis has revealed it to be an independent risk factor for mortality in critically ill patients. To prevent hospital-acquired aspergillus infections, high-risk patients are usually placed in protective isolation rooms in which positive air pressure is maintained compared with surrounding areas. These special rooms are provided with high-efficiency particulate air (HEPA) filters and an air flow of at least 12 air changes/h because HEPA filtration significantly reduces the concentration of fungal spores and the incidence of IA. In addition, horizontal laminar air flow (LAF) is provided in some facilities which drives contaminants out through the ducts. However, additional protection due to LAF remains a matter of debate and the use of LAF is not explicitly recommended by the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA) or the American Society of Blood and Marrow Transplantation (ASBMT) for the care of haematopoietic stem cell transplant recipients. Despite such guidelines for the care of highly susceptible patients and maximum protective efforts, nosocomial outbreaks of IA do occur. This systematic review was carried out to summarize the data from all nosocomial aspergillus outbreak reports published to date.

Methods

Collection of data

The outbreak database (www.outbreak-database.com), a web-based register of nosocomial epidemics, was searched for outbreaks due to any type of Aspergillus spp. Furthermore, a PubMed search (1 January 1966–15 August 2005) was performed to identify additional aspergillus outbreaks by using the term ‘outbreak’ in combination with ‘aspergillus’ or ‘aspergillosis’. References were subsequently screened for additional descriptions of aspergillus epidemics in hospital settings.

Extraction of data

The following data were obtained: (1) number of patients involved in the outbreak; (2) number of patients that died due to aspergillus infection; (3) underlying diseases of affected patients; (4) primary site of mycosis; (5) distribution of Aspergillus spp. in clinical specimens; (6) concentration of airborne mould spores in diverse hospital areas; (7) genotyping of fungal isolates to confirm an epidemiological relationship; (8) source of the outbreak.

Evaluation of data

Outbreak data were evaluated by both authors independently. Patients were grouped depending upon underlying diseases into the following classes: (1) haematology and bone marrow transplantation; (2) solid organ transplantation; (3) other immunodeficiency; (4) no known severe immunodeficiency. If a relevant immunodeficiency could not be excluded but definite classification of underlying disease was not possible either, patients were grouped as ‘other immunodeficiency’. Mortality was calculated for all groups and then compared. Statistically significant differences in mortality rates in diverse patient groups were determined using Chi-squared test (Epi-Info software, Version 3.3.2). Outbreak sources were considered ‘probable’ if stated so by the authors of the outbreak. Sources were considered ‘possible’ if there were circumstances that may have been the source of the outbreak but no exact link could be made with infection.

Results

A total of 53 outbreaks and 458 affected patients were included in this review. Comprising a total of 299 individuals (65.3%), haematological malignancies were the predominant underlying disease. In all but one outbreak, air was the route of fungal spore transmission and the major site of primary infection (356 patients) was the lower respiratory tract. Surgical site infections and superficial skin infections were observed far less frequently (24 patients each). Interpatient spread was only described on one occasion. Species identified most often from clinical samples were Aspergillus fumigatus (154 patients) and Aspergillus flavus (101 patients). Species differentiation was not
<table>
<thead>
<tr>
<th>Author (year, country)</th>
<th>Patient group (N patients)</th>
<th>Patients (N fatal)</th>
<th>Primary site of infection (N)</th>
<th>Clinical Aspergillus spp. isolates (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gage et al. (1970, USA)</td>
<td>T-SURG (4)</td>
<td>4 (3)</td>
<td>Endocarditis (4)</td>
<td>fumigatus (3); glaucus (1)</td>
</tr>
<tr>
<td>Burton et al. (1972, USA)</td>
<td>RTX (4)</td>
<td>4 (0)</td>
<td>LRTI (4)</td>
<td>fumigatus (4)</td>
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<tr>
<td>Rose (1972, USA)</td>
<td>HEMA (?)</td>
<td>Total: 23 (total: 12)</td>
<td>LRTI (23)</td>
<td>fumigatus (≥12)</td>
</tr>
<tr>
<td>Aisner et al. (1976, USA)</td>
<td>HEMA (8)</td>
<td>8 (≥3)</td>
<td>LRTI (7); sinusitis (1)</td>
<td>Unknown (8)</td>
</tr>
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<td>Kyriakides et al. (1976, USA)</td>
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<td>LRTI (3)</td>
<td>fumigatus (3)</td>
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<td>Arnow et al. (1978, USA)</td>
<td>RTX (3)</td>
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<td>LRTI (2)</td>
<td>fumigatus (3)</td>
</tr>
<tr>
<td>Mahoney et al. (1979, USA)</td>
<td>HEMA (5)</td>
<td>5 (3)</td>
<td>Sinusitis (3); LRTI (2)</td>
<td>Unknown (4)</td>
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<td>Lentino et al. (1982, USA)</td>
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<td>LRTI (10)</td>
<td>Unknown (10)</td>
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<td>LRTI (23)</td>
<td>fumigatus (12)</td>
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<td>Gustafson et al. (1983, USA)</td>
<td>RTX (9)</td>
<td>9 (7)</td>
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<td>fumigatus (3); unknown (6)</td>
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<td>Grossman et al. (1985, USA)</td>
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<td>Rotstein et al. (1985, USA)</td>
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<td>fumigatus (7); flavus (3)</td>
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<td>Opal et al. (1986, USA)</td>
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<td>LRTI (11)</td>
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<td>Allo et al. (1987, USA)</td>
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<td>Perraud et al. (1987, France)</td>
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<td>22 (18)</td>
<td>LRTI (22)</td>
<td>fumigatus (22)</td>
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<td>Ruutu (1987, Finland)</td>
<td>HEMA (8)</td>
<td>8 (8)</td>
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<td>fumigatus (8)</td>
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<td>Shergert et al. (1987, USA)</td>
<td>HEMA (14)</td>
<td>14 (13)</td>
<td>LRTI (14)</td>
<td>fumigatus (?)</td>
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<td>Weems et al. (1987, USA)</td>
<td>HEMA (3)</td>
<td>3 (3)</td>
<td>LRTI (3)</td>
<td>Unkown (3)</td>
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<tr>
<td>Harvey et al. (1988, UK)</td>
<td>ICU patients low risk (2); high risk (2)</td>
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<td>Endocarditis (3)</td>
<td>fumigatus (≥3)</td>
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<tr>
<td>Barnes and Rogers (1989, UK)</td>
<td>HEMA (6)</td>
<td>6 (6)</td>
<td>LRTI (6)</td>
<td>Unkown (6)</td>
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<tr>
<td>Hara et al. (1989, USA)</td>
<td>HEMA (1); steroids (1)</td>
<td>1 (1)</td>
<td>LRTI (1); sinusitis (1)</td>
<td>terreus (2); fumigatus (1)</td>
</tr>
<tr>
<td>Hopkins et al. (1989, USA)</td>
<td>RTX (3); HEMA (2); ONCO (1)</td>
<td>3 (1)</td>
<td>LRTI (6)</td>
<td>fumigatus (6)</td>
</tr>
<tr>
<td>Mehta et al. (1990, India)</td>
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<td>4 (4)</td>
<td>Endocarditis (4)</td>
<td>fumigatus (1); unknown (3)</td>
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<tr>
<td>Weber et al. (1990, USA)</td>
<td>HEMA (18)</td>
<td>18 (18)</td>
<td>LRTI (17)</td>
<td>fumigatus (1); unknown (3)</td>
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<td>Arnow et al. (1991, USA)</td>
<td>HEMA (12); LiTX (3)</td>
<td>12 (?)</td>
<td>LRTI (15)</td>
<td>flavus (9); fumigatus (6)</td>
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<tr>
<td>Humphreys et al. (1991, UK)</td>
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<td>LRTI (≥4)</td>
<td>flavus (6); fumigatus (1)</td>
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<td>Loosveld et al. (1992, The Netherlands)</td>
<td>HEMA (5); ONCO (1)</td>
<td>5 (3)</td>
<td>LRTI (6)</td>
<td>fumigatus (6)</td>
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<tr>
<td>Pla et al. (1992, Spain)</td>
<td>LiTX (2)</td>
<td>2 (2)</td>
<td>SSI (2)</td>
<td>fumigatus (2)</td>
</tr>
</tbody>
</table>
performed in 108 clinical isolates. Genotyping of clinical and environmental isolates was performed in 11 studies, and revealed similar or identical band patterns of at least some isolates in all but four of those investigations. Detailed data concerning patients’ characteristics and causative Aspergillus spp. in each outbreak are summarized in Table I.

Table II shows mortality rates in various groups of patients. In 49 patients, the distribution of

<table>
<thead>
<tr>
<th>Author (year, country)</th>
<th>Patient group (N patients)</th>
<th>Patients (N fatal)</th>
<th>Primary site of infection (N )</th>
<th>Clinical Aspergillus spp. isolates (N )</th>
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</thead>
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<tr>
<td>Richet et al. (1992, USA)</td>
<td>T-SURG (6); HEMA (3); ONCO (1)</td>
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<td>SSI (6)</td>
<td>fumigatus (6)</td>
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<td>Flynn et al. (1993, USA)</td>
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<td>Tritz and Woods (1993, USA)</td>
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<td></td>
<td>fumigatus (4); flavus (2); other (2)</td>
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<td>Buffington et al. (1994, USA)</td>
<td>HEMA (7)</td>
<td>4 (4)</td>
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<td>terreus (4); fumigatus (3); flavus (2); other (2)</td>
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<td>Iwen et al. (1994, USA)</td>
<td>HEMA (5)</td>
<td>7 (6)</td>
<td>LRTI (7)</td>
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<td>Tang et al. (1994, UK)</td>
<td>RTX (2); Surgery (?)</td>
<td>2 (1)</td>
<td>LRTI (2)</td>
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<td>Bryce et al. (1996, Canada)</td>
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<td>5 (?)</td>
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<td>Leenders et al. (1996, The Netherlands)</td>
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<td>Total: 10; Total: 6</td>
<td>fumigatus (10); flavus (10)</td>
</tr>
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<td>36 (17)</td>
<td>LRTI (34); Sinusitis (2)</td>
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<td>Skin infection (4)</td>
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<td>Tabbara and al Jabarti (1998, Saudi Arabia)</td>
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<td>5 (?)</td>
<td>Eye infection (5)</td>
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<td>21 (6)</td>
<td>LRTI (21)</td>
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<td>Thio et al. (2000, USA)</td>
<td>HEMA (6); HEMA (3)</td>
<td>6 (?)</td>
<td>LRTI (6)</td>
<td></td>
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<td>Burwen et al. (2001, USA)</td>
<td>HEMA (10)</td>
<td>3 (2)</td>
<td>LRTI (3)</td>
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<td>HEMA (31)</td>
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<td>Oren et al. (2001, Israel)</td>
<td>HEMA (10)</td>
<td>10 (8)</td>
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<td>9 (6)</td>
<td>LRTI (6)</td>
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<tr>
<td>Pegues et al. (2002, USA)</td>
<td>LITX (3)</td>
<td>3 (?)</td>
<td>Ssi (2); LRTI (1)</td>
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<tr>
<td>Lutz et al. (2003, USA)</td>
<td>Surgery (3); RTX (1); T-SURG (2)</td>
<td>3 (1)</td>
<td>SSI (6)</td>
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<tr>
<td>Myoken et al. (2003, Japan)</td>
<td>HEMA (3)</td>
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<td>Stomatitis (3)</td>
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<tr>
<td>Panackal et al. (2003, USA)</td>
<td>RTX (4); T-SURG (9)</td>
<td>4 (4)</td>
<td>LRTI (3)</td>
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<tr>
<td>Heinemann et al. (2004, Belgium)</td>
<td></td>
<td>9 (2)</td>
<td>SSI (9)</td>
<td></td>
</tr>
</tbody>
</table>

?, exact number unknown; T-SURG, thoracic surgery; RTX, renal transplantation; HEMA, haematology and bone marrow transplantation; ONCO, non-haematologic malignancy; ICU, intensive care unit; LiTX, liver transplantation; LRTI, lower respiratory tract infection; SSI, surgical site infection.
underlying diseases was not described in detail but all of those diseases did show a relevant immunodeficiency. Therefore, these patients were grouped as described in the Methods section. Mortality was greatest (57.6%) among patients suffering from haematological malignancies. The mortality in this group was significantly higher compared with the mortality of patients without any known immunodeficiency (39.4%; $P < 0.05$).

In 24 outbreaks, volumetric air samples in the hospital and outdoors were taken during the environmental investigation (Table III). The concentration of airborne fungi in patient care areas

Table II  Number of patients with different underlying diseases and associated mortality

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>No. of patients</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematologic malignancy</td>
<td>299</td>
<td>57.6</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>36</td>
<td>55.9</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Other immunocompromised patients</td>
<td></td>
<td>52.3</td>
</tr>
<tr>
<td>High-dose steroid therapy</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Neonates</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other malignancy</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ICU patients (‘high risk’)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>No exact classification possible</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>
| Patients without severe immunodefi
| cency                           | 39.4           |
| Thoracic surgery                   | 25             |              |
| Cataract surgery                   | 5              |              |
| ICU patients (‘low risk’)          | 5              |              |
| Other surgical patients            | 3              |              |
| Total                              | 458            | 55.0         |

ICU, intensive care unit.

Table III  Concentration of airborne aspergillus spores (colony-forming units/m$^3$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Site of renovation</th>
<th>Operating theatres</th>
<th>Wards, stairs, elevators</th>
<th>Rooms (no HEPA)</th>
<th>Rooms (HEPA)</th>
<th>Outdoor samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnow et al. $^{57}$</td>
<td>&gt;235.0</td>
<td>&gt;235.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentino et al. $^{49}$</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotstein et al. $^{66}$</td>
<td>0.0–5.0</td>
<td>0.0–5.0</td>
<td></td>
<td>3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opal et al. $^{68}$</td>
<td>5.9</td>
<td>1.7</td>
<td></td>
<td>&lt;0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Allo et al. $^{69}$</td>
<td>0.0–400.0</td>
<td>0.0–400.0</td>
<td></td>
<td>6.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Perraud et al. $^{70,71}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sherertz et al. $^{3}$</td>
<td>0.2</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvey et al. $^{75}$</td>
<td>0.0</td>
<td>0.0</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barnes and Rogers $^{18}$</td>
<td>133.0</td>
<td></td>
<td></td>
<td>12.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnow et al. $^{44}$</td>
<td>1.1–90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humphreys $^{48}$</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richet et al. $^{50}$</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flynn et al. $^{82}$</td>
<td>&gt;71.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffington et al. $^{24}$</td>
<td>Took volumetric air samples but did not describe exact results of environmental investigation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leenders et al. $^{26,84}$</td>
<td>0.0–&lt;0.1</td>
<td>0.0–&lt;0.1</td>
<td>0.9–1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loo et al. $^{85}$</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer et al. $^{22}$</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gazpar et al. $^{87}$</td>
<td>48.0</td>
<td>5.0–35.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thio et al. $^{28}$</td>
<td>0.8–18.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li $^{38}$</td>
<td>0.0–5.9</td>
<td>0.0</td>
<td></td>
<td>0.2</td>
<td></td>
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</tr>
<tr>
<td>Oren et al. $^{89}$</td>
<td>15.0</td>
<td>15.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hahn et al. $^{90}$</td>
<td>&lt;4.0–150.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegues et al. $^{23}$</td>
<td>1.1–106.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heinemann et al. $^{33,91,92}$</td>
<td>5.0–115.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HEPA, high-efficiency particulate air.

Figure 1  Distribution of sources of nosocomial aspergillus outbreaks.

In 24 outbreaks, volumetric air samples in the hospital and outdoors were taken during the environmental investigation (Table III). The concentration of airborne fungi in patient care areas
Outbreaks of nosocomial aspergillosis

During outbreak investigations ranged from 0 to more than 100 spores/m³.

As shown in Figure 1, construction work or renovation activities within the hospital or in surrounding areas were most commonly (49.1%) considered to be the probable or possible source of the nosocomial aspergillus outbreak, followed by a contaminated or defective air supply system (17%). In 12 of the 53 outbreaks, the source remained unknown or was not described.

Discussion

Today, construction in or around hospitals is a never-ending phenomenon. This review suggests that construction, renovation, demolition and excavation activities are the main causes of nosocomial aspergillus outbreaks. This is plausible because renovation and demolition work have been shown to increase the amount of airborne fungal spores dramatically, and in consequence increase the risk for aspergillus infection in susceptible patients. Routes of aspergillus transmission in nosocomial outbreaks other than airborne spores are rarely described. Although aspergilli have also been detected in water supply systems, there is no evidence that nosocomial outbreaks derive from the plumbing system.

No Aspergillus spp. may be disregarded with respect to severity of infection. Instead, any Aspergillus spp. in air samples from special care areas should raise concern of invasive infection, although certain Aspergillus spp. are more commonly involved in nosocomial outbreaks than others. This may, in part, be explained by an increased pathogenicity of this species, but it may also reflect the natural distribution of aspergilli in the environment.

Environmental investigations are usually initiated in order to assess the quality of air and to identify potential sources of the epidemic. In many studies, the burden of fungal spores in air has been evaluated by gravity sedimentation methods alone (e.g. open Petri dish method). However, this method is not volumetric, cannot be calibrated, and hence provides qualitative rather than quantitative results. In preference, air samples should be drawn by impacting particles from an air stream on to agar surfaces after centrifugal acceleration (e.g. Anderson sampler). This technique is more sensitive, allows determination of aspergillus spores in a standardized volume, and is recommended for calculation of the actual density of fungal contamination. To date, the minimal airborne concentration of aspergillus spores necessary to cause infection in patients with significant immunodeficiency remains unknown. Even concentrations of airborne aspergillus spores below 1 colony-forming unit (cfu)/m³ have been shown to be sufficient to cause outbreaks in immunocompromised patients. In contrast, the rate of nosocomial IA did not increase in other studies when a median spore count of 0 cfu/m³ was maintained or high-efficiency filtration face masks were used for neutropenic patients outside patient rooms during the construction period.

In accordance with guidelines published by the Healthcare Infection Control Practices Advisory Committee of the CDC, the Association for Professionals in Infection Control and Epidemiology, the IDSA and the ASBMT, the authors’ recommend application of the following measures for nosocomial IA prevention:

1. Avoid non-emergent admissions during heavy construction periods;
2. If possible, locate high-risk patients as far as possible from areas of demolition or construction;
3. Seal off patient care areas with adequate and impermeable barriers, and keep doors and windows closed;
4. Verify that HEPA air filtration is sufficient and proper air exchange rates are maintained. Check possible plugging or leakage of air filters. Ensure that air pressure relationships are adequate compared with adjunct rooms. Aim for positive pressure in patient rooms and for negative pressure in in-house construction areas;
5. Provide treatment in the patient’s room if possible. Transport via an alternate route, schedule transportation during periods with minimal construction activity, minimize waiting times outside, and use appropriate face masks for susceptible patients if it is necessary for them to leave their rooms and pass through potentially contaminated areas;
6. Wet-clean wards thoroughly without raising dust;
7. Surveillance of infections in patients that are at increased risk for IA should be performed.

