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Framework for Evaluating Measures to Control Nosocomial Tuberculosis Transmission

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Abstract Diverse control measures can be applied to reduce tuberculosis infection risk in health-care facilities. Selecting optimal controls requires methods for predicting the dependence of infections risk on underlying parameters. A common model for infection risk only explicitly accounts for control by ventilation. This paper proposes a more complete model for evaluating tuberculosis infection control methods in health-care settings. An infection risk parameter is defined as the probable number of infectious droplet nuclei inhaled by all susceptible persons from a single infectious person. Algebraic model equations are presented for two exposure cases. In one, the susceptible and infectious persons are together in a well-mixed indoor environment; in the second, the infectious person is in respiratory isolation. Model equations are used to explore many common tuberculosis control measures: identification, isolation and treatment of tuberculosis cases; surgical masks and treatment booths applied at the source; environmental controls such as ventilation, air filtration, and ultraviolet germicidal irradiation; and respiratory protection for susceptible persons. Experimental data are limited or lacking on some key variables, such as emissions of infectious droplet nuclei by contagious persons and air leakage rates from isolation rooms. Methods are outlined for collecting additional data.

Key words Bioaerosol; Disease transmission; Filtration; Indoor air quality; Respiratory disease; Ultraviolet disinfection.

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Introduction

After several decades of neglect that extended into the 1980s, the control of tuberculosis has reemerged as an important public health topic. The resurgent interest has been precipitated by increased disease incidence, triggered in part by the appearance of multidrug resistant strains of *Mycobacterium tuberculosis* and by an increasing population of immunocompromised individuals.

The transmission of tuberculosis (TB) in health-care facilities is a specific topic of concern (Gordin, 1992), with many papers documenting nosocomial, or hospital-acquired, tuberculosis (Ehrenkranz and Kicklighter, 1972; Cantanzaro, 1982; Haley et al., 1989; Dooley et al., 1992; Pearson et al., 1992; Jarvis, 1993; Ikeda et al., 1995; Jereb et al., 1995; Ussery et al., 1995; Zaza et al., 1995). In response, the Centers for Disease Control and Prevention (CDC) issued comprehensive guidelines for controlling TB transmission in health-care facilities (Centers for Disease Control and Prevention, 1994) and the Occupational Safety and Health Administration established an enforcement policy for protecting exposed workers (Decker, 1993; Occupational Safety and Health Administration, 1993). Review articles summarize the current state of knowledge of TB transmission and control in hospitals from the perspective of the medical profession (McGowan, 1995; Menzies et al., 1995; Sepkowitz, 1995; Dooley et al., 1996). The status and effectiveness of implementing TB control programs has been reported for many specific health-care settings (Blumberg et al., 1995; Fridkin et al., 1995a, 1995b; Maloney et al., 1995; Stroud et al., 1995; Wenger et al., 1995).

The CDC recommendations contain many components, including administrative and engineering controls plus protective equipment for health-care workers. Overall, these recommendations target all aspects in the chain of transmission from an infectious host to a susceptible receptor. There is no known safe level of exposure to TB ''infectious droplet nuclei''. Furthermore, none of the control measures is perfect in practice. Consequently, to strictly minimize the risk of

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transmission, each of the control components must be fully applied. In practice, a balance is sought between the risk of infection and the cost of control, tempered by the special concerns that apply for patient care. The current approach for establishing an appropriate balance seems to be based largely on experience and intuitive judgment, rather than on specific objective criteria.

Lacking a means of quantitatively evaluating the relative merits of different control strategies, it is no surprise that specific CDC recommendations have sparked controversy. Much of the debate has focused on whether health-care workers need to use high-efficiency particle filters for respiratory protection (Decker, 1993; Voelker, 1993; Winters, 1994; Adal et al., 1994; Nettleman et al., 1994; Hodous and Coffey, 1994; Catanzaro, 1995; Jarvis et al., 1995). Another controversial issue is the efficacy and safety of using ultraviolet germicidal irradiation (UVGI) to inactivate airborne bacilli (Macher, 1993; Riley, 1994; Heinsohn, 1996).

Some progress in reducing nosocomial TB transmission has been achieved in the United States (Cookson and Jarvis, 1997), but outbreaks continue to be reported (e.g., Kenyon et al., 1997; Nirvin et al., 1998). We know of no surveillance data establishing that the overall TB infection rate among U.S. health-care workers has been decreasing. The problem of nosocomial transmission of tuberculosis has worldwide significance, and control strategies implemented in the United States may not be appropriate for less-developed countries (Harries et al., 1997).

To develop efficient and cost-effective control strategies for preventing nosocomial transmission of TB, an analytical framework is required that allows the costs and benefits of various control measures to be evaluated. The purpose of this paper is to contribute to the development of such a framework. We define a parameter that quantifies the risk of infection and serves as a basis for evaluating the relative effectiveness of a variety of control techniques. Then, model equations are presented that link this risk parameter to important variables, such as the efficiency of prospective control measures. We provide a few illustrative examples, summarize what is known about the input parameters and point out deficiencies in the current data.

This approach combines principles from industrial hygiene with those from environmental engineering, building on the work of early investigators (e.g., Wells, 1955), and complementing the current TB control literature which emphasizes epidemiology, occupational medicine and infectious disease management. Most recent studies on engineering control of nosocomial TB transmission focus on individual technologies (Macher, 1993; Nardell et al., 1991; Fraser et al., 1993; Marier and Nelson, 1993; Nardell, 1995; Nicas, 1995; Rutala et al., 1995; Miller-Leiden et al., 1996). The papers that explore multiple techniques assess them in isolation or by largely qualitative means (Nardell, 1993; Conroy and Franke, 1994; Nagin et al., 1994; Segal-Maurer and Kalkut, 1994). The present paper offers advances towards quantitative synthesis.

Although this paper focuses on TB transmission in health-care facilities, we note that much of what is discussed here is relevant to the broader problem of occupational tuberculosis control. The United States Occupational Safety and Health Administration (OSHA) has recently proposed a health standard to control occupational TB exposure that will use many of the same methods required in health-care facilities (Occupational Safety and Health Administration, 1997).

