Estimates of risk associated with a tuberculosis patient and air travel

Primary authors: Yoshifumi Masago[1] and Rachael Jones[2]
Secondary authors: Tim Bartrand[3], Charles N. Haas[3], Mark Nicas[2] and Joan B. Rose[1]
(Michigan State University[1], University of California Berkeley[2], Drexel University[3])

CAMRA ALERT: On May 12th, 2007, a man who had an infection of multi-drug-resistant *Mycobacterium tuberculosis* (XDR-TB) traveled from Atlanta to Paris and again he traveled from Prague to Montreal on May 24th, 2007. These two transatlantic flights lasted approximately 8 hours each. After he was hospitalized in Atlanta, the CDC began attempting to address the risk of infection focusing on about 80 people who sat in the five rows surrounding the man during the flights. TB transmission had been previously reported to nearby passengers during a flight to Hawaii in 1996 (Tracy, 1996)

While it has been acknowledged by CDC that this risk is low (no estimate of how low has been given), the consequence of subsequent infections could be high because of the rare, extensively drug-resistant type of infection that the patient has.

CAMRA investigators pooled knowledge and worked to address quickly the potential risk of infection and the range of potential outcomes to those exposed.

The assessment involved dose-response models developed in Monkeys with mortality and skin-test as an end point and an exposure model developed for respiratory impact. The airplanes and the airflow were used to define the space. The range of bacilli emission from the patient is one of the components that drives the risk, thus this estimate examines two scenarios which bound the range of potential human emissions by infected individuals through exhalation and coughing.

In addition, research questions were developed which would be extremely helpful to further elucidate the risk thus improving communications and risk management strategies.

In the future it may be possible to develop tests and advice regarding travel and risks based on measurement of emission (e.g. bacilli in the saliva) and estimated intensity of exposure. This could be followed with prudent advice regarding prevention of exposure and thus transmission. While, the view of what is deemed as "SAFE" may be very individual, professionals along with those representing the social aspects of the community can build a consensus about their views of safe with evidence-based approaches with appropriate consideration of overall benefits at the societal level.

The goals of this assessment were to address, as rapidly as possible, a quantitative microbial risk assessment and identify key scientific gaps with the current knowledge.

SUMMARY OF THE RESULTS OF THE ANALYSES (See sections below for model descriptions and Appendix for parameters used)

Risk of infection on average ranged from 1/1000 to 4/10,000, with detectable average ranges of bacilli in the saliva, however with non-detectable bacilli, the risk was seen as less that 2/100 million to approximately 6/billion. .The estimated probabilities of producing infections or deaths (assuming NO treatment) during an 8 hour flight are summarized in Table 1 and Figure 1. Because we did not have the concentration of *M. tb* in saliva of the patient at the time of the trip, the concentrations were assumed based on data from symptomatic patients (Yeager et al., 1967).

Table 1. Estimated probabilities of 1 or more infection, and 1 or more death, among passengers seated in 5 rows around the source patient.

M. tb concentration in saliva [CFU/ml]	Model A		Model B	
	Infection	Death [a]	Infection	Death [a]
Non-detectable (Assumed < 1 CFU/ml)	$< 5.8 \times 10^{-9}$	$< 1.3 \times 10^{-10}$	$< 1.9 \times 10^{-8}$	$< 4.2 \times 10^{-10}$
Low : 1×10^{2} [b]	5.8×10^{-7}	1.3×10^{-8}	1.9×10^{-6}	4.2×10^{-8}
Average : 7×10^{4} [b]	4.0×10^{-4}	8.9×10^{-6}	1.3×10^{-3}	2.9×10^{-5}
High : 6×10^{5} [b]	3.5×10^{-3}	7.6×10^{-5}	1.1×10^{-2}	2.5×10^{-4}

a: assuming no treatment and based on monkey dose-response
b: based on samples from 22 pulmonary TB patients (Yeager et al., 1967)

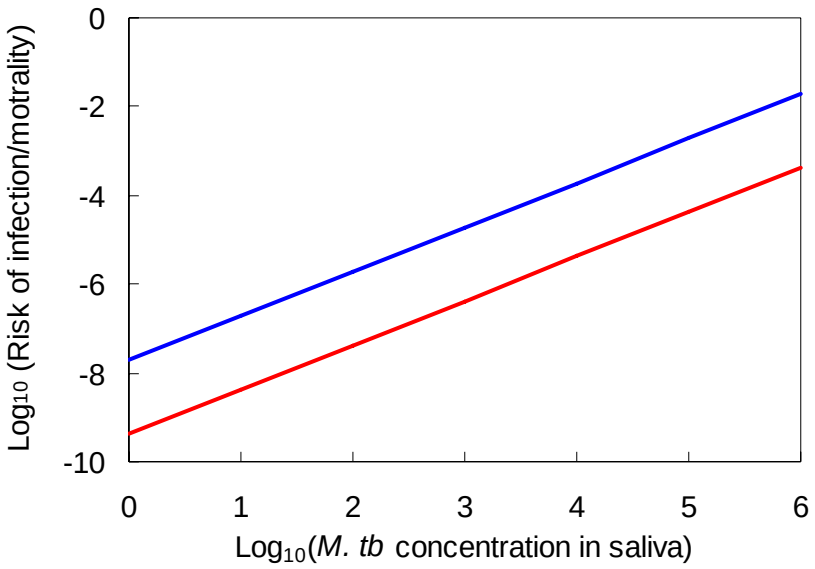

Figure 1. Estimated probability of one or more infection (blue line), and one or more death (red line), among 39 passengers seated in 5 rows around the source patient (result from Model B).

NOTE: There are many terms used by the medical community and by the news to describe the disease status. These are often confusing. Thus one goal may be to harmonize the terms with a clear understanding of the meanings to improve communications.

