Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Tuberculosis (TB) is the best known, and most studied, occupational respiratory infectious disease. The wealth of published information regarding nosocomial transmission of TB can provide insight into the risks, mechanisms, and potential preventive measures for the nosocomial transmission of other airborne infections including severe acute respiratory syndrome (SARS), influenza, measles, varicella, and anthrax. The study of occupational TB is particularly informative because transmission can be monitored in 2 ways. The cumulative or periodic incidence of latent infection can be estimated using tests of immune reactions to TB antigens, such as the tuberculin skin test (TST). Transmission that results in disease can be measured with a high degree of specificity using molecular epidemiologic tools such as restriction fragment length polymorphism (RFLP) analysis.

Much of the information regarding risk, risk factors, and prevention of nosocomial transmission is derived from studies conducted in high-income countries. There was considerable interest in this topic in the preantibiotic era, but this waned with the introduction of effective antibiotics. However, the coincident advent of human immunodeficiency virus (HIV) infection and multidrug-resistant (MDR) TB resulted in several major outbreaks in high-income countries, particularly the United States. In a few of these outbreaks more than half of exposed patients became infected, developed disease, and died. In the same hospitals a large number of health care workers were infected, although few developed disease and even fewer died. These outbreaks led to renewed interest in the prevention of transmission of airborne respiratory infections. In the past decade attention has shifted to workers in low- and middle-income countries (LMIC), where risk of disease may be high.
RISK AND RISK FACTORS FOR TB INFECTION AND DISEASE

Several narrative and systematic reviews have been published on the risk of TB infection and disease among health care workers in high-income and LMIC. Nosocomial TB transmission has also been reviewed in guidelines issued by authoritative agencies including the US Centers for Disease Control and most recently the World Health Organization.

Until recently prevalence and incidence of latent TB infection (LTBI) could be measured only with the TST. In the past decade interferon release assays (IGRA) have been increasingly used to measure LTBI prevalence. However, few studies have measured incidence of TB infection through serial performance of IGRA. Although IGRA have significantly better specificity in bacille Calmette-Guérin (BCG)-vaccinated populations, their ability to predict who will develop active TB is unclear. In addition, studies of serial IGRA testing have reported substantial rates of conversion and spontaneous reversion. Until these issues are clarified the usefulness of IGRA for estimation of nosocomial transmission remains questionable, although this is an area of active research. Hence this review focuses on studies using TST to detect prevalent and incident LTBI.

As summarized in Table 1 a large number of studies have estimated risk of TB infection or disease. Although the estimates are variable, there is consistent evidence that the prevalence and incidence of LTBI in health care workers is substantially higher than the general population, in all settings. In high-income countries the pooled risk of TB disease among workers is only twice that of the general population, whereas the risk of infection is 10 times higher. In low-income countries disease and infection are about 5-fold higher than the general population. The reason for the difference in relative risk between infection and disease in high-income countries may reflect the healthy worker effect or may reflect overestimation of LTBI because of the nonspecificity of tuberculin skin testing in BCG-vaccinated populations.

Risk factors associated with TB infection and disease in all countries are summarized in Table 2. Despite the differences in levels of exposure, risk factors are similar. Most of these risk factors can be interpreted to indicate simply that infection and disease are proportionate to likelihood of exposure to patients with TB. It is self-evident that more years of work, in jobs that involve direct patient care, and in hospitals or units caring for more patients with TB, are more likely to result in TB infection and disease. One useful indicator is the number of patients with TB per worker, because the same number of patients with TB inevitably creates greater probability of exposure if cared for by a small group of workers, than the per-worker exposure

| LTBI | Studies (N) | Relative Risk | References |
|------|-------------|---------------|------------|
| High-income countries | 27 | 10.1 | 13-38 |
| LMIC | 9 | 5.8 | 39-47 |
| Active TB disease | | | |
| High-income countries | 12 | 2.0 | 48-57 |
| LMIC | 20 (222) | 5.7 | 58-79 |

Data from World Health Organization, Stop TB Department. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva (Switzerland): World Health Organization; 2009.
risk in a larger hospital. Other risk factors relate to increased chance of exposure to undiagnosed patients; these include work in emergency departments, or HIV services (the latter because of the atypical clinical manifestations of TB in HIV-coinfected patients). The third category of risk factor relates to specific activities that increase patients’ contagiousness. For example, respiratory therapists,52,92 and pathology workers2,90,93 have been consistently identified as high-risk workers, because certain of their tasks can result in aerosolization of TB bacilli (eg, intubation,94,95 sputum induction,96,97 bronchoscopy,98 or autopsy99,100).

These epidemiologic observations have improved our understanding of nosocomial transmission, and guided the development of infection control recommendations. The consistent observation that risk is proportional to the number of patients with TB per worker has resulted in risk-stratified recommendations: large hospitals with few patients with TB are required to implement fewer measures to prevent nosocomial TB transmission than hospitals with more TB cases. The knowledge that workers in high-incidence countries have 5 times greater risk of infection and disease than the general population has led to the realization that TB is the most common and serious occupational illness in these countries. This finding has stimulated concerted efforts to raise awareness, not least among the workers themselves, many of whom have a stoic and fatalistic approach to occupational TB. This finding also resulted in development of guidelines for TB control in resource poor settings,101 which have been updated recently.8

Table 2
Occupational risk factors for TB

| General          | Specific                                | LMIC References | High-income References |
|------------------|-----------------------------------------|-----------------|------------------------|
| LTBI             | Years of work                           | 44,45,47,58,80-82 | 37                     |
|                  | TB admissions                           | —               | 37                     |
|                  | Known TB contact                        | 43,58           | 18,37,83              |
| Type of work     | Health care/patient care                | 45,84           | 83,85                  |
|                  | Physicians                              | 80,86           | 37,87                  |
|                  | Nurses                                  | 45,80,86        | 21,37,85,88           |
|                  | Respiratory therapists                   | 58              | 85                     |
|                  | Trainees                                | —               | 18                     |
| Location of work | Medical ward                            | 58,81,89        | 21,88                  |
|                  | HIV ward/care                           | —               | 21                     |
|                  | Emergency                               | 86              | 16                     |
|                  | Laboratory/pathology                    | 86              | 88,90                  |
|                  | TB ward/clinic                          | —               | 18                     |
| TB disease       | Exposures                               | —               | —                      |
| Type of work     | Health care/patient care                | —               | 49,50,53,56           |
|                  | Physicians                              | 63,68,72,73     | 51,53,55              |
|                  | Nurses                                  | 61,63,67,68,70-73 | 52,53,55             |
|                  | Respiratory therapists                   | —               | 52                     |
|                  | Trainees                                | —               | 54                     |
| Location of work | Medical ward                            | 58,70,72,91     | —                      |
|                  | TB ward/clinic                          | 58,59,62,66,70,72 | —                    |
|                  | HIV ward/clinic                         | —               | —                      |
|                  | Emergency                               | 58,70           | —                      |
|                  | Laboratory/pathology                    | 58,63           | —                      |
The identification of high-risk professionals such as respiratory therapists or pathology workers led to the realization that certain tasks were high-risk activities, such as bronchoscopy or autopsy. This finding in turn led to specific infection-control measures for these activities. The identification of increased risk associated with work in emergency departments resulted in administrative measures in these departments to improve triage and separation of patients suspected of TB.

**INTERVENTIONS TO PREVENT NOSOCOMIAL TB TRANSMISSION**

Interventions to prevent nosocomial TB transmission are generally divided into 3 broad categories: administrative, personal, and engineering.\(^7\) These categories are often referred to as a hierarchy of control measures. Administrative controls are institutional policies that have the general aim of reducing the time between arrival of a patient at a health care facility and their placement in respiratory isolation, definitive diagnosis, and initiation of effective treatment. These controls include rapid triage of patients suspected of active TB, rapid performance of chest radiographs or other screening tests, expeditious processing of sputum samples for acid-fast bacillus (AFB) smear and culture, and more rapid separation of patients with TB (usually in isolation rooms). Personal controls are measures directed at individual workers. These measures include use of personal respirators (masks) and screening for, and treatment of, latent or active TB. Engineering controls are environmental measures that act to reduce the likelihood of workers’ exposure to viable airborne TB bacilli. These controls include ventilation to remove and/or dilute airborne bacilli, and to ensure correct direction of flow of contaminated air, and ultraviolet germicidal irradiation (UVGI), which kills airborne bacilli.

