Airborne Infection

Theoretical Limits of Protection Achievable by Building Ventilation[1,2]

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SUMMARY Of 67 office workers 27 (40%) had documented tuberculin skin test conversions after an estimated 4-wk exposure to a coworker with cavitary tuberculosis. Worker complaints for more than 2 yr before the tuberculosis exposure prompted investigations of air quality in the building before and after the tuberculosis exposure. Carbon dioxide concentrations in many parts of the building were found to be above recommended levels, indicating suboptimal ventilation with outdoor air. We applied a mathematical model of airborne transmission to the data to assess the role of building ventilation and other transmission factors. We estimated that ventilation with outside air averaged about 15 feet³/min (cfm) per occupant, the low end of acceptable ventilation, corresponding to CO_2 levels of about 1,000 ppm. The model predicted that at 25 cfm per person 18 workers would have been infected (a 33% reduction) and at 35 cfm, a level considered optimal for comfort, that 13 workers would have been infected (an additional 19% reduction). Further increases in outdoor air ventilation would be impractical and would have resulted in progressively smaller increments in protection. According to the model, the index case added approximately 13 infectious doses (quanta) per hour (qph) to the office air during the exposure period, 10 times the average infectiousness reported in a large series of tuberculosis cases. Further modeling predicted that as infectiousness rises, ventilation would offer progressively less protection. We conclude that outdoor air ventilation that is inadequate for comfort may contribute to airborne infection but that the protection afforded to building occupants by ventilation above comfort levels may be inherently limited, especially when the level of exposure to infection is high.

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Introduction

Measles transmitted by infectious air in a pediatrician's waiting room; influenza spread on an airplane; tuberculosis transmitted within a shelter for the homeless, a nursing home, a prison, a hospital, or a clinic administering aerosolized pentamidine—are all current examples of airborne infection (1–7). If inadequate outdoor air ventilation is considered a contributing factor, it is often assumed that improved ventilation should prevent transmission. However, there is little in the medical literature to support or refute this assumption. We were stimulated to analyze the role of building ventilation and other transmission factors by the contact investigation of a case of tuberculosis occurring in an office building that was the source of air quality complaints.

The exposure was unusual because air quality measurements were available from which the outdoor air ventilation of the building could be estimated, because the duration of exposure was well defined, and because the other major determinants of airborne infection were either known or estimable. The data permitted the application of a mathematical model of airborne infection to assess the relationship between infection rate, building ventilation, exposure duration, and infectivity of the source case. Specifically, we sought to predict how many exposed workers would have been infected had the ventilation been optimal for comfort purposes, to examine the theoretical limits of protection achievable by further increases in ventilation, and to explore the relationship of protection to the intensity of exposure.

Methods

This study was prompted by the contact investigation of a case of tuberculosis. Although the methods and results of that investigation are presented here in some detail, the purpose is solely to establish a realistic starting point for the theoretical analysis that follows. Countless variables over a 4-wk period defy the precise description of exposure conditions for each worker. Such detail is not necessary for our purposes. Had the actual duration of exposure for some workers, for example, been somewhat shorter or longer than the average figures used, the true infectivity of the index case might be slightly higher or lower than the calculated figure used but the outcome of the analysis would not change substantially, as demonstrated by sensitivity studies over a wide range of possible exposure conditions.

Epidemiology

The index case was a 30-yr-old woman who became symptomatic with cough, fatigue, and fever during a monthlong holiday out of the country. She had progressive worsening of her symptoms on returning to the office where she worked but remained at work for 4 wk before seeking medical attention. A chest radiograph at that time revealed a cavitary infiltrate suspicious for tuberculosis, and a sputum smear was strongly positive for acid-fast bacilli. Sputum culture revealed *Mycobacterium tuberculosis*, which was subsequently found to be resistant to isoniazid.

