Indoor Air 2016; 26: 79–87
wileyonlinelibrary.com/journal/ina

INDOOR AIR
doi:10.1111/ina.12232

Keynote: Indoor Air 2014

Indoor environmental control of tuberculosis and other airborne infections

Abstract Tuberculosis (TB) remains the airborne infection of global importance, although many environmental interventions to control TB apply to influenza and other infections with airborne potential. This review focuses on the global problem and the current state of available environmental interventions. TB transmission is facilitated in overcrowded, poorly ventilated congregate settings, such as hospitals, clinics, prisons, jails, and refugee camps. The best means of TB transmission control is source control— to identify unsuspected infectious cases and to promptly begin effective therapy. However, even with active case finding and rapid diagnostics, not every unsuspected case will be identified, and environmental control measures remain the next intervention of choice. Natural ventilation is the main means of air disinfection and has the advantage of wide availability, low cost, and high efficacy—under optimal conditions. It is usually not applicable all year in colder climates and may not be effective when windows are closed on cold nights in warm climates, for security, and for pest control. In warm climates, windows may be closed when air conditioning is installed for thermal comfort. Although mechanical ventilation, if properly installed and maintained, can provide adequate air disinfection, it is expensive to install, maintain, and operate. The most cost-effective way to achieve high levels of air disinfection is upper room germicidal irradiation. The safe and effective application of this poorly defined intervention is now well understood, and recently published evidence-based application guidelines will make implementation easier.

E. A. Nardell

Harvard Medical School, Harvard School of Public Health, Brigham & Women's Hospital, Boston, MA, USA

Key words: Tuberculosis; Airborne Infection; Environmental Control; Ultraviolet air disinfection.

E. A. Nardell
Harvard Medical School
Harvard School of Public Health
Brigham & Women's Hospital
641 Huntington Avenue
3A-03, Boston, MA, USA
Tel.: 617 877 9412
Fax: 617 432 6958
e-mail: endardell@gmail.com

Received for review 27 December 2014. Accepted for publication 3 July 2015.

Practical Implications
Tuberculosis remains an indoor airborne hazard of global importance. Administrative control—finding and treating cases—is the most effective strategy, but environmental control interventions are a necessary secondary intervention. Natural ventilation is the most available, but not the most reliable environmental intervention. Upper room UVGI is by far the most cost-effective air disinfection strategy, but improved international guidelines are required.

Historical background

Before effective treatments were developed in the 20th century and still today, hospitals have been as much a cause of human suffering as places of relief. Writing of the infamous 18th century *Hotel-Dieu* in Paris, Stevenson quotes a translation of Foucoult in her monograph on the history of hospital design:

> 'A fragment of space closed on itself, a place of internment of men and disease, its ceremonious but inept architecture multiplying the ills of its interior without preventing their outward diffusion, the hospital is more of a centre of death *(foyer de mort)* for the cities where it is sited, than a therapeutic agent for the population as a whole'(Stevenson, 2000).

Awareness of the impact of hospital design, of crowding, and of fresh air were growing, however, stimulated by 1859 landmark publication of Florence Nightingale's '*Notes on Hospitals'*(Nightingale, 1859). In it, she specified the spacing of beds, their relation to windows, the amount of ventilation needed, and many other details that were far ahead of their time. With the discovery of the microbial cause of tuberculosis (TB) by Robert Koch in 1882, it was concluded that the 'white plague', a killer of perhaps one in four humans historically, impacting entire families, was not genetic as some thought—even though the exact mode of

person-to-person transmission would remained unproven for nearly another century (Riley and O'Grady, 1961). The airborne route was proposed by some observers, given the prominence of cough, lung involvement, and the presence of *Mycobacterium tuberculosis* in sputum, but it was difficult to prove, and there was also a counter movement to earlier beliefs that many diseases were caused by noxious vapors (Riley and O'Grady, 1961). Finally, mid-20th century, Wells and Riley theorized that bacteria and viruses could be spread in the dried residua (*droplet nuclei*) of aerosols generated by coughs, sneezes, and other respiratory maneuvers and proved that patients with TB would regularly infect vulnerable guinea pigs breathing the exhaust air from special hospital rooms, as detailed below (Riley et al., 1959; Wells, 1934, 1955).

In the 21st century, tuberculosis still remains the second greatest infectious killer of adults worldwide, the first *officially* being HIV (WHO 2013). That statistic is misleading, however, because the majority of deaths among HIV-infected persons in TB endemic areas are due to TB, but attributed by to HIV by international convention. Although TB transmission can theoretically occur outside of buildings, nearly infinite dilution and generally less crowded conditions outside make that much less likely. For that reason, tuberculosis is arguably the world's most important building-associated illness, occurring in homes, congregate settings of every description, including modes of transportation such as minibuses, trains, and ships. Few infections other than TB are almost exclusively airborne, but many respiratory viruses appear to have airborne potential under the right conditions (Roy and Milton, 2004).

