Tuberculosis in the Global Aging Population

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KEYWORDS

• Tuberculosis • Aging • Epidemiology • Prevention

EPIDEMIOLOGIC TRANSITION OF TUBERCULOSIS

Aging of the Tuberculosis Patient Population

Tuberculosis (TB) can attack people of any sex, age, or socioeconomic class. In reality, TB is likely to claim its greatest toll from certain strata of the population, and it is important to identify these for the purpose of planning and implementing TB control. **Fig. 1** presents the age-specific incidence rate of TB and the age distribution of TB patients in the United States[1] and Africa[2] (countries belonging to the African Region of the World Health Organization), representing countries with a low and high prevalence of TB, respectively. Here, ''TB'' refers to smear-positive TB for Africa, and TB of all forms for the United States. Also, for the United States it is limited to TB in whites, as 58% of the TB patients in the United States are foreign-born and have clearly distinct epidemiologic characteristics.

The epidemiologic situations with respect to TB in Africa and the United States are tremendously different, with incidence rates of smear-positive TB for the entire population of 124 and 1.1, respectively. A similar difference appears with regard to age-specific statistics. The incidence rate curve in Africa has a peak at 25 to 44 years of age that goes downward thereafter, whereas in the United States it goes up monotonically with age. As for the age composition of the patients, in Africa the age group of 15 to 44 years comprises 74% of the population, whereas in the United States it is only 24%, and instead the age group of 65 years and older occupies 35% (vs only 4% in Africa). It is apparent that in high-prevalence settings TB is badly affecting the most productive age groups. On the other hand, TB is now becoming a serious health issue of elderly persons in low-prevalence countries.

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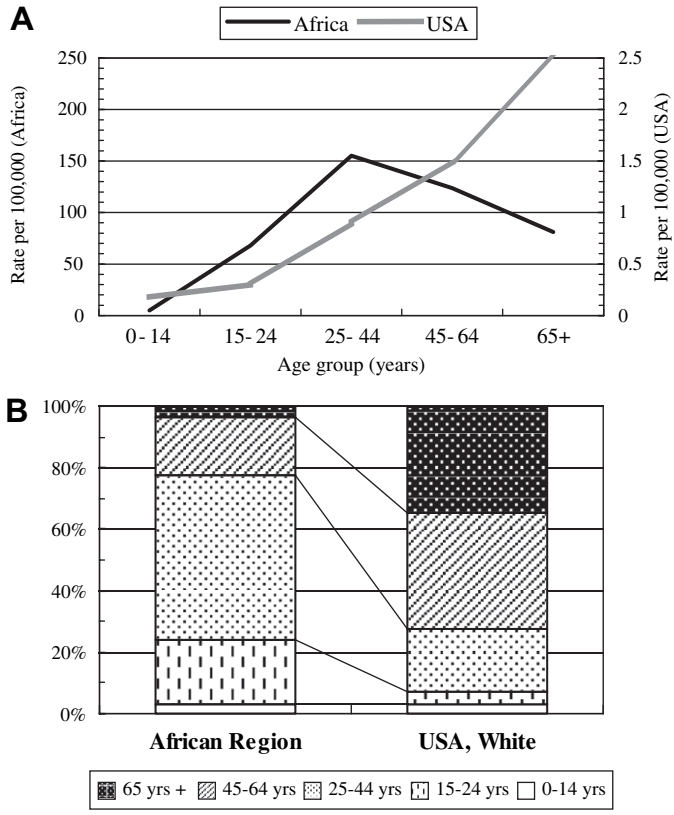

Fig. 1. (*A*) Age-specific notification rate (Africa: smear-positive TB; United States, white: all forms, 2007). (*B*) Newly notified cases according to age groups (Africa: smear-positive TB; United States, white: all forms, 2007). (*Data from* CDC. Reported tuberculosis in the United States, 2007. Atlanta (GA): US Department of Health and Human Services, CDC; 2008; and World Health Organization. Global tuberculosis control: epidemiology, strategy, financing. Geneva: WHO report; 2009. WHO/HTM/TB/2009.411.)

A similar comparison can be observed in the historical changes of TB within the same population. In Japan, TB mortality has changed dramatically in its level and age pattern from 1940 through 1990 (**Fig. 2**). **Fig. 3** presents the TB notification rates as well as the age composition of newly notified patients for the years 1962 and 2005 in Japan.[3] The notification rate for all ages was 303 (per 100,000 population) in 1962 and had fallen greatly to 22 by 2005. At the same time, the age strata of the population affected by the disease have changed drastically. The age-specific notification rate increased continuously with age during both years, but the gap between the young and the aged groups has recently become wider. Also, in 1962 a majority (65%) of the patients were aged 20 to 59 years, whereas in 2005 this group was replaced by those aged 60 years or older (60%), a group that accounted for only 16% in 1962.

When TB was prevalent globally, covering Europe and the United States during the nineteenth and early twentieth centuries, it was a problem of youth or middle age and was supposed to be rare in old age.[4,5] Such is characteristic of the current situation in Africa and that of the Japan in the past. When the level of epidemics is reduced, the problem of old age emerges to a varying extent.

