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Original Article

Ambulatory independence is associated with higher incidence of latent tuberculosis infection in long-term care facilities in Taiwan

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KEYWORDS
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Abstract *Background/purpose:* Tuberculosis (TB) in the elderly population remains a major challenge in areas with intermediate disease burden like Taiwan. Despite the increasing burden and high risks of TB in the elderly population, particularly those living in long-term care

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Long-term care facility;
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facilities (LTCFs), diagnostic testing for latent tuberculosis infection (LTBI) has not been carefully evaluated in this group. This study aimed to investigate the prevalence and predictors of LTBI in older adults living in LTCFs.

Methods: Older adults living in seven LTCFs in Taiwan were prospectively enrolled between January and July 2017. Interferon-gamma release assay (IGRA) through QuantiFERON-TB Gold In-tube was used to determine presence of LTBI. Predictors for LTBI were analyzed.

Results: A total of 258 participants were enrolled, including 240 older residents (mean age, 81.6 years; male, 51.2%) and 18 employees (mean age, 64.8 years; male, 22.2%). The proportion of independent status in ambulation assessments significantly declined with aging ($p < 0.001$). The IGRA-positivity rate in LTCFs was 31.4% (81/258), which consisted of 73 (30.4%) residents and 8 (44.4%) employees. The IGRA results were different with respect to the ambulation status ($p = 0.052$). In the multivariate logistic regression analysis, the only independent predictor of LTBI among older adults in LTCFs was independent ambulation (odds ratio, 2.16; 95% confidence interval, 1.09–4.28; $p = 0.027$).

Conclusions: There was a high prevalence of LTBI among older adults in LTCFs in Taiwan. Independent ambulation was the only independent predictor of LTBI.

Introduction

Tuberculosis (TB), which is caused by the bacterium *Mycobacterium tuberculosis* and involves various organs, remains one of the top 10 causes of death and is a significant global health concern. It was estimated that TB affected 10 million people and caused 1.3 million deaths worldwide in 2017.[1–4] Taiwan is an endemic TB area, with an intermediate burden of the disease. Although there has been an overall decline in the absolute number of TB cases, the incidence rate of TB was 41.4 per 100,000 people in Taiwan in 2017, which is higher than those in other developed countries.[5]

Older adults across all racial and ethnic groups and in both sexes are at substantial risk for active TB.[6] Age-related changes, such as progressive decline in both innate and adaptive immune responses, lead to decreased immunological protection from active TB in the elderly population.[7] Other factors, such as nonspecific clinical manifestation, poor nutrition, low socioeconomic status, decreased access to health services, and comorbidities, also contribute to the higher risk of TB infection in aging populations.[8–11]

The global pace of population aging is rapidly accelerating because of longer life expectancy and lower childbirth rates.[12] It was estimated that the world's population aged >60 years will increase by more than twofold, from 900 million people in 2015 to more than two billion people in 2050, gradually contributed by the developing world.[12] TB prevalence increases with age in Asia and some African countries.[1] Moreover, the 2017 Global Burden of Disease estimates also show that 60% of all TB deaths globally occurred among individuals aged >50 years, with approximately half of these deaths in those aged >70 years.[13]

There is a high burden of TB in older adults (≥65 years), who represented 57% of all TB cases in Taiwan, and >80% of TB deaths occurred in individuals aged ≥65 years.[5,14] Because older adults are more likely to have comorbid chronic diseases and disabilities, it has been estimated that about 10% of reported TB cases originated in long-term care facilities (LTCFs).[15] Within this population, the incidence rate of active TB is higher than that of people living in the community.[16] Institutionalized older adults are more likely to have more comorbidities, and residence in congregate settings can promote active TB transmission.

The American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC) guidelines recommend that latent tuberculosis infection (LTBI) screening in LTCFs is one of the important strategies of TB control and prevention.[17,18] Both the tuberculin skin test (TST) and interferon gamma release assays (IGRAs) are commonly used in LTBI screening diagnostic tools, and IGRAs are supposed to offer improved specificity over the TST.[19] However, there were insufficient data on IGRA as a diagnostic tool for LTBI in older adults living in LTCFs.[20,21] In light of the burden of TB in older adults in Taiwan, there is a need to perform LTBI screening and prevent TB in older adults, particularly those living in LTCFs. This study aimed to (1) investigate the prevalence of LTBI using the IGRA in LTCFs and (2) determine the risk factors associated with IGRA positivity in LTCFs.