Investigation of all household and workplace contacts began immediately after the diagnosis of tuberculosis (TB). The patient's husband had completed 14 months of tuberculosis treatment in another country years before they had met. He was asymptomatic at the time of the current contact investigation, and his chest X-ray showed only scarring. The patient's 3½-yr-old daughter had a positive Mantoux skin test but no evidence of current tuberculosis. A 14-yr-old niece tested positive and had an abnormal X-ray. Although sputum cultures were negative, her physician elected to treat her as a secondary case.

In addition to the index case, there were 92 persons working in the offices during the exposure period. The first round of skin testing occurred 1 wk after the index case was diagnosed; a second round followed 4 months later. The majority of Mantoux skin tests were applied and read by two experienced state public health department nurses. Some test-

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ing was done by private providers. The antigen used for testing was Tween®-stabilized purified protein derivative (PPD) (Connaught Laboratories, Inc., Swiftwater, PA), 5 tuberculin units (5 TU). Tests resulting in induration of 10 mm or more after 48 to 72 h were considered significant for tuberculosis infection. An increase of 6 mm or more, resulting in more than a 10-mm induration, was considered a conversion, which indicated recent infection. Nine workers were documented tuberculin reactors in the past and were not tested. Seven workers without a history of previous testing were positive at the time of the first testing. Another nine workers tested positive at the second round of testing but were unavailable for the initial testing. Of the remaining 67 workers who had negative Mantoux tests initially and were retested after 4 months, 27 (40%) converted to positive. Although two-stage testing was not done, both the young mean age (41.1 yr) of the 27 converters and the large size of the PPD conversion (mean increase in induration, 16.2 mm) made skin test boosting an unlikely contributor to the conversion rate. Only 6 of the 27 workers were over 50 yr of age, and their mean increase in Mantoux induration was 15.2 mm. There was no evidence of additional sources of tuberculosis transmission in the workplace or among the family contacts. Of the 27 skin test converters who decided against preventive therapy, 1 subsequently developed clinical tuberculosis and was successfully treated.

The 40% conversion rate is likely an underestimate. Some of the 16 Mantoux-positive workers who were tested only once, during the first or the second screenings, with no prior skin test information, may have been infected through this exposure. These workers were disregarded for the purposes of this analysis. For the remaining 67 workers, however, it was possible to estimate the duration of exposure. The index case was asymptomatic before she left on vacation and was apparently less contagious than on her return. Had any of the 67 workers been infected before the patient left on vacation, they would have developed skin test reactivity during the 4 wk she was away and the additional 4 wk that passed before her diagnosis and the first round of testing. Thus, the 27 documented infections resulted from an average 4-wk exposure between the return of the index case to the office and the time of her diagnosis, during which she became progressively more symptomatic. We have assumed that the exposure averaged 40 h/wk for most workers, or about 160 h.

Air Quality Measurements

The office building had been the source of chronic complaints concerning air quality, and consultation with the Massachusetts Division of Occupational Hygiene (MA-DOH) resulted in air quality measurements. The offices occupied about 13,000 feet^2 of floor space on two floors. In October 1983, 2 yr before diagnosis of the tuberculosis case, ambient carbon dioxide (CO_2) measurements in various parts of the building were as follows: 800, 800, 900, 1,000, 1,000, and 1,000 parts per million (ppm). In December 1985, just weeks after the tuberculosis exposure, CO_2 measurements were repeated by an outside consultant, with similar results: 600, 800, 1,000, 1,000, and 1,500 ppm. Testing on both occasions used a Draeger detector tube (National Draeger Co., Pittsburgh, PA) and the hydrazine reaction. Based on these measurements, we concluded that outdoor air ventilation in the building averaged about 15 feet^3/min (cfm) per occupant at the time of the exposure. Outdoor air ventilation of 15 cfm per occupant corresponds to a CO_2 level of about 1,000 ppm, less than the current minimum standard of 20 cfm per person for offices (8). For greater worker comfort, however, the MA-DOH currently recommends 25 cfm per occupant for offices in the absence of smoking and 35 cfm per occupant where smoking is permitted (9). This higher rate of outdoor air ventilation results in CO_2 concentrations under 600 ppm, a level under which complaints about air quality are less frequently encountered.

