



Tuberculosis: 11. Nosocomial disease

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The tuberculosis (TB) series, which has been running in *CMAJ* since March 1999, has already reviewed the changes in populations at risk¹ and the emergence of HIV-related² and multidrug-resistant³ TB in Canada. Since the occurrence of several highly publicized outbreaks of multidrug-resistant TB in US hospitals,⁴ the transmission of TB within hospitals and other institutions has been increasingly recognized as a hazard for patients and workers. Using a fictitious case for illustration, this article reviews the major determinants of nosocomial transmission of TB, as well as the key administrative, engineering and personal measures that can be taken to minimize transmission of the disease in health care facilities.

Early diagnosis

Mr. B, a 68-year-old male smoker, arrives in the emergency department of an urban community hospital complaining of persistent dry cough, fatigue, anorexia and a weight loss of 22 kg over the previous month. One week earlier, bronchitis had been diagnosed at a walk-in clinic, and an oral cephalosporin had been prescribed. Mr. B was born in Canada and denies previous illness, medication use or allergy. He is retired, lives alone in a rooming house and drinks several beers per day.

The physician performs a physical examination and finds the patient thin and apparently malnourished. The patient's temperature is 38.3°C, and he is coughing but not acutely distressed. Chest radiography shows extensive noncavitary air space disease involving the apical and posterior segments of the right upper lobe. The leukocyte count is $9.5 \times 10^9/L$, with 80% neutrophils. The results of other laboratory tests are normal.

Mr. B is admitted with a diagnosis of pneumonia and is moved to a 4-bed room on a general medical ward. He receives ceftriaxone and clindamycin intravenously. However, over the next 48 hours he remains febrile, and a respiratory consultation is requested. The respirologist arranges a bronchoscopy procedure for the next morning (day 3). A Ziehl-Neelsen smear of bronchial washings reveals 5–10 acid-fast bacilli (AFB) per high-powered field (considered heavily positive). Antituberculous therapy consisting of isoniazid, rifampin, pyrazinamide and ethambutol is started, along with vitamin B₆. The intravenous antibiotics are discontinued.

Potential delays in TB management include failure to suspect the diagnosis, which leads to delays in appropriate testing; delays in the reporting of results of laboratory tests, which might include deficient communication of results from the laboratory to the treating physician; delays in institution of respiratory isolation for patients who have been admitted to hospital; and delays in initiating antituberculous therapy. Missed or delayed diagnosis and treatment lead to increased risk of death and increased risk of transmission in both community and institutional settings.

Community-based outbreaks have been reviewed in detail elsewhere.⁵ Common to these outbreaks were long intervals between the onset of symptoms and diagnosis in the index case and a consistent relation between duration of exposure and transmission, as predicted from classic animal experiments.^{6,7} A long delay between initial evaluation and diagnosis was also a common feature in 8 institutional outbreaks involving single patients and 5 hospital epidemics involving

Education

Éducation

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numerous patients, most of whom had HIV infection and multidrug-resistant TB.⁸ For the period 1991 to 1993, the median duration between onset of symptoms and initiation of treatment was 44 days for 142 patients with culture-positive pulmonary TB in an Australian hospital.⁹ There was no difference between sputum smear-positive and smear-negative patients, which suggested that the delay related to the initiation of appropriate medical evaluation. One retrospective study in the United States found that the median interval between admission and treatment was 6.5 days, and only 42% of cases were suspected on admission.¹⁰ In another series only 16% of patients were isolated upon admission.¹¹

These reports cannot be used to estimate the risk of infection per day of exposure for workers, but they underline the importance of prompt recognition and management of the disease. A recent study in Montreal found that the cumulative frequencies of positive tuberculin test results (43%) and conversions (20%) among health care personnel working on several surgical wards actually exceeded those among their colleagues on medical wards at the same hospital.¹² There were very few patients in whom TB had been diagnosed on these surgical units, so the high conversion rates were likely the result of unrecognized cases.