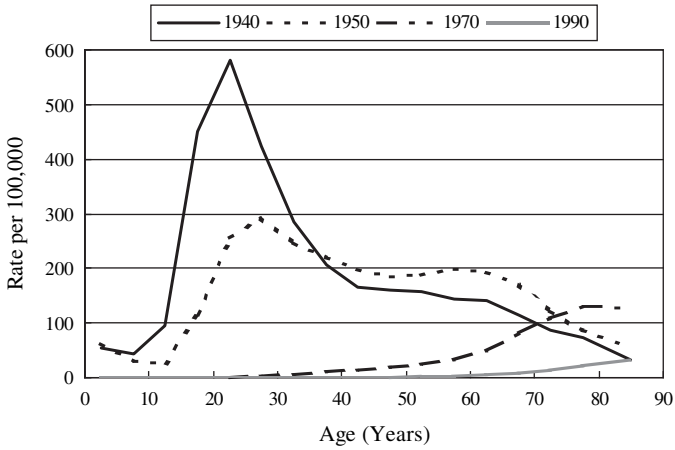

Fig. 2. Age-specific tuberculosis mortality rate of selected years, Japan. (*Data from* Ministry of Health, Labor & Welfare of Japan. Tuberculosis surveillance annual report 2006.)

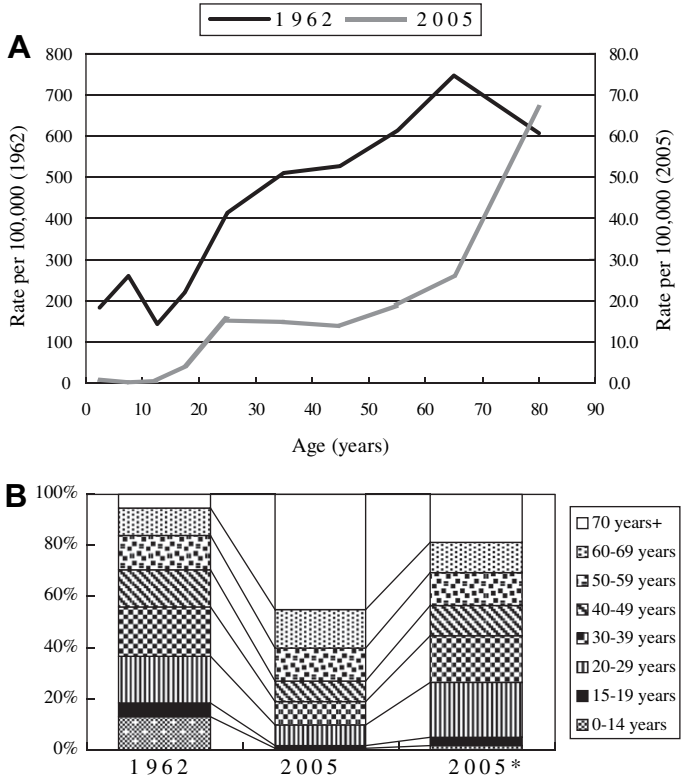

Fig. 3. (*A*) Case notification rates for 1962 and 2005, Japan, TB of all forms. (*B*) Distribution of notified cases according to age group, Japan, 1962 and 2005, TB of all forms. (*Data from* Ministry of Health, Labor & Welfare of Japan. Tuberculosis surveillance annual report 2006. Tokyo: Japan Anti-Tuberculosis Association; 2006.)

Aging of the Population

In many countries and areas, the decline of TB epidemics and the aging of the population are occurring in parallel. The drift of TB into aged people is ascribed greatly to the aging of the entire population, distinct from any epidemiologic changes. Taking the aforementioned example of the United States and Africa, the proportion of population older than 65 years is 13% and 6%, respectively, meaning that a considerable part of the predominance of the aged seen in the United States could be attributed to its aged population. Similarly, in Japan the proportion of those older than 60 years has increased from 9% in 1962 to 28% in 2005. The impact of this change is illustrated in **Fig. 3**B, in which the age composition of new cases in 2005 was adjusted by applying the age-specific rates of that year to the population structure of 1962. If it were not for the population aging, the proportion of those 60 years and older would have been 31%, meaning that about half (but not all) of the observed proportion of elderly patients could be explained by the aging population.

However, the effects of the aging population on TB epidemiology are complicated. If the aged population grows together with a decline in the overall incidence rate, the latter may slow down due to the higher level and slower decline of incidence in the elderly, as observed in Japan after the 1980s. As a result, the decline of infection sources within the population may be hampered. Infection can be transmitted to all age groups, thereby retarding the decline in age-specific case rates. Also, in the growing elderly population segment, there are more subjects with various health problems, such as underlying illnesses or risk factors that would predispose them to TB, and these may in turn have repercussions on the TB problem for the entire population.

Burden of Infection in the Older Age Group

The most basic index of TB epidemiology is annual risk of infection (ARI). The accumulated effect of ARI on each cohort is indicated by the age-specific prevalence of TB infection, as seen in **Fig. 4** for Japan.[6] This estimate is based on the tuberculin survey results and mathematical modeling. The prevalence of infection thus estimated for 1950, when the TB mortality rate was 146 per 100,000, was 50% at age 20 and older, and 90% at age 60. In those days, mortality was highest in the 20s and 30s age groups. In 2005, the prevalence of infection was as low as 1% at age 20, but as high as 56% in the 60s and 70% in the 70s. This trend implies that the current aging of TB disease rates is a reflection of the overwhelming concentration of the infected into the older age segments of the population. In 2005, out of all infected subjects, 74% were 60 years or older, and 91% were older than 50.

At the same time, the risk of progression from infection to disease is not excessively high in the older subjects as compared with those of younger age. By dividing the incidence rate by the prevalence of infection for each age group, one can derive the risk of progression to clinical disease. As shown in **Fig. 4**B, an age-dependent profile with a young adult peak is seen, rather similar to what is observed for TB incidence rate in high-prevalence settings (see **Fig. 2**). The gradually declining risk after the 30s may be due to the passing of time after the primary infection. Indeed, for those aged 70 to 74 years in 2005, it is estimated that 80% of the infection was acquired before 1950.