Conceptual Framework

Tuberculosis transmission occurs predominantly by the airborne route. The causative agent, *M. tuberculosis*, is emitted in the form of small particles from persons with active pulmonary or laryngeal tuberculosis. Expelled respiratory particles rapidly shrink by evaporation of water; some fraction decrease to the size of ''droplet nuclei'', which have aerodynamic diameters thought to be in the range 1 to 5 μm (Centers for Disease Control and Prevention, 1994; Wells, 1955; Riley and O'Grady, 1961). Inhalation and deposition—especially in the alveolar region—of a single droplet nucleus carrying a viable bacillus appears sufficient to cause infection (Wells, 1955; Riley and O'Grady, 1961).

In summarizing pioneering research, Riley and O'Grady (1961) pointed out that ''the key to understanding the transmission and control of airborne infection is contained in the study of the origin, behavior and means of elimination of infectious airborne particles''. They also articulated that control measures can be applied at any of three stages: (i) at the source; (ii) during transmission; and (iii) at the receptor.

An ideal nosocomial TB control program would completely eliminate the risk of transmission at minimum cost without undue burden on patients or health-care workers. Although complete control (i.e., zero risk) is theoretically possible, it appears to be unattainable in complex health-care environments, and therefore the practical objective is to reduce the probability of transmission to an acceptably small value. What constitutes an ''acceptably small'' risk involves subjective judgment. However, such judgment can and should incorporate objective information. A rational

control strategy would achieve cost that is near minimum at a given acceptable level of risk. This objective cannot be achieved without a consistent basis for quantitatively comparing the effectiveness of various prospective control measures and estimating the associated risks. The primary objective of this paper is to describe such a basis.

We begin by defining an infection risk parameter. An individual's cumulative inhaled dose, d, is the probable number of infectious droplet nuclei deposited in the lungs of a susceptible health-care worker per TB patient over the course of the patient's stay in the health-care facility. Then, the choice for an infection risk parameter is the "cohort inhaled dose", D, defined as the sum of all d values across N individuals in the cohort of susceptible occupants of the health-care environment:

$$D = \sum_{N} d \tag{1}$$

D is treated as a continuous real number, even though the true number of infectious droplet nuclei inhaled in any circumstance must be a discrete integer.

According to the traditional risk model for TB infection, a susceptible individual's risk of infection, r, is an increasing function (asymptotically approaching one) of d (Wells, 1955; Catanzaro, 1982; Nardell et al., 1991; Nicas, 1996a):

$$r = 1 - e^{-d} \tag{2}$$

The mean risk in the cohort is the arithmetic average of the individual r-values:

$$\bar{r} = \frac{1}{N} \sum_{N} r \tag{3}$$

The expected number of new infections in the susceptible cohort is simply the sum of the r-values, which is equivalent to N $\bar{r}$ (Nicas, 1996a).

In addition to being related to the cohort mean risk, $\bar{r}$, the infection risk parameter, D, can be influenced by administrative controls (for example, respiratory isolation and prompt onset of chemotherapy), engineering controls (ventilation, UVGI), and personal respiratory protection. Thus, with sufficient data, all major aspects of a TB control program can be assessed on a consistent basis by evaluating D.

The second step towards establishing an analytical framework is to specify one or more conceptual model representations of health-care environments that can be used to describe the key features of all important classes of nosocomial exposure. Two models are used to describe the system. A single, well-mixed volume represents exposures in which both the infectious person and the susceptible persons are in the same room or zone of the facility. A dual-chamber representation is applied to evaluate exposure in which the infectious and susceptible persons are segregated. This approach allows several exposure scenarios to be simulated: (a) an undiagnosed patient or health-care worker is the index case and everyone else in that zone of the facility is at risk; (b) a diagnosed patient emits infectious droplet nuclei over extended periods in an isolation room with exposure occurring to health-care workers in the room and, in the case of isolation failure, elsewhere in the facility; and (c) a patient undergoes treatment that induces a high episodic emission rate such as bronchoscopy or intubation and exposure occurs in the treatment room and possibly elsewhere in the facility.

The principle of mass conservation is applied to generate quantitative relationships for the dependence of the infection risk parameter on the governing variables. The resulting equations for infection risk include terms whose values vary according to the nature and efficiency of control measures. The specific control measures that are incorporated into the analytical framework are summarized in Table 1. The approach can be adapted to incorporate other control measures.

Table 1 Control techniques to limit nosocomial transmission of tuberculosis

Control technique	Key parameter(s) in model equations[a]
Case identification/effective chemotherapy	N_e
Isolation	L, Q_p
Emission controls applied at source	η_e
General ventilation	Q
Ultraviolet germicidal irradiation (unducted)	λ, λ_p
Recirculating air filtration[b]	$Q_r\eta_r$, $Q_{pr}\eta_{pr}$
Respiratory protection of susceptibles	η_s

[a] Parameter definitions: N_e – total number of infectious droplet nuclei emitted by an infectious person while in a health-care facility; L – fractional leakage of air from isolation room into a general health-care facility; Q_p, Q – ventilation rates ($m^3\ h^{-1}$) for an isolation room and a general health-care facility, respectively; η_e, η_s – fractional removal efficiency for emissions control measure and respiratory protection for a susceptible person, respectively; λ_p, λ – rate coefficients (h^{-1}) for inactivation of *M. tuberculosis* by ultraviolet disinfection in an isolation room and a general health-care facility, respectively; Q_{pr}, Q_r – recirculation flow rates ($m^3\ h^{-1}$) for air filtration in an isolation room and a general health-care facility, respectively; η_{pr}, η_r – fractional single-pass removal efficiency of *M. tuberculosis* by air filtration in an isolation room and a general health-care facility, respectively.

[b] Includes ultraviolet germicidal irradiation within ducts or portable air cleaning devices.

Model Equations

Background

In previous studies, the mean risk of TB infection in a cohort was predicted by an equation of this form (Catanzaro, 1982; Nardell et al., 1991; Riley and Nardell, 1989):

$$\bar{r} = 1 - \exp\left(-\frac{I\,E\,t\,b\,f}{Q}\right) \tag{4}$$

where I is the number of infectors, E is the emission rate (h^{-1}) of infectious droplet nuclei per infector, t is the exposure duration (h), b is the volume inhalation rate ($m^3\ h^{-1}$) per susceptible, and Q is the ventilation rate ($m^3\ h^{-1}$) of the indoor space. In the traditional risk model, f, the deposition fraction of inhaled viable *M. tuberculosis*, was omitted. Note that Equation (4) strictly assumes that the dose rate is constant during exposure, that it is the same for all N individuals in the cohort, and that infection is a one-hit phenomenon (that is, the deposition of one droplet nucleus carrying one or more viable bacilli can initiate infection) (Nicas, 1996b).