As shown in Table 3, several studies have examined the effect on indicators of nosocomial transmission when multiple interventions were applied simultaneously. Harries and colleagues\(^{65}\) implemented a program in 40 facilities in Malawi to train workers to triage, and separate patients with TB, and to enhance natural ventilation. These efforts resulted in a modest decline in overall TB incidence, which was not statistically significant. However, compliance with these measures was suboptimal. In Thailand, 1202 health care workers had serial tuberculin testing before and after administrative, personal, and engineering measures were instituted in one provincial referral hospital. Incidence of LTBI declined substantially but incidence of disease increased.\(^{47}\) However, the increase in disease may have been a result of a concomitant increase in HIV prevalence, and because the number of patients with TB almost doubled at the same time. In 2 Brazilian hospitals incidence of TST conversion was 8 per 1000 person-months following implementation of the full hierarchy of administrative, personal, and engineering controls, compared with 16 per 1000 person-months in 2 other hospitals without any TB infection-control measures.\(^{45}\)

Delays in institution of adequate isolation, or diagnosis and institution of effective therapy, have been consistently identified as important factors in almost all reports of nosocomial TB outbreaks.\(^5\) The importance of administrative measures has been identified in a modeling study,\(^{107}\) but the epidemiologic evidence of the effectiveness of these measures is limited, because, as shown in Table 4, few studies have implemented these measures alone. In one Italian hospital, the occurrence of new MDR disease among patients was eliminated after implementation of administrative measures alone.\(^{108}\) In a US hospital TST conversion was reduced 80% by administrative measures alone.\(^{109}\) In the Malawi study most of the changes were administrative; these had minimal effect, but as noted earlier, compliance with the measures was poor.\(^{65}\) In 2 US hospitals administrative measures were introduced first, and interim
tuberculin testing was performed before implementation of the rest of the infection control measures. In both hospitals incidence of TST conversion decreased significantly after the implementation of the administrative measures.\textsuperscript{110,111} Administrative controls are the cheapest and simplest measures to implement, and all evidence suggests that they are effective and important. Hence, implementation of administrative control measures should be the first priority in all health care facilities.

Personal respirators or masks were the subject of considerable confusion in the early 1990s. Infection control and occupational health practitioners, regulatory agencies, and researchers struggled with conflicting recommendations and confusing terminology regarding personal respirators. In 1994 a single standard was recommended: that personal respirators (masks) should filter at least 95% of particles of 1 μm or larger, with less than 10% face seal air leak.\textsuperscript{112} Respirators meeting these standards are referred to as N-95. Given that TB bacilli are 3 to 5 μm in length, these masks should filter at least 95% of TB bacilli out of the air inhaled by health care workers. Modeling studies have concluded that personal respirators should work well.\textsuperscript{113} On the other hand, there is no epidemiologic evidence of their effectiveness. No studies have been published in which only personal respirators were implemented. Some modeling studies have found that the effect of personal respirators is modest if they are used in a setting with proper engineering control measures.\textsuperscript{114} Fit testing of personal respirators is particularly controversial because studies have shown that the results of fit testing are not reliable or reproducible.\textsuperscript{115,116} Nevertheless, most regulatory authorities and most health care institutions insist on fit testing because in theory a better-fitting personal respirator should provide more protection than one that allows some leakage.

Virtually all TB transmission occurs indoors. The risk of TB transmission outdoors is considered virtually nil, because of the bactericidal effect of sunlight as well as the rapid dispersion and dilution of airborne bacilli.\textsuperscript{117} Ventilation can reduce the risk of indoor transmission by removal and dilution of airborne TB bacilli.\textsuperscript{118} As shown in Fig. 1, the concentration of any airborne particles, including TB bacilli, can be reduced effectively with greater air exchange rates. However, the incremental gains diminish as air exchange rates are progressively increased, and the energy costs and construction/capital costs to achieve these higher air exchange rates increase considerably.\textsuperscript{119} Natural ventilation, through open windows and doors, can achieve high air exchange rates,\textsuperscript{120} but the direction of airflow within the building is unpredictable, as it is largely determined by outdoor temperature and wind direction.\textsuperscript{85,121} This situation means that contaminated air from a TB patient’s room can move to other occupied areas including staff rooms and other patient rooms. Natural ventilation also has limitations when outdoor temperatures are very high or very low.

When properly designed and installed, mechanical ventilation can control direction of airflow and achieve adequate outdoor air exchange rates. However, the initial capital costs for mechanical ventilation systems are high, as are the operating costs. The latter reflect the need for trained personnel to operate mechanical ventilation systems constantly, and to inspect and maintain them regularly. Energy costs of mechanical ventilation can be substantial in very cold or very hot climates,\textsuperscript{119} particularly if high outdoor air exchange rates are mandated.

The effect of ventilation alone has been examined in only 3 studies, summarized in Table 5. In a Canadian study of 1274 workers in 17 hospitals, nurses and respiratory therapists who worked on units with ventilation of less than 2 air changes per hour in general patient rooms and wards (ie, nonisolation rooms) had a 3.8 times higher risk of tuberculin conversion than those who worked on units with better ventilation in general wards.\textsuperscript{92} Air exchange rates in respiratory isolation rooms were not associated with
| Author, Year Country Facilities Year of intervention | Preventive Strategy Used | Epidemiologic Measure in Absence of Preventive Measure | Epidemiologic Measure in Presence of Preventive Measure | Effect |
|---------------------------------------------------|--------------------------|--------------------------------------------------------|--------------------------------------------------------|--------|
| Harries 2002, Malawi 40 TB care facilities (1998) | Administrative: (1) Priority to patients with chronic cough in OPD (2) Rapid sputum collection, transport and reporting (3) Visitors kept to a minimum (4) CXR at quiet times of the day (5) Patients with TB spend more day time outdoors when possible Personal: (1) Proper cough hygiene (2) Mask worn by patients with TB when undergoing surgical procedures Engineering: (1) Increased natural ventilation (2) Windows left open most of the time | Incidence of TB disease before prevention (1996) Clin officer 7407 Pt attd 5014 Wd attd 3543 TB officer 3030 Nurses 2835 Overall 3707 | Incidence of TB disease after prevention (1999) Clin officer 3603 Pt attd 4348 Wd attd 3954 TB officer 1785 Nurses 2060 Overall 3222 | Incidence of TB disease declined after preventive measures used. Statistically NS |
| Yanai 2003, Thailand Provincial referral hospital (1997–98) | Administrative: (1) Early suspicion of TB (2) Early sputum collection and reporting (3) Early initiation of TB treatment (4) Isolation of patients with TB (5) One-stop OPD TB service Personal: (1) N95 mask use by HCWs (2) HEPA filter in laboratory areas Engineering: (1) TB isolation room in wards (2) Maximizing ventilation in wards (3) Class II safety cabinets in laboratory (4) UVGI system in laboratory | Incidence of TB disease control measures (1995–1999) All HCWs 179.21 Annual incidence of LTBI before control measures (1995–97) 9.3% (3.3%–15.3%) | Incidence of TB disease after control measures (1999) All HCWs 252.68 Annual incidence of LTBI after control measures (1999) 2.2% (0%–5.1%) | Increase in TB disease Statistically NS Decrease in LTBI rates Statistically significant |
| Roth 2005, Brazil. 2 hospitals with, and 2 without control measures (1998) | Administrative: (1) Rapid diagnosis and treatment of Patients with TB (2) Isolation of patients with TB in private rooms Personal: (1) N95 mask use by HCWs (2) HEPA filter in laboratory areas Engineering: (1) Negative pressure rooms (one hospital) (2) Class II biosafety cabinets in laboratory areas | Incidence of LTBI in 2 hospitals without control measures (1998–99) 16 per 1000 person-months | Incidence of LTBI in 2 hospitals with control measures (1998–99) 8 per 1000 person-months | Difference in LTBI rates Statistically significant |
| Author, Year | Workers, Year of Intervention | TST Baseline Conversion Definition | Infection Control Strategy Used | Outcomes |
|--------------|-------------------------------|------------------------------------|-------------------------------|----------|
| **High-Income Countries** |                               |                                    |                               |          |
| Wenger, 1990 | United States, 1991           | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: ↑ Isolation, ↑ Speed for AFB, Sputum induction in respiratory isolation rooms. Personal: TST every 4 mo, Sub-μm masks, Dust-mist masks. Engineering: Auto door closers, Negative pressure isolation rooms. | Conv/tested ARI, 7/25 28%, 3/17 18% |
| Maloney, 1991 | United States, 1991           | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: ↑ Isolation, ↑ Treatment, ↑ Speed for AFB. Personal: Molded surgical masks, Window exhaust fans. Engineering: Window exhaust fans, Upper-air UV light. | Conv/tested ARI, 26/840 3.1%, 22/727 3.0% |
| Fella, 1991 | United States, 1991–1993      | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: ↑ Isolation. Personal: Better mask (dust-mist), Window exhaust fans, Upper air UV light. Engineering: Window exhaust fans, Upper-air UV lights. | Conv/tested ARI, 30/145 21%, 51/1007 5.1% |
| Bangsberg, 1992 | United States, 1992         | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: ↑ Isolation. Personal: Respiratory masks, Negative pressure rooms in ER+OPD, Upper-air UV lights. Engineering: Window exhaust fans. | Conv/tested ARI, 11/90 5.4%, 1/90 0.7% |
| Blumberg, 1992 | United States, 1991–1992      | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: ↑ Isolation. Personal: Better masks, TST every 6 months, Sub-μm masks, Sputum induction booth, UV lights. Engineering: Window exhaust fans. | Conv/tested ARI, 118/3579 3.3%, 185/17618 1.1% |
| Boudreau, 1997 | United States, 1989–1992     | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: Drug therapy improved, ↑ Isolation procedures, Worker education. Personal: Better masks, Sputum induction booth, UV lights. Engineering: ARI in HCW. | ARI in HCW, 6.9% 1.9% |
| Blumberg, 1998 | United States, 1992–1997      | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: Isolation procedures, TB infection control nurse. Personal: Better masks, TST of HCWs. Engineering: 50 respiratory isolation rooms. | ARI in HCW, 6% 1.1% |
| Louther, 1997 | United States, 1991–1994      | 1-Step: T₁<10, T₂≥10 mm, TST ≥10 mm and ↑ 6+ mm | Administrative: ↑ Isolation. Personal: Better masks, ↑ Ventilation. Engineering: ARI in HCW. | ARI in HCW, 7.2% 4.8% |

**Abbreviations:** ARI, annual risk of infection; Clin officer, clinical officer; Conv, conversions; CXR, chest radiograph; ER, emergency room; HCW, health care worker; HEPA, high-efficiency particulate air; NS, nonsignificant; OPD, outpatient department; Pt attd, patient attendant; Wd attd, ward attendant.