In Canada, TB is rare in the general population. However, it remains relatively common in certain risk groups:¹³ people born in countries where the incidence of TB is high, aboriginal Canadians, elderly people (particularly single men), people with dual HIV and tuberculous infection, and the urban poor (particularly homeless people and drug and alcohol abusers). People from these risk groups with 2 or more key symptoms (cough for more than 4 weeks, fever for more than 1 week or weight loss) or a chest radiographic abnormality of any sort should be suspected of having active TB. They should be isolated immediately upon presentation to a health care facility, and 3 sputum smears for acid-fast bacilli should be ordered. If the patient is unable to provide sputum spontaneously, these smears should be obtained by induction with hypertonic saline.¹⁴ If sputum induction is either unsuccessful or not feasible, bronchoscopy for such patients should be the last procedure of the day in the bronchoscopy suite.

Clues to the diagnosis in Mr. B's case include his persistent symptoms and his demographic risk factors, as well as the extensive radiographic abnormality. However, cavitation is often absent in active pulmonary TB. For example, only 29% of patients diagnosed with active pulmonary TB in Montreal from 1992 to 1995 had cavitory disease.¹⁵ This underscores the importance of a high index of suspicion, accompanied by prompt examination of respiratory specimens.

Hierarchy of controls

Prevention of nosocomial transmission of TB is best achieved by a variety of measures — the so-called hierarchy

of administrative, engineering and personal controls. Administrative controls include efforts to reduce any delay in diagnosis and policies to ensure more extensive and rapid respiratory isolation. These measures were reviewed in the previous section. Engineering controls include ventilation and ultraviolet (UV) light, and personal controls include masks and personal respirators, BCG (bacille Calmette-Guérin) vaccination,¹⁶ tuberculin skin testing¹⁶ and preventive therapy with isoniazid.¹⁶

In addition to the hierarchy of controls there is a fundamental step that patients with TB can take to reduce the risk of transmission. Every patient with TB should be clearly instructed to cover his or her mouth and nose when coughing or sneezing. This simple behavioural intervention reduces the aerosolization of infectious particles and hence the transmission of disease.

Mr. B is immediately placed in a respiratory isolation room and is instructed to wear a mask at all times when outside the room. Staff and visitors are instructed to don masks upon entering the patient's room. The head nurse wants to know what type of mask should be used and whether the room is in fact a proper isolation room for this type of patient.

Engineering controls

At present, the major engineering method used to prevent nosocomial transmission is room ventilation. The rate of exchange of contaminated air with clean air within a room is referred to as the ventilation rate, expressed as the number of air changes per hour (ACPH). A ventilation rate of 1 ACPH means that the ventilation system delivers a volume of air equal to the room volume each hour. For example, to achieve 1 ACPH the ventilation system must deliver 27 m³ of air for a room measuring 3 × 3 × 3 m. One ACPH will reduce the concentration of a given contaminant within a room by 67% in 1 hour, whereas a ventilation rate of 6 ACPH will reduce the contaminant concentration by more than 99% in the same period.¹⁷

Table 1 summarizes the recommended ventilation rates for different patient care areas in acute care hospitals. These recommendations are based entirely on theoretical

Table 1: Recommended rate of ventilation and direction of air flow for various patient care areas in Canadian hospitals

Area of hospital	Ventilation rate, ACPH	Direction of air flow
General ward	2	NA
Isolation room	6	Inward
Bronchoscopy and sputum induction rooms	15	Inward
Autopsy suite	15	Inward

Note: ACPH = air changes per hour, NA = not applicable.



evidence, as there is no proof from field studies that ventilation is effective in reducing transmission of infection. If anything, field studies have repeatedly demonstrated that ventilation systems in many hospitals fail to work properly because of poor design or construction or because of inadequate maintenance.⁴ Therefore, verification of ventilation rates is important. Although this is potentially difficult, a simple protocol using carbon dioxide has recently been described.¹⁸

The other objective of ventilation is to direct the movement of contaminated air so that it is removed at its source without contaminating other areas of the hospital. In a properly ventilated respiratory isolation room, air should move from the corridor into the room and out through the exhaust system. This directional air flow (so-called negative pressure) can be achieved by directly exhausting room air to the outdoors, as with a window fan unit, or ensuring that the flow of air back into the ventilation return or exhaust system exceeds by 10% to 20% the in-flow of air through the ventilation supply system. If contaminated air is to be recirculated, it must pass through a high-efficiency filter to remove all airborne pathogens.

