# Canadian Tuberculosis Standards

7th Edition

## Chapter 2: Pathogenesis and Transmission of Tuberculosis

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# CHAPTER 2

# PATHOGENESIS AND TRANSMISSION OF TUBERCULOSIS

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## KEY MESSAGES/POINTS

- Infection with *Mycobacterium tuberculosis* is acquired by inhalation of bacilli-containing droplet nuclei small enough (diameter 1-5 microns) to reach the alveoli.

- Through innate immune mechanisms, alveolar macrophages eradicate the bacteria in some individuals; in others, the bacteria are able to replicate and establish tuberculosis (TB) infection. Bacterial factors and host genetic factors that promote or limit acquisition of infection are not well understood.

- After infection with *M. tuberculosis*, early primary TB disease develops in 5% of people unless they first receive treatment for latent infection. Rapid progression to primary active TB is most frequent in infants and young children, and in people with immune compromise.

- In another 5% of infected people there is later development of reactivation TB in the absence of treatment for latent TB infection (LTBI). Risks are much higher for people with immune compromise, notably HIV infection.

- In the remaining 90% progression to active disease never occurs.

- Intact cell-mediated immunity (CMI) is required to control and contain *M. tuberculosis* infection. Beyond evident clinical and radiographic risk factors, it is impossible to predict which infected people will ultimately develop active TB.

- Transmission of *M. tuberculosis* occurs, with very few exceptions, via droplet nuclei, which can then be inhaled by those who are exposed. For this reason, only those with active pulmonary and/or laryngeal TB are likely to be contagious.

- The probability of transmission increases with the following:
  - bacterial burden (smear positivity), cavitary and upper lung zone disease, and laryngeal disease;
  - amount and severity of cough in the source case;
  - duration of exposure;
  - proximity to the source case;
  - crowding and poorer room ventilation;
  - delays in diagnosis and/or effective treatment.

- The most effective way to reduce transmission is to diagnose and treat patients with active TB disease as soon as possible.

## PATHOGENESIS

The pathogenesis and transmission of TB are inter-related. *M. tuberculosis* is almost exclusively a human pathogen. How it interacts with the human host determines its survival. From the

perspective of the bacterium a successful host-pathogen interaction is one that results in pathogen transmission. Initial infection is usually self-limited and followed by a variable period of latency, which ultimately, in a proportion of those infected, results in infectious pulmonary TB. Transmission from a case of infectious pulmonary TB is by the airborne route in minute droplets of moisture that become increasingly reduced by evaporation, creating "droplet nuclei".[1]

## EVOLUTION OF INITIAL INFECTION AND HOST RESPONSE

At the time of initial infection, the distribution of inhaled droplet nuclei in the lung is determined by the pattern of regional ventilation. It thus tends to follow the most direct path to the periphery and to favour the middle and lower lung zones, which receive most of the ventilation.[2] In immunocompetent hosts, it is theorized that alveolar macrophages ingest the *M. tuberculosis* organisms and may or may not destroy them, depending on the degree to which phagocytosing cells are nonspecifically activated, on host genetic factors and on resistance mechanisms in the bacteria.[3] If bacteria are successfully cleared, then test results will remain negative on the tuberculin skin test (TST) or interferon-gamma release assay (IGRA).

When innate macrophage microbicidal activity is inadequate to destroy the initial few bacteria of the droplet nucleus they replicate logarithmically, doubling every 24 hours until the macrophage bursts to release the bacterial progeny.[3] New macrophages attracted to the site engulf these bacilli, and the cycle continues. The bacilli may spread from the initial lesion via the lymphatic and/or circulatory systems to other parts of the body. After a period lasting from 3 to 8 weeks the host develops specific immunity (cell-mediated immunity [CMI] and delayed-type hypersensitivity [DTH]) to the bacilli, and individuals typically show positive results on the TST or IGRA. The resulting *M. tuberculosis*-specific lymphocytes migrate to the site of infection, surrounding and activating the macrophages there. As the cellular infiltration continues, the centre of the cell mass, or granuloma, becomes caseous and necrotic. Radiographically demonstrable fibrocalcific residua of the initial infection include a Ghon focus (a calcified granuloma in the lung) alone or in combination with a calcified granulomatous focus in a draining lymph node (Ghon complex).[4,5] Infection and immune conversion are usually asymptomatic; any symptoms that do occur are self-limited. In a small proportion of those infected, erythema nodosum (a cutaneous immunologic response to an extracutaneous TB infection) or phlyctenular conjunctivitis (a hypersensitivity reaction) may develop.

