Using a Mathematical Model to Evaluate the Efficacy of TB Control Measures

Laura Gammaitoni and Maria Clara Nucci
University of Perugia, Perugia, Italy

We evaluated the efficacy of recommended tuberculosis (TB) infection control measures by using a deterministic mathematical model for airborne contagion. We examined the percentage of purified protein derivative conversions under various exposure conditions, environmental control strategies, and respiratory protective devices. We conclude that environmental control cannot eliminate the risk for TB transmission during high-risk procedures; respiratory protective devices, and particularly high-efficiency particulate air masks, may provide nearly complete protection if used with air filtration or ultraviolet irradiation. Nevertheless, the efficiency of these control measures decreases as the infectivity of the source case increases. Therefore, administrative control measures (e.g., indentifying and isolating patients with infectious TB) are the most effective because they substantially reduce the rate of infection.

After decades of steady decline and a subsequent relaxation of infection control practices in health-care facilities, the number of tuberculosis (TB) cases has been increasing dramatically in the United States (1) and Western Europe (2) since 1985; the increase is due to human immunodeficiency virus (HIV) infection, immigration, poverty, homelessness, and drug addiction.

Epidemiologic studies have shown that primary pulmonary TB is caused by inhaling the tubercle bacillus in a droplet nucleus form (3). Airborne contagion is crucial in the indoor transmission of all respiratory infections from person to person (4,5). Infective persons may contaminate the air by coughing, sneezing, and spitting (4,5), which generate a large number of small respiratory droplets that evaporate almost instantly into small droplet nuclei, disperse into the environment, and implant themselves in the lung when inhaled (4). Droplet nuclei have a leading role in airborne contagion (3-5).

Outbreaks of TB have been reported from prisons, nursing homes, residential centers for HIV-infected persons, urban homeless shelters, aircraft, schools, and bars. All outbreaks occurred under crowded living conditions with prolonged close exposure to an infectious person.

Address for correspondence: Maria Clara Nucci, Dipartimento di Matematica, Università di Perugia, 06123 Perugia, Italy; fax: 011-39-75-585-5024; e-mail: nucci@unipg.it.

Nosocomial TB transmission is also associated with cough-generating procedures (6), bronchoscopy (7), endotracheal intubation and suctioning (8), open abscess irrigation (9), and autopsy (10). Workers involved in such procedures are at high and increasing risk for TB (11) because of the resurgence of the disease, the emergence of multidrug-resistant (MDR) strains causing outbreaks in hospitals among patients and health-care workers, and compromised TB control due to decreased funding of health-care agencies responsible for TB control.

After studying hospital outbreaks that resulted in TB transmission to health-care workers, various authorities have recommended measures to prevent nosocomial TB transmission (12-15). The implementation of a TB infection control program requires risk assessment and development of a TB infection control plan including early identification, treatment, and isolation of infectious TB patients; effective engineering controls (environmental controls such as general ventilation, high-efficiency particulate air [HEPA] filters, or ultraviolet germicidal irradiation [UVGI]); the adoption of appropriate respiratory protection (surgical masks and particulate respirators such as HEPA masks); health-care worker TB training, education, counseling, and screening; and evaluation of the program's effectiveness (13). Several reviews of environmental control measures and respiratory protective

devices are available (16-20). Implementing recommended measures would require massive expenditures in all hospitals that admit TB patients. At several hospitals where MDR-TB outbreaks have occurred, measures similar to those recommended in TB prevention guidelines have been implemented. Such implementation halted and prevented MDR-TB transmission to healthcare workers and patients (21-23), but which of the many implemented control measures played a key role in reducing risk is not clear. However, data suggest that implementing administrative control measures, in particular identifying and isolating patients with infectious TB, substantially reduces the risk for transmission (22).

In this article, we review the most important TB infection control measures and evaluate their efficacy in various settings by a deterministic mathematical model for airborne contagion (24). The model describes how a person can become infected by staying in a room where a source of airborne infection and an air disinfection device are present.