As in past centuries, hospitals today in high-TB-burden areas often act, essentially, as *factories* for the production of TB cases, drug-resistant TB cases in particular. In Tomsk, Siberia, for example, Gelmanova reported that the risk for developing multidrug resistance (MDR-TB) for treatment adherent patients was more than 6 times higher if they were hospitalized for any portion of their treatment rather than being treated entirely in ambulatory settings (Gelmanova et al., 2007). The reasons for this observation are clear. Patients admitted to the hospital are assumed to have drug-susceptible TB, and, if true, effective treatment rapidly stops transmission (Rouillon et al., 1976; Dharmadhikari et al., 2014). However, if they fail to respond to weeks or months of treatment, only then are further tests ordered for drug resistance, and by the time the results are known, additional weeks or months have passed during which *transmission and reinfection of drug-susceptible patients occurs in tightly sealed,* poorly ventilated Soviet-style hospitals in that cold climate. In the above example, the source was unsuspected drug resistance in known TB cases. Another important source of hospital transmission in congregate settings is simply unsuspected TB among patients admitted for respiratory and non-respiratory symptoms. In Lima, Peru, for example, testing every consenting admission to a general medical ward over a one-year period yielded 40 culture-proven TB cases, one-third of which were unsuspected but likely to be infectious (Willingham et al., 2001). Very similar findings were recently reported for both a general hospital ward and an obstetrics ward in Zambia (Bates et al., 2012; Bates et al., 2013).

With the advent of rapid molecular diagnostic testing of sputum, the presence of *Mycobacterium tuberculosis* and resistance to one of the key drugs, rifampin, can be determined within two hours (Boehme et al., 2010). Combined with active case finding through cough surveillance upon entry to congregate settings, in theory, there is no reason for patients with unsuspected TB or unsuspected drug resistance to remain undiagnosed, untreated, and infectious. In pilot sites in Bangladesh, Vietnam, Nigeria, Russia, and Peru, hospitals are introducing an intensified, focused administrative control strategy called 'F-A-S-T' (Find cases Actively, Separate, and Treat effectively, based on molecular diagnosis with drug susceptibility testing). Early experience suggests that this strategy is feasible and results in many fewer unsuspected infectious cases (Barrera et al., 2015).

Airborne infection

The foundation of what we know of airborne transmission of infections, TB in particular, can be attributed to William Firth Wells, and his student, Richard Lord Riley (Riley and O'Grady, 1961; Wells, 1955). Wells conceived of exposing hundreds of sentinel guinea pigs to the exhaust air from a TB ward, and his student, Riley, conducted those studies mid-twentieth century at a Veterans Administration Hospital in Baltimore (Riley et al., 1959). It has not yet been possible to culture human-generated *Mycobacterium tuberculosis* from ambient air. Tens of thousands of environmental airborne microorganisms grow faster and easier than *M. tuberculosis*. Molecular detection methods have been tried, but determining numbers of organisms and viability, much less infectivity, has proven elusive (Nardell, 1999). Using the sentinel guinea pig model, Wells and Riley demonstrated that TB was an airborne infection, that infectiousness varied greatly from person to person, but was almost immediately stopped by effective treatment (Riley et al., 1962). The effect of treatment on transmission is critical in a discussion of environmental control of TB because it means that once on *effective* therapy, transmission essentially stops, and isolation, air disinfection, masks on patients, and respirators on workers becomes much less important. However, *effective* is a key word here. Routine TB treatment may be *ineffective* if there is

unsuspected drug resistance or if effective treatment delivery systems, such as directly observed therapy (DOT), are lacking.

Few human-to-human pathogens are transmitted preferentially by the airborne route. There are several reasons why *Mycobacterium tuberculosis* is an airborne infection: (i) *Mycobacterium tuberculosis* has evolved to be, initially, an infection of the alveolar macrophage, located deep in the lung periphery, accessible primarily to so-called *respirable* particles in the 1–3 micrometer size range; (ii) *Mycobacterium tuberculosis* is virulent enough to be able to initiate infection at the very low doses that result from dilution in room air; and (iii) the unusual, thick waxy coat of *Mycobacterium tuberculosis* may serve many functions, but among them is likely resistance to the environmental stresses of otherwise intracellular pathogens traveling in air as nearly dry particles.

Infectious droplet nuclei result from the rapid dehydration of larger respiratory droplets sheared off of the wet surface of the human respiratory tract by the high-velocity airflow generated by cough, sneezing, and other respiratory maneuvers (Riley and O'Grady, 1961). They are rapidly diluted in room air. In Riley's 4-year human-to-guinea pig studies, the average concentration was one infectious dose (probably a single droplet nucleus) in 311 m^3 (Riley et al., 1995). That very low concentration, however, was high enough to explain the rate at which student nurses became infected with *Mycobacterium tuberculosis* working on hospital wards in the days before chemotherapy for TB (Riley, 1957).

Little is known of the aerobiology of *Mycobacterium tuberculosis*, that is, how this normally intercellular pathogen survives in room air. Much more is known about what happens from the point that it lands in the alveolar macrophage, begins to replicate, and triggers host innate and adaptive immune responses, but that is beyond the scope of this article. We have long had a vaccine against TB, *BCG (Bacille de Calmette et Guérin)*, but it has failed to control the disease in the way that vaccines for smallpox, diphtheria, and polio have been successful. Indeed, all of the highest TB-risk countries administer BCG, with high coverage rates. However, recently several reports support the fact that household contacts of infectious TB cases are less likely to become infected if they had been vaccinated at birth with BCG (Lalvani et al., 2006). Recent recommendations suggest BCG vaccination for medical workers traveling to areas where drug-resistant TB is common (Seaworth et al., 2014).