If the probability of infection for each susceptible individual is much less than one, Equation (4) can be simplified by applying the approximation $e^{-x} \approx 1-x$ which is valid for $|x| << 1$. In this case,

$$\bar{r} = \frac{I\,E\,t\,b\,f}{Q} \tag{5}$$

and r=d. Multiplying by the number of susceptibles exposed, the following expression would be obtained for D:

$$D = (I\,E\,t) \times \left(\frac{N\,b}{Q}\right) \times f \tag{6}$$

This expression is written as the product of three terms: (i) the total number of infectious droplet nuclei emitted into the indoor air (I E t); (ii) the fraction of indoor air that is inhaled before it is removed by ventilation ($N\,b\,Q^{-1}$); and (iii) the deposition probability for an infectious droplet nucleus (f). The full form of Equation (4) is needed only when the probability of any individual inhaling more than one infectious droplet nucleus is large; in this case, the risk per infectious droplet nucleus emitted diminishes because any individual can only be infected once.

As formulated, Equation (6) can be used directly to evaluate the effectiveness of ventilation as a control measure. Other control options, however, cannot be directly assessed. In the new framework presented below, model equations are developed to explicitly incorporate parameters that represent all of the major TB control measures in health-care facilities.

Before proceeding, two technical points regarding Equation (4) merit further comment. First, it assumes that all individuals are equally susceptible to infection. It is plausible that biological susceptibility to infection varies across individuals. Available evidence on one factor that could influence susceptibility, race, is contradictory (Stead et al., 1990; Hoge et al., 1994). Second, Equation (4) implicitly assumes that infection risk is the complement of the probability that *no* particles carrying viable bacilli deposit in the alveolar region, and thereby assumes that the deposition of just one particle carrying one or more bacilli is sufficient to infect. We believe this "one-hit" model is a reasonable descriptor, because the available animal evidence indicates that one bacillus can infect a mammalian host (Riley, 1957). If multiple droplet nuclei must be deposited to initiate infection, an alternative formulation of the risk equation is required (Nicas, 1996b).

Case 1: Single-Zone Exposure

For Case 1, emission and exposure occur in the same air zone. Depending on the ventilation system and the configuration of the health-care facility, this zone might represent an entire wing or only a single room. Specifically, this case would be used to assess exposure of a health-care worker in a facility that results from the presence of an undiagnosed infectious patient or the exposure of a susceptible person in the same room as a diagnosed infectious person.

Figure 1 presents a schematic representation of this case, indicating the important variables. On the basis of a governing material balance equation, the following equation is derived to predict the infection risk parameter (see appendix):

$$D = \frac{[N_e\,(1-\eta_e)]\,\Sigma_N\,[b\,f\,(1-\eta_s)]}{Q + \lambda\,V + Q_r\,\eta_r} \tag{7}$$

The infection risk parameter, D, represents the total expected number of infectious droplet nuclei inhaled by all susceptible persons due to one source case. The variables b, f, and Q have the meaning previously described. The variable N_e (=E t) represents the total number of infectious droplet nuclei emitted by the infectious person while present in a Case 1 environment (number); η_e is the efficiency of a source-oriented control measure, such as a surgical mask or treatment booth (dimensionless); η_s is the efficiency of a respir-

atory protection device used by a susceptible person (dimensionless); λ is the first-order decay rate of infectious droplet nuclei due to ultraviolet irradiation or other open-air removal processes (h^{-1}); V is the volume of the zone (m^3); Q_r is the air flow rate through a recirculating filter ($m^3\ h^{-1}$); and η_r is the single-pass removal efficiency for infectious droplet nuclei passing through the recirculating filter (dimensionless). Each of the efficiency terms (η) has a value ranging from 0 to 1 and represents the fraction of infectious droplet nuclei presented to the control device that are removed from the air stream or otherwise inactivated. If the parameters vary across the exposed population, the breathing rate and effectiveness of respiratory protection can be separately evaluated and summed over all exposed susceptible persons, N.

Equation (7) is derived from a steady-state material balance. Some of the parameters may be time dependent; if so, the equation should be modified accordingly, as illustrated in the following example. In Figure 1, emission of infectious droplet nuclei is represented by E, a rate parameter (number emitted per unit time). Over the course of stay in a health-care facility, E may vary markedly with time, for example, because of successful chemotherapy or invasive treatment processes. The emission parameter, N_e, in Equation (7) represents the time integral of E(t). If a source-oriented control measure is applied for only part of the time that nuclei are emitted, then the first term in brackets in the numerator of Equation (7) should be replaced by $\int E(t)\,[1-\eta_e(t)]\,dt$.

In analogy with Equation (6), Equation (7) can be seen as the product of three terms: (i) the number of infectious droplet nuclei escaping from the source into the general indoor environment [$N_e\ (1-\eta_e)$]; (ii) the ratio of the rate at which infectious droplet nuclei are inhaled [the sum of b $(1-\eta_s)$ over the exposed population] to the sum of the rates of all other removal processes (ventilation, air ultraviolet irradiation, and recirculation/filtration); and (iii) the probability of deposition following inhalation (f).

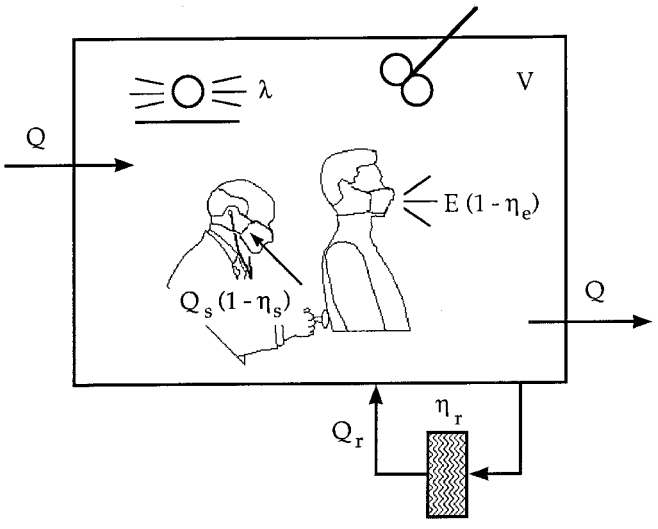

Fig. 1 Schematic representation of infection risk model for Case 1 in which the infectious and susceptible persons are in the same well-mixed room or zone.

