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Original Article

Determinants of latent tuberculosis infection and treatment interruption in long-term care facilities: A retrospective cohort study in Taiwan

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KEYWORDS
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Abstract *Background/purpose:* Latent tuberculosis infection (LTBI) treatment is challenging in long-term care facilities (LTCFs) residents due to the occurrence of medical complexities. However, factors associated with treatment interruption have not been extensively studied. This retrospective cohort study aimed to determine LTBI-associated factors and treatment interruption in LTCF residents and employees in Taiwan.
Methods: From May 2017 through September 2020, the residents and employees of 20 LTCFs in Taipei, Taiwan, were screened for LTBI by using QuantiFERON-TB Gold In-Tube test. The LTBI individuals underwent directly observed preventive therapy (DOPT), including regimens of 9-month daily isoniazid (9H) and 3-month weekly isoniazid plus rifapentine (3HP). All the LTBI cases were followed up till treatment completion, death, or treatment interruption.
Results: Among 2207 LTCF subjects, 16.8% had LTBI. After controlling for other covariates, residents of public facilities had a significantly higher LTBI prevalence than those of private

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facilities (adjusted odds ratio [AOR] = 1.43; 95% confidence interval [CI]: 1.08—1.88). Among 264 LTBI cases receiving preventive therapy, 52 (19.7%) had treatment interruption. LTBI cases receiving 3HP were less likely to have treatment interruption than those receiving 9H (AOR = 0.22; 95% CI: 0.07—0.71).

Conclusions: LTCF residents, particular those living in public facilities, had a high LTBI prevalence. 3HP with DOPT is considered the priority regimen for preventive therapy among LTBI cases in LTCFs.

Introduction

One-fourth of the world's population is latently infected with tuberculosis (TB),[1] and approximately 10.0 million incident TB cases are reported each year.[2] In 2015, the World Health Organization (WHO) implemented the "End TB strategy" to reduce TB deaths by 95% and lower the incidence of new TB cases by 90% between 2015 and 2035.[3] The strategy implies the importance of case finding intensification and preventive therapy provision for individuals with latent TB infection (LTBI),[3] which carries an approximately 10% lifetime risk of progression to active TB.[4]

In Taiwan, among all notified infectious diseases, TB has had the highest annual number of incident cases for decades.[5] In 2006, Taiwan's Centers for Disease Control (CDC) adopted a directly observed therapy, a short course program, to halve TB incidence within 10 years.[6] Since then, the TB incidence rate has significantly decreased from 72.5 per 100,000 in 2005 to 37.0 in 2019.[5] In response to the WHO's End TB strategy,[3] the Taiwan CDC initiated an aggressive LTBI Eradication Program in 2016 to proactively screen LTBI in high-risk groups and provide directly observed preventive therapy (DOPT) for those with LTBI.

Residents of long-term care facilities (LTCFs) have multiple risk factors for progression from LTBI to active TB. It has been estimated that 10% of the reported TB cases in Taiwan originate in LTCFs.[7] Since LTCF residents with active TB are highly likely to cause a TB outbreak in congregate settings,[8,9] these residents form one of the priority groups for LTBI screening and treatment in Taiwan's LTBI Eradication Program. However, LTBI treatment in LTCF residents is challenging due to the occurrence of medical complexities and comorbidities.[10] Therefore, evaluating the treatment compliance and identifying the factors associated with treatment interruption in LTCF residents with LTBI is important.

LTBI treatments include 9-month daily isoniazid (9H), 4-month daily rifampin (4R), or 3-month weekly isoniazid plus rifapentine (3HP).[11] Although LTBI therapy can stop the progression of latent TB to active TB, treatment interruption is common in LTBI cases receiving preventive therapy.[12] Treatment interruption has been reported to jeopardize the efficacy of preventive therapy and increase the risk of developing active TB.[13] Previous reports showed that risk factors associated with LTBI treatment interruption included systemic adverse reactions during preventive therapy[14] and homelessness.[12] However, foreign-born individuals[12,15] and those with recent exposure to TB[16] were less likely to default on LTBI therapy.