Materials and methods

Setting and participant enrollment

This cross-sectional study was conducted between January 1, 2017 and July 31, 2017 in seven LTCFs in Taiwan (one in northern, five in southern, and one in eastern Taiwan).[22] The target population for this study was older residents (≥60 years). After obtaining informed consent from the residents, their baseline characteristics, including demographic data, comorbidity status, and history of bacille Calmette-Guerin (BCG) vaccination (presence or absence of BCG scar), and previous TB infection, were prospectively

collected. All enrolled participants (residents and employees) underwent chest radiography before the IGRA. Chest radiography and clinical history were obtained to exclude active TB disease. Urbanization level was accessed by Liu et al.'s classification method.[23] The study was reviewed and approved by the Institutional Review Board of Kaohsiung Medical University Chung-Ho Memorial Hospital (IRB. No. KMUHIRB-SV (I)-20160057).

IGRA

Peripheral blood samples of the enrolled residents were examined for LTBI using QuantiFERON-TB Gold In-Tube assay (Qiagen, Hilden, Germany). The procedure was performed and results were reported (positive, negative, or indeterminate) according to the respective manufacturer's instructions and our previous study.[22]

Assessment of activities of daily living (ADL) of the residents

ADLs of the residents were assessed using the Barthel index (BI) on enrollment. The BI includes eight domains: feeding, bathing, grooming, dressing, bowel, bladder, toilet, and transfers, mobility, and stairs. Performance on these domains is rated by level of assistance needed, with each task yielding a maximum score of 100 points.[24] In this study, ADL was classified into three categories according to the BI score: independent (BI, 60—100), partially dependent (BI, 40—60), and totally dependent (BI, 0—40). In order to assess "ambulation," individuals who are able to walk 50 m without assistance are considered "independent," even if they use the help of a walking stick, crutches, prosthesis, or a walker. Elderly individuals who can walk 50 m but need help or supervision were classified as "assistance dependent."

Statistical analysis

Statistical analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were compared using Student's t-test or the Mann—Whitney U test, as appropriate. The BI scores and ambulation status according to age were examined using the linear regression model. Variables with a P-value <0.1 in the univariate analysis were incorporated into a multivariate analysis. Multivariate logistic regression analysis was used to identify factors associated with IGRA positivity. A multivariate backward logistic regression was performed to evaluate the independent effects on IGRA positivity after adjustments for factor discrepancies between groups. A P-value <0.05 was considered statistically significant.

Results

Demographics of the participants in LTCFs

A total of 258 participants (mean age, 80.5 years; male, 49.2%) with length of stay in LTCFs of 6 years (median, 6 years; interquartile range (IQR), 2—7 years) were enrolled in the study (Table 1), including 240 older residents (mean age, 81.6 years; male, 51.2%) and 18 employees (mean age, 64.8 years; male, 22.2%). A total of 150 (58.2%) participants were aged >80 years, and 126 (52.5%) residents lived in an enclosed environment with rooms consisting of more than 5 beds. The employees had worked in LTCFs for a mean duration of 10.9 years. A total of 84 (35.0%) residents were bedridden, and 106 (44.2%) were totally dependent according to the assessment of the BI. Moreover, 146 (56.6%) participants had previously received BCG vaccination. Hypertension and diabetes were the most common comorbidities (Table 1).

ADL of the residents

The BI scores and ambulation status for each age category are presented in Fig. 1. There were no differences between the BI scores and age (Fig. 1A, $p = 0.401$). However, the independent status in ambulation assessments significantly declined with aging (Fig. 1B, $p < 0.001$).