* Single rooms, R6 air changes per hour, negative pressure or inward airflow, automatic door closing.
workers’ tuberculin conversion rates. In the same study laboratory workers had greater rates of tuberculin conversions if they worked in laboratories or autopsy suites with lower ventilation levels. A single study has reported on TST conversion rates before and after improvements in ventilation only. In the emergency department of a US hospital, 4 respiratory isolation rooms were created, recirculation of air was eliminated, and laminar airflow introduced. Following these measures tuberculin conversion declined substantially among staff in the emergency department and in other departments (possibly because of reduced recirculation of air from the emergency departments to these other departments).

UVGI is an older technology that was evaluated extensively in the preantibiotic era. With the advent of effective antibiotic therapy, UVGI fell into disuse (along with most aspects of TB infection control). UVGI also fell into disrepute because of concerns regarding skin cancer. These concerns were completely unfounded because the type of ultraviolet irradiation generated by the lamps (UV-C) does not penetrate the skin and so cannot cause mutagenesis in the skin. Direct exposure to UVGI can cause skin rash (similar to sunburn) and keratoconjunctivitis (similar to snow blindness). Outbreaks of both conditions have been reported, and all have been mild and self-limited. In every instance these outbreaks were caused by errors in the installation, or operation of the lamps.

Modern lamps are designed to minimize risk of direct exposure. Usually these are installed above eye level in rooms with reflectors so that only the upper air in the

| Author (References) | Country | Year of Intervention | Effect Measured in | Outcome Measure | Before | After |
|---------------------|---------|---------------------|--------------------|----------------|--------|-------|
| Moro108             | Italy   | 1993                | Patients           | New MDR disease | 26/90  | 0/44  |
| Jarvis109           | United States | 1995   | HCWs               | TST conversion  | 14.6%  | 2.9%  |

Abbreviation: HCW, health care worker.

Fig. 1. Percent of airborne bacteria remaining after 1 hour of ventilation at different exchange rates.
Table 5
Effect of ventilation on nosocomial TB transmission (studies in which effect of ventilation alone was studied)

| Author (References) | Country | Year of Intervention | Ventilation | Outcome Measure | Type | N  | Lower Ventilation | Higher Ventilation |
|---------------------|---------|----------------------|-------------|-----------------|------|----|-------------------|-------------------|
| Menzies^90,92       | Canada  | 1996–98              | Mechanical  | Relative risk of cumulative TST conversion | Nurses, respiratory therapists, laboratory workers | 1270 | 3.8               | 1.0               |
|                     |         |                      |             |                 |      |    |                   |                   |
| Behrman^16          | United States | 1993–96  | 4 respiratory isolation rooms, non-recirculating air laminar airflow | TST conversion per 6 months | Emergency department staff, other departments | 88 | 10.5% | 0 |
|                     |         |                      |             |                 |      |    |                   |                   |
|                     |         |                      |             |                 |      |    |                   |                   |

Health Care Workers and Nosocomial Infections 663
room is irradiated. Occasionally such lamps have caused eye irritation as a result of reflected UV light from glossy ceilings.\textsuperscript{122} This reflection can be eliminated by use of low-gloss ceiling paint or louvered lamps so that the UV light is emitted only in a narrow beam in the upper air. Effectiveness of UVGI is summarized in Table 6. Effect of UVGI installation on TST conversion among hospital workers has been reported in 4 studies. In all 4, the incidence of tuberculin conversion declined substantially, but this may have been a result of other interventions, because UVGI was one of several interventions introduced at the same time. Two studies have irradiated upper air in rooms of patients with TB with UVGI; the air exhausted from these rooms was fed through an animal enclosure. In both studies, animals exposed to air from rooms with UV irradiation had substantially reduced incidence of TB infection and disease.\textsuperscript{123,124,128} In vitro studies have also shown the high potency of UVGI in reducing the number of viable airborne BCG,\textsuperscript{129} or viable mycobacterial cultures in solid media. Despite solid animal evidence of efficacy and clear evidence that it is safe for humans, authoritative agencies remain reluctant to endorse use of UVGI. As summarized in Table 7, UVGI has many advantages compared with mechanical ventilation in terms of proven effectiveness, low initial and recurrent costs, as well as proven safety, yet authoritative agencies continue to recommend it only as an adjunct measure.

SARS

The SARS epidemic from November 2002 until July 2003 provided many important observations regarding determinants and prevention of nosocomial transmission. Interest in infection control with SARS was high because no effective vaccine or treatment was available at the time of the epidemic, and a high proportion of all SARS cases occurred as a result of nosocomial transmission. Ultimately the epidemic subsided following strict enforcement of control measures within health care facilities and in the community. Hence, this epidemic provides many important lessons that are applicable for prevention of nosocomial transmission of TB and influenza.

Several features of SARS were unusual. First, the incubation period was longer than typical for influenza or other respiratory tract viral infections (4–6 days instead of 1–2 days; see Table 8) and the course of the illness was slower.\textsuperscript{147} Of particular relevance for nosocomial transmission, in most patients the viral load and viral shedding increased to a peak about 10 to 12 days after the onset of symptoms, following which there was a slow decline.\textsuperscript{146,147} Because patients typically sought medical care and were hospitalized after a few days of symptoms they became progressively more contagious after their arrival in health care facilities. This situation may have accounted for the disproportionate share of transmission that occurred within health care facilities; it was estimated that 78% of all cases in Singapore, among patients and health care workers, resulted from nosocomial transmission.\textsuperscript{150} Overall, health care workers accounted for 21% of all cases,\textsuperscript{132} although in most countries they account for only 2% to 3% of the adult population. A rough estimate is that the risk of disease in health care workers was approximately 10-fold higher than the general population. A similar estimate can be derived from Hong Kong, where there was more extensive community transmission, yet the rates in health care workers were more than 10 times higher than the community rates in the worst affected areas.\textsuperscript{141}

This situation is similar to TB in high-income countries; community transmission is rare, and patients are often hospitalized when they present with symptoms. After admission, contagiousness and transmission often increase, because the diagnosis is missed or delayed by days to weeks.\textsuperscript{156}
Table 6
Effect of improved UVGI only on nosocomial TB transmission

| Author (References) | Country     | Year of Intervention | Intervention Measured in | Type    | N    | Outcomes       | Before UVGI | After UVGI | Reduction (%) |
|---------------------|-------------|----------------------|--------------------------|---------|------|----------------|-------------|------------|---------------|
| Studies of HCWs^a   |             |                      |                          |         |      |                |             |            |               |
| Bourdeau^18         | United States | 1989–91              | All HCWs                 | TST conv/y | 21%  | 5.1%            |             |            | 76            |
| Fella^104           | United States | 1991                 | All HCWs                 | TST conv/y | 6.9% | 1.9%            |             |            | 72            |
| Bangsberg^105       | United States | 1991–92              | Trainees (residents)     | TST conv/y | 5.4% | 0.7%            |             |            | 87            |
| Yanai^b,47          | Thailand    | 1997–98              | All HCWs                 | TST conv/y | 9.3% | 2.2%            |             |            | 76            |
| Studies of laboratory animals |           |                      |                          |         |      |                |             |            |               |
| Riley^123           | United States | 1957                 | Guinea pigs              | ns      | BCG infection | 100%  | 0   | 100            |
| Escombe^124         | Peru        | 2008                 | Guinea pigs              | 150     | MTB infection | 106   | 29  | 72            |
|                     |             |                      |                          |         | MTB disease    | 26    | 11  | 60            |
| Studies of microbes |             |                      |                          |         |      |                |             |            |               |
| Ray^125             | United States | 1957                 | Culture plates           | Viable MTB | 150-350 | 15–30 | 90  |               |
| Riley^126           | United States | 1976                 | Airborne BCG            | BCG killing | 9      | 1     | 90  |               |
| Xu^127              | United States | 2003                 | Airborne BCG            | Viable airborne BCG | 5.7 $\times$ 10^4 | 3.2 $\times$ 10^3 | 96  |               |

Abbreviations: conv, conversions; HCW, health care worker; MTB, *Mycobacterium tuberculosis*.

