Airborne Infection Isolation Rooms – A Review of Experimental Studies

Marko Hyttinen, Anna Rautio, Pertti Pasanen, Tiina Reponen, G. Scott Earnest, Andrew Streifel and Pentti Kalliokoski

Indoor and Built Environment 2011 20: 584 originally published online 18 July 2011
DOI: 10.1177/1420326X11409452

Review Paper

Indoor and Built Environment

Indoor Built Environ 2011;20;6:584–594

Accepted: March 11, 2011

Airborne Infection Isolation Rooms – A Review of Experimental Studies

Marko Hyttinen[a] Anna Rautio[a] Pertti Pasanen[a]
Tiina Reponen[b] G. Scott Earnest[c] Andrew Streifel[d]
Pentti Kalliokoski[a]

[a]Department of Environmental Science, University of Eastern Finland, Kuopio, Finland
[b]Department of Environmental Health and institution(s), University of Cincinnati, Cincinnati, OH, USA
[c]Division of Applied Research and Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH, USA
[d]Department of Environmental Health and Safety, University of Minnesota, Minneapolis, MN, USA

Key Words
Isolation room · Airborne infection · Ventilation strategies

Abstract

Ventilation guidelines for airborne infection isolation rooms (AIIRs) are highly variable in different countries indicating lack of actual knowledge about the guidance needed. However, US guidelines for AIIRs are extensive and have been widely adopted outside the US. AIIR performance has also been evaluated in numerous studies. For a long time, the aim has mainly been to evaluate how well the existing AIIRs meet US guidelines. For historical reasons, mixing-type ventilation has been emphasised and attention has been paid to air exchange rates, although the use of auxiliary devices, such as portable room-air cleaners and ultraviolet germicidal irradiation systems, has also been examined. Recently, the scope of the investigations has been widened. The most crucial issue is to minimise the potential for disease transmission and prevent the escape of contaminated air from the AIIR. Airflow direction inside the AIIR is also important and AIIRs minimise air leakage to save energy. On the other hand, it has been observed that efficient containment can be achieved even by using simple and inexpensive construction by considering pressure differential and air flow patterns. Nevertheless, additional research is needed to assist hospitals with improving their preparedness to cope with the threat of pandemics by building and using effective AIIRs.

Introduction

Airborne infection isolation rooms (AIIRs) are used for patients with known or suspected infectious disease that spread via small particles originating from mucus and skin. These diseases include tuberculosis (TB), varicella (chicken pox) and rubella (measles). Very hazardous infections, such as Ebola and severe acute respiratory syndrome (SARS) also require infection isolation, and it is important to implement isolation strictly in the early stage

DOI: 10.1177/1420326X11409452
Accessible online at http://ibe.sagepub.com

Marko Hyttinen,
Department of Environmental Science, University of Eastern Finland, P.O. Box 1627, FI-70211, Kuopio, Finland, Tel. +358-40 355 3220, Fax +358-17-163 191, E-Mail marko.hyttinen@uef.fi

of the outbreak; e.g. the SARS outbreak in Canada in 2003 was initiated by a single case. In addition, suspected influenza patients may be isolated if there is a threat of pandemic outbreak (avian, swine influenzas).

When airborne transmission is a concern, isolation is usually achieved by negative pressure in an AIIR. In addition to general ventilation, other control methods such as local exhaust ventilation, high-efficiency particulate air (HEPA) filtration and ultraviolet germicidal irradiation (UVGI) are applied to prevent the spread of infectious agents. Considerable research has been done in this area in the US, and several AIIR guidelines have been produced. Much of this work has been done during the past 15 years. In the UK, guidance has also been issued for the design of a neutral pressure isolation room with a positively pressurised anteroom [1,2].

This paper presents a review of the current scientific knowledge of performance of AIIRs. The review focuses on airborne transmission of infections, ventilation strategies and current conception of the use of auxiliary devices in AIIRs, such as portable room-air cleaners and UVGI systems to prevent the spread of infectious agents.

Pathogen-Containing Particles

Among infections that are transmitted through air, tuberculosis (TB) has been studied most widely. It has been generally assumed that pathogen-containing droplets produced by coughing and sneezing quickly evaporate to droplet nuclei, the size of which is $\leq 5\,\mu m$ and which remain airborne for a long time [3]. The facile transmission of TB in air was demonstrated in the 1950 s through experiments in which guinea pigs were exposed to the air vented from a TB ward and became infected. However, these size estimates were based mainly on the assumption that the alveolar region is the target size. Even though 2 μm TB bacilli droplets seem to be clearly more infective than 12 μm particles, infection can also occur in the upper respiratory tract [4].

Historically, the risk of droplet transmission has been thought to reach only to a distance of 1 m. This is partly because of the limitations of sampling methodology used in those days. Based on results obtained by high-speed photography or counting of droplets after collection on a slide or plate, it was concluded that droplets were coarse and they settled quickly. Even though 1 m is still considered to be the limit between short-range and long-range airborne infection routes, the distinction between droplet and airborne transmission has been found to be difficult. Aerosolised particles up to 100 μm can remain suspended in air when room-air currents exceed the particle-settling velocities [5]. Droplet sizes are often classified as large droplets ($>60\,\mu m$), small droplets ($<60\,\mu m$) and droplet nuclei ($<10\,\mu m$). ASHRAE [6] considers the mass median aerodynamic diameter (MMAD) of 10 μm as the upper size limit for airborne transmission. Small droplets may participate in short-range transmission, but before falling out of the air, they are more likely than large droplets to evaporate to become droplet nuclei and have the potential for long-range airborne transmission. However, estimates given by different researchers for droplet emission and their behaviour in the air vary with measurement methodology, tested individuals, expiratory activities, environmental conditions (relative humidity, temperature), and timing used in the investigation, which largely explains different results. In addition, test subjects have usually been healthy young individuals, which probably emit droplets with different size and concentration than unhealthy persons. According to theoretical estimates, Xie et al. [7] have shown that droplets with initial sizes between 60 and 100 μm can totally evaporate before falling a distance of 2 m. These droplets can be carried over 6 m away by exhaled air at velocities produced by sneezing ($50\,m{\cdot}s^{-1}$) and over 2 m away at a velocities produced by coughing ($10\,m{\cdot}s^{-1}$), but less than 1 m away at velocities produced by breathing ($1\,m{\cdot}s^{-1}$). Yang et al. [8] analysed coughed droplets from 54 healthy test subjects, found the droplet size to range from 0.6 to 16 μm. They also analysed the size of initial droplets, and found that the mode was at 8.4 μm. The size of droplet nuclei formed was in the range of 0.6–5.4 μm, 82% of them being smaller than 2.1 μm.