Air should continue to flow into the isolation room when the door is open, but this is often difficult to achieve. That is why it is essential to keep the doors to isolation rooms and other potentially contaminated areas closed as much as possible. Devices that automatically close such doors may be required. In high-risk areas such as bronchoscopy suites or autopsy rooms, anterooms should be considered to maintain inward air flow even when the doors are open.

UV light has been recommended for institutional TB control, because of its proven efficacy in eradicating airborne pathogens in experimental studies.¹⁹⁻²¹ UV light is attractive for TB control because the fixtures are relatively cheap, and the maintenance and energy costs are also low. It appears to be particularly useful in settings where there is high risk of exposure to unrecognized cases, such as shelters for the homeless and emergency departments. It may also be a useful adjunct in high-risk areas of the hospital such as bronchoscopy suites and autopsy rooms.

Direct exposure to UV light can result in keratoconjunctivitis (so-called welder's eye), and prolonged direct exposure is associated with skin cancer. Because of fear of these potential complications, the use of UV light has been limited to date. However, these complications are easily prevented by installing the fixtures within ventilation systems, or by using wall- or ceiling-mounted fixtures with baffles to block rays directed downward so that only the air in the upper room is irradiated.

An important limitation, however, is the absence of data from field studies on the effectiveness of UV light in reducing the concentration of airborne pathogens and in reducing nosocomial transmission. Nonetheless, given its low cost, ease of installation and maintenance, and theoretical efficacy, UV light seems underused at present.

Masks and personal respirators

Between 1990 and 1993, nosocomial outbreaks of multi-drug-resistant strains of TB with high rates of transmission to health care workers generated enormous concern as well as demands for improved protection. Considerable controversy, compounded by inconsistent recommendations from various authorities, surrounded the designation of appropriate protective masks. Standard surgical masks, designed to prevent operative wound contamination by catching droplets in air expired by the mask wearer, are less than 50% efficient in filtering the airborne droplet nuclei containing viable tubercle bacilli, which have a diameter of 1–5 μm .²² A much finer filter is needed to prevent inhalation of such small particles; these are referred to as personal respirators and were originally developed to prevent occupational lung disease in workers labouring in dusty industries (Table 2).

The present consensus regarding masks and respirators is that the optimal balance of worker protection with comfort and ease of use, as well as cost, is afforded by personal respirators that filter at least 95% of respirable particles of 1–5 μm diameter and that allow less than 10% leak around the mask. These so-called N95 respirators should be worn by anyone entering a room potentially contaminated with airborne tubercle bacilli. Because the patients themselves release relatively large droplets, standard surgical masks are in fact adequate for their use when they leave their rooms. However, it is often more practical, and certainly less confusing, if patients wear the same devices as health care workers, that is, personal respirators.

There are a number of pitfalls related to mask use. The most common is non-use. Health care workers commonly dart into patients' rooms while "holding their breath" to avoid having to put on a mask for just a short time. This strategy is successful only if the worker does not breathe at all while in the room, which severely curtails communication. The second problem is leakage around the mask because of poor fit, which commonly occurs in people with

Table 2: Filter efficiency and cost of various respirators and masks

Type of mask*	Filter efficacy, % respirable particles†	Particle size (μm)	Unit cost, \$
Surgical	50	1–5	0.02–0.06
Dust–mist	Not tested	1.0	0.40–0.65
N-95-HCW	95	1.0	0.65–1.00
HEPA	99.97	0.3	10.50–12.70
Personal air-powered	100	0.3	450.00–600.00

*Dust–mist type mask is a mask developed for use in industry. N-95-HCW is a new type of mask certified as a personal respirator according to the N-95 requirements of the US National Institute for Occupational Safety and Health; specifically, they filter at least 95% of particles 1 μm in diameter or larger. HEPA masks are high-efficiency particulate air filter masks, which filter 99.97% of particles 0.3 μm in diameter or larger. Personal air-powered masks are full face masks, for which air is supplied under pressure.