^a All 4 studies in health care workers involved multiple interventions applied concurrently. Hence, the reduction seen may have been caused by other interventions (partially or entirely).

^b UVGI applied in laboratory areas only. In this study there was no reduction in incidence of disease.
Another feature of the SARS epidemic was that a few patients were identified as more contagious than others, so-called superspreaders of the epidemic (SSEs).\textsuperscript{137,152,157} One of these persons transmitted SARS to several others on the same floor in a hotel,\textsuperscript{141} and another to more than 50 others living in the same apartment complex but different buildings.\textsuperscript{137} Neither patient had any direct contact with these secondary cases, supporting the possibility of airborne spread. Reasons for this contagiousness were not identified, but again there is a close parallel with TB. In several studies, the contagiousness of patients with TB has varied widely.\textsuperscript{123,158,159} Although contagiousness is generally correlated with extent of pulmonary disease, it is substantially increased if there is laryngeal involvement.\textsuperscript{123,159} One can only speculate why the phenomenon of SARS superspreaders occurred, but it seems these few patients were efficient generators of infectious aerosols.

Delayed diagnosis was common to all outbreaks of SARS, as with TB. Triage and separation of patients proved important in containing SARS epidemic, as shown in Table 9, another parallel with TB. Other administrative measures, particularly

| Parameters | Mechanical Ventilation | UVGI |
|------------|------------------------|------|
| Maximum air exchange rate\textsuperscript{a} | 12–15 | 20–25 |
| Effectiveness | — | — |
| Proved | — | — |
| In workers | Partially | Partially |
| In animals | No | Yes |
| In vitro | No | Yes |
| Safety | — | — |
| In theory | Yes | Yes |
| Shown in workers | No | Yes |
| Costs | — | — |
| Initial capital costs | Very high | Moderate |
| Recurrent costs | — | — |
| Maintenance | High | Low |
| Energy | Moderate-High | Low |
| Personnel (operation) | Moderate | None |
| Personnel (inspection) | Low | Low |

Recommendations (reference)

| Parameters | United States\textsuperscript{7} | Canada\textsuperscript{130} | WHO\textsuperscript{8} |
|------------|---------------------------------|--------------------------|---------------------|
| Primary mode | Use when recommended ventilation cannot be achieved | Use when recommended ventilation cannot be achieved |

\textsuperscript{a} Maximum outdoor air exchange rate that can reasonably be achieved in occupied spaces, yet maintain noise, draft, and temperature within human comfort range. For UVGI this refers to the removal of viable airborne organisms that would be achieved with equivalent levels of ventilation.
isolation of symptomatic health care workers, limited the health care workers as a source of nosocomial transmission, an important message for influenza control (see later discussion). Personal protective measures seemed the most important in containing the spread of SARS. In almost all situations in which full protective measures were implemented, there was no further nosocomial transmission.\textsuperscript{135,145} In an analysis of workers who became infected with SARS despite using full personal protective equipment, lapses or breaches in infection-control procedures were found that could explain every apparent failure.\textsuperscript{142} In one ward in a Hong Kong hospital, more than 20 patients were placed on noninvasive positive ventilation, a significant Table 8

| Features                        | Influenza A | SARS |
|---------------------------------|-------------|------|
| **Incubation**                  | 1.4 days\textsuperscript{131} | 4.6–6.4 days\textsuperscript{132,133} |
| **Transmission**                |             |      |
| Mode                            | Primary droplet\textsuperscript{134} | Primary droplet\textsuperscript{132} |
|                                 | Possible contact\textsuperscript{134,136} | Fecal-oral\textsuperscript{135} |
|                                 | Possible airborne\textsuperscript{134,136} | Possible contact\textsuperscript{135} |
|                                 |             | Possible airborne\textsuperscript{137,138} |
| **Asymptomatic**                | Minimal\textsuperscript{139} | None\textsuperscript{140,141} |
| **Increased by**                | Intubation  | Intubation\textsuperscript{142–144} |
|                                 |             | NIPPV\textsuperscript{144,145} |
| **Infectiousness (new infections per case)** | 1.8–20.0 | 2.4–2.7\textsuperscript{146,147} |
| **Duration of contagiousness**  | 3 days\textsuperscript{b,131} | 10–20 days\textsuperscript{146,147} |
| **Nosocomial transmission**     |             |      |
| Outbreaks shown                 | Yes\textsuperscript{139,148,149} | All reports |
| % Nosocomial                     | Unknown–low\textsuperscript{148,149} | 78% in Singapore\textsuperscript{150} |
| **Transmission to HCWs**        | No estimates | 1%–3% per h\textsuperscript{143,151} |
| **HCW as % of all cases**       | No estimates | 21%\textsuperscript{132} |
| **Incidence**                   |             |      |
| Total global cases              | 401, 276 (H1N1, as of September 25, 2009)\textsuperscript{c} | 8098 (as of July 2003)\textsuperscript{132} |
| Severity (% admitted to ICU)    | 3.8% (Quebec) | 19%–34%\textsuperscript{132,141,152} |
| Mortality (overall)             | 1.1%\textsuperscript{153} | 9.6%\textsuperscript{132} |
| age <60 y                       | — | 2.9%–7.0%\textsuperscript{141,143} |
| age >60 y                       | — | 53%–55%\textsuperscript{141,143} |
| HCWs (all ages)                 | — | 2%\textsuperscript{141} |

Abbreviations: HCW, health care worker; ICU, intensive care unit; NIPPV, nasal intermittent positive pressure ventilation.

\textsuperscript{a} Noninvasive positive pressure ventilation such as continuous positive airway pressure or bilevel positive airway pressure.

\textsuperscript{b} Contagiousness estimate for nonimmunocompromised adult. Duration is longer if immunocompromised,\textsuperscript{154} severely ill\textsuperscript{155} or young infant.\textsuperscript{154}

\textsuperscript{c} US estimates were that more than 1 million cases had occurred in the United States alone by September 12, 2009.\textsuperscript{153}
risk factor for aerosolization of infectious particles. All workers on this ward were required to be meticulous in their infection-control procedures and use of personal protective equipment; despite the intense exposure, none became infected with SARS.

One controversial issue with regard to personal protective measures remains the type of respiratory protection, or masks. In one survey, nonuse of masks was clearly associated with increased risk of SARS, whereas in another use of either surgical or N-95 masks was protective, although use of paper masks was not. In a Toronto study, use of N-95 masks was associated with greater protection than use of surgical masks, and both type of masks were associated with greater protection than no masks.

| Influence Control Measures | Influenza Studies Showing Benefit, N (References) | SARS Studies Showing Benefit, N (References) |
|----------------------------|--------------------------------------------------|---------------------------------------------|
| Administrative             |                                                  |                                             |
| Triage/separation of patients | 2154,160                                         | 2135,150                                    |
| Reduce crowding            | 1136                                             | 1144                                        |
| Screen/furlough sick workers | 2154,161                                         | 2144,150                                    |
| Personal                   |                                                  |                                             |
| Vaccination of health care worker | 3162–164                                        | No vaccine available                        |
| Knowledge/training in infection control | —                                               | 1165                                        |
| Hand washing               | —                                                | 2144,166                                    |
| Masks: surgical or N-95    | 1167, a                                          | 2151,166, b,c                              |
| Compliance with all measures | —                                              | 3142,165,166                                |
| Engineering                |                                                  |                                             |
| UVGI                       | 1168                                             | —                                           |
| Ventilation (risk factor, not intervention) | 2136,169                                         | 1 (Ha 2004)                                 |
| Full hierarchy of measures | 1160                                             | 2143,150                                    |
| Most important measure     | Vaccination                                      | Infection control                           |

a Loeb 2009: Randomized controlled trial of surgical versus N-95 masks: no difference in seroconversion of workers.
b Seto 2003: paper masks were not effective; surgical and N-95 were not different.
c Loeb 2004: N-95 masks were better than surgical masks, which were better than no masks.
that superspreaders are identified only in retrospect, it may be more prudent for workers to wear N-95 masks at all times.

Ventilation of occupied indoor spaces is important for diluting and removing airborne contaminants. This practice can help prevent nosocomial transmission of airborne pathogens. As reviewed earlier there is some evidence that SARS could be transmitted by the airborne route; this was the most plausible explanation for the community outbreak. The ward in which nasal intermittent positive pressure ventilation was used achieved high air exchange rates with exhaust fans, which may have helped prevent nosocomial transmission. The efficacy of UVGI was not studied with SARS.