Although prompt diagnosis and effective treatment are the best TB transmission control strategy, a variety of other interventions are employed (WHO, 2009a,b). Surgical masks on (untreated) patients can stop many respiratory droplets before they evaporate into droplet nuclei, reducing transmission by about 50% in a recent study (Dharmadhikari et al., 2012). Patients can be physically separated or isolated from other vulnerable people, and air can be disinfected by dilution (ventilation), filtration, or germicidal irradiation. Those exposed to patients with TB can wear protective respirators, and as mentioned, immunization with BCG appears to reduce the risk of infection (Roy et al., 2014). A WHO policy covers these administrative, environmental, and respiratory protection approaches in great detail (WHO, 2009a,b). Here, we will focus on control by environmental and engineering interventions, germicidal ultraviolet air disinfection in particular.

Environmental and Engineering approaches to the control of airborne infection

Not knowing how many tubercle bacilli were required to cause infection, Wells used the term, '*quanta'* for whatever that number was (Wells, 1955). In the highly vulnerable guinea pig that number may be low, possibly just one droplet nucleus (containing 1 or more tubercle bacilli), but it probably varies due to strain virulence and other factors (Wells, 1955).

Under steady-state conditions (unlikely under real-world conditions), the risk of infection (C) is a function of several factors: (i) the number of infectious persons (I) and source strength (q)—number of infectious quanta generated per hour or day; (ii) the number of susceptible people breathing the same air (S); (iii) the breathing rate of exposed persons (p); (iv) the exposure time (t); and (v) the ventilation rate of the room or rooms where exposure occurs (Q). The relationship of these factors is captured by a mass balance relationship known as the *Wells–Riley equation*—adapted from an epidemiological model by Edward Riley, Richard's brother, an engineer, to explain measles transmission in a school (Riley et al., 1978).

$$C = S\,(1\text{-}e^{-Iqpt/Q}).$$

More recently, Rudnick and Milton have made the case that human-generated indoor CO_2 levels (above ambient outdoor levels) are a good surrogate of rebreathed air exposure, arguably a surrogate for airborne infection risk if an infectious source is present, and representing a more dynamic model of infection, accommodating the ever changing non-steady-state conditions of real exposures (Rudnick and Milton, 2003).

Source factors

There have been several outbreaks where many of the essential transmission factors in the Wells–Riley equation were known or estimated. In an office building TB exposure, for example, where building ventilation rates were known, one infectious source infected 27 of 67 susceptible occupants (40%) over a one-month period, and the calculated q (source strength) was 13 quanta

per hour. Other exposures have shown q values as high as 250 quanta per hour compared to Riley's ward average figure of 1.25 quanta per hour (Catanzaro, 1982; Nardell et al., 1991; Riley et al., 1962). This leads to a fundamental observation about TB transmission—that patients vary greatly in infectiousness. It has been estimated that only one in three patients with TB infects any close contacts (Fennelly, 2007; Fennelly et al., 2004). Further, it appears that a minority of infectious cases, so-called disseminators account for much of observed transmission (Sultan et al., 1960). Variability in infectiousness is believed to relate to characteristics of the source patient, strain virulence, the vulnerability of exposed hosts, and environmental factors, but they are difficult to separate. The same source patient and strain will infect more contacts in a crowded, poorly ventilated environment with highly susceptible hosts. Frequency of cough, viscosity of respiratory secretions, presence of lung cavities or laryngeal disease, and duration of exposure are important variables (Loudon and Spohn, 1969). Among potential interventions to reduce transmission, however, nothing is as rapidly and completely effective as is treatment with the appropriate drug regimen (Rouillon et al., 1976; Dharmadhikari et al., 2014).

Concentrations of contagion—implications for building ventilation

As noted, a key finding of the Riley ward studies was the average low concentration of infectious *doses* in ward air (Riley, 1957). In his first 2-year study, as noted earlier, Riley found the average concentration of infectious doses of *Mycobacterium tuberculosis* to be low, just 1 in 311 m^3 of air (Riley et al., 1995). The engineering implications of this finding are important. At very low average concentrations, large amounts of ventilation are required for effective dilution and removal, and the difficulty only gets worse (and more expensive) as concentrations of infectious droplet nuclei fall further, but never reaching zero (Nardell et al., 1991). According to the Wells–Riley equation (above), doubling the ventilation rate reduces the risk of infection by approximately half, but unless the initial ventilation rate is low, doubling ventilation may be difficult and expensive, and reducing risk by half may not be adequate (Nardell et al., 1991). As discussed below, this is an important rationale for air disinfection by upper room germicidal ultraviolet irradiation (UVGI) where large volumes of air are treated at once (Nardell, 1993). Just the opposite conclusion is true for air disinfection by room air cleaners (using filters and/or UVGI) due to the difficulty of moving sufficiently large volumes of air through the device, as further discussed below (Nardell, 1993).

