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Current Status of Latent Tuberculosis Infection Treatment Among Pediatric Patients in Korea: Prescription and Treatment Completion

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ABSTRACT

Background: The treatment of pediatric patients with latent tuberculosis infection (LTBI) is a crucial TB control strategy. LTBI is not a reportable communicable disease, and data regarding LTBI treatment in pediatric patients in Korea are scarce. This study aimed to investigate the prescription patterns and treatment completion rates among pediatric patients with LTBI in Korea by analyzing National Health reimbursement claims data.

Methods: We retrospectively analyzed outpatient prescription records for pediatric patients aged 18 or younger with LTBI-related diagnostic codes from 2016 to 2020. We compared the frequency of prescriptions for the standard treatment regimen (9 months of isoniazid [9H]) and an alternative treatment regimen (3 months of isoniazid plus rifampicin [3HR]). We also assessed the treatment incompleteness rates by age group, treatment regimen, treatment duration, the level of medical facility, physician's specialty, and hospital location. We performed multivariable analysis to identify factors influencing treatment incompleteness.

Results: Among the 11,362 patients who received LTBI treatment, 6,463 (56.9%) were prescribed the 9H regimen, while 4,899 (43.1%) received the 3HR regimen. Patients in the 3HR group were generally older than those in the 9H group. The proportion of 3HR regimen prescriptions significantly greater in the later period (2018–2020), in primary hospitals, under the management of non-pediatric specialists, and in metropolitan regions. The overall treatment incompleteness rate was 39.7% (9H group: 46.9%, 3HR group: 30.3%). In the multivariable analysis, 9H regimen prescription was the strongest factor associated with treatment incompleteness (adjusted odds ratio, 2.42; 95% confidence interval, 2.20–2.66; $P < 0.001$). Additionally, management in a primary hospital, a hospital's location in a non-metropolitan region, and management by a non-pediatric specialist were also significant risk factors for treatment incompleteness.

Conclusion: Our study results suggest that promoting the use of 3HR regimen prescriptions could be an effective strategy to enhance treatment completion. Physicians in primary hospitals, hospitals located in non-metropolitan regions, and physicians without a pediatric specialty require increased attention when administering LTBI treatment to pediatric patients to ensure treatment completion.

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Choi UY, Kim JH. Data curation: Choi UY. Formal analysis: Choi UY. Funding acquisition: Choi UY. Methodology: Choi UY, Kim JH. Validation: Kim Y, Bae KS, Han SB, Kim JH. Writing - original draft: Kim Y, Choi UY. Writing - review & editing: Kim Y, Bae KS, Choi UY, Han SB, Kim JH.

Keywords: Latent Tuberculosis Infection; Treatment; Prescription; Completion; Regimen; Children

INTRODUCTION

Latent tuberculosis (TB) infection (LTBI), characterized by an infection with *Mycobacterium tuberculosis*, denotes a state of persistent bacterial viability in which the host remains asymptomatic, showing no evidence of clinically active infection. When the host's immune function weakens, LTBI can progress to active TB disease.¹ Hence, treating LTBI effectively prevents new TB cases. Pediatric patients are at higher risk of transitioning from LTBI to active TB disease, frequently presenting with severe forms of TB like TB meningitis and miliary TB. Moreover, pediatric patients with LTBI serve as potential sources of new TB cases throughout their lives. Therefore, the identification and treatment of pediatric patients with LTBI are essential components of TB-control strategies.²⁻⁴

Korea has made significant strides in reducing TB incidence and mortality over the past few decades, yet it still falls under the category of countries with moderate TB incidence (35.7 new cases per 100,000 people in 2021). The Korean government consistently supports TB control initiatives, which encompass investigating close contacts of TB cases, mandatory LTBI screening for healthcare workers, and LTBI treatment for high-risk groups.⁵⁻⁷ Following TB control guidelines, pediatric patients diagnosed with LTBI are recommended to undergo treatment. Currently, the standard regimen is 9 months of isoniazid (9H), with 3 months of isoniazid plus rifampicin (3HR) treatment as a recommended alternative.^{8,9}

In contrast to TB, LTBI is not classified as a reportable communicable disease, and routine data collection on LTBI treatment is limited. Information about the specific regimens administered to children or their treatment completion rates is scarce. This study aimed to explore the status of LTBI treatment among pediatric patients in Korea, delineate patient and medical facility characteristics, describe the implementation of treatment regimens, assess the incompleteness rate, and identify contributing factors to treatment non-completion.