INFLUENZA

There is less information regarding the determinants, and effective prevention, of nosocomial transmission. This situation reflects the availability, for more than 20 years, of an effective vaccine. Also, influenza is typically less severe, with lower case fatality rates than SARS. Influenza also has a shorter incubation period, so that patients are more quickly contagious during the symptomatic phase than with SARS. Hence, there is greater community transmission, making it difficult to identify and study nosocomial influenza transmission. The new pandemic of H1N1, which spread rapidly through air travel, and caused millions of cases, before a vaccine became available, underscores the importance of understanding the determinants of nosocomial transmission of influenza, to implement effective infection control.

The effect of nosocomial transmission of influenza is difficult to estimate but there have been well-documented outbreaks in nursing homes, intensive care units, and general medical facilities. Attack rates in these outbreaks ranged from 11% to 59% overall, and from 8% to 63% in exposed health care workers. Mortality among patients ranged from 0% to 66%, with highest mortality among elderly nursing home residents and very young infants. Individuals with other immunocompromising conditions are also highly susceptible. An additional problem created by nosocomial influenza transmission is the large number of health care workers who may become ill and unable to work. Their absenteeism may create significant problems in delivery of care, at a time when they are needed most.

As with SARS and TB, delayed diagnosis of cases is a common feature of nosocomial influenza outbreaks. In these outbreaks, health care workers were the most commonly identified source cases, as well as frequently playing a major role in spreading the infection from patient to patient. Two studies have reported that screening workers to identify those with influenza and send them home was an effective measure to prevent nosocomial outbreaks.

Little attention has been given to the importance of personal protective equipment such as gowns, gloves, and masks in practice and in guidelines for prevention and management of influenza. This situation is because vaccination of health care workers has been shown to reduce or prevent nosocomial transmission. In one randomized trial, vaccinating health care workers reduced mortality among elderly people in nursing homes. Treatment of influenza with antivirals is effective for individual benefit, but the effect of antiviral therapy on community or nosocomial transmission has not been studied.

The role of airborne transmission of influenza in nosocomial outbreaks is controversial, because the evidence is limited. As reviewed elsewhere, there is convincing animal and in vitro evidence that airborne transmission of influenza can occur. There is also evidence from a limited number of outbreaks that supports the role of airborne
transmission. As with SARS and TB, a few individuals may be extremely contagious and contribute to airborne transmission, or particularly contagious during aerosol-generating procedures such as intubation or noninvasive ventilation. Given this uncertainty, it seems prudent for nonvaccinated workers to use N-95 masks, particularly during high-risk procedures or with very ill patients.

There is limited evidence, from an older study, that upper-air UVGI is effective in reducing influenza transmission rates. Upper-air UVGI was also shown to be effective in reducing measles transmission among schoolchildren.

**SUMMARY**

1. The risk of TB infection in health care workers is 5 to 10 times greater than that in the general population, and risk of disease is 2 to 5 times higher. Risk factors for TB infection and disease are mostly associated with greater risk of exposure to patients with TB, particularly undiagnosed patients. Some risk factors relate to specific work activities that can cause aerosolization of TB bacilli.

2. The simplest, cheapest, and quickest interventions to implement, with proven effectiveness, are the administrative measures of triage and separation of patients. These measures should be a part of all TB infection-control programs in all health care facilities.

3. There is little direct evidence for the effectiveness of N-95 personal respirators for protection against occupational TB. Nevertheless, on theoretic grounds alone, their use is supported.

4. There are sound theoretic reasons why air exchange (ventilation) should help reduce nosocomial TB transmission. There is evidence from several observational studies and one interventional study that higher levels of ventilation reduce risk of TB transmission. Natural ventilation can achieve high air exchange rates and should be effective as well as feasible in health facilities in LMIC. However, resultant airflow patterns within buildings are unpredictable, so natural ventilation may result in inadvertent exposure of workers or other patients.

5. UVGI is grossly underused. This is a low-cost, simple, and safe technology. All available evidence suggests that it should be safe and highly effective in reducing nosocomial TB transmission.

6. There are few epidemiologic studies on the effectiveness of infection control measures, alone or in combination, and their effect on reducing nosocomial TB transmission.

7. For the prevention of nosocomial transmission of influenza, the most important action is vaccination of health care workers. However, if an effective vaccine is not available, then other infection-control measures become of paramount importance. For TB, SARS, and influenza, delayed diagnosis (or delayed institution of an effective treatment, if available) is the most common and important factor in nosocomial transmission. Hence, the most important measures are to promptly identify patients with these illnesses and separate them from other patients and from susceptible health care workers.

8. Personal protective equipment including gowns, masks, and gloves is important to prevent transmission by droplet. This is a major mechanism of transmission for SARS and influenza, so should be the major method of protection for health care workers and prevention of spread by health care workers from one patient to another.

9. However, there is clear evidence that airborne transmission of influenza and SARS can occur. Transmission is most likely during performance of procedures that
cause aerosolization of infectious droplets, or with severely ill patients. Therefore, N-95 personal respirators, which should be more effective in preventing acquisition of airborne infections, should be used by workers caring for severely ill patients, or workers performing aerosol-generating procedures. In addition, these patients should be cared for, and procedures performed, in rooms with adequate ventilation and/or upper-air UVGI, as these environmental measures can further reduce the risk of airborne transmission.

REFERENCES

1. Menzies D, Doherty TM. Diagnosis of latent tuberculosis infection. In: Raviglione MC, editor. Reichman and Hershfield’s tuberculosis, a comprehensive international approach. New York: Informa Healthcare USA; 2006. p. 215–63.

2. Harrington JM, Shannon HS. Incidence of tuberculosis, hepatitis, brucellosis, and shigellosis in British medical laboratory workers. Br Med J 1976;1:759–62.

3. Joshi R, Reingold A, Menzies D, et al. Tuberculosis among healthcare workers in low and middle income countries: a systematic review. PLoS Med 2006;3(12):e494.

4. Sepkowitz K. Tuberculosis and the health care worker: a historical perspective. Ann Intern Med 1994;120:71–9.

5. Menzies RI, Fanning A, Yuan L. Tuberculosis among health care workers. N Engl J Med 1995;332:92–8.

6. Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. Int J Tuberc Lung Dis 2007;11(6):593–605.

7. Centers for Disease Control. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. MMWR Recomm Rep 2005;54(RR–17):1–141.

8. World Health Organization, Stop TB Department. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva (Switzerland): World Health Organization; 2009.

9. Menzies D, Pai M, Comstock GW. New tests for diagnosis of latent tuberculosis infection - areas of uncertainty and recommendations for research. Ann Intern Med 2007;146(5):340–54.

10. Pai M, Zwerling A, Menzies D. Systematic review: T-cell based assays for the diagnosis of latent tuberculosis infection–an update. Ann Intern Med 2008;149(177):184.

11. Pai M, Joshi R, Dogra S, et al. T-cell assay conversions and reversions among household contacts of tuberculosis patients in rural India. Int J Tuberc Lung Dis 2009;13(1):84–92.

12. Pai M, Joshi R, Dogra S, et al. Serial testing of health care workers for tuberculosis using interferon-gamma assay. Am J Respir Crit Care Med 2006;174(3):349–55.

13. Adal KA, Anglim AM, Palumbo CL, et al. Preventing nosocomial tuberculosis with HEPA respirators: a cost-effectiveness analysis. N Engl J Med 1994;331(3):169–73.

14. Aitken ML, Anderson KM, Albert RK. Is the tuberculosis screening program of hospital employees still required? Am Rev Respir Dis 1987;136:805–7.