Cohort Effect

Apart from the changing pattern of the age-specific prevalence of infection in the face of declining epidemics, the generation or cohort effect is another important epidemiologic mechanism that drives the change in age pattern of TB with time. This theory assumes that a generation of people born during a certain time period, that is, a cohort,

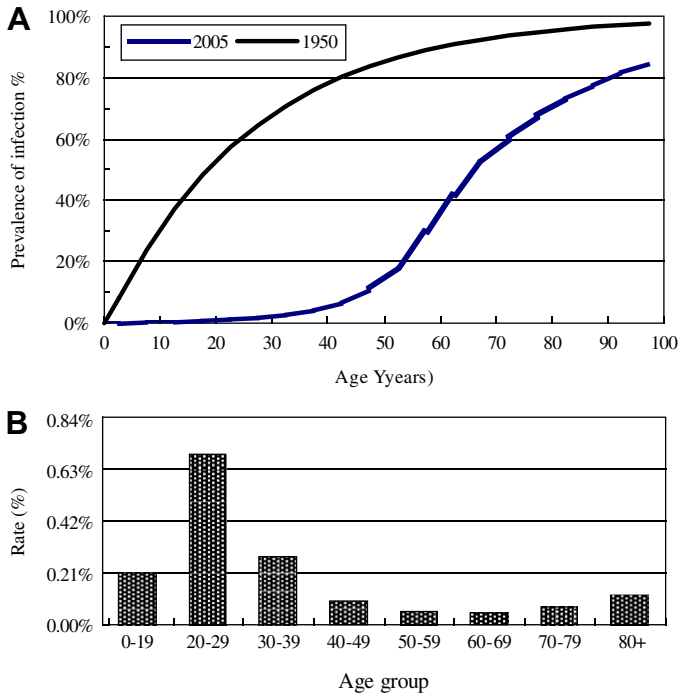

Fig. 4. (*A*) Estimated age-specific prevalence of infection, Japan, 1950 and 2005. (*B*) Estimated rate of development of TB from the infected, Japan, 2005. (*Data from* Mori T. Some recent aspects of tuberculosis infection in Japan (2). Kekkaku 1988;63:39–48 [in Japanese].)

shares the same age-dependent risk of disease development as cohorts born at other time. However, if the exposure level decreases with time, a higher burden of infection remains in the older cohorts, which is manifest by increasing disease risk with age at cross-sectional analysis. Thus, high levels of disease risk in old age indicate the residual effects of higher risks of infection earlier in life.[7] As Powell has said,[8] the fact that the pool of infected persons from which cases of disease arise is becoming older signifies the continuing success of the battle against TB.

Not Just Cohort Effect

However, there are some cases that indicate a deviation from the cohort model when analyzed closely. Tocque and colleagues[9] performed cohort analyses of the TB notification rates in Hong Kong and in England and Wales. In Hong Kong, each birth cohort exhibited a similar age pattern of notification rates, peaking in the 25 to 39 age group and gradually declining thereafter. After 1978, all cohorts exhibited an increase in rates with increasing age (**Fig. 5**). For England and Wales, the decline of the rates with age ceased in 1984. A similar discontinuation of the decline in the incidence rate in later life was observed in Japan after 1990. As shown in **Fig. 4**B, there is also an increase in the risk of developing disease after 60 years of age, even after controlling for difference in the prevalence of infection. Regarding the reasons for this recent irregular trend, Tocque and colleagues argued for the possibility of immunologic incompetence due to the pattern of aging leading to exogenous reinfection and reactivation. In England

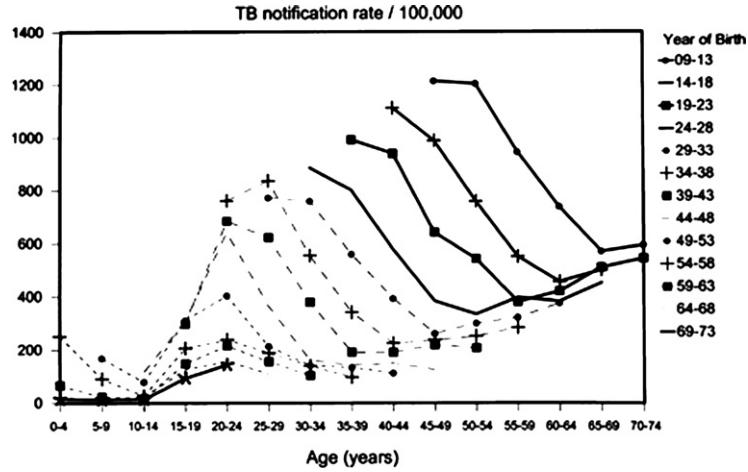

Fig. 5. Age-specific pattern of TB in 13 cohorts born between 1909 to 1913 and 1969 to 1973 in Hong Kong males. (*From* Tocque K, Bellis MA, Tam CM, et al. Long-term trends in tuberculosis. Comparison of age-cohort data between Hong Kong and England and Wales. Am J Respir Crit Care Med 1998;158:485; with permission.)

and Wales, increased infection during the War years is suspected as a possible cause.[10] For Japan, it has been argued that the cohorts infected around the end of the War under conditions of serious malnutrition may run a higher risk of disease that has lasted to the present day. A more plausible reason that could explain such a phenomenon across different localities might have been the attenuation of the natural selective forces for survival with the continuing socioeconomic development and improvement in health care. Whereas only few of the fittest could have survived beyond 70 years in the early part of the last century, most children born nowadays are expected to live beyond that age in developed countries. With the increasing prevalence of chronic degenerative diseases among the elderly nowadays, it is perhaps not surprising to see a rising incidence of TB at this extreme of age nowadays. The effect of tobacco smoking on TB has been established,[11] and differences in prevalence of this habit among cohorts could also have contributed.