1. **Exposure**: In the modeling world this means that the individual **actually received some dose**; HOWEVER in the real-world situation it means that the individual was **exposed to the source** of the contaminant (not knowing if they really received a dose or not, e.g. exposed to the airplane air, sat next to the patient); in the medical world one may look to see if there is **evidence of exposure from some clinical test** (antibody response or identification of a biomarker or the biological agent itself; for TB this may be a skin test to look for antibody).
2. **Infection**: In the modeling world this means that the microorganism has been able to begin it's **replication in the host**, this is measurable in experiments by antibody response or identification of the biological agent at the site of replication (SEE EXPOSURE ABOVE FOR MEDICAL); in the real-world many use infection to be synonymous with **disease** (impairment of the persons health status or impairment of some function)**;** in the medical world in Webster's Medical Dictionary the following definition of **Active Tuberculosis** is presented as "The presence of *Mycobacterium tuberculosis* infection with a positive chest X-ray. Treatment of active tuberculosis is mandatory by law in the US.". The presence of the bacilli in the sputum is also indicative of **infection and disease**. In the development of tuberculosis, the initial infection is usually self-limited, such that no clinical symptoms of illness are observed. The bacteria can stop replicating (become dormant) but remain viable in the lungs. This dormant stage can be termed latent tuberculosis. If the initial infection is not treated with antibiotics, these dormant bacteria can reactivate years later and cause clinical disease. The usual statistics cited are that among those infected and not treated with antibiotics, 5% develop clinical disease within the first two years of infection, and another 5% develop clinical disease at some point in their remaining lifetimes subsequent to the first two years.
3. **Contagion**: in the modeling world, one can estimate **the probability of transmission** of the microorganism from the one person who is infected to a susceptible individual based on exposure scenarios and the characteristics of the microorganism, estimates of very low risks can be made: 1 in million (10^{-6})or 1 in 10 million (10^{-7}), or 1 in a billion (10^{-9}); in the real-world **and** medical world very high levels of disease transmission can be evaluated through investigations (1 in 10; 1/100) but generally this is addressed as **YES or NO** without quantification of probability. In this case, a NO or VERY LOW was suggested based on bacilli in the sputum.
4. **Sputum versus saliva:** Sputum is the material that is brought up into the mouth from the lungs with persistent deep coughing and includes some saliva. Saliva is the liquid produced in the mouth which aids in initial digestion of food as we eat. However, saliva is easier to collect and measure. In the mouth, the sputum mixes with saliva. The numbers of bacilli can be 100 times higher in sputum than in saliva.

Research Needs:

1) This is clearly an organism where risk from repeated exposures may be an issue, and so experiments on multiple dosing (and proliferation/decay of the organism in vivo) would be important.

2) Effect of host factors (nutritional status, immune suppression) on infectivity and emissions needs to be better understood.

3) The levels of emissions of bacilli as measure in the sputum, saliva and coughs needs to be better quantified.

4) Airflow and microbial transport within confined spaces needs to be assessed, particularly given people movement.

5) Aircraft decontamination strategies need to be examined, and the approach for environmental sampling -- due to hydrophobicity of *M. tb*, the sampling issues may be more interesting/complex than other organisms. While fomite contamination is not an issue in regard to disease spread with TB, this is not the case with other pathogens and other possible types of biological agents that could be used intentionally.

QUANTITATIVE MICROBIAL RISK ASSSESMENT FOR TB

DOSE-RESPONSE ANALYSIS

Background

Cynomolgus monkeys are believed to be the best animal models for human *Mycobacterium tuberculosis* infection because their pathology and response are nearest that of humans (Walsh, Tan et al., 1996; Capuano, Croix et al., 2003; Flynn, Capuano et al., 2003). In particular, Cynomolgus monkeys have lower low-dose mortality than Rhesus monkeys (Barclay, Anacker et al., 1970) and can exhibit latent tuberculosis, whereas latent tuberculosis has not been shown conclusively for guinea pig and rabbit models (Capuano, Croix et al., 2003).

For Cynomolgus monkeys, survival time after intratracheal infection with *Mycobacterium tuberculosis* was a strong function of dose (Walsh, Tan et al., 1996). Animals receiving a dose of 1000 CFU or more died, with time to death ranging from 31 days for a dose of 10^5 CFU to 152 days for a dose of 10^3 CFU. Mortality was observed for all animals exposed to doses at and above 1000 CFU. Mortality for animals receiving doses of 100 and 10 CFU was 75% and 50%, respectively.

At low doses (15-25 CFU), Cynomolgus monkeys exhibited a range of responses (Capuano, Croix et al., 2003; Flynn, Capuano et al., 2003). In a group of 25 monkeys given low-dose exposure via bronchoscope instillation, 2 monkeys progressed to disease rapidly, 8 monkeys had active chronic infections and 7 monkeys had latent infections. These findings are

significant because Cynomolgus infection was demonstrated to be similar to that of humans and because the potential for infection at very low dose was demonstrated. *Mycobacterium tuberculosis* is a facultative pathogen, capable of evading immune responses by harboring in cells between periods of infection (Brock, Madigan et al., 1991).

Immune system responses of inbred and outbred rabbits (Dorman, Hatem et al., 2004) to aerosol exposure to *M. tuberculosis* were significantly different, with inbred rabbits less able to contain disease than their outbred counterparts.

The ratio of the sensitivity of *M. tuberculosis* to ultraviolet radiation to the sensitivity of *E. coli* is 0.4 (Barksdale and Kim, 1977).

Inhalation Dose and Mortality

Inhalation dose-mortality response data from Walsh et al. (1996) were fit with exponential, beta-Poisson and log-probit dose-response models. Dose response data from the study are found in Table 2. The endpoint of the experiments was mortality.

Table 2: Dose-Response Data for Intratracheal Instillation Exposure of Cynomolgus Monkeys to Mycobacterium tuberculosis

Dose	Number of monkeys	Number of positives (Mortality)
10 CFU	4	2
100 CFU	4	3
1000 CFU	4	4
10000 CFU	4	4
100000 CFU	4	4

Best fits for the three dose-response models are shown in Figure 2. Goodness of fit was realized for all dose-response fits. The two-parameter log-probit and beta-Poisson models do not provide a statistically significant improvement in fit over the exponential model. The best fit model is then the exponential model with parameter $k = 0.022$.