†Minimum size of particles filtered varies;⁴¹ see first footnote.



beards. Masks increase resistance to air flow, potentially making breathing and talking more difficult. As a result, health care workers may fail to wear them properly. Infection control departments can minimize these problems by providing workers with comprehensive training in the indications, benefits and proper techniques for mask use.

Discontinuation of isolation

Two days later (day 5), the microbiology laboratory reports that the acid-fast organisms from the bronchial washings have been presumptively identified as *Mycobacterium tuberculosis*, by polymerase chain reaction. On day 10, sputum induction yields 3+ AFB on direct smear. Sputum induction is repeated 1 week later (day 17), and 2+ AFB are seen. Mr. B has gained 3 kg, is now afebrile and wishes to leave the hospital. The ward staff wonder whether this is advisable.

Most studies of nosocomial TB have measured transmission to health care workers. In fact, this is only because the incidence of infection and disease is much easier to measure in this group. Other hospital patients are exposed to at least the same extent. Moreover, once such patients become infected, the risk of progression to disease is much greater because of underlying medical conditions (such as HIV infection, diabetes, renal failure and malnutrition) or treatments (with corticosteroids, chemotherapy or other immunosuppressive agents). Therefore, before patients with active pulmonary TB can be transferred from respiratory isolation to non-isolation rooms on a general ward their lack of contagiousness must be established with certainty.

In the past there were dogmatic claims that smear-negative patients were not contagious and smear-positive patients were no longer contagious after 2 weeks of therapy. Neither statement is correct. (The categorization according to the result of direct smear testing refers equally to spontaneous or induced sputum samples and to bronchial secretions obtained by bronchoscopy.) Smear-negative patients *are* contagious, although less so than smear-positive patients. Once effective treatment has begun, patients who were initially smear negative should become noncontagious after 2 weeks of therapy.²³ However, patients who are initially smear positive are likely to remain contagious as long as their smears and cultures are positive. Among initially smear-positive patients, 50% to 70% will be culture positive after 4 weeks of therapy, and 5% to 10% will still be culture positive after 12 weeks of therapy.²⁴⁻²⁷ If viable organisms are still present in sputum (i.e., if sputum or bronchial secretions are culture positive), then presumably they can still be disseminated into the air and transmitted to others.²³

In approximately 20% to 30% of initially smear-positive patients, there is a transient phase when sputum smears remain positive but cultures from the same specimens are negative.²⁸ It is important to remember that this is a transient phase occurring in only a minority of patients. More than 90% of all smear-positive specimens obtained from initially smear-positive patients while they are receiving

therapy prove culture positive, which means that these patients are still potentially contagious.²³

However, patients *can* be discharged home while still potentially contagious. This step can be taken if all those in the home environment have already been evaluated and if high-risk contacts are already receiving preventive therapy (for further details, see Menzies and associates¹⁶). Before discharge is considered, there must be some clinical response such as a lessening of symptoms or a microbiologic response, with a diminished degree of smear positivity. Patients with known or suspected drug resistance will remain contagious longer²⁹ and must be kept in isolation until it is certain they are receiving effective therapy and are no longer smear or culture positive.

Investigation of hospital contacts

The hospital infection control nurse estimates that 10 other patients, 15 visitors, 20 nurses, 3 physicians, 1 inhalation therapist, 3 orderlies, 3 housekeeping workers, 2 social workers and 1 dietician were potentially exposed during the 72 hours between Mr. B's arrival in the emergency department and his isolation. She suggests that these people be contacted for tuberculin skin testing and chest radiography.

Contact investigations are often extremely difficult to conduct in institutional settings. The extent and nature of contact between the index patient and other patients, visitors and workers may be difficult to determine, given the movement of patients and the changing work assignments of personnel. There may be an element of panic among staff members, and administrators and infection control authorities may be worried about workers' demands for compensation. This makes it tempting to test everyone.