Modern optical on-line instruments are capable of measuring wide particle size distributions with real-time response. These new devices have given new perspective to the formation of droplet nuclei. Morawska et al. [9] measured particles in exhaled air at a distance of 10 mm from the mouth by aerodynamic particle sizer (TSI model 3312 A; detects particles in diameter range 0.3–20 μm) and found that most of the particles were below 0.8 μm. The highest number of particles was generated during speaking (average concentration in the size range of 0.5–10 μm with $1.088\,particles{\cdot}cm^{-3}$), followed by coughing (respective average was $0.678\,particles{\cdot}\,cm^{-3}$). Their results were similar to those obtained by Papineni and Rosenthal who were using an optical particle counter (Climet model C17300) [10]. They also noticed that exhaled droplets from healthy human subjects were mainly (80–90%) less than 1 μm, much smaller than previously detected.

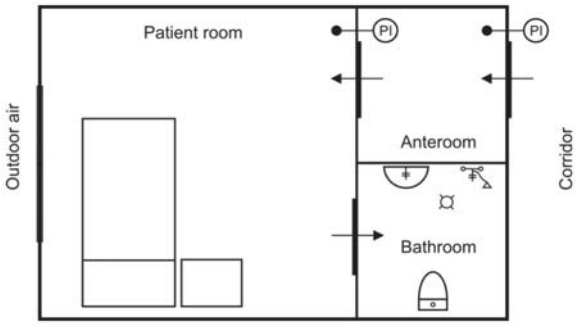

Fig. 1. Diagram of an airborne infection isolation room. Note: The arrows show the direction of air flows.

They did not investigate sneezing, which appears to generate the highest number of particles. Sneezing introduces up to 40,000 droplets [5], whereas a cough or talking for 5 min generates 3000 droplet nuclei [11]. A flow rate of $8.1\,L{\cdot}s^{-1}$ has been given for coughing with the initial velocity of $30\,m{\cdot}s^{-1}$, which decreased to about $2\,m{\cdot}s^{-1}$ one metre away from the mouth [12]. The particle numbers were approximately 10^2 for coughing ($<10\,\mu m$) and 10^5 for sneezing ($<40\,\mu m$) [13]. As a summary, there is no clear unanimity on the issue. ASHRAE [6] has concluded that there is not enough data to describe the particle size distributions of cough-generated aerosols. In addition, it has been advised to pay attention also to agents, which, under special circumstances, may be transmitted through the air [14]. This group includes, in addition to SARS-causing corona virus and influenza viruses, several other pathogens; for example, *Staphylococcus aureus*, adenoviruses, respiratory syncytial virus (RSV) and rhinoviruses [15]. Even though coughing generates the highest particle concentrations, it should be kept in mind that infectious aerosols may also be generated during normal breathing; for example, influenza patients have been shown to emit submicron particles containing influenza virus also during their tidal breathing [16].

Pressure Difference and Ventilation

A diagram of a typical negative pressure isolation room with designed air paths and pressure monitoring is shown in Figure 1. The isolation room is a single-patient room with a bathroom and anteroom. The protection between the isolation room and adjoining areas is established by pressure differential, while staff protection inside the AIIR (outside the 1-m droplet transmission range) depends on air flow patterns within the AIIR, which are affected by the location of supply and exhaust diffusers [17]. The patient should be placed in a well-ventilated area of the room [18]. Mixing ventilation systems are commonly used in hospital rooms, but displacement ventilation systems are also used [19,20]. To maintain the negative pressure, the exhaust air flow rate must be greater than the supply air flow rate.

In the US, the pressure difference recommendation was only 0.25 Pa until the year 2000. According to the most recent US guidelines, the negative pressure of the room should be at least 2.5 Pa and ventilation ≥ 12 ACH (air exchanges per hour) for new AIIRs and 6 ACH for existing rooms [15,21–23]. However, national and international guidelines for AIIRs vary considerably. For example, a high pressure difference (Δp) of 30 Pa is recommended in Australia [24]. There is not sufficient scientific evidence for the pressure difference limit values needed to prevent the escape of infectious air from the AIIR. Technically, small Δp is difficult to maintain constantly in variable weather conditions, especially if the AIIR is untight. In addition, even if Δp between the corridor and AIIR is adequate, some air always escapes during ingress and egress of staff between corridor and AIIR. There should be a permanently installed pressure monitor. Airflow movement should be from clean area towards the patient. The velocity of air should not exceed $0.25\,m{\cdot}s^{-1}$ [25]. The door should be self-closing. However, AIIRs with an anteroom may deviate from the above ventilation guidelines, especially if the patient is also immunocompromised [21].

The ventilation characteristics have been widely investigated. Studies have usually included mechanical supply and exhaust flow rates, air velocities and directions, and differential pressures. In addition, blower door and smoke tube tests have been conducted to investigate AIIR leakage.

Tracer gas measurements have been done to determine effective air exchange rates and to study exfiltration of air into the anteroom and hallway. The dispersion of infectious particles has been simulated with tracer gases and aerosols. Sulphur hexafluoride has been widely used to test isolation rooms [26]. Aerosol tracers have included fluorescent oleic acid [27], mineral oil [28], fluorescent plastic microspheres [29], and potassium iodide [26]. The generated particles should ideally have similar aerodynamic size as the actual airborne pathogens. However, the air velocity in AIIRs are so high due to efficient ventilation that tests conducted using a gas tracer and 3–5 μm salt particles provide a good representation of the behaviour of two bacteria (*Bacillus subtilis* and *S. aureus*) [30]. A patient in the bed generates a turbulent thermal plume, which may

affect the spread of small infectious particles released by the patient [31]. The study made by Cheong and Phua used computational fluid dynamics (CFD) modelling supplemented with tracer gas tests indicated that exhaust openings should be located at low levels and near the patient [32]. Tests were made in single-patient isolation room (16 m^2) with unrealistic high ventilation rates of 29.9 ACH. Controversially, Qian and Li came to conclusion by using experimental (tracer gas SF_6 and particles) and computational (CFD) methods that more efficient removing of fine particles and gaseous compounds were achieved by using ceiling-level exhaust than using floor-level exhaust close to the bed heads [33]. They came to the conclusion that impurities flow upwards more easily than downward because of the thermal plume by the patient. Even for the large particles ($\geq$40 μm), deposition played a major role for removing; indicating that floor-level exhaust was not much more efficient in removing particles than the ceiling-level exhausts. Floor-level exhausts were also said by healthcare workers to be inconvenient, because they were located close to the bed heads where space is needed for clinical use. Qian and Li made tests in six-bed isolation room with supply ventilation rate of 12 ACH, while the exhaust was 13.2 ACH.