Factors associated with IGRA positivity

The IGRA-positivity rate in LTCFs was 31.4% (81/258), consisting of 73 (30.4%) residents and 8 (44.4%) employees. Seven (2.9%) residents had indeterminate IGRA results. Although statistical significance was not achieved in a proportion of IGRA results among different age categories ($p = 0.647$), we observed that the prevalence of IGRA positivity declined in those aged >70 years (Fig. 2). However, the IGRA results were different with respect to the ambulation status ($p = 0.052$) (Fig. 3). Compared with the bedridden group, IGRA-positivity rates were significantly higher in the independent ambulation groups (odds ratio [OR], 2.24; 95% CI, 1.14—4.41; $p = 0.020$) (Table 2). In the multivariate logistic regression, the only independent predictor of LTBI in older adults in LTCFs is independent ambulation (OR, 2.16; 95% CI, 1.09—4.28; $p = 0.027$) (Table 2).

Discussion

This cross-sectional study reported the prevalence of LTBI in a large number of older adults living in LTCFs in Taiwan. In this enclosed environment, there was a high prevalence (31.4%) of LTBI in the elderly population in LTCFs. The IGRA results were not different with respect to aging. The only independent predictor of LTBI in older adults in LTCFs is independent ambulation (OR, 2.16; 95% CI, 1.09—4.28; $p = 0.027$).

Previous studies revealed that the prevalence of IGRA positivity in LTCFs were 16.3%—26.5%.[20,21,25] Our study revealed the highest LTBI prevalence (31.4%) in this population. Consistent with previous studies,[20,21] most participants in this study were aged >70 years. Seven (2.9%) residents had indeterminate IGRA results, and 6/7 (85.7%) were aged >70 years. Although our study revealed that there was no difference in the IGRA results with respect to aging, we observed that the prevalence of IGRA positivity declined in those aged >70 years. The decrease in

Table 1 Demographic and clinical characteristics of the studied population.

	Residents (n = 240)	Employee (n = 18)	*P*-value
Age, mean ± SD	81.6 ± 8.3	64.6 ± 4.4	<0.001
<70 years	29 (12.1)	17 (94.4)	
70–79 years	72 (30.0)	1 (5.6)	
80–89 years	108 (45.0)	0	
>90 years	31 (12.9)	0	
Male, n (%)	123 (51.2)	4 (22.2)	0.026
BMI (kg/m^2)	21.7 ± 4.1	25.2 ± 4.6	0.002
BCG vaccination, n (%)	138 (57.5)	8 (61.5)	0.774
Location, n (%)			0.260
Urban, 66 (25.6)	59 (89.4)	7 (10.6)	
Suburban, 192 (74.4)	181 (94.3)	11 (5.7)	
Lengths of stay, (year) mean (IQR) (range)	5.6 (2.0–7.0) (1.0–40.0)	10.9 (4.0–18.0) (2.0–22.0)	<0.001
Bedroom configurations, n (%)			
Private room and room with two beds	38 (15.8)		
Room with 3 and 4 beds	76 (31.7)		
Room with >5 beds	126 (52.5)		
Ambulation, n (%)			<0.001
Bedridden	82 (34.0)	0	
Assistance dependent	52 (21.7)	0	
Independent	106 (44.2)	18 (100)	
Barthel index score			<0.001
>60	82 (34.2)	0	
41–59	52 (21.7)	0	
<40	106 (44.2)	18 (100)	
Smoking, n (%)			0.275
Never	173 (72.1)	16 (88.9)	
Ever	56 (23.3)	2 (11.1)	
Current	11 (4.6)	0	
Comorbidities, n (%)			
Hypertension	147 (61.3)	4 (22.2)	0.002
Diabetes	79 (32.9)	4 (22.2)	0.439
Dementia	66 (27.5)	0	0.009
Cerebrovascular accident	77 (32.1)	0	0.002
Chronic obstructive pulmonary disease	18 (7.5)	0	0.623
Malignancy	11 (4.6)	0	1
Chronic kidney disease	18 (7.5)	0	0.623
Laboratory tests			
HbA1c (%), mean ± SD	6.5 ± 1.3	5.9 ± 0.9	0.01
Albumin (g/dL), mean ± SD	3.7 ± 0.5	4.5 ± 0.2	<0.001
Creatinine (mg/dL), mean ± SD	0.7 ± 0.2	1.1 ± 1.1	0.117
IGRA results			0.389
Positive	73 (30.4)	8 (44.4)	
Indeterminate	7 (2.9)	0	