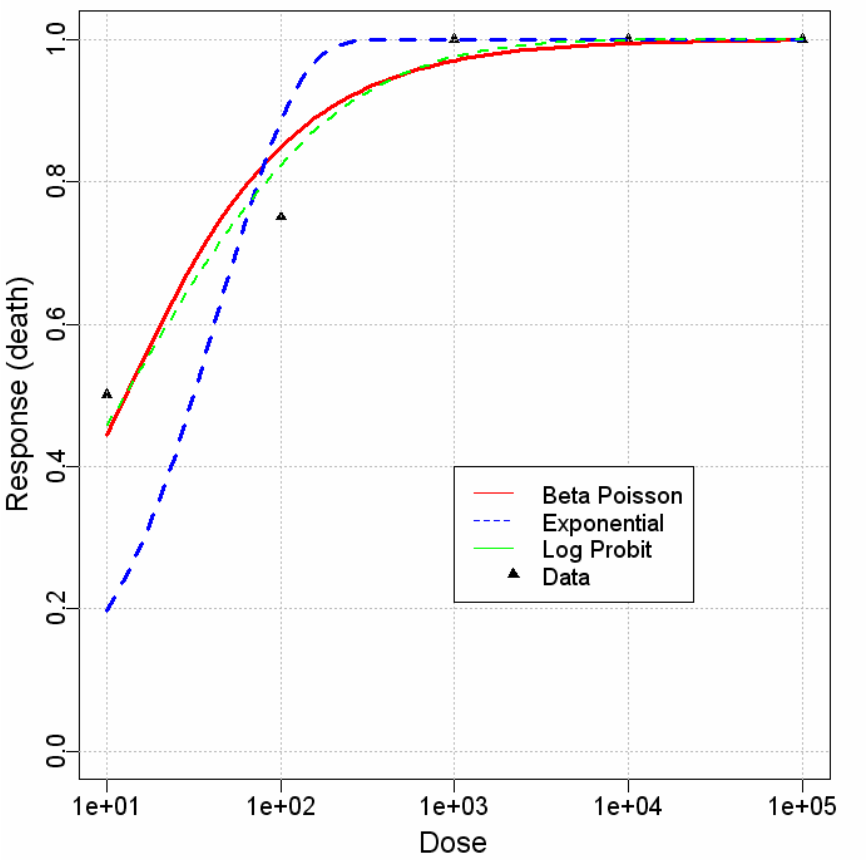

Figure 2: Cynomolgus monkey response (mortality) to intratracheal exposure to Mycobacterium tuberculosis

Inhalation Dose and Infection Response: Barclay et al. (1970) exposed unvaccinated rhesus monkeys and monkeys vaccinated with BCG to aerosols *of Mycobacterium tuberculosis* H37Rv in a Henderson apparatus. Experiments on non-vaccinated monkeys were intended to simulate the "natural infection" of humans and involved low doses of the pathogen delivered in aerosols. Groups of 4 monkeys were exposed to cumulative doses of 12, 25 and 49 infectious units and infection was assessed via abdominal skin reactions to 10 tuberculin units of purified protein derivative and by X-ray examination of monkeys' lungs. The two tests provided contradictory results; the X-ray examination showed that visible lesions were present in all the monkeys after 8 weeks, although the numbers of tubercles were not quantified. The skin tests showed 0 out of 4, 2 out of 4 and 3 out of 4 monkeys were positive eight weeks subsequent to receiving doses of 12, 25 and 49 infectious units, respectively.

Dose response analysis was possible only for the skin test data of Barclay et al. (1970). The best fit to the dose response data was provided by the log-probit model, but the improvement of fit over the exponential model was not justified by the improvement in deviation, so the exponential model (k = 0.0217) was accepted as the best fit. The data and best fit models are shown in Figure 3.

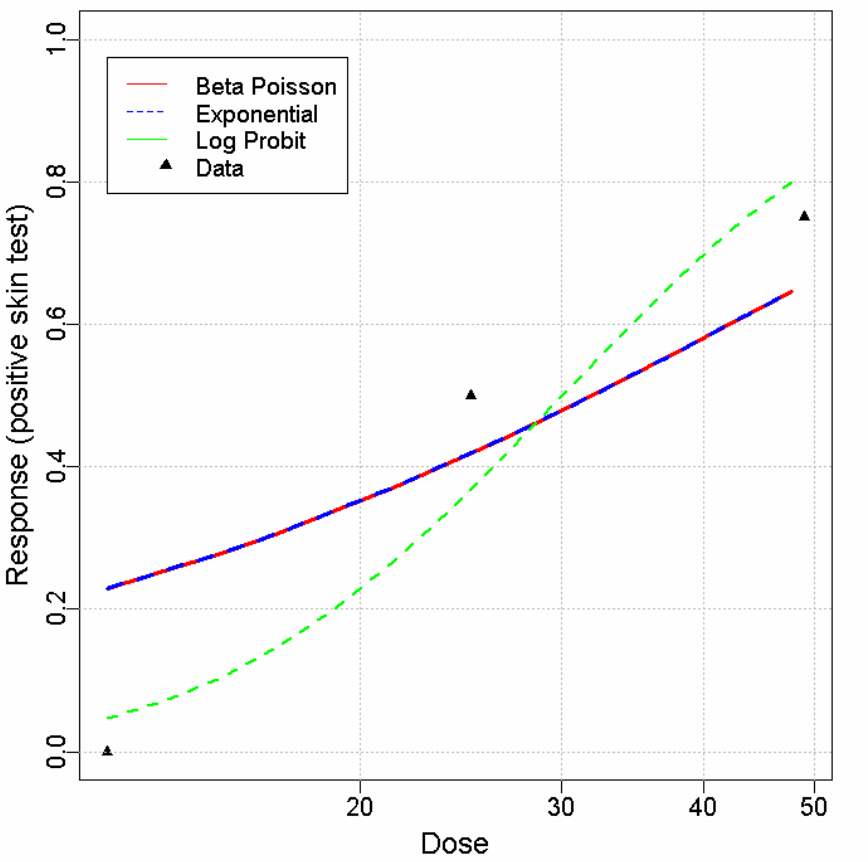

Figure 3: Rhesus monkey response (positive skin test) to aerosol exposure to Mycobacterium tuberculosis

Infectious dose data for *M. tb* come primarily from animal inhalation studies of the following nature. Small animals (rabbits, mice, rats, guinea pigs, hamsters) were exposed to fine aerosol particles (estimated aerodynamic diameters less than 4 μm) carrying strains of bovine or human *M. tb*. The inhaled dose was estimated based on the concentration of viable bacilli in the aerosol (# per m^3), the inhalation rate of the animals (m^3 per minute), and the duration of exposure (minutes). Several weeks after exposure, the animals were sacrificed and the number of distinct tubercles (foci of infection) was enumerated in the lungs. The general observation was that the estimated number of inhaled bacilli was comparable to the number of tubercles observed in the lungs (Wells, 1955). For example, in one experiment, 8 rabbits inhaled an estimated 20 *M. tb* bacilli (a bovine strain) carried by particles with aerodynamic diameters less than 4 μm; the mean number of observed tubercles per rabbit was 26.4 with a range of 15 to 40 (Ratcliffe, 1952). We note that in the human respiratory tract, about 20% of particles in the 1 μm to 4 μm range which are inhaled via the nose deposit in the alveolar region; if the same deposition percent held for rabbits (nose breathers), and if 20 bacilli were inhaled, the observed number of tubercles per lung should have been 4, not 26. On the other hand, when the inhaled *M. tb* bacilli were from a human strain, the mean number of observed tubercles per rabbit was about 20% of the estimated number inhaled; this finding is consistent with 20% particle deposition in the alveolar region.