Tracer gas studies done in a test chamber simulating an AIIR (one supply air vent on ceiling and one exhaust vent behind bed) indicated that best protection for the healthcare workers was achieved with the highest pressure difference (−15 Pa) and ventilation rate (24 ACH). However, the former was more important so that −15 Pa/12 ACH was more effective than −8 Pa/24 ACH. This was attributed to larger air flow through door gaps in the former situation [34].

Alevantis et al. [35] studied the leakage of environmental tobacco smoke from 23 smoking areas to adjacent non-smoking areas and concluded that some of the smoking areas had characteristics similar to those of AIIRs. Based on tracer gas measurements in five such smoking areas, they suggested that the negative pressure in an AIIR should be at least −7 Pa to prevent the leakage from exceeding 1%. However, the similarity of these smoking areas with AIIRs was limited to exhaust to the outside and no intended air recirculation. Their ventilation rates were lower and two of these five smoking areas were overpressurised.

Ideally, room airflow should be laminar. This is, however, difficult to achieve in reality due to spatial restrictions and, consequently, turbulence eddies cause airborne pathogens to recirculate within the room space [36]. There should be no furniture in the path of the airflow from the air supply vent to the exhaust terminal, which should locate near the patient [32,33].

Studies done in the US indicate that the US ventilation guidelines are often violated in AIIRs. The large surveys conducted in the 1990s, showed that 28–45% of the rooms investigated were even positively pressurised relative to surrounding areas [37–39]. Saravia et al. [40] found that only 32% of the 672 AIIRs investigated achieved the recommended pressure difference of −2.5 Pa relative to surrounding areas, 9% of the rooms were positively pressurised. The ventilation recommendation of 12 ACH was fulfilled in 51% of the rooms. Permanently installed pressure monitors were in 76% of the rooms. Self-closing doors were installed in 36% of the rooms. The particle concentrations in the AIIRs were more similar to concentrations in the surrounding areas than in the supply air, suggesting that more of the air entering the AIIRs came from the surrounding areas than from the supply air. Presumably air flow leakage rates were responsible for similar particle concentrations. Li et al. [41] evaluated ventilation performance of SARS isolation wards in nine hospitals in Hong Kong. They found that the pressure difference criteria of −2.5 Pa was met in 97% of the 38 rooms tested (mean −7.7 Pa for all the rooms tested). However, high fluctuation of the pressure difference (highest value 38 Pa) was detected, and it was found to depend on age of HEPA filter and the supply and exhaust fans. Replacement of the exhaust HEPA filter increased the pressure difference. In spite of using state-of-the-art technologies, 28% of the tested AIIRs had ACH < 12.

Pressure difference fluctuation was also monitored in four AIIRs with anterooms and eight standard rooms at the University of Minnesota Hospital [42]. The study was conducted in 1996 when the pressure difference guideline for AIIRs was still −0.25 Pa. The mean pressure difference (−0.3 Pa) was only slightly higher in the AIIRs than in the standard rooms (−0.2 Pa). In addition, the AIIRs with anterooms had more pressure fluctuation than the standard rooms. However, most of the AIIRs and their anterooms had an overall negative pressure as intended. The ventilation rates were greater than 6 ACH but less than 12 ACH.

Door-slot and other types of leakage are important for the performance of AIIRs. Hayden et al. [43] studied leakage area, flow differential, and pressure difference in an experimental room where leakage areas were known. He developed the following model (in SI units) between leakage area (A), pressure difference (Δp) and the flow differential (ΔQ = exhaust flow rate − supply flow rate): $A = 4.891 \cdot \Delta Q^{1.170} / \Delta p^{0.602}$. This model can be useful in

helping to design an AIIR that performs well and is energy efficient. In the US, the gap under a standard door is approximately 1 cm ($0.02\,m^2$). If the pressure difference is 2.5 Pa, the air velocity in the slot would be about 2 m/s [44].

Insufficient tightness in joints and penetrations in the room envelope makes it difficult to control air flow rates and pressure differentials. Often, unintended leakage sources, such as electrical and other outlets, ceiling, and plumbing dominate. The tests conducted in 8 real isolation rooms indicated that, in addition to the door, the ceiling is the other major contributor to the leakage [45]. Isolation rooms with solid ceilings had an average pressure differential of −4.4 Pa whereas the differential was −2.0 Pa in the rooms with suspended ceilings. The calculated airflow differential required for the pressure difference of 2.5 Pa was also smallest (20–29 $L{\cdot}s^{-1}$) in two rooms with solid ceilings and which were made as airtight as possible during construction. The corresponding offset flow requirements ranged from 99 to 148 $L{\cdot}s^{-1}$ in rooms with suspended ceilings. However, it was possible to decrease the leakage about 50% (achieving offset flow requirements of 68 and 79 $L{\cdot}s^{-1}$) by remodelling (two rooms) of the suspended ceiling by replacing them with tighter ones. The study also indicated that the (125 cfm, 59 $L{\cdot}s^{-1}$) airflow differential which has been used as an US guideline is too low for suspended ceiling rooms.

Flow rate differential between the exhaust and supply air was the only statistically significant factor in determining the migration of air from the AIIR to the area outside of the room during ingress or egress in the tracer gas tests conducted by Hayden et al. [46]. The type of door (swinging or sliding), nominal leakage areas into the AIIR, or pressure differential showed no major effect (as pressure difference was mostly lost when the door opened as did the overwhelming effect of the area of the open door negate existing AIIR leakage area effect). Marshall [18] suggested that the ventilation standards should, in principle, be based on airflow per patient instead of using air changes per hour according to the general principles of source control. The patient is the source of infectious agents in an AIIR. The recommendation of at least 12 ACH would correspond to 410 $m^3{\cdot}h^{-1}$ per patient in a standard 23 m^3 room. However, the present practice is convenient if dilution ventilation is applied, because the number of air changes affects the decrease rate (via dilution) of the concentration of the infectious aerosol after a release event, such as cough or sneeze. There is some evidence that low ventilation rates (ACH below 2 h^{-1}) are associated with increased infection rates or outbreaks of airborne diseases in healthcare settings [47].