For much of the high-TB-burden world in tropical or temperate climates, natural ventilation is the only available means of air disinfection in buildings. In optimal settings such as breezy, seaside Lima, Peru, CO_2 decay studies have shown that very high levels of ventilation can be achieved (Escombe et al., 2007). However, at night even in warm climates windows are often closed for cold or security, and ventilation is usually variable in amount and direction. Wind direction that is favorable for preventing transmission one minute may be unfavorable the next. Natural ventilation is generally less applicable to northern Europe and other cold regions for much of the year. But even in very warm climates like India, windows may be closed as split system air conditioners are introduced for thermal comfort. In cold climates, mechanical ventilation may be used in newer buildings, but it is often in poor repair, as in the following observational study in Lima, Peru.

Nursing and medical students in high-burden settings are commonly TB-infected during their training, especially as they transmitted from the classroom to the wards. At one Peruvian university, medical students start out about 15% TB skin test positive, but after 7 years are about 55% positive (Accinelli and Alvarez, 2002). Of great interest, medical students who were assigned to hospital A for their clinical training had roughly half the TB infection rate as those assigned to hospital B. Although the hospital patient population is similar, hospital A, an older colonial-style facility with high ceilings and large windows, had more than twice the room volume per bed (41.4 m^3) compared to hospital B (16.2 m^3), a newer hospital with lower ceilings, small windows, and a dysfunctional mechanical ventilation system. Although observational, there are few other examples where building design and engineering appear to correlate so clearly with risk of infection.

Building occupancy correlates with risk for at least two synergistic reasons: the greater the number of room (or building) occupants rebreathing each others' air, the greater the risk of an infectious source or sources in that population, and the greater the number of exposed occupants (Rudnick and Milton, 2003). Simplistically, if there are two infectious sources in a population of 100 persons breathing the same air, 98 vulnerable occupants are at risk. Divide that same population of 100 into ten rooms of 10 occupants each and 8 or 9 rooms will, by chance, have no infectious risk, a >80% risk reduction by separation alone—assuming no communication between rooms. The Indus Hospital drug-resistant TB clinic has implemented a patient flow system whereby most patients wait in sheltered outside areas until called, moving through the building in relatively small groups with a lower risk of person-to-person transmission. Designing buildings and patient flow systems that *should* work is one thing, but demonstrating that they *are effective* has proven to be extremely difficult. Recently, as noted above, ambient CO_2 levels

have been shown to be a good surrogate for the percentage of air that is rebreathed, which in turn should correlate with risk of airborne infection (Rudnick and Milton, 2003). Researchers in Cape Town are using portable CO_2 monitors with GPS tracking to determine where in the course of a person's day they are exposed to greater fractions of rebreathed air (Richardson et al., 2014). This same concept is being applied to populations of building occupants (nurses for example) to determine their percentage rebreathed air during a work day—the integrated result of building design, engineering, climatic conditions, and building-use patterns.

Progress in building design and engineering for airborne infection control

Although the design principles for good natural ventilation go back hundreds of years, they are being revived and updated for use in new construction and renovations around the world. WHO has published guidelines on natural ventilation for airborne infection control (WHO, 2009a,b). A continuing education program at Harvard School of Public Health targeting architects, engineers, and public health professionals from around the world has been credited, in part, for some award-winning designs, for example, a clinic for drug resistance TB in Karachi, Pakistan (Fig. 1a) and a district hospital in Butaro, Rwanda (Fig. 1b). Measuring the efficacy of natural ventilation and other interventions on institutional TB transmission, however, remains a challenge.

Where natural ventilation is judged inadequate, the first impulse is often to install extraction fans. While logical, it is easy to demonstrate with a smoke source that even appropriately sized fans often have difficulty in moving air (smoke) from even a short distance away. Full ventilation systems are designed to produce a prescribed number of air changes per hour (ACH), but such systems require good planning and maintenance to remain functional. Hospitals in high-burden settings often have inadequately trained engineering staff and little or no maintenance budgets, and ventilation systems commonly become dysfunctional, as in the Peru example, above. Ideally, mechanical ventilation systems should be commissioned after installation to assure that they work as designed and then maintained through a contract with a company certified to make the necessary measurements, adjustments, and repairs to assure ongoing proper function. This uncommonly happens in resource-limited settings, and the problem is compounded by building renovations over the years without adjustments to the ventilation system.

Portable air cleaners

If a mechanical ventilation system does not exist in a building, it is expensive, disruptive, and sometimes simply not feasible to install. Another common solution specifically to deal with airborne contagion is air disinfection through installed or portable room air cleaners. These are essentially boxes containing fans drawing air through filters, ultraviolet germicidal irradiation, or both technologies (Miller-Leiden et al., 1996). Although many such devices can be shown to disinfect contaminated air that goes through on a single pass, there are major problems with this approach. The most important problem is flow rate. Unless extremely well designed, it is difficult for such devices to move enough air to produce the equivalent of 12 or more equivalent air changes recommended for airborne infection control. This is worsened by a tendency for short circuiting, the return of just filtered air back into the device, while the air furthest from the device is not entrained at all. The clean air delivery rate (CADR) is a measure of the airflow through the device, but the effective air exchange rate (equivalent ACH) may be far less, especially by relatively small devices in large rooms. With few exceptions (very small rooms), room air cleaners are not recommended for airborne infection control. Data on their relative cost-effectiveness compared to other interventions are presented below.