In a different study design, the numbers of *M. tb* bacilli (bovine strain) present in the left lungs of three mice about 30 minutes after inhalation exposure were enumerated via microscopy of lung sections (Nyka, 1962). All the observed acid-fast bacilli (2 to 3 μm in length) were associated with alveoli, and were reported to be randomly dispersed in the lung. The author stated that one acid-fast bacillus was found per 65 lung sections, and that approximately 2,000 sections comprised a left lung, such that the estimated number of bacilli deposited per left lung was $1/65 \times 2{,}000 = 31$ bacilli. In two other mice that were simultaneously exposed with the first three mice but sacrificed 54 days post-exposure, the numbers of tubercles observed in the left lung were 20 and 30, respectively; the tubercles were randomly dispersed in the lung. Due to the parity between the numbers of deposited bacilli and tubercles, the author concluded that each tubercle had been induced by one bacillus; that is, the infectious dose of *M. tb* is one bacillus.

EXPOSURE ASSESSMENT and RISK CHARACTERIZATION

It should be noted that these analyses does not provide information on the "actual" risk. It was reported that the patient had very low in most cases non-detectable bacilli numbers in a sputum slide (lower than "usual", although specific details have not been available thus far) and that he seldom coughed. **However, two parameters in this risk assessment, *M. tb* concentration in sputum and saliva and number of coughs per hour, were derived from data of symptomatic patients.**

Model A: Markov chain model for transmission of *M. tb* in Boeing 767-300

A Markov chain model for transmission of *M. tb* emitted from a patient in an aircraft is developed based on our previous research (Jones, 2007). Although the aircraft modeled here (Boeing 767-300) is different from the ones used in the patient's trips (Boeing 747-400 and Airbus 310), we believe that this model can represent the actual situation because characteristics of the aircrafts (e.g. dimensions of aircrafts, air ventilation system) are similar to each other.

Estimates of Exposure and Dose: The emission of *M. tb* was assumed to occur via coughing. Only the respirable size range of cough droplets was considered because only respirable particles reach the alveolar region, which is the initial site of *M. tb* infection. The features of the cough droplet size distribution are indicated in Table 3 (Nicas, et al, 2005). The initial fluid volume in the respirable cough particles in Table 3 is approximately 6×10^{-8} mL.

Yeager et al. (1967) found that the concentration of viable *M. tb* bacilli in the saliva to ranged from 1×10^2 per mL to 6×10^5 bacilli per mL, with an average of 7×10^4 per mL; the concentration of viable *M. tb* bacilli in the sputum ranged from 6.6×10^4 per mL to 3.4×10^7 bacilli per mL, with an average of 8.4×10^6 per mL. For the dose calculations presented here, the maximum measured concentration of *M. tb* in the saliva ($C_{tb} = 6 \times 10^5$ bacilli per mL) has been used, because coughs are likely to contain more saliva than sputum. However, to estimate the dose received if other concentrations of *M. tb* are considered, one can multiply the dose estimates presented in Tables 4 – 7 by the ratio of the new concentration of interest to 6×10^5 bacilli per mL. Note that the estimated average emission rate of respirable *M. tb* from a pulmonary TB patient is approximately one per hour (Riley, et al, 1962). Given our posited $6 \times$

10^5 bacilli per mL and our posited cough rate of 10 per hour, our source case emits respirable M. tb at 36% of the cited patient-average rate, or:

$$(6 \times 10^5 \text{ bacilli mL}^{-1}) \times (6 \times 10^{-8} \text{ mL cough}^{-1}) \times (10 \text{ cough hr}^{-1}) = 0.36 \text{ bacilli hr}^{-1}$$

The concentrations of *M. tb* in the breathing zones of seated passengers in a Boeing 767-300 aircraft were predicted using a Markov chain model (Jones, 2007; Nicas, 2001). This aircraft features seven seats in each row, two seats near each window and three seats in the center. The cabin volume was divided into rectangular volumes ("states") of size 0.50 m × 0.4 m × 0.2 m (V = 0.04 m^3). The air within each volume was assumed to be well-mixed. The cabin air inflow is through diffusers located in the ceiling above the aisles, and the air outflow is at floor level under the windows. For each row of seats, the air inflow is at rate 2.52 m^3 min^{-1} (NRC, 2002). The air flow pattern involves two eddies centered in the aisles at the top of seats that circulate outward towards the windows and then down toward the floor (NRC, 2002). The air velocity in these eddies was deter-mined by the volumetric inflow rate. In addition, there is a steady advective flow towards the rear (aft) of the cabin at speed 6 m min^{-1} (Thibeault, 2002; Eklund, 1996). The magnitude of the turbulent diffusion coefficient was estimated based on mixing length theory and found to be D_T = 5.3 m^2 min^{-1} (Kundu and Cohen, 1996). The modeling accounted for the gravitational settling of particles based on the terminal settling velocity which, in turn, is a function of particle aerodynamic diameter (Hinds, 1999). The Markov chain model predicted the probability that a particle emitted in location *i* was in location *j* at some time *n* subsequent to emission at location *i*, where $n = T \div \Delta t$ for $\Delta t = 0.5$ s, and where T is the total time (s) subsequent to emission. This probability value is denoted $P_{ij}^{(n)}$. The Markov chain model was simulated for each of the four respirable particle size bins.

The breathing rate of the seated passengers was assumed to be 0.54 m^3 h^{-1}, which is the value for seated males in the ICRP model (Hinds, 1999). The fraction of the particles in a given state of volume 0.04 m^3 that are inhaled in time step $\Delta t = 0.5$ s is 0.0019, or:

$$f_{inh} = \frac{0.54 \text{ m}^3}{\text{h}} \times \frac{1 \text{ h}}{3600 \text{ s}} \times (0.5 \text{ s}) \times \frac{1}{0.04 \text{ m}^3} = 0.0019$$

If the cough is emitted in state *i*, and the breathing zone of a fellow passenger is located in state *j*, the bacilli dose deposited in the alveolar region of the fellow passenger, D, is computed as follows:

$$\text{D} = \sum_{k=1}^{4} \sum_{n=1}^{T \div \Delta t} P^{(n)}{}_{ij,k} \times f_{inh} \times f_{alv,k} \times C_{tb} \times V_{bin,k}$$

where *k* indexes the droplet bin, and *n* indexes the time after the cough. T indicates the total duration of the exposure.