## EARLY DISEASE PROGRESSION (PRIMARY TB)

A proportion of those who are recently infected are unable to contain the infection despite the stimulation of CMI and DTH, and there is progression to disease in a matter of months. Such early disease progression is a function of age and immunologic response, disease being especially likely to occur in young children and the immunocompromised. A progressive Ghon focus, disseminated (miliary) disease and central nervous system disease may occur as early as 2 to 6 months after infection in infants and the severely immunocompromised.[6,7] Uncomplicated and asymptomatic lymph node disease (hilar or mediastinal lymphadenopathy without airway involvement) may also occur in the first 2-6 months of infection, although there is debate about whether this should be called active disease (see Chapter 9, Pediatric Tuberculosis).[6,8]
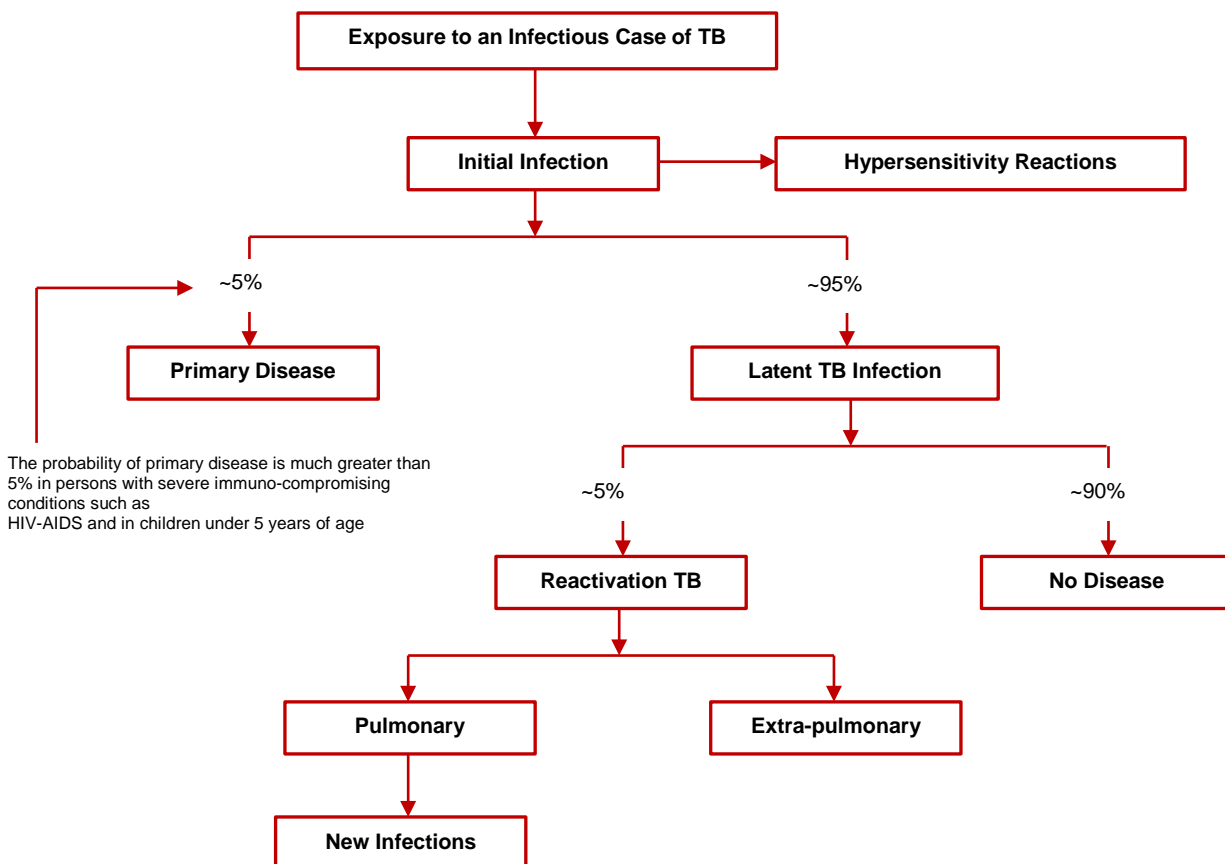
At 4-12 months after infection, early disease manifestations include complicated lymph node disease (airway compression, expansile caseating pneumonia, infiltration of adjacent anatomic structures), pleural disease (most commonly a lymphocyte-predominant exudative effusion) and peripheral lymphadenitis (usually in the neck).[6] In immunocompetent children and adolescents

early disease is more likely to manifest as intrathoracic adenopathy and in adults as a unilateral pleural effusion. In severely immunocompromised people of any age (e.g. those with advanced HIV or AIDS), early disease may manifest as intrathoracic adenopathy.[9,10] Rarely, in newly infected people who are 10 years of age or older (pubertal) adult-type pulmonary disease (see Figure 1) or other types of extrapulmonary TB (for example bone and joint TB) may develop within the first 24 months of infection.[11]

While early disease progression may or may not result from lympho-hematogenous spread, late disease progression (see Figure 1) is almost always the result of the lympho-hematogenous spread of bacilli. Recent infection with early disease progression probably accounts for many cases of TB in recently arrived immigrants.[12] For purposes of disease reporting, everyone with a diagnosis of TB made within 18-24 months of infection is considered to have "primary" disease (on balance about 5% of those infected). Those newly infected people in whom TB does not develop within this period of time will either be left with LTBI and will never experience disease (on balance about 90% of those infected) or, after a variable period of latency, they will develop late disease progression (on balance about 5% of those infected, see Figure 1).

**Figure 1:   The Pathogenesis of Tuberculosis in the Infected Host**
(Adapted from the 6th Edition of the *Canadian TB Standards*)



The probability of primary disease is much greater than 5% in persons with severe immuno-compromising conditions such as HIV-AIDS and in children under 5 years of age

## LATENT TUBERCULOSIS INFECTION (LTBI)

In the classical concept of LTBI, *M. tuberculosis* bacteria are believed to survive for years in Ghon foci and complexes and in the small granulomas or solid caseous material of lympho-hematogenously seeded foci. Presumably, local conditions, an intact CMI or the presence of inhibitors result in conditions unfavourable to replication. Recent mapping of the complete genome sequence of the bacterium demonstrates that the organism has the potential to synthesize enzymes involved in anaerobic metabolism.[13] Although rapid death and autolysis occur after abrupt depletion of oxygen, the organism can shift into a state of dormancy if allowed to settle through gradual reductions in oxygen tension.[14,15] Therefore, although *M. tuberculosis* thrives in an aerobic environment, it possesses the genetic and biochemical capability of anaerobic survival and can persist experimentally in oxygen-depleted media. Tubercle formation, with its oxygen-depleted environment, is a defining characteristic of TB. LTBI is usually identified by a positive TST or IGRA in the absence of active disease (see Chapter 4, Diagnosis of Latent Tuberculosis Infection).

More recently LTBI and active TB have been considered as two ends of a spectrum of states ranging from asymptomatic infection to overt disease.[16,17] In this more nuanced concept, patients whose LTBI progresses to overt disease may pass through a continuum of asymptomatic intermediate states with detectable manifestations indicative of disease.[16] Such asymptomatic disease states frequently remain undiagnosed, and their manifestations and duration are mostly dependent on host immune response. Defining these intermediate states in concrete terms is considered to be important for pragmatic reasons, as they might have an impact upon the performance of TB biomarkers or other diagnostic measures and could also present targets for therapeutic interventions.[16,18]

## REINFECTION

The elegant studies of Ferguson strongly suggest that it takes up to 18 months after the initial infection for CMI to mature.[19] During this period of time a reinfection carries the same risk of disease as the initial infection, perhaps explaining why disease is much more common in newly infected close contacts of smear-positive cases than it is in newly infected close contacts of smear-negative cases – the former having a greater likelihood than the latter of repeated exposure and reinfection.[20-22] Reinfection of immunocompetent hosts that occurs 18 months or more after the initial infection carries a much lower risk of progression to TB disease, estimated to be 21% of the risk of an initial infection progressing to disease.[22] It is not known whether this is because prior infection without development of overt disease is simply a marker for people who are less susceptible to disease development or better able to overcome it once it has developed. Nevertheless, in highly endemic areas the majority of TB cases occurring in those with prior LTBI may be due to reinfection rather than reactivation; in Canada, where repeat exposure is much less common, most active TB reflects reactivation and not reinfection.[23-25] In the severely immunocompromised host, reinfection and initial infection carry a similarly high risk of disease regardless of when the reinfection occurred (see Chapter 6, Treatment of Latent Tuberculosis Infection).