Anterooms and Restrooms

Anterooms provide additional protection, especially when the isolation room door is opened. The anteroom also provides a convenient location for hand washing and possibly for storage of respirators. There are three main anteroom airflow strategies: (1) negative isolation room/balanced anteroom strategy, (2) positive pressure in the anteroom, and (3) negative pressure in the anteroom [21,48]. Strategy 1 is probably the most commonly used. In this scenario, exhaust flow clearly exceeds the supply air flow in the isolation room but there is balanced ventilation in the anteroom. It provides dilution and two door barriers. In addition, healthcare workers do not need to wear respiratory protection prior to entry into the anteroom. In strategy 2, positive pressure in the anteroom can improve negative pressure in the isolation room but may push microbes into the corridor if those, nevertheless, leak to the anteroom. In strategy 3, negative pressure in the anteroom helps to prevent leakage to the corridor but simultaneously can reduce the negative pressure of the isolation room. In this case, healthcare workers must also wear respiratory protection prior to entering the anteroom. Strategy 2 is recommended especially for contagious patients who also are immunocompromised. The British version of strategy 2 is described later as a neutral pressure isolation room.

Tracer gas test conducted in four similar, strategy 3-type AIIRs in a new Norwegian hospital indicated that complete containment could not be achieved in spite of high negative pressure differentials (approximately, 15 and 30 Pa for corridor–anteroom and corridor–patient room, respectively) and high ventilation rates (15–21 ACH in the patient room and 44–47 ACH in the anteroom) [49]. The initial dilution factor in the anteroom after moving from the patient room to the anteroom was only about 16 but increased to 150 by waiting 3 min in the anteroom. The dilution factor was about 3000 in the corridor at 10 min after the release of the tracer.

Surprisingly, few studies on the effect of the anteroom on pressure differences of AIIRs have been conducted. Dahl et al. [50] investigated 156 AIIRs with smoke tests and found that 51% of them were under negative pressure, and that the presence of an anteroom was associated with negative pressure. On the other hand, Saravia et al. [40] did not find any significant influence of the presence of an

anteroom upon the pressure differential of AIIRs. Streifel et al. [51] followed the pressure conditions in an un-occupied AIIR over a week during which the doors were occasionally opened. The supply air flow was $80\,L{\cdot}s^{-1}$ and exhaust rate $110\,L{\cdot}s^{-1}$. The offset flow was thus only $30\,L{\cdot}s^{-1}$. The ceiling had many small holes. The average pressure difference between the patient room and the anteroom (its ventilation data were not given) was low, −0.36 Pa. The average difference between the patient room and the hall was even lower, only −0.03 Pa. During door openings between the anteroom and the patient room, the pressure differential between these rooms increased to −30 Pa for a few seconds. However, there was a reverse pressure pulse of 10 Pa after closing the door.

The bathroom should always be negatively pressurised relative to the patient room. The bathroom of the AIIR studied by Streifel et al. [51] had a negative pressure of −0.50 Pa relative to the patient room. However, in a recent study, Li et al. [41] noticed that there were air flows outwards in 40% of 57 bathrooms tested when the doors were closed although there was no mechanical air supply in bathrooms [41]. The reason for this was due to wrong sealing of the pipes in the suspended ceiling. Bi-directional flow was also detected in over 90% of the other doors tested (corridor–anteroom or anteroom–AIIR).

Neutral Pressure Isolation Room

The principle of a neutral pressure isolation room incorporates a positively pressurised ventilated anteroom (lobby) providing a barrier to airborne infection originating within the isolation room, whereas the pressure differential between the isolation room and the adjacent corridor is close to zero [2]. This kind of isolation also provides protection against microbes originating in the corridor (i.e. protective isolation) and is an alternative for switchable isolation rooms that can be set to function with either negative or positive pressure rooms. However, the design offers no pressure differential to protect against airflow from the patient room into adjacent (non-anteroom) areas by means of cracks or gaps around room penetrations. The design pressure in the anteroom is 10 Pa above that in the corridor when all the doors are closed. The isolation room is intended to have 10 ACH mixing ventilation [2].

In the tracer gas tests conducted in a full-scale experimental facility with suspended ceiling and air leakage of $1\,L{\cdot}s^{-1}{\cdot}m^{-3}$ at 20 Pa ($5\,m^3{\cdot}h^{-1}{\cdot}m^{-2}$ at 50 Pa), there was only small migration from the isolation room to the corridor when all the doors were closed (the protection factor i.e. dilution ratio was 10^5). However, tracer gas entered the anteroom after door opening but only a very small loss of tracer from the anteroom to the corridor was observed. On the other hand, this kind of arrangement does not provide protection to healthcare workers within the isolation room and the use of appropriate personal protection equipment (PPE) is needed [2].

Local Exhausts, Filtration and Portable Air Cleaners

Source-control techniques can prevent or reduce the spread of infectious aerosols into the air. Due to the thermal plume generated by the patient, local exhausts control infection spread most effectively when placed above the patient's head [27,31]. However, room-air motion affects the dispersion of expiratory droplets [52]. In addition, it is difficult to achieve a capture velocity high enough without causing thermal discomfort and noise for the patient.

On the other hand, source-control techniques have been used especially during critical procedures of TB patients (e.g. bronchoscopy, sputum induction, endotracheal intubation, and aerosol treatment). According to the Centers for Disease Control and Prevention (CDC) guidelines, [21] HEPA filter should be incorporated at the discharge duct of exhaust from enclosing devices (booths and tents) and local exhaust hoods. A HEPA filter can arrest 99.97% of 0.3 μm particles. It is crucially important to capture infectious microbes near the source before they are dispersed throughout the room. If a hood is used, the patient should face directly into the opening of the hood and the control velocity should be $1\,m{\cdot}s^{-1}$. HEPA filters can also be used to remove infectious particles (especially TB droplet nuclei) from air that is recirculated or exhausted directly to the outside. The exhaust fan should be located on the discharge side of the HEPA filter to ensure negative pressure before the filter. Commercially available booths, tents, and hoods generally include HEPA filtration and no additional filtration is needed [21].