Germicidal ultraviolet air disinfection

Another way to achieve high rates of air disinfection is through the application of germicidal (254 nm wave-

Fig. 1 Two hospitals designed with principals of airborne infection control, including natural ventilation (2a and 2b), and upper room UVGI (2b): 2a Indus Hospital, Karachi, Pakistan, 2b Butaro District Hospital, Rwanda

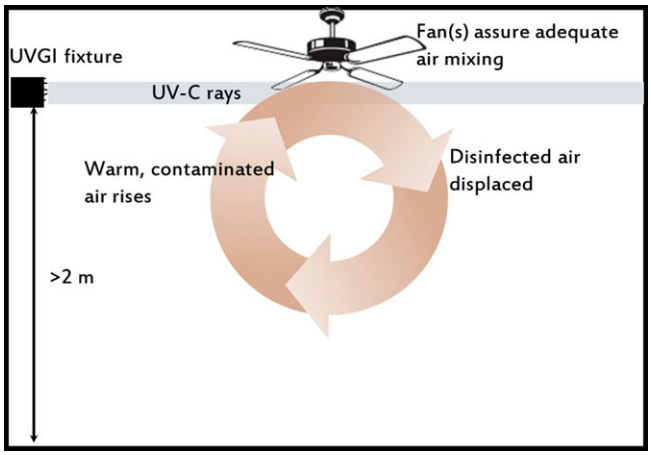

Fig. 2 Schematic of an upper room UVGI wall fixture with an ordinary low-velocity ceiling fan to assure good room air mixing

length) ultraviolet (UV) air disinfection (Riley and Nardell, 1989). Although germicidal UV can be used in ventilation ducts and portable air cleaners, as noted above, by far the most efficient use of this technology in occupied spaces is upper room germicidal UV fixtures with ceiling fans to assure good air mixing (see Fig. 2).

In contrast to room air cleaners that struggle to capture and process all room air at rates approaching 12 ACH, upper room germicidal UV air disinfection takes advantage of the entire upper room as a disinfection chamber, and the tendency of air to rise on occupied rooms due to body head and warm expired air. Low-velocity ceiling fans assure good air mixing. Chamber studies with aerosolized test organisms routinely show air disinfection rates equivalent to 10 to 20 or more ACH (Miller et al., 2002). A hospital study in Peru showed that upper room UVGI was 72% effective over a period of almost 2 years in preventing transmission of *Mycobacterium tuberculosis* to hundreds of sentinel guinea pigs breathing the exhaust air from the ward (Escombe et al., 2009). A similar hospital study in South Africa demonstrated 80% efficacy, the equivalent of adding 24 ACH, and is the basis for proposed new application guidelines (Mphaphlele et al., 2015).

Like mechanical ventilation and room air cleaners, upper room germicidal UV air disinfection suffers from poor implementation in many parts of the world where it is needed—in the case of South Africa, resulting in a temporary moratorium on its use. In theory, however, upper room germicidal UV has great potential for use in high-burden, resource-limited settings because of its simplicity, ease of maintenance, and cost-effectiveness, but that potential has yet to be realized. A USAID-funded effort aimed at producing international application guidelines including fixture performance and maintenance specifications is underway. Likewise, South Africa is in the process of producing evidence-based guidelines and fixture manufacturers are producing safer and more effective equipment. New, even more effective and efficient application modes of upper room germicidal UV have been recently published, and LED UV sources promise to transform this technology once their price falls and their power and reliability improve (Linnes et al., 2014). LED UV can run on batteries and solar power, providing continuous protection in areas prone to electrical blackouts. For now, standard mercury lamp technology provides an extremely cost-effective means to achieve high levels of air disinfection where needed.

Until recently, upper room germicidal UV air disinfection was dosed (number, size, and location of fixtures) based on old formulas that used the electrical input to the fixture, not the UV output (NIOSH 2009; Riley et al., 1976). The problem is that, depending on fixture design, the output for the same electrical input can vary by as much as 10-fold (Mphaphlele et al., 2015). A recent NIOSH guideline recommended an average upper room UV intensity (fluence rate, defined below), but not how to predict that rate in the planning stage before installing fixtures (NIOSH 2009). In response, we adapted and validated a commercial lighting computer-assisted design (CAD) program (Visual™, Acuity Lighting) for use with upper room UV fixtures (Rudnick et al., 2012). The program allows planners to place well-characterized fixtures (UV output defined in all directions from the fixture) on the walls of imported architectural CAD drawing, calculating the resulting average fluence rates anywhere in the room, or for the entire room. *UV 'fluence rate'* refers to the germicidal irradiation experienced by airborne organisms from all directions throughout the room. Based on the hospital transmission control study in South Africa, we recommend a target fluence rate for entire rooms of approximately 5–7 $\mu W/cm^2$. As a first approximation, planners can estimate specifying fixtures *to deliver* a total output of 15–20 mW/m^3 room volume. In the South African study, tested commercial wall germicidal UV wall fixtures produced 220–500 mW depending on their design characteristics. However, UV output is not yet routinely specified by manufacturers. To rationally apply upper room germicidal UV, total fixture output must be specified, ideally by full gonioradiometry to allow the use of Visual™, or at a minimum, total fixture output by the integrated sphere method to approximate dosage, as suggested above. The Visual™ method has the advantage of automatically incorporating UV ray length into calculated average fluence rates—maximizing germicidal effect of UV rays before they are absorbed by walls, ceilings, and other surfaces. If these dosing guidelines gain acceptance, manufacturers will be under commercial pressure to provide full output data on their fixtures, performed by a reliable lighting laboratory by standard methods.