RISK FACTORS FOR TB

Demographic Factors

Aging itself is generally not an important risk factor of TB disease. As remote infection is much more likely in elderly subjects, they often run a lower risk of developing disease, primarily due to the longer time lapse since the primary infection and their status as selected survivors. However, at the same time they are likely to have various risk factors commonly associated with aging that may enhance the risk of disease development, or modify/complicate the clinical picture of TB.

As cited by Perez-Guzman and colleagues[12] in their meta-analysis of comparative studies between elderly and nonelderly TB patients, most of the available studies reported a male predominance among elderly TB patients. For Japan in 2005, notification rates of males and females per 100,000 population considered separately were 10.2 versus 8.7 for 0 to 39 years, 24.5 versus 9.0 for 40 to 59 years, and 70.5 versus 30.2 for 60 years and older,[3] indicating a remarkable sex difference beyond

the age of 40 years. For the United States in 2007, the rates were 4.0 versus 3.1 for age group of 0 to 44 years, 7.4 versus 3.3 for 45 to 64 years, and 9.4 versus 4.9 for 65 years and older,[1] also demonstrating a wider gap after the age of 45 years. The similar male predominance was reported from Hong Kong.[13] The reason for this male predominance in the TB rate may be at least partly ascribed to the more extensive social activity of males, exposing them to infection and in turn leading to TB disease.[12]

Smoking and Comorbidities

In a prospective study of older subjects on the risk of TB development, Leung and colleagues[14] found that TB incidence was clearly higher in current smokers (2.6 times that of nonsmokers). These investigators also calculated that 33% of male TB cases and 9% of female TB cases is attributable to smoking, which may partly explain these sex differences. Moreover, the recent deviations in the cohort pattern of notification rates can be related to recent changes in smoking habits within the cohorts.

Other factors analyzed by Perez-Guzman and colleagues[12] that were found to be significantly more common in elderly patients included cardiovascular diseases, chronic obstructive pulmonary disease, diabetes mellitus, a history of gastrectomy, and malignancy. These diseases or conditions are more common in the elderly than in the general population, and the contribution of diabetes, gastrectomy, and malignancy to TB has been well documented.

As for diabetes, Ponce-de-Leon and colleagues[15] found in a survey in Mexico that subjects with diabetes had a prevalence rate of TB 6.8 times higher than the general population. In a prospective study conducted in Korea from 1988 to 1990, people with diabetes were found to have an incidence rate of TB 3.47 times higher (5.15 times for bacteriologically confirmed TB) than those without diabetes.[15,16] In Japan's surveillance report, the proportion of reported diabetes cases among newly notified TB patients was 7.0% for those younger than 60 years but 15.2% for those aged 60 years and older.[17] The contribution of diabetes to TB appears not only in its higher disease development but also in causing rapid progress of the illness, a poor treatment response,[18] and a greater risk of relapse.

In Hong Kong, TB patients older than 60 years were known to have more underlying diseases, including diabetes (in 16.6%, compared with 6.2% for those younger than 60 years), silicosis (2.3% vs 1.0%), liver disease (2.1% vs 1.4%), lung cancer (1.6% vs 0.3%), and other malignancies (1.2% vs 0.2%).[19] Korzeniewska-Kosela and colleagues[20] also reported that elderly patients had cancers other than lung cancer 3.94 times more frequently than younger patients.

Interacting Effects/Environment

The changes in immunity associated with advanced age is well known from many observations of waning tuberculin reactions, or even anergy, among both TB patients and healthy subjects at the upper extreme of age.[21,22] All of the illnesses or conditions cited above are supposed to promote these immunity changes, thus creating a predisposition for the development of clinically manifest disease.

Finally, there is the issue of elderly subjects living in nursing homes or other congregate facilities. In such facilities in the United States, tuberculin positivity has been reported at higher levels and outbreaks of TB have not been rare.[23,24] Staff members at these facilities are also known to have a higher risk of TB. Similar observations were made in Hong Kong as well.[25] However, no such problem was found in similar facilities in Canada.[26] Further studies are warranted to address this issue properly.

PREVENTIVE TREATMENT

Goal of Intervention

Infection is the prerequisite for development of disease. Preventive treatment for TB generally refers to the screening and treatment of latent TB infection (LTBI). Like that for other infectious diseases, it serves 2 main functions: personal protection and public health control.

TB is a chronic infection. Although the risk of disease is highest in the first 2 years after infection, considerable magnitude of risk persists for their lifetime.[27] As discussed earlier, there is generally excess risk of LTBI among the elderly segment of the indigenous population in developed countries,[28,29] likely reflecting the much higher burden of TB in the past decades. With the waning immunity associated with advance age and increasing prevalence of multiple comorbidities, there is often an excess risk for the development of clinical disease. Indeed in Hong Kong, there is up to a 100-fold risk differential between elderly men aged 75 or older and those aged 14 or younger (**Fig. 6**).[30] Smoking,[13] low body mass index,[31] and poorly controlled diabetes mellitus[32] have been associated with an increased risk of TB among an elderly cohort in the same locality. Furthermore, TB often presents atypically among the elderly.[12,13] Delay in diagnosis and treatment, coupled with poorer drug tolerance, accounts for the much higher mortality among this group.[13] Screening and treatment of LTBI can, at least in theory, help to avert morbidity and mortality in this age group.