Carbon dioxide is generated primarily by building occupants, and its concentration in indoor air is a function of both occupancy and the adequacy of ventilation with outdoor air. This convenient natural contaminant of indoor air is used by air quality engineers to estimate building ventilation with outside air. This requires accurate measurements and no important nonhuman sources of carbon dioxide (such as a faulty furnace). The result is an estimate of outdoor air ventilation relative to occupancy, rather than total ventilation. Only a small fraction of a building's total ventilation is ordinarily nonrecirculated, outdoor air. Whereas recirculated air may cool, heat, and distribute odors and other contaminants (possibly reducing their concentration locally), only the portion of ventilation that is outdoor air truly dilutes the concentration of contaminants within the building. Moreover, outdoor air replaces an equal volume of exhaust air that is removing contaminants from the building. If the occupancy of a room (or an entire building) is known, ventilation per person can be converted to total outdoor air ventilation and, if room volume is known, to room air changes (outdoor air, not total) per hour.

Knowing that 27 of 67 workers converted over a defined exposure period and that outdoor air ventilation averaged an estimated 15 cfm per person, we were able to apply the mathematical model to assess the role of ventilation relative to other transmission factors.

Analysis

We analyzed this exposure by using a modification of the Soper equation for airborne transmission, $C = S(1 - e^{-Iqpt/Q})$, where C is the number of new infections, S is the total number of susceptibles, I is the number of infectors, p is the volume of air sampled (minute ventilation) per occupant per unit time, t is the exposure time, Q is the volume of outdoor air building ventilation per unit time, and q is the number of quanta of infection added to the air per unit time ("infectiousness" of the case) (10). Because the number of droplet nuclei required to infect a susceptible person is usually not known, Wells (11) used the term "quantum" to represent a dose of airborne infection; however, many droplet nuclei are necessary. This statement of the theoretical relationship among the factors determining the probability of infection has been derived from basic principles, with the appropriate units indicated, in a recent review of air disinfection (12). Similar expressions have been used in the past to analyze airborne infection in a variety of circumstances (13–15), and more recently, a mass balance equation has been used to predict the effects of ventilation, filtration, and production rate on the concentration of respirable allergens (16). In the latter experiments, the concentrations predicted by the model correlated closely with air sampler measurements of airborne particles.

The contact investigation found that 27 new infections (C) resulted from the exposure of 67 susceptible occupants (S) for 160 h (t) to one source case (I). Room air sampling per occupant (minute ventilation) was assumed to average the standard 0.353 cfm (p). Assuming outdoor air building ventilation (Q) averaged 15 cfm per person, it was approximately 1,395 cfm for 93 occupants (including the index case). The only unknown, q, was the number of quanta of airborne infection added to the air per hour (qph). Once q was calculated, it was possible to recalculate C for a variety of theoretical exposure conditions in which Q, outdoor air ventilation, varied while other factors remained constant. It was also possible to predict the protection afforded to occupants at any assumed level of ventilation while q varied within the wide range of infectiousness reported in the tuberculosis literature. The calculation of q and the probability of infection at various levels of ventilation, using these values as an illustrative example, are detailed in the appendices of the previously cited review of air disinfection (12).

Assumptions

For the purposes of this theoretical analysis, exposure to tuberculosis was assumed to have occurred throughout the building, assisted by the largely recirculated ventilation. Had all or most of the transmission taken place in one or more poorly ventilated areas of the building, much of the analysis concerning total ventilation would be irrelevant. However, although some regional variation in outdoor air ventilation was indicated by the carbon dioxide measurements in different parts of the building, the free movement of workers within the building may have counterbalanced some of this inequality. Skin test conversions were distributed among the occupants of all six work areas and were nearly equally divided between the two floors. By area, the infection rate ranged from 25 to 53% of susceptible occupants. Although 52% of susceptibles in the work area of the index case converted, two areas with similar conversion rates were neither adjacent to that of the index case nor downstream to its ventilation. A formal case control investigation of the infected and uninfected workers failed to uncover specific risk

factors for infection, other than working in the building during the exposure period. Similarly, working in a clinic during the exposure period was the single greatest risk factor in the case control analysis of another building-associated tuberculosis epidemic in which much of the air was recirculated (7).