Comparative costs of air disinfection by ventilation, air filtration, and upper room UVGI

Based on studies in his TB hospital in Vladimir, Russia, Volchenkov (personal communication, December, 2014) found that for his multistory hospital, floor area 17 000 m^3, the capital cost of a new, high-capacity ventilation system with negative pressure isolation rooms was $345 000 (2005–2007 prices), and maintenance, $4425 per year. Average power consumption is 37 KW for the entire facility. The air disinfection efficacy of this modern mechanical ventilation system for one 32 m^3 test room was compared to three different room air-cleaning devices and an upper room UVGI system using two different aerosolized surrogate test organisms and mechanical biological air sampling. For the test room only, per equivalent air change (equivalent to ventilation for air disinfection purposes only), mechanical ventilation cost approximately $126 per year to install and operate. Two of the room air cleaners produced one equivalent air changes at similar costs of $143 and $109 per year. One very expensive room air cleaner cost $287 per year per equivalent air change. In contrast, the upper room UVGI system was least expensive intervention at $14 per year per equivalent room air change. Upper room UVGI was more than nine times more cost-effective per room air change. It is for this reason, and because germicidal technology is not well understood, that it receives more discussion in this review than better known (but not better studied) ventilation and air filtration.

Summary

Tuberculosis remains a major global health problem, the epidemic being amplified by institutional transmission in high-burden settings, especially where HIV and drug resistance are prevalent. While early detection, diagnosis, and effective treatment is the best way to prevent transmission, cough surveillance in some settings, crowded waiting rooms, for example, may not be feasible, and environmental control measures remain essential. Buildings designed for effective natural ventilation and patient flow (reduced crowding) can greatly reduce transmission—as long as the windows are open and outside conditions are conducive. When natural ventilation is inadequate, unreliable, or not possible, in very cold climates or on cold nights, by far the most cost-effective technology to achieve high rates of air disinfection is upper room germicidal UV. However, for rational implementation, upper room UVGI requires good guidelines based on fixture output, using well-designed fixtures fully characterized in terms of output in a qualified lighting laboratory. If dosing guidelines are followed and good air mixing are provided, and installations are commissioned for both safety and efficacy, high levels of air disinfection can be assumed based on decades of evidence, even if outcomes are difficult to measure in terms of infections prevented. Other than the two controlled trials of upper room UVGI in hospitals cited, controlled field trials of other environmental controls in wide use do not exist because of the variable nature of TB transmission and the limitations of current assessment tools. Perhaps the most pressing area of research in the environmental control of airborne infections is finding new, validated ways to demonstrate efficacy in the field. This advance would likely provide a pathway to entirely new approaches to air disinfection.

References

Accinelli, R. and Alvarez, L. (2002) Annual Risk of Infection Among Medical Students of Universidad Peruana Cayetano Heredia in Lima, Peru, American Thoracic Society Annual Meeting, Atlanta, GA.

Barrera, E., Livchits, V. and Nardell, E. (2015) F-A-S-T; a refocused, intensified, administrative tuberculosis transmission control strategy, *Int. J. Tuberc. Lung Dis.*, **19**, 381–384.

Bates, M., O'Grady, J., Mwaba, P., Chilukutu, L., Mzyece, J., Cheelo, B., Chilufya, M., Mukonda, L., Mumba, M., Tembo, J., Chomba, M., Kapata, N., Rachow, A., Clowes, P., Maeurer, M., Hoelscher, M. and Zumla, A. (2012) Evaluation of the burden of unsuspected pulmonary tuberculosis and co-morbidity with non-communicable diseases in sputum producing adult inpatients, *PLoS ONE*, **7**, e40774.

Bates, M., Ahmed, Y., Chilukutu, L., Tembo, J., Cheelo, B., Sinyangwe, S., Kapata, N., Maeurer, M., O'Grady, J., Mwaba, P. and Zumla, A. (2013) Use of the Xpert(R)-MTB/RIF assay for diagnosing pulmonary tuberculosis comorbidity and multidrug-resistant TB in obstetrics and gynaecology inpatient wards at the University Teaching Hospital, Lusaka, Zambia, *TM & IH*, **18**, 1134–1140.

Boehme, C.C., Nabeta, P., Hillemann, D., Nicol, M.P., Shenai, S., Krapp, F., Allen, J., Tahirli, R., Blakemore, R., Rustomjee, R., Milovic, A., Jones, M., O'Brien, S.M., Persing, D.H., Ruesch-Gerdes, S., Gotuzzo, E., Rodrigues, C., Alland, D. and Perkins, M.D. (2010) Rapid molecular detection of tuberculosis and rifampin resistance, *N. Engl. J. Med.*, **363**, 1005–1015.

Catanzaro, A. (1982) Nosocomial tuberculosis, *Am. Rev. Respir. Dis.*, **125**, 559–562.