TB is an airborne infectious disease and a major killer in the history of mankind. There is, perhaps, a more important public health dimension in the screening and treatment of LTBI. It is estimated that 2 billion people worldwide have LTBI.[33] There is little doubt that treatment of active disease by DOTS (Directly Observed Treatment Short-course) remains the key strategy to bring the transmission risk under rapid control in most high-incidence countries. However, such a strategy alone cannot

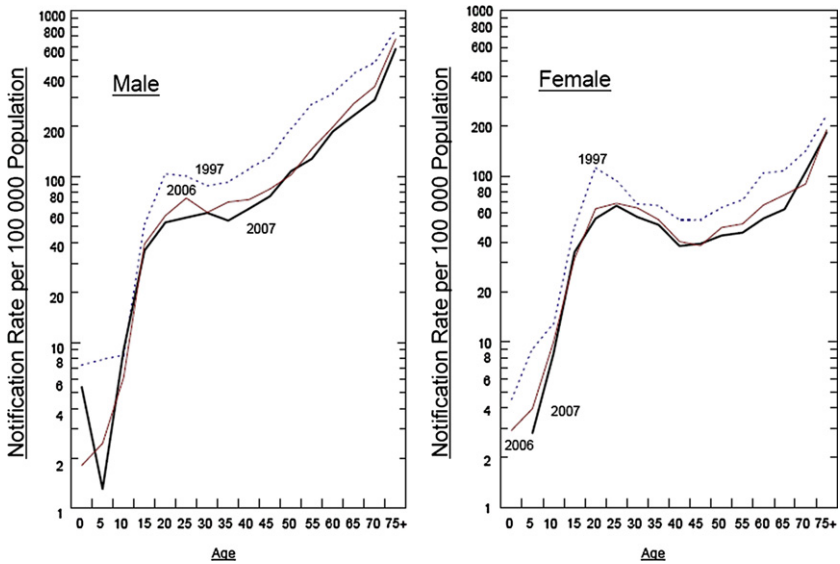

Fig. 6. Sex- and age-specific tuberculosis notification rate in Hong Kong, 1997, 2006 and 2007. (*Data from* Tuberculosis and Chest Service. Annual Report of Tuberculosis and Chest Service 2007. Hong Kong (China): Department of Health; 2009.)

tackle the continuing development of disease by endogenous reactivation among those latently infected. In many intermediate burden areas, where the transmission risk has been brought under control either by natural decline or the introduction of effective chemotherapy, endogenous reactivation of LTBI among the elderly segment of the population accounts for the increasing proportion of TB cases.[30,34] In contrast to the treatment of active disease by DOTS, screening and treatment of LTBI, if implemented on a population scale, has the potential to tackle the large pool of infected individuals across successive birth cohorts, and thereby to bring the disease under more rapid control. However, the limitations of existing diagnostic and treatment tools must be overcome before such an ambitious goal can be realized.

Screening Tools for LTBI

With a very low bacillary load and in the absence of clinical manifestations, the diagnosis of LTBI involves measurement of the specific host immune responses to the pathogen. Serologic tests have contributed remarkably in the diagnosis of many viral infections, even when the there is difficulty in isolating the causative organism. For TB, the situation is much more complex. The human body appears to rely mainly on cellular immune response to defend against the tubercle bacillus. Humoral responses are variable and inconsistent. No serologic test has been conclusively found to be useful for the diagnosis of either TB infection or disease.[27,35,36] The diagnosis of LTBI therefore relies on the measurement of cellular responses to TB antigens, either in vivo with the tuberculin skin test or in vitro with the interferon-γ release assays (IGRAs). **Table 1** summarizes the characteristics of the currently available diagnostic tools for TB infection. The tuberculin skin test (TST), which measures the in vivo cellular immune response to intradermally injected purified protein derivatives (PPD) of the human tubercle bacillus, has been the gold standard test for diagnosis of LTBI for many years. As TST is cross-reactive to bacillus Calmette-Guérin (BCG) and nontuberculous mycobacteria, a relatively high specificity is attainable often at the expense of sensitivity, especially among BCG-vaccinated populations. However, cross-reactivity to BCG is usually not a major issue among the elderly, as few of them would have the opportunity of being vaccinated with BCG during their childhood. On the other hand, the immunologic response to the injected antigens does vary with age and host immunologic status. Multiple cut-offs are therefore recommended to give the best predictive values under different clinical[27] and epidemiologic situations.[27,30,37] The tuberculin response is often found to be diminished among the elderly,[22,38] but substantial disease risk is still found among those with a negative tuberculin response, especially among those with a body mass index (weight in kilograms divided by height in meters squared) below 18.5.[29] The need for a separate test-reading visit and potential boosting of response on serial testing also affect its field application, especially in marginalized population segments or institutional settings.[27] Although repeat testing within 2 weeks is sometimes recommended to pick up infected negatives among the elderly, this has been found to decrease the specificity of TST in identifying active TB on follow-up in a recent Hong Kong study.[29]

With advances in immunology and genomics, several relatively specific antigens have been discovered in the pathogenic *Mycobacterium tuberculosis* complex. These antigens include the early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10), which are encoded by genes located in the Region of Difference (RD-1) of the bacillary genome, and are absent in all BCG strains and most environmental mycobacteria (with the exception of *Mycobacterium szulgai*, *Mycobacterium marinum*, *Mycobacterium flavescens*, and *Mycobacterium kansasii*). The newly introduced IGRAs, QuantiFERON TB Gold (QFT-G), QuantiFERON TB Gold in-Tube