Case 2: Two-Zone Exposure

A second case is introduced to describe exposures that occur elsewhere in a health-care facility when a patient is in a separate treatment or isolation room. Ideally, such rooms provide for complete air isolation. However, in practice, some leakage may occur (Pearson et al., 1992; Fraser et al., 1993; Blumberg et al., 1995).

Figure 2 presents a schematic representation of this case. The room with the infectious patient has volume V_p. Ventilation is provided to this room at a flow rate Q_p. A fraction, L, of this flow rate may leak into the general health-care environment leading to exposure of susceptible individuals. It is assumed that the leakage flow rate, $L\ Q_p$, is much less than the total ventilation air flow rate to the general environment, Q. Both the patient room and the general environment may be equipped with UV germicidal lamps which yield first-order inactivation rates of λ_p and λ, respectively. Likewise, both zones may be equipped with recirculating air filters with distinct flow rates (Q_{pr} and Q_r) and removal efficiencies (η_{pr} and η_r). Although it is unlikely in this exposure scenario that susceptible individuals would be using respiratory protection devices, for completeness this measure is included in the model equation.

In analogy with Case 1, the following equation is derived by applying a material balance to predict the infection risk parameter:

$$D = [(N_e\,(1-\eta_e)] \times \frac{L\,Q_p}{Q_p+\lambda_p\,V_p+Q_{pr}\eta_{pr}} \times \frac{\sum_N [bf(1-\eta_s)]}{Q+\lambda\,V+Q_r\eta_r} \quad (8)$$

Equation (8) is written as the product of three terms. The first term again represents the total release of infectious droplet nuclei into indoor air. The second term represents the fraction of these infectious droplet nuclei that escape from the isolation room into the general health-care environment. The third term represents the ratio of the rate of lung deposition of infectious droplet nuclei to the total rate of removal by all mechanisms from the general indoor environment.

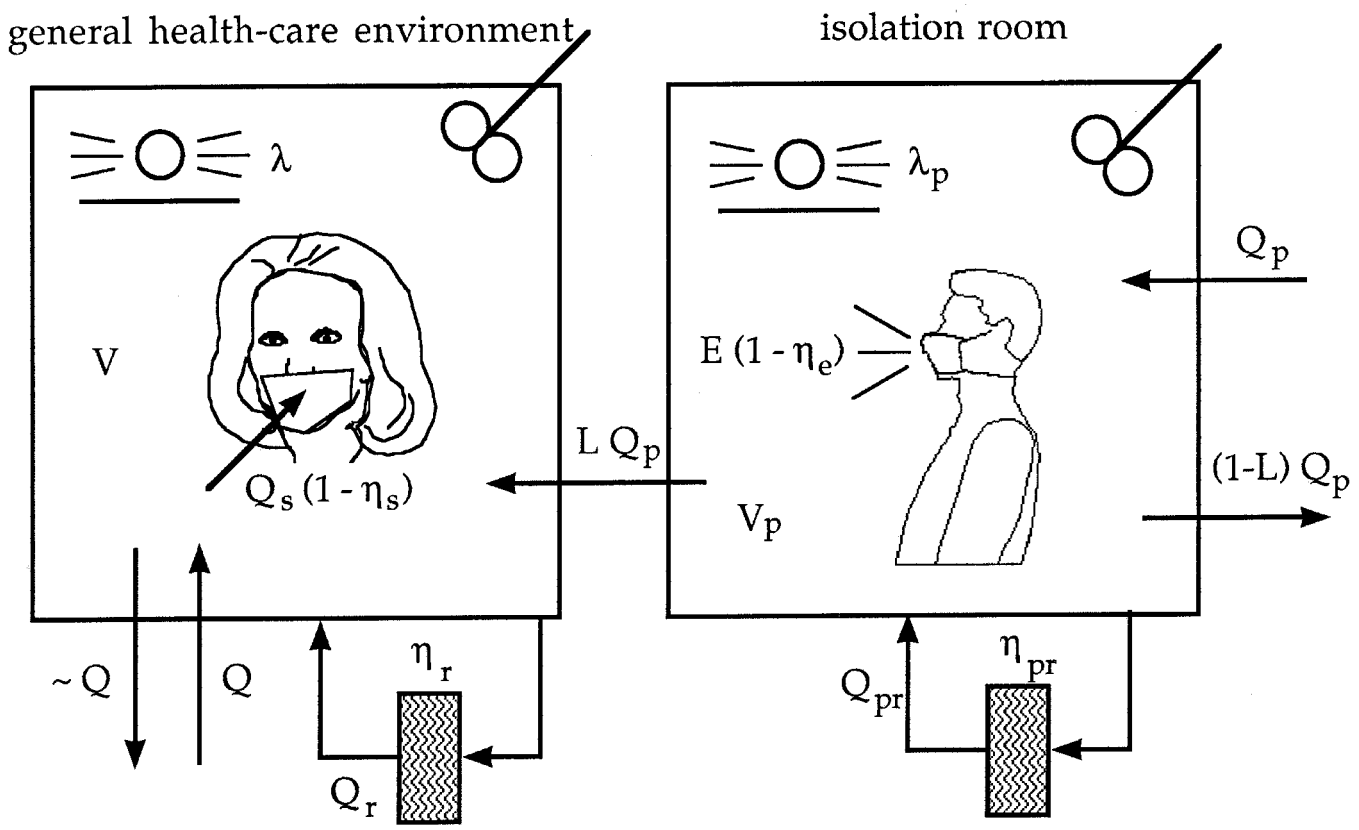

Fig. 2 Schematic representation of infection risk model for Case 2 in which the infectious person is in respiratory isolation with respect to the remainder of the health-care environment.

Discussion: Control Opportunities, Model Parameters, and Data Needs

Critical Data Need: Respiratory Emission of Infectious Droplet Nuclei

Six decades have passed since Wells (1934) introduced the hypothesis that frames our current understanding of tuberculosis transmission. In the intervening years, remarkably little has been learned about the rate of emission of infectious droplet nuclei from individuals with pulmonary tuberculosis and the factors that influence this rate. Standard bioaerosol sampling techniques are incapable of measuring the small emission rates of the slowly reproducing *M. tuberculosis*. Instead, available data are based on inferences using Equation (4) or a similar expression and observations on the rate of new infections following identifiable exposures. Using this approach, Riley et al. (1962) reported an average emission rate of 0.25 infectious droplet nuclei per hour for a tuberculosis ward; the maximum rate from an individual patient in this study was 60 per hour (averaged over a three-day period) for a case of laryngeal tuberculosis. Nardell et al. (1991) inferred an emission rate of 13 infectious droplet nuclei per hour for an office worker with cavitary tuberculosis. Likewise, Catanzaro (1982) reported an emission rate of 249 infectious droplet nuclei per hour for a single patient undergoing bronchoscopy, a cough-inducing procedure. Note that the emission rates in these studies were actually given in terms of "quanta" per hour, where a quantum is that number of inhaled bacilli required to initiate infection. However, the form of Equation (4) implies that a quantum is equal a single infectious droplet nucleus (Nicas, 1996b).