LTBI screening and preventive therapy is an important aspect of TB control and prevention. By understanding the factors associated with LTBI and treatment interruption in high-risk groups, one can determine the best allocation of medical resources and provide important guidelines for future TB control programs. Therefore, this cohort study identifies the factors associated with LTBI and treatment interruption in Taiwanese LTCFs.

Methods

Study population and participants' eligibility

This study utilized LTBI surveillance data from Taipei, Taiwan. The study population included residents and employees from 20 LTCFs in Taipei, Taiwan, for LTBI evaluation between May 2017 and September 2020. At the time of the evaluation, all participants underwent chest radiography and took the QuantiFERON-TB Gold In-Tube (QFT) test for LTBI screening.[17] Moreover, LTBI treatment was provided to participants who tested positive in QFT testing. All LTBI cases receiving preventive therapy were followed up till treatment completion, death, treatment interruption, or December 31, 2020. Treatment interruption was defined as (1) not taking all necessary doses of LTBI treatment and (2) missing $\geq$7 days of medication for any LTBI therapy regimen.[18] This study was approved by the Institutional Review Board of Taipei City Hospital (TCHIRB-11001012-E).

Latent tuberculosis infection treatment regimens

The Taiwan LTBI Eradication Program recommends 9H, 4R, or 3HP regimens for LTBI treatment. The treatment regimen for each LTBI case was determined following a thorough discussion between the participants, their families, and the doctor in charge. However, participants who were in contact with isoniazid-resistant TB cases received the 4R regimen. During the study period, Taipei TB Prevention Center informed physicians about the participants' contact history with drug-resistant TB. All medical expenses related to LTBI therapy in the Taiwan LTBI Eradication Program were subsidized by the government and insurance.

In LTBI therapy, blood tests to monitor blood count and liver function tests were conducted every month. Hepatotoxicity was defined as ALT elevation more than three times the upper limit of normal (ULN) in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms.[19] Primary care physicians discontinued preventive therapy for those who developed hepatotoxicity or drug-induced liver injury (2 ULN$<$ALT$\leq$3 ULN) after receiving LTBI treatment.

Directly observed preventive therapy

Since 2016, the Taiwan CDC has been implementing the DOPT strategy for LTBI cases to improve adherence to preventive therapy. DOPT observers are trained by the government and supervised by public health nurses. In this study, DOPT observers monitored treatment complications in LTBI cases and reported any adverse effect of the treatment to the public health nurses every day. Whenever LTBI cases developed hepatotoxicity-related (e.g., loss of appetite and jaundice) or flu-like (e.g., fever and headache) symptoms, public health nurses contacted doctors and arranged hospital visits.

Data collection

Participants' information was collected at the time of the study enrollment, which included sociodemographic characteristics (age, sex, body mass index [BMI], and smoking status), LTCF attributes, TB contact history, and details of end-stage renal disease. LTCF attributes included details of private and public LTCFs. BMI was categorized as underweight ($<$18.5 kg/m^2), normal (18.5—23.9 kg/m^2), overweight (24—26.9 kg/m^2), and obese ($\geq$27 kg/m^2).[21]

Outcome variables

The primary outcomes of this study were LTBI-positivity and treatment interruption of preventive therapy. In study participants, LTBI-positivity was determined using the QFT test.[17]

Statistical analyses

The demographic data of the study participants were analyzed. Continuous data were presented as the mean (standard deviation [*SD*]), and the two-sample *t*-test was used to compare groups. Categorical data were analyzed using Pearson's χ^2 test, where appropriate.