Table 1
Comparison of available tests for TB infection

	Tuberculin Skin Test	QuantiFERON TB-Gold/IT	T-Spot.TB
Antigens	Complex: purified protein derivative Cross reaction: BCG, other mycobacteria	Specific:ESAT6, CFP10, TB7.7 Absent in BCG and most NTM	Specific: ESAT6, CFP10 Absent in BCG and most NTM
Test method	Skin test: intradermal/multiple puncture; 2 visits	Whole blood interferon assay; single visit	Blood monocyte spot test; single visit
Laboratory support	No; clinic/bedside procedure	High; fresh blood delivery	Highest; fresh blood delivery
Cell separation	No	No	Yes
Cost	Relatively low	High	Highest
Interference by BCG	Yes	No	No
Booster effect	Yes (2 tests >1 wk to exclude booster)	No (good for serial testing)	No (good for serial testing)
Choice of cut-off	5, 10, 15 mm in different clinical scenarios Trade-off: sensitivity and specificity Higher disease risk with larger induration	Single Not fully clarified yet Not fully clarified yet	Single Not fully clarified yet Not fully clarified yet
Conversion	Criterion established for recent conversion	Not fully clarified yet	Not fully clarified yet
Infection or disease	Do not distinguish	Do not distinguish	Do not distinguish
Recent versus remote	Do not distinguish	Do not distinguish adequately	Do not distinguish adequately
Exposure correlation	Some	Higher	Higher/highest
Immune compromise	Affected significantly	Less affected	Least affected
Advance age	Significantly affected	Less affected	Less affected
Proxy sensitivity[a]	71%–82%	QFT-Gold: 73%–82%; QFT-Gold IT: 63%–78%	86%–93%
Proxy specificity[b]	No BCG: 95%–99%; BCG: low and heterogeneous	No BCG: 98%–100%; BCG: 94%–98%	86%–100%
Longitudinal data	Abundant	Scant	Scant

Abbreviations: BCG, bacillus Calmette-Guérin; NTM, nontuberculous mycobacteria.
[a] Positive rate among patients with culture confirmed tuberculosis.
[b] Negative rate among low risk individuals.

(QFT-G-IT) (Cellestis Ltd, Carnegie, Victoria, Australia), and the T-SPOT.TB test (Oxford Immunotec, Oxford, UK) measure the release of interferon-γ by blood monocytes on stimulation by these specific antigens. In the absence of a gold standard for LTBI, surrogate measures like positive rate among culture-confirmed TB (for sensitivity) and negative rate among subjects with low risk for TB infection (for specificity) were used in most of the available studies evaluating the performance of TST and IGRAs.[39] The performance of IGRA has also been evaluated by correlating test results with TB exposure factors[40] and BCG status.[39] In general, studies have demonstrated similar levels of specificity for IGRAs and independence from BCG status.[39] The sensitivity of IGRAs has been shown to be at least equivalent to that of TST and superior with T-SPOT.TB among human immunodeficiency virus (HIV)-infected children, the severely malnourished, and children younger than 3 years. The IGRAs also appear to be less affected by advance age in comparison with the TST.[41–44] It should be noted, however, that the IGRAs still measure the host's immunologic reaction to the tubercle bacillus. As such, they might be affected by the host immune status, though possibly by a lesser degree than TST. Although they have several operational advantages, such as completion of test in one visit, results available in 24 hours, absence of inter- and intraobserver divergence, detection of potential immunodepression, and avoidance of the booster phenomenon, the need for delivery of fresh blood, lengthy laboratory processes, and high costs may limit their large-scale application in most TB-endemic areas.

In the clinical application of both TST and IGRAs, it is of importance that clinically manifest disease only develops in a minority of infected subjects after a highly variable latent period. Using development of active disease as the end point, the predictive values of all available LTBI tests are necessarily low. None of these tests are able to distinguish satisfactorily between recent and remote infection, latent infection and active disease, or untreated and treated infection/disease. Remote infection generally carries a much lower risk of disease development than recent infection.[27] The prevalence of background infection tends to increase with advance age and varies greatly between different places and settings, depending on past disease incidence and exposure pattern. These factors must be taken into careful consideration in the implementation of LTBI screening, either with traditional TST or the more specific IGRAs, among the elderly, especially in high TB burden settings. Better cost-effectiveness can often be achieved by a more targeted approach, focusing on defined risk groups such as those with a higher chance of recent infection (eg, recent household or institutional contacts) or a higher risk of reactivation (eg, HIV-infected subjects, silicosis, and immunosuppressive therapy, and so forth).