Two existing mathematical models describe the propagation of airborne contagion indoors. The first model was developed in 1955 by William F. Wells (4), who introduced the so-called quantum theory. Wells defined a quantum to be the number of infectious droplet nuclei required to infect 1 - 1/ *e* of susceptible persons. His ninth postulate states, "The response to inhaled droplet nuclei contagium is quantal; the Poisson equation expresses reasonably well the relation between dosage and initial response, a quantum infecting 63.2% of homogeneously exposed hosts by definition." Wells explains, "When on the average one animal breathes one quantum, (omissis) 36.8% of the animals will survive, since this is the fraction whose negative natural logarithm is 1. Thus 1 quantum of contagium has been breathed per animal when 63.2% of the animals become infected (4, p. 124)." In 1978, Edward R. Riley, G. Murphy, and Richard L. Riley elaborated another model (25), which deals with the probability of a susceptible person becoming infected by inhaling a quantum of infection. They used the Reed Frost modification of the Soper equation for airborne transmission and Poisson's law of small chances. This model contains Wells' model as a particular case.

Our model is based on Wells' experiments and postulates and includes the Riley/Murphy/Riley model as a particular case (24). In this article, we describe some of the most important TB infection control measures, such as environmental controls and respiratory protective devices, and review recommendations made by various agencies and organizations. Then, we consider four recent TB outbreaks during which healthcare workers became infected while performing bronchoscopy, jet irrigation of a thigh abscess, autopsy, and intubation. Using our deterministic mathematical model, we simulate the adoption of different environmental control strategies and respiratory protective devices, and we give the number of purified protein derivative (PPD) conversions predicted to occur under various exposure conditions. Moreover, we use our mathematical model to evaluate the efficacy of administrative control measures by analyzing data related to PPD conversions found on an HIV ward before and after implementing such control measures.

Environmental Control Strategies and Respiratory Protective Devices

A TB infection control program should be based on control measures that address the most important factors involved in TB transmission: the concentration of droplet nuclei in the air and the rate at which droplet nuclei are inhaled by susceptible persons. The concentration of infectious droplet nuclei in the air can be reduced by environmental controls. These controls include diluting and removing contaminated air by general ventilation and air cleaning by air filtration (e.g., through HEPA filters) or UVGI.

In general ventilation systems, uncontaminated supply air mixes with contaminated room air (dilution), which is subsequently removed from the room by the exhaust system (removal). Two types of general ventilation systems can be used for dilution and removal of contaminated air: single-pass systems and recirculating systems. In single-pass systems the supply air is uncontaminated fresh outside air, and after it passes through the ventilated area, 100% of that air is exhausted to the outside. In a recirculating system, a small portion of the exhaust air is discharged to the outside and is replaced with fresh outside air, which mixes with the portion of exhaust air that was not discharged to the outside. The resulting mixture, which can contain a large proportion of contaminated air, is then recirculated. The rate at which airborne particles are removed from an enclosed space (e.g., a room) by ventilation is usually expressed

as the number of air changes per hour (ACH), which is the ratio between the volume of air entering the room per hour and the room volume. A minimum of 6 ACH is recommended for TB isolation rooms and treatment rooms (26-28). Where feasible, this airflow rate should be increased to 12 ACH or more, and in areas where the nature of work is exceptionally hazardous, such as autopsy rooms, airflow rates of 15-25 ACH have been recommended (29,30).

HEPA filtration units or UVGI can be used as a supplement to ventilation control measures in settings where adequate airflow cannot be provided with the general ventilation system alone (13). HEPA filters have a demonstrated and documented minimum removal efficiency of 99.97% of particles whose diameter is ≥ 0.3 µm (droplet nuclei are an estimated 1 to 5 µm in size [13], but they can have an aerodynamic diameter of less than 1 µm [31]). They can be used in fixed or portable HEPA recirculation systems that can achieve 12 ACH or more (13). UVGI can kill or inactivate tubercle bacilli under experimental conditions (32), especially where air mixing is accomplished mainly by convection (13). The effect of UVGI in a room without supplemental ventilation (33) and in another with a ventilation rate of 6 ACH (34) is estimated at 10 and 39 ACH, respectively. Greater rates of ventilation may decrease the killing of bacteria (34), but the optimal relationship between ventilation and UVGI is not known. However, general ventilation plus UVGI has a disinfection rate of 45 ACH if properly installed (34).

Personal protective devices are recommended when engineering controls are not likely to protect against inhaling infectious airborne droplet nuclei (e.g., in TB isolation rooms, treatment rooms in which cough-inducing or aerosol-generating procedures are performed, and ambulances during the transport of infectious TB patients) (13). The respiratory protective devices used in these settings should have a filter efficiency $\geq 95\%$ with an obtainable face-seal leakage not greater than 10% (13). The efficiency of standard cup-shaped surgical masks in preventing the inhalation of droplet nuclei with a diameter of 1 to 5 µm is less than 50% (11) with a face-seal leakage of 0% to 20% (35). Since 1990, the use of particulate respirators including HEPA masks tested to filter 99.97% of 0.3 µm particles with a face-seal leakage less than 2% has been recommended (13).