## LATE DISEASE PROGRESSION (REACTIVATION TB)

In Canada, most TB is understood to be "reactivation" TB, i.e. occurring 18-24 months or more after the initial infection. It usually presents as adult-type pulmonary disease (upper lung zone fibrocavitary disease – previously referred to as postprimary TB – beginning in small foci that are the result of remote lympho-hematogenous spread), although it may also present as extrapulmonary TB. As mentioned earlier, adult-type pulmonary TB may on occasion be a manifestation of primary TB or a reinfection. In any population group, reactivation of LTBI, leading to reactivation TB, is much more likely to occur in people who are immunocompromised.

There are a number of theories, most of them speculative, as to why adult-type pulmonary TB tends to localize in the upper lung zones. These are described elsewhere.[2,5] People with a history of untreated or inadequately treated pulmonary TB or a "high-risk" lung scar (upper lung zone fibronodular abnormality) on chest radiograph are understood to have a higher bacillary burden than those without such a history/radiograph, and to be at increased risk of reactivation TB.[26,27]

From the standpoint of public health and the organism's survival as a species, adult-type pulmonary TB is the most important phenotypic expression of the disease. Patients with adult-type pulmonary TB are much more likely to show lung cavitation, created when caseous material liquefies (possibly related to hydrolytic enzymes released from inflammatory cells during their destruction and DTH to tuberculin-like proteins) and erodes into the bronchi.[28] Within the unique extracellular environment of cavities, host defences are ineffectual, and bacteria multiply in large numbers. Because cavities are open to, and discharge their contents into, nearby bronchi these same bacteria are directly communicable to the outside air when the patient coughs. Transmission from patients with adult-type pulmonary TB is facilitated by the concurrent involvement of both the airways and their contiguous pulmonary blood supply at sites of disease in the lung. This minimizes the respiratory limitation experienced by the patient, extending the life of the host within the community and creating further opportunities for transmission before the patient either seeks medical attention or succumbs.[29]

## EXTRAPULMONARY TB

Outside of the extrapulmonary sites of disease alluded to in the section Early Disease Progression and cases of bone and joint TB, whose timeline from infection to disease in children may be as short as a year, most extrapulmonary TB is reactivation disease. Extrapulmonary TB or combined pulmonary and extrapulmonary TB is more common in those who are severely immunocompromised; in those coinfected with HIV the occurrence of extrapulmonary TB increases as the CD4 count decreases (see Chapter 7, Non-respiratory Tuberculosis).[9,10]

## RISK FACTORS FOR PROGRESSION FROM INFECTION TO DISEASE

The risk of transition from LTBI to active TB, primary or reactivation, is largely dependent on the immune competency of the host. Age and sex appear to directly affect the immunologic response and the risk of disease: morbidity is greater among young children (<5 years of age), especially infants, among young adults, especially females, and among older adults, especially males. In high-burden countries, the population attributable fraction of undernutrition for TB is 27% according to the WHO.[30] The seasonality of TB (with the highest incidence in spring and early summer) has been attributed to reduced sunlight and vitamin D deficiency during the winter months in some studies but not in others.[31-33] Ethnic differences have been offered as

factors determining host immune response, with some support,[34] but differences among ethnic groups in all clinical forms of TB are probably best explained as phase differences in an epidemic wave.[35] All races initially exposed in an epidemic as a group are equally susceptible, but eventually death and survival outcome select out people who are relatively more resistant. A growing body of evidence suggests that host genetic factors are important in determining susceptibility to TB.[36-38] Most important from a clinical perspective are the many medical conditions that are well known to affect host immunologic response and increase the risk of progression from LTBI to active TB disease. These are reviewed in detail in Chapter 6, Treatment of Latent Tuberculosis Infection. To identify entry points for interventions aimed at addressing TB risk factors as well as social determinants, Lönnroth and colleagues developed a framework for proximate risk factors and upstream determinants of TB (see Figure 2).[39]