However, a more rational approach to contact investigation remains preferable. As in the community, the infectiousness of the index case should first be evaluated. Transmission is only possible if tubercle bacilli are aerosolized and inhaled by others, meaning that only pulmonary (parenchymal) and laryngeal TB are contagious. Contagiousness is greater in patients with positive smears (such as Mr. B) and more extensive pulmonary disease. The investigation should follow the "concentric circle approach."¹⁶ With this approach, the people with the greatest exposure must be identified: those in close proximity to the index patient for a prolonged period or those exposed at times of heightened contagiousness, such as during cough-inducing procedures (bronchoscopy, sputum induction, administration of aerosolized pentamidine, endotracheal intubation and suctioning).

Hence, appropriate contacts for initial evaluation in Mr. B's case would be the inhalation therapist who assisted during bronchoscopy, the respirologist who performed the bronchoscopy, the patient who underwent bronchoscopy immediately after Mr. B, the patients who shared his ward room and the nurses who were directly assigned to care for him on the ward — all of whom were in contact with Mr. B before initiation of isolation and therapy. Contact occur-



ring only after isolation and initiation of therapy does not require investigation, provided that isolation has been properly instituted. Contact investigation should be done only after confirmation that the infecting organism is indeed *M. tuberculosis*. In Mr. B's case, presumptive identification of *M. tuberculosis* was made possible by polymerase chain reaction. In smear-negative cases, it may be necessary to wait for culture results.

If the results of screening the initial group of hospital contacts suggest a high frequency of transmission, the scope of the investigation should be broadened. Transmission is suggested when the prevalence of tuberculin reactors exceeds that expected in the community, according to the age and ethnic origin of the group tested. For instance, among non-aboriginal Canadian-born people under 50 years of age, the expected prevalence of tuberculin reactors is 10% or less. If the observed prevalence is greater than this level, it becomes reasonable to target people who had briefer contact with the index case, such as patients in adjacent beds in the emergency department and housekeeping personnel who cleaned the patient's room.

All targeted contacts should be evaluated for clinical signs and symptoms of TB (Fig. 1). Those with either a previously documented negative result on tuberculin skin testing or no previously documented skin test should undergo this type of testing. Since tuberculin skin test conversion takes 3 to 7 weeks, it is reasonable to wait 8 weeks from the time of first exposure before evaluating immunocompetent contacts (be they patients or health care workers). As in the community, close contacts with a high risk of

active disease if infected (because of immunosuppression related to HIV infection or other medical conditions and treatments) should be strongly considered for immediate chemoprophylaxis, once active disease has been excluded. Their skin test results can be disregarded, because they are likely to have false-negative results,³⁰⁻³² and it may be advisable not to perform skin testing at all in such cases. In immunocompetent contacts, induration of 5 mm or greater is considered a positive result, regardless of prior BCG vaccination status.³³ People with such reactions should be referred for chest radiography and medical evaluation. If there is no evidence of active TB, they should be considered for chemoprophylaxis.

Contacts with a previously documented positive skin test result (or a documented history of antituberculous prophylaxis or therapy) should be referred for chest radiography if symptoms such as persistent cough, fever or weight loss raise any suspicion of active disease. They should not undergo further tuberculin testing. For those with a previous tuberculin reaction, the risk of active disease after new exposure is 80% lower than that of previously tuberculin-negative people, presumably because of acquired immunity.³⁴ However, reinfection can and does occur, so compatible symptoms in a recently exposed worker should prompt radiographic evaluation even if there was a previously documented tuberculin reaction.