The cumulative alveolar retained dose over 6 minutes (due to one cough) is presented in Tables 4 – 7 for emission in the central seat, the central-aisle seat, the window-aisle seat, and the window seat, respectively. The exposure pattern is spatially symmetric, so the dose is only

presented for these four emission locations. The Markov chain model predicted the removal of *M. tb* from the breathing zones of seated passengers within five minutes of emission; thus, the concentration of *M. tb* is not predicted to build-up in the aircraft cabin for cough frequencies of 10 to 12 per hour. The doses due to a series of coughs are additive. Thus, to find the cumulative dose received due to N coughs, one multiplies the doses presented in Tables 4 – 7 by N. For example, if the source case coughs 10 times per hour, then N = 80 for an 8-hr flight, and the cumulative dose for a passenger in a given seat is N × D.

For comparison, Tables 8 and 9 indicate the expected dose to seated passengers subsequent to the emission of one cough in the central seat, for the average and minimum concentrations of *M. tb* in saliva.

Infection Risk and Incidence: Infection risk R is computed by the following exponential function for which k = 1:

$$R = 1 - \exp(-k \times Dose)$$

For a passenger seated next to the source case, dose per cough ranges from 0.084×10^{-5} to 0.97×10^{-5} bacilli, according to Tables 4 – 7. Given N = 80 coughs during an 8-hour flight, the cumulative dose ranges from 6.7×10^{-5} to 7.8×10^{-4} bacilli. The corresponding infection risks range from 6.7×10^{-5} (0.00067%) to 7.8×10^{-4} (0.078%).

The expected incidence of infection among all the passengers is the sum of the individual infection risks (Nicas, 1996). Given 80 coughs in an 8-hour trip, the sum of the risks among the 55 fellow passengers shown in the eight rows (assumed to be full) in Tables 4 – 7 is, respectively, 0.005, 0.0049, 0.0048 and 0.0044. In turn, the Poisson probability that no infections would occur among this group is 99.5% or more, or: exp(–0.005) = 0.995.

If the concentration of *M. tb* in the saliva was the average level observed by Yeager et al (1967), 7×10^{4} mL^{-1}, the expected incidence of infection among the 55 fellow passengers in the eight rows is 7.2×10^{-6} after one cough emitted in the central seat, and 5.8×10^{-4} after 80 coughs emitted in the central seat. The Poisson probability that no infections would occur among this group is 99.999% and 99.94% for one and 80 coughs, respectively.

If the concentration of *M. tb* in the saliva was the lowest level observed by Yeager et al (1967), 1×10^{2} mL^{-1}, the expected incidence of infection among the 55 fellow passengers in the eight rows is 1.0×10^{-8} after one cough emitted in the central seat, and 8.3×10^{-7} after 80 coughs emitted in the central seat. The Poisson probability that no infections would occur among this group is greater than 99.999%.

The Boeing 747 Aircraft: The Boeing 747-400 aircraft is larger and has a different ventilation configuration than the Boeing 767 aircraft family (http://www.boeing.com/commercial/airports/acaps/7474sec2.pdf). Like the 767 aircraft the 747-400 has two aisles, but in the economy cabin there are ten seats per row: 3 seats are next to each window, and four seats are in the center. Like the 767 aircraft, the 747-400 has exhaust ventilation located at the floor level, under the window. The air inlets in the 747-400, however,

are located above the windows, under the overhead luggage bins, rather than above the aisles. Computational fluid dynamics simulation of airflow in an empty 747-400 cabin has found that the air at the inlet follows the underside of the luggage bins, and moves towards the center of the cabin (Garner et al, 2004). This results in stable eddies within each row that would be expected to circulate towards the center of the cabin above the passengers seated by the windows, down through the breathing zones of passengers seated in the center of the cabin, and along the floor to the exhaust points under the windows. Notably, these eddies circulate in the opposite direction to those predicted by computational fluid dynamics simulations for the 767-300 (Lin et al, 2005).

It is intuitive that the longer the air has been in the cabin, the more likely it is to carry pathogens. This was evidenced in the Markov model simulations of exposures in the 767-300 cabin, where it was found that passengers seated near the windows (the last passenger breathing zones through which the air passed before reaching the exhaust points) had relatively higher exposure than other passengers, regardless of the emission location. [NOTE: This statement is contradicted in Table 4. Passengers seated next to the source case had the highest doses.]This implies that in the 747-400, the passengers in the central seats would have higher exposure levels than those at the windows, because after passing through the breathing zones of the passengers in the central seat, the airflow follows the floor to the windows.

The magnitude of the exposures and risk on the population level in the aircraft are likely to be similar because the general features of the airflow – the stable eddies within each row and the advective velocity towards the cabin rear – are similar in the 767 and 747 aircraft.

Model B: Box-based model for Airbus 310

Here we depict another model to estimate average concentration of *M. tb* in the aircraft using simpler box-based model. Three "boxes" of cabin space, each of them consists of five rows of seats were included in the model (see Figure 4). The dimension of Airbus 310 was used in the model because it is smaller than Boeing 747-400, thus presumed to produce higher dose for passengers. Doses of *M. tb* by inhalation and risk of infection/mortality for passengers in each box were estimated. This simpler model allowed us to use parameters from the aircraft actually used by the patient.

This model employed the same emission pattern (concentration of *M. tb* in saliva, amount and size distribution of particles emitted by coughing) as the Model A. The emitted particles are well mixed in the box immediately, and transferred among three boxes at the air exchange rate of 4.2 m^3/hour (10 % of volume of each box was exchanged per hour). Ko and colleagues (2004) said the air ventilation rates of most aircrafts are between 20 and 30 air changes per hour (ACH). To obtain conservative risk estimates, 20 ACH was adopted in the model. HEPA filter installed in the air ventilation system was considered to remove all aerosol particles in the inflow air. Decay rate of the *M. tb* in air or aerosol was not considered. Air inhalation rate for each passenger was set at 0.54 m^3/hour, the same rate as the Model A. As this model assumes *M. tb* is equally distributed in each box, passengers in a box are exposed to equal amount of *M. tb* cells. The risk of infection and mortality were calculated using the following model:

$$R = 1 - \exp(-k \times Dose)$$

where k=1 for infection and k=0.022 for mortality. The probabilities that one or more infection or death were occurred among the passengers in each box were calculated using as follows:

$$P_{incidence} = 1 - \left(1 - R_{personal}\right)^{N}$$

where $R_{personal}$ is risk of infection/mortality for one person in the box, and N is the number of passengers in each box except the source patient; thus N = 39 for middle box and N = 40 for other boxes. Estimated risks of infection/mortality of passengers in each box were summarized in Tables 10 and 11. With the highest possible concentration of *M. tb* in saliva (6×10^5 CFU/mL), the probability of observing one or more infection among passengers near the source patient was 1.1%, which was about 3 times higher than the estimates from the Model A.