**Figure 2: Framework for proximate risk factors and upstream determinants of TB[39]**
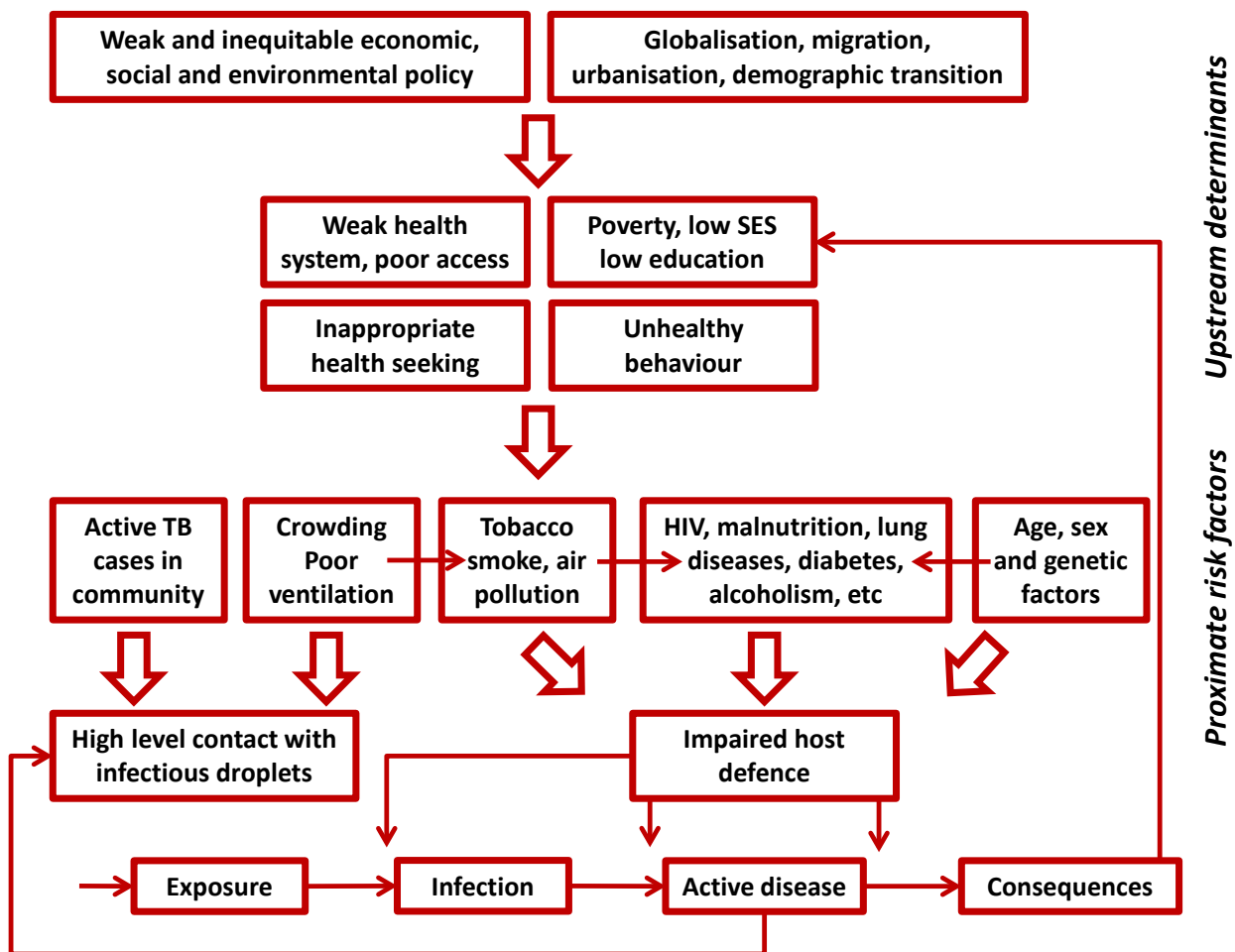
## TRANSMISSION[40-43]

*M. tuberculosis* is communicable from one human to another mainly by the aerosol route and rarely through ingestion or percutaneous inoculation (e.g. through laboratory or hospital accident). Bovine TB, which in the past was caused by ingestion of milk heavily infected by *M. bovis* that then penetrated the mucosa of the oropharynx or the gastrointestinal tract, has been largely eradicated as a result of the pasteurization of milk and the tuberculin testing of cattle, followed by the slaughter of animals found to be infected.

The reservoir for *M. tuberculosis* is humans. Other animals, in particular primates, may be infected but are rarely a source of infection.[40-43] Droplet nuclei, sometimes referred to as "the quanta of contagion", are created by forceful expiratory efforts, such as coughing, sneezing, singing, playing wind instruments and even speaking. Before droplets reach the airspace of a room and have had an opportunity to evaporate down to a "droplet nucleus" their numbers can be reduced by wearing a simple gauze (surgical) mask or covering the mouth and nose during coughing. Certain procedures, for example, bronchoscopy, sputum induction, processing of specimens, autopsy and even irrigation or other manipulation of tuberculous abscesses, may also produce infectious aerosols. The droplets have an extremely slow settling rate (0.5 mm per second or less), which permits their transport by air currents, duct systems or elevator shafts for significant distances from the source case. Large particles settle quickly and are either not inhaled by contacts or, if inhaled, are trapped in the mucus of the upper airway.

If the organism reaches the trachea and bronchi it is usually swept back to the larynx by ciliary action and cough, and then swallowed. For practical purposes, only the droplet nuclei in the size range 1 to 5 microns reach the terminal air spaces or alveoli; each is understood to contain only a few bacteria. In most instances only one such droplet nucleus is believed to be responsible for establishing infection in the host. Bacteria that are lodged on fomites (linen, furniture, books, floors) do not constitute a significant source of infection: most die quickly through the action of drying, heat or sunlight.[5,40-43]

The rate of transmission can be measured by the percentage of close contacts (household and non-household) whose TST or IGRA responses are converted from negative to positive or in whom active TB disease develops. The percentage will depend on the number of infectious droplet nuclei per volume of air (infectious particle density) and the length of time that the uninfected individual spends breathing that air. In the past, drug susceptibility patterns and phage typing of *M. tuberculosis* isolates have helped to confirm the transmission between source case and contact. More recently, DNA fingerprinting of *M. tuberculosis* isolates has greatly refined the identification of this relation.[44]

Because of the highly variable latency period of *M. tuberculosis* infection it is difficult to precisely document transmission using currently available tools. People found to have positive TSTs and/or IGRAs during contact investigation may have been infected in the past (remotely) rather than by the recent source case of concern, though for contact management and public health purposes these contacts are treated as if recently infected if there is no way to determine the duration of infection. DNA fingerprinting techniques will only detect transmission to the small group of people in whom active disease develops following transmission. If most TB disease in a community reflects recent/ongoing transmission, the first priority for public health authorities should be to prevent further transmission. On the other hand, if most TB reflects reactivation of remotely acquired infection, the priority should shift to identification and treatment of people with LTBI, notably those with risk factors for reactivation.