While isolation of *Mycobacterium tuberculosis* complex is often regarded as the gold standard in the diagnosis of active TB disease, conventional cultures take a very long time and bacteriologic confirmation is never established in at least 15% to 20% of cases. As TB disease must be preceded by infection, attempts have been made to evaluate the potential roles of the new IGRAs in the diagnosis of active TB disease, especially among children[43] and the elderly.[22] Unfortunately, conflicting results are obtained depending on the prevalence of the target conditions in the study population and the background prevalence of LTBI.[45,46] Untreated active TB disease carries very substantial morbidity and mortality, especially among the elderly. The sensitivity and specificity of both TST and IGRAs are not adequate to rule in or rule out active disease,[27,39] even though a positive or negative result might affect the likelihood of the presence or absence of disease. Account must therefore be taken of the overall clinical and epidemiologic situation in reaching a sensible diagnosis.[47]

Treatment of LTBI

Isoniazid monotherapy, either daily or twice weekly, for 9 months is currently the recommended regimen for treatment of LTBI in United States,[27] while a 6-month regimen is adopted in Hong Kong.[30,48] In the International Union Against Tuberculosis (IUAT) Trial, a daily 52-week regimen of isoniazid was slightly more effective in reducing the risk of TB than a 24-week regimen (75% vs 65%) in persons with fibrotic lung disease.[49] The risk of hepatotoxicity with isoniazid was reported to be in the range of 0.5% to 1% in that trial and the United States Public Health Service (PHS) multicenter study.[50] The 24-week regimen prevented more cases of TB per case of drug-induced hepatitis in the IUAT trial,[51] and the cost per case of TB prevented by 6-month isoniazid was also shown to be half of that under the 12-month regimen.[52]

The risk of hepatotoxicity increases with age. In the PHS study, isoniazid-associated hepatitis occurred in 0% of those aged under 20, 0.3% from 20 to 34, 1.2% from 35 to 49, and 2.3% from 50 to 64 years.[50] In these early studies, the hospitalization rates were up to 5.0 per 1000 treatment initiations[49] and a mortality rate of 0.6 per 1000 persons was reported in the PHS study, even though liver cirrhosis might have been a confounding factor.[50] More recently, the rate of symptomatic hepatitis has been estimated to be 1 to 3 per 1000, and much lower hospitalization rates (0.1–0.2 per 1000) and mortality rates (0.0–0.3 per 1000) have been reported.[52,53]

Treatment with rifampicin at a dose of 10 mg/kg daily (maximum 600 mg) for 4 months is currently an acceptable alternative for treatment of LTBI.[27] Unlike isoniazid, there are only scant clinical data on its clinical efficacy, but hepatotoxicity risk appears to be low in the limited number of clinical studies.[48,54] The combination of rifapentine, 900 mg and isoniazid, 900 mg once weekly for 12 weeks was found to be well tolerated in a recent human trial.[55] Further clinical studies to address the tolerance and efficacy of this combination are ongoing. Despite initial favorable reports on the use of 2 months of rifampicin plus pyrazinamide in the treatment of LTBI among the HIV-infected persons,[56,57] such a regimen was associated with an unacceptably high incidence of hepatotoxicity in subsequent field surveillance[52] and clinical trials.[58,59] This result could not be entirely accounted for by risk factors like alcohol use or chronic viral hepatitis, but older age and concomitant use of other medications could have contributed.[59,60]

To minimize the risk of hepatotoxicity during the treatment of LTBI among the elderly, careful pretreatment assessment is needed to balance the benefit against the potential risk.[61] Close clinical monitoring is necessary during treatment. Patients should be thoroughly educated about the symptoms of hepatitis, and advised to report them promptly for early evaluation. Baseline and monthly (or biweekly) laboratory testing of liver enzymes is generally recommended for high-risk patients, especially for chronic alcohol users, HIV-infected persons, and those with chronic liver disease, or those taking concomitant hepatotoxic medications.[27,52] Isoniazid or rifampicin should be withheld as recommended if serum transaminase level is higher than 3 times the upper limit of normal in a symptomatic patient or 5 times the upper limit of normal in the absence of symptoms.[27,62]

OTHER PREVENTION STRATEGIES

Modification of Host Factors

As smoking[13] and poorly controlled diabetes mellitus[32] are proven risk factors for TB among the elderly, careful control of these risk factors by healthy lifestyle and careful management of comorbidities could make substantial contributions in reducing the TB morbidity and mortality among the elderly. Evidence is also accumulating in both

human and animal studies that undernutrition is associated with increased risk and severity of TB.[31,63,64] Maintaining a balanced diet with adequate protein, calories, and micronutrient intake is therefore important not only for general health but also for protection against the human tubercle bacillus, at no additional cost or potential risk. Both macronutrient and micronutrient deficiencies should be aggressively treated. Vitamin D deficiency has been implicated as a risk factor for TB,[65] but the role of vitamin supplementation in the absence of clinical deficiency has yet to be clarified.[66]

Tuberculosis Control in Elderly Institutions

In elderly institutions, the concentration of both potential infectious sources and susceptible contacts is conducive to the spread of TB. Although TB is an airborne disease, its infectivity decreases rapidly with effective treatment unless there is significant drug resistance. Early identification, separation, and treatment of symptomatic infectious cases therefore play a key role in infection control. Maintaining good ventilation and avoiding overcrowding are also important in reducing the risk of transmission. For nursing homes and other health care facilities, the established hierarchy of administrative, environmental, and personal protective measures should be followed to contain the infectious sources, reduce the environmental pathogen level, and protect those at risk of exposure.[67] Although indiscriminate chest radiography screening is unlikely to be cost-effective, preadmission examination of both staff and clients may serve a dual purpose: to avoid inadvertent introduction of infectious cases into the high-risk environment and to provide baseline results for later comparison. As intradermal injection of antigens is not involved in the new IGRAs, they have an advantage over TST in the serial surveillance of LTBI among staff and/or clients in some of these high-risk settings. However, previous sensitization by the antigens used for TST might still affect their own interpretation. Further studies are required to clarify their exact role, especially in high-burden settings.