Multivariate logistic regression was used to identify LTBI-associated factors among LTCF residents and employees. Moreover, this study used multivariate analysis to determine the factors associated with treatment interruption among LTBI individuals receiving preventive therapy. Variables with $p < 0.05$ were considered significant

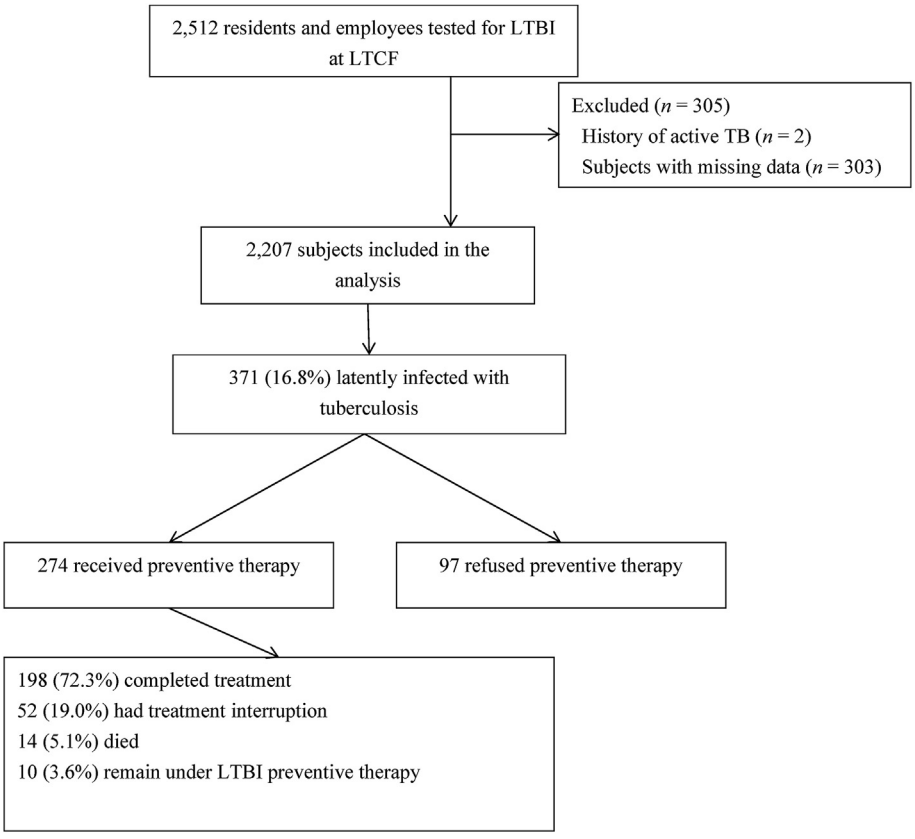

Figure 1. Enrollment and follow-up of residents and employees in long-term care facilities. Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis.

factors associated with LTBI and treatment interruption in the multivariate analysis. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were reported to indicate the strength and direction of these associations. All the data management and analyses in this study were performed using the SAS 9.4 (SAS Institute, Cary, NC) and IBM SPSS 19.0 (IBM Corp., Armonk, NY) software packages.

Results

Participant selection

This cohort study included 2512 LTCF residents and employees who were tested for LTBI between May 2017 and September 2020. After excluding those with a history of active TB ($n = 2$) and those with missing data ($n = 303$), the remaining 2207 subjects were included in the analysis (Fig. 1). The overall mean (*SD*) age was 70.4 (19.8) years; 57.9% of the subjects were female; and 16.8% were tested positive for LTBI. The prevalence of LTBI among LTCF residents and employee was 19.5% and 11.3%, respectively.

Of 371 LTBI individuals, 274 (73.9%) agreed to undergo preventive therapy. During the follow-up period, among the 274 subjects who received preventive therapy, 198 (72.3%) completed treatment, 14 (5.1%) died, 52 (19.0%) experienced treatment interruption, and 10 (3.6%) remained under preventive therapy. Of the 14 deceased LTBI cases, 7 (50.0%) died of pneumonia and 3 (21.4%) died of congestive heart failure (Supplementary table 1). All the deceased LTBI cases received 9H regimen.