There are limitations in this approach to determine the minimal infectious dose of aspergillus spores by outbreak analysis. First, environmental investigation starts some time after an increased incidence of nosocomial aspergillosis is recognized, but the concentration of environmental airborne fungal spores varies constantly, e.g. due to climate changes or phases of spores’ dissemination from construction work. As such, a single peak of increased spore concentrations at the time of
infection may not be detected. Spores may have settled down in the meantime, and can be detected by environmental swabs while volumetric air samples remain free of fungi.49,50 Second, after an outbreak has occurred, air sampling should be conducted using large volumes (>1000 L) to increase the likelihood of detecting a low level of spores;28 however, that was not the case in many outbreak reports. Third, standardized criteria for definite, probable or possible IA were not used in all the studies included in this review. In 2002, international definitions for IA in immunocompromised patients were proposed, but data of earlier outbreak investigations may be influenced by different criteria for IA determination.51 Finally, despite wide diversity within each species of aspergillus,52 genotyping was seldom performed to ascertain a common source of infection.23–33 Even if indistinguishable strains are found, it is also noteworthy that nosocomial aspergillosis is one of the few settings where nosocomial outbreaks can, and probably usually, occur due to a variety of unrelated strains. Thus, findings of similar strains in the nosocomial outbreak setting may also represent inadequate sensitivity of typing methods.

Prospective approaches where the actual airborne fungal concentration is determined in small time intervals in patient care areas during hospital construction periods could be helpful to identify an increase of airborne mould concentrations at an early stage before cases of nosocomial aspergillosis are observed. Detection of airborne aspergilli in high-risk patient care areas should always draw attention to the potential risk of a serious infection. Based on the data available at present, it is concluded that airborne mould spores at any concentration may represent a threat for severely immunocompromised patients.

References

Outbreaks of nosocomial aspergillosis

253


63. Gerson SL, Talbot GH, Lusk E, Hurwitz S, Strom BL, Cassileth PA. Invasive pulmonary aspergillosis in adult acute
The Potential for Airborne Dispersal of Clostridium difficile from Symptomatic Patients

Das Potenzial luftübertragener Verbreitung von Clostridium difficile bei symptomatischen Patienten

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1Microbiology Department, Old Medical School, Leeds General Infirmary, Leeds Teaching Hospitals National Health Service Trust, and 2University of Leeds, Leeds, United Kingdom

(See the editorial commentary by Donskey, on pages 1458–1461.)


Clostridium difficile infection (CDI) is a major burden to health care facilities [1], with increasing rates since 2002 in the United States [2], Canada [3–5], and Europe [6, 7]. C. difficile is transmissible between hospitalized patients, and control measures to limit cross-infection are part of routine practice. Pragmatically, it is desirable to nurse patients with CDI in isolation, although there is a lack of robust evidence to support the utility of single rooms in preventing transmission. However, limited availability of single rooms in some settings can lead to the frequent management of CDI cases in open wards [8, 9]. With the recognition and emergence of virulent strains associated with CDI outbreaks, such as ribotype 027/NAP1 [1–7], it has become increasingly important to determine how transmission is occurring and to establish effective interventions to minimize these risks.

It has been estimated that a patient with CDI can excrete between $1 \times 10^9$ and $1 \times 10^{10}$ of C. difficile per gram of feces [10]. C. difficile spores may be resistant to disinfectants and can survive for months or years on contaminated surfaces [11–14]. Environmental contamination with C. difficile spores occurs at as many as 34%–58% of sites despite cleaning, with surfaces of fomites being most frequently contaminated [15–17]. Crucially, the hands of health care workers are significantly more likely to be positive for C. difficile if the environment is heavily contaminated with the bacterium [18].

There are few data to substantiate the risks associated with airborne transmission of C. difficile in hospitals. A number of studies have alluded to the possibility that C. difficile could potentially spread through the air [15,
We aimed to determine the extent of *C. difficile* contamination in ward environments by recovery of *C. difficile* from air and environmental surfaces in the immediate vicinity of patients with symptomatic CDI. We aimed to establish an epidemiological link between patients and their surroundings, using highly discriminatory DNA fingerprinting, as well as the relationship between near-patient activity and *C. difficile* aerosolization.

**METHODS**

**Organization of Air Sampling**

Approval for the study was obtained from the Leeds Teaching Hospitals’ Research Committee. The first phase of the investigation (6 months) comprised air sampling (total, 50 h) for 1 h adjacent to 50 patients with confirmed CDI (including 13 in general medical wards, 25 in elderly care wards, and 12 in the *C. difficile* ward, of whom 43 were in single rooms and 7 were in multioccupied bays). All air was maintained by standard ventilation. The second and third phases of sampling (4 months) involved 10 h of air sampling over 2 days (total, 130 h for proven CDI cases [see below]) and 40 environmental samples per patient in elderly care wards and the *C. difficile* ward; 19 of 20 patients in these phases were in single rooms. The second phase of sampling comprised 10 patients with CDI identified by nursing staff as having suspected cases (not laboratory confirmed). The third phase of sampling focused on 10 patients with symptomatic (cytotoxin-positive) CDI.

Control air sampling consisted of the following. During phase 1, 11 air samples (11 h) were obtained adjacent to patients without a history or symptoms suggestive of CDI. During phase 2, 7 of the 10 patients with suspected CDI proved to be cytotoxin negative and were therefore counted as control tests (70 h). During phase 3, air sampling was conducted adjacent to a patient without a history of CDI (10 h) and in the corridor of the same ward (10 h). Air sampling totaled 180 and 101 h for CDI cases and control subjects. During sampling, we observed and recorded ongoing activities that could be associated with marked air disturbance (eg, bed changing and frequency of visitors). Routine environmental cleaning was done each morning, using a detergent/chlorine (1000 ppm) agent.

**Environmental Surface Sampling**

*Initial in vitro tests for determining the efficiency of Polywipe sponges.* Polywipe sponges (Medical Wire & Equipment) were initially examined as a pilot to this investigation to determine their efficiency for recovery of *C. difficile* from environmental surfaces. In vitro tests (in triplicate) were conducted using 200-μL aliquots of diluted spore suspensions (2.4–2.4×10⁸) spread onto an aluminum surface (30×15 cm) and left to dry for 1 h. Duplicate test-seeded areas were sampled using both standard environmental swabs and sponges. Each sponge or swab tip was placed into a Stomacher bag (Seward) with 50 mL of Ringer solution and processed for 30 s. Aliquots were cultured on CCEYL and anaerobically enriched in cooked-meat fastidious anaerobe broth (E&O Laboratories) at 37°C for 48 h.

*Patient environment sampling.* Following the pilot study, sponges were used for environmental sampling (Table 1). After sampling, 50 mL of Ringer solution was added to each sponge, followed by 30-s processing in a Stomacher bag. Liquid from the bag was passed through a 0.45-μm filter (Millipore), which was then placed in 10 mL of cooked-meat broth and subcultured on CCEYL, as described above.

**Culture of Patient Fecal Samples**

Patient fecal samples (pea-sized aliquots) were alcohol-shocked by immersion in 1 mL of 50% ethanol solution. After being vortexed for 10 s and left to stand at room temperature for ≥1 h, samples were cultured on CCEYL plates, as described above.

**Polymerase Chain Reaction Ribotyping and Multilocus Variable-Number Tandem-Repeat Analysis**

Polymerase chain reaction ribotyping was performed on all *C. difficile* isolates as described previously [24]. Multilocus variable-number tandem-repeat analysis (MLVA) was conducted as described elsewhere [25], using 7 loci (A6, B7, C6, E7, F3, G8, and H9). Fragments were analyzed using GeneMapper software (version 4.0; Applied Biosystems), and copy numbers were determined. The summed absolute difference between 2 MLVA-typed isolates is the calculated summed tandem-repeat difference (STRD) at all 7 loci [26]. MLVA types with a STRD ≤2 plate. Plates (140-mm diameter) contained Brazier’s cycloserine-cefoxitin-egg yolk agar (Bioconnections) supplemented with 5 mg/mL lysozyme (CCEYL) (not prereduced) [23]. The plate rotated constantly; thus, after culture the location of the colonies represented the time of recovery from air, making it possible to link it to activities near to the sampler. Plates were transported to the laboratory and incubated anaerobically (37°C for 48–72 h). After each sampling session or day, the machine was cleaned externally and internally with a sporidical disinfectant (Trigene; Medichem).
were indicative of a high degree of genetic relatedness among *C. difficile* isolates.

**RESULTS**

**Polywipe sponge in vitro tests.** Sponges were significantly more effective than swabs (*P* = .006) at recovering *C. difficile* from surfaces (Table 2). In tests comprising 2400 colony-forming units (CFUs) spread on a test surface, a recovery of 52% with sponges versus zero with swabs was achieved. To increase the detection limit further (2 CFUs), an enrichment step was added, on the basis of previous experience with recovering *C. difficile* from environmental sites [23]. Sponges also allowed sampling of larger surface areas, and so these were used in preference to swabs during phases 2 and 3.

**First-phase sampling of 50 patients with confirmed CDI.** Of the first 50 patients examined (1 h), only 6 (12%) had positive cultures from the air sampling. There was a trend toward there being more positive air samples from patients with active diarrheal symptoms, compared with those without diarrheal symptoms (10% vs 2%; *P* = .1). Of the 5 symptomatic patients with positive air samples, 2 were in beds on different 6-bedded bays (fully occupied), and 3 were in single rooms. During air sampling, cleaning and bed making were taking place close to 2 of the positive patients. No *C. difficile* was recovered from any of the control air samples (*n* = 11).

**Second-phase air and environmental sampling of symptomatic patients with suspected but unconfirmed CDI.** Results from phase 1 suggested that airborne dissemination of *C. difficile* spores may be occurring before laboratory confirmation of CDI was obtained. Of 10 patients identified by nursing staff as having suspected CDI, only 3 proved to have laboratory confirmed cases. Patient U4, who had a positive air sample, was in a single room and underwent air sampling on 15 December 2008 and 16 December 2008, with CDI confirmed on 16 December 2008. *C. difficile* colonies were recovered on 3 occasions (day 1, at 1115, 1130, and 1315), corresponding to ward cleaning at 1130 and to curtain closure around the bed at 1315. Ribotyping and MLVA confirmed that indistinguishable isolates were recovered from the patient and air at each time point (ribotype 106; MLVA profile 23-13-23-2-6-4-2). Patients U2 and U5 were also confirmed to be positive for CDI, but no positive air or environmental samples were obtained. The remainder of the patients (*n* = 7) were confirmed to be negative for cytotoxin and were thus considered as control (albeit diarrheal) patients. A positive air sample was collected from one of these control patients (U8), and positive environmental samples were collected from patient U6 (commode) and from patient U9 (bed, floor, table, sink, and the ward storeroom handle). *C. difficile* with the same ribotype and MLVA type (027; 31-22-17-12-5-8-2) was obtained from the bed, floor, table, and sink, but *C. difficile* with a different ribotype and MLVA type (106; 24-14-22-2-6-4-2) (STRD, >10) was recovered from the storeroom door.

**Third-phase air and environmental sampling of symptomatic patients with confirmed CDI.** Of the 10 patients tested (10 h), 7 had at least 1 positive air sample, 4 on multiple occasions. The most common times when *C. difficile* was recovered from the air corresponded with activity close to patients (Figure 1). Between 1000 and 1100, a drinks delivery occurred for patients, which corresponded to the recovery of *C. difficile* from 2 patients. The peak at 1145 corresponded with ward rounds between 1100 and 1200. The second peak comprising a total recovery of 8 colonies (from 4 patients) corresponded to lunch delivery (1200) and visiting time (1200–1400).

In total, 346 environmental surface samples were obtained during this phase, of which 10% yielded *C. difficile* (from 9 of 10 patients). For the single patient without a positive environmental sample, *C. difficile* was recovered from the air. The highest levels of recovery of *C. difficile* were from surfaces closest to the patients and the areas frequently handled, including the patients’ bed, bedside table, sink, and bin (6 or more isolations). There were fewer (<2) positive environmental samples from infrequently touched surfaces.

Six patients had *C. difficile*-positive environmental and air samples (Table 3). For 3 patients, *C. difficile* recovered from the air and at least 1 environmental sample had identical MLVA

<table>
<thead>
<tr>
<th>Surface tested</th>
<th>Surface Area, (~30 cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfaces in vicinity of patient</td>
<td></td>
</tr>
<tr>
<td>Inside door handle</td>
<td></td>
</tr>
<tr>
<td>Outside door handle</td>
<td></td>
</tr>
<tr>
<td>Bed rails</td>
<td></td>
</tr>
<tr>
<td>Bedside table</td>
<td></td>
</tr>
<tr>
<td>Hand-wash sink</td>
<td></td>
</tr>
<tr>
<td>Clinical waste bin</td>
<td></td>
</tr>
<tr>
<td>Overbed light</td>
<td></td>
</tr>
<tr>
<td>Medical equipment</td>
<td></td>
</tr>
<tr>
<td>Commode</td>
<td></td>
</tr>
<tr>
<td>Floor (adjacent to patent bed)</td>
<td></td>
</tr>
<tr>
<td>Walking frame</td>
<td></td>
</tr>
<tr>
<td>Communal area surfaces tested</td>
<td></td>
</tr>
<tr>
<td>Ward door</td>
<td></td>
</tr>
<tr>
<td>Desk surface of nurses’ station</td>
<td></td>
</tr>
<tr>
<td>Patient toilet</td>
<td></td>
</tr>
<tr>
<td>Patient sink</td>
<td></td>
</tr>
<tr>
<td>Patient bath</td>
<td></td>
</tr>
<tr>
<td>Sluice room door</td>
<td></td>
</tr>
<tr>
<td>Notes trolley</td>
<td></td>
</tr>
<tr>
<td>Store room door</td>
<td></td>
</tr>
<tr>
<td>Staff room door</td>
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</tbody>
</table>
Table 2. Mean *Clostridium difficile* Counts from In Vitro Surface Recovery Tests for Polywipes and Swabs

<table>
<thead>
<tr>
<th>No. of CFUs spread onto test surface</th>
<th>No. of colonies on plate</th>
<th>No. recovered</th>
<th>Percent recovery</th>
<th>No. of colonies on plate</th>
<th>No. recovered</th>
<th>Percent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Environmental swabs</td>
<td></td>
<td></td>
<td>Polywipe sponges</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4 × 10^3</td>
<td>1</td>
<td>2500</td>
<td>1</td>
<td>82</td>
<td>2 × 10^6</td>
<td>83</td>
</tr>
<tr>
<td>24,000</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>17,500</td>
<td>72</td>
</tr>
<tr>
<td>240</td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
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<td>52</td>
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</tr>
<tr>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** The test surface area was 30 × 15 cm. CFUs, colony-forming units.

types. For the other 3 positive patients, the *C. difficile* recovered from the air in each environment was considered to be highly related to at least 1 environmental sample obtained within the same environment (either a single- or double-locus variant, with a STRD ≤6). It was also possible to confirm an epidemiological link for the *C. difficile* isolates from air, diagnostic fecal samples, and environmental surfaces. For example, for patient C1 the *C. difficile* isolates from feces, air (1045 and 1050), and a table were all ribotype 027, with highly related MLVA types and 6 identical loci (31-22-15-12-5-10-2 and 31-22-15-12-5-8-2; a single-locus variant with a STRD of 2). *C. difficile* was not recovered from 20 h of control air samples.

**DISCUSSION**

Airborne transmission and environmental contamination of *C. difficile* was first suspected in hamster experiments [27]. Studies reported significant contamination of objects in the immediate environment and suggested that airborne cross-contamination appeared to be less important than that from contact surfaces.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Date tested</th>
<th>Date confirmed positive</th>
<th>Sample type (time of day)</th>
<th>Ribotype</th>
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<td></td>
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<td>24-21-22-2-6-4-2</td>
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</table>
counts that were orders of magnitude larger [19]. Because we sampled air from the air around patients with C. difficile ribotypes [25, 28], most commonly during periods of activity, particularly around the busy lunchtime period. These observations suggest that the air within the patient’s immediate environment is contaminated with C. difficile spores either directly from symptomatic patients or from environmental surfaces and that people movement, including the opening and closing of doors, contributes to the circulation and dispersal of airborne C. difficile. It has been demonstrated previously that areas associated with much air movement, such as air vents, are frequently contaminated with C. difficile [27]. Fekety et al [22] used a slit-impaction air sampler and failed to isolate C. difficile from the air around patients with CDI but demonstrated extensive environmental and hand contamination. Roberts et al [19] recovered C. difficile from air using a cyclone air sampler in a hospital but did not recover C. difficile from associated environmental surfaces. Our study appears to be the first to recover C. difficile from the air and environment within the same time period and provide confirmation of a link between isolates.

We have shown that C. difficile is commonly (from 7 of 10 patients intensively studied) but sporadically present in the air close to symptomatic patients with CDI. By MLVA, we confirmed the presence of indistinguishable or very highly related strains of C. difficile in the environment, patient fecal specimens, and air. Several studies have confirmed the utility of MLVA for discrimination within C. difficile ribotypes [25, 28], including ribotype 106 (authors’ unpublished data). Thus, our findings help explain the widespread dissemination of C. difficile in the hospital environment, including to infrequently touched or cleaned sites [11–13, 15, 16]. For example, we previously showed that 69% of infrequently touched (“high dust”) surfaces were positive for C. difficile in an elderly medical ward within 6 months of ward opening [29]. We emphasize that without prolonged sampling of air we would have underestimated the sporadic nature of airborne C. difficile dispersal. This may explain the failure of some investigators to detect C. difficile in air [21, 22, 27].