Dharmadhikari, A.S., Mphahlele, M., Stoltz, A., Venter, K., Mathebula, R., Masotla, T., Lubbe, W., Pagano, M., First, M., Jensen, P.A., van der Walt, M. and Nardell, E.A. (2012) Surgical face masks worn by patients with multidrug-resistant tuberculosis: impact on infectivity of air on a hospital ward, *Am. J. Respir. Crit. Care Med.*, **185**, 1104–1109.

Dharmadhikari, A.S., Mphahlele, M., Venter, K., Stoltz, A., Mathebula, R., Masotla, T., van der Walt, M., Pagano, M., Jensen, P. and Nardell, E. (2014) Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis, *Int. J. Tuberc. Lung. Dis.*, **18**, 1019–1025.

Escombe, A.R., Oeser, C.C., Gilman, R.H., Navincopa, M., Ticona, E., Pan, W., Martinez, C., Chacaltana, J., Rodriguez,

R., Moore, D.A., Friedland, J.S. and Evans, C.A. (2007) Natural ventilation for the prevention of airborne contagion, *PLoS Med.*, **4**, e68.

Escombe, A.R., Moore, D.A., Gilman, R.H., Navincopa, M., Ticona, E., Mitchell, B., Noakes, C., Martinez, C., Sheen, P., Ramirez, R., Quino, W., Gonzalez, A., Friedland, J.S. and Evans, C.A. (2009) Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission, *PLoS Med.*, **6**, e43.

Fennelly, K.P. (2007) Variability of airborne transmission of Mycobacterium tuberculosis: implications for control of tuberculosis in the HIV era, *Clin. Infect. Dis.*, **44**, 1358–1360.

Fennelly, K.P., Martyny, J.W., Fulton, K.E., Orme, I.M., Cave, D.M. and Heifets, L.B. (2004) Cough-generated aerosols of *Mycobacterium tuberculosis*: a new method to study infectiousness, *Am. J. Respir. Crit. Care Med.*, **169**, 604–609.

Gelmanova, I.Y., Keshavjee, S., Golubchikova, V.T., Berezina, V.I., Strelis, A.K., Yanova, G.V., Atwood, S. and Murray, M. (2007) Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance, *Bull. World Health Organ.*, **85**, 703–711.

Lalvani, A., Bakir, M., Millington, K.A., Dosanjh, D. and Soysal, A. (2006) BCG and protection against *Mycobacterium tuberculosis* infection, *Lancet*, **367**, 391–392.

Linnes, J.C., Rudnick, S.N., Hunt, G.M., McDevitt, J.J. and Nardell, E.A. (2014) Eggcrate UV: a whole ceiling upper-room ultraviolet germicidal irradiation system for air disinfection in occupied rooms, *Indoor Air*, **24**, 116–124.

Loudon, R.G. and Spohn, S.K. (1969) Cough frequency and infectivity in patients with pulmonary tuberculosis, *Am. Rev. Respir. Dis.*, **99**, 109–111.

Miller, S.L., Hernandez, M., Fennelly, K., Martyny, J. and Macher, J. (2002) Final Report CDC/NIOSH Contract No. 200-97-2602; NTIS PB2003-103816, Efficacy of ultraviolet irradiation in controlling the spread of tuberculosis, http://www.cdc.gov/niosh/reports/contract/pdfs/ultrairrTB.pdf

Miller-Leiden, S., Lobascio, C., Nazaroff, W.W. and Macher, J.M. (1996) Effectiveness of in-room air filtration and dilution ventilation for tuberculosis infection control, *J. Air Waste Manag. Assoc.*, **46**, 869–882.

Mphaphlele, M., Dharmadhikari, A.S., Jensen, P.A., Rudnick, S.N., van Reenen, T.H., Pagano, M.A., Leuschner, W., Sears, T.A., Milonova, S.P., van der Walt, M., Stoltz, A.C., Weyer, K. and Nardell, E.A. (2015) Institutional tuberculosis transmission: controlled trial of upper room ultraviolet air disinfection - a basis for new dosing guidelines, *Am. J. Respir. Crit. Care Med.*, **192**, 477–484.

Nardell, E. (1993) Fans, filters, or rays? Pros and cons of the current environmental tuberculosis control technologies, *Infect. Control Hosp. Epidemiol.*, **14**, 681–685.

Nardell, E.A. (1999) Air sampling for tuberculosis- homage to the lowly guinea pig, *Chest*, **116**, 1143–1145.

Nardell, E.A., Keegan, J., Cheney, S.A. and Etkind, S.C. (1991) Airborne infection. Theoretical limits of protection achievable by building ventilation, *Am. Rev. Respir. Dis.*, **144**, 302–306.

Nightingale, F. (1859) *Notes on Hospitals*, London (reprinted by ARUP), John W Parker and Son.

NIOSH (2009) *Environmental Control of Tuberculosis: Basic Upper-Room Ultraviolet Germicidal Irradiation Guidelines for Healthcare Settings*, Cincinnati, OH, National Institute for Occupational Safety and Health, (NIOSH Publication 2009-105).

Richardson, E.T., Morrow, C.D., Kalil, D.B., Bekker, L.G. and Wood, R. (2014) Shared air: a renewed focus on ventilation for the prevention of tuberculosis transmission, *PLoS ONE*, **9**, e96334.