METHODS**Data source**

This study utilized administrative data from the Health Insurance Review and Assessment Service (HIRA), an agency under the Ministry of Health and Welfare in Korea. HIRA is responsible for monitoring reimbursement claims submitted by medical providers participating in the National Health Insurance (NHI) program. NHI is a universal health insurance system in Korea, mandatory for all Korean nationals, covering 97% of the country's population (with the remaining 3% enrolled in medical aid due to an inability to afford insurance premiums). HIRA data reliably reflect healthcare practice patterns in Korea. We conducted an analysis of de-identified prescription records for pediatric patients with LTBI, encompassing demographic information (sex, age), medical facility characteristics (bed capacity, specialty, location), and drug details (prescription duration, dose, cost).

Study population and treatment regimen

LTBI is defined by a positive tuberculin test (TST) result and/or a positive interferon-gamma release assay (IGRA) result, a normal chest radiograph, and the absence of signs or symptoms of TB disease.^{1,10} In accordance with Korean TB guidelines for LTBI screening, pediatric patients aged ≤ 18 years with a history of close contact with TB are advised to undergo a two-step TST protocol. The second TST should be conducted 8–12 weeks after the last exposure to TB. If the initial test yields a positive result, LTBI treatment is initiated. If the first test is negative, the second TST is recommended. For the first TST, a positive result is defined as an induration with a diameter ≥ 10 mm. In the second TST, a positive result is indicated by an induration with a diameter ≥ 10 mm or an increase ≥ 6 mm compared to the first test. IGRA is not suggested for children under 5 years of age. In LTBI treatment for children aged ≤ 18 years, the standard regimen is 9H (10–15 mg/kg once daily, with a maximum dose of 300 mg). An alternative regimen is the 3HR (10 mg/kg once daily for both isoniazid and rifampicin, with a maximum dose of 300 mg for isoniazid and 600 mg for rifampicin).⁹

We collected outpatient prescription records for pediatric patients aged ≤ 18 years with the principal diagnostic code for LTBI (R7680) between January 2016 and December 2020. Patients without an LTBI diagnosis but receiving neonate or window period prophylaxis were excluded. In line with the increased risk of progression to severe TB in children under 2 years of age, Korean TB guidelines recommend window period prophylaxis for neonates aged ≤ 28 days who have been exposed to TB. This involves a 3-month course of isoniazid prophylaxis, followed by a TST. If the TST result is negative, prophylaxis is halted; if it is positive, further evaluation for active TB is required. If LTBI is confirmed, an additional 6 months of isoniazid is administered to complete the 9H regimen. For children aged 29 days to 23 months, window period prophylaxis is similarly recommended. Isoniazid is given until the second TST, even if the first TST result is negative. If the second TST also yields a negative result, prophylaxis is discontinued. However, if the second TST is positive (induration diameter ≥ 10 mm or an increase ≥ 6 mm), isoniazid is continuously administered to complete the 9H regimen for LTBI treatment.⁹ To exclude patients receiving neonate or window period prophylaxis, we excluded patients aged ≤ 23 months who were prescribed isoniazid for ≤ 3 months. We also excluded those patients prescribed medication neither part of the 9H regimen nor the 3HR regimen (e.g., other anti-TB medication), and we considered principal diagnostic miscoding in these patients.

Variables

The medical facility level was categorized according to the domestic hospital classification system as follows: primary hospital (clinic or hospital with a bed capacity of < 100), general hospital (bed capacity ≥ 100), or tertiary referral center (bed capacity ≥ 100 and designated as a referral center by the Ministry of Health and Welfare of Korea). Hospital location was classified as metropolitan (capital city [Seoul] or Gyeonggi-do, the area surrounding Seoul) or non-metropolitan (areas outside Seoul and Gyeonggi-do). Specialization was categorized as pediatrics or non-pediatrics (non-pediatric specialties included internal medicine, family medicine, and general practice).