These guidelines highlight the importance of obtaining and recording baseline tuberculin skin test results, since they are crucial to the management of exposed workers. Two-step testing upon hiring is recommended (i.e., a sec-

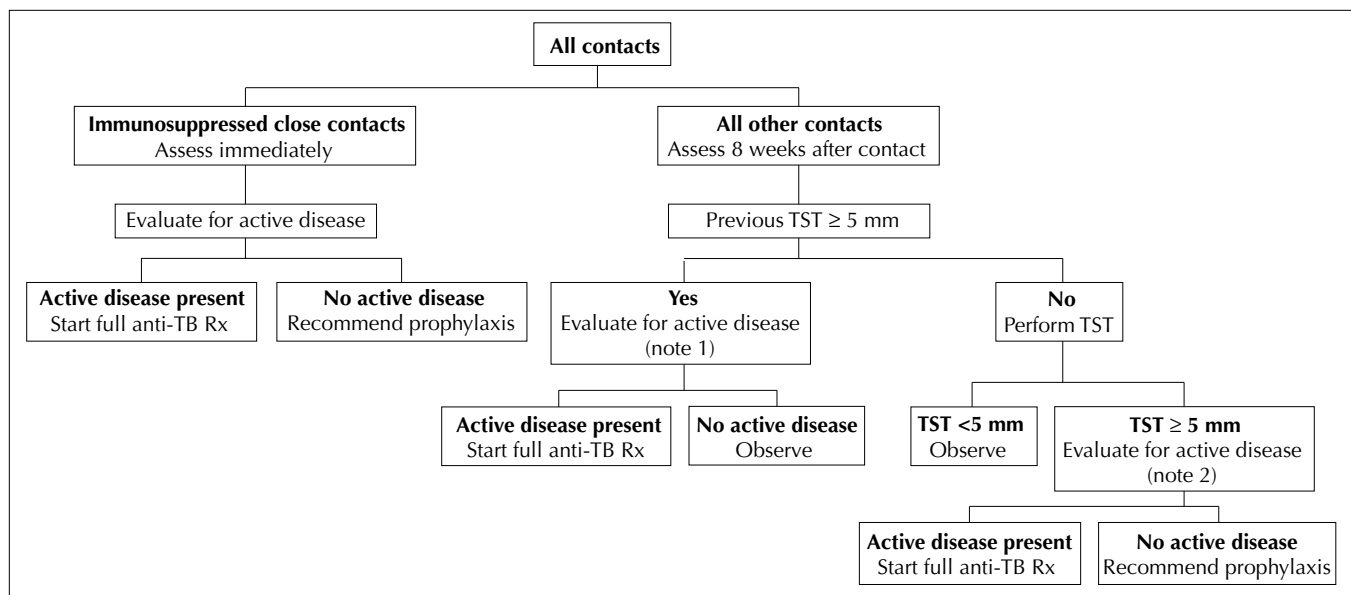


Fig. 1: Algorithm for evaluating tuberculosis contacts in an institutional setting. TST = tuberculin skin test, full anti-TB Rx = full (combination) antituberculous chemotherapy. Note 1: For contacts with a previously documented tuberculin reaction 5 mm or more in diameter, evaluation for active disease should include a check for symptoms and a physical examination. Chest radiography should also be performed if active disease is suspected. Note 2: For contacts without a previously documented positive result on a tuberculin test, evaluation for active disease should always include a check for symptoms, a physical examination and chest radiography.



ond tuberculin test within 7 to 21 days of an initial negative result). This permits detection of boosting related to remote exposure or BCG vaccination. Subsequent tests will thus be limited to those without boosting, which will permit much more reliable interpretation of positive results. Single-step retesting should be undertaken after significant exposure. Depending on the type of work and the facility, routine surveillance every 6 to 12 months may be appropriate, as summarized in Table 3.¹⁷

The actual risk to exposed health care workers varies tremendously, depending on the infectivity of the source case, the type and extent of contact, the delay in isolation and treatment, and the adequacy of isolation measures. In the most dramatic instances of hospital transmission, up to 50% of exposed workers have been infected, and active disease has occurred in as many as 10% of those infected.⁸ Aerosolization of infected secretions, as occurs during bronchoscopy, endotracheal intubation, suctioning and autopsies, figured prominently.