prevalence observed in older age groups is also consistent with those in previous studies.[26–28] A relative inadequacy of phytohemagglutinin-induced interferon gamma responses, likely reflecting immune maturation and subsequent immunosenescence, which infer the immune response to this test, may be a possible explanation.[29] Another possible explanation is earlier birth cohorts that we observed could be influenced by selective mortality. Individuals with LTBI in earlier birth cohorts may die from TB or comorbid conditions at a young age, resulting in lower LTBI rates among survivors.[27] The high prevalence of LTBI in older adults in LTCFs combined with the risk of an outbreak if a case of TB develops make LTBI screening and treatment an important prevention opportunity. Although isoniazid remains the primary drug recommended for the treatment of LTBI in all age groups, elderly individuals have been considered at increased risk for drug-induced liver injury.[30] A short-course regimen with 3 months of weekly rifapentine plus isoniazid (3HP) is less hepatotoxic than 9 months of daily isoniazid for LTBI.[31] However, some studies revealed that development of adverse effects of 3HP was frequent in the elderly population.[31–33] Therefore, efficiency and tolerability of 3HP in the elderly population need further investigation.

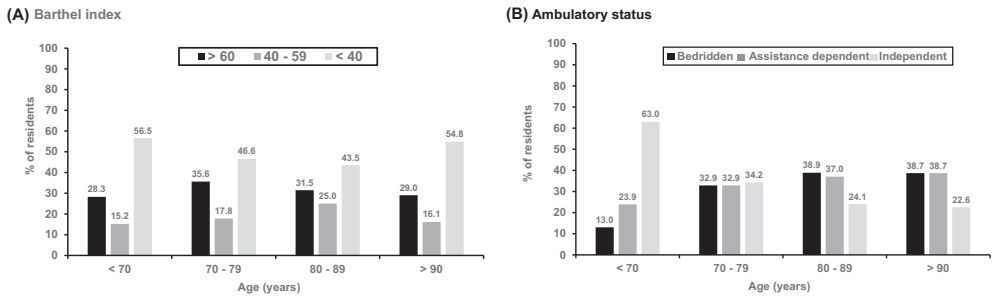

Figure 1. (A) Association of age with Barthel index score in older adults living in long-term care facilities ($p = 0.401$). (B) Ambulatory status declined with aging ($p < 0.001$).

There are no gold standard methods in the diagnosis of LTBI. The TST and IGRA indirectly measure TB infection by detecting T-cell response, which reveals only the presence of host sensitization to *M. tuberculosis* antigens.[34] Previously, the Society for Healthcare Epidemiology of America and American Geriatric Society have recommended LTBI screening using the TST at the time of admission to a LTCF.[35,36] Recently, the ATS/Infectious Diseases Society of America and CDC guidelines updated in 2017 support the use of IGRAs instead of TSTs for LTBI screening in certain conditions.[17] Overall, IGRAs might be an incremental improvement over the TST, with advantages of having no cross-reaction with the BCG vaccine and being convenient, only requiring one patient visit. Moreover, sensitivity to TST in older adults may also decrease due to waning immunity, with a 5% decline in test positivity per decade after the age of 65 years.[37] An outbreak investigation reported that a nosocomial TB outbreak was associated with a delayed diagnosis in a TST-negative elderly patient and resulted in 2 secondary cases and evidence of transmission to 12 other patients and healthcare facility staff.[38] Although data on the use of IGRA in the elderly population were limited,[20,21,25] IGRA might be more useful than TST in diagnosing LTBI in this population.[39]

Our study indicated that older adults with independent ambulation status are associated with IGRA positivity (OR, 2.16; 95% CI, 1.09—4.28; $p = 0.027$). It is assumed that older adults with independent ambulation were more likely to have been exposed to TB during their lifetime compared with bedridden individuals. Because older adults in LTCFs are at increased risk of LTBI reactivation, other residents in this setting are therefore at risk for outbreaks of TB that is the consequence of transmission from a source case with LTBI reactivation.[36,40] A genotyping surveillance study in Taiwan also reported that patients with clustered TB infection were less likely to be ADL dependent (adjust OR, 0.07; 95% CI, 0.007—0.758).[41]