Characteristics and predictors for latent tuberculosis infection among long-term care facility residents and employees

Table 1 shows the characteristics of participants with and without LTBI. Compared with LTBI-negative individuals, LTBI subjects were likely to be older, male, smoker, residents living in LTCF, and enrolled from public LTCFs.

After controlling for demographics and other covariates, participants enrolled from public LTCFs indicated a higher prevalence of LTBI than those enrolled from private LTCFs

Table 1 Participant characteristics by LTBI status.

Characteristics	Number of subjects (%)*			P value
	Total, n = 2207	LTBI positivity, n = 371	LTBI negativity, n = 1836	
Age, yrs				
Mean ± SD	70.4 ± 19.8	70.9 ± 15.8	69.4 ± 20.3	<0.001
18-49	392 (17.8)	27 (7.3)	365 (19.9)	<0.001
50-64	344 (15.6)	60 (16.2)	284 (15.5)	
65-79	587 (26.6)	118 (31.8)	469 (25.5)	
≥80	884 (40.1)	884 (40.1)	718 (39.1)	
Sex				
Male	930 (42.1)	176 (47.4)	754 (41.1)	0.023
Female	1277 (57.9)	195 (52.6)	1082 (58.9)	
Body mass index (kg/m^2)				
Normal (18.5–23.9)	1165 (52.8)	197 (53.1)	968 (52.7)	0.813
Underweight (<18.5)	292 (13.2)	44 (11.9)	248 (13.5)	
Overweight (24–26.9)	444 (20.1)	79 (21.3)	365 (19.9)	
Obese (≥27)	306 (13.9)	51 (13.7)	255 (13.9)	
Smoker				
No	1924 (87.2)	305 (82.2)	1619 (88.2)	0.002
Yes	283 (12.8)	66 (17.8)	217 (11.8)	
Source of subjects				
Resident	1483 (67.2)	289 (77.9)	1194 (65.0)	<0.001
Employee	724 (32.8)	82 (22.1)	642 (35.0)	
Attribute of long-term care facilities				
Private facility	1386 (62.8)	209 (56.3)	1177 (64.1)	0.005
Public facility	821 (37.2)	162 (43.7)	659 (35.9)	
History of TB contact				
No	1300 (58.9)	211 (56.9)	1089 (59.3)	0.384
Yes	907 (41.1)	160 (43.1)	747 (40.7)	
End-stage of renal disease				
No	2191 (99.3)	367 (98.9)	1824 (99.3)	0.379
Yes	16 (0.7)	4 (1.1)	12 (0.7)	
LTBI treatment				
No	1933 (87.6)	97 (26.1)	1836 (100.0)	<0.001
Yes	274 (12.4)	274 (73.9)	0	

LTBI, latent tuberculosis infection; SD, standard deviation; TB, tuberculosis; *Unless stated otherwise.

(AOR = 1.37; 95% CI: 1.08—1.74) (Table 2). Other independent predictors for LTBI included smoker (AOR = 1.44; 95% CI: 1.03—2.01), age 50—64 (AOR = 2.46; 95% CI: 1.50—4.03), age 65—79 (AOR = 2.47; 95% CI: 1.32—4.62), and age ≥80 years (AOR = 2.48; 95% CI: 1.30—4.73) (age 18—49: reference).

This study conducted a subgroup analysis to determine the risk of LTBI in LTCFs residents and employees, respectively. The subgroup analysis showed that residents of public LTCFs had a significantly higher LTBI prevalence than those of private LTCFs (23.8% vs. 17.3%; AOR = 1.43; 95% CI: 1.08—1.88). However, employees working at public LTCFs did not show significantly higher LTBI prevalence than those working at private LTCFs (13.4% vs. 9.7%; AOR = 1.14; 95% CI: 0.70—1.87).