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date tested</th>
<th>Ribotype</th>
<th>MLVA result</th>
</tr>
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<tr>
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<tr>
<td></td>
<td></td>
<td>Feces 106</td>
<td>24-15-22-26-4-2</td>
</tr>
</tbody>
</table>

**NOTE.** MLVA, multilocus variable-number tandem-repeat analysis.

The environmental surface sampling results were consistent with previous studies showing that frequently touched areas are most often C. difficile positive [17, 31, 34]. C. difficile was not recovered from the least-touched areas, such as the light. The patient room door handles were very infrequently found to harbor C. difficile, which presumably reflects the frequent use of hand hygiene practices immediately before entering or leaving rooms. Conversely, C. difficile was recovered from sluice room door handles, likely reflecting contamination by staff disposing of feculent material. It might be expected to recover C. difficile from the patients’ communal bathrooms [17, 31, 34]. However, such facilities were unlikely to be frequented by patients with CDI during this study, because they tended to use en-suite rooms and/or their own commodes. There are some limitations to the present study. C. difficile recovery was generally modest, which may reflect methodological problems or a genuine low environmental microbial burden. The air sampler used was reliant on a slit-to-agar impaction method. A similar study [19] used a machine that recovered airborne material directly into solution but recorded airborne C. difficile counts that were orders of magnitude greater than our results. It is possible that positioning of the air sampler next to a toilet may have partly explained the higher airborne counts of C. difficile [19]. Because we sampled air close to patients for 5-h periods, we had to use the machine contained within a soundproof box and collect samples via an extension tube. The tube may have resulted in a loss of particulate matter collected onto the plates. The practicalities of

[21, 27], Roberts et al [19] recovered C. difficile from the air using a cyclone air sampler in a hospital but did not recover C. difficile from associated environmental surfaces. Our study appears to be the first to recover C. difficile from the air and environment within the same time period and provide confirmation of a link between isolates. We have shown that C. difficile is commonly (from 7 of 10 patients intensively studied) but sporadically present in the air close to symptomatic patients with CDI. By MLVA, we confirmed the presence of indistinguishable or very highly related strains of C. difficile in the environment, patient fecal specimens, and air. Several studies have confirmed the utility of MLVA for discrimination within C. difficile ribotypes [25, 28], including ribotype 106 (authors’ unpublished data). Thus, our findings help explain the widespread dissemination of C. difficile in the hospital environment, including to infrequently touched or cleaned sites [11–13, 15, 16]. For example, we previously showed that 69% of infrequently touched (“high dust”) surfaces were positive for C. difficile in an elderly medical ward within 6 months of ward opening [29]. We emphasize that without prolonged sampling of air we would have underestimated the sporadic nature of airborne C. difficile dispersal. This may explain the failure of some investigators to detect C. difficile in air [21, 22, 27].

We detected airborne C. difficile most commonly during periods of activity, particularly around the busy lunchtime period. These observations suggest that the air within the patient’s immediate environment is contaminated with C. difficile spores either directly from symptomatic patients or from environmental surfaces and that people movement, including the opening and closing of doors, contributes to the circulation and dispersal of airborne C. difficile. It has been demonstrated previously that areas associated with much air movement, such as air vents, are contaminated with C. difficile [29, 30]. These findings have implications for cleaning practices. Unless cleaning is done frequently around symptomatic patients with CDI, including in frequently touched places, reaccumulation of C. difficile will occur on surfaces via the air. Disturbance of already-contaminated articles, such as the bin or bed linen, may contribute to spore aerosolization. It has been demonstrated previously that bed linen can be contaminated [31], and during this study we demonstrated that 3 of 30 bed curtains were culture positive for C. difficile on a ward with 2 confirmed CDI cases (authors’ unpublished data). Therefore, activities known to liberate particles into the air, such as bed making and curtain drawing [32, 33], as well as contact with these items may contribute to the spread and aerosolization of C. difficile.
prolonged sampling close to patients may have caused inconsistencies; for instance, during testing the air sampler or tube may have been moved because of visitors or patient care activities. A further difficulty was the timing and extent of symptoms, particularly because our phase 1 data suggested that air contamination by C. difficile was more likely while diarrhea was occurring. Although we had confirmation that patients were C. difficile toxin positive, we had to rely on health care staff to inform us of symptoms, and so sampling likely occurred at different times relative to the onset of CDI. For future studies, it would be useful to conduct air sampling before (this would also increase sampling of control subjects, which was limited in our study) and during the course of CDI to determine the frequency of C. difficile aerosolization in symptomatic patients.

It remains unclear whether the frequent presence of particular strains in health care environments reflects the burden of CDI caused by epidemic types or whether these have enhanced capacity to persist—for example, because of greater sporulation [30, 35, 36]. Nevertheless, our results suggest that there is a clear risk for C. difficile contamination via the air, particularly in patients with active CDI symptoms. The efficacy of these approaches as a control mechanism for CDI remains unproven. By contrast, the results of the present study do justify the use of single rooms for patients with suspected or proven CDI, even when such resources are limited [8]. In particular, we believe our findings underscore the importance of early patient isolation, as soon as possible after the onset of diarrhea and before laboratory diagnosis of CDI is confirmed. Allowing even a few hours before patient isolation or the wait until laboratory diagnosis is obtained, even with rapid tests, may not be adequate to prevent environmental dissemination of C. difficile via the air. Such a mechanism would at least partly explain the rapid spread and large outbreaks of CDI typified by epidemic strains, such as C. difficile ribotype 027 [1–7]. Recognition of the risk of airborne dissemination provides an opportunity to reduce transmission, especially of epidemic C. difficile strains.

Acknowledgments

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Studies Show Great Variation in Contact Precautions, Impact on Patients and Care Delivery

By Kelly M. Pyrek

*Editor's note: This is a two-part series examining viral size, transmission of disease, and implications for respiratory protection worn by healthcare workers.*

Clinicians and infection preventionists may need to rethink what they currently know about respiratory protection in light of several recent studies indicating that the influenza virus can be carried in smaller particles than previously thought. Additionally, there is debate over airborne transmission and what kind of PPE healthcare workers should don in these situations where exposure is imminent. As Lindsley and Blachere, et al. (2010) explain, "Although influenza is known to be transmitted by infectious secretions, these secretions can be transferred from person to person in many different ways, and the relative importance of the different pathways is not known. The likelihood of the airborne transmission of influenza virus by infectious aerosols is particularly unclear, with some investigators concluding that airborne transmission is a key route, while others maintain that it rarely, if ever, occurs. The question of airborne transmission is especially important in healthcare facilities, where influenza patients tend to congregate during influenza season, because it directly impacts the infection control and personal protective measures that should be taken by healthcare workers. During the 2009 H1N1 pandemic, for example, a United States Institute of Medicine (IOM) panel recommended that healthcare workers in close contact with influenza patients wear respirators to avoid infectious aerosols. This recommendation was subsequently adopted by some health authorities such as the Centers for Disease Control and Prevention (CDC), but not by others, such as the World Health Organization (WHO). The IOM panel also noted that many questions about the airborne transmission of influenza are unresolved, and the issue remains controversial."

One recent study published in the *Journal of Infectious Diseases* suggests that patients with influenza can emit small virus-containing particles into the surrounding air during routine patient care, potentially exposing healthcare providers to influenza. Published in *The*, the findings raise the possibility that current influenza infection control recommendations may not always be adequate to protect providers from influenza during routine patient care in hospitals.

Werner E. Bischoff, MD, PhD, and colleagues from the Wake Forest School of Medicine in North Carolina screened 94 patients for flu-like symptoms during the 2010-2011 influenza season. Study participants had been admitted to the emergency department (52 patients) or an inpatient care unit (42 patients) of Wake Forest Baptist Medical Center, where vaccination for influenza is mandatory for healthcare providers. Nasopharyngeal swabs were collected from each patient. Samples were analyzed by rapid testing and by PCR analysis. Air samples were obtained by placing three six-stage air samplers from within 1 foot, 3 feet, and 6 feet of patients. No aerosol-generating procedures—such as bronchoscopy, sputum induction, intubation, or cardiopulmonary resuscitation—were conducted while air sampling took place. During air sampling, the number of patients’ coughs and sneezes were counted and assessed for severity. Patients also completed a questionnaire at admission to report symptoms and the number of days they were sick.

Of the 94 patients enrolled, 61 patients (65 percent) tested positive for influenza virus. Twenty-six (43 percent) released influenza virus into the air. Five patients (19 percent) emitted up to 32 times more virus than others. This group of patients with influenza, described by the researchers as “super-emitters,” suggested that some patients may be more likely to transmit influenza than others. High concentration of influenza virus released into the air was associated with high viral loads in nasopharyngeal samples. Patients who emitted more virus also reported greater severity of illness.

The current belief is that influenza virus is spread primarily by large particles traveling up to a maximum of 3 feet to 6 feet from an infected person. Recommended precautions for health providers focus on preventing transmission by large droplets and following special instructions during aerosol-generating procedures. In this study, Bischoff and his team discovered that the majority of influenza virus in the air samples analyzed was found in small particles during non-aerosol-generating activities up to a 6-foot distance from the patient’s head, and that concentrations of virus decreased with distance. The study addressed only the presence of influenza-containing particles near patients during routine care, not the actual transmission of influenza infection to others.

As Bischoff, et al. (2013) explain, "Influenza virus can be transmitted by air. Breathing, talking, coughing, and sneezing release influenza virus into air, with sizes ranging from submicron particles (during breathing) to large droplets (during
The Centers for Disease Control and Prevention (CDC), the Institute of Medicine, the European Centre for Disease Control and Control, and the World Health Organization (WHO) have expressed lack of knowledge and the urgent need for research in influenza virus transmission routes. CDC and WHO state that influenza virus transmission primarily occurs by large-particle respiratory droplets traveling within a short distance of the source and that such particles are blocked during encounters between patients and healthcare professionals (HCPs) by face masks worn by HCP." Fit-tested respirators are only required during aerosol-generating procedures such as bronchoscopy. During routine, non-aerosol-generating patient care, the current precautions recommend that providers wear a non-fitted face mask.

The researchers add, "The size of airborne particles determines how influenza virus is transmitted. Large particles (diameter, ≥20 µm) have limited travel distance, while smaller particles (diameter, <5 µm) stay airborne longer and spread widely. We found that up to 89 percent of influenza virus–carrying particles were <4.7 µm in diameter. Notably, no aerosol-generating procedures were undertaken during air sampling. The predominance of small particles has been reported previously, with influenza virus detected in the exhaled breath of 4 of 12 subjects (33%) breathing normally. Although the majority of particles (>87%) were <1 µm in diameter, the sizes containing virus were not identified. The effect of coughing was studied in 47 influenza virus–positive patients. Thirty-eight (81 percent) released influenza virus, with 65 percent of RNA contained in particles <4 µm in diameter. The published data and our findings indicate that small particles carry the majority of influenza virus other than virus released during aerosol-generating procedures. We consider it unlikely that, during routine care, influenza virus is transmitted solely by droplet-sized particles."

Based on their findings, Bischoff and investigators are concerned that providers may still be exposed to infectious dosages of influenza virus up to 6 feet from patients with small wide-spreadening particles potentially exceeding the current suggested exposure zones. These findings suggest that current infection control recommendations may need to be reevaluated, the study authors say.

Another recent study suggests that people may more likely be exposed to the flu through airborne virus than previously thought, according to new research from the University of Maryland School of Public Health. The study also found that when flu patients wear a surgical mask, the release of virus in even the smallest airborne droplets can be significantly reduced.

"People are generally surprised to learn that scientists don't know for sure how flu spreads," says Donald Milton, MD, DrPH, who directs the Maryland Institute for Applied Environmental Health and led the study of influenza virus aerosols published in the journal PLOS Pathogens on March 7, 2013. "Our study provides new evidence that there is nearly nine times more influenza virus present the smallest airborne droplets in the breath exhaled from those infected with flu than in the larger droplets that would be expected to carry more virus," explains Milton. "This has important implications for how we prevent the spread of flu."

Routes of flu transmission include: 1) direct or indirect (e.g., doorknobs, keyboards) contact with an infected person, 2) contact via large droplet spray from a respiratory fluid (via coughs and sneezes), and 3) inhalation of fine airborne particles, which are generated by the release of smaller, virus-containing droplets via normal breathing and coughing. The relative importance of these modes of influenza transmission has not been well understood, but is critical in devising effective interventions to protect healthcare workers and vulnerable people, such as infants and the elderly. The Centers for Disease Control and Prevention (CDC) recommends that persons with influenza wear surgical masks to prevent transmission to susceptible individuals. Yet, this recommendation has been supported so far by only one study of mask impact on the containment of large droplet spray during influenza infection. Maryland's study is the first to provide data showing that using a surgical mask can reduce the release of even the smallest droplets containing infectious virus. For this reason, healthcare facilities should put surgical masks on those suspected of having influenza, and individuals with influenza can protect their families by wearing a mask.

Milton and his research team, including scientists from Harvard and Boston University Schools of Public Health and the University of Hong Kong, collected the exhaled breath from 38 flu patients and tested both the coarse (≥ 5 µm) and fine (< 5 µm) particles for the number of viruses using molecular methods. They found that the fine particles had 8.8 times more virus than the coarse particles (larger but still airborne droplets). They also tested the airborne droplets for "culturable" virus and found that virus was not only abundant in some cases, but infectious. However, there was a big range of how many viruses people put into the air – some were undetectable while others put out over 100,000 every 30 minutes. The researchers also tested the impact of wearing a surgical mask on the virus shedding into airborne droplets. Wearing a surgical mask significantly decreased the presence of virus in airborne droplets from exhaled breath. There was a 2.8 fold reduction in the amount of virus shed into the smallest droplets, and a 3.4 fold overall reduction in virus shed in both the coarse and fine and airborne particles. As Milton, et al. (2013) note, "Surgical masks reduced the overall number of RNA copies by 3.4 fold. These results suggest an important role for aerosols in transmission of influenza virus and that surgical facemasks worn by infected persons are potentially an effective means of limiting the spread of influenza."

The researchers report that when study volunteers were not wearing surgical masks, they detected virus RNA in
coarse particles exhaled by 43 percent and in fine particles exhaled by 92 percent of influenza patients. Milton, et al. (2013) say their findings contrast with a study by Johnson et al. (2009), who detected influenza virus RNA in cough generated large droplet spray from 100 percent of influenza patients over two brief sampling trials, and from 78 percent on each trial. "These discrepant findings are likely due to the very different collection techniques and particle sizes collected in these two studies," the researchers explain. "We used a specially designed aerosol sampler to collect particles from 0.05 to 50 µm in diameter. Johnson et al., by contrast, used simple deposition on petri dishes, and based on particle settling rates and collection times, that method would have been unlikely to collect particles with diameters of less than approximately 50 µm because smaller particles would have remained suspended in air and flowed around the petri dishes. We view results from Johnson et al and the present study as complementary. Together the studies show that surgical masks can limit the emission of large droplet spray and aerosol droplets larger than 5 µm. However, surgical masks are not as efficient at preventing release of very small particles. It is well known that surgical masks are not effective for preventing exposure to fine particles when worn as personal protection. We had hypothesized that when used as source control, exhaled droplets might be large enough prior to evaporation to be effectively captured, primarily through impaction. This appears to be true for virus carried in coarse particles. But the majority of virus in the exhaled aerosol appear to be in the fine fraction that is not well contained. Nevertheless, the overall 3.4 fold reduction in aerosol copy numbers we observed combined with a nearly complete elimination of large droplet spray demonstrated by Johnson et al. suggests that surgical masks worn by infected persons could have a clinically significant impact on transmission. For example if one hypothesized that all transmission were due to aerosol particles <50 µm, and estimated a reproductive number of 1.5 for influenza (i.e. each infection generates 1.5 new infections on average at the start of the epidemic) [19], then the use of surgical masks by every infected case could reduce the reproductive number below 1. Compliance, however, would be a major limitation resulting in lower efficacy in real-world practice." Milton, et al. (2013) add, "While it is generally assumed that large droplets shed from the respiratory tract contain infectious virus, there are limited data that indicate that fine particle aerosols released from the human respiratory tract contain infectious virus. In one previous study by Lindsley et al. (2010), infectious virus was detected in 2 of 21 cough aerosol samples, once with a sampler that did not discriminate between coarse and fine particles and once in the coarse particle fraction of a second instrument. This observation, along with our observation that it was possible to recover culturable virus from the fine-particle fraction using our device demonstrates that humans generate infectious influenza aerosols in both coarse and fine particle fractions. This lends support to the hypothesis that aerosols may be a common pathway for influenza transmission among humans. However, a clear test of the hypothesis requires intervention studies that can interrupt only one mode of transmission without interfering with others."

In that aforementioned study, Lindsley and Blachere, et al. (2010) measured the amount and size of aerosol particles containing influenza virus that were produced by coughing. Subjects were recruited from patients presenting at a student health clinic with influenza-like symptoms. Nasopharyngeal swabs were collected from the volunteers and they were asked to cough three times into a spirometer. After each cough, the cough-generated aerosol was collected using a NIOSH two-stage bioaerosol cyclone sampler or an SKC BioSampler. The amount of influenza viral RNA contained in the samplers was analyzed using quantitative real-time reverse-transcription PCR (qPCR) targeting the matrix gene M1. For half of the subjects, viral plaque assays were performed on the nasopharyngeal swabs and cough aerosol samples to determine if viable virus was present. Fifty-eight subjects were tested, of whom 47 were positive for influenza virus by qPCR. Influenza viral RNA was detected in coughs from 38 of these subjects (81 percent). Thirty-five percent of the influenza RNA was contained in particles >4 µm in aerodynamic diameter, while 23 percent was in particles 1 to 4 µm and 42 percent in particles <1 µm. Viable influenza virus was detected in the cough aerosols from 2 of 21 subjects with influenza. These results show that coughing by influenza patients emits aerosol particles containing influenza virus and that much of the viral RNA is contained within particles in the respirable size range. Lindsley and Blachere, et al. (2010) say their results support the idea that the airborne route may be a pathway for influenza transmission, especially in the immediate vicinity of an influenza patient. They say that additional research is needed on the viability of airborne influenza viruses and the risk of transmission.

Milton, et al. (2013) note that in their study, the lack of strong correlation between the viral load in the nasopharyngeal and aerosol samples may of interest: "This may merely be a result of nasopharyngeal sample variability; in future studies, control for sample quality by PCR of a cellular gene may be helpful. Our sampler, as is the case with all samplers for fine and ultrafine particles, has an upper limit to the size droplet that can be pulled into its inlet airstream. Thus, a second possible explanation for the lack of correlation is that the nasopharynx is primarily a source for very large droplets (>50 µm) that we would not have detected. Furthermore, none of our subjects sneezed; an efficient method of generating droplets from the upper respiratory tract. This may imply that the smaller droplets we detected were generated in the lower respiratory tract and that the viral load at that location is not strongly correlated with the nasopharyngeal load. Alternatively, shedding into aerosol droplets may be driven by other host factors (e.g. asthma, symptom severity, and immune response), co-infection with other agents, virus factors affecting release from the epithelium, or the nature of the
resident microbiome. If shedding into aerosol is determined in large part by the location of infection in the respiratory tract, this may have implications for experimental studies of transmission. Such studies will need to monitor aerosol shedding to determine whether nasal inoculation of donors results in aerosol shedding that mimics naturally acquired infection to validate the experimental design and aid the interpretation of results."

The viral size debate begs the question of what to do about individuals who produce and are able to spread an inordinate number of virus particles. The detection of "super-emitters" raises concerns about how individuals with high viral load may impact the spread of influenza, Bischoff, et al. (2013) emphasize. "Our study offers new evidence of the natural emission of influenza and may provide a better understanding of how to best protect health care providers during routine care activities," the study authors write. However, studies of influenza virus transmission will be necessary before the role of super-emitters can be firmly established, they note.