Reported systematic surveys of health care workers suggest that the overall risk is more modest. The annual risk of infection appears to increase as the ratio of the number of workers to the annual number of admissions of patients with active TB decreases. In reports from institutions with 100 or more workers per annual TB admission, the estimated annual risk of infection was 0.2% or less, but the risk was 1.7% to 3.9% in hospitals with 11 to 100 workers per annual TB admission, and as high as 10% in institutions with 10 or fewer workers per admission.⁸ In contrast, the estimated annual risk of TB infection in the community is 0.02% to 0.08%.³⁶⁻³⁸ At 2 Montreal hospitals, workers' estimated annual risk of infection was 1.7% to 2.7%.¹²

Tuberculosis transmission in other institutions

The director of the public health department telephones. A

Table 3: Recommended frequency of worker surveillance for tuberculosis (TB) in Canadian health care facilities*

Worker activity risk‡	Health care facility risk‡	
	High	Low
High	Every 6 mo	Annually
Intermediate	Annually	Only if exposed
Low	Only if exposed	Only if exposed

*Modified from Health Canada.¹⁷

‡High = 6 or more patients with TB seen annually or one or more patients with TB seen annually with ratio of health care workers to patients with TB less than 100:1; low = fewer than 6 patients with TB seen annually and ratio of health care workers to patients with TB greater than 100:1.

‡High = personnel involved with cough-inducing procedures, autopsies, pathology examinations or designated mycobacterial laboratory procedures; intermediate = personnel with regular, direct patient contact and those working on units where patients with active TB are cared for (includes housekeeping, clerical and maintenance staff working on those units); low = personnel with minimal patient contact (e.g., administration and kitchen staff) or with patient contact limited to areas where TB patients are rarely cared for (e.g., obstetrics and neonatology units).

month earlier Mr. B had been held for 2 days in a short-term detention centre. The director wants to know whether contact investigation should be undertaken at that facility.

In these circumstances, contact investigation is appropriate. Depending on the environment, Mr. B's detention (although relatively brief) may have represented a real risk to workers and other detainees. Indeed, transmission of TB has been reported in numerous institutions other than hospitals, such as prisons, shelters for homeless people, nursing homes and hospices. Prisons are particularly important because of the increased prevalence of dual infection with TB and HIV in inmates, which can result in high rates of reactivation. Transmission is enhanced by overcrowding and poor ventilation. In addition, diagnosis may be delayed, and therapy, if started, may be interrupted. Outbreaks with high rates of transmission have been reported in a number of prisons, as has transmission in the community after inmates' release.³⁹

Efforts to prevent nosocomial transmission must be tailored to the particular circumstances of each institution. In nursing homes, the greatest problem is delay in diagnosis, so a high index of suspicion must be maintained. TB should be suspected in any nursing-home resident with nonresolving pneumonia, persistent fever, or simply fatigue and weight loss. The role of tuberculin testing and preventive therapy in nursing home residents remains controversial.^{40,41}

In prisons systematic record-keeping is essential to identify patients with confirmed TB and to ensure that they complete therapy, particularly after their release. Screening of high-risk inmates, such as foreign-born or aboriginal Canadians, as well as injection drug users, should be considered. The most important and effective strategy for controlling transmission within shelters for homeless people in New York City was simply to verify whether those using the shelter were registered as receiving therapy for active TB.⁴² Close collaboration between the public health department and authorities of shelters and prisons is therefore essential, to maintain confidentiality yet to rapidly identify known active cases and thereby prevent transmission to others.

Conclusion

In this article we have reviewed the key elements of institutional control of TB. As this disease becomes increasingly concentrated in high-risk subgroups, hospitals, prisons and other communal settings represent focal points for transmission between these high-risk groups and the general population, a group that is less and less likely to have been previously exposed and so remains susceptible. In addition, the emergence of multidrug-resistant TB strains has made it imperative to prevent transmission in these settings, given the difficulty of treating infection and disease caused by these strains. Every Canadian facility must develop a plan to control TB appropriate to the level of risk in that institution, which is roughly proportional to the number of patients with active TB admitted each year. This plan could be as simple as a contingency plan to trans-



fer out all known or suspected cases. This strategy would be appropriate for a community hospital with 1 or 2 such patients each year. In contrast, a large urban general hospital should have a full hierarchy of administrative, engineering and personal controls. Such efforts will ensure that this uncommon disease remains uncommon.

Competing interests: None declared.

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