Table 3. Size and count distribution of cough droplets (Nicas et al, 2005), and the alveolar deposition fraction according to the ICRP deposition model, f_{alv} (Hinds, 1999).

Droplet Bin	Mean Equilibrium Diameter, d_a (μm)	Number of Droplets	Bin Volume $\times 10^{-8}$ mL, V_{bin}	Alveolar Deposition Fraction, f_{alv}
1	2.1	120	0.47	0.117
2	4.5	100	3.8	0.065
3	7.3	6.2	1.0	0.034
4	9.4	1.7	0.6	0.022

Table 4. Dose ($\times 10^{-5}$ bacilli) deposited in the alveolar region of the lungs of seated passengers in the six minutes subsequent to the emission of a single cough in the central seat (Seat 4) of Row 3 given the maximum concentration of *M. tb* in saliva, 6×10^5 mL^{-1} . Note that aisles separate Seats 2 and 3, and Seats 5 and 6. Seats 1 and 7 are next to the windows. Bold text indicates the site of emission.

	Seat 1	Seat 2	Seat 3	Seat 4	Seat 5	Seat 6	Seat 7
Row 1	0.0007	0.0005	0.0003	0.0003	0.0004	0.0006	0.0008
Row 2	0.0176	0.0122	0.0076	0.0076	0.0082	0.00129	0.0179
Row 3	0.2595	0.2072	0.3203	**0.4429**	0.3327	0.2152	0.2652
Row 4	0.3138	0.2192	0.1453	0.1519	0.1526	0.2246	0.3112
Row 5	0.2342	0.1624	0.1067	0.1115	0.1127	0.1679	0.2343
Row 6	0.1704	0.1182	0.0778	0.0815	0.0824	0.1229	0.1715
Row 7	0.1241	0.0861	0.0568	0.0595	0.0602	0.0897	0.1253
Row 8	0.0924	0.0639	0.0419	0.0439	0.0445	0.0668	0.0935

Table 5. Dose ($\times 10^{-5}$ bacilli) deposited in the alveolar region of the lungs of seated passengers in the six minutes subsequent to the emission of a single cough in the central-aisle seat (Seat 3) of Row 3 given the maximum concentration of *M. tb* in saliva, 6×10^5 mL^{-1}. Note that aisles separate Seats 2 and 3, and Seats 5 and 6. Seats 1 and 7 are next to the windows. Bold text indicates the site of emission

	Seat 1	Seat 2	Seat 3	Seat 4	Seat 5	Seat 6	Seat 7
Row 1	0.0007	0.0005	0.0003	0.0003	0.0003	0.0005	0.0007
Row 2	0.0195	0.0135	0.0080	0.0074	0.0073	0.0110	0.0151
Row 3	0.3615	0.3074	**0.4325**	0.3979	0.2333	0.1543	0.1937
Row 4	0.3557	0.2467	0.1553	0.1497	0.1386	0.1900	0.2608
Row 5	0.2426	0.1674	0.1071	0.1083	0.1061	0.1540	0.2139
Row 6	0.1697	0.1174	0.0764	0.0789	0.0789	0.1162	0.1621
Row 7	0.1215	0.0842	0.0552	0.0575	0.0580	0.0861	0.1200
Row 8	0.0899	0.0621	0.0406	0.0425	0.0430	0.0644	0.0901

Table 6. Dose ($\times 10^{-5}$ bacilli) deposited in the alveolar region of the lungs of seated passengers in the six minutes subsequent to the emission of a single cough in the window-aisle seat (Seat 2) of Row 3 given the maximum concentration of *M. tb* in saliva, 6×10^5 mL^{-1}. Note that aisles separate Seats 2 and 3, and Seats 5 and 6. Seats 1 and 7 are next to the windows. Bold text indicates the site of emission

	Seat 1	Seat 2	Seat 3	Seat 4	Seat 5	Seat 6	Seat 7
Row 1	0.0007	0.0005	0.0003	0.0003	0.0003	0.0004	0.0006
Row 2	0.0212	0.0145	0.0082	0.0069	0.0061	0.0084	0.0114
Row 3	0.9719	**0.7392**	0.3514	0.2135	0.1194	0.0932	0.1186
Row 4	0.3869	0.2643	0.1568	0.1385	0.1157	0.1425	0.1927
Row 5	0.2357	0.1618	0.1005	0.0979	0.0923	0.1294	0.1787
Row 6	0.1579	0.1089	0.0699	0.0711	0.0699	0.1019	0.1417
Row 7	0.1108	0.0767	0.0500	0.0518	0.0518	0.0766	0.1067
Row 8	0.0812	0.0561	0.0366	0.0382	0.0385	0.0577	0.0806

Table 7. Dose ($\times 10^{-5}$ bacilli) deposited in the alveolar region of the lungs of seated passengers in the six minutes subsequent to the emission of a single cough in the window seat (Seat 1) of Row 3 given the maximum concentration of *M. tb* in saliva, 6×10^{5} mL^{-1}. Note that aisles separate Seats 2 and 3, and Seats 5 and 6. Seats 1 and 7 are next to the windows. Bold text indicates the site of emission

	Seat 1	Seat 2	Seat 3	Seat 4	Seat 5	Seat 6	Seat 7
Row 1	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001
Row 2	0.0022	0.0015	0.0008	0.0007	0.0006	0.0008	0.0011
Row 3	**0.1514**	0.0836	0.0277	0.0175	0.0102	0.0082	0.0105
Row 4	0.0384	0.0259	0.0148	0.0129	0.0103	0.0129	0.0174
Row 5	0.0025	0.0154	0.0095	0.0092	0.0086	0.0119	0.0165
Row 6	0.0149	0.0103	0.0066	0.0067	0.0065	0.0095	0.0132
Row 7	0.0104	0.0072	0.0047	0.0048	0.0048	0.0072	0.0100
Row 8	0.0076	0.0053	0.0034	0.0036	0.0036	0.0054	0.0075

Table 8. Dose ($\times 10^{-6}$ bacilli) deposited in the alveolar region of the lungs of seated passengers in the six minutes subsequent to the emission of a single cough in the central seat (Seat 4) of Row 3 given the average concentration of *M. tb* in saliva, 7×10^{4} mL^{-1} . Note that aisles separate Seats 2 and 3, and Seats 5 and 6. Seats 1 and 7 are next to the windows. Bold text indicates the site of emission.