The issue of super-emitters or super-shedders received attention in 2003-2004 when the rapid spread of severe acute respiratory syndrome (SARS) was aided by "numerous 'superspreading events' in which certain individuals infected unusually large numbers of secondary cases," according to Lloyd-Smith, et al. (2005) who add that superspreading is a normal feature of disease transmission. As Galvani and May (2005) note, "Initial work in this area largely treated individuals in populations as having an equal chance of transmitting disease — that is, as being homogeneous — and ignored stochastic fluctuations in transmission capability. However, studies of gonorrhea and of HIV/AIDS could not explain epidemiological patterns without acknowledging heterogeneities in patterns of sexual-partner acquisition, including the disproportionate influence of superspreaders ... These observations led to the proposal of the 20/80 rule, which suggests that roughly 20 percent of the most infectious individuals are responsible for 80 percent of the transmission. This rule has been applied mainly to helminthic and sexually transmitted diseases; for other directly transmitted diseases, such as smallpox or influenza, heterogeneity in infectiousness has been neglected. The superspreading that seemed to fuel the 2003 SARS epidemic was largely treated as anomalous in most models, but it highlighted the need for a reassessment of heterogeneous infectiousness."

Lloyd-Smith et al.(2005) addressed this point by posing infectiousness as a continuous variable and formulating an unambiguous and universally applicable definition of superspreaders as those who transmit more infection than is predicted by a homogeneous 'null model'. In their study, the researchers analyzed data from eight human infections, including SARS, measles, smallpox, monkeypox and pneumonic plague, to show that superspreading occurs across the board, although to a greater or lesser extent depending on the disease. They indicated that heterogeneity is greatest for SARS and least for Ebola haemorrhagic fever.

References


Q&A With Werner E. Bischoff, MD, PhD

Q: What prompted you to conduct your study?
A: There is only limited knowledge of how influenza is transmitted. Based on the explosive nature of influenza epidemics and pandemics the airborne route appears to play a major role in the transmission of this pathogen.
We decided to determine the virus load present in the environment that healthcare providers are exposed to during their routine care activities. This will help to better understand how we can best protect our healthcare providers against influenza.

Q: Do you believe that there are more “super-emitters” in the patient population/community population than healthcare providers are currently aware of, and how can awareness be raised?
A: The presence of “super-spreaders” has been suggested in other respiratory viruses such as SARS. However, we did not assess transmission but only release of influenza (emission). The transmission aspect needs to be confirmed before the importance of our findings can be determined. If the 20/80 rule of 20 percent of infectious individuals cause 80 percent of infections applies to influenza, our findings may reflect the true percentage of “super-spreaders.” At this point any changes in infection prevention measures including staff behavior should be very carefully considered based on our results.

Q: Should greater attention be paid to measuring viral loads so that these super emitters can be identified more rapidly and precautions be taken? Given the workload of most healthcare providers and crushing workloads on labs, is this even feasible?
A: We looked at factors that may help identify super-emitters. However, due to the small number of these individuals (n=5) none were found. There is also no ‘easy’ laboratory test available. Since rapid identification of super-emitters is currently not available, the feasibility of these measures remains unclear.

Q: Your findings completely upset the long-standing belief that influenza virus is spread primarily by large particles traveling up to a maximum of 3 to 6 feet from an infected person — what was the reaction to your findings in the medical community? Have you seen facilities reconsidering what they formerly presumed about influenza transmission?
A: The main concern regarding our findings was the proof of transmission. We measured emission and subsequent environmental burden of influenza in a care setting but could not address if the viral loads we found at increasing distances from the source actually pose an infection risk. As outlined in our article our study offers new evidence of the transmission dynamics of influenza but requires further research to assess the role of super-emitters and distance in influenza transmission.

Q: In light of your findings, how would you suggest that hospitals approach influenza-transmission prevention strategies? Do you think current clinical thought regarding respiratory protection needs to be revamped?
A: Based on our findings and the new questions posed by it we believe that it would be too early to change influenza-transmission prevention strategies. Our study demonstrated that some influenza patients emit influenza in much higher concentration than others and that the current recommendations regarding distance may need to be revisited. This new evidence will hopefully help to promote additional research and funding opportunities that will build on our findings and answer questions regarding the efficacy of the current prevention and control measures recommended for our healthcare providers.

Q: You say that studies of influenza virus transmission will be necessary before the role of super-emitters can be firmly established – are you and your colleagues planning on conducting a follow-up study? What’s next in your research?
A: We are currently working on follow-up studies looking into the characteristics of super-emitters and also the transmission of live influenza virus over distance. We hope that these projects will shed further light into the way influenza is spread.

Additional Research

NIOSH has undertaken a number of studies to help inform the debate about virus size and transmission.

- Bioaerosol Sampling for the Detection of Aerosolized Influenza Virus
  Coughing, sneezing, talking, and breathing generate an aerosol of airborne particles with diameters that can range from a few millimeters to less than 1 µm. This study investigated the potential for influenza virus to be carried by small particles. Researchers at NIOSH developed a two-stage cyclone bioaerosol sampler that can collect air samples and separate airborne particles into three size fractions (greater than 4 µm, 1-4 µm, and less than 1 µm). Attenuated influenza virus was aerosolized in a laboratory calm-air settling chamber and airborne particles collected with the NIOSH bioaerosol.
The presence of influenza virus laden particles in a healthcare setting. This study addressed the potential for influenza virus to be carried and potentially transmitted by viral-laden particles in a healthcare setting. The researchers concluded that airborne particles were efficiently collected by the NIOSH sampler and 2009 H1N1 influenza and H3N2 influenza virus were predominately found in the 1-4 µm and less than 1 µm size fractions. The viability of the collected virus was not determined.


- Detection of Airborne Influenza in Healthcare Facilities During Influenza Seasons
Two studies measuring the amount of airborne influenza viral RNA in healthcare facilities during influenza seasons were conducted. In 2008 and 2009, air samples were collected from the West Virginia University Hospital's emergency room and urgent care clinic, respectively, to determine the amount and size of airborne particles containing influenza and whether this correlated with the number and location of patients. These studies directly addressed whether influenza is present on respirable particles that could potentially place healthcare workers at risk for infection during influenza outbreaks. Both studies found that the highest concentrations of influenza RNA were detected in locations where, and during times when, the number of influenza patients was highest. The studies also found that 42 percent to 53 percent of the influenza viral RNA was contained in airborne particles less than 4 µm in aerodynamic diameter (the respirable size fraction). Aerosol particles in this size range are of particular concern because they can remain airborne for an extended time and because they can be drawn down into the alveolar region of the lungs during inhalation. The viability of the collected virus was not determined.

References:

- Measurements of Airborne Influenza Virus in Aerosol Particles from Human Coughs
Researchers completed one influenza season measuring the amount and size distribution of aerosol particles containing influenza viral RNA that were produced by influenza patients as they coughed. This study addressed whether influenza patients could potentially place healthcare workers at risk for infection during a routine examination. Results show that influenza patients produce aerosol particles containing measurable amounts of influenza virus while coughing. Further, 65 percent of the viral RNA was contained within particles in the respirable size fraction. Our study was also able to demonstrate that at least some influenza patients expelled airborne particles containing viable virus.


- Cough Aerosol Particles Produced by Influenza Patients During and After Illness
Little is known about the quantity and size of potentially infectious airborne particles produced by people with influenza. Because respiratory infections generally increase airway mucus production, it is typically assumed that aerosol production also increases, but the actual amount of any change is unknown, and it is also unclear whether the particle size distribution of the aerosol is shifted. The purpose of this study was to measure and compare aerosol production by influenza patients while they were ill and after they had recovered. By performing the first direct comparison of respiratory aerosol production during and after illness, these results show more clearly how influenza affects aerosol generation. A better understanding of the effects of influenza on aerosol production will help with efforts to study the potential for the airborne transmission of this illness and to devise interventions to reduce its spread.
Individuals with influenza produce a significantly greater volume of aerosol when ill compared to afterwards. The number of particles produced per cough was also higher when subjects had influenza compared to afterwards, although the difference did not reach statistical significance. The average number of particles expelled per cough varied widely from patient to patient. When the subjects had influenza, an average of 60 percent of the cough aerosol particle volume was in the respirable size fraction, indicating that these particles could reach the alveolar region of the lungs if inhaled by another person. This enhancement in aerosol generation during illness may play an important role in influenza transmission.


Factors Influencing the Transmission of Influenza

The overall purpose of this program is to develop improved methods for the collection and evaluation of virus-laden bioaerosols in order to better characterize the parameters that influence the transmission of the influenza virus. Studies are being conducted to measure and understand the parameters important for the persistence of infectivity of the influenza virus in aerosols. An environmental chamber has been built that contains a cough manikin that "coughs" influenza virus into the room to simulate a patient with influenza, and a breathing manikin to simulate a healthcare worker. The manikins can be outfitted with a mask or respirator to study how well they can protect workers. NIOSH aerosol samplers are used to collect the airborne particles containing influenza virus from the breathing manikin and at locations throughout the room. Specific questions being addressed include; how long does infectious influenza virus remain airborne, what is the distance over which infectious virus can be transmitted, and what is the effect of room temperature and humidity on infectivity of the virus? These studies will better our understanding of the mechanisms of transmission of influenza in occupational settings and directly assess the risk of infection when workers are exposed for short periods to infected individuals in a confined environment.

Extensive testing in the environmental chamber using potassium chloride aerosols indicate that the immediate exposure to aerosol particles from a cough depends on the location of the simulated healthcare worker, but within 5–10 minutes the particles are dispersed throughout the room and the worker is exposed regardless of location. As expected, N95 respirators reduced exposure levels to negligible levels, while surgical masks typically admitted 20 percent of the airborne particles even when the mask was sealed to the breathing machine head. This work has now been expanded to include testing using influenza virus. We have demonstrated that viable influenza was present in all three aerosol fractions collected and that surgical masks sealed to the manikin head admitted approximately 15% of viable virus while N95 respirators further significantly reduced exposure.

References:
Gastrointestinal Flu: Norovirus in Health Care and Long-Term Care Facilities


Once given the diminutive name “small, round structured viruses,” noroviruses have emerged as a growing threat in the community and in health care facilities. Noroviruses are now recognized as the leading cause of viral gastroenteritis, estimated to affect at least 23 million people yearly in the United States alone [1] and to contribute to an expanding number of outbreaks in hospitals and long-term care facilities.

Noroviruses were originally named for the places where they were identified, but these single-stranded, nonenveloped RNA viruses are now grouped within the Caliciviridae family and are classified into 5 genogroups; groups I, II, and IV affect humans. Genogroups are further divided into genotypes (or clusters) and then strains; group I contains ≥8 genotypes, group II contains 17 genotypes, and group IV contains 1 genotype [2, 3]. Characterized by diarrhea, vomiting, abdominal pain, malaise, and, typically, a low-grade fever, norovirus illnesses quickly resolve, most often on their own. However, viral shedding may be protracted [4, 5]. Prolonged asymptomatic shedding, noroviral persistence in the environment, and a low infectious dose contribute to the sustained transmission of these viruses.

Traditionally, the illness caused by this group of viruses has been diagnosed clinically. The Kaplan criteria for diagnosis of presumptive norovirus infection, developed in 1982, include stool cultures negative for bacterial pathogens, vomiting in ≥50% of cases, an incubation period of 24–48 h, and a mean or median illness duration of 12–60 h [6]. Specific diagnosis can be made through use of electron microscopy and ELISA, although these methods lack sensitivity. The benchmark for diagnosis is RT-PCR, developed for norovirus in the 1990s. With this method, the Kaplan criteria have been found to have a sensitivity of 68% and a specificity of 99% [7].

For years, noroviruses have remained under the radar for most clinicians. The inability to culture the virus and the lack of an animal model have restricted research. Surveillance, notably for endemic norovirus disease, is limited, because laboratory diagnosis is currently confined to state and national public health facilities. In addition, acute attacks of gastroenteritis, even when clustered, are frequently not reported to health officials. Because of the difficulty of diagnosing the disease and its lack of perceived morbidity, no national surveillance system for acute gastroenteritis exists in the United States [8]. Despite these limitations, the growing number of reported no-
Although norovirus was originally identified as a cause of gastroenteritis, its significance has grown as it has been recognized as a leading cause of community-acquired gastroenteritis, especially among vulnerable populations such as children, older adults, and immunocompromised individuals. This recognition has highlighted the need for improved surveillance and control measures to prevent norovirus outbreaks, especially in health care facilities, which cannot be ignored.

**Evolving Epidemiology of Norovirus Infection**

**Overall importance of norovirus to enteric disease.** Noroviruses are now recognized as, by far, the most common viral cause of gastroenteritis [8], and given the often short-term symptoms and the lack of easy diagnostic techniques, the number of reported norovirus cases is thought to vastly underestimate the true number of cases. Wheeler et al. [9] note that only 1 case is identified for every 1562 cases that likely exist.

The ability of noroviruses to persist in the environment for at least 12 days allows many unreported norovirus outbreaks to occur in health care settings. Outbreaks in hospitals, nursing homes, and long-term care facilities can be very difficult to contain and can lead to significant morbidity and mortality, especially in vulnerable populations.

**Increase in outbreaks and emergence of new viral strains.** Although surveillance for norovirus is incomplete, available data suggest that outbreaks of norovirus infection are increasing [8]. Although multiple norovirus outbreaks are often dominated by 1 strain, new ones are frequently identified and tracked using PCR [13]. Noroviruses replicate only in the gastrointestinal tract and are highly adaptable, evolving mostly by antigenic drift (and sometimes recombination) that leads to changes in viral capsid protein binding to oligosaccharides on host gut mucosal surfaces [15]. As a result, new norovirus strains, all GII.4 (genogroup II, genotype 4) viruses, were responsible for pandemics in 1995–1996 (US95/96 norovirus strain), 2002 (Farmington Hills strain), 2004 (Hunter strain), and 2006 (2006a/Minerva and 2006b/Laurens strains). Typically, additional local epidemics also occur because of other norovirus genogroups/genotypes [3, 8, 13, 16, 17]. This link between outbreaks and new norovirus variants was elucidated, in part, by data collected in Europe that demonstrated a marked increase in outbreaks of norovirus infection in 2002 that coincided with the emergence of a new variant, first noticed in Germany and The Netherlands and later found to have spread throughout continental Europe and beyond [17]. This pattern represents a recurring theme—new norovirus variant, new epidemic wave—in norovirus epidemiology. Antigenic drift or recombination resulting in the emergence of new norovirus strains suggests that the kindred spirit of noroviruses is the influenza virus, well known for antigenic drift and reassortment that yields epidemic and pandemic disease.

Increasing outbreaks of norovirus disease have fueled international efforts to improve surveillance. The European Foodborne Viruses Network collects epidemiological and molecular data from 13 European countries. As of 2008, the Centers for Disease Control and Prevention is requesting reports of all acute gastroenteritis outbreaks through the National Outbreak Reporting System, whereas previously, only data on food-borne outbreaks were collected [8]. It is expected that this request for voluntary reporting will help provide a national estimate of norovirus disease. The Centers for Disease Control and Prevention has also developed Calicinet, a centralized database of different norovirus sequences, intended to help determine links between outbreaks. Improved surveillance may well impact public health; for example, there is evidence that cruise-ship outbreaks might predict winter norovirus outbreaks and could be used as an early warning system [18].

**Increased outbreaks in nursing homes and long-term care facilities.** Although norovirus was originally identified as a cause of community-associated gastroenteritis [19], it is now clear that 30%–50% of outbreaks occur in closed facilities, such as hospitals, retirement centers, and nursing homes [8, 13, 20]. Additional analysis of acute gastroenteritis outbreaks reported to the Centers for Disease Control and Prevention during 2000–2004 indicated that an additional 28% of outbreaks occurred in restaurants and catered-meal events, 16% on cruise ships, and 8% in day care centers [13]. The GII.4 strain, in particular, has gained importance in outbreaks in closed institutions, where transmission appears to often occur by person-to-person contact [13, 20]. The reason for the GII.4 predominance is unknown but has been thought to be attributable to enhanced environmental stability of these strains and/or decreased herd immunity that promotes their transmissibility.

**Increased illness severity?** It is unclear how variable the virulence of noroviruses is. The Farmington Hills strain demonstrated higher attack rates and longer persistence on cruise ships than do other strains, although this difference did not reach statistical significance [16]. The GII.4 variant strain that affected Europe in 2002 was associated with excess deaths; however, this could be attributed to its predominance among hospital and nursing home residents [17], where individuals might have been more vulnerable than the general population. Norovirus gastroenteritis, although generally a mild, self-limited disease, can be less benign when patients are older; recently, confirmed norovirus-associated mortality has been recognized in long-term facilities in the United States [8]. Illnesses among hospital inpatients and even in the community are frequently reported to last 5 days [4, 21]. Additional data suggest that noroviruses may trigger severe outcomes in some hosts, such as older or immunocompromised patients or those with cardiovascular disease. Complications may include acute renal fail-
Although norovirus is ∼ Downloaded from http://cid.oxfordjournals.org/ A little norovirus goes a long way. Less

HIGHLY TRANSMISSIBLE. A little norovirus goes a long way. Less than 10–100 virions can be enough to infect a healthy adult

MULTIPLE MODES OF TRANSMISSION. Norovirus transmission occurs by food, water, and airborne routes, as well as incidental hand contact with contaminated surfaces or fomites and through person-to-person contact. It is primarily fecal-oral contamination that drives the spread of norovirus. Estimates suggest that one-half of all outbreaks of food-borne infection in the United States are caused by norovirus [27]. Large outbreaks have implicated oysters, raspberries, and water, among other vehicles [28–30]. As another example, a single ill employee contaminated 76 L of iced coffee distributed on various baked goods, which resulted in ∼3000 outbreak-associated cases of norovirus infection over 4 days [31]. The potential for food-borne spread extends to the global economy of food distribution, as evident by reports of recent norovirus outbreaks in Australia that were traced to oysters imported from Japan [32].

It is now recognized that vomiting with airborne norovirus dispersion is an important route of virus dissemination. An analysis of an outbreak in a large hotel demonstrated that victims’ attack rates were inversely related to their distance from a woman who vomited during her meal [33]. An outbreak in an elementary school demonstrated that attack rates were directly related to the number of times pupils were exposed to vomiting episodes, suggesting that spread occurred by the inhalation and swallowing of viral particles [34]. Transmission has even occurred to individuals walking through an emergency department in which a vomiting patient was being evaluated [35].