In the elderly population, an estimated 90% of TB cases were due to reactivation of LTBI acquired earlier in life rather than a result of recent transmission.[42,43] Although LTCF caring the elderly population are generally characterized by the limited living space, poorly ventilated facility, and relatively enclosed environments that lead to the inevitable close contact between residents, increasing the possibility of TB transmission, our study revealed that IGRA positivity was not confined to the same bedrooms (Table 2).

It has been reported that TB case rates are threefold higher among LTCF workers compared with those working in any other job.[44] As regards LTCF employees in this study, LTBI prevalence (44.4%) is higher than that in general healthcare workers (3.8—8.4%) and hemodialysis unit staff (11%).[45,46] Targeted strategies of TB control and prevention in LTCFs are essential to protect both the residents and employees in these settings.

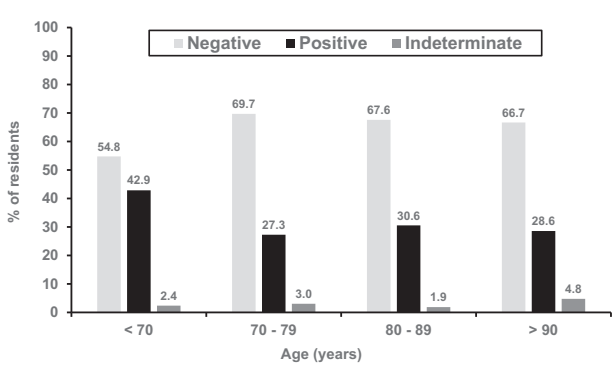

Figure 2. Association of age with the prevalence of latent TB infection in older adults living in long-term care facilities ($p = 0.647$). IGRA, interferon-gamma release assay.

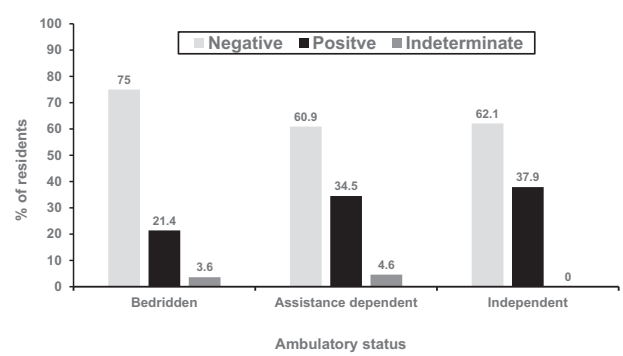

Figure 3. The IGRA results in bedridden, assistance-dependent, and independent older adults ($p = 0.052$). The proportion of IGRA positivity in assistance-independent participants was significantly higher than in bedridden participants (37.9% [33/87] *vs.* 21.4% [18/84], $p = 0.018$). No indeterminate IGRA results were detected in assistance-independent participants. IGRA, interferon-gamma release assay.

Table 2 Univariate and multivariate analysis of the association between risk factors and interferon-gamma release assay positivity in older adults in long-term care facilities.