This analysis assumed approximately equal host susceptibility to an initial infection with tuberculosis. Although laboratory and clinical research indicates individual and group variability in the effectiveness of host defenses against tuberculosis, at present there are no clinical tests to assess susceptibility in otherwise healthy persons (17, 18). There were few black workers, and ethnic group was not noted in the skin test data.

Results

After the various units of the transmission factors were reconciled with one another, q was calculated as 12.7 qph. The number of workers predicted to have been infected, had the outdoor air ventilation in the office been lower or higher than the estimated 15 cfm, with q at 13 qph and other conditions unchanged, is shown in figure 1. The curve indicates that a decrease in ventilation of 10 cfm, to 5 cfm per occupant, would have nearly doubled the infection rate (78%), whereas an increase of 10 cfm, to 25 cfm, would have reduced the infection rate by only a third. A further increase of 10 cfm, to 35 cfm, the level of ventilation recommended in offices where smoking is permitted, would have reduced the theoretical infection rate another 19%, to about half the original rate. Further increases in outdoor air ventilation are not practical but would be predicted to result in progressively smaller reductions in infection, as indicated by the curve.

The effect of outdoor air ventilation on infection rate is again represented in figure 2, in which the curves derived for hypothetical exposures at four levels of infectiousness (q), where all other exposure factors correspond to the conditions observed in the office building, are compared. The average tuberculosis patient reported by Riley and coworkers (19) generated relatively few infectious particles (1.25 qph) and, at 15 cfm outdoor air ventilation per occupant, would have infected only about 3 of 67 workers over the 4-wk exposure. As in the previous situation, the curve shows that less ventilation would have increased contagion somewhat, but increased ventilation could protect only some of the very few individuals likely to be infected under these conditions. At 60 qph, a laryngeal case reported in Riley's series, the curve shows that the probability of infection over 4 wk would have been high at 15 cfm ventilation, reducible, but somewhat less sensitive to increasing ventilation to 35 cfm than was the case at 13 qph. Finally, at 250 qph, an extraordinary tuberculosis exposure that occurred during an intubation and bronchoscopy, the curve predicts that nearly all susceptibles would have been infected over a 4-wk exposure, regardless of the level of achievable outdoor air ventilation (15).

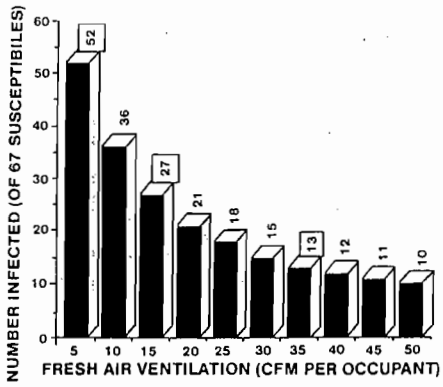

Fig. 1. Predicted number of workers infected with tuberculosis at various levels of outdoor air ventilation. Exposure conditions: 67 susceptible subjects exposed for 160 h to one source case generating 13 infectious quanta per hour (qph). See text for description of the model used for predictions.