## PATIENT, PATHOGEN AND ENVIRONMENTAL DETERMINANTS OF TRANSMISSION

Several patient, pathogen and environmental factors determine whether transmission occurs, largely by affecting the number of infectious droplet nuclei per volume of air (see Table 1). Although the probability of being infected after contact with an infectious source decreases with decreasing duration and decreasing closeness of contact, the absolute number of casual contacts infected may exceed the number of infected close contacts, since the former may far outnumber the latter.[45] DNA fingerprint data have highlighted the limits of contact tracing in settings where there is exposure of a large number of people unknown to source cases and in settings where social connections are tenuous at best.[46,47] At this point very little is known about what, if any, host determinants influence the acquisition of initial infection after inhalation of a droplet nucleus. Some individuals are able to achieve complete or "sterile" elimination of *M. tuberculosis* bacteria rather than developing latent infection.[48] Observational studies suggest that BCG vaccination in infancy offers some protection against infection with *M. tuberculosis* as detected by an IGRA.[49-52]

**Table 1. Patient, pathogen and environmental factors affecting transmission**

| Patient | Pathogen | Environment |
|---|---|---|
| Disease type | Strain variability | Indoor/outdoor |
|     Pulmonary | | |
|         Smear-positive/smear-negative<br>        Cavitary/non-cavitary on CXR*<br>        Typical/atypical on CXR<br>        Laryngeal | | Air circulation/ventilation<br><br>Sunlight |
|     Extrapulmonary | | Proximity to the source case |
| Symptomatology | | Duration of exposure |
| Delayed diagnosis | | |
| Treatment | | |

*CXR = chest radiograph

## PATIENT FACTORS

With rare exception (e.g. transmission related to an inadequately sterilized bronchoscope or a needle stick injury), transmission requires that a TB patient be able to produce airborne infectious droplets.[41-43] This most often limits the potential for transmission to adolescent or adult patients with adult-type pulmonary TB. Younger children can on occasion be infectious,[53] but as a general rule they have few bacilli in their lesions, often do not produce sputum and rarely have communicable disease.[54] Of patients with TB involving the respiratory tract not all are equally efficient at transmission.

1. **Sputum smear status**

   Patients with smear-positive/culture-positive pulmonary TB are more infectious than patients with smear-negative/culture-positive pulmonary TB, and the latter are more infectious than patients with smear-negative/culture-negative pulmonary TB (see Table 2 for a summary of the epidemiologic studies on the risk of infection in household [close] contacts grouped according to the bacteriologic status of the source cases).[55-62] Sputum that is smear-positive contains 5,000 or more organisms per millilitre of sputum.[57,58,63,64]

   Patients with smear-positive bronchoalveolar lavage fluid are considered just as infectious as those with smear-positive sputum.[65] Smear-positive induced sputum is for practical purposes considered to indicate the same degree of contagiousness as smear-positive spontaneously expectorated sputum, though there are currently no data that prove this assertion.[55] With the use of molecular epidemiologic tools the relative transmission rate of smear-negative compared with smear-positive patients has been determined to be 0.17-0.22 or roughly one-fifth the likelihood of transmission.[66,67] In addition to the greater infectivity of smear-positive cases, as mentioned in the section Pathogenesis, the risk of disease after infection from a smear-positive case is greater, by virtue of the higher probability of repeated infection, than it is after infection from a smear-negative case.

**Table 2.\* Risk of infection among household (close) contacts according to bacteriologic status of index case (pulmonary TB only)**

| Ref no. | Year of survey | Location | Contacts | | Number and % infected contacts by bacteriologic status of index case | | | | | | General population % positive PPD[†] |
|---------|----------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| | | | | | S+C+ | | S-C+ | | S-C- | | |
| | | | Age | Total no. | N | %+ | N | %+ | N | %+ | |
| 56 | 1949-56 | England | 0-14 | 545 | 262 | 63% | 126 | 21% | 157 | 18% | 13% |
| 57 | 1950-53 | England | 0-14 | 823 | 374 | 65% | 228 | 27% | 221 | 18% | 22% |
| 58 | 1963-64 | Holland | all ages | 858[‡] | 391 | 20% | 467 | 1% | – | – | <<1% |
| 20 | 1966-71 | Canada-Whites | 0-19 | 2406 | 1210 | 38% | 655 | 12% | 541 | 10% | 2% |
| | | Canada-Aboriginals | 0-19 | 1168 | 592 | 45% | 377 | 31% | 199 | 27% | NA |
| 59 | 1967-69 | Rotterdam | 0-14 | 134 | 40 | 50% | 43 | 5% | 51 | 8% | 1% |
| 60 | 1969 | USA | all ages | 130 | 88 | 44% | 14 | 21% | 28 | 14% | NA |
| 61 | 1971-74 | USA | all ages | 761 | 504 | 46% | 257 | 28% | – | – | NA |
| 62 | 1975-77 | USA | all ages | 541 | 368 | 40% | 173 | 27% | – | – | NA |

\*Adapted from reference number 55

† Taken from the same reference, i.e. a comparable reference population.

‡ In this study contacts were considered infected only if tuberculin conversion and/or primary TB had been documented.

S = smear, C = culture, PPD = purified protein derivative

2. **Disease type on plain chest radiograph**

Pulmonary TB patients with cavitation on chest radiograph are more infectious than pulmonary TB patients without cavitation after bacteriologic findings have been taken into account.[68-70] Pulmonary TB patients with "typical" chest radiographic findings (upper lung zone disease, with or without cavitation, and no discernable intrathoracic adenopathy) are more infectious than pulmonary TB patients with "atypical" chest radiographic findings (all others).[71]

3. **Laryngeal disease**

Patients with laryngeal TB are more infectious than those with pulmonary TB.[72] Most patients with laryngeal TB (hoarseness associated with inflammation and ulceration of the vocal cords) have far advanced pulmonary disease upstream from the larynx.[73]

4. **Symptomatology**

In general, normal breathing produces few infectious particles, a bout of coughing or five minutes of speaking in a normal tone produce many more, and a sneeze produces the most.[74,75] The likelihood that household contacts will be infected increases with the frequency of cough in the source case.[60] When the aerial infectivity of the droplets from smear-positive patients was evaluated by artificially atomizing sputum and exposing guinea pigs to a standard dose, there was marked variability in the infectivity of aerosolized sputum, perhaps explaining the extraordinary heterogeneity of infectiousness among patients with smear-positive pulmonary TB.[76-78] Thus, although patients may appear to have an equal number of bacteria in their sputum, the physical and chemical properties of their sputum, as well as their effectiveness as an aerosolizer, may determine whether they produce a large or small number of droplet nuclei. The role of smoking, allergy or coincidental viral upper respiratory tract infection in aerosol formation is unknown.[79]

5. **Delayed diagnosis**

The number of contacts and the duration of exposure of each contact may increase as time to diagnosis increases. The longer the duration of symptoms in the source case the greater the risk of transmission.[65]

6. **Treatment**

Effective treatment (see Chapter 5, Treatment of Tuberculosis Disease) appropriate to the drug susceptibility test results rapidly reduces cough frequency and sputum bacillary counts.[60,80] Even faster than the rate of decrease of the latter is the rate of decrease of bacillary counts in cough-generated aerosol cultures.[81] With treatment those bacteria that continue to be expectorated may be expected to be less metabolically active and/or are inhibited by the drugs, two effects that may decrease the chances of the organism establishing an infection in the host.[76,82] However, in theory, any residual viable bacteria in respiratory secretions can be transmitted, although the chances of this occurring decrease rapidly with effective treatment.[83] Given the frequency of drug resistance, the determination that treatment is effective in reducing the infectiousness of a given patient should reflect objective clinical, radiographic and/or microbiologic improvement, and not simply time elapsed since treatment initiation.