	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Age, mean ± SD	0.98	0.95–1.01	0.099	–	–	–
Male, n (%)	1.09	0.64–1.84	0.762			
BMI (kg/m^2)	1.05	0.99–1.12	0.130			
BCG vaccination	0.89	0.52–1.52	0.663			
Rural location	0.62	0.34–1.11	0.106			
Lengths of stay, year	1.04	1.00–1.09	0.044	–	–	–
Resident	0.55	0.21–1.44	0.222			
Private room and room with two beds	Reference					
Room with 3 and 4 beds	0.67	0.30–1.50	0.327			
Room with >5 beds	0.59	0.28–1.26	0.172			
Bedridden	Reference					
Assistance dependent	1.93	0.97–3.82	0.059	1.94	0.97–3.85	0.060
Assistance independent	2.24	1.14–4.41	0.020	2.16	1.09–4.28	0.027
Barthel index score >60	Reference					
Barthel index score, 41–59	0.80	0.39–1.66	0.548			
Barthel index score <40	0.60	0.33–1.09	0.091	–	–	–
Smoking, Never	Reference					
Ever	1.04	0.55–1.97	0.899			
Current	2.78	0.82–9.48	0.102			
Hypertension	0.58	0.34–0.99	0.045	0.60	0.35–1.02	0.059
Diabetes mellitus	0.68	0.39–1.21	0.192			
Dementia	0.85	0.46–1.56	0.597			
Cerebrovascular accident	1.27	0.72–2.24	0.408			
Chronic obstructive pulmonary disease	0.83	0.29–2.41	0.732			
Malignancy	0.81	0.21–3.15	0.764			
Chronic kidney disease	0.61	0.19–1.90	0.389			
HbA1c, per % increase	0.87	0.65–1.16	0.335			
Albumin, per g/dL increase	1.75	1.01–3.03	0.046	–	–	–
Creatinine, per mg/dL increase	0.92	0.70–1.20	0.539			

There are several limitations of this study. First, although IGRA conversions were better predictors for progression of active TB,[20,47] we did not perform serial IGRAs in all participants. It will require a series of IGRAs in the future to predict development of active TB. Second, only 18 employees underwent IGRA in this study. It is difficulty to evaluate the association between LTBI prevalence in residents and employees in LTCFs. However, the size of this occupational group will gradually increase in the coming years if LTCF resident populations increase as expected. Therefore, it is reasonable for employees to undergo LTBI screening because inadequately screened LTCF workers would serve as sources of infection of other employees and residents. Third, because the sampling of this study was not standardized (ex, systematic, stratified or cluster) from these facilities, the data would not totally be respecting the prevalence of LTBI in geographic regions in Taiwan. In addition, urbanization level is associated with TB risk.[48] Therefore, we used urbanization level to instead of geographic differences for analysis in this study.

In conclusion, a high LTBI prevalence (31.4%) among elderly residents and employees was found in LTCFs in Taiwan. Independent ambulation is the only independent predictor of LTBI. Prioritized screening policy including both residents and employees in long-term care facilities needs to be integrated into the national policy, Long-term Care 2.0, in the future.

Declaration of Competing Interest

All authors have no conflicts of interest to declare and have no association with Qiagen.

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References

1. World Health Organization. *Global tuberculosis report 2018*. Geneva, Switzerland: World Health Organization; 2018.
2. Huang TY, Hung CH, Hsu WH, Peng KT, Hung MS, Lai LJ, et al. Genitourinary tuberculosis in Taiwan: a 15-year experience at a teaching hospital. *J Microbiol Immunol Infect* 2019;**52**: 312–9.
3. Tang VK, Hsu HL, Hsieh TC, Lee WS. Vertebral tuberculosis complicated with retropharyngeal, parathoracic, and huge iliopsoas abscess, successfully treated with image-guided percutaneous drainage. *J Microbiol Immunol Infect* 2017;**50**: 263–4.