Additional estimates could be generated by similar analysis of published reports on TB transmission. However, because published case reports usually constitute a self-selected set of positive findings, the results would be biased towards high emitters.

It should be an important priority to develop a method capable of quantitatively measuring the airborne concentration of *M. tuberculosis* in hospitals and other settings. This goal would appear within reach of modern techniques of molecular biology (Schafer, 1994; Mukoda et al., 1994; MacNeil et al., 1995). With appropriate methods of analysis, time-integrated samples of airborne *M. tuberculosis* in the exhaust ducts of hospital isolation rooms might be used in concert with air flow measurements to measure generation rates of infectious droplet nuclei, although the small emission rates would still pose substantial experimental challenges.

Identification, Isolation and Treatment of Tuberculosis Cases

The CDC recommendations state that "the most important factors in preventing transmission of *M. tuberculosis* are the early identification of patients who may have infectious tuberculosis, prompt implementation of tuberculosis precautions for such patients, and prompt initiation of effective treatment for those who are likely to have tuberculosis" (Centers for Disease Control and Prevention, 1994). Cases of nosocomial tuberculosis outbreaks are commonly traced to delayed recognition of infectious cases (Dooley et al., 1996).

The importance of identification and respiratory isolation can be seen by considering an example in which an infectious patient is admitted to a hospital for a one-week stay. We evaluate D for three situations. In the base case, we assume that the patient is not diagnosed to have TB and therefore enters a general ward. The only removal of droplet nuclei is by ventilation. Assuming that the occupancy is 10 people per 100 m^2, that the ceiling height is 2.5 m, and that the ventilation rate is 25 cfm/person (=47 $m^3\ h^{-1}$ person) (ASHRAE, 1990), the air-exchange rate would be 1.9 h^{-1}. If the untreated patient emits 0.25 infectious droplet nuclei per hour and the susceptible individuals inhale 1 $m^3\ h^{-1}$, the infection risk parameter estimated from Equation (7) is D=0.89 (168 h $\times$ 0.25 per hour $\times$ 1 $m^3\ h^{-1}$ $person^{-1}$ $\div$ 47 $m^3\ h^{-1}$ $person^{-1}$). In the second situation, the patient remains undiagnosed. Enhanced ventilation, ultraviolet disinfection, or recirculating filtration increase the removal rate from 1.9 h^{-1} to 6 h^{-1}. According to Equation (7), the infection risk parameter would be correspondingly reduced to 0.28. For the third situation, we return to base-case building conditions, but consider rapid diagnosis, effective treatment, and isolation. Assume that the patient is in the general hospital environment for 2 h before being placed in respiratory isolation and beginning chemotherapy. Assume that once chemotherapy begins, the rate of emission of infectious droplet nuclei diminishes linearly to zero over a 48-h period. Further assume that the rate of leakage from the isolation room is 5% (L= 0.05 and $\lambda_p=Q_{pr}=0$). The cumulative infection risk parameter for occupants in the general hospital environment would be reduced to 0.017, about 2% of the base-case value. More than half of this residual risk would occur during the first two hours in the hospital (Figure 3), again stressing the importance of rapid diagnosis.

The impact of effective drug therapy on TB transmission risk is captured in the N_e term in the model equations. The evolution of respiratory emissions in response to treatment is unknown (Noble, 1981). However, the potential impact on reducing transmission risk scales roughly with the change in the duration of infectivity of a patient. Clearly, this can be an important factor if the period of infectiousness can be reduced from weeks or months to days (Iseman, 1995).

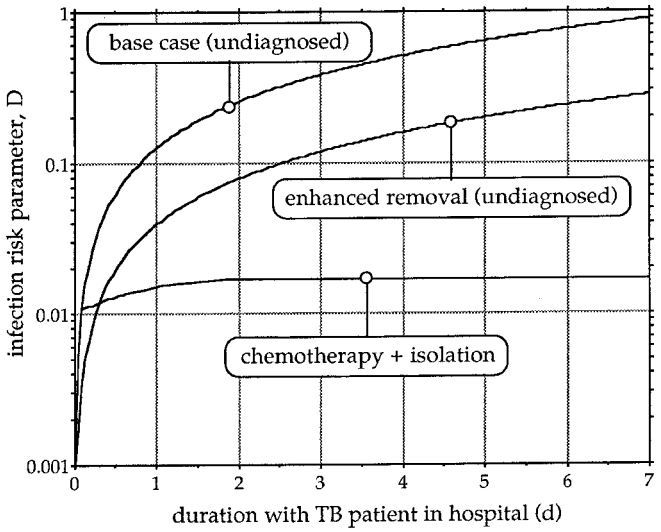

Fig. 3 Predicted infection risk parameter vs. time since admission for a single infectious patient in a health care facility, demonstrating the importance of rapid diagnosis, effective chemotherapy, and respiratory isolation in managing nosocomial transmission. Curves are generated from Equations (7) and (8). See text for parameter values.

Direct empirical data on air leakage from hospital isolation rooms are lacking. The design goal for respiratory isolation is to maintain negative pressure in the isolation room such that any air flow through openings or leaks in the room envelope will be inwards. Consequently, L=0 for ideal respiratory isolation, and the risk of transmission to those in the general health-care environment would be zero, as predicted by Equation (8). Many hospitals lack adequate isolation rooms for treating TB patients (Nicas et al., 1993). Also, in a field study of seven hospitals, Fraser et al. tested 115 isolation rooms and found that 45% did not have negative pressure (Fraser, 1993). Blumberg et al. (1995) reported a 16.5% failure of negative pressure in retrofitted isolation rooms in a university-affiliated, inner-city hospital that sought to control nosocomial TB transmission.