Although aerosol spread may initiate an outbreak, continued propagation of a norovirus disease outbreak can, in some instances, be attributed to the role of subsequent environmental or fomite contamination [26]. For example, in a concert hall-linked outbreak in Wales involving 300 people, the epidemic investigation suggested a point source outbreak initiated by an attendee who had vomited in the auditorium, with continued case accumulation through environmental contact by people coming to the concert hall over several subsequent days [36].

Health care facilities, in particular, are susceptible to environmental and fomite contamination. Sampling swabs taken from a pediatric intensive care unit demonstrated norovirus to be the most common virus detected, present in 18% of swabs, most frequently from such sites as toilet door handles and toilet taps that are readily soiled with minute amounts of feces [37]. Swabbing of environmental surfaces in a long-term care veterans facility a full 2 weeks after the peak of a norovirus outbreak demonstrated norovirus on toilet seats, a bed rail, a dining table, and an elevator button, even after extensive cleaning of the facility [38].

Finally, person-to-person transmission occurs. During a collegiate football game in Florida, numerous members of the visiting North Carolina football team became ill, presumably from contaminated turkey sandwiches that they had eaten from box lunches the day before. The day after the football game, despite not having shared any food, members of the Florida team became ill as well [39]. Person-to-person contact is especially important in the health care and long-term care settings, where close living quarters, shared bathrooms, and incontinent patients increase the risk that norovirus can spread from one person to another. Prospective studies of >170 inpatient units in England demonstrated that outbreak rates increased with the number of beds in a unit and shorter lengths of stay and were especially high in geriatric and general medical care units [40].

HIGHLY RESISTANT TO DISINFECTANTS. Although norovirus is easy to spread, it is much more difficult to remove. Simple detergent cleaning is not sufficient to remove norovirus from fomites or surfaces. Experiments suggest that clean surfaces are obtained only after wiping the surface first with a detergent to remove particulate debris and then applying hypochlorite bleach at 5000 ppm as a disinfectant. Other disinfectants, such as quaternary ammonium compounds or alcohols, are not as effective in removing norovirus [26, 34]. Recent outbreak management provides evidence of the importance of appropriate disinfectant use. When illness continued in a Michigan restaurant in 2006, public health workers discovered that a quaternary ammonium–based sanitizer had been used, and it was not until a bleach solution was used that the restaurant could reopen [11]. New disinfectants, mainly peroxygen compounds, exhibit enhanced activity and appear promising [41]. Proper hand washing—using liquid soap and water for 1 min, rinsing for 20 s, and drying with disposable paper towels—is recommended to eliminate noroviral hand contamination [26].

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Because there are multiple, common sources of virus transmission, the key to management is use of a multidisciplinary and comprehensive prevention-and-control strategy that encompasses all potential transmission modes. Airborne transmission of norovirus has been reported. The measures proposed to prevent and contain spread of norovirus in this table also apply if airborne transmission of norovirus is considered to be possible. Some experts may recommend masks while in the rooms of actively vomiting patients. 

### Table 1. Prevention and control of norovirus in health care facilities.

<table>
<thead>
<tr>
<th>General</th>
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<tbody>
<tr>
<td>Ensure hand hygiene: experiments demonstrated that virus could no longer be identified on hands that had been washed with soap and water for 1 min, rinsed for 20 s, and dried with disposable paper towels [26]; visitors to long-term facilities should be instructed about proper hand washing techniques as well.</td>
</tr>
<tr>
<td>Ensure that all individuals clean their hands before eating or drinking, after using the bathroom, or after contact with an ill patient.</td>
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<tr>
<td>Do not share equipment between affected and unaffected patients.</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Person-to-person contact</th>
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<tbody>
<tr>
<td>First tier: single case or cluster without single source</td>
</tr>
<tr>
<td>Always use standard precautions.</td>
</tr>
<tr>
<td>Immediately implement contact precautions for anyone with suspected norovirus until patient has been asymptomatic for 48–72 h.</td>
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<tr>
<td>Isolate ill patients in single rooms or cohort together.</td>
</tr>
<tr>
<td>Prevent visitation of any sick visitors through use of signs, and perform active screening for symptomatic patients.</td>
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<tr>
<td>Identify and furlough sick employees for 48–72 h after symptoms have resolved.</td>
</tr>
<tr>
<td>Eliminate sharing of food and drinks.</td>
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<tr>
<td>Second tier: transmission after implementation of tier 1</td>
</tr>
<tr>
<td>Cohort staff members and employees to limit contact with ill patients.</td>
</tr>
<tr>
<td>Screen employees who are exposed and potentially incubating infection with rapid furlough if signs of infection develop.</td>
</tr>
<tr>
<td>Assign unexposed employees to work with unexposed patients.</td>
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<tr>
<td>Third tier: ongoing transmission after implementation of tier 2 recommendations</td>
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<tr>
<td>Consider closure of entire units or facilities if initial measures do not prevent additional transmission.</td>
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<th>Transmission by food and water</th>
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</thead>
<tbody>
<tr>
<td>Ensure clean water supply and proper food preparation, storage, and serving.</td>
</tr>
<tr>
<td>Comply with US FDA guidelines 2005 [25].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean spills with detergent to remove particulate matter, then disinfect with hospital-approved disinfectant.</td>
</tr>
<tr>
<td>Disinfect with a solution of a minimum of 1:50 hypochlorite (bleach) to water of all high-touch surfaces (e.g., doorknobs, light switches, tables, counter tops, computer keyboards) frequently (e.g., every shift).</td>
</tr>
<tr>
<td>Clean bathrooms every shift, with special attention to toilets and fixtures.</td>
</tr>
<tr>
<td>Clean common areas and staff rooms, including refrigerators and freezers.</td>
</tr>
<tr>
<td>Clean rooms every 24 h and on patient discharge; walls, windows, beds, chairs, ledges should be included in this process.</td>
</tr>
<tr>
<td>Provide different toilet facilities for ill and nonill patients.</td>
</tr>
<tr>
<td>Remove all supplies from a room before an infected patient is housed in the room; any supplies left in these rooms after the infected patient's release should be discarded.</td>
</tr>
<tr>
<td>Clean floors with approved disinfectant, and change solution and mop head every 3 rooms.</td>
</tr>
<tr>
<td>Clean rooms that have housed patients who vomited and/or had diarrhea after all other rooms have been cleaned; ensure that the mop head and solution are changed after cleaning rooms of infected patients.</td>
</tr>
<tr>
<td>Remove and replace curtains if soiled or contaminated.</td>
</tr>
</tbody>
</table>

**NOTE.** Because there are multiple, common sources of virus transmission, the key to management is use of a multidisciplinary and comprehensive prevention-and-control strategy that encompasses all potential transmission modes. Airborne transmission of norovirus has been reported. The measures proposed to prevent and contain spread of norovirus in this table also apply if airborne transmission of norovirus is considered to be possible. Some experts may recommend masks while in the rooms of actively vomiting patients. 

on alcohol-based cleansers suggest that they are insufficient for noroviral disinfection. Feline calicivirus, a surrogate for norovirus, is incompletely decontaminated with alcohol-based cleansers, although a 95% ethanol hand rub was superior to a 70% hand rub in disinfecting calicivirus [42]. Of note, common hospital hand rubs contain an alcohol content of only 60%–62%. No studies address whether increased hospital use of alcohol hand rubs is permissive in the persistence of norovirus outbreaks.

**Determinants of host susceptibility to norovirus infection.** Despite the impressive transmissibility of noroviruses, not everyone is susceptible to norovirus infection. Overall, symptomatic attack rates in outbreaks infrequently exceed 70% whereas 70%–90% of individuals may exhibit serological evidence of prior norovirus infection [43]. Together, these observations and other data suggest that a small subset of individuals are absolutely resistant to norovirus infection, whereas another subset may acquire only asymptomatic infection. The host determinants of norovirus resistance are complex and incompletely defined. Individuals who are secretor-status positive for histoblood group antigens that are also displayed on mucosal surfaces are susceptible to norovirus infection, because histoblood group antigens serve as receptors for most, but not all, noroviruses [14, 43]. Blood group antigen status (O, A, B, or AB) also affects the host-norovirus interaction, at least for genotype I noroviruses [43–45]. Individuals with an O phenotype more often have symptomatic infection with genotype I noroviruses than do those with a B phenotype, who experience less clinical.
morbidity. Individuals infected with noroviruses likely develop both humoral and cellular immune responses, but these do not necessarily constitute protective immunity against subsequent norovirus infection [46]. The difficulty of understanding what comprises protective immunity to noroviruses is compounded by the ever-changing diversity of noroviruses, with display of antigen epitopes that may or may not induce cross-protective immunity to other noroviral strains. Short-term immune protection to homologous viral strains has been shown in volunteer studies [43]. Thus, it seems that most individuals can expect to acquire multiple, symptomatic norovirus infections in a lifetime.

WHAT APPROACHES WILL INTERRUPT NOROVIRUS SPREAD?

Challenges and costs of norovirus outbreak containment.

A nosocomial outbreak of norovirus at Johns Hopkins Hospital involving >500 patients and health care workers illustrated some of the strategies and challenges in containing the virus within the hospital setting [47]. When the outbreak was recognized, disinfection and isolation protocols were instituted, and asymptomatic health care workers were instructed to stay home for 72 h after symptoms resolved, consistent with 2005 Federal Food Code and Michigan guidelines for norovirus control (see below) [8, 11, 25]. However, ongoing cases prompted more-stringent measures, including the prohibition of visitors, cohorting of nursing staff, universal use of gowns and gloves in affected units, and cessation of new admissions to the involved hospital unit. Even group therapy sessions in the affected psychiatric unit were halted. Similarly, in several norovirus disease outbreaks in English hospitals, prevention and control measures were rapidly escalated, and units were closed within 3 days, resulting in outbreaks being shortened by a startling 7.5 days, which suggests the need, at times, for seemingly extreme containment measures [48]. Hospital-based norovirus disease outbreaks are expensive. The Johns Hopkins Hospital outbreak cost an estimated $650,000 for the 946-bed hospital [47]. Outbreaks in the United Kingdom have been estimated to cost $1 million per 1000 hospital beds [48].

Outbreaks of norovirus gastroenteritis on cruise ships prove equally difficult to control and may continue on consecutive cruises, despite cleaning measures [10, 16]. This has been attributed to inadequate disinfection, shedding of virus by asymptomatic crew members, and repeated introduction of noroviruses as new passengers and crew members board the ships. This flow of people might be compared to an emergency department; therefore, hospitals, like these ships, are at high risk of acquiring new viruses.

A multistrain outbreak of norovirus gastroenteritis in a Houston, Texas, shelter during the aftermath of Hurricane Katrina (2005) proved extremely difficult to control because of the close quarters among evacuees, insufficient toilet and hand hygiene facilities, and an inability to cohort symptomatic patients and to separate exposed from unexposed individuals, as well as delayed cleaning. Together, these factors resulted in ongoing transmission until the shelter was closed [49]. Although public health measures require separation and isolation of sick people, the reality of separating family members after such a traumatic experience made this intervention untenable.

**Recommendations for prevention and control of norovirus.**

Prevention and control efforts should focus on the potential transmission modes suggested by the epidemiologic investigation. For example, the recognition of increasing food-borne outbreaks in Michigan with enhanced severity prompted officials to amend their Food Laws, adopting and strengthening the recommendations contained in the 2005 Federal Food Code for norovirus control [8, 11, 25]. Included in the Michigan rules are instructions for employees to wash their hands with warm running water and soap, exclusion from work until asymptomatic for 48–72 h, and, on return to work, further restriction from handling kitchenware and ready-to-eat foods for an additional 72 h. Vomiting incidents in food establishments are to be treated as emergencies that require discarding anything potentially contaminated by vomitus and cleaning with diluted bleach (1/10–1/50 dilution) the area (a 7–8-m radius) of the vomiting incident. Depending on where vomiting occurred, restaurant or bathroom closure is to be considered to be a public health containment measure. The recommendations to exclude infected employees from work for at least 48–72 h is based on older data that suggest that viral shedding ceases within 100 h after symptom resolution [50]. Recent data, in contrast, suggest that protracted norovirus excretion may occur after illnesses, lasting a median of 28 days, with ~10^4 viral copies/g of stool [5]. The precise contributions of person-to-person spread, environmental contamination, and/or other factors to ongoing transmission in outbreak situations are unclear.

On the basis of prior efforts to prevent and control norovirus epidemics, we make recommendations for containment of outbreaks in health care and long-term care facilities, as specified in table 1. The proposed interventions target the various means by which the virus spreads and aim to prevent the introduction, dissemination, and continuation of norovirus transmission. As learned at our institution [47], aggressive interventions at the onset of an outbreak are likely necessary to reduce both morbidity and cost. Norovirus will continue to evolve and likely evade the host immune response. Therefore, combating this common infection requires marked diligence to public health education and infection-control measures. Vigilance in surveillance, isolation, and disinfection is required to keep our health care and long-term care facilities free of noroviruses and to protect those who are most vulnerable.
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Potential conflicts of interest. All authors: no conflicts.

References

Air and surface contamination patterns of meticillin-resistant *Staphylococcus aureus* on eight acute hospital wards

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**ZUSAMMENFASSUNG**


Ziel: Untersuchung der Beziehung zwischen MRSA Isolaten nachgewiesen in der Luft und auf Oberflächen mit jenen bei Patienten durch intensive Testreihen in der Umgebung und bei Patienten


Ergebnisse: MRSA wurde bei 30/706 (4,3%) der Patienten und in 19/132 (14,4%) der Luftproben nachgewiesen. In 9/132 (6,8%) der Fälle enthielten sowohl die Probe des Patienten als auch der Luft MRSA. In den 32 getesteten Räumen der Intensivüberwachung wurde MRSA bei 12/161 (7,4%) der Patienten, 8/32 (25%) der Luftproben und 21/644 (3,3%) der Oberflächenentnahmen gefunden.

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Introduction

Numerous studies have shown that the hospital environment is frequently contaminated with potential pathogens that pose a risk of cross-transmission to patients.1,2 Meticillin-resistant *Staphylococcus aureus* (MRSA) can survive for long periods on environmental surfaces, and may be transmitted to patients via healthcare workers’ hands or the environment.3,4 Studies on MRSA in the environment have mostly related to outbreaks, intensive care units (ICUs), or isolation rooms with MRSA patients, rather than in routine ward areas over a period of time.5–9 There is relatively little information on the dispersal of airborne MRSA and this may be an often underestimated method of transmission that results in clusters or outbreaks. It is not clear what impact MRSA in the environment and in air may have on patient acquisition and cross-transmission, and many studies involving the sampling of air in the vicinity of patients have been one-off investigations. Previous studies have strongly suggested or confirmed the transmission of bacteria by air, especially when carriers of *S. aureus* have viral infection.10,11 However, the extent to which MRSA may be recovered from the air and how commonly this occurs in an acute hospital outside of an outbreak are unclear.

The current study describes the pattern of MRSA recovered from air and surfaces on a number of wards where MRSA is endemic over a period of time, and investigates patient and environmental links using spa typing and DNA microarray profiling of isolates.

Methods

Patients

The study was conducted on patients and their environment on eight wards, four general surgical and four general medical, in a 700-bed tertiary referral acute care hospital during 2010–2011. The study was undertaken as part of a larger study of MRSA that was approved by the Hospital Ethics (Medical Research) Committee. Patient and environmental sampling were conducted on a scheduled basis, and were not in response to an outbreak investigation. Bed occupancy was ~ 100%.

Sampling was carried out accordingly in three ways. First, sampling was conducted on 132 occasions on eight wards between March 2010 and February 2011. From March to June 2010, eight wards were sampled successively; three wards were sampled once, and five were sampled twice. From September 2010 to February 2011, the patients and the environment of four wards were each sampled for 4 weeks consecutively. Patient screening involved the taking of swabs from the nose, groin and non-intact skin/wound if available (n = 706), with one air sample taken in each ward bay.

Second, on 32 occasions, extended environmental sampling was conducted in the immediate area of patients in two high-dependency bays (HDBs) on eight wards, where more vulnerable and sicker patients are cared for. Patients were screened for MRSA on study wards as previously described.12,13 At-risk patients were those as defined in national guidelines, i.e. patients known to be previously MRSA positive, patients transferred from another hospital or a long-term care facility, patients with chronic ulcers or urinary catheters, and patients who had been hospitalized within the last 18 months.1 Environmental sampling involved surface sampling of each patient’s mattress, pillow, bed rail or bed frame and locker. In addition, a settle-plate was placed on each patient’s locker and one air sample was collected at the window-ledge of each ward bay.

Third, air sampling was conducted on HDBs at different times over a 24 h period: 07:30–09:00, 09:30–11:30, 14:00–16:00, 17:00–19:00, and 20:00–22:00 h, but without simultaneous patient sampling. However, during this study phase, routine ward screening revealed no MRSA-positive patients in the HDBs during these periods of sampling. No area sampled had any form of artificial ventilation. Cleaning was performed daily by the cleaning services, using water and detergent. A hypochlorite, 1000 ppm available chlorine, was used for MRSA and other infected/contaminated patients. Terminal decontamination of the bed and bed area after a patient’s discharge of the bed and bed area was performed by a designated cleaning team.

Air and environmental surface sampling

Samples of air (1000 L) were taken using an impact air sampler (AES Chemunex Air Sampler, Department SAV, Rue Maryse Bastié–Ker Lann, 35172 BRUZ cedex, France) with MRSASelect chromogenic agar (CA) plates (Bio-Rad Life Science Group, Marnes La Coquette, France) which was placed on the ledges of outer wall windows in ward bays. CA settle plates were also placed on patients’ lockers for 1 h. Neutralizing buffer swabs (Technical Services Consultants, Heywood, UK) were used to sample mattresses, pillows, bed rail or bed frames and patient lockers. An area, 10 × 10 cm, of each surface was sampled. In addition, mattresses were assessed by sweeping a CA plate over the surface of the mattress. Most wards consisted of 35 beds, each with one four-bedded and one six-bedded HDB, three other six-bedded bays, one two-bedded bay and five single rooms (Figure 1a). HDBs mainly comprised of four-bedded (wards A) or six-bedded (wards B) ward bays, but one ward had a five-bedded bay. The environmental sampling sites were those immediately associated with the patient’s bed area and are shown in Figure 1b. All environmental swabs were enriched in tryptone soy broth with 6% (w/v) NaCl (TB055-100, Cruinn Diagnostics, Dublin, Ireland) and incubated at 37 °C for 18 h. These were subsequently subcultured on to CA and incubated along with settle plates and sweep plates for 24 h at 37 °C. Presumptive MRSA was confirmed by coagulase and clumping factor production using Staphaurex Plus (Remel, Dartford, UK) and meticillin resistance determination using.
oxacillin minimum inhibitory concentration (MIC) evaluator strips (Oxoid, Basingstoke, UK) and detection of resistance with cefoxitin, 30 μg discs (Oxoid).