Factors associated with treatment interruption among LTBI individuals receiving preventive therapy

To determine the factors associated with treatment interruption among LTBI individuals undergoing preventive therapy, this study analyzed 264 LTBI cases who completed treatment, died, or experienced treatment interruption during the study period. Of 264 LTBI cases undergoing preventive therapy, 52 (19.7%) had treatment interruption. The most frequent etiology of treatment interruption is drug-induced liver injury (n = 15; 28.8%), followed by patients' refusal to continue LTBI treatment (n = 15; 28.8%), and development of flu-like symptom (n = 12; 23.1%) (Supplementary table 2).LTBILTBI.

After controlling for participants' demographics and other covariates, multivariate analysis revealed that LTBI individuals receiving 3HP were less likely to undergo treatment interruption than those receiving 9H (AOR = 0.22; 95% CI: 0.07—0.71) (Table 3).

Adverse drug reactions among LTBI individuals receiving 3HP and 9H preventive therapy

Table 4 depicts the adverse drug reactions experienced by LTBI individuals who received 3HP and 9H. Among 155 LTBI individuals receiving 9H, 9 (5.8%) developed hepatotoxicity. However, none of the 105 LTBI individuals receiving 3HP developed hepatotoxicity (p = 0.001). Moreover, the

Table 2 Univariate and multivariate analysis of factors associated with latent tuberculosis infection among residents and employees in long-term care facilities.

Variables	Number of subjects	LTBI	Univariate	Multivariate analysis
		n (%)	OR (95%CI)	AOR (95%CI)
Age, yrs				
18-49	392	27 (6.9)	1	1
50-64	344	60 (17.4)	2.86 (1.77—4.62)***	2.46 (1.50—4.03)***
65-79	587	118 (20.1)	3.40 (2.19—5.28)***	2.47 (1.32—4.62)**
≥80	884	166 (18.8)	3.13 (2.04—4.78)***	2.48 (1.30—4.73)**
Sex				
Male	930	176 (18.9)	1	1
Female	1277	195 (15.3)	0.77 (0.62—0.97)*	1.00 (0.78—1.29)
Body mass index (kg/m^2)				
Normal (18.5—23.9)	1165	197 (16.9)	1	1
Underweight (<18.5)	292	44 (15.1)	0.87 (0.61—1.24)	0.76 (0.53—1.09)
Overweight (24—26.9)	444	79 (17.8)	1.06 (0.80—1.42)	1.09 (0.81—1.46)
Obese (≥27)	306	51 (16.7)	0.98 (0.70—1.38)	1.08 (0.76—1.53)
Smoker				
No	1924	305 (15.9)	1	1
Yes	283	66 (23.3)	1.61 (1.19—2.18)**	1.44 (1.03—2.01)*
Source of subjects				
Resident	1483	289 (19.5)	1	1
Employee	724	82 (11.3)	0.53 (0.41—0.69)***	0.73 (0.44—1.21)
Attribute of long-term care facilities				
Private facility	1386	209 (15.1)	1	1
Public facility	821	162 (19.7)	1.38 (1.10—1.74)**	1.37 (1.08—1.74)*
History of TB contact				
No	1300	211 (16.2)	1	1
Yes	907	160 (17.6)	1.11 (0.88—1.39)	1.06 (0.84—1.35)
End-stage of renal disease				
No	2191	367 (16.8)	1	1
Yes	16	4 (25.0)	1.66 (0.53—5.17)	1.46 (0.46—4.62)

*<0.05; **<0.01; ***<0.001.
LTBI, latent tuberculosis infection; AOR, adjusted odds ratio; CI, confident interval; TB, tuberculosis.

Table 3 Univariate and multivariate analysis of factors associated with treatment interruption among LTBI-positive individuals receiving preventive therapy in long-term care facilities.