CLINICAL DISEASE AMONG THE ELDERLY

Clinical Presentation and Diagnosis

Most TB in elderly persons occurs as a result of endogenous reactivation of remote infections. However, in low-prevalence situations, it includes many more cases of clinical disease in immunologically compromised subjects as compared with the younger age strata. This scenario often affects the clinical presentation of TB in elderly persons. Among a total of 25,311 newly notified patients in Japan in 2007, 17% had TB in sites other than the lung in those aged 14 to 59 years, while it was 24% in those older than 60 years. Miliary TB accounted for 3.3% of all TB for those aged 60 years or older, which was significantly high compared with 0.9% for younger subjects. Schluger[68] also mentioned that elderly patients are more likely to have extrapulmonary TB including miliary disease, although this was not supported in recent United States statistics[69] or in Hong Kong.[19] In Japan, 74% of pulmonary TB patients were bacteriologically confirmed cases for the age group 15 to 59 years, compared with 86% for those aged 60 years or older. A similar tendency was also seen in Hong Kong[13,19] and in the meta-analysis by Perez-Guzman and colleagues.[12]

Regarding the clinical presentation of TB, the meta-analysis of Perez-Guzman and colleagues[12] suggested that fever, sweating, and hemoptysis were less frequent in older patients, but dyspnea was more frequent, while there was no significant difference for coughing, sputum, loss of body weight, and fatigue or malaise. Leung and colleagues[13] also reported the same findings in their systematic comparison of old and young patients in Hong Kong. Laboratory findings

indicated that the tuberculin-positive rate, serum total protein level, and white blood cell counts were lower in elderly patients.[12,13] There was no difference between the two age groups in hemoglobin concentration or in liver transaminase activity.

Radiographic findings such as cavity formation and lesions in the upper lung area are supposed to be characteristic of the adult type (reactivation) TB. The meta-analysis by Perez-Guzman and colleagues[12] revealed that cavity formation is rare in elderly patients and that the upper zone predominance was similar for both age groups, whereas Leung and colleagues[13] found that the elderly patients have more extensive disease and lower zone involvement on chest radiograph. Chan-Yeung and colleagues[19] reported that cavitary lesions were seen in 16% of the aged patients, slightly lower than the 19% of younger patients. Morris[70] pointed out that the most common radiographic findings in the elderly or immunocompromised TB patients are opacity in the lower zone accompanied by basal effusion or thickening, and that the apical as well as lower lung cavity are rare. He also noted that disseminated lesions are rare but can occur in the absence of significant host reaction, resulting in an apparently normal radiograph.

The atypical clinical presentation of TB in the elderly can often make diagnosis difficult, and can be further complicated due to the coexistence of underlying illnesses. Diagnosis is sometimes made at a very late stage of the disease.[71] Perez-Guzman and colleagues[12] found a longer evolution time in elderly patients in their meta-analysis. The longer delay in presentation and start of treatment was seen in elderly patients in Hong Kong.[13] Thus, Iseman[72] stresses the importance of considering TB and careful history taking of exposure, followed by 3 sputum examinations. He also recommends sputum induction or gastric juice aspiration if voluntary production of sputum is difficult.

Treatment of Active Disease

In general, TB in elderly patients should be treated with the same treatment used for younger patients. However, special attention must be paid to preventing, detecting, and managing the adverse reactions of anti-TB drugs. Higher risk of hepatotoxicity is seen for isoniazid in those aged 50 years or older and in those with a previous history of liver disease. Similar caution should be taken when using rifampicin and pyrazinamide. Ethambutol can cause problems with the optic nerve, including disturbances of visual acuity and color sensation, which might be difficult to detect in presence of cataract or other preexisting causes of visual impairment often more common at this age. Although these visual disturbances are often assumed to be reversible, some reports indicate that there are irreversible changes that warrant special attention in the case of long-term use of the drug.[2]

The outcomes of treatment are not always favorable in elderly patients. The 12-month treatment success rate in the study of Chan-Yeung and colleagues[19] in Hong Kong was 83% for those younger than 60 years compared with 77% for the elderly, and the death rate was 1% (59 years and younger) and 9% (60 years and older). The treatment success rate in Hong Kong was only 72.5% and mortality 16% for those aged 65 or older.[13]

In Japan, the 9-month treatment success rate was 87% for young patient cohorts and 71% for elderly patient cohorts; the death rates were 21% (elderly) and 3% (young).[17] On the other hand, the death risk relative to that of the general population was 12.5 times higher for the 30 to 49 age group, 11.7 times for the 50 to 59 age group, 8.8 times for the 60 to 74 age group, and 4.5 times for the 75 and older age group. The lower relative risks at the upper age ranges reflect the high background mortality, rather than decreased lethality of TB, at these ages.

FUTURE PERSPECTIVE

Despite the decline in the overall incidence of TB in many developed countries, TB remains an important problem among the older population. The epidemiologic transition will take several decades in most of the intermediate-burden areas, as very high disease rates were observed in these areas in the middle of the last century. The control of TB in the elderly will remain a major challenge in the coming years because of the limitations of the existing tools for the diagnosis and treatment of both LTBI and clinically active disease. Diagnostic tests with better predictive values for the development of clinical disease will be required for tackling the large infection pool at this age. Shorter, more effective, and less toxic treatment regimens will also be required if any large-scale treatment of LTBI is to be contemplated among the elderly. Better diagnostic tools and new TB drugs are also required to manage patients with clinically active disease, especially in the face of the global emergence of drug resistance. Until these become available, a high index of suspicion will continue to be required to detect the often atypically presenting disease. A careful, holistic approach is also needed in the management of elderly TB patients because of the often late presentation, poorer drug tolerance, and sometimes less satisfactory outcome.

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