Molecular typing

spa typing was carried out on one isolate per MRSA-positive patient and/or the patients’ environment in the HDBs using the European Network of Laboratories for Sequence Based Typing of Microbiol Pathogens and amplicron sequencing was performed by Source BioScience (Guinness Enterprise Centre, Dublin, Ireland). Where two sampling methods (e.g. swab and sweep-plate) were MRSA-positive from mattress sampling, only one MRSA isolate was included in the analysis. DNA microarray profiling was performed using the StaphyType Kit (Alere, Jena, Germany) on all except two of the isolates that underwent spa typing; these two isolates were not available for DNA microarray profiling. The StaphyType Kit detects 334 S. aureus gene sequences and alleles including typing and species-specific markers as well as virulence-associated and antimicrobial resistance genes. DNA microarray procedures were performed according to the manufacturer’s instructions.

Statistical analysis

Statistical analysis was performed using Epi Info 6 (version 6.04c; Centers for Disease Control and Prevention, Atlanta, GA, USA) and odds ratios were calculated. The Mantel–Haenszel chi-square method was used to assess the significance of the difference between proportions.

Results

Patient and air sampling

Overall, 30/706 (4.3%) patients and 19/132 (14.4%) air samples yielded MRSA (Table I). Two of the 30 MRSA-positive patients had infections; the remainder were colonized only. On 9/132 (6.8%) sampling occasions both patient and air...
samples were MRSA positive, but on 10/132 (7.6%) occasions, air samples yielded MRSA but no MRSA-positive patients were identified. When four wards were sampled consecutively for a 4-week period, MRSA was isolated on week 1 (five patients, two air samples), week 2 (four patients, two air samples), week 3 (one patient, no air samples), and week 4 (two patients, one air sample). Three of the five air samples were linked to an MRSA-positive patient in a specific ward bay.

Environmental sampling on 32 occasions in high-dependency bays

MRSA was recovered from 9/85 (10.6%) male and 3/76 (4%) female patients on nine environmental sampling occasions resulting in 12/161 (7.4%) positive patients. MRSA was recovered from 8/32 (25%) air samples, from 12/161 (7.5%) settle plates and from 21/644 (3.3%) surface environmental sites. On five occasions, MRSA was isolated from two patients in a ward bay. Ten of 161 (6.2%) mattresses, 2/161 (1.2%) pillows, 3/161 (1.9%) bed rail/frames and 6/161 (3.7%) bedside lockers yielded MRSA. MRSA was isolated from at least one sample (patient or environment) on 16/32 (50%) occasions. On 2/32 (6.3%) occasions, MRSA was recovered from one or more patients as well as from air samples, settle plates and one or more environmental surface sites. For three of 12 MRSA-positive patients, MRSA was recovered from the patient’s mattress, plus the locker for another patient, from the mattress and locker for another patient, and from the mattress, bed frame and pillow of another patient. Two of these MRSA-positive patients were associated with extensive contamination (ward 2 in June 2010 and ward 7 in January 2011). Patient risk factors for the 12 MRSA patients included previous MRSA (1/12), transfer from another hospital (1/12), the presence of a urinary catheter (3/12) and admission within the previous 18 months (7/12). MRSA patients included previous MRSA (1/12), transfer from another hospital (1/12), the presence of a urinary catheter (3/12) and ward 7 in January 2011. Patient demographic data combined with spa typing and DNA microarray profiling suggested four clusters, where closely related MRSA was isolated from one or more patients and their environment or from two or more patients without any environmental sites positive for MRSA (Table II). The first of these was on 6th November 2010 and involved 19 spa type t557 isolates from three patients with 16 environmental sites in two bays of ward 2; these isolates all yielded indistinguishable DNA microarray profiles. The second spa typing cluster was recovered on 14th June 2010 and involved two spa type t032 isolates from two patients in two ward bays of ward 3; these isolates differed by one gene combination only using the DNA

Air sampling over a 24 h period

Thirteen of 128 (10%) air samples in HDBs yielded MRSA: 7/32 (22%) between 07:30 and 09:00; 3/32 (9%) between 09:30 and 11:30; 1/32 (3%) between 14:00 and 16:00; 0/16 between 17:00 and 19:00; and 2/16 (13%) between 20:00 and 22:00. Significantly more MRSA-positive samples were recovered between 07:30 and 09:00 compared with other times [i.e. 7/32 (22%) versus 6/96 (6%); odds ratio: 4.20; 95% confidence interval: 1.13–15.81; \( P = 0.01 \)].
Table II
The distribution of MRSA recovered from patients, air, settle plates and environmental surfaces on 32 occasions of high-dependency bays with spa typing of 42/52 isolates and DNA microarray profiling of 40/52 isolates

<table>
<thead>
<tr>
<th>Date</th>
<th>Ward</th>
<th>Bay</th>
<th>Patients</th>
<th>Air sampling</th>
<th>Air settle plates</th>
<th>Surface environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n/total)</td>
<td>(n/total)</td>
<td>(n/total)</td>
<td>(n/total)</td>
</tr>
<tr>
<td>08/06/10</td>
<td>1</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>1/4</td>
<td>0/16</td>
</tr>
<tr>
<td>08/06/10</td>
<td>1</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>2/24</td>
</tr>
<tr>
<td>11/06/10</td>
<td>2</td>
<td>Bay A</td>
<td>3/6</td>
<td>1/1</td>
<td>3/6</td>
<td>10/24</td>
</tr>
<tr>
<td>11/06/10</td>
<td>2</td>
<td>Bay B</td>
<td>0/6</td>
<td>1/1</td>
<td>1/6(^c)</td>
<td>1/24</td>
</tr>
<tr>
<td>14/06/10</td>
<td>3</td>
<td>Bay A</td>
<td>1/4 (^d)</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>14/06/10</td>
<td>3</td>
<td>Bay B</td>
<td>1/5</td>
<td>0/1</td>
<td>0/5</td>
<td>0/20</td>
</tr>
<tr>
<td>16/06/10</td>
<td>4</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>16/06/10</td>
<td>4</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>23/06/10</td>
<td>5</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>1/16</td>
</tr>
<tr>
<td>23/06/10</td>
<td>5</td>
<td>Bay B</td>
<td>0/6</td>
<td>1/6</td>
<td>1/6</td>
<td>2/24 (^c)</td>
</tr>
<tr>
<td>28/06/10</td>
<td>6</td>
<td>Bay A</td>
<td>1/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>28/06/10</td>
<td>6</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>20/09/10</td>
<td>1</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>20/09/10</td>
<td>1</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>27/09/10</td>
<td>1</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>27/09/10</td>
<td>1</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>04/10/10</td>
<td>1</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>04/10/10</td>
<td>1</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>18/10/10</td>
<td>5</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>18/10/10</td>
<td>5</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>26/10/10</td>
<td>5</td>
<td>Bay A</td>
<td>1/4</td>
<td>1/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>26/10/10</td>
<td>5</td>
<td>Bay B</td>
<td>2/6 (^*)</td>
<td>1/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>08/11/10</td>
<td>5</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>08/11/10</td>
<td>5</td>
<td>Bay B</td>
<td>0/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>04/01/11</td>
<td>7</td>
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<td>0/4</td>
<td>1/1</td>
<td>1/4</td>
<td>0/16</td>
</tr>
<tr>
<td>04/01/11</td>
<td>7</td>
<td>Bay B</td>
<td>1/6</td>
<td>1/1</td>
<td>5/6</td>
<td>5/24</td>
</tr>
<tr>
<td>10/01/11</td>
<td>7</td>
<td>Bay A</td>
<td>0/4</td>
<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>10/01/11</td>
<td>7</td>
<td>Bay B</td>
<td>0/6</td>
<td>1/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td>31/01/11</td>
<td>8</td>
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<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
<td>31/01/11</td>
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<td>0/1</td>
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<td>0/24</td>
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<tr>
<td>21/02/11</td>
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<td>0/1</td>
<td>0/4</td>
<td>0/16</td>
</tr>
<tr>
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<td>Bay B</td>
<td>1/6</td>
<td>0/1</td>
<td>0/6</td>
<td>0/24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8</strong></td>
<td><strong>32</strong></td>
<td><strong>12/161(7.5%)</strong></td>
<td><strong>8/32(25%)</strong></td>
<td><strong>12/161(7.5%)</strong></td>
<td><strong>21/644(3.3%)</strong></td>
</tr>
</tbody>
</table>

\(^a\) Wards 1-8

\(^b\) Mattress, pillow, bedrail/frame or locker.

\(^c\) One isolate not spa typed.

\(^d\) Using DNA microarray, one t032 spa type isolate lacked the sec & sel gene cluster

\(^e\) Total 2/6 isolates MRSA-positive, one t515 spa type, one t022

Cell shading indicates the combined spa types and DNA microarray profiles of isolates within the four clusters;

- **spa type t557; DNA microarray profile blaZ, erm(C), sec & sel, egc and IEC B**
- **spa type t515, DNA microarray profile blaZ, erm (C), egc and IEC B**
- **spa type t032, DNA microarray profile blaZ, erm (C), sec & sel, egc and IEC B**
microarray and are considered to be closely related. The next spa typing cluster was recovered on 26th October 2010 and again involved two spa type t032 isolates, one recovered from a patient and the other from an environmental site of ward bay A on ward 5; these isolates exhibited indistinguishable DNA microarray profiles. The final spa typing cluster involved 12 spa type t515 isolates recovered on 1st April 2011 and involved one patient and 11 environmental isolates on ward A; again these isolates exhibited indistinguishable DNA microarray profiles. Three of four other environmental isolates yielded indistinguishable spa (t515) and microarray pattern profiles, on 23rd June 2011, in two bays of ward 5. However, no positive MRSA patients were identified as being epidemiologically associated with these isolates.

Discussion

MRSA is endemic in most Irish hospitals and this study was part of a programme of research to determine whether current methods of screening underestimate the extent of MRSA colonization and environmental contamination. Through a combination of admission screening of all patients (not just those in at-risk categories such as patients being transferred from another hospital), follow-up screening while inpatients, air and environmental sampling, and the prospective collection of detailed demographic data and molecular typing, we have endeavored to gain a deeper understanding of the extent of MRSA colonization and transmission. Results showed that some patients are MRSA-positive even though not in an at-risk category and who would not normally be routinely screened; that transmission can occur but remain undetected if solely relying on routine screening; and that the method of environmental sampling influences the density of MRSA recovered from the healthcare environment.12-15

In this study, MRSA was mainly isolated from the air in ward bays where MRSA-positive patients were identified (air sampling sites outlined in Figure 1b). However, on 7.6% of 132 sampling occasions, MRSA was detected from air samples when no known MRSA-positive patients were identified, possibly because of unidentified MRSA-positive individuals in the vicinity, recently discharged MRSA-positive patients, or environmental contamination. When patient screening and air sampling were conducted on four wards over a consecutive 4-week period, more MRSA-positive patients and environmental samples were identified during the first 2 weeks than during weeks 3–4. This may suggest that the early identification of MRSA patients arising from this study and their subsequent isolation may have contributed to fewer MRSA-positive samples during the last 2 weeks of screening.

In HDBs, MRSA was recovered on 50% of occasions from either patients or their environment, probably due to the greater risk of these more vulnerable patients having MRSA. Apart from the presence of a urinary catheter in 3/12 patients, no other MRSA risk factors were associated with environmental contamination. Skin scales can travel significant distances when patient screening and air sampling influences the density of MRSA recovered from the healthcare environment.6-13,15 Effective cleaning and the decontamination of environmental surfaces have been associated with reduced MRSA in the patient’s environment, but cleaning may not always be effective.14 In the present study, mattresses were the items of equipment from which MRSA was most frequently isolated and these may be a significant reservoir in the environment. Patients may acquire MRSA from a previous MRSA-positive patient if decontamination of that clinical area before patient admission is inadequate.25 The surface of patients’ lockers was also contaminated, possibly from aerial transmission, but also due to direct patient contact and indirect contact with MRSA-positive patients via healthcare staff combined with inadequate cleaning.

The use of spa typing as a standalone typing method for differentiating between highly clonal ST22-MRSA-IV isolates has been shown to be inadequate.26 In the present study spa typing was combined with DNA microarray profiling to attempt to enhance discrimination of the ST22-MRSA-IV isolates based on the presence or absence of virulence-associated and antimicrobial resistance genes. This combined molecular typing approach together with epidemiological data identified four clusters, three of which were on different wards involving patients and the environment. In addition, three of four isolates that were linked epidemiologically and isolated from the
environment were indistinguishable but these were not associated with MRSA-positive patients. Whereas it is important not to rely on spa typing alone for typing of MRSA particularly in an endemic setting, in the present study DNA microarray profiling did not result in isolates clustered based on spa typing being further differentiated. However, the DNA microarray permits identification of characteristic resistance and virulence genes among isolates, as we have demonstrated for a collection of isolates causing MRSA bloodstream infection. 

Patterns of air dispersal of S. aureus are not generally well understood in the healthcare environment or elsewhere. A recent study of livestock-associated MRSA traced the spread of MRSA in the vicinity of pig barns, and spa typing indicated that MRSA spread was influenced by the season and the wind direction. The clinical areas sampled in our study were naturally ventilated and therefore air flow would have been influenced by open doors and windows and the movement of patients and staff.

The limitations of this study include taking samples mainly in HDBs and not as frequently throughout the rest of the ward, as this would have more accurately determined the full extent of MRSA dispersal. We sampled mainly nasal and groin patient sites but not other sites such as throat, sputum, urine, etc. which may be associated with significant additional air dispersal. Because of logistical and resource reasons, active air sampling was conducted at one position only, i.e. the outer window of each ward bay and not beside each patient in all ward bays; thus, our sampling possibly missed MRSA dispersion from patients further away from the window. Sampling was conducted during the day and early night periods, but not between 22:00 and 07:30, when patients were asleep and there was less activity on the ward. Broth enrichment was not used for patient samples and healthcare staff were not screened; both may have underestimated the true number of MRSA-positive carriers on the ward and may explain the presence of MRSA in the air without known MRSA-positive patients in the immediate vicinity. One study found that the average limit of detection for direct culture and broth enrichment in an in vitro study was about 750 and 40 cfu/mL, respectively. Hence broth enrichment significantly enhances the sensitivity of MRSA detection but with a longer time to confirmation of MRSA status.

In conclusion, MRSA was recovered from either patients or their environment on 50% of sampling occasions with patterns suggesting dispersal from patients to the surrounding air. This suggests that aerial transmission from patient to patient may be common. While not conclusive, patients appear to shed their environment on 50% of sampling occasions with patterns of air dispersal of meticillin-resistant Staphylococcus aureus are not generally well understood in the healthcare environment or elsewhere. A recent study of livestock-associated MRSA traced the spread of MRSA in the vicinity of pig barns, and spa typing indicated that MRSA spread was influenced by the season and the wind direction. The clinical areas sampled in our study were naturally ventilated and therefore air flow would have been influenced by open doors and windows and the movement of patients and staff.

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Conflict of interest statement

H.H. has received research support from Steris Corporation, Inov8 Science, Pfizer and Cepheid in recent years. He has also recently received lecture and other fees from Novartis, Astellas and AstraZeneca. No conflict of interest is reported by the other co-authors.

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Role of air changes per hour (ACH) in possible transmission of airborne infections

Die Bedeutung von Lufterneuerungen pro Stunde (ACH) bei möglichen Übertragungswegen von Infektionen in der Luft

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Abstract


1 Introduction

The role that airborne transmission plays in nosocomial or hospital acquired infections (NI/HAI) has been highly debated for well over 40 years. Although transmission of nosocomial pathogens from people via an airborne route in the hospital setting is well established, it is a common misconception that most hospital acquired infections (HAI) are spread by aerosol transmission and that the number of air changes per hour (ACH) used to ventilate the occupied space directly impacts the transmission. Many studies on the transmission of infectious disease particles suggest that ventilation is one of the major methods for reduction and control of the spread of pathogens via the airborne route in hospitals (Streifel 1999; Kaushal et al. 2004; Beggs et al. 2008). ASHRAE 170 2008 and the CDC guidelines 2005 recommend ventilation rates of minimum 12 ACH for hospital insulation rooms. Although increasing ventilation airflow rate does dilute concentrations better when the contaminant source is constant, it does not increase ventilation effectiveness.

Li et al. (2005, 2007) discuss the role that ventilation systems play in cross infection between people. They conclude...
that there is a close connection between the ventilation systems and the infectious transmission in the air. Recently, engineers have begun to examine the effect that physical factors such as location of supply and exhaust vents, surfaces, object placement and composition and thermodynamic factors such as temperature, humidity and air currents have on aerosol transmission and particle migration. For health care facilities, the studies specifically examine infectious particle transmission. However, these studies rarely take into account length of exposure time and particle virulence. Furthermore, an extensive literature review (Memarzadeh 2011a) indicates that not every exposure to an infectious agent will necessarily cause a recipient infection. Individual risk factors exist that make one person more vulnerable to contracting a disease than another. Risk factors for HAI are factors that are not a direct cause of the disease, but appear to be associated in some way with infection. Risk factors may be inherent in an individual due to genetics, health status, or gender. Risk factors may also be present in the local environment. Examples of environmental risk factors include the age and operational status of the ventilation equipment, temperature and humidity. Risk factors are also related to behaviors such as compliance to use of standard operating procedures (SOP) involving personal protective equipment (PPE), decontamination or control of isolation procedures for example. Although the existence of a risk factor for an HAI increases the chances of contracting an illness, it does not always lead to a HAI, whereas the absence of any single risk factor or the existence of a protective factor, does not necessarily guard against getting a HAI (Memarzadeh 2011b). Fisk (2000) estimates that changes in building characteristics and ventilation could reduce indices of respiratory illness by 15% to 76%. The estimated productivity gains by reducing respiratory illness, utilizing 1996 data are 16 to 37 million avoided cases of common cold or influenza, with a potential of $6 to $14 billion in 1996 dollars (Fisk 2000).

There is sufficient evidence to support the truly “airborne” mode of transmission for tuberculosis (TB) caused by Mycobacterium tuberculosis and M. africanum, measles (rubeola virus) and chickenpox (varicella zoster virus) (Wells et al. 1942; Riley et al. 1978; Langmuir 1980). Noting that each of these are physiologically dissimilar, never-the-less they are all vaccine-preventable diseases. There is further evidence that mumps (Habel 1945) bacterial meningitis (American College Health Association) and pertussis may also be transmitted via the airborne route. Couch (1981) notes that the prevailing concept, although unsupported by objective evidence, is that other respiratory viruses are transmitted primarily by direct and indirect droplet contact. The WHO states that “Human Influenza is transmitted by inhalation of infectious droplets and droplet nuclei, by direct contact and perhaps by indirect (fomite) contact … the relative efficiency of the different routes of transmission has not been defined” (Beigel et al. 2005). Other pathogens spread via multiple modes of transmission include smallpox, Methicillin Resistant Staphylococcus Aureus (MRSA), Legionnaire’s disease, Pseudomonas aeruginosa, environmental sources of Aspergillus spp., Serratia marcescens, and some Clostridium difficile infections. It is a generally accepted fact that the remainder of HAIs are caused by potentially infectious particles that are transmitted via direct and indirect contact with droplet nuclei through a fomite, a surface, or some other intermediary (Couch 1981) and that these particles may be affected by local environmental conditions.