	Seat 1	Seat 2	Seat 3	Seat 4	Seat 5	Seat 6	Seat 7
Row 1	0.0008	0.0006	0.0004	0.0004	0.0004	0.0006	0.0009
Row 2	0.0205	0.0143	0.0089	0.0089	0.0095	0.0150	0.0209
Row 3	0.3028	0.2415	0.3736	**0.5167**	0.3882	0.2511	0.3094
Row 4	0.3661	0.2557	0.1696	0.1772	0.1781	0.2620	0.3630
Row 5	0.2733	0.1895	0.1245	0.1301	0.1314	0.1959	0.2733
Row 6	0.1988	0.1379	0.0908	0.0951	0.0962	0.1433	0.2001
Row 7	0.1448	0.1004	0.0662	0.0694	0.0702	0.1047	0.1461
Row 8	0.1078	0.0746	0.0489	0.0512	0.0519	0.0780	0.1091

Table 9. Dose ($\times 10^{-9}$ bacilli) deposited in the alveolar region of the lungs of seated passengers in the six minutes subsequent to the emission of a single cough in the central seat (Seat 4) of Row 3 given the minimum concentration of *M. tb* in saliva, 1×10^{2} mL^{-1} . Note that aisles separate Seats 2 and 3, and Seats 5 and 6. Seats 1 and 7 are next to the windows. Bold text indicates the site of emission.

	Seat 1	Seat 2	Seat 3	Seat 4	Seat 5	Seat 6	Seat 7
Row 1	0.0012	0.0008	0.0005	0.0005	0.0006	0.0009	0.0013
Row 2	0.0293	0.0204	0.0127	0.0127	0.0136	0.0215	0.0299
Row 3	0.4326	0.3450	0.5338	**0.7381**	0.5545	0.3586	0.4420
Row 4	0.5230	0.3653	0.2422	0.2532	0.2544	0.3743	0.5186
Row 5	0.3904	0.2706	0.1779	0.1859	0.1878	0.2798	0.3904
Row 6	0.2841	0.1969	0.1297	0.1358	0.1374	0.2048	0.2858
Row 7	0.2069	0.1425	0.0946	0.0991	0.1003	0.1496	0.2088
Row 8	0.1541	0.1065	0.0698	0.0731	0.0742	0.1114	0.1558

Table 10. Estimated risk for passengers in the same box of the source patient (middle box).

Scenario	Concentration	Risk of infection (k=1)		Risk of mortality (k=0.022)	
	[CFU/mL]	personal	39 people	personal	39 people
Low	100	4.9×10^{-8}	1.9×10^{-6}	1.1×10^{-9}	4.2×10^{-8}
Average	70000	3.4×10^{-5}	1.3×10^{-3}	7.5×10^{-7}	2.9×10^{-5}
High	600000	2.9×10^{-4}	1.1×10^{-2}	6.4×10^{-6}	2.5×10^{-4}
Detection limit	1	4.9×10^{-10}	1.9×10^{-8}	1.1×10^{-11}	4.2×10^{-10}

Table 11. Estimated risk for passengers in the front or rear boxes.

Scenario	Concentration	Risk of infection (k=1)		Risk of mortality (k=0.022)	
	[CFU/mL]	personal	40 people	personal	40 people
Low	100	2.6×10^{-10}	1.1×10^{-8}	5.8×10^{-12}	2.3×10^{-10}
Average	70000	1.9×10^{-7}	7.4×10^{-6}	4.1×10^{-9}	1.6×10^{-7}
High	600000	1.6×10^{-6}	6.4×10^{-5}	3.5×10^{-8}	1.4×10^{-6}
Detection limit	1	2.6×10^{-12}	1.1×10^{-10}	5.8×10^{-14}	2.3×10^{-12}

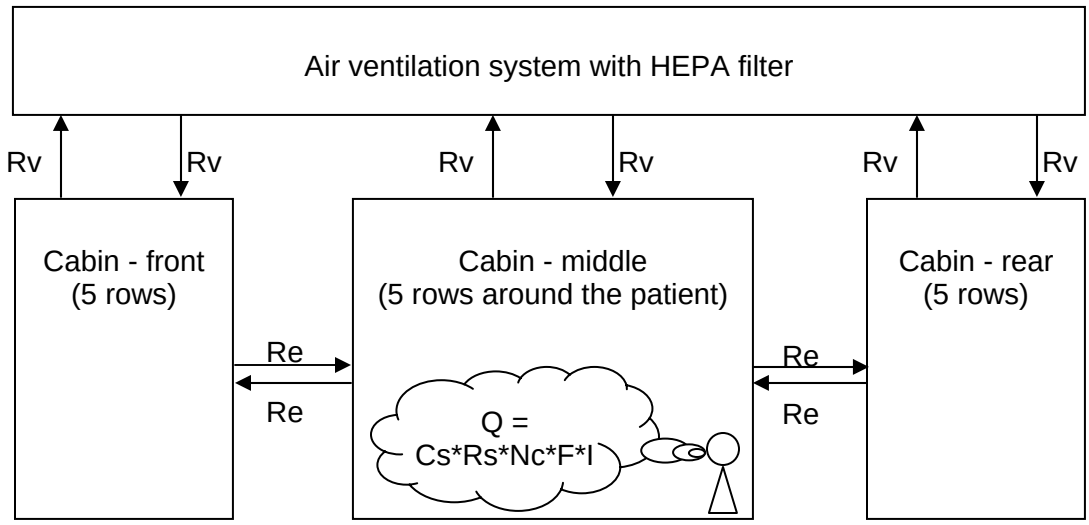

Figure 4. Schematic representation of the Box-based model (Model B).