Because of the very high costs of HEPA masks, the breathing difficulties they may cause, and the odd appearance of people wearing them, which may have a psychological impact on patients, the recommendation for personal respiratory devices is the most controversial aspect of existing TB guidelines. Reported cases of TB and skin-test conversions among health-care workers have led many to conclude that HEPA respirators are justified. On the other hand, many believe that less stringent personal protective devices, such as dust/mist respirators, may provide sufficient protection, with less discomfort and lower cost (31). New certification rules (42 CFR 84) have been recently approved that allow the use of dust/mist respirators, in addition to HEPA respirators, in TB control settings (36).

The Model

In the case of an airborne infection outbreak in a single room (e.g., a hospital room) of volume V, where a certain number $I_0 \geq 1$ of infective persons and S_0 of susceptible persons are present at initial time t = 0, the number of susceptible persons can be expressed as a function of the time interval from the beginning of the exposure (the time of exposure t, measured in minutes), the rate at which quanta are produced by the infective persons (the infection rate q), and the number of effective or equivalent air changes (AC) in the unit time (the disinfection rate C) (24).

The following assumptions (4,24,25) are taken into consideration: differences in susceptibility are neglected; the rate at which quanta of infection are added to the air by infectious persons is considered constant; the latent period of the disease is longer than the time scale of the model, and the number of infective persons in the room is constant; droplet nuclei are instantaneously and evenly distributed in the room; droplet nuclei are assumed to be removed by fresh air ventilation of the room and ultraviolet irradiation at a constant rate; fresh air is at the same temperature and pressure as the air already present in the room; and the number of infected persons is proportional to the number of encounters between susceptible persons and quanta of infection, (and the encounter rate is proportional to both the number of susceptible persons and quanta of infection in the room [law of mass action]).

If the constant of proportionality between the number of infected persons and the number of

susceptible persons times the number of quanta of infection Q is the ratio between the pulmonary ventilation p (we assume p = 0.01 m ^{3}/min) and the volume V of the room, the following equations can be derived:

1. $$\frac{dS}{dt} = -\frac{p}{V}QS,$$
$$\frac{dQ}{dt} = -CQ + q, \quad t \geq 0,$$

with the initial conditions

2. $$S(0) = S_0 > 0,$$
$$Q(0) = Q_0 \geq 0.$$

The solution of equation 1 - equation 2 is

3. $$S(t,q,C) = S_0 \exp\left\{-\frac{pq}{V}\frac{Ct + e^{-Ct} - 1}{C^2}\right\},$$

4. $$Q(t,q,C) = \left(Q_0 - \frac{q}{C}\right)e^{-Ct} + \frac{q}{C}.$$

The percentage of PPD conversion among health-care workers is the following:

5. $$I_w(t,q,C) = \left[1 - \frac{S(t,q,C)}{S_0}\right] \times 100.$$

The rate of production of quanta of infection during each outbreak is not known a priori. Therefore, we do not know the real value of q during a specific epidemic. However, it can be derived a posteriori when the number S of susceptible persons who were not infected is known. In fact, solving equation S(t,q,C) = S with respect to q, with S given by formula 3 yields

6. $$q = \frac{V}{p}\frac{C^2}{Ct + e^{-Ct} - 1}\log\frac{S_0}{S}$$

By substituting the given values of p, V, S_0, $\bar{S}$, t, and C in the right-hand side of formula 6, we obtain the value for q during each epidemic.

In this article, we simulate the adoption of various environmental control strategies (e.g., HEPA filtration devices or UVGI combined with ventilation) by giving suitable values to the parameter C. Also, we simulate the adoption of personal protective devices (e.g., surgical masks, dust/mist respirators, and HEPA masks) by scaling the rate at which quanta of infection are breathed (pulmonary ventilation p), which depends both on the mask's filter efficiency and face-seal leakage. If the masks adopted have a filter efficiency of X% and a face-seal leakage of Y%, then we can describe the effective filter efficiency of the mask as Z%, with Z = (X-XY/100). The scaling factor for p, therefore, is (100-Z)%.