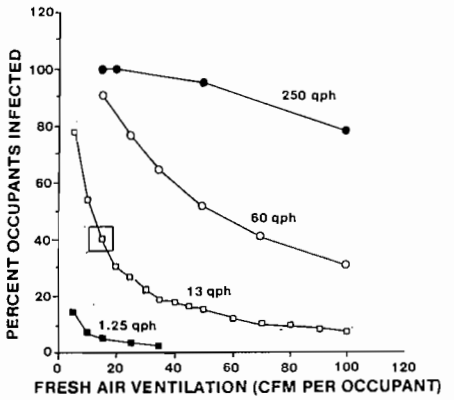

Fig. 2. Predicted percentage of 67 exposed workers infected with tuberculosis at various levels of outdoor air ventilation at four levels of infectiousness (q). Exposure conditions: 67 susceptible subjects exposed for 160 h to one source case generating from 1.25 to 250 infectious quanta per hour (qph). See text for description of the model used for predictions.

Discussion

Although the importance of airborne microbial infection in human disease has long been recognized, the role of building ventilation in preventing person-to-person transmission has received little attention in the recent medical literature (11, 20). In the early 1900s, a generous 30 cfm per person of outdoor air ventilation was recommended in public buildings, not to control infection but to control human body odor (21). By 1930, personal hygiene had improved and the recommendation for ventilation with outdoor air was reduced to 10 cfm per person, where it remained until 1973, when new standards and the oil embargo led to the widespread implementation of even lower ventilation rates, still dictated primarily by considerations of comfort but also influenced by economic constraints (22). Fortunately, as building designs called for greater dependence on recirculated air, tuberculosis was declining and rendered less contagious by chemotherapy, and immunizations reduced the chance of transmission of several viral illnesses. Thus, only small portions of three recent reviews of the health consequences of indoor air were devoted to microbial illnesses, primarily fungal and bacterial contamination of building ventilation systems (23–25). However, people, not buildings, remain the principal source of indoor airborne infection. Person-to-person transmission of influenza, measles, tuberculosis, and other airborne infections continues in homes, workplaces, schools, and, of increasing importance, in such indoor environments as shelters for the homeless, nursing homes, prisons, hospital intensive care units, and bronchoscopy rooms (1–6, 15). Like bronchoscopy, treatment and prophylaxis for pneumocystis infection with pentamidine aerosol may induce coughing and has recently been associated with extensive tuberculosis transmission in a clinic (7). Sputum induction for diagnosing lung diseases, another cough-generating procedure of increasing importance in managing patients with the acquired immunodeficiency syndrome (AIDS), may also increase the risk of tuberculosis transmission. Among human immunodeficiency virus (HIV)-infected patients, 29 cases of isoniazid- and rifampin-resistant tuberculosis have been reported, believed to have been transmitted on a specialized hospital ward and in a HIV clinic where cough-generating procedures were performed (26). A recent editorial and official guidelines from the Centers for Disease Control address the problem of nosocomial tuberculosis transmission in the AIDS era (27, 28).

In the office exposure under discussion, the high infection rate was immediately associated with the workers' long-standing complaints about air quality. However, outdoor air ventilation averaging 15 cfm per occupant is commonly found in buildings designed in the post-oil embargo era. Had the outdoor air ventilation been the recommended 35 cfm per person, theoretical modeling predicted that about half the persons infected would have been protected. Although a considerable improvement, the infection

of 13 rather than 27 workers would have been cause for continued concern. Therefore, although relatively low outdoor air ventilation contributed to the high infection rate, other factors, especially the infectiousness of the index case (q) and the duration of exposure (t), were also important.

The estimated 12.7 qph generated by this patient was approximately 10 times the average infectiousness (1.25 qph) of tuberculosis cases studied by Riley and colleagues in Baltimore over a 4-yr period (19). It should be noted, however, that the Baltimore patients had been started on chemotherapy and that a few highly infectious subjects accounted for much of the transmission. A case of laryngeal tuberculosis in that series, for example, generated approximately 60 qph. The wide range of tuberculosis infectiousness in the literature is topped by the pulmonary case reported by Cantazaro (15), who produced nearly 250 qph during an intubation and bronchoscopy. Thus, the index case in the current exposure was relatively highly infectious but well within the wide range reported for tuberculosis.