Even in a properly functioning isolation room, some leakage may occur when the door is open. A magnitude estimate for the average volumetric leakage rate ($L\ Q_p$) is 5 $m^3\ h^{-1}$ obtained as the frequency of door openings (say one per hour) times half the area of the door ($\sim$ 1 m^2), times a characteristic air velocity ($\sim$ 0.5 m s^{-1} considering the disturbance of a swinging door and a person entering), times the duration of the door opening ($\sim$ 10 s). For a 50 m^3 room with an air-ex-

change rate of 6 h^{-1}, this leakage rate would be ~ 2%. Experiments to measure leakage directly could be readily conducted using tracer gas techniques (Decker, 1995; Marshall et al., 1996).

Technological Controls at the Source: Surgical Masks and Treatment Booths

Source-oriented controls aim to prevent emitted infectious droplet nuclei from entering the general room air. The two techniques most suitable for this approach are local exhaust ventilation and filtration.

The CDC recommendations for controlling TB transmission include use of treatment booths for cough-inducing procedures (Centers for Disease Control and Prevention, 1994). Conroy and Franke discuss design considerations for TB treatment booths from the perspective of industrial hygiene practice (Conroy and Franke, 1994). They recommend evaluation of such units using a capture-efficiency approach, which is analogous to the use of η_e in our model equations.

Surgical masks have long been used in operating rooms to prevent infection of a patient by respiratory secretions from health-care workers. Despite the long history of their application in practice, use of surgical masks in operating rooms is controversial (Mitchell and Hunt, 1991). Their effectiveness has been demonstrated in reducing near-field deposition of bacteria emitted from the respiratory tract (Phillips et al., 1992). However, near-field deposition may be dominated by droplets that are much larger than infectious droplet nuclei. One study measuring airborne bacterial concentrations near surgical wounds showed no dependence on use of masks by surgical staff (Tunevall and Jörbeck, 1992). Our search of the literature revealed no studies specifically determining the efficiency of surgical masks in reducing the expulsion of infectious droplet nuclei from the respiratory tract.

Having a patient cover his/her mouth when coughing, sneezing or laughing is a frequently recommended, source-oriented control method (Riley, 1974; Bass et al., 1992; Daugherty et al., 1993; Grimes and Grimes, 1995). As with other measures, the effectiveness of this method in preventing the release of infectious droplet nuclei is unknown.

Given modern aerosol measurement techniques, it should be a straightforward matter to directly study the efficiency of source-oriented controls. The experiments could entail measuring the emitted particle size distribution from coughing or sneezing, with and without use of a control method. The efficiency of the control measure would be indicated by the reduction in emissions of particles in the size range of the infectious droplet nuclei, that is 1–5 μm in aerodynamic diameter. Physical measurements of the aerosol should suffice; it would not seem necessary to measure the infectivity of these particles.

Environmental Controls: Ventilation, Air Filtration and Ultraviolet Germicidal Irradiation (UVGI)

Once released into the general indoor environment, infectious droplet nuclei can be removed by ventilation or filtration. The bacteria can also be inactivated by UVGI. Germicidal lamps emit ultraviolet and visible radiation. More than 95 percent of the radiant energy is emitted at a wavelength of 253.7 nm (Nagy, 1964), which is near the optimum for inactivating microorganisms (Luckiesh, 1946).

Baseline recommended outdoor air ventilation rates for general hospital environments are in the vicinity of $Q/V=2\ h^{-1}$ when the spaces are occupied at design levels (ASHRAE, 1990). For TB isolation rooms, the CDC recommends a combination of ventilation and filtration ($Q_p/V_p + \eta_{pr}\ Q_{pr}/V_p$) that corresponds to at least 6 h^{-1} for existing facilities and 12 h^{-1} for renovations and new construction (Centers for Disease Control and Prevention, 1994).

Miller-Leiden et al. (1996) found moderate to good improvement resulting from enhanced ventilation and recirculating air filtration in a test facility designed to represent a respiratory isolation room. In that study, a ventilation rate of 2 h^{-1} was used to establish baseline conditions. At a total ventilation plus filtration rate of 6 h^{-1}, room-averaged steady-state particle concentrations were reduced to 33–56% of the baseline values. For total ventilation plus filtration rates of 12 h^{-1} or higher, the steady-state room-averaged concentrations were 3–21% of the baseline values. The model for Case 1 predicts reductions to 33% and 17%, respectively, for changes from 2 to 6 h^{-1} and from 2 to 12 h^{-1}. In the immediate vicinity of the particle source, or under transient circumstances as might be associated with a cough-inducing treatment procedure, the degree of improvement with enhanced ventilation and filtration was not as large as for the room-averaged, steady-state values.

Ultraviolet germicidal irradiation can be applied as a TB control measure in three configurations: (1) in mechanical ventilation system ducts; (2) in locally recirculating enclosed units; and (3) in an open configuration irradiating room air (Nagin et al., 1994). For the Case 1 and Case 2 model equations, the impact of UVGI on infection risk would be represented by the terms $Q_r\ \eta_r$ and $Q_{pr}\ \eta_{pr}$ for the ducted and enclosed configurations (1) and (2), and by the first-order rate constants λ and λ_p for the open configuration (3).

Animal studies have compellingly demonstrated

that UVGI in air ducts effectively prevents the spread of TB (configuration 1) (Riley et al., 1957, 1962). Data from a test room study suggest that open-air irradiation can achieve relatively large rate constants for inactivation of TB, λ=10–25 h^{-1}, depending on the total power of the UV lamps (configuration 3) (Riley et al., 1976). In the latter study, however, room air mixing was not characterized, and the estimation of λ from the slope of a concentration decay curve may have led to an overestimate of UV efficiency (Nicas, 1996c).

Clinical trials of the effectiveness of ultraviolet irradiation (or, for that matter, of any other engineering control) in preventing nosocomial TB transmission have not been conducted (McGowan, 1995; Nardell, 1995). Such trials are difficult to undertake for this (or any other) TB control technology because of the highly variable infectivity of patients with active TB (Nardell, 1993, 1995).

The merits of using germicidal irradiation for TB control are debated (Macher, 1993; Heinsohn, 1996). The CDC recommendations do not include as large a role for UVGI as advocates of the technology believe appropriate (Centers for Disease Control and Prevention, 1994; Nardell, 1995). Potential limitations of room air irradiation include reduced effectiveness under high humidity conditions, ineffective room air mixing, and health problems associated with elevated or excessive UV exposure (Nagin et al., 1994). The concern of air mixing also applies for enhanced ventilation and recirculating filtration (Miller-Leiden et al., 1996). Given the large potential effectiveness and relatively low cost of UVGI, further experimental investigation of its efficacy in realistic physical scenarios should be pursued.