Room-air cleaning and recirculation can be used if the general ventilation system is incapable of providing sufficient air exchange. Recirculation of HEPA-filtered air can be done with the general ventilation system or using separate HEPA recirculation units [21]. The efficiency of room-air recirculation systems is often expressed as equivalent ventilation rate, i.e. the ventilation

rate that is needed to achieve the same disappearance rate of microbes. Usually, clean air delivery rate (measures how much clean air an air purifier delivers to a room per unit time) is also given. Commercial portable filtration units have flow rates from 200 to 2000 $m^3 \cdot h^{-1}$. Equivalent ACH can exceed 20 [21]. When a portable unit provided 13 ACH in a hospital room it removed 90% of particles larger than 0.3 μm within 5–8 min. The flow rate appeared to be the most important factor for particle removal [28].

With the exception of electrets filter media, the pressure drop across the filter increases with the efficiency of the filter. Although new HEPA filters having large surface areas cause relatively low pressure drop compared to the previous HEPA types, they, nevertheless, cause larger pressure drop (i.e. higher energy demand) than 90% efficient filters. In applications, where air flow is crucial, such as in-rooms air filtration and dilution ventilation for TB infection control, the use of a 90% efficient filter instead of a HEPA filter presumably reduces the removal efficiency only marginally. The efficiency of in-room air filtration can be estimated reasonably well using a completely mixed room model [53].

When filters are installed, care must be taken to prevent leakage between the filter segments and between the filter bed and its frame. Persons performing maintenance and replacing filters should wear respirators, eye protection, and gloves [21].

UVGI and Ionisation

Both UVGI and negative air ionisation appeared to provide effective control against airborne transmission of tuberculosis when the classical experiment where guinea pigs were exposed to exhaust air from a TB ward was recently replicated. In this test that lasted for 535 days, UVGI prevented 70% of TB infection and 54% of TB disease. The corresponding percentages for ionisation were 60% and 51% [54]. UVGI lamps are used especially in the AIIRs of TB patients. The optimal germicidal effect is obtained with UV-C ($\lambda = 254$ nm) radiation [1,55]. In order to prevent human exposure (the main risk is inflammation of the cornea of the eye), the irradiation should be arranged either as induct or upper-room air irradiation. In the former, UV lamps are installed inside the exhaust ducts of the recirculating air-handling system. In the latter system, UV lamps are mounted on the ceiling or on the upper parts of the walls. The lamps must be shielded to direct radiation upward to prevent exposing people. The ceiling and wall should be painted with non-reflecting coatings. The upper-room UV is generally used [36,56].

Portable filter units and UVGI can be applied simultaneously, and their removal rates are additive [57]. The cost of UVGI is low; therefore, it can also be used in resource-limited settings [54]. UVGI is silent, draftless and energy efficient. Even though the efficiency of UVGI was demonstrated long ago, little research followed after development of effective antibiotics. The widely applied US guidelines; one 17-W suspended lamp or one 30-W wall lamp per 19 m^2 of floor area is largely based on experiments done in the 1970 s [36]. However, after the rise of multi-drug-resistant tuberculosis, the research has been activated again. The spread of infections caused by human immunodeficiency virus (HIV) is another reason for increased concern about tuberculosis, because reduced immunity may lead to activation of a dormant tuberculosis infection.

Recently, CDC/NIOSH [58] published new comprehensive UVGI guidelines, which provide an overview of the current knowledge concerning upper-room UVGI systems. Although other pathogenic microorganisms may be killed or inactivated by UVGI, the guidelines were developed especially to control mycobacteria.

The effectiveness of UVGI is also often expressed as equivalent ventilation. Equivalent ventilation rates as high as 10 ACH were reported for mycobacteria in the experiments conducted in the 1970 s [59]. This was also the experiment on which the above US recommendations are based. However, the shields added to the lamps to improve their safety to occupants also reduce their efficiency [36]. The efficiency also depends on the particle size of the airborne microbes (microbes contained in small particles are more sensitive) and humidity of air (decreased susceptibility at high humidity). In addition, the sensitivity of microbes varies. Mycobacteria are intermediate in their sensitivity [1,36,60] However, equivalent ventilation rates of 4–6 ACH were detected even for *B. subtilis*, which is tolerant microbe with a single 15-W lamp in a 36 m^3 room [61]. On the other hand, little is known concerning the effective practical application of UVGI in hospitals [36]. In addition, UVGI suffers from an inherent problem: as the ventilation rate increases, the length of air irradiation time decreases. The optimal relationship between them is not known and is likely to be organism specific. According to CFD simulations, the optimum ventilation rate is about 6 ACH when UVGI is used [62]. The simulations also suggest that particle deposition on surfaces is an important factor. The buoyancy effects are also important in the

CFD simulations and non-isothermal simulations should be performed [63].

The recommended threshold limit value for an 8-h period for UV-C is 6.0 $mJ \cdot cm^{-2}$. For other exposure times, the permissible exposure time in seconds is 0.006 $J \cdot cm^{-2}$ per measured irradiance level ($W \cdot cm^{-2}$). This exposure limit may be exceeded by the use of UVGI and, therefore, the exposure levels should always be measured [60].

Artificial ionisation of air (usually with negative charge) leads to unipolar ionisation of airborne particles, which consequently repel and migrate towards surfaces and are eventually deposited onto walls and other charged surfaces. Ionisation is a controversial method. It has been claimed to have beneficial biological effects, but the results have been inconsistent. In addition, the ion generators may also produce ozone. Air ionisation has its maximum effect on particles that are about 0.02 μm in size; efficiency decreases below this size due to slow charging rate and above this size due to small electrical mobility of particles [64]. Ionisation was found to prevent the transmission of Newcastle virus-containing particles in experiments carried out with chickens [65]. Ionisation was also found to decrease the concentration of rather large *S. aureus* bearing skin particles in a burn unit [66]. As a possible explanation, it was suggested that the shedding of microbial particles was inhibited by their immediate charging causing their fixing to their origin. Recent studies have shown that most of the reduction of biological particles due to air ionisation occurs though the physical removal of charged particles and not through inactivation of viable microorganisms [67]. As mentioned earlier, negative ionisation caused a significant reduction of TB infection and disease in guinea pigs exposed to air from a TB ward [54]. Even though negative air ionisation has not yet been studied in conjunction with human TB infections, it has been found to reduce Acinetobacter infections in an intensive care unit. On the other hand, no change in methicillin resistant *S. aureus* cases was detected [68].