4. Liu YC, Wu CJ, Ko PS, Chien SH, Fan NW, Wang HY, et al. Mycobacterial infections in adult recipients of allogeneic hematopoietic stem cell transplantation: a cohort study in a high endemic area. *J Microbiol Immunol Infect* 2018 Jul 26. https://doi.org/10.1016/j.jmii.2018.07.001. pii: S1684-1182(18)30269-X [Epub ahead of print].
5. Centers for Disease Control. *Statistics of communicable diseases and surveillance report, Republic of China*. Taiwan: Centers for Disease Control; 2017. [Accessed 15 January 2019].
6. Schaaf HS, Collins A, Bekker A, Davies PD. Tuberculosis at extremes of age. *Respirology* 2010;**15**:747—63.
7. Byng-Maddick R, Noursadeghi M. Does tuberculosis threaten our ageing populations? *BMC Infect Dis* 2016;**16**:119.
8. Donald PR, Marais BJ, Barry 3rd CE. Age and the epidemiology and pathogenesis of tuberculosis. *Lancet* 2010;**375**:1852—4.
9. Lee CH, Lee MC, Shu CC, Lim CS, Wang JY, Lee LN, et al. Risk factors for pulmonary tuberculosis in patients with chronic obstructive airway disease in Taiwan: a nationwide cohort study. *BMC Infect Dis* 2013;**13**:194.
10. Lee CH, Wang JY, Lin HC, Lin PY, Chang JH, Suk CW, et al. Treatment delay and fatal outcomes of pulmonary tuberculosis in advanced age: a retrospective nationwide cohort study. *BMC Infect Dis* 2017;**17**:449.
11. Yen YF, Feng JY, Pan SW, Chuang PH, Su VY, Su WJ. Determinants of mortality in elderly patients with tuberculosis: a population-based follow-up study. *Epidemiol Infect* 2017;**145**:1374—81.
12. World Health Organization. *Ageing and health*. 2018. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health. [Accessed 15 January 2019].
13. Collaborators GBDCoD. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1736—88.
14. Cruz-Hervert LP, Garcia-Garcia L, Ferreyra-Reyes L, Bobadilla-del-Valle M, Cano-Arellano B, Canizales-Quintero S, et al. Tuberculosis in ageing: high rates, complex diagnosis and poor clinical outcomes. *Age Ageing* 2012;**41**:488—95.
15. Lai CC, Hsieh YC, Yeh YP, Jou RW, Wang JT, Pan SL, et al. A pulmonary tuberculosis outbreak in a long-term care facility. *Epidemiol Infect* 2016;**144**:1455—62.
16. Hochberg NS, Horsburgh Jr CR. Prevention of tuberculosis in older adults in the United States: obstacles and opportunities. *Clin Infect Dis* 2013;**56**:1240—7.
17. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American thoracic society/infectious diseases society of America/Centers for disease control and prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis* 2017;**64**:e1—33.
18. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am Thora Soc MMWR Recomm Rep* 2000;**49**:1—51.
19. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. *Clin Microbiol Rev* 2014;**27**:3—20.
20. Tsou PH, Huang WC, Huang CC, Lin CF, Wu KM, Hsu JY, et al. Quantiferon TB-Gold conversion can predict active tuberculosis development in elderly nursing home residents. *Geriatr Gerontol Int* 2015;**15**:1179—84.
21. Katsenos S, Nikolopoulou M, Gartzonika C, Manda-Stachouli C, Gogali A, Grypaiou C, et al. Use of interferon-gamma release assay for latent tuberculosis infection screening in older adults exposed to tuberculosis in a nursing home. *J Am Geriatr Soc* 2011;**59**:858—62.
22. Chien JY, Chiang HT, Lu MC, Ko WC, Yu CJ, Chen YH, et al. QuantiFERON-TB gold plus is a more sensitive screening tool than QuantiFERON-TB gold in-tube for latent tuberculosis infection among older adults in long-term care facilities. *J Clin Microbiol* 2018;**56**. e00427-18.
23. Liu CY, Hung YT, Chuang YL, Chen YJ, Weng WS, Liu JS, et al. A stratification study on the urbanization of Taiwan. *J Health Manag* 2006;**4**:1—22.
24. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965;**14**:61—5.
25. Kruczak K, Duplaga M, Sanak M, Cmiel A, Mastalerz L, Sladek K, et al. Comparison of IGRA tests and TST in the diagnosis of latent tuberculosis infection and predicting tuberculosis in risk groups in Krakow, Poland. *Scand J Infect Dis* 2014;**46**:649—55.
26. Dorken E, Grzybowski S, Allen EA. Significance of the tuberculin test in the elderly. *Chest* 1987;**92**:237—40.
27. Winston CA, Navin TR. Birth cohort effect on latent tuberculosis infection prevalence, United States. *BMC Infect Dis* 2010;**10**:206.
28. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao TC. The prevalence of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med* 2016;**194**:501—9.
29. Tebruegge M, de Graaf H, Sukhtankar P, Elkington P, Marshall B, Schuster H, et al. Extremes of age are associated with indeterminate QuantiFERON-TB gold assay results. *J Clin Microbiol* 2014;**52**:2694—7.
30. Stine JG, Sateesh P, Lewis JH. Drug-induced liver injury in the elderly. *Curr Gastroenterol Rep* 2013;**15**:299.
31. Bliven-Sizemore EE, Sterling TR, Shang N, Benator D, Schwartzman K, Reves R, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. *Int J Tuberc Lung Dis* 2015;**19**:1039—44.
32. Lin SY, Chiu YW, Lu PL, Hwang SJ, Chen TC, Hsieh MH, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection in hemodialysis patients: high rates of adverse events. *J Microbiol Immunol Infect* 2019;**52**:158—62.
33. Schein YL, Madebo T, Andersen HE, Arnesen TM, Dyrhol-Riise AM, Tveiten H, et al. Treatment completion for latent tuberculosis infection in Norway: a prospective cohort study. *BMC Infect Dis* 2018;**18**:587.
34. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. The immune response in tuberculosis. *Annu Rev Immunol* 2013;**31**:475—527.
35. Finucane TE. The American Geriatrics Society statement on two-step PPD testing for nursing home patients on admission. *J Am Geriatr Soc* 1988;**36**:77—8.
36. Thrupp L, Bradley S, Smith P, Simor A, Gantz N, Crossley K, et al. Tuberculosis prevention and control in long-term-care facilities for older adults. *Infect Control Hosp Epidemiol* 2004;**25**:1097—108.
37. Hochberg NS, Rekhtman S, Burns J, Ganley-Leal L, Helbig S, Watts NS, et al. The complexity of diagnosing latent tuberculosis infection in older adults in long-term care facilities. *Int J Infect Dis* 2016;**44**:37—43.
38. Harris TG, Sullivan Meissner J, Proops D. Delay in diagnosis leading to nosocomial transmission of tuberculosis at a New York City health care facility. *Am J Infect Contr* 2013;**41**:155—60.
39. Kobashi Y, Mouri K, Yagi S, Obase Y, Miyashita N, Okimoto N, et al. Clinical utility of the QuantiFERON TB-2G test for elderly patients with active tuberculosis. *Chest* 2008;**133**:1196—202.
40. Pratt RH, Winston CA, Kammerer JS, Armstrong LR. Tuberculosis in older adults in the United States, 1993-2008. *J Am Geriatr Soc* 2011;**59**:851—7.
41. Chao WC, Chuang PC, Wu DH, Wu CL, Liu PY, Shieh CC, et al. Using genotyping to delineate tuberculosis transmission in long-term care facilities: single facility 4-year experience. *BMC Infect Dis* 2017;**17**:421.