## PATHOGEN FACTORS

Data are emerging to suggest that one or more virulence properties of *M. tuberculosis* may affect its ability to be transmitted.[84] For example, one strain may be better suited than another to overcoming the innate resistance of the host. Although drug-resistant strains have shown reduced virulence in animal models,[85] clinical evidence of their transmissibility is compelling,[86-89] and for practical purposes they should be considered just as transmissible as drug-susceptible strains. Beijing/W strains have been reported to be hypervirulent, but indices of transmission have been found to be no greater in patients with these strains than in those without them.[90]

## ENVIRONMENTAL FACTORS

Outdoor exposures are very unlikely to result in transmission unless the source and the susceptible person are in talking distance. Bacillary dispersion is immediate, and sunlight rapidly kills any viable bacilli.[91,92] For practical purposes outdoor exposures are not investigated during a contact tracing exercise.

1. **Air circulation and ventilation**

   Given a defined number of bacteria expelled into the air, the volume of air into which the bacteria are expelled determines the probability that a susceptible individual breathing that air will become infected. A high concentration of viable bacteria in the inhaled air of the contact is favoured by indoor exposure, poor ventilation or recirculation of air, and little sunlight (ultraviolet rays). Ventilation dramatically dilutes the concentration of infectious droplet nuclei (see Chapter 15, The Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings, for further information on clearance times).

2. **Proximity to the source case**

   Proximity to the source case is also a determinant of transmission. Related to this is overcrowding: if, as a result of there being many people in a room, an individual is forced into close proximity with an infectious case his or her risk of infection is likely to increase.

3. **Duration of exposure**

   Because of the dilution of infected air and the low concentration of infectious droplet nuclei, the duration of exposure required to ensure that transmission occurs is commonly prolonged (days, months or even years), and yet reports have confirmed that exposures as short as a few minutes may be sufficient to infect a close contact. The latter would appear to be supported by the high proportion of active cases that deny any history of exposure.

## MEASURES TO PREVENT TRANSMISSION

The highest priority should be given to early diagnosis and prompt, effective treatment of the source case together with isolation of the patient when necessary. The insidious development of symptoms in most cases of TB commonly results in a delay of weeks or months before the patient presents for diagnosis. At that point, when the patient is often at his or her most infectious, any further delay caused by the physician, nurse or system allows unnecessary transmission to others. Maintaining an appropriate awareness of TB among health care providers is thus critical to reducing transmission and initiating early prevention and treatment. Administrative and engineering controls that aim to reduce exposure in health care and other congregate settings complement—but cannot replace—prompt diagnosis and appropriate therapy. Methods once thought to be important in preventing the transmission of TB – disposing of such personal items as cloths or bedding, sterilizing fomites, using caps and gowns, gauze or paper masks, boiling dishes and washing walls – are unnecessary, because they have no bearing on airborne transmission.

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# REFERENCES

1. Wells WF. *Airborne Contagion and Air Hygiene.* Cambridge, MA: Harvard University Press, 1995.

2. Murray JF. Bill Dock and the location of pulmonary tuberculosis: how bed rest might have helped consumption. *Am J Respir Crit Care Med* 2003;168:1029-33.

3. Woolwine SC, Bishai WR. Overview of the pathogenesis of tuberculosis from a cellular and molecular perspective. In: Raviglione MC, ed. *Reichman and Hershfield's Tuberculosis, A Comprehensive International Approach, 3rd Edition.* New York: Informa Healthcare, 2006;101-16.

4. Ghon A. *The Primary Lung Focus of Tuberculosis in Children.* London, UK: Churchill, 1916.

5. Allen EA. Tuberculosis and other mycobacterial infections of the lung. In: Thurlbeck WM, Churg AM, eds. *Pathology of the Lung* (2nd edition). New York: Thieme Medical Publishers Inc., 1995;229-302.

6. Perez-Valez CM, Marais BJ. Current concepts: tuberculosis in children. *N Engl J Med* 2012;367(4):348-61.

7. Daley CD, Small PM, Schecter GS, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *N Engl J Med* 1992;326:231-35.

8. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intrathoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004;8:392-402.

9. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4$^+$ T lymphocyte count. *Tubercle Lung Dis* 1995;76:518-21.

10. Burman WJ, Jones BE. Clinical and radiographic features of HIV-related tuberculosis. *Semin Respir Infect* 2003;18:263-71.

11. Stead WW, Kerby GR, Schleuter DP, Jordahl CW. The clinical spectrum of primary tuberculosis in adults. Confusion with reinfection in the pathogenesis of chronic tuberculosis. *Ann Intern Med* 1968;68:731-44.

12. Langlois-klassen D, Wooldrage KM, Manfreda J, et al. Piecing the puzzle together: foreign-born tuberculosis in an immigrant receiving country. *Eur Respir J* 2011;38:895-902.

13. Wilson RJ, Pillay DG, Sturm AW. *Mycobacterium tuberculosis* is not an obligate aerobe. *J Infection* 1999;38:197-8.

14. Wayne LG, Diaz GA. Autolysis and secondary growth of *Mycobacterium tuberculosis* in submerged culture. *J Bacteriol* 1967;93:1374-81.

15. Wayne LG, Lin KY. Glyoxylate metabolism and adaptation of *Mycobacterium tuberculosis* to survival under anaerobic conditions. *Infect Immun* 1982;37:1042-49.