For example, dust/mist respirators should have a filter efficiency X% equal to 95% and a face-seal leakage Y% not greater than 10%; then, their effective filter efficiency is Z = X-XY/100 = 85.5%, and the scaling factor for p is (100-Z)% = 14.5%. We derive a scaling factor of 60% and 3% for surgical and HEPA masks, respectively (13). Moreover, we assume C = 6 ACH (0.1 AC/min) for general ventilation alone, and C = 18 ACH (0.3 AC/min) or C = 45 ACH (0.75 AC/min) when HEPA filtration or UVGI is adopted in combination with ventilation (34).

Model Application

We consider two types of nosocomial exposure to TB infection: exposure during high-risk procedures and exposure during normal working conditions on a ward where a source of TB infection is present. Using data from published TB outbreaks among health-care workers and assuming the use of different environmental control strategies (general ventilation, HEPA filtration, UVGI) and respiratory protective devices (surgical masks, dust/mist respirators, HEPA masks), we derive the percentage of PPD conversions that can occur.

High-Risk Procedures

We use data from four published TB outbreaks during which health-care workers were infected while performing bronchoscopy (7), jet irrigation of a thigh abscess (9), autopsy (10), and intubation (8) (Table 1). The values for q vary from six (7) to 514 (8) quanta per minute (qpm), indicating a high level of infectiveness of the index case in each outbreak. The patient with the highest rate of quanta production was considered a dangerous disseminator of TB (8).

Table 2 shows the percentage of PPD conversions that can occur during four procedures (bronchoscopy, abscess irrigation, autopsy, intubation) if

Table 1. Nosocomial TB outbreaks involving health-care workers who performed high-risk procedures

	Pulmonary ventilation p(m^3/min)	Room volume V(m^3)	No. of susceptible persons S_0	No. of uninfected persons $\overline{S}$	Exposure time t (min)	Infection rate q (qpm)	Disinfection rate C (ACH)
Bronchoscopy	10^{-2}	200	13	3	150	6	1.26
Abscess irrigation	6 x 10^{-3}[a]	200[b]	5	1	150[b]	38	6[b]
Autopsy	10^{-2}	200[b]	4	0[c]	150[b]	94	11
Intubation	6 x 10^{-3}[a]	3000	3	1	66	514	2.4[d]

[a]Surgical masks were adopted.
[b]Estimated value; actual data are not available
[c]We assumed S=0.001≅ 0.
[d]In the emergency department where this outbreak developed, 60% of the air was recirculated without filtration; we assumed an airflow rate of 6 ACH, obtaining an effective disinfection rate equal to 40% of 6 ACH.

different environmental control strategies were adopted, with and without the adoption of surgical masks, dust/mist respirators, or HEPA masks.

The percentage of PPD conversions that can occur as a function of the time of exposure t during the least risky procedure—bronchoscopy—if different environmental control strategies were adopted, no personal protective devices were used, and the time of exposure varied from 50 to 400 minutes is shown in Figure 1.

Normal Working Conditions

We consider an MDR-TB outbreak that occurred on an HIV ward (21). During the initial period, the percentage of PPD conversions among health-care workers was 28%. Inadequate TB control programs or facilities (delays in TB diagnosis and in determining drug susceptibility and inadequate patient isolation precautions) facilitated the transmission. Administrative measures similar to those subsequently recommended (37) were implemented on the HIV ward, and early follow-up period showed a decrease in PPD conversions among healthcare workers (18%), who were required to wear surgical masks.

The actual time of exposure during the initial period is not available. Assuming that the ratio between the time of exposure t_{in} and the time span T_{in}=150 days of the initial period (January–May 1990) is equal to the ratio between the time of exposure t_{ef}=135 days (average between 139 and 129 days) and the time span T_{ef}=270 days of the early follow-up period (June 1990–February 1991), we assume that $t_{in}=T_{in} \times t_{ef}/T_{ef} \cong 75$ days. The remaining data are summarized in Table 3.

We calculate the rate of infection in the initial period to be q = 0.006; and after administrative control measures were implemented, it decreased to q = 0.003 in the early follow-up period. Administrative control measures decreased the rate of infection by 50%, thus confirming their key role in preventing TB transmission.

Figure 2 shows the percentage of PPD conversions predicted to occur during the initial period with the use of different environmental control strategies and respiratory devices.