Temporary Negative Pressure Isolation

During large-scale airborne infectious disease outbreaks, the normal AIIR capacity is insufficient to meet the increased needs. In the US, several authorities and organisations have provided instructions on building temporary negative pressure isolation (TNPI) installations for such situations. Researchers from Minnesota [69] and Oklahoma [70] have given detailed instructions for building TNPIs.

The Minnesota guidelines limit the use of curtain TNPI for non-ambulatory patients. The plastic sheeting must also be fire-rated. The preferred method to clean contaminated air and induce negative pressure is to provide an ordinary room with a portable HEPA filter machine and to discharge the air to the outside or to a return air system. TNPI can be provided with a portable anteroom [69].

The expedient isolation zones of the Oklahoma guidelines, which were constructed by using portable particulate air filtration and full-length plastic curtains, have also been tested. In the tests conducted in containments erected around two adjacent beds, the total HEPA unit flow rate was 930 $m^3 \cdot h^{-1}$, which provided 32 ACH within the enclosures. In the aerosol generation tests, the containments were effective in maintaining particle containment. Mean respirable particle counts were from 30% to 87% lower at the healthcare worker position than those measured near the patient. Particle concentrations outside the containments could not be distinguished from background [70,71]. The results of these tests have also been presented as protective time equivalent (PTE), which indicates the equivalent waiting time (provided immediately) for safe entry (99% of airborne particles cleaned) into potentially contaminated area as compared to a traditionally isolation room with 12 ACH. A 69-min wait before re-entry is needed with the recommended ventilation rate of 12 ACH. The mean PTE was similar, 87–88 min, for both of the configurations studied [72].

Conclusion

There is a great variation in national AIIR guidelines. Even the US guidelines, which are the most extensive ones and periodically updated, do not contain definite background data. The performance of AIIRs has been tested in numerous studies. The main aim has traditionally been to find out how well the existing AIIRs would fulfil the national, especially US guidelines. Probably due to historical reasons, mixing-type ventilation has been emphasised. Thus, a lot of attention has been paid to air exchange rates. However, it is easy to calculate that even if the ventilation rate exceeds the recommended 12 ACH, the waiting time for safe entry after release of airborne pathogens into an AIIR would be unrealistically long, about 1 h. Nevertheless, because the risk of infection is proportional to the concentration of infectious agents in the air, adequate ventilation reduces the risk of infection. In addition, studies have shown that a better protection of the healthcare workers is achieved by providing supply air from the ceiling in the

front part of the room and directing air flow towards the patient. However, results obtained about the location of exhaust air whether the near patient head or ceiling level are diverse and need to be studied more. Nevertheless, personnel should always wear proper respirator protection when entering an AIIR with a contagious patient. The most crucial requirement for the proper function of the ventilation system is that it should minimise the escape of contaminated air from the AIIR. This can be accomplished by removing or diluting infectious agents in the air and maintaining sufficient negative pressure between the AIIR and adjacent spaces. It is also important that the AIIR structures minimise air leakage because a tight room saves energy by minimising offset and exhaust volume to achieve the desired pressure differential. It is important to inspect the AIIR for air leakage already during and after construction. An anteroom increases the protection of an AIIR, especially during door opening. There are, however, insufficient data to optimise pressurisation between the corridor, anteroom, and AIIR.

Recent investigations on TNPI have demonstrated that good containment can be achieved through simple and inexpensive construction if good air flow patterns are created. On the other hand, complete containment seems to be impossible in spite of the use of very high pressure differential and exchange rate. Control efficiency can be enhanced by using auxiliary devices, such as portable air cleaners and UVGI systems. Tuberculosis is an especially serious problem in poor countries and often worsened by widely spread HIV infection. Low-cost control methods, such as UVGI and possibly ionisation, provide realistic remedies to alleviate the situation.

Management of these expensive spaces requires knowing what controls are necessary for cost-effective risk management. Minimising discharge of tempered air, while maintaining consistent airflow direction in AIIR, would provide an effective method for airborne infection control. However, these control experiences require continuous updating for developing infectious disease prevention best practice.

Disclaimer

The findings and conclusions in this report have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

References

1 Booth W, Arribas BB: Characterisation of contaminant distribution in a neutral pressure isolation room: in Roomvent 2007, Helsinki, June 2007, pp. 13–15.
2 Fletcher A, Booth W, Arribas BB: Validation of a neutral pressure isolation room: in Proceedings of Clima 2007 WellBeing Indoors, Helsinki, 10–14 June, 2007, pp.8.
3 Nardell EA: Disinfecting air: in Spengler JD, Samet JM, McCarthy JF (eds): Indoor Air Quality Handbook, Vol. 11, Ch. 13, New York, McGraw-Hill, 2000, pp. 1–11.
4 Nicas M, Nazaroff WW, Hubbard A: Toward understanding the risk of secondary airborne infection: emission of respirable pathogens: J Occup Environ Hyg 2005;2:143–154.
5 Cole EC, Cook CE: Characterization of infectious aerosols in health care facilities: Am J Infect Control 1998;26:453–464.
6 ASHRAE: ASHRAE Position Document on Airborne Infectious Diseases: Atlanta, GA, American Society of Heating, Refrigerating and Air-Conditioning Engineers, 2009, p. 17.
7 Xie X, Li Y, Chwang ATY, Ho PL, Seto WH: How far droplets can move in indoor environments – revisiting the Wells evaporation-falling curve: Indoor Air 2007;17:211–225.
8 Yang S, Lee GWM, Chen C-M, Wu C-C, Yu K-P: The size and concentration of droplets generated by coughing in human subjects: J Aerosol Med 2007;20:484–494.
9 Morawska L, Johnson GR, Ristovski ZD, Hargreaves M, Mengersen K, Corbett S, Chao CYH, Li Y, Katoshevski D: Size distribution and sites of origin of droplets expelled from the human respiratory tract during expiratory activities: J Aerosol Sci 2009;40:256–269.
10 Papineni RS, Rosenthal FS: The size distribution of droplets in the exhaled breath of healthy human subjects: J Aerosol Med 1997;10:105–116.
11 Fitzgerald D, Haas DW: Mycobacterium tuberculosis: in Mandell GL, Bennet JE, Dolin R (eds): Principles and Practice of Infectious Diseases, 6th edn, Philadelphia, Churchill Livingstone, 2005, pp. 2852–2886.
12 Liu L, Li Y, Nielsen PV, Jensen RL, Litewnicki M, Zajas J: An experimental study of human exhalation during breathing and coughing in a mixed ventilated room: in Proceedings of Healthy Buildings 2009, Syracuse, NY, 13–17 September, 2009, paper 162.
13 Chen SC, Chio CP, Jou LJ, Liao CM: Viral kinetics and exhaled droplet size affect indoor transmission dynamics of influenza infection: Indoor Air 2009;19:401–413.
14 Roy CJ, Milton DK: Airborne transmission of communicable infection: the elusive pathway: N Engl J Med 2004;350:1710–1712.
15 Siegel JD, Rhinehart E, Jackson M, Chiarello L: Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings, the Healthcare Infection Control Practices Advisory Committee 2007. Available at: http:/www.cdc.gov/ncidod/dhgp/isolation2007.pdf (accessed November 20, 2009).
16 McDevitt J, Fabain P, Milton D: Influenza virus in fine particles exhaled breath: in Proceedings of Healthy Buildings 2009, Syracuse, NY, 13–17 September, 2009, paper 546.
17 Booth W, Beato B, Noakes C, Fletcher L, Sleigh A, Tomlinson N: Characterisation of the protection provided by the ventilation strategy in hospital isolation rooms: in Proceedings of Healthy Buildings 2009, Syracuse, NY, 2009, paper 685.
18 Marshall JW, Vincent JH, Kuehn TH, Brosseau LM: Studies of ventilation efficiency in a protective isolation room by the use of a scale model: Infect Control Hosp Epidemiol 1996;17:5–10.
19 Gulick B, Guity A, Marmion P: Healthcare ventilation research collaborative displacement ventilation research report, Phase II summary report 12/20/09, 2009.
20 Tang JW, Li Y, Eames I, Chan PKS, Ridgway GL: Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises: J Hosp Infect 2006;64:100–114.