42. France AM, Grant J, Kammerer JS, Navin TR. A field-validated approach using surveillance and genotyping data to estimate tuberculosis attributable to recent transmission in the United States. *Am J Epidemiol* 2015;**182**:799—807.
43. Horsburgh Jr CR, O'Donnell M, Chamblee S, Moreland JL, Johnson J, Marsh BJ, et al. Revisiting rates of reactivation tuberculosis: a population-based approach. *Am J Respir Crit Care Med* 2010;**182**:420—5.
44. Prevention and control of tuberculosis in facilities providing long-term care to the elderly. Recommendations of the advisory committee for elimination of tuberculosis. *MMWR Recomm Rep* 1990;**39**:7—13.
45. Shu CC, Hsu CL, Lee CY, Wang JY, Wu VC, Yang FJ, et al. Comparison of the prevalence of latent tuberculosis infection among non-dialysis patients with severe chronic kidney disease, patients receiving dialysis, and the dialysis-unit staff: a cross-sectional study. *PLoS One* 2015;**10**: e0124104.
46. Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among health care workers. *Emerg Infect Dis* 2011;**17**:488—94.
47. Machingaidze S, Verver S, Mulenga H, Abrahams DA, Hatherill M, Hanekom W, et al. Predictive value of recent QuantiFERON conversion for tuberculosis disease in adolescents. *Am J Respir Crit Care Med* 2012;**186**:1051—6.
48. Prasad A, Ross A, Rosenberg P, Dye C. A world of cities and the end of TB. *Trans R Soc Trop Med Hyg* 2016;**110**: 151—2.