15. Baussano I, Bugiani M, Caros ELA, et al. Risk of tuberculin conversion among healthcare workers and the adoption of preventive measures. Occup Environ Med 2007;64(3):161–6.
16. Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. Ann Emerg Med 1998;31(3):370–5.
17. Blumberg HM, Sotir M, Erwin M, et al. Risk of house staff tuberculin skin test conversion in an area with a high incidence of tuberculosis. Clin Infect Dis 1998;27:826–33.
18. Bourdreaux AY, Baron SL, Steenland NK, et al. Occupational risk of Mycobacterium tuberculosis infection in hospital workers. Am J Ind Med 1997;32:528–34.
19. Chan CC, Tabak JI. Risk of tuberculous infection among house staff in an urban teaching hospital. South Med J 1985;78:1061–4.
20. Christie CD, Constantinou P, Marx ML, et al. Low risk for tuberculosis in a regional pediatric hospital: nine-year study of community rates and the mandatory employee tuberculin skin-test program. Infect Control Hosp Epidemiol 1998;19:168–74.
21. Dooley SW, Villarino ME, Lawrence M, et al. Nosocomial transmission of tuberculosis in a hospital unit for HIV-infected patients. JAMA 1992;267(19):2632–4.
22. Fraser VJ, Kilo CM, Bailey TC, et al. Screening of physicians for tuberculosis. Infect Control Hosp Epidemiol 1994;15(2):95–100.
23. Lainez RM, Consul M, Olona M, et al. Tuberculous infection in nursing students: prevalence and conversion during a 3-year follow-up. Med Clin 1999;113(18):685–9.
24. Larsen NM, Biddle CL, Sotir MJ, et al. Risk of tuberculin skin test conversion among health care workers: occupational versus community exposure and infection. Clin Infect Dis 2002;35(7):796–801.
25. LoBue PA, Catanzaro A. Effectiveness of a nosocomial tuberculosis control program at an urban teaching hospital. Chest 1998;113(5):1184–9.
26. Louther J, Riviera P, Feldman J, et al. Risk of tuberculin conversion according to occupation among health care workers at a New York City hospital. Am J Respir Crit Care Med 1997;156:201–5.
27. Manusov EG, Bradshaw RD, Fogarty JP. Tuberculosis screening in medical students. Fam Med 1996;28(9):645–9.
28. Menzies D, Fanning A, Yuan L, et al. The Canadian Collaborative Group in Nosocomial Transmission of Tuberculosis. Tuberculosis in health care workers: a multicentre Canadian prevalence survey: preliminary results. Int J Tuberc Lung Dis 1998;2(9):S98–102.
29. Plitt SS, Soskolne CL, Fanning EA, et al. Prevalence and determinants of tuberculin reactivity among physicians in Edmonton, Canada: 1996–1997. Int J Epidemiol 2001;30(5):1022–8.
30. Price LE, Rutala WA, Samsa GP. Tuberculosis in hospital personnel. Infect Control 1987;8:97–101.
31. Ramirez JA, Anderson P, Herp S, et al. Increased rate of tuberculin skin test conversion among workers at a university hospital. Infect Control Hosp Epidemiol 1992;13(10):579–81.
32. Ruben FL, Norden CW, Schuster N. Analysis of a community hospital employee tuberculosis screening program 31 months after its inception. Am Rev Respir Dis 1977;115:23–8.
33. Rullan JV, Herrera D, Cano R, et al. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in Spain. Emerg Infect Dis 1996;2(2):125–9.
34. Stuart RL, Bennett NJ, Forbes AB, et al. Assessing the risk of tuberculosis infection among healthcare workers: the Melbourne Mantoux Study. Melbourne Mantoux Study Group. Med J Aust 2001;174(11):569–73.
35. Bailey TC, Fraser VJ, Spitznagel EL, et al. Risk factors for a positive tuberculin skin test among employees of an urban, midwestern teaching hospital. Ann Intern Med 1995;122:580–5.

36. Vogeler DM, Burke JP. Tuberculosis screening for hospital employees: a five-year experience in a large community hospital. Am Rev Respir Dis 1978;117:227–32.

37. Zahnow K, Matts JP, Hillman D, et al. Rates of tuberculosis infection in healthcare workers providing services to HIV-infected populations. Terry Beirn Community Programs for Clinical Research on AIDS. Infect Control Hosp Epidemiol 1998;19(11):829–35.

38. Zarzuela-Ramirez M, Cordoba-Dona JA, Perea-Milla E, et al. Factors associated with tuberculin conversion among staff at a university-affiliated hospital. Infect Control Hosp Epidemiol 1999;20(9):589–90.

39. Bonifacio N, Saito M, Gilman RH, et al. High risk for tuberculosis in hospital physicians, Peru. Emerg Infect Dis 2002;8(7):747–8.

40. Corbett EL, Muzangwa J, Chaka K, et al. Nursing and community rates of Mycobacterium tuberculosis infection among students in Harare, Zimbabwe. Clin Infect Dis 2007;44(3):317–23.

41. Hohmuth BA, Yamanjia JC, Dayal AS, et al. Latent tuberculosis: risks to health care students at a hospital in Lima, Peru. Int J Tuberc Lung Dis 2006;10(10):1146–51.

42. Lopes LK, Teles SA, Souza AC, et al. Tuberculosis risk among nursing professionals from Central Brazil. Am J Infect Contr 2008;36(2):148–51.

43. Maciel EL, Viana MC, Zeitoune RC, et al. Prevalence and incidence of Mycobacterium tuberculosis infection in nursing students in Vitoria, Espirito Santo. Rev Soc Bras Med Trop 2005;38(6):469–72.

44. Pai M, Gokhale K, Joshi R, et al. Mycobacterium tuberculosis infection in health care workers in rural India – comparison of a whole-blood interferon gamma assay with tuberculin skin testing. JAMA 2005;293(22):2746–55.

45. Roth VR, Garrett DO, Laserson KF, et al. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals. Int J Tuberc Lung Dis 2005;9:1335–42.

46. Silva VM, Cunha AJ, Oliveira JR, et al. Medical students at risk of nosocomial transmission of Mycobacterium tuberculosis. Int J Tuberc Lung Dis 2000;4(5):420–6.

47. Yanai H, Limpakarnjanarat K, Uthaivoravit W, et al. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis 2003;7(1):36–45.

48. Center for Disease Control. Proportionate mortality from pulmonary tuberculosis associated with occupations–28 states, 1979–1990. MMWR Morb Mortal Wkly Rep 1995;44(1):14–9.

49. Diehl R, Seidler A, Nienhaus A, et al. Occupational risk of tuberculosis transmission in a low incidence area. Respir Res 2005;6(1):35.

50. Driver CR, Stricof RL, Granville K, et al. Tuberculosis in health care workers during declining tuberculosis incidence in New York State. Am J Infect Contr 2005;33(9):519–26.

51. Hill A, Burge A, Skinner C. Tuberculosis in National Health Service hospital staff in the west Midlands region of England, 1992–5. Thorax 1997;52(11):994–7.

52. McKenna MT, Hutton M, Cauthen G, et al. The association between occupation and tuberculosis. A population-based survey. Am J Respir Crit Care Med 1996;154:587–93.
53. Meredith S, Watson JM, Citron KM, et al. Are healthcare workers in England and Wales at increased risk of tuberculosis? BMJ 1996;313(7056):522–5.
54. Pleszewski B, FitzGerald JM. Tuberculosis among health care workers in British Columbia. Int J Tuberc Lung Dis 1998;2(11):898–903.
55. Raitio M, Helenius H, Tala E. Is the risk of occupational tuberculosis higher for young health care workers? Int J Tuberc Lung Dis 2003;7(6):556–62.
56. Sepkowitz KA, Friedman CR, Hafner A, et al. Tuberculosis among urban health care workers: a study using restriction fragment length polymorphism typing. Clin Infect Dis 1995;21:1098–102.
57. van DH, Gerritsen JJ, van SD, et al. A molecular epidemiological approach to studying the transmission of tuberculosis in Amsterdam. Clin Infect Dis 1997;25(5):1071–7.
58. Alonso-Echanove J, Granich RM, Laszlo A, et al. Occupational transmission of Mycobacterium tuberculosis to health care workers in a university hospital in Lima, Peru. Clin Infect Dis 2001;33(5):589–96.
59. Babus V. Tuberculosis morbidity risk in medical nurses in specialized institutions for the treatment of lung diseases in Zagreb. Int J Tuberc Lung Dis 1997;1(3):254–8.
60. Balt E, Durrheim DN, Weyer K. Nosocomial transmission of tuberculosis to health care workers in Mpumalanga [8]. S Afr Med J 1998;88(11):1363–6.
61. Cuhadaroglu C, Erelel M, Tabak L, et al. Increased risk of tuberculosis in health care workers: a retrospective survey at a teaching hospital in Istanbul, Turkey. BMC Infect Dis 2002;2:14.
62. Dimitrova B, Hutchings A, Atun R, et al. Increased risk of tuberculosis among health care workers in Samara Oblast, Russia: analysis of notification data. Int J Tuberc Lung Dis 2005;9(1):43–8.
63. Eyob G, Gebehyhu M, Goshu S, et al. Increase in tuberculosis incidence among the staff working at the Tuberculosis Demonstration and Training Centre in Addis Ababa, Ethiopia: a retrospective cohort study (1989–1998). Int J Tuberc Lung Dis 2002;6(1):85–8.
64. Gopinath KG, Siddique S, Kirubakaran H, et al. Tuberculosis among healthcare workers in a tertiary-care hospital in South India. J Hosp Infect 2004;57(4):339–42.
65. Harries AD, Hargreaves NJ, Gausi F, et al. Preventing tuberculosis among health workers in Malawi. Bull World Health Organ 2002;80(7):526–31.
66. Harries AD, Kamenya A, Namareka D, et al. Delays in diagnosis and treatment of smear-positive tuberculosis and the incidence of tuberculosis in hospital nurses in Blantyre, Malawi. Trans R Soc Trop Med Hyg 1997;91(1):15–7.
67. Harries AD, Nyirenda TE, Banerjee A, et al. Tuberculosis in health care workers in Malawi. Trans R Soc Trop Med Hyg 1999;93(1):32–5.
68. Hosoglu S, Tanrikulu AC, Dagli C, et al. Tuberculosis among health care workers in a short working period. Am J Infect Contr 2005;33(1):23–6.
69. Jelip J, Mathew GG, Yusin Y, et al. Risk factors of tuberculosis among health care workers in Sabah, Malaysia. Tuberculosis 2004;84(1–2):19–23.
70. Jiamjarasrangsi W, Hirunsuthikul N, Kamolratanakul P. Tuberculosis among health care workers at King Chulalongkorn Memorial Hospital, 1988–2002. Int J Tuberc Lung Dis 2005;9(11):1253–8.
71. Kanyerere HS, Salaniponi FM. Tuberculosis in health care workers in a central hospital in Malawi. Int J Tuberc Lung Dis 2003;7(5):489–92.
72. Kilinc O, Ucan ES, Cakan MD, et al. Risk of tuberculosis among healthcare workers: can tuberculosis be considered as an occupational disease? Respir Med 2002;96(7):506–10.