Exposure time is another highly variable transmission factor. Compared with any one exposure for workers in an acute care hospital, for example, the 4-wk exposure period reported here is relatively long, but it is short compared with many household exposures in which symptomatic disease may go undiagnosed for months. Even a brief exposure, however, can result in transmission when q is high, as in the bronchoscopy case, in which 10 of 13 susceptible individuals were infected during a 150-min procedure. The outdoor air ventilation in the intensive care unit where the transmission occurred, however, averaged only 11.5 cfm per occupant, less than ventilation estimates for the office building. We performed similar mathematical modeling using the actual conditions of the bronchoscopy exposure and predicted that tripling the ventilation rate to 35 cfm per person would have reduced infection by half. Another threefold increase in ventilation would have reduced infection by only an additional 20%. Therefore, the limited protection achievable by ventilation does not appear to be peculiar to the conditions extant in the office building, as similar findings result from analysis of a shorter, more intensive exposure.

Drainage and irrigation of a tuberculous hip abscess was the source of another recent hospital exposure, resulting in nine secondary cases and 59 skin test conversions (6). The wound was estimated to contain extraordinarily high concentrations of tubercle bacilli, and the method of jet irrigation may have contributed to their aerosolization. Relevant to the present discussion, transmission occurred in three separate hospital environments—a surgical suite, an isolation room, and an intensive care unit—under three different ventilation conditions, only one of which was found to be deficient.

For both comfort and safety, ventilation should always meet or exceed current building standards (8, 28). Should higher rates of outdoor air ventilation be recommended, beyond the requirements of comfort, specifically to reduce the risk of airborne infection? This decision depends upon the setting, the type of infection, the relative risk, the protection predicted by increased ventilation under specific circumstances, cost and design considerations, and the availability of alternative methods of control. The number of infections theoretically prevented, as a percentage of susceptible occupants, by increased outdoor air ventilation, as a function of q, is shown in figure 3. The lower curve shows the protection predicted by increasing from 15 to 35 cfm per person. At low levels of q there would be few infections at 15 cfm and, therefore, very few infections prevented by increasing to 35 cfm. At 13 qph, as previously noted, 14 infections would be prevented (21% of occupants protected). As q increases, the increasing infections predicted are less and less preventable by the added ventilation, with a maximum of about 20 infections prevented (30% of occupants protected). Finally, with increases in q above 60 qph, the percentage of susceptible workers predicted to become infected at 15 cfm approaches 100%, but a progressively smaller percentage of them would be protected at 35 cfm. Thus, under the conditions described here, increased outdoor air ventilation appears inherently able to protect only a portion of exposed occupants.

Increased outdoor air ventilation is not the only way to disinfect building air. The ability of ultraviolet (UV) irradiation of the 254 nm wavelength to render indoor air noninfectious has been demonstrated in experimental exposure chambers, in experimental rooms, and, to a lesser extent, by field trials (12, 29–31). Species of microorganisms vary in their susceptibility to UV irradiation, but many bacteria, including tubercle bacilli, and some airborne viruses are killed with levels of UV irradiation that are both practical and safe for certain applications (32, 33). Experiments with aerosolized tubercle bacilli demonstrated that a 30 W suspended fixture, designed to irradiate only the upper air of a 200 foot² room, was about four times more effective than average outdoor air ventilation (25 cfm per occupant) in disinfecting air (34). Because the benefit is additive to existing outdoor air ventilation, for the purpose of comparison, the potential benefit of upper room air ultraviolet air disinfection equivalent to 125 cfm outdoor air per occupant (100 cfm UV equivalent plus 25 cfm outdoor air) is superimposed in figure 3. The number of infections theoretically prevented by UV irradiation peaks at more than twice that predicted by increasing from 15 to 35 cfm. At 13 qph, the case reported here, all but about three infections would have been prevented by UV fixtures. However, in situations of more intensive exposure, neither UV irradiation nor equivalent high levels of outdoor air ventilation can eliminate airborne transmission.