At the 1970 International Conference on Nosocomial Infection held at the Centers for Disease Control (CDC) in Atlanta, Georgia, Brachman (1971) reviewed modes of transmission of nosocomial infections and concluded that although airborne transmission certainly accounted for some nosocomial infections, the exact impact of the aerosol mode of transmission was unknown. Based largely on data available from the National Nosocomial Infections Study (NNIS), he estimated that airborne transmission accounted for 10% to 20% of all endemic nosocomial infections or about a one percent incidence of infection among hospitalized patients.

Maki et al. (1982) did extensive environmental microbiological sampling of a new university hospital in Madison, Wisconsin before and after it was put into use. The rate of nosocomial infections in the new hospital was no different from the rate in the old hospital, thus suggesting that organisms in the inanimate environment contributed little if at all to endemic nosocomial infections. Schaal (1991) estimated that the relative incidence of airborne infections is about 10% of the whole of endemic nosocomial infection. However, Kowalski (2007) estimated that more than a third of all nosocomial infections possibly involve airborne transmission at some point. He stated that “various sources estimate that between 2 million and 4 million nosocomial infections occur annually, resulting in 20,000 to 80,000 fatalities.” The increase from 10% to 33% or greater may be indicative of the identification of new pathogenic microorganisms such as SARS CoV and other mutated forms of influenza virus. After many empirical and observational studies, the jury is still out on the exact mode of transmission for most of the recently identified diseases.

The evidence clearly shows that no single factor is responsible for the spread of infectious disease, regardless of the offending microorganism. A combination of many factors and variables influence the modes of particle transmission. These include but are not necessarily limited to:

- aerosol and droplet transmission dynamics,
- the nature of the dust levels,
• the health and condition of individuals naso-pharyngeal mucosal linings,
• population density,
• ventilation rate,
• air distribution pattern,
• humidity and temperature,
• number of susceptibles,
• length of exposure,
• number of infected people producing contaminated aerosols,
• infectious particle settling rate,
• lipid or non-lipid viral envelope or microorganism cell wall,
• surrounding organic material,
• UV light or antiviral chemical exposure,
• vitamin A and D levels,
• microorganism resistance to antibiotic or antiviral therapy,
• type and degree of invasive procedures,
• spatial considerations,
• contact with a carrier,
• persistence of pathogens within hosts,
• immuno-epidemiology,
• transmission of resistance and role of host genetic factors.

The mucociliary clearance apparatus also affects infectivity and is an important defense mechanism for clearing the lung of foreign particulate matter. Bennett (2002) notes that secretory cells that line airway passages produce mucus and afford protection from disease etc. Pollutant exposure and viral or bacterial infections may cause disruption of mucociliary clearance and likewise affect the natural rheological properties such as adhesiveness of nasal mucus and/or slowing of ciliary beating according to Salah et al. (1988) and Waffaa et al. (2006).

Again, not every exposure to an infectious agent leads to infection nor is there evidence that virulence of a particular strain causes the same intensity of illness in all individuals. Detection alone does not necessarily imply infectivity. For example, other factors such as host response, receipt of vaccine against the strain of influenza in circulation, use of respiratory hygiene practices and avoiding crowded environments by the individual with acute infection all influence any one person’s risk of infection following exposure. (Memarzadeh 2011a).

It is important to understand the interaction and the role that particle size and particle transmission dynamics play in infectious disease transmission. It is generally accepted in the current mechanical engineering and medical community that particles with an aerodynamic diameter of 5 μm or less are aerosols, whereas particles of 20 μm are large droplets. There is substantial literature on cough droplet size distribution (Duguid 1945; Fairchild and Stamper 1987; Papineni and Rosenthal 1997; Fennelly et al. 2004; Morawska et al. 2009) and exhaled air temperature (Hoppe 1981). Infectious diseases are transmitted by several mechanisms. One such mechanism is by direct contact and fomites, which are inanimate objects that transport infectious organisms from one individual to another. A second mechanism is by large droplets generally with a mass median aerodynamic diameter (MMAD) of >10 micrometers (μm) and particles with MMAD <10 μm sometimes termed droplet nuclei. Recent work by Xie and colleagues (2007) indicate that large droplets are those larger than 5—100 μm at the original time of release. Nicas and colleagues (2005) show by modeling that emitted large droplets will evaporate to 50% of their initial value (under varying temperature and humidity conditions) and that if the initial diameter is <20 μm this process will happen instantaneously.

Particle size is a consequence of the process that led to its generation, and thus it is also 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 and the larynx and seldom at the front of the mouth. Thus to assess the potential for infection via airborne droplet route, it is important to develop an understanding about the localities from which droplets originate during various expiratory activities, and the numbers of droplets arising from each site (Morawska 2006).

The distance droplets travel depends on the velocity and mechanism by which respiratory droplets are propelled from the source, the density of respiratory secretions, environmental factors such as temperature and humidity, and the ability of the pathogen to maintain infectivity over that distance. Pathogen-laden droplets are expelled into air by an infected person by coughing, sneezing, breathing or talking (Duguid 1945). Zhu et al. (2006) indicated the peak cough velocity varied from 6 to 22 m/s with an average of 11.2 m/s or about 2000 fps. Variations in this velocity depend on gender, individual size and relative health status.

The pathogen-laden droplets dry out and produce droplet nuclei that may be transmitted over a wide area. Cole and Cook (1998) and Wells (1955) report that sneezing can introduce as many as 40,000 droplets which can evaporate to produce droplets of 0.5 to 12 μm. Fitzgerald and Haas (2005) report that a cough can generate about 3000 droplet nuclei, the same number as talking for 5 minutes. Duguid (1945) notes that a single cough typically produces about 1% of this amount, but coughs occur about ten times more frequently than sneezes. Normal breathing actually generates more bio-aerosols than a cough or sneeze. The particles making up aerosol in normal exhalation are less than 1 micron in size and these smallest particles are primary vectors of contagion.

It is equally important to take into account the physical
position of occupants in the room. Studies have shown that the position of the “coughing” patient and the “staff” have a pronounced effect on the “staff” exposure to potentially infective particles (Kierat 2010). The evidence from these studies suggest that the recommendations in the Standard for 12 h in hospital isolation rooms with mixing ventilation do not reduce the risk of airborne cross infection due to coughing. The posture of the coughing infected patient has great impact on the exposure of medical staff and other patient (Kierat 2010). Exposure of the doctor is a result of the interaction of several factors: the airflow pattern in the space, the distance between the exposed person and the sick patient, the posture of the doctor etc. (Bolashikov 2010). Kierat (2010) suggests that for a patient coughing upwards (towards the ceiling exhaust vent) contaminants were successfully exhausted whereas the total volume (TV) ventilation did not have as significant impact on the exposure level as in the studied case when the patient coughed sideways towards the face of the doctor. Kierat suggests that a good contaminant control solution in hospital rooms is to position the TV exhaust as close as possible to the polluting source: the sick coughing patient in this case. Similar arrangement has been suggested by others (Cheong and Phua 2006; Noakes et al. 2009; Tung et al. 2009a, b). The results of our computational fluid dynamics (CFD) analysis leads us to the same conclusion.

If the disease-causing microorganisms are inhaled by or come to rest on or near a susceptible person, infection may occur. Short-range airborne infection routes between individuals are less than approximately 1-m apart and long-range routes are greater than approximately 1-m apart. 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. Such is the case for TB, measles and chickenpox. Larger droplets are influenced more by gravity than by airflows and fall to the ground more quickly (Wan and Chao 2007; Chen et al. 2009). There is so much inertial force in the large particles that they have to be forced to the recipient whereas, when small particles enter the air, air creates enough resistance so that they cannot easily reach the recipient and these particles follow air flow (Couch 1981). Large droplets released in short range aerosols (e.g., sneezing) are sometimes confused with airborne droplets, but such released particles do not typically transmit over long distances. 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.

The evidence suggests that very few respiratory viruses are exclusively transmitted via one route. There is no exact particle size cut-off at which pathogen transmission changes from exclusively droplet to airborne or vice versa. Preventing droplet and contact transmission would require very different control measures. It is important to re-emphasize that numerous factors influence the transmission of infectious disease. Not every exposure to an infectious virus leads to infection nor is there evidence that virulence of a particular strain causes the same intensity of illness in all individuals.

1.1 Importance of performing a risk analysis

Increasing or decreasing ventilation rate by as little as one air change per hour can result in a difference of $150–$250 per year in heating and cooling costs. This is a significant expenditure that is often overlooked but that can be managed through proper ventilation system design. We are not suggesting here that the ACH should be indiscriminately increased or decreased to save money. What we are suggesting is that “good” versus “poor” design based on an initial and on-going risk assessment can help determine the optimal ACH for the proposed use of the space, thereby selecting an ACH that is both cost effective and efficient.

Other costs associated with infectious disease include absence from work for health care workers (HCW) and productivity of any single individual due to illness acquired as an HAI. Therefore, determining the appropriate ACH for a facility, whether it is for the whole building or a specialized section of the building such as an emergency room, operating room, or isolation unit requires a careful risk analysis early in the design process or when there is a change of use. The current evidence strongly suggests that no single physical, environmental or epidemiologic variable can be unilaterally altered to make accommodations for the function of that designated space. A thorough risk assessment to optimize design options may result in higher first costs but provide long term savings in a variety of healthcare facilities.

ASHRAE (2003) defines risk assessment and management as “a systematic approach to the discovery and treatment of risks facing an organization or facility.” There are certain general principles that should be considered for any risk assessment (ASHRAE 2003):

(1) identifying the risk,
(2) estimating the level of exposure,
(3) estimating the probability of risk occurrence,
(4) determining the value of the loss,
(5) ranking risks,
(6) identifying vulnerabilities.

The risk assessment approach outlined in the Facilities Guideline Institute’s “Design and Construction of Health Care Facilities” considers both the susceptibility of the patients and health care worker versus the degree of environmental contamination. This infection control risk assessment or
“ICRA” supports communication between clinical and facility staff and includes both design and remediation issues to protect patients and staff both long and short term. Risk assessment design strategies for infection prevention and control include consideration of the patient population served, range and complexity of services provided, and settings in which care is provided. Other variables include status (e.g., infectious or susceptible), the area under consideration (e.g., isolation or protective), the type of filtration, ventilation and pressurization and the operations and maintenance procedures and management that are in place. Risk assessment design strategies for environmental controls include the use of PPE for the HCW, the type of isolation necessary (e.g., protective or containment) and the ventilation standards that apply to the type of facility being assessed. (Kosar 2002)

Involvement of professionals from the medical and building sciences including architects, engineers, epidemiologists, and industrial hygienists and infection preventionists is required to provide effective indoor air quality (IAQ) practices in healthcare facilities. Acceptable IAQ can be achieved by using ventilation in conjunction with air filtration on recirculated and fresh air, mechanical arrestance media to clean air of microbial and other particulate matter; and irradiation in targeted applications, using ultra violet germicidal irradiation (UVGI) to alter airborne and surface borne microbes and limit the proliferation of the infectious agents.

The role that environmental factors, such as air temperature and relative humidity (RH) play in surface survival is important for risk assessment and the development of control measures. In an attempt to control environmental factors in the healthcare environment, we must find a balance between reducing infectious disease transmissibility while maintaining occupant comfort.

1.2 Experimental (empirical) and numerical approaches

To study various factors that affect airborne infectious disease transmission, engineers and researchers have employed experimental and numerical methods. Carefully conducted experiments replicate reality in a controlled environment and provide most reliable information.

Olmedo et al. (2011) performed an empirical study that examined exhalation flow in order to create a description of the velocity distribution and the concentration distribution around the person. The measurements were made in a room with three different air distribution systems creating different environments around the person in which the exhalation flow of a person is considered as the pollutant in order to investigate the mechanism of spreading respiratory diseases. Additional studies examined how this exhalation flow might provoke a high exposure to other persons situated in the same room. The level of exposure was measured for different positions and separation distances between the manikins, and for three ventilation strategies: displacement ventilation, mixing ventilation and non-mechanical ventilation in a room with otherwise similar conditions. A preliminary report that focused on the displacement ventilation conditions was published (Nielsen et al. 2011). Continuing this work, Olmedo provided a more thorough analysis, considering three different ventilation modes in further details.

However, often times the cost and time required limit the amount of experimental data. Interferences from environment and instruments, equipment and human error can also reduce the accuracy of experimental results. Numerical analysis, commonly known as computational fluid dynamics (CFD), on the other hand, is a very cost effective tool and does not suffer from these interferences. With the development of computer technology and ever increasing computing power, a numerical approach has become increasingly more popular. A numerical approach is frequently used to confirm or disprove an empirical approach. Care has to be taken to deal with model building, mesh creation, turbulence model selection and results analysis etc. The best approach is to combine the two methods to some extent. The study presented in this paper mainly employs a numerical approach to analyze the transmission and control of airborne contaminants, with references to the experimental results in similar situations.

2 Methodology

Building ventilation systems help prevent building-associated illness by providing dilution and removal of unknown airborne microbial and some viral contaminants. The movement of airborne contaminants is closely linked to the movement of air in built environments. When the contaminant particle size is less than a few microns, it can be safely considered as a “gas” that obeys transport equations of continuum (Yin et al. 2009). When solved using CFD technique, the transport equation of contaminant concentration, along with transport equations of mass, momentum and energy gives detailed information on the mechanism of air movement and contaminant transmission. The generalized transport equation can be written as

\[
\frac{\partial \phi}{\partial t} + \nabla \cdot (\mathbf{u} \phi) = \nabla \cdot (D \nabla \phi) + S
\]

where \( \mathbf{u} \) denotes the velocity field, \( \phi \) is the variable in question, \( \Gamma \) is the diffusion coefficient.
when \( \phi \) is 1, Eq. (1) represents mass conservation equation, \( u \), momentum equation, \( h \), energy equation, \( C \), concentration equation.

As nearly all indoor airflows are turbulent, turbulence models are also needed to assess the effects of turbulence in momentum and heat transfer. Historically, there have been numerous efforts to establish turbulence models for various applications. This paper uses a model that combines LVEL (Agonafer et al. 1996) and the popular \( k-\varepsilon \) model (Launder and Spalding 1974). Equation (1) remains applicable. This turbulence model adds two additional partial differential equations for turbulence kinetic energy \( k \) and turbulent energy dissipation \( \varepsilon \) to solve.

Solving the above set of equations numerically requires changing the form of the equations from differential to algebraic. This process is called discretization. The most widely used discretization method is called the “finite volume” method, which divides the solution domain into many finite volumes and then solves the discretized equations within each volume. The general form of a discretized equation can be written as

\[
a_{P} \phi = \sum a_{NB} \phi_{NB}
\]

where \( a_{P} \), and \( a_{NB} \) are coefficients derived from discretized equations, \( P \) stands for the point to be solved, \( NB \) stands for neighboring points, \( \phi \) is the variable in question. The equations are non-linear and coupled, therefore, iterations are usually required to obtain a solution.

Many commercially available CFD programs take the complexity of mathematics and numerical methods away from the end user. They are equipped with powerful model building and post processing tools that makes it possible to solve engineering problems within a reasonable amount of time. This analysis used FloVENT® as the CFD tool.

2.1 Cases considered

In this numerical study, a total of 16 cases were examined. Four initial cases with simple configurations were chosen to understand the underlying principle that governs the contaminant transmission in a room.

Figures 1 and 2 illustrate these four cases. They consist of a room measured at 432 cm \( \times \) 490 cm \( \times \) 272 cm; a small object measured at 20 cm \( \times \) 15 cm \( \times \) 15 cm; a small contaminant source measured at 4 cm \( \times \) 4 cm; a ventilation supply (55 cm \( \times \) 70 cm) and return (exhaust) (30 cm \( \times \) 30 cm). The small object represents the patient for purposes of this illustration.

In Cases 1 and 2 the ventilation supply is located on the side wall, as shown in Fig. 1. In Cases 3 and 4 the supply is located below the contamination source. Cases 1–4 are “theoretical cases” to show the “principle” in a hypothetical environment. Cases 1 and 3 use a contamination source that emits tracer gas sulfur hexafluoride (SF\(_6\)) at a constant or steady-state rate of 300 mL/min, which is similar to what has been used in an experimental study (Yin et al. 2009). Tracer gas simulates the droplet nuclei because the air distribution of tracer gas is identical to the distribution of droplet nuclei (Tang et al. 2011). Cases 2 and 4 use a contamination source that is transient with a flow rate vs. time profile identical to the coughing characteristics of a 1.8 m, 70 kg male (Gupta et al. 2009). The contaminant concentration of the transient flow is assumed to be 100%. The small object representing the patient in the room dissipates roughly 30 W. Supply flow rate is 120 cfm and temperature is set at 67°F. Approximately 234,000 finite volume cells were used to represent contaminant for each of the four cases. Simulation was conducted for 300 seconds. Table 1 shows additional details of the four cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Type</th>
<th>Supply flow rate</th>
<th>Supply location, direction</th>
<th>Exhaust location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Steady-state</td>
<td>4 ACH</td>
<td>Side wall, towards source</td>
<td>Right above source</td>
</tr>
<tr>
<td>2</td>
<td>Transient</td>
<td>4 ACH</td>
<td>Side wall, towards source</td>
<td>Right above source</td>
</tr>
<tr>
<td>3</td>
<td>Steady-state</td>
<td>4 ACH</td>
<td>Floor, below source</td>
<td>Right above source</td>
</tr>
<tr>
<td>4</td>
<td>Transient</td>
<td>4 ACH</td>
<td>Floor, below source</td>
<td>Right above source</td>
</tr>
</tbody>
</table>
Using these four cases, we were able to identify the underlying “path” principle that affects contaminant transport in rooms.

Twelve additional application cases (Cases 5–16) were chosen to further validate the principle in a more realistic patient room setup.

Figure 3 illustrates the room configuration of these 12 cases. The room resembles a typical hospital patient room, with a patient, a caregiver, bed, equipment, bathroom, ventilation supply and returns (exhaust). Table 2 lists the dimensions of the included geometries and other pertinent information.