Receptor Controls: Respiratory Protection

The effectiveness of respiratory protection is captured in the model equations through the term η_s, where $1-\eta_s$ represents the number of *M. tuberculosis* bacteria inhaled relative to the number that would be inhaled without the protective device. This representation applies equally well to filtering face-piece respirators (for example, disposable Type N95 particulate respirators) and powered air-purifying respirators (PAPRs), and includes the effects of penetration of bacteria through filter material plus face-seal leakage.

As reviewed by Hodous and Coffey (1994), a hierarchy of respiratory protection devices is available, including surgical masks, disposable filtering face-piece half-mask respirators, elastomeric half-mask respirators, and PAPRs. As a rule, as the device effectiveness improves (η_s approaches 1), the cost increases. The elastomeric respirators and PAPRs are also more cumbersome than the disposable units. On the other hand, for prolonged wearing times, a hooded PAPR can be more comfortable than a disposable respirator and, unlike a mask, a hooded PAPR permits the patient to see the facial expressions of the wearer. Based on a review of published data, Nicas (1995) estimated the respective device effectiveness for protection against *M. tuberculosis* to be 0.58 for surgical masks, 0.94 for disposable dust/mist particulate respirators, 0.98 for elastomeric halfmask respirators with high-efficiency filters, and 0.996 for PAPRs with elastomeric halfmask facepieces. It is OSHA policy to enforce the CDC recommendations that call for the use of, at a minimum, the equivalent of Type N95 particulate respirators for health-care workers in isolation rooms, while present for cough-inducing procedures, and when transporting patients suspected of infectious TB (Centers for Disease Control and Prevention, 1994, Occupational Safety and Health Administration, 1993).

Figure 4 illustrates the benefits associated with effective respiratory protection. The baseline condition corresponds to the conditions reported by Catanzaro (1982). Thirteen health-care workers were present without respiratory protection for 150 min during bronchoscopy of a TB patient. The room volume and air-exchange rates were 208 m^3 and 1.2 h^{-1}, respectively. From these data and the observation that ten of the health-care workers became infected, Catanzaro estimated that the effective emission rate of infectious droplet nuclei was 249 h^{-1}. Figure 4 shows the predicted effects, according to Equation (7), of two classes

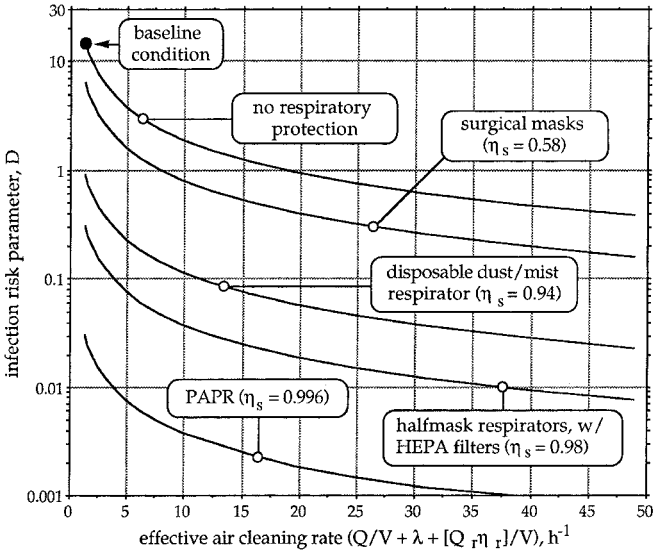

Fig. 4 Predicted infection risk parameter for exposure of 13 health-care workers for 150 min to a highly infectious patient during bronchoscopy (Catanzaro, 1982). Effects of respiratory protection and enhanced environmental control are shown, as predicted by Equation (7).

of control measures: environmental controls (by ventilation, UVGI, or air filtration) and respiratory protection. Even with a low ventilation rate, the use of half-mask respirators (η_s=0.98) would have reduced the infection risk parameter to about 0.3, better than what could be achieved with even 50 h^{-1} as an overall effective air cleaning rate without respiratory protection. Use of powered air purifying respirators in combination with moderately high environmental removal rates ($\sim$ 10 h^{-1}) could have reduced the infection risk parameter by more than three orders of magnitude, to well below 0.01.

Additional Remarks

Theoretically, it is possible to completely eliminate the risk of infection (i.e., achieve D=0) by perfect control at the source (η_e =1), at the receptors (η_s=1), or, for the general health-care environment, by perfect respiratory isolation (L=0). In contrast, it is not possible to completely eliminate the risk of infection by increasing general ventilation (Q), recirculation through a particle filter ($Q_r\ \eta_r$ or $Q_{pr}\ \eta_{pr}$), or ultraviolet irradiation (λV or $\lambda_p V_p$). In the former cases, the control measure interrupts the transmission route at sites where it is contained or confined. In the latter cases, this confinement is lacking. As a consequence, there are diminishing returns in the benefit of reduced risk associated with increasing ventilation (Nardell et al., 1991), recirculating air filtration, or UVGI.

Data on the emission rate of infectious droplet nuclei are not required to explore the relative merits of source-oriented, receptor-oriented, or general environmental controls. For these comparisons, one can use D/N_e as the quantitative indicator of risk. This indicator represents the fraction of emitted infectious droplet nuclei that are inhaled. On the other hand, rational efforts that seek to balance benefits of control against their costs do require emission data. The cost-benefit calculation requires this information because the per-patient cost of implementing a control program is independent of the emission characteristics, whereas the risk of infection increases in proportion to the total emissions per patient.

Similarly, the number of infectious persons in the health-care setting is an important variable in the design of a rational control strategy. For a control program that includes more than isolation and source-oriented controls, the cost scales at a rate that is less than proportional to the number of infectious patients, although the risk of infection is proportional to the number of these patients. Consequently, as the number of infectious patients increases, more elaborate and costly control measures can be justified to manage the larger risk.