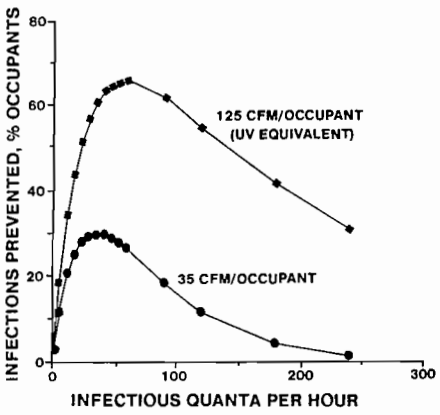

Fig. 3. Predicted infections prevented by increasing outdoor air ventilation from 15 to 35 cfm per occupant and from 15 to 125 cfm per occupant, as a function of infectiousness (q). Exposure conditions: 67 susceptible subjects exposed for 160 h to one source case generating from 1.25 to 250 infectious quanta per hour (qph). Infections prevented expressed as a percentage of the 67 exposed occupants. See text for description of the model used for predictions.

We are not suggesting that this or any other office building be equipped with UV fixtures for air disinfection. Most offices are not regular sites of tuberculosis transmission; however, where tuberculosis transmission and other airborne infections are more likely (intensive care units, isolation rooms, bronchoscopy rooms, clinics, shelters, and jails, for example) it may be possible to improve the protection provided by conventional outdoor air ventilation. Under these circumstances, properly installed and maintained UV air disinfection offers advantages of greater potential efficacy and reduced cost compared with high levels of outdoor air ventilation—hence Wells' recommendation: "Ventilate for comfort, but irradiate for infection control" (personal communication, Richard L. Riley,

M.D.). Planning and installation guidelines for safe and effective UV air disinfection have been published (12, 33).

Both outdoor air ventilation and UV irradiation help control airborne infection by diluting infectious droplet nuclei with infection-free air. From the perspective of air quality engineers, however, ventilation as a means of dilution control "may be the most energy-intensive and costly of the control methods available today" (35). As emphasized in this analysis, the dilution approach concedes ongoing exposure to air contaminants, however much reduced. The two other engineering approaches, source control and removal control, are also relevant to containing indoor airborne infection. Source control entails physically isolating the infectious individual from susceptible individuals (or rendering the person noninfectious by treatment from a nonengineering point of view). This strategy is especially important when the q factor is potentially large, as in aerosol-generating procedures like sputum induction or pentamidine aerosol treatment, in which dilution may be particularly ineffective. If these procedures are performed in a small room or booth that is adequately exhausted to the outside, other building occupants are protected primarily by the physical barrier. Removal control means using high-efficiency particle air (HEPA) filters to remove droplet nuclei. Ventilation with properly filtered air is equivalent to diluting droplet nuclei with outdoor air. HEPA filtration on a large scale is expensive, and like ventilation, it is limited as a means of infection control. However, using the source control approach, Riley has effectively used a HEPA filter to disinfect the air exhausted from a booth designed for administering pentamidine aerosol treatments and for sputum induction. Because the booth is self-contained and need not be exhausted to the outside, it is readily relocated, saving considerable energy and installation costs (personal communication, Richard L. Riley, M.D.).

Finally, it should be emphasized that the environmental control interventions discussed in this paper are not presented as substitutes for the prompt diagnosis and effective treatment of source cases, when possible. These measures acknowledge that transmission often occurs before the disease is diagnosed and the treatment initiated.

The main conclusion derived from this theoretical analysis is that, because the relationship between ventilation and risk of airborne infection is a logarithmic curve, large reductions in risk are predicted from increases in ventilation at low levels, but much smaller reductions are predicted from increases at the higher end of ventilation. The data from a contact investigation of an office building exposure was sufficient to approximate its location on the exposure curve and to predict the protection achievable by increased outdoor air ventilation. At levels of ventilation considered optimal for comfort purposes, only half the observed infections would have been prevented, according to this model.

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