73. Kruuner A, Danilovitch M, Pehme L, et al. Tuberculosis as an occupational hazard for health care workers in Estonia. Int J Tuberc Lung Dis 2001;5(2):170–6.

74. Laniado-Laborin R, Cabrales-Vargas N. Tuberculosis in healthcare workers at a general hospital in Mexico. Infect Control Hosp Epidemiol 2006;27(5):449–52.

75. Naidoo S, Mahommed A. Knowledge, attitudes, behaviour and prevalence of TB infection among dentists in the western Cape. SADJ 2002;57(11):476–8.

76. Rao KG, Aggarwal AM, Behera D. Tuberculosis among physicians in training. Int J Tuberc Lung Dis 2004;8(11):1392–4.

77. Skodric V, Savic B, Jovanovic M, et al. Occupational risk of tuberculosis among health care workers at the Institute for Pulmonary Diseases of Serbia. Int J Tuberc Lung Dis 2000;4(9):827–31.

78. Sotgiu G, Arbore AS, Cojocariu V, et al. High risk of tuberculosis in health care workers in Romania. Int J Tuberc Lung Dis 2008;12(6):606–11.

79. Wilkinson D, Gilks CF. Increasing frequency of tuberculosis among staff in a South African district hospital: impact of the HIV epidemic on the supply side of health care. Trans R Soc Trop Med Hyg 1998;92(5):500–2.

80. Do AN, Limpakarnjarat K, Uthaivoravit W, et al. Increased risk of *Mycobacterium tuberculosis* infection related to the occupational exposures of healthcare workers in Chiang Rai, Thailand. Int J Tuberc Lung Dis 1999;3(5):377–81.

81. Kassim S, Zuber P, Wiktor SZ, et al. Tuberculin skin testing to assess the occupational risk of *Mycobacterium tuberculosis* infection among health care workers in Abidjan, Cote d’Ivoire. Int J Tuberc Lung Dis 2000;4(4):321–6.

82. Orrett FA. Prevalence of tuberculin skin test reactivity among health care workers at a teaching hospital in Trinidad. Clin Microbiol Infect 2000;6(1):45–8.

83. Liss GM, Khan R, Koven E, et al. Tuberculosis infection among staff at a Canadian community hospital. Infect Control Hosp Epidemiol 1996;17(1):29–35.

84. Keskiner R, Ergonul O, Demiroglu Z, et al. Risk of tuberculous infection among healthcare workers in a tertiary-care hospital in Ankara, Turkey. Infect Control Hosp Epidemiol 2004;25(12):1067–71.

85. Schwartzman K, Loo V, Pasztor J, et al. Tuberculosis infection among health care workers in Montreal. Am J Respir Crit Care Med 1996;154:1006–12.

86. Garcia-Garcia ML, Jimenez-Corona A, Jimenez-Corona ME, et al. Factors associated with tuberculin reactivity in two general hospitals in Mexico. Infect Control Hosp Epidemiol 2001;22(2):88–93.

87. Warren DK, Foley KM, Polish LB, et al. Tuberculin skin testing of physicians at a midwestern teaching hospital: a 6-year prospective study. Clin Infect Dis 2001;32(9):1331–7.

88. Berman J, Levin ML, Orr ST, et al. Tuberculosis risk of hospital employees: analysis of a five-year tuberculin skin testing program. Am J Public Health 1981;71:1217–22.

89. Kayanja HK, Debanne S, King C, et al. Tuberculosis infection among health care workers in Kampala, Uganda. Int J Tuberc Lung Dis 2005;9(6):686–8.

90. Menzies D, Fanning A, Yuan L, et al. Factors associated with tuberculin conversion in Canadian microbiology and pathology workers. Am J Respir Crit Care Med 2003;167(4):599–602.
91. Harries AD, Maher D, Nunn P. Practical and affordable measures for the protection of health care workers from tuberculosis in low-income countries. Bull World Health Organ 1997;75(5):477–89.

92. Menzies RI, Fanning A, Yuan L, et al. Hospital ventilation and risk of tuberculous infection in Canadian Health Care Workers. Ann Intern Med 2000;133(10):779–89.

93. Sugita M, Tsutsumi Y, Suchi M, et al. Pulmonary tuberculosis: an occupational hazard for pathologists and pathology technicians in Japan. Acta Pathol Jpn 1990;40:116–27.

94. Ehrenkranz NJ, Kicklighter JL. Tuberculosis outbreak in a general hospital: evidence for airborne spread of infection. Ann Intern Med 1972;77:377–82.

95. Haley CE, McDonald RC, Rossi L, et al. Tuberculosis epidemic among hospital personnel. Infect Control Hosp Epidemiol 1989;10:204–10.

96. Calder RA, Duclos P, Wilder MH, et al. *Mycobacterium tuberculosis*: transmission in a health clinic. Bull Int Union Tuberc Lung Dis 1991;66:103–6.

97. Menzies D, Adhikari N, Arieta M, et al. Efficacy of environmental measures in reducing potentially infectious bioaerosols during sputum induction. Infect Control Hosp Epidemiol 2003;24(7):483–9.

98. Catanzaro A. Nosocomial tuberculosis. Am Rev Respir Dis 1982;125:559–62.

99. Kantor HS, Poblete R, Pusateri SL. Nosocomial transmission of tuberculosis from unsuspected disease. Am J Med 1988;84:833–8.

100. Lundgren R, Norrman E, Asberg I. Tuberculosis infection transmitted at autopsy. Tubercle 1987;68:147–50.

101. International Union Against Tuberculosis and Lung Disease, World Health Organization. Control of tuberculosis transmission in health care settings. Tuberc Lung Dis 1994;75:94–5.

102. Wenger PN, Otten J, Breeden A, et al. Control of nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* among healthcare workers and HIV-infected patients. Lancet 1995;345:235–40.

103. Maloney SA, Pearson ML, Gordon MT, et al. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med 1995;122:90–5.

104. Fella P, Rivera P, Hale M, et al. Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Contr 1995;23:352–6.

105. Bangsberg DR, Crowley K, Moss A, et al. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol 1997;18:566–70.

106. Blumberg HM, Watkins DL, Jeffrey PA-C, et al. Preventing the nosocomial transmission of tuberculosis. Ann Intern Med 1995;122:658–63.

107. Nicas M. Assessing the relative importance of the components of an occupational tuberculosis control program. J Occup Environ Med 1998;40(7):648–54.

108. Moro ML, Errante I, Infuso A, et al. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy. Int J Tuberc Lung Dis 2000;4(1):61–8.

109. Jarvis WR. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*. Am J Infect Contr 1995;23(2):146–51.

110. Otten J, Chen J, Cleary T. Successful control of an outbreak of multi-drug resistant tuberculosis in an urban teaching hospital [abstract 51D]. World Congress on Tuberculosis; 1992.
111. Stroud LA, Tokars JI, Grieco MH, et al. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* in a New York City hospital. Infect Control Hosp Epidemiol 1995;16(3):141–7.

112. Centers for Disease Control and Prevention. Recommendations and Reports. Guidelines for preventing the transmission of mycobacterium tuberculosis in health-care facilities. MMWR Recomm Rep 1994;43(RR13):1–132.

113. Nicas M. Respiratory protection and the risk of mycobacterium tuberculosis infection. Am J Ind Med 1995;27:317–33.

114. Fennelly KP, Nardell EA. The relative efficacy of respirators and room ventilation in preventing occupational tuberculosis. Infect Control Hosp Epidemiol 1998;19(10):754–9.

115. Coffey CC, Lawrence RB, Campbell DL, et al. Fitting characteristics of eighteen N95 filtering-facepiece respirators. J Occup Environ Hyg 2004;1(4):262–71.

116. Lee MC, Joffe M, Long R, et al. Qualitative fit testing does not ensure health care worker protection. Can J Infect Dis Med Microbiol 2005;16(2):172.

117. Nardell EA. Fans, filters, or rays? Pros and cons of the current environmental tuberculosis control technologies. Infect Control Hosp Epidemiol 1993;14:681–5.

118. Nardell EA, Keegan J, Cheney SA, et al. Airborne infection: theoretical limits of protection achievable by building ventilation. Am Rev Respir Dis 1991;144(2):302–6.