21 CDC: Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-care Settings: MMWR 2005:54, Washington, DC, CDC, 2005.
22 American Institute of Architects: Guidelines for Design and Construction of Health Care Facilities, Washington, DC, American Institute of Architects, 2006.
23 American Institute of Architects: Guidelines for Design and Construction of Health Care Facilities, Washington, DC, American Institute of Architects, 2001.
24 Victorian advisory committee on infection control: Guidelines for the Classification and Design of Isolation Rooms in Health Care Facilities. Victoria, Victorian Advisory Committee on Infection Control, 1999.
25 ANSI/ASHRAE Standard 55-1992: Thermal Environmental Conditions for Human Occupancy. Atlanta, GA, American Society of Heating, Refrigerating and Air-Conditioning Engineers, 1992.
26 Walker JT, Hoffman P, Bennet AM, Vos MC, Thomas M, Tomlinson N: Hospital and community acquired infection and the built environment – design and testing of infection control rooms: J Hosp Infect 2007;65:43–49.
27 Chau O, Liu C-H, Leung M: CFD analysis of the performance of a local exhaust ventilation system in a hospital ward: Indoor Built Environ 2006;15:257–271.
28 Rutala WA, Jones SM, Worthington JM, Reist PC, Weber DJ: Efficacy of portable filtration units in reducing aerosolized particles in the size range of *Mycobacterium tuberculosis*: Infect Control Hosp Epidemiol 1995;16:391–398.
29 Johnson DL, Lynch RA, Mead KR: Containment effectiveness of expedient patient isolation units: Am J Infect Control 2009;37: 94–100.
30 Noakes CJ, Fletcher LA, Sleigh PA, Booth WB, Beato-Arribas B, Tomlinson N: Comparison of tracer techniques for evaluating the bahaviour of bioaerosols in hospital isolation rooms: in Proceedings of Healthy Buildings 2009, Syracuse NY, 13–17 September, 2009, paper 504.
31 Holmberg S, Alenius S, Chen S-Y: Drug-resistant bacteria in hospital wards – the role of ventilation: in Proceedings of Healthy Buildings 2009, Syracuse, NY, 13–17 September, 2009, paper 596.
32 Cheong KWD, Phua SY: Development of ventilation strategy for effective removal of pollutant in the isolation room of a hospital: Build Environ 2006;41:1161–1170.
33 Qian H, Li Y: Removal of exhaled particles by ventilation and deposition in a multibed airborne infection isolation room: Indoor Air 2010;20:284–297.
34 Tung Y-C, Hu S-C, Tsai T-I, Chang I-L: An experimental study on ventilation efficiency of isolation room: Build Environ 2009;44:271–279.
35 Alevantis LE, Offermann FJ, Loiselle S, Macher JM: Pressure and ventilation requirements of hospital isolation rooms for tuberculosis (TB) patients: existing guidelines in the United States and a method for measuring room leakage: in Maroni M (ed): Ventilation and Indoor Air Quality in Hospitals, Netherlands, Kluwer Academic Publishers, 1996, pp. 101–116.
36 Beggs CB, Donnelly JK, Kerr KG, Sleigh PA, Mara DD, Cairns G: The use of engineering controls to disinfect mycobacterium tuberculosis and airborne pathogens in hospital buildings: Indoor Built Environ 2000;9: 7–27.
37 Fraser VJ, Johnson K, Primack J, Jones M, Medoff G, Dunagan WC: Evaluation of rooms with negative-pressure ventilation used for respiratory isolation in seven Midwestern hospitals: Infect Control Hosp Epidemiol 1993;14:623–627.
38 Sutton PM, Nicas M, Reinisch F, Harrison RJ: Evaluating the control of tuberculosis among healthcare workers: adherence to CDC guidelines of three urban hospitals in California: Infect Control Hosp Epidemiol 1998;19:487–493.
39 Pavelchak N, DePersis RP, London M, Stricof R, Oxtoby M, DiFerdinando G: Identification of factors that disrupt negative air pressurization of respiratory isolation rooms: Infect Control Hosp Epidemiol 2000;21:191–195.
40 Saravia SA, Raynor PC, Streifel AJ: A performance assessment of airborne infection isolation rooms: Am J Infect Control 2007;35: 324–331.
41 Li Y, Ching WH, Qian H, Yuen PL, Seto WH, Kwan JK, Leung JKC, Leung M, Yu SCT: An evaluation of the performance of new SARS isolation wards in nine hospitals in Hong Kong: Indoor Built Environ 2007;16:400–410.
42 Rice N, Streifel A, Vesley D: An evaluation of hospital special-ventilation-room pressures: Infect Control Hosp Epidemiol 2001;22:19–23.
43 Hayden CS, Earnest GS, Jensen PA: Development of an empirical model to aid in designing airborne infection isolation rooms: J Occup Environ Hyg 2007;4:198–207.
44 Streifel AJ: Health-care IAQ: Guidance for infection control: HPAC Heating/Piping/Air Conditioning Engineers, 2000, pp. 28–36.
45 Geeslin A, Streifel A, Nelson G: Air leakage analysis of special ventilation hospital rooms: ASHRAE Trans 2008; 114, SL-08-044: p. 6.
46 Hayden CS, Johnston OE, Hughes RT, Jensen PA: Air volume migration from negative pressure isolation rooms during entry/exit: Appl Occup Environ Hyg 1998;13:518–527.
47 WHO 2009: Natural ventilation for infection control in health care settings. Atkinson J, Chartier Y, Pessoa-Silva CL, Jensen P, Li Y and Seto W-H (eds.), WHO Press. Switzerland. 133.
48 Cali S, Franke J, Conroy L, Scheff P: First, do not harm: indoor air quality in hospitals: J Environ Monit 2000;10:22–29.
49 Rydock JP, Eian PK: Containment testing of isolation rooms: J Hosp Infect 2004;57:228–232.
50 Dahl KM, L'Ecuyer PB, Jones M, Fraser VJ: Follow-up evaluation of respiratory isolation rooms in 10 midwestern hospitals: Infect Control Hosp Epidemiol 1996;17:816–818.
51 Streifel AJ, Bridges BB, Grimsrud DT, Krafthefer BC: Pressure relationships in hospital critical-care facilities: in Proceedings of Indoor Air 99, Edinburgh, Vol. 5, 8-13 August, 1999, pp. 31–36.
52 Pantelic J, Wai TK: Effect of the room air motion on the dispersion of expiratory droplets in the personalized ventilated room: in Proceedings of Healthy Buildings 2009, Syracuse, NY, 13–17 September, 2009, paper 633.
53 Miller-Leiden S, Lobascio C, Nazaroff WW, Macher JM: Effectiveness of in-room air filtration and dilution ventilation for tuberculosis infection control: J Air Waste Manage Assoc 1996;46:869–882.
54 Escombe AR, Moore DAJ, Gilman RH, Navicncopa M, Ticona E, Mitchell B, Frieland JS, Gonzalez A, Sheen P, Evans CA, Ramirez A, Quino W, Martinez C: Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission: PLoS Med 2009;6:312–323.
55 Grossi L: Control of the biologically active particulate by means of filters UV irradiation: in Proceedings of Healthy Buildings 2000, Vol. 2, 6–10 August, 2000, Espoo, Finland, pp. 107–112.
56 First MW, Weker RA, Yasui S, Nardell EA: Monitoring human exposure to upper-room germicidal ultraviolet irradiation: J Occup Environ Hyg 2005;2:285–292.
57 Kujundzic E, Howard C, Hernandez M, Miller S: Effectiveness of portable air cleaners and upperroom ultraviolet germicidal irradiation for infection control: in Proceedings of Indoor Air 2002, Vol. 2, Monterey, CA, 2002, pp. 718–723.
58 CDC: Environmental control for tuberculosis: upper-air ultraviolet germicidal irradiation. US. DHHS, CDC, NIOSH, Cincinnati, OH. DHHS (NIOSH) Pub No 2009-105.
59 Riley RI, Knight M, Middlebrook G: Ultraviolet susceprtibility of BCG and virulent tubercle bacilli: Am Rev Respir Dis 1976;113:413–418.
60 Macher JM, Alevantis LE, Chang Y-L, Liu K-S: Effect of ultraviolet germicidal lamps on airborne microorganisms in an outpatient waiting room: Appl Occup Environ Hyg 1992;7: 505–513.
61 Miller SL, Macher J: Evaluation of a methodology for quantifying the effect of room air ultraviolet germicidal irradiation on airborne bacteria: Aerosol Sci Tech 2000;33:274–295.
62 Memarzadeh F, Jiang J: Methodology for minimizing risk from airborne organisms in hospital isolation rooms: MN-00-11-2, ASHRAE Trans. 2000. pp. 733–749.
63 Heidarinejad M, Srebric J: Importance of non-isothermal indoor conditions for the prediction of upper-room UVGI lamps performance in patient rooms: in Proceedings of Healthy Buildings 2009, Syracuse, NY, 13–17 September, 2009, paper 671.
64 Lehtimaki M and Graeffe G: The effect of the ionization of air on aerosols in closed spaces: in Proceedings of the 3rd International Symposium on Contamination Control, Vol. 2, Copenhagen, 1976, pp. 370–382.
65 Estola T, Mäkelä P, Hovi T: The effect of air ionization on the air-borne transmissions of experimental Newcastle disease virus in-fections in chickens: J Hyg Camb 1979;83:59–67.
66 Mäkelä P, Orajärvi J, Graeffe G: Studies on the effects of ionization on bacterial aerosols in a burns and plastic surgery unit: J Hyg Camb 1979;83:199–206.