16. Achkar JM, Jenny-Avital ER. Incipient and subclinical tuberculosis: defining early disease in the context of immune response. *J Infect Dis* 2011;204:S1179-86.

17. Lawn SD, Wood R, Wilkinson RJ. Changing concepts of "latent tuberculosis infection" in patients living with HIV infection. *Clin Devop Immunol* 2011;doi:10.1155/2011/980594.

18. Robertson BD, Altmann D, Barry C, et al. Detection and treatment of subclinical tuberculosis. *Tuberculosis* 2012;92:447-52.

19. Ferguson RG. *Studies in Tuberculosis*. Toronto: University of Toronto Press, Canada, 1955.

20. Gryzbowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Report #3 of TSRU. *Bull Int Union Tuberc* 1975;50:90-106.

21. Houk V, Kent D, Baker J, et al. The Byrd Study. *Arch Environ Health* 1968;16:4-6.

22. Houk V, Baker J, Swensen K, Kent D. The epidemiology of tuberculosis in a closed environment. *Arch Environ Health* 1968;16:26-35.

23. Andres JR, Farzad N, Wolensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with *Mycobacterium tuberculosis. Clin Infect Dis* 2012;54:784-91.

24. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect* 1997;119:183-201.

25. Cohen T, Murray M. Incident tuberculosis among recent US immigrants and exogenous reinfection. *Emerg Infect Dis* 2005;11;725-8.

26. Krivinka R, Drapela J, Kubik A, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia. Second report (1965-1972). *Bull World Health Organ* 1974;51:59-69.

27. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bull World Health Organ* 1982;60:555-64.

28. Dannenburg AM, Sugimoto M. Liquefaction of caseous foci in tuberculosis. *Am Rev Respir Dis* 1976;113:257-9.

29. Long R, Maycher B, Dhar A, Manfreda J, Hershfield E, Anthonisen N. Pulmonary tuberculosis treated with directly observed therapy: serial changes in lung structure and function. *Chest* 1998;113:933-43.

30. Lönnroth K, Castro K, Chakaya JM, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. *Lancet* 2010;375(9728):1814-29. DOI: 10.106/S0140-6736(10)60483-7.

31. Martineau AR, Nhamoyebonde S, Oni T, et al. Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa. *Proc Natl Acad Sci U S* 2011;108:19013-17.

32. Fares A. Seasonality of tuberculosis. *J Glob Infect Dis* 2011;3:46-55.

33. Willis MD, Winston CA, Heilig CM, Cain KP, Nicholas DW, Mac Kenzie WR. Seasonality of tuberculosis in the United States 1993-2008. *Clin Infect Dis* 2012;54:1553-60.

34. Stead WW, Lofgren JP, Senner JW, Reddick WT. Racial differences in susceptibility to infection with *M. tuberculosis. N Engl J Med* 1990;322:422-27.

35. Grigg ERN. Arcana of tuberculosis. *Am Rev Respir Dis* 1958;78:151-72.

36. Greenwood C, Fujiwara T, Boothroid L, et al. Linkage of tuberculosis to chromosome 2q35 loci, including *NRAMP 1*, in a large Aboriginal family. *Am J Hum Genet* 2000;67:405-16.

37. Bellamy R. Susceptibility to mycobacterial infections: the importance of host genetics. *Genes Immun* 2003;4:4-11.

38. Pan H, Yan B-S, Rojas M, et al. *IPR1* gene mediates innate immunity to tuberculosis. *Nature* 2005;434:767-72.

39. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009;68(12):2240-06. DOI:10.1016/j.socscimed.2009.03.041

40. Mycobacteria. In: Fraser RS, Müller NL, Colman N, Paré PD, eds. *Diagnosis of Diseases of the Chest* (4th edition). Toronto: W.B. Saunders Company, 1999;798-873.

41. Adler JJ, Rose DN. Transmission and pathogenesis of tuberculosis. In: Rom WN, Garey S, eds. *Tuberculosis*. Toronto: Little, Brown and Company, 1996:129-40.

42. Bates JH. Transmission, pathogenesis, pathology and clinical manifestations of tuberculosis. In: Kubica GP, Wayne LG, eds. *The Mycobacteria: A Sourcebook. Part B (Microbiology Series, Vol. 15)*. New York: Marcel Dekker, Inc., 1984;991-1005.

43. How is tuberculosis transmitted? In: Iseman MD, ed. *A Clinician's Guide to Tuberculosis.* New York: Lippincott Williams and Wilkins, 2000;51-62.

44. Barnes P, Cave D. Molecular epidemiology of tuberculosis. *N Engl J Med* 2003;349:1149-56.

45. Rieder H. Infection with tubercle bacilli. In: Rieder H, ed. *Epidemiologic Basis of Tuberculosis Control.* Paris: International Union Against Tuberculosis and Lung Disease, 1999;17-63.

46. Barnes PF, Yang Z, Preston-Martin S, et al. Patterns of tuberculosis transmission in central Los Angeles. *JAMA* 1997:278:1159-63.

47. von Rie A, Warren R, Richardson M, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. *N Engl J Med* 1999;341:1174-79.

48. Ottenhoff THM. The knowns and unknowns of the immunopathogenesis of tuberculosis. *Int J Tuberc Lung Dis* 2012;16:1424-32.

49. Soysal A, Millington KA, Bakir M, et al. Effect of BCG vaccination on risk of *Mycobacterium tuberculosis* infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005;366:1443-51.

50. Eisenhut M, Paranjothy S, Abubakar I, et al. BCG vaccination reduces risk of infection with *Mycobacterium tuberculosis* as detected by gamma interferon release assay. *Vaccine* 2009;27:6116-20.

51. Eriksen J, Chow JH, Mellis V, et al. Protective effect of BCG vaccination in a nursery outbreak in 2009: time to reconsider the vaccination threshold? *Thorax* 2010;65:1067-71.

52. Roy RB, Sotgiu G, Altet-Gómez N, et al. Identifying predictors of interferon-γ release assay results in pediatric latent tuberculosis: a protective role of bacillus Calmette-Guérin? A pTB-NET collaborative study. *Am J Respir Crit Care Med* 2012;186:378-84.

53. Curtis AB, Ridzon R, Vogel R, McDonough S, et al. Extensive transmission of *Mycobacterium tuberculosis* from a child. *N Engl J Med* 1999;341(20):1491-95.