119. Nardell EA. Environmental infection control of tuberculosis. Semin Respir Infect 2003;18(4):307–19.

120. Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med 2007;4(2):e68.

121. Menzies RI, Schwartzman K, Loo V, et al. Measuring ventilation of patient care areas in hospitals: description of a new protocol. Am J Respir Crit Care Med 1995;152:1992–9.

122. Nardell EA, Bugher SJ, Brickner PW, et al. Safety of upper-room ultraviolet germicidal air disinfection for room occupants: results from the Tuberculosis Ultraviolet Shelter Study. Public Health Rep 2008;123(1):52–60.

123. Riley RL, Mills CC, O’Grady FO, et al. Infectiousness of air from a tuberculosis ward: ultraviolet irradiation of infected air – comparative infectiousness of different patients. Am Rev Respir Dis 1962;85:511–25.

124. Escombe AR, Moore DAJ, Gilman RH, et al. Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission. PLoS Med 2009;6(3):e1000043.

125. Ray KC, Johnson BH. An evaluation of ultraviolet lamps in a dental clinic (tuberculosis hospital). Dent Items Interest 1951;73:521–9.

126. Riley RL, Knight M, Middlebrook G. Ultraviolet susceptibility of BCG and virulent tubercle baccilli. Am Rev Respir Dis 1976;113:413–8.

127. Xu P, Peccia J, Fabian P, et al. Efficacy of ultraviolet germicidal irradiation of upper-room air in inactivating airborne bacterial spores and mycobacteria in full-scale studies. Atmos Environ 2003;37:405–19.

128. Riley RL, Nardell EA. Controlling transmission of tuberculosis in health care facilities: ventilation, filtration, and ultraviolet air disinfection. In: Tomasik KM, editor. Plant, technology, safety management series. 1st edition. Oakbrook Terrace (IL): Joint Commission Accreditation of Healthcare Organizations; 1993. p. 25–31.

129. Riley RL, Nardell EA. Clearing the air: the theory and application of ultraviolet air disinfection. Am Rev Respir Dis 1989;139:1286–94.
130. Long R. Canadian tuberculosis standards 6th edition - 2007. Ottawa (Canada): Canadian Lung Association and Public Health Agency of Canada; 2007.

131. Lessler J, Reich NG, Brookmeyer R, et al. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis 2009;9:291–300.

132. Chan-Yeung M, Ooi GC, Hui DS, et al. Severe acute respiratory syndrome. Int J Tuberc Lung Dis 2003;7(12):1117–30.

133. Donnelly CA, Chani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 2003;361:1761–6.

134. Brankston G, Gitterman L, Hirji Z, et al. Transmission of influenza A in human beings. Lancet Infect Dis 2007;7:257–65.

135. Ho AS, Sung J, Chan-Yeung M. An outbreak of severe acute respiratory syndrome among hospital workers in a community hospital in Hong Kong. Ann Intern Med 2003;139:564–7.

136. Moser MR, Bender TR, Margolis HS, et al. An outbreak of influenza aboard a commercial airliner. Am J Epidemiol 1979;110(1):1–6.

137. Li Y, Yu I, Xu P, et al. Predicting super spreading events during the 2003 severe acute respiratory syndrome epidemics in Hong Kong and Singapore. Am J Epidemiol 2004;160:719–28.

138. Yu I, Li Y, Wong T, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med 2004;350:1731–8.

139. Patrozou E, Mermel LA. Does influenza transmission occur from asymptomatic infection or prior to symptom onset? Public Health Rep 2009;124(2):193–6.

140. Gamage B, Moore D, Copes R, et al. Protecting health care workers from SARS and other respiratory pathogens: a review of the infection control literature. Am J Infect Contr 2005;33:114–21.

141. Leung GM, Hedley AJ, Ho LM, et al. The epidemiology of severe acute respiratory syndrome in the 2003 Hong Kong epidemic: an analysis of all 1755 patients. Ann Intern Med 2004;141:662–73.

142. Ofner-Agostini M, Gravel D, McDonald LC, et al. Cluster of cases of severe acute respiratory syndrome among Toronto healthcare workers after implementation of infection control precautions: a case series. Infect Control Hosp Epidemiol 2006;27(5):473–8.

143. Varia M, Wilson S, Sarwal S, et al. Investigation of a nosocomial outbreak of severe acute respiratory syndrome (SARS) in Toronto, Canada. CMAJ 2003;169(4):285.

144. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? Clin Infect Dis 2007;44(8):1017–25.

145. Dwosh AH, Hong H, Austgarden D, et al. Identification and containment of an outbreak of SARS in a community hospital. CMAJ 2003;168(11):1415.

146. Cheng P, Wong DA, Tong L, et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet 2004;363(9422):1699–700.

147. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767–72.

148. Bridges CB, Kuehnert J, Hall CB. Transmission of influenza: implications for control in health care settings. Clin Infect Dis 2003;37(8):1094.
149. Voirin N, Barret B, Metzger MH, et al. Hospital-acquired influenza: a synthesis using the Outbreak Reports and Intervention Studies of Nosocomial Infection (ORION) statement. J Hosp Infect 2009;71:1–14.

150. Tan CC. SARS in Singapore – key lessons from an epidemic. Ann Acad Med Singap 2006;35:345–9.

151. Loeb M, McGreer A, Henry B, et al. SARS among critical care nurses, Toronto. Emerg Infect Dis 2004;10(2):251–5.

152. Chan P, Tang J, Hui D. SARS: clinical presentation, transmission, pathogenesis and treatment options. Clin Sci 2006;110:193–204.

153. Center for Disease Control. Update: influenza activity – United States, April–August 2009. MMWR Morb Mortal Wkly Rep 2009;58(36):1009–12.

154. Salgado SD, Farr BM, Hall KK, et al. Influenza in the acute hospital setting. Lancet Infect Dis 2002;2(3):145–55.

155. Sandrock C, Stollenwerk N. Acute febrile respiratory illness in the ICU: reducing disease transmission. Chest 2008;133:1221–31.

156. Greenaway C, Menzies D, Fanning A, et al. Delay in diagnosis among hospitalized patients with active tuberculosis–predictors and outcomes. Am J Respir Crit Care Med 2002;165(7):927–33.

157. Riley S, Fraser C, Donnelly CA, et al. Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science 2003;300(5627):1961.

158. Escombe AR, Moore DA, Gilman RH, et al. The infectiousness of tuberculosis patients coinfected with HIV. PLoS Med 2008;5(9):e188.

159. Riley RL, Mills CC, Nyka W, et al. Aerial dissemination of pulmonary tuberculosis: a two year study of contagion in a tuberculosis ward. Am J Hyg 1959;70:185–96.

160. Munoz F, Campbell J, Atmar R, et al. Influenza A virus outbreak in a neonatal intensive care unit. Pediatr Infect Dis J 1999;18(9):811–5.

161. Low JGH, Wilder-Smith A. Infectious respiratory illnesses and their impact on healthcare workers: a review. Ann Acad Med Singap 2005;34:105–10.

162. Carman WF, Elder AG, Walce LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet 2000;355:93–7.

163. Maltezou HC. Nosocomial influenza: new concepts and practice. Curr Opin Infect Dis 2008;21:337–43.

164. Pachucki CT, Pappas SA, Fuller GF, et al. Influenza A among hospital personnel and patients. Implications for recognition, prevention, and control. Arch Intern Med 1989;149(1):77–80.

165. Lau JT, Fung KS, Wong TW, et al. SARS transmission among hospital workers in Hong Kong. Emerg Infect Dis 2004;10(2):280–6.

166. Seto WH, Tsang D, Yung RWH, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 2003;361:1519.

167. Loeb M, Dafoe N, Mahony J, et al. Surgical mask vs N95 respirator for preventing influenza among health care workers. JAMA 2009;302(17):1865–71.

168. McLean RL. The effect of ultraviolet radiation upon the transmission of epidemic influenza in long-term hospital patients. Am Rev Respir Dis 1961;83:36–8.

169. Drinka PJ, Krause P, Schilling M, et al. Clinical investigation: reporting of an outbreak: nursing home architecture and Influenza-A attack rates. J Am Geriatr Soc 1996;44(8):910–3.
170. Khan K, Arino J, Hu W, et al. Spread of novel influenza A (H1N1) virus via global airline transportation. N Engl J Med 2009;361(2):212.
171. Morens DM, Rash VM. Lessons from a nursing home outbreak of influenza A. Infect Control Hosp Epidemiol 1995;16:275–80.
172. Committee on Infectious Diseases. Infection prevention and control in pediatric ambulatory settings. Pediatrics 2007;120:650.
173. Uhnoo I, Linde A, Pauksens K, et al. Treatment and prevention of influenza: Swedish recommendations. Scand J Infect Dis 2003;35(1):3–11.
174. Wells WF. Airborne contagion and air hygiene. Cambridge (MA): Harvard University Press; 1955.