67 Grinshpun SA, Adhikari A, Honda T, Kim KY, Toivola M, Rao KSR, Reponen T: Control of aerosol contaminants in indoor air: combining the particle concentration reduction with microbial inactivation: Environ Sci Tech 2007;41:606–612.
68 Kerr KG, Beggs CB, Dean SG, Thornton J, Donnelly JK, Todd NJ, Sleigh PA, Qureshi A, Taylor CC: Air ionization and colonization/infection with methicillin-resistant Staphylococcus aureus and Acininetobacter species in an intensive care unit: Intensive Care Med 2006;32:315–317.
69 Anderson J, Geeslin A, Streifel A: Airborne Infectious Disease Management. Methods for Temporary Negative Pressure Isolation, Minnesota Department of Health, St. Paul, MN, 2007.
70 Johnson DL: Oklahoma State Department of Health Design and Implementation Guidelines for airborne infectious isolation under epidemic emergency response conditions. Available at: http://www.coph.ouhsc.edu/coph/oeh/Isolation%20Guidance%20Document.pdf. 2005 Accessed on 22 April 2010.
71 Mead K, Johnson DL: An evaluation of portable high-efficiency particulate air filtration for expedient patient isolation in epidemic and emergency response: Ann Emerg Med 2004;44:635–645.
72 Mead K: Expedient methods for patient isolation during natural or manmade epidemic response: PhD dissertation, The University of Oklahoma Health Sciences Center Graduate College, Oklahoma City, Oklahoma, 2008.