Table 2. Percentage of purified protein derivative conversions predicted to occur during various procedures, by using various environmental control strategies and respiratory protective devices

Control measures [a]	Bronchoscopy q=6, t=150 min [b]	Abscess irrigation q=38, t=150 min	Autopsy q=90, t=150 min	Intubation q=514, t=66 min
GV	34.3	93	99.9	61.7
GV+HF	13.6	60.5	90	30.1
GV+UVGI	5.8	31.4	60.5	13.7
GV+SM	22.3	79.7	98.1	43.8
GV+HF+SM	8.4	42.7	74.8	19.3
GV+UVGI+SM	3.5	20.2	42.8	8.5
GV+DMR	5.9	32	61.5	13
GV+HF+DMR	2.1	12.6	28.3	5.1
GV+UVGI+DMR	0.9	5.3	12.6	2.1
GV+HM	1.3	7.7	17.9	2.8
GV+HF+HM	0.4	2.7	6.7	1.1
GV+UVGI+HM	0.2	1.1	2.8	0.4

[a]GV=general ventilation; HF=HEPA filtration; SM=surgical masks; DMR=dust/mist respirators; HM=HEPA masks
[b]q=infection rate; t=exposure time.

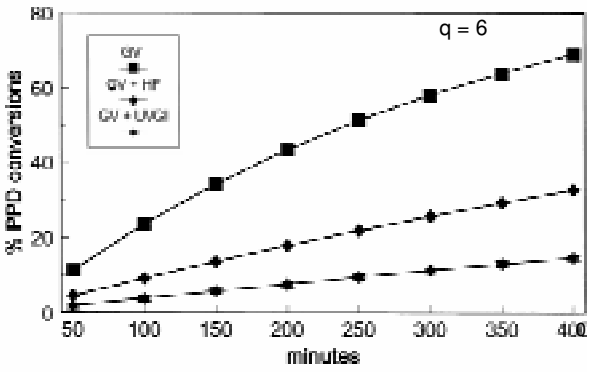

Figure 1. Percentage of PPD conversions predicted to occur as a function of time of exposure t during bronchoscopy, if different environmental control strategies were adopted, no personal protective devices were used, and the time of exposure varied from 50 to 400 minutes.

Conclusions

Our mathematical model indicates that a certain number of persons exposed to a source of TB infection will be infected in spite of all precautions. Nevertheless, if the infection rate is known, this number can be kept low by increasing the disinfection rate and decreasing the time of exposure.

We have evaluated the probability of acquiring TB infection under various exposure conditions and found that the efficacy of environmental control strategies depends on the duration of exposure and the infection rate. In particular, if the recommended levels of airflow are the only means of reducing the concentration of droplet nuclei in a room, they can neither eliminate TB contagion nor provide tolerable value for the risk of contagion. If HEPA filtration or UVGI is combined with general ventilation, protection against TB transmission is ensured at low infection rates, especially for brief exposures. As the infection rate increases, higher disinfection rates appear less and less effective in reducing the risk for transmission, and in situations of very intensive exposure, not even HEPA filtration or UVGI combined with general ventilation can keep the risk for transmission low enough. In these circumstances, respiratory protective devices may be used to protect health-care workers from inhaling droplet nuclei. The adoption of HEPA

q = 0.006, t = 75 days

Figure 2. Percentage of PPD conversions predicted to occur on the HIV ward during the initial period, if different environmental control strategies were adopted and with and without the adoption of surgical masks (SM), dust/mist respirators (DMR), or HEPA masks (HM).

Table 3. Nosocomial TB outbreaks involving health-care workers under normal working conditions

	Pulmonary ventilation p (m^3/min)	Room volume V (m^3)	No. of susceptible persons S_o	No. of uninfected persons S	Exposure time t (days)	Infection rate q (qpm)	Disinfection rate C (ACH)
Initial period	10^{-2}	200 [a]	25	18	75	0.006	6
Early follow-up period	6×10^{-3} [b]	200 [a]	17	14	135	0.003	6

[a]Estimated value; actual data are not available.
[b]Surgical masks were adopted.

masks would provide nearly complete protection, even for long exposures, if used together with HEPA filtration or UVGI. Neverthless, the efficacy of these control mea-sures decreases as the infectivity of the source case increases; therefore, the only control measures that significantly reduce the infection rate are administrative.

Dr. Gammaitoni is a postgraduate fellow at the University of Perugia and a computer specialist for ALENIA-Italy. Her research interests include mathematical models applied to environmental health problems.

Dr. Nucci is a researcher at the University of Perugia. Her recent interests include application of mathematical modeling techniques to epidemiology. Her work is supported in part by Ministero Università Ricerca Scientifica Tecnologica: Fondi (60% and 40%).

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