54. Starke JR. Transmission of tuberculosis to and from children and adolescents. *Semin Pediatr Infect Dis* 2001;12:115-23.

55. Menzies D. Issues in the management of contacts of patients with active pulmonary tuberculosis. *Can J Public Health* 1997;88:197-201.

56. Van Zwanenberg D. The influence of the number of bacilli on the development of tuberculosis disease in children. *Am Rev Respir Dis* 1960;82:31-44.

57. Shaw JB, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. *Am Rev Tuberc* 1954;69:724-32.

58. Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. *Tubercle* 1976;57:275-99.

59. Van Geuns HA, Meijer J, Styblo K. Results of contact examination of Rotterdam, 1967-1969. *Bull Int Union Tuberc* 1975;50:107-21.

60. Loudon RG, Romans WE. Cough frequency and infectivity in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1969;99:109-11.

61. Rose CE, Zerbe GO, Lantz SO, Bailey WC. Establishing priority during investigation of tuberculosis contacts. *Am Rev Tuberc* 1979;119:603-09.

62. Snider DE, Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug susceptible bacilli. *Am Rev Resp Dis* 1985;132:125-32.

63. Yeager H Jr, Lacy J, Smith LR, et al. Quantitative studies of mycobacterial populations in sputum and saliva. *Am Rev Respir Dis* 1967;95:998-1004.

64. Gryzbowski S, Allen E. The challenge of tuberculosis in decline. *Am Rev Respir Dis* 1964;90:707-20.

65. Lohmann EM, Koster BFPJ, le Cassie S, et al. Grading of positive sputum smear and the risk of *Mycobacterium tuberculosis* transmission. *Int J Tuberc Lung Dis* 2012;16(11):1477-84.

66. Behr MA, Warren SA, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* 1999;353:444-49.

67. Hernandez-Garduno E, Cook V, Kunimoto D, et al. Transmission of tuberculosis from smear negative patients: a molecular epidemiology study. *Thorax* 2004;59:286-90.

68. Catanzaro A. Nosocomial tuberculosis. *Am Rev Respir Dis* 1982;125:559-62.

69. Bailey WC, Gerald LB, Kimerling ME, et al. Predictive model to identify positive tuberculosis skin test results during contact investigations. *JAMA* 2002;287:996-1002.

70. Marks SM, Taylor Z, Qualls NL, et al. Outcomes of contact investigations of infectious tuberculosis patients. *Am J Respir Crit Care Med* 200;162:2033-8.

71. Lau A, Barrie J, Winter C, et al. The public health consequences of smear-positive pulmonary tuberculosis in patients with typical versus atypical chest radiographs. International Union against Tuberculosis and Lung Disease North American Regional Meeting. February 24-26, 2011, Vancouver, BC.

72. Muecke C, Isler M, Menzies D, et al. The use of environmental factors as adjuncts to traditional tuberculosis contact investigation. *Int J Tuberc Lung Dis* 2006;10:530-35.

73. Rieder HL. The infectiousness of laryngeal tuberculosis: appropriate public heath action based on false premises. *Int J Tuberc Lung Dis* 2009;13:4-5.

74. Louden RG, Roberts RM. Droplet expulsion from the respiratory tract. *Am Rev Respir Dis* 1967;95:435-42.

75. Louden RG, Roberts RM. Singing and the dissemination of tuberculosis. *Am Rev Respir Dis* 1968;98:297-300.

76. 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.

77. Sultan L, Nyka W, Mills C, et al. Tuberculosis disseminators: a study of the variability of aerial infectivity of tuberculosis patients. *Am Rev Respir Dis* 1960;82:358-69.

78. Riley RL, Mills CC, O'Grady F, 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.

79. Stein RA. Super-spreaders in infectious diseases. *Int J Infect Dis* 2011;15:e510-e513.

80. Jindani A, Aber VR, Edwards EA, et al. The early bacteriocidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1980;121:939-49.

81. Fennelly KP, Martyny JW, Fulton KA, et al. Cough generated aerosols of *Mycobacterium tuberculosis. Am J Respir Crit Care Med* 2004;169;604-09.

82. Long R, Bochar K, Chomyc S, et al. Relative versus absolute noncontagiousness of respiratory tuberculosis on treatment. *Infect Control Hosp Epidemiol* 2003;24:831-38.

83. Hopewell PC. Factors influencing the transmission and infectivity of *Mycobacterium tuberculosis*: implications for clinical and public health management. In: Sande MA, Hudson LD, Root RK, eds. *Respiratory Infections*. New York: Churchill Livingstone, 1986;191-216.

84. Albanna AS, Reed MB, Kotar KV, et al. Reduced transmissibility of East African Indian Strains of *Mycobacterium tuberculosis. PLoS One* 2011; 6:e25075.doi:10.1371/journal.pone.0025075.

85. Middlebrook G, Cohn ML. Some observations on the pathogenicity of isoniazid-resistant variants of tubercle bacilli. *Science* 1953;118 (3063):297-99.

86. Schaaf HS, Marais BJ, Hesseling AC, et al. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. *Acta Paediatr* 2006;95:523-8.

87. Moss AR, Alland D, Telzak E, et al. A city wide outbreak of a multiple-drug-resistant strain of *Mycobacterium tuberculosis* in New York. *Int J Tuberc Lung Dis* 1997;1:115-21.

88. Drobniewski F, Balabanova Y, Nikolayevsky V, et al. Drug-resistant tuberculosis, clinical virulence, and the dominance of the Beijing strain family in Russia. *JAMA* 2005;293:2726-31.

89. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006;368:1575-80.

90. Langlois-Klassen D, Senthilselvan A, Chui L, et al. Transmission of *Mycobacterium tuberculosis* Beijing strains, Alberta, Canada, 1991-2007. *Emerg Infect Dis* (in press).

91. Edwards LB, Tolderlund K. BCG vaccine studies. 3. Preliminary report on the effect of sunlight on BCG vaccine. *Bull World Health Organ* 1952;5:245-48.

92.    Edwards LB, Dragsted I. BCG vaccine studies. 4. Further observations on the effect of light on BCG vaccine. *Bull World Health Organ* 1952;5:333-36.