Riley, R. (1957) Aerial dissemination of pulmonary tuberculosis - The Burns Amberson Lecture, *Am. Rev. Tuberc. Pulmon. Dis.*, **76**, 931–941.

Riley, R.L. and Nardell, E.A. (1989) Clearing the air. The theory and application of ultraviolet air disinfection, *Am. Rev. Respir. Dis.*, **139**, 1286–1294.

Riley, R. and O'Grady, F. (eds) (1961) *Airborne Infection*, New York, The Macmillan Company.

Riley, R.L., Mills, C.C., Nyka, W., Weinstock, N., Storey, P.B., Sultan, L.U., Riley, M.C. and Wells, W.F. (1959) Aerial dissemination of pulmonary tuberculosis: a two-year study of contagion in a tuberculosisward: 1959, *Am. J. Epidemiol.*, **142**, 3–14 (republished as a classic in epidemiology: *Am. J. Epidemiol.* 1995 Jul 1;142(1):3–14)

Riley, R.L., Mills, C.C., O'Grady, F., Sultan, L.U., Wittstad, F. and Shivpuri, D.N. (1962) Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients, *Am. Rev. Respir. Dis.*, **85**, 511–525.

Riley, R., Knight, M. and Middlebrook, G. (1976) Ultraviolet susceptibility of BCG and virulent tubercle bacilli, *Am. Rev. Resp. Dis.*, **113**, 413–418.

Riley, E., Murphy, G. and Riley, R. (1978) Airborne spread of measles in a suburban elementary school, *Am. J. Epidemiol.*, **107**, 421–432.

Riley, R.L., Mills, C.C., Nyka, W., Weinstock, N., Storey, P.B., Sultan, L.U., Riley, M.C. and Wells, W.F. (1995) Aerial dissemination of pulmonary tuberculosis: a two-year study of contagion in a tuberculosis ward: 1959, *Am. J. Epidemiol.*, **142**, 3–14.

Rouillon, A., Perdrizet, S. and Parrot, R. (1976) Transmission of tubercle bacilli: the effects of chemotherapy, *Tubercle*, **57**, 275–299.

Roy, C.J. and Milton, D.K. (2004) Airborne transmission of communicable infection–the elusive pathway, *N. Engl. J. Med.*, **350**, 1710–1712.

Roy, A., Eisenhut, M., Harris, R.J., Rodrigues, L.C., Sridhar, S., Habermann, S., Snell, L., Mangtani, P., Adetifa, I., Lalvani, A. and Abubakar, I. (2014) Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis, *BMJ*, **349**, g4643.

Rudnick, S.N. and Milton, D.K. (2003) Risk of indoor airborne infection transmission estimated from carbon dioxide concentration, *Indoor Air*, **13**, 237–245.

Rudnick, S.N., First, M.W., Sears, T., Vincent, R.L., Brickner, P.W., Ngai, P., Zhang, J., Levin, R.E., Chin, K., Rahn, R.O., Miller, S.L. and Nardell, E.A. (2012) Spatial distribution of fluence rate from upper room ultraviolet germicidal irradiation: experimental validation of a computer-aided design tool, *HVAC&R Res.*, **18**, 774–794.

Seaworth, B.J., Armitige, L.Y., Aronson, N.E., Hoft, D.F., Fleenor, M.E., Gardner, A.F., Harris, D.A., Stricof, R.L. and Nardell, E.A. (2014) Multidrug-resistant tuberculosis. Recommendations for reducing risk during travel for healthcare and humanitarian work, *Ann. Am. Thorac. Soc.*, **11**, 286–295.

Stevenson, C. (2000) *Medicine and Magnificence: British Hospital and Asylum Architecture, 1660–1815*, New Haven, Yale University Press, 155.

Sultan, L., Nyka, C., Mills, C., O'Grady, F. and Riley, R. (1960) Tuberculosis disseminators - A study of variability of aerial infectivity of tuberculosis patients, *Am. Rev. Respir. Dis.*, **82**, 358–369.

Wells, W. (1934) On air-borne infection: II Droplets and droplet nuclei, *Am. J. Hyg.*, **20**, 611–618.

Wells, W. (ed.) (1955) *Airborne Contagion and Air Hygiene: An Ecological Study of Droplet Infections*, Cambridge, Harvard University Press for the Commonwealth Fund.

WHO (2009a) *WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households*, Geneva, World Health Organization (WHO/HTM/TB/2009.419).

WHO (2009b) Natural Ventilation for Infection Control in Health-care settings, World Health Organization (http://www.who.int/water_sanitation_health/publications/natural_ventilation.pdf)

WHO (2013) *Global Tuberculosis Report 2013*, Geneva, World Health Organization (WHO/HTM/TB/2013.11).

Willingham, F.F., Schmitz, T.L., Contreras, M., Kalangi, S.E., Vivar, A.M., Caviedes, L., Schiantarelli, E., Neumann, P.M., Bern, C. and Gilman, R.H. (2001) Hospital control and multidrug-resistant pulmonary tuberculosis in female patients, Lima, Peru, *Emerg. Infect. Dis.*, **7**, 123–127.