Variables	Number of subjects	Treatment interruption	Univariate	Multivariate analysis
		n (%)	OR (95%CI)	AOR (95%CI)
Treatment regimens				
9H	155	43 (27.7)	1	
3 HP	105	9 (8.6)	0.24 (0.11—0.53)***	0.22 (0.07—0.71)*
4R	4	0	—	—
Age, yrs				
18-64	75	8 (10.7)	1	1
65-79	89	25 (28.1)	3.27 (1.38—7.78)**	1.03 (0.24—4.45)
≥80	100	19 (19.0)	1.96 (0.81—4.77)	0.50 (0.11—2.45)
Sex				
Male	121	32 (26.4)	1	1
Female	143	20 (14.0)	0.45 (0.24—0.84)*	0.62 (0.30—1.29)
Body mass index (kg/m^2)				
Normal (18.5—23.9)	140	31 (22.1)	1	1
Underweight (<18.5)	26	3 (11.5)	0.46 (0.13—1.63)	0.39 (0.10—1.51)
Overweight (24—26.9)	59	10 (16.9)	0.72 (0.33—1.58)	0.62 (0.27—1.45)
Obese (≥27)	39	8 (20.5)	0.91 (0.38—2.17)	1.14 (0.44—2.96)
Smoker				
No	216	43 (19.9)	1	1
Yes	48	9 (18.8)	0.93 (0.42—2.06)	0.64 (0.24—1.65)
Source of subjects				
Resident	192	45 (23.4)	1	1
Employee	72	7 (9.7)	0.35 (0.15—0.82)*	0.84 (0.16—4.40)
Attribute of long-term care facilities				
Private facility	139	22 (15.8)	1	1
Public facility	125	30 (24.0)	1.68 (0.91—3.10)	1.56 (0.76—3.20)
History of TB contact				
No	140	31 (22.1)	1	1
Yes	124	21 (16.9)	0.72 (0.39—1.33)	0.71 (0.35—1.44)

*<0.05; **<0.01; ***<0.001.
LTBI, latent tuberculosis infection; AOR, adjusted odds ratio; CI, confident interval; 9H, 9-month daily isoniazid; 3HP, 3-month weekly rifapentine plus isoniazid; 4R, 4-month daily rifampin; TB, tuberculosis.

proportions of individuals developing flu-like symptoms in 3HP and 9H groups were 5.7% and 3.9%, respectively ($p = 0.487$).

Discussion

This cohort study found that LTBI prevalence was 16.8% among LTCF residents and employees in Taiwan. After controlling for demographics and other covariates, residents of public LTCFs had a significantly higher prevalence of LTBI than those of private LTCFs. During the follow-up period, among 264 LTBI cases receiving DOPT, 52 (19.7%) had treatment interruption. LTBI cases receiving 3HP were less likely to indicate treatment interruption than those receiving 9H.

This study found that the prevalence of LTBI among LTCF residents in Taiwan was 19.5%, which was similar to 19.9% among LTCF residents in the United States[22] and 21.0% among LTCF residents in Portland.[23] Since LTCF residents with LTBI are at high risk of progression to active TB[10] and, subsequently, may cause TB outbreak in the crowded settings,[8] it is important to screen LTCF residents and provide preventive therapy to those who are LTBI.

Our study showed that LTCF residents living in public facilities had a significantly higher LTBI prevalence than those living in private facilities. The low socioeconomic status (SES) of public LTCF residents may explain the higher LTBI prevalence in this population. In Taiwan, individuals with low SES (e.g., people without homes) are prioritized in public LTCF admission, which has been subsidized by the government. Previous studies report that individuals with low SES have a higher risk of LTBI.[24,25] Since LTCF residents suffering from active TB may experience diagnosis delays and transmit TB to others,[26] the findings of our study suggest that the LTBI Eradication Program should focus on LTCF residents, particularly those living in public LTCFs.

This study found that the rate of treatment interruption was 19.7% among LTBI cases receiving preventive therapy in Taiwan, which was similar to 21.6% in an earlier Taiwan report[14] but lower than 48.4% in the United States.[16] The adoption of a comprehensive DOPT program may explain the lower rate of treatment interruption among LTBI cases receiving preventive therapy in Taiwan. Since 2016, the

Table 4 Comparison of adverse drug reactions between LTBI cases receiving 3HP and 9H.