In all 12 cases, the geometries are identical in size. The variables in the 12 cases are the supply flow rates, airflow direction and the ventilation exhaust locations. For purposes of this analysis, the 12 cases are divided into 2 groups. The first group, Cases 5–10, represents a “typical” ventilation design in a hospital room where the supply is on the ceiling and flows towards the inside of the room. The return (exhaust) is located further away, as shown in Fig. 3(a). In the second group, Cases 11–16, the supply is similarly located on the ceiling, but airflow is directed towards the walls and the return (exhaust) is located directly above the patient. Each group was analyzed at airflow rates of 4, 6 and 12 ACH. The contaminant sources in both steady-state and transient situations are the same as those used in Cases 1–4. Approximately 500 000 finite volume cells were used to represent contaminant for each of the 12 cases. Table 3 lists the details of each case.

### 2.2 Results and discussions

The results from the first four cases illustrate the principle discovered in this study and are very revealing. Figure 4(a) shows how the contaminant concentration in Case 1 where the ventilation supply is located on the side wall, flows in a wide path across the room. In contrast, Case 3 shown in Fig. 4(b), where the supply is located on the floor below the source, the contaminant flow is contained in a narrow space above the source. Figure 4(c) and (d) compare Cases 2 and 4 at various moments after the contaminant injection. In Case 2 shown in Fig. 4(c) where the ventilation supply is on the

### Table 2 Patient room configuration & pertinent information

<table>
<thead>
<tr>
<th>Item</th>
<th>Dimension</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room</td>
<td>432 cm × 490 cm × 272 cm</td>
<td>Adiabatic walls</td>
</tr>
<tr>
<td>Patient</td>
<td>175 cm tall, consist of various body parts such as arms and legs</td>
<td>Dissipates 85 W</td>
</tr>
<tr>
<td>Exhaust</td>
<td>Main exhaust B: 25 cm × 25 cm located at ceiling</td>
<td>Flow rate of B: various according to the supply flow rate</td>
</tr>
<tr>
<td></td>
<td>Bathroom exhaust B’: under the bathroom door</td>
<td>Flow rate of B’: fixed at 75 cfm</td>
</tr>
<tr>
<td>Supply</td>
<td>Located on the ceiling, flow rate and flow direction varies by case</td>
<td>Supply temperature 67°F</td>
</tr>
<tr>
<td>Caregiver</td>
<td>Same as the patient, standing position</td>
<td>Dissipates 85 W</td>
</tr>
<tr>
<td>Equipment</td>
<td>40 cm × 40 cm × 110 cm</td>
<td>Dissipates 50 W</td>
</tr>
<tr>
<td>Cabinet</td>
<td>60 cm × 140 cm × 272 cm</td>
<td></td>
</tr>
<tr>
<td>Bathroom</td>
<td>110 cm × 165 cm with an angled door</td>
<td>75 cfm going through the gap under the angled door</td>
</tr>
</tbody>
</table>

### Table 3 Flow conditions of Cases 5–16

<table>
<thead>
<tr>
<th>Case #</th>
<th>Type</th>
<th>Supply flow rate</th>
<th>Supply location, direction</th>
<th>Main exhaust location</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Steady-state</td>
<td>4 ACH</td>
<td>Ceiling, towards patient</td>
<td>Ceiling, away from patient</td>
</tr>
<tr>
<td>6</td>
<td>Steady-state</td>
<td>6 ACH</td>
<td>Ceiling, towards patient</td>
<td>Ceiling, away from patient</td>
</tr>
<tr>
<td>7</td>
<td>Steady-state</td>
<td>12 ACH</td>
<td>Ceiling, towards patient</td>
<td>Ceiling, away from patient</td>
</tr>
<tr>
<td>8</td>
<td>Transient</td>
<td>4 ACH</td>
<td>Ceiling, towards patient</td>
<td>Ceiling, away from patient</td>
</tr>
<tr>
<td>9</td>
<td>Transient</td>
<td>6 ACH</td>
<td>Ceiling, towards patient</td>
<td>Ceiling, away from patient</td>
</tr>
<tr>
<td>10</td>
<td>Transient</td>
<td>12 ACH</td>
<td>Ceiling, towards patient</td>
<td>Ceiling, away from patient</td>
</tr>
<tr>
<td>11</td>
<td>Steady-state</td>
<td>4 ACH</td>
<td>Ceiling, away from patient</td>
<td>Ceiling, right above patient</td>
</tr>
<tr>
<td>12</td>
<td>Steady-state</td>
<td>6 ACH</td>
<td>Ceiling, away from patient</td>
<td>Ceiling, right above patient</td>
</tr>
<tr>
<td>13</td>
<td>Steady-state</td>
<td>12 ACH</td>
<td>Ceiling, away from patient</td>
<td>Ceiling, right above patient</td>
</tr>
<tr>
<td>14</td>
<td>Transient</td>
<td>4 ACH</td>
<td>Ceiling, away from patient</td>
<td>Ceiling, right above patient</td>
</tr>
<tr>
<td>15</td>
<td>Transient</td>
<td>6 ACH</td>
<td>Ceiling, away from patient</td>
<td>Ceiling, right above patient</td>
</tr>
<tr>
<td>16</td>
<td>Transient</td>
<td>12 ACH</td>
<td>Ceiling, away from patient</td>
<td>Ceiling, right above patient</td>
</tr>
</tbody>
</table>
side wall, contaminant is transmitted in a wide path whereas in Case 4, shown in Fig. 4(d), the contaminant was more “controlled” when the supply was placed below the source.

Figure 5 compares the concentration and the contaminant captured at exhaust during the 300 s simulation period. It is clear that for Case 4, in which the supply is on the floor, there is a surge of high concentration between 1 and 10 s, which results in twice as much contaminant being captured during this period.

The results of this study suggest that the most important contributing factor to contaminant transmission in enclosed and mechanically ventilated environment is the path between the contaminant source and the exhaust, not the ACH. When this path is interrupted by air streams, the contaminant is most likely to migrate to other places in the room. If this path is kept intact from an intercepting air stream, then the contaminant is unlikely to migrate.

This principle of room ventilation is analogous to how a laboratory fume hood captures contaminant. A fume hood is designed to remove hazardous substances. It usually has an enclosure and an exhaust right above the contaminant agent and is able to remove the contaminant effectively using appropriate airflow dynamics. A room ventilation system, on the other hand, is typically designed to mix room air with supply air to create a uniform thermal condition. This, however, is not ideal for the purpose of removing contaminants that might be found for example in a healthcare setting. The most effective ventilation system for
contaminant removal is the one that can produce the effect of a fume hood or a “virtual” fume hood. Instead of a physical boundary of the real fume hood, the ideal ventilation system should be able to produce an invisible air curtain that confines contaminant inside. Figure 6(a) is a sketch of a typical room ventilation system; 6(b) shows a sketch of a fume hood; 6(c) shows an ideal ventilation system, which is capable to create the effect of a fume hood (6(b)) but without the physical structure.

Applying the “path” principle to Group 1 (Cases 5–10) (see Fig. 3), it becomes clear that when the main exhaust is far away from the contaminant source and is intercepted by supply air, the contaminant migrates to other places in the room. In contrast, Group 2 (Cases 11–16) where the exhaust is right above the patient (contaminant source) and the supply air is directed away from the path we should see much better contaminant control in the simulation if the hypothesis is correct.

To quantitatively compare the contaminant control of Cases 5–16, two metrics are selected. The first one is ventilation effectiveness defined by Chapter 27 of ASHRAE Fundamental Handbook 2005.

\[
V_e = \frac{C_e - C_s}{C_e - C_a}
\]

where \(C_e\) is the concentration at exhaust, \(C_s\) is the average concentration at breathing level, 1.1 m and 1.7 m, \(C_a\) is the concentration at supply, which is set to 0 in the current study. A perfect mixing room has a \(V_e\) value of 1. Values greater than 1 indicated better contaminant containment than perfect mixing condition. This parameter is appropriate for steady-state contaminant sources. Table 4 shows the \(V_e\) values for the steady-state cases among the 12 cases.

It is clear from the Table 4 that ventilation designs that conform with the principle gives much higher ventilation effectiveness.

Figure 7 shows the iso-surface contour with value at exhaust level. It further proves that when a ventilation system design conforms with the “path” principle, the contaminants are well controlled.

The second parameter chosen to evaluate the ventilation systems, and more appropriate for transient cases, is contaminant exposure, which can be defined as

<table>
<thead>
<tr>
<th>Case #</th>
<th>Type</th>
<th>Supply flow rate</th>
<th>Conform with the principle?</th>
<th>Ventilation effectiveness at 1.1 m</th>
<th>Ventilation effectiveness at 1.7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Steady-state</td>
<td>4 ACH</td>
<td>No</td>
<td>1.11</td>
<td>1.05</td>
</tr>
<tr>
<td>6</td>
<td>Steady-state</td>
<td>6 ACH</td>
<td>No</td>
<td>0.75</td>
<td>1.08</td>
</tr>
<tr>
<td>7</td>
<td>Steady-state</td>
<td>12 ACH</td>
<td>No</td>
<td>0.99</td>
<td>1.01</td>
</tr>
<tr>
<td>11</td>
<td>Steady-state</td>
<td>4 ACH</td>
<td>Yes</td>
<td>1.76</td>
<td>1.69</td>
</tr>
<tr>
<td>12</td>
<td>Steady-state</td>
<td>6 ACH</td>
<td>Yes</td>
<td>2.38</td>
<td>2.27</td>
</tr>
<tr>
<td>13</td>
<td>Steady-state</td>
<td>12 ACH</td>
<td>Yes</td>
<td>3.37</td>
<td>3.24</td>
</tr>
</tbody>
</table>

Fig. 5 Concentration (a) and captured contaminant mass (b) at exhaust

Fig. 6 Sketch of (a) a typical room ventilation system mixes room air and contaminants; (b) a laboratory fume hood removes contaminant efficiently; (c) an ideal ventilation system that is capable to produce “fume-hood-like” effects
where $\bar{C}(t)$ the average concentration within a selected volume.

In order to assess the infection risk vs. distance to the contaminant source, the average contaminant concentration is evaluated in a series of volumes that are 1 ft (0.3 m) apart, starting from the volume right above the patient. The height of the volume starts from 1.1 m (3.6 ft) and ends at 1.7 m (5.6 ft). Figure 8 shows the location and size of the volumes.

Figure 9 compares the exposure concentration in the first volume, which is right above the patient. Figure 9(a) suggests that in a “poor” ventilation design that does not conform to the “path” principle, increasing airflow rate from 4 ACH to 12 ACH has little impact on the infection risk. In contrast, Fig. 9(b) indicates that with an “optimized” ventilation design that conforms to the “path” principle, increasing the airflow rate does reduce the infection risk. This observation of the impact of ventilation flow rate and infection risk is consistent with recent experimental studies (Kierat et al. 2010; Olmedo et al. 2011), which also found increasing airflow rates to 12 ACH does not necessarily reduce the infection risk in a mixing ventilation setting. Further, several studies (Edwards et al. 2004; Zhu et al. 2006; Sun and Ji 2007; Gupta et al. 2009) indicate that the interaction of coughed flow with high initial velocity ranging from 6 m/s (1181.1 fpm) up to 30 m/s (5905.51 fpm) with the free convection flow around the human body and the ventilation flow will be different than the flow of exhalation with much low initial velocity (Gupta et al. 2010). This suggests that the strategy of supplying extra amounts of outdoor air aiming to dilute the polluted room air may not be effective in protecting from airborne cross-infection due to coughing.

![Fig. 7 Comparison of contaminant concentration iso-surface between (a) Case 5 (poor design); (b) Case 11 (good design)](image)

![Fig. 8 Volumes used to evaluate contaminant exposure](image)

![Fig. 9 Comparison of contaminant exposure in the volume right above the patient: (a) poor ventilation design; (b) optimized ventilation design](image)
Figure 10 compares the rest of the volumes that were examined in this study. This data reveals a more complex nature of infection risk. First, consistent with Figs. 9, 10 suggests that an optimized ventilation design provides significant reduction of contaminant in most scenarios. Second, also consistent with Fig. 9, it appears that increasing the supply airflow rate does not reduce the risk with a poor design. With the optimized design, it appears that increased airflow rate does help at later time (>150 s), but at earlier time points, airflow rate can have the opposite effect, especially when considering the distance l away from the source. This may suggest that if the caregiver is too close to the patient, the ventilation system plays a secondary role in terms of preventing exposure to infectious particles. Third, as would be expected, the data suggests that in most cases moving away from the patient does help to reduce exposure. However, note that the benefit of keeping a distance from the patient can be offset by poor ventilation design, and under the low airflow rate of 4 ACH, moving away from the patient is not an effective way to reduce the risk regardless of the design.

In summary, the results of this numerical study confirm previous empirical studies (Kierat et al. 2010; Olmedo et al. 2011) and define a “path” theory between “Source” and “Exhaust” of contaminants. A poor design as in, for example, Case 6 shows a wide path of contaminant whereas Case 12, having a good design, shows a contained path of contaminant.

For a constant contaminant source, the benefit of an “optimized design” is apparent at all flow rates. It produces better ventilation efficiency and results in more benefits for increasing airflow rate, while poor design does not, although increasing airflow rate does reduce absolute concentration level for a constant source.

For a “strong” transient (coughing) source, the benefit of an “optimized design” is not obvious when the airflow rate is low. However, with increased airflow rate, good design starts to help limiting contaminant migration in transient situations as well.

Contaminant exposure risk is greatest directly above the patient’s bed. Increasing the ventilation airflow rate does not reduce the infection risk with a poor ventilation design, whereas with an optimized design, it does. Moving away from the patient’s bed does reduce the infection risk slightly and the effect is more pronounced when ventilation airflow rate is high.

Therefore, it is not always helpful to increase airflow rate. Increasing ventilation airflow rate does dilute concentrations better when the contaminant source is constant. However, it does not increase ventilation effectiveness. With poor design of the ventilation system, it can make the infection risk greater when the contaminant source is transient. Moving away from the patient’s bed helps reduce the infection risk as was demonstrated by moving away l from the source. After the first l, the effectiveness of moving away from the contaminant source is reduced. At higher ventilation rates, the infection risk reduces more quickly with distance; at lower rate, the risk can rise after the first l.

The results seem to suggest that the most important contributing factor to contaminant transmission in enclosed and mechanically ventilated environment is the path between the contaminant source and the exhaust, not the ACH. When this path is interrupted by air streams, the contaminant is most likely to migrate to other places in the room. If this path is kept intact from an intercepting air stream, then the contaminant is unlikely to migrate.

The general principle and application simulations indicated that a good ventilation design is crucial to contaminant control. Good design practice includes:

- Placing the return as close to the patient’s head as possible.
- This reduces the chance for “the path” to be disturbed.
- Not allowing air streams to directly intercept “the path”.
- Optimizing and verifying ventilation design with simulation.
- Increasing ventilation airflow rate only when the design is optimized.

![Fig. 10 Contaminant exposure under (a) poor ventilation design; (b) optimized ventilation design](image-url)
2.3 Future studies

The present study focuses on the impact of ventilation system design to the transmission of infectious disease agents, and assumes the disease agents are airborne and relatively small (<5 micron), and therefore can be safely modeled as concentration. The transport behavior of larger particles (>10 microns) might not be the same, as larger particles will be affected by gravitational forces and large droplet dynamics (Chen et al. 2009; Chao and Wan 2007). Studies, such as those by Chao et al. 2008, Wan et al. 2009, and Sze To et al. 2009, which focus more on the transport mechanism of large droplets, could be complementary to the present study to give a full picture of infectious disease transmission in enclosed spaces.

In addition, this study assumes the patient is stationary. Obviously, in real life patients do move around the room, go to bathroom, meet guests and caregivers etc. Under these situations, a ventilation system designed to work best under stationary condition is no longer optimal, and we intended to study the impact of occupant movements in future researches. However, following the “path” principle to design a ventilation system for the position that a patient would spend most of his/her time is still a good practice.

Keirat et al. (2010) note that the exposure of medical staff and patients in a hospital room to air coughed by an infected patient has not been studied in depth. It is generally accepted that no single factor is responsible for the spread of infectious disease, regardless of the offending microorganism. A combination of many factors and variables influence the modes of particle transmission and not every exposure to an infectious agent will necessarily cause a recipient infection. It is evident from an extensive literature review and after many empirical and observational studies, that there is still a great deal of investigation needed to determine the exact mode of transmission for most of the recently identified diseases.

3 Conclusions

Not every exposure to an infectious virus leads to infection nor is there evidence that virulence of a particular strain causes the same intensity of illness in all individuals. Furthermore, is does not appear from the results of this study and others that ASHRAE 170 2008 and the CDC guidelines 2005 recommendations for ventilation rates of minimum 12 ACH for hospital insulation rooms is necessarily the optimum ACH to control infections transmission. Although increasing ventilation airflow rate does dilute concentrations better when the contaminant source is constant, it does not increase ventilation effectiveness.

The results of this study suggest that the most important contributing factor to contaminant transmission in enclosed and mechanically ventilated environment is the path between the contaminant source and the exhaust, not the ACH. When this path is interrupted by air streams, the contaminant is most likely to migrate to other places in the room. If this path is kept intact from an intercepting air stream, then the contaminant is unlikely to migrate.

The results shown in Fig. 9(a) suggest in the presence of a “poor” ventilation design that does not conform to the “path” principle, increasing airflow rate from 4 ACH to 12 ACH has little impact on the infection risk. In contrast, the results shown in Fig. 9(b) indicate that with an “optimized” ventilation design that does conform to the “path” principle, increasing the airflow rate does reduce the infection risk. This observation of the impact of ventilation flow rate and infection risk is consistent with recent experimental studies (Kierat et al. 2010; Olmedo et al. 2011), which also found increasing airflow rates to 12ACH does not necessarily reduce the infection risk in a mixing ventilation setting. Other studies indicate that the interaction of coughed flow with high initial velocity with the free convection flow around the human body and the ventilation flow will be different than the flow of exhalation with much lower initial velocity (Gupta et al. 2010) suggesting that the strategy of supplying extra amounts of outdoor air aiming to dilute the polluted room air may not be effective in protecting from airborne cross-infection due to coughing.

Hospital acquired infections result in significant economic consequences on the nation’s healthcare system. The most comprehensive national estimate of the annual direct medical costs due to HAI was published in 1992 by Martone. With an incidence of approximately 4.5 HAI for every 100 hospital admissions, the annual direct costs on the healthcare system were estimated to be $4.5 billion in 1992 dollars. Adjusting for the rate of inflation using the consumer price index (CPI) for all urban consumers, this estimate is approximately $6.65 billion in 2007 dollars. However, more recent published evidence indicates that the underlying epidemiology of HAI in hospitals has changed substantially along with the costs of treating HAI. (Haas 2006; Stone 2005; et al. Scott, 2009). Modifying ventilation, humidity and filtration to meet infectious disease control criteria will result in significant personal, energy, and equipment savings. Modifying surface finish and materials may potentially provide a passive solution for reducing spread of viral and bacterial infection, to augment active purification solutions.

References

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