APPENDIX

Table A1. Parameters used in both models

Description		Unit	Value	Reference
Detection limit of TB in sputum/saliva		CFU/ml	1	
TB concentration in saliva	Cs	CFU/ml	Low: 1×10^2 Average: 7×10^4 High: 6×10^5	Yeager et al., 1967
Emission rate of respiratory fluids	Rs	ml/cough	1 - 2.9 μm: 4.7×10^{-9} 2.9 - 5.8 μm: 3.8×10^{-8} 5.8 - 8.7 μm: 1.0×10^{-8} 8.7 - 10 μm: 6.0×10^{-9}	Nicas et al., 2005
Number of coughs [a]	Nc	cough/min	0.17 (= 10 cough/hour)	Nicas et al., 2005
Droplet nuclei deposition fraction in the alveolar region	F	-	1 - 2.9 μm: 0.32 2.9 - 5.8 μm: 0.21 5.8 - 8.7 μm: 0.023 8.7 - 10 μm: 0.003	Nicas et al., 2005
Removal efficiency of bacilli by HEPA filter	X	%	100	
Breathing rate of exposed passengers	Rb	m^3/min	0.0090 (=0.54 m^3/hour)	Hinds, 1999
Number of infected patients	I	person	1	
Duration of exposure	T	min	480	

a: Based on data that one-fifth of 96 TB patients coughed an average of 12 times or more per hour (Loudon and Roberts, 1967).

Table A2. Additional parameters used in Model A

Description	Unit	Value	Reference
Air volume modeled (8 rows) [a]	m^3	46.72	
Ventilation rate	m^3/min	20.16	NRC, 2000
Turbulent Diffusion Coefficient	m^2/min	5.28	

a: Model based on technical specifications of the Boeing 767 aircraft family (http://www.boeing.com/commercial/airports/acaps/767sec2.pdf)

Table A3. Additional parameters used in Model B

Description		Unit	Value	Reference
Air volume modeled (5 rows)[a]		m^3	41.6	
Ventilation rate of the occupied space	Rv	ACH [b]	20	Ko et al., 2004
Frontward/backward air exchange rate	Re	%/hour	10	Ko et al., 2004

a: Based on specification of Airbus 310 (http://www.airbus.com/en/aircraftfamilies/a300a310/a310/specifications.html); 2 m height was assumed

b: ACH = air change per hour

REFERENCES

Barclay, W. R., R. L. Anacker, et al. (1970). "Aerosol-Induced Tuberculosis in Subhuman Primates and the Course of Disease After Intravenous BCG Vaccination." Infection and Immunity **2**(5): 574-582.

Barksdale, L. and K.-S. Kim (1977). "*Mycobacterium*." Bacteriological Reviews **41**(1): 217-372.

Brock, T. D., M. T. Madigan, et al. (1991). Biology of Microorganisms. Englewood Cliffs, NJ, Prentice-Hall.

Capuano, S. V., D. Croix, et al. (2003). "Experimental *Mycobacterium tuberculosis* Infection of Cynomolgus Macaques Closely Resembles the Various Manifestations of Human *M. tuberculosis* Infection." Infection and Immunity **71**(10): 5831-5844.

Dorman, S. E., C. L. Hatem, et al. (2004). "Susceptibility to Tuberculosis: Clues from Studies with Inbred and Outbred New Zealand White Rabbits." Infection and Immunity **72**(3): 1700-1705.

Eklund, T.I. (1996). "In-flight cabin smoke control." Toxicology **155**: 135-144.

Flynn, J. L., S. V. Capuano, et al. (2003). "Non-Human Primates: a Model for Tuberculosis Research." Tuberculosis **83**: 116-118.

Garner, R.P., K.L. Wong, S.C. Ericson, A.J. Baker and J.A. Orzechowski. (2004). "CFD Validation for Contaminant Transport in Aircraft Cabin Ventilation Flow Fields." DOT/FAA/AM-04/7.

Hinds, W.C. (1999). Aerosol Technology, 2nd Edition. New York: John-Wiley & Sons, Inc.

Jones, R.M. (2007). "Quantitative Risk Assessment of Viral Aerosols." NIOSH Contract #211-2006-M-162553.

Ko, G., K. M. Thompson et al. (2004). "Estimation of Tuberculosis Risk on a Commercial Airliner." Risk Analysis **24**(2): 379-388.

Kundo, P.K. and I.M. Cohen (2004). "Fluid Mechanics, 3rd Eition." Amsterdam: Elsevier Academic Press.

Lin, C.H., R.H. Horstman, M.F. Ahlers, L.M. Sedgwick, J.L. Dunn, J.L. Topmiller, J.S. Bennett, and S. Wirogo. (2005). "Numerical simulation of airflow and airborne pathogen transport in aircraft cabins – Part I: Numerical simulation of the flow field." ASHRAE Transactions. **111**: OR-05-8-4.

Loudon, R.G., and R.M. Roberts (1967). "Cough frequency in patients with respiratory disease." American Reviews of Respiratory Diseases **96**:1137–1143.

National Research Council Committee on Air Quality in Passenger Cabins of Commercial Aircraft. (2002) The Airliner Cabin Environment and the Health of Passenger and Crew. Washington, D.C.: National Academy Press.

Nicas, M. (1996). "An Analytical Framework for Relating Dose, Risk, and Incidence: An Application to Occupational Tuberculosis Infection." Risk Analysis **16**(4): 527-538.

Nicas, M. (2001). Modeling turbulent diffusion and advection of indoor air contaminants by Markov chains. American Industrial Hygiene Association Journal **62**: 149-158.

Nicas, M., W. W. Nazaroff et al. (2005). "Toward Understanding the Risk of Secondary Airborne Infection: Emission of Respirable Pathogens." Journal of Occupational and Environmental Hygiene **2**(3): 143-154.

Nyka W. (1962): "Studies on the infective particle in airborne tuberculosis. I. Observations in mice infected with a bovine strain of ***M. tuberculosis***." American Review of Respiratory Disease **85**:33-39.

Ratcliffe H.L. (1952): "Tuberculosis induced by droplet nuclei infection." American Journal of Hygiene **55**:36-48.

Riley, R.L., C.C. Mills, F. O'Grady, L.U. Sultan, et al. (1962): "Infectiousness of air from a tuberculosis ward." American Review of Respiratory Disease **85**: 511-525

Thibeault, C. (2002). "Airliner cabin air quality." Occupational Medicine: State of the Art Reviews. **17**: 279-292.

Walsh, G. P., E. V. Tan, et al. (1996). "The Phillipine Cynomolgus Monkey (*Macaca fasicularis*) Provides a New Nonhuman Primate Model of Tubersulosis that Resembles Human Disease." Nature Medicine **2**(4): 430-436.

Wells WF (1955): "Airborne Contagion and Air Hygiene." Cambridge University Press, Cambridge, MA

Yeager, H., J. Lacy, L. et al. (1967). "Quantitative studies of mycobacterial populations in sputum and saliva." American Reviews of Respiratory Diseases **95**:908–1004.