Variables	Number of subjects (%)*		p Value
	3HP (n, 105)	9H (n, 155)	
Hepatotoxicity			
AST, ALT>3 ULN, or T-Bil>2 mg/dL	0	9 (5.8)	0.012
AST, ALT>5 ULN	0	5 (3.2)	0.083
Flu-like symptom	5 (5.7)	6 (3.9)	0.487
Fatigue	3 (2.9)	2 (1.3)	0.396
Dizziness	2 (1.9)	4 (2.6)	0.722
Vomiting	2 (1.9)	1 (0.6)	0.567
Fever	1 (1.0)	0	0.404
Headache	2 (1.9)	0	0.162
Poor appetite	1 (1.0)	1 (0.6)	0.781
Cutaneous reaction	0	3 (1.9)	0.275

LTBI, latent tuberculosis infection; 3HP, 3-month weekly rifapentine plus isoniazid; 9H, 9-month daily isoniazid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limited normal; T-Bil, total bilirubin.

Taiwan CDC has been implementing DOPT for LTBI cases to improve their adherence to preventive therapy. All the LTBI cases in our study considered to receive LTBI treatment under the DOPT strategy. The government-trained DOPT observers delivered medicines daily to individuals receiving 9H or 4R and weekly to those receiving 3HP, according to LTBI treatment guidelines.[11] The DOPT observers interviewed the LTBI subjects about their treatment complications under the supervision of public health nurses. When LTBI subjects receiving preventive therapy on DOPT have, for example, poor appetite or skin rash, public health nurses contacted doctors and arranged hospital visits. Taiwan's LTBI DOPT experience demonstrates that comprehensive interdisciplinary collaborations can improve the compliance of LTBI cases to preventive therapy.

Our study revealed that LTBI cases receiving 3HP were less likely to experience treatment interruption than those receiving 9H. The lower rate of 3HP-related hepatotoxicity[27] may explain the good adherence to preventive therapy in LTBI individuals receiving 3HP. Among our cohort participants, 8.4% of LTBI cases receiving 9H developed hepatotoxicity, whereas none of the subjects receiving 3HP developed hepatotoxicity during prophylactic therapy. Since treatment completion plays an important role in LTBI eradication, our study suggests that 3HP should be considered the priority regimen for treating individuals with LTBI.

This study found that the rates of drug-related hepatotoxicity in LTBI cases receiving 3HP was lower than those receiving 9H. A meta-analysis showed that the risk of hepatotoxicity among participants given 3HP was significantly lower than those on 9H (Relative risk 0.16, 95%CI 0.10—0.27).[27] Since 3HP has a similar efficacy to daily INH regimens[27] and is associated with a higher treatment completion rate, our study suggests that 3HP can contribute significantly to the scale-up of LTBI preventive program.

The present study nevertheless has two limitations. First, the treatment regimen for each LTBI case was determined through a discussion between the participant and the doctor in charge, rather than through randomization. However, all the LTBI cases receiving preventive therapy came under the DOPT program. The treatments' adverse effects in LTBI cases were monitored by the DOPT observers. Second, the external validity of our findings may be concerning because all our enrollees were Taiwanese. The generalizability of our results to other non-Asian ethnic groups requires further verification.

In conclusion, this cohort study found that LTBI prevalence was 19.5% in LTCF residents in Taiwan. The residents living in public facilities had a significantly higher LTBI prevalence than those living in private facilities. Under the DOPT strategy, the treatment interruption rate was 19.7% in LTBI cases receiving preventive therapy. The LTBI cases receiving 3HP were less likely to undergo treatment interruption than those receiving 9H. Since the presence of LTCF residents with LTBI increases the risk of a TB outbreak in congregate settings, it is imperative that LTCF residents are screened for LTBI and DOPT with 3HP is considered the priority regimen for preventive therapy for positive cases.

Declaration of competing interest

No conflict of interest exists for the author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.09.013.