The model Equations (7) and (8) are based on an important simplifying assumption about mixing in indoor air. Specifically, we assume that the time-averaged concentration of infectious droplet nuclei is the same at the receptor and at the inlet of any control measure as for the spatial average throughout the indoor zone. This assumption is satisfied if the indoor air is completely and rapidly mixed; however, mixing is not instantaneous and the rate varies with indoor air flow conditions (Drescher et al., 1995). The uniform mixing assumption is particularly important in two circumstances: (i) when evaluating the effectiveness of general engineering controls, such as recirculating filtration, ventilation, and upper-air ultraviolet irradiation; and (ii) when a susceptible person is in close proximity to an infectious person. In the former case, the uniform mixing assumption can lead to either overestimating or underestimating efficacy (Miller-Leiden et al., 1996); in the latter circumstance, the uniform mixing assumption can lead to substantially underestimating exposure intensity (Nicas, 1996c; Drescher et al., 1995).

In considering the effects of mixing, it is important to recognize that instantaneous, complete mixing represents *idealized* conditions, not *ideal* conditions. Depending on the detailed air flow patterns and the source and receptor locations, it is possible, for example, for a ventilation system to perform either better or worse than predicted for perfect mixing. To obtain the best possible performance of ventilation or recirculating air filtration as an infection control measure, one should strive to apply this principle: supply clean air in the proximity of susceptible individuals and remove air containing relatively high concentrations of infectious droplet nuclei from the proximity of the source. Lidwell and Towers (1969) have discussed the idea of using directional air flow to improve the effectiveness of infection control by ventilation. The CDC recommendations for TB control include provisions to exploit incomplete mixing: "To provide optimal airflow patterns, the air supply and exhaust should be located such that clean air first flows to parts of the room where health-care workers are likely to work, and then flows across the infectious source and into the exhaust" (Centers for Disease Control and Prevention, 1994).

Although Equations (7) and (8) do not account for incomplete mixing, it is possible to incorporate these effects into engineering models using computational fluid dynamics or multizone box models (Awbi, 1991; Chen et al., 1992; Nicas, 1996c; Furtaw et al., 1996).

Substantial research effort would be required before one could formulate predictive capability for infection risk under conditions that lack complete mixing.

Conclusion

In this paper, we have defined an approach for quantitatively evaluating the relative effectiveness of various control measures in limiting tuberculosis infection risk in health-care settings. Previous studies employing a quantitative approach have tended to focus on single control methods in isolation. Studies that have presented a synthesis of control methods have tended to do so qualitatively.

Some of the empirical data required to use this modeling framework do not yet exist. The framework we have proposed can help define the variables that should be experimentally measured to support the further development of control strategies.

Although the research presented in this paper has focused on TB in health-care settings, the analytical framework can be modified to address the broader issue of airborne infection control in indoor environments. TB is transmitted in buildings other than health-care facilities and several other diseases are transmitted by airborne routes. The pendulum for environmental health concerns has swung far in the direction of chemical toxicity at the expense of microbial pathogens. A strong case can be made for the importance of better understanding the factors that govern exposure to airborne pathogens, the associated disease risks, and the potential for control. The framework we have presented can be viewed as a small step in that effort.

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Appendix

The purpose of this appendix is to provide a compelling argument for the form of Equation (7). Equation (8) follows directly.

Figure 1 depicts a well-mixed indoor environment, such that the concentration of infectious droplet nuclei is uniform throughout the space at all times. More properly, given that the total number of airborne infectious droplet nuclei is small, uniform mixing implies that a single infectious droplet nucleus is likely to be found with equal probability at any point in the indoor zone. Four factors influence the number of airborne infectious droplet nuclei: (1) emission from the source; (2) removal by ventilation; (3) removal by recirculating air filtration; and (4) removal by ultraviolet irradiation. As will be explained, removal by deposition onto room surfaces is relatively unimportant for infectious droplet nuclei.

Consider a single *M. tuberculosis* bacterium emitted within an infectious droplet nucleus. With respect to the infection risk, there are four possible fates that must be considered: the three removal processes cited above plus inhalation by a susceptible person. Given the assumption of uniform mixing, the relative probability of each fate in a small time interval is proportional to the rate of each process, as follows:

$$\text{probability of inhalation followed by respiratory deposition} \propto \frac{bf}{V}(1-\eta_s)$$

$$\text{probability of removal by ventilation} \propto \frac{Q}{V}$$

$$\text{probability of removal by recirculating filtration} \propto \frac{Q_r\,\eta_r}{V}$$

$$\text{probability of removal by ultraviolet irradiation} \propto \lambda$$

The first term represents the fractional rate of inhalation and deposition of infectious droplet nuclei (nuclei entering and depositing in the lung per nuclei in room per time). Each of three latter terms represents the fractional removal rate by the given mechanism.

An emitted infectious droplet nucleus will persist in indoor air through a time scale that is approximated by the inverse of the sum of the removal rates:

$$\tau \sim \frac{1}{(Q/V) + (Q_r\eta_r/V) + \lambda} \tag{9}$$

Given CDC and ASHRAE recommendations, this time scale would be the range of approximately 5 to 30 min for health-care settings (Centers for Disease Control and Prevention, 1994; ASHRAE, 1990). If the exposure period is much longer than τ, then the large majority of emitted nuclei will no longer be present in the indoor air. The fraction inhaled and deposited is represented by the probability of inhalation/deposition divided by the sum of the probabilities of all fates; removal by inhalation is small compared with the other

fates and can be neglected in the denominator. In Equation (7), multiple susceptible individuals are permitted, such that the fraction of bacteria inhaled and deposited is the sum of the inhalation/deposition probabilities over all exposed divided by the probability of removal by all mechanisms. This ratio is then multiplied by the total number of infectious droplet nuclei emitted by the infectious individual, $N_e(1-\eta_e)$, where N_e represents the total emissions without control, and η_e is the fraction captured by a source-oriented control measure.

As formulated, Equations (7) and (8) apply equally well for both episodic and chronic emissions, provided that the period of exposure is much longer than τ. Miller-Leiden et al. (1996) point out that general room-air control measures are less effective for episodic emissions than would be predicted by Equations (7) and (8) when the exposure period is short.

In addition to removal or inactivation by engineered control measures, infectious droplet nuclei may settle under the influence of gravity onto indoor surfaces. Settling velocities range from 0.13 to 2.8 m h^{-1} for particles with the density of water with diameters in the range 1–5 μm (Hinds, 1982). Given a 2.5 m high room, the removal rate associated with settling is equivalent to additional air exchange in the range 1.1 h^{-1} (for the largest particles) to a negligible 0.05 h^{-1} for the smallest. The effect of this removal mechanism could be included in model equations as a separate loss rate added to ventilation, recirculating filtration and UVGI. The effect would be fairly small and is not included here to keep the equations as simple as possible.

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