The completion of LTBI treatment was determined based on prescribed days within a specified period for each regimen, as in previous studies. For the 9H regimen, individuals who received treatment for ≥ 270 days within a 365-day period were considered as having completed treatment. For the 3HR regimen, individuals treated for ≥ 90 days within a 120-day period were considered as having completed treatment.^{9,11,12}

Statistical analysis

We employed descriptive statistics to calculate frequencies. For comparing continuous variables, we used a multiple *t*-test with Bonferroni correction. In the case of discrete variables, such as proportions, the χ^2 test was applied. Treatment completion was determined as the percentage of individuals who met the specified criteria for completion. To assess the factors influencing the completion of LTBI treatment, we conducted multivariate logistic regression analysis, estimating adjusted odds ratios (aORs) along with 95% confidence intervals (CIs). Statistical analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R statistical software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-tailed, and a significance level of $P < 0.05$ was used to determine statistical significance.

Ethics statement

Our data usage was approved by the HIRA data access committee (HIRA research data M20220326894). This study was approved by the Institutional Review Board (IRB) of Eunpyeong St. Mary's Hospital (IRB No. PC22ZISI0125). No informed consent was required from patients due to the nature of public data from HIRA.

RESULTS

Between 2016 and 2020, 11,362 patients aged 0–18 received LTBI treatment. **Table 1** presents demographic data, treatment durations, and information about the medical facilities utilized by these patients. Most enrolled patients received care in general hospitals (62.3%) or tertiary referral centers (29.2%), with a smaller proportion in primary hospitals (8.5%). Over 80% of patients (80.5%) received their prescriptions from pediatricians.

Table 2 summarizes prescribed regimens by various variables. Among the 11,362 patients, 6,463 (56.9%) were prescribed the 9H regimen, while 4,899 (43.1%) received the 3HR

Table 1. Baseline characteristics of pediatrics patients with latent tuberculosis infection treated during 2016–2020

Variables	Total (N = 11,362)
Sex	
Male	5,966 (52.5)
Female	5,396 (47.5)
Age, yr	
0–6	4,713 (41.5)
7–12	2,889 (25.4)
13–18	3,760 (33.1)
Treatment period	
2016–2017	6,021 (53.0)
2018–2020	5,341 (47.0)
Medical facility	
Tertiary referral center	3,321 (29.2)
General hospital	7,074 (62.3)
Primary hospital	967 (8.5)
Specialty of clinicians	
Pediatrics	9,150 (80.5)
Non-pediatrics	2,212 (19.5)
Hospital location	
Metropolitan	5,977 (52.6)
Non-metropolitan	5,385 (47.4)

Categorical variables are presented as number (%).

Table 2. Prescribed latent tuberculosis infection treatment regimens by variables

Variables	Treatment regimen		Total (N = 11,362)	P value ^a
	9H (n = 6,463)	3HR (n = 4,899)		
Age, yr	6.92 ± 4.98	11.5 ± 5.87	8.89 ± 5.84	< 0.001
Treatment period				< 0.001
2016–2017	3,809 (63.3)	2,212 (36.7)	6,021 (100.0)	
2018–2020	2,654 (49.7)	2,687 (50.3)	5,341 (100.0)	
Medical facility				< 0.001 ^b
Tertiary referral center	1,699 (51.2)	1,622 (48.8)	3,321 (100.0)	
General hospital	4,377 (61.9)	2,697 (38.1)	7,074 (100.0)	
Primary hospital	387 (40.0)	580 (60.0)	967 (100.0)	
Specialty of clinicians				< 0.001
Pediatrics	6,192 (67.7)	2,958 (32.3)	9,150 (100.0)	
Non-pediatrics	271 (12.3)	1,941 (87.7)	2,212 (100.0)	
Hospital location				< 0.001
Metropolitan	3,283 (54.9)	2,694 (45.1)	5,977 (100.0)	
Non-metropolitan	3,180 (59.1)	2,205 (40.9)	5,385 (100.0)	

Values are presented as mean ± standard deviation or number (%).

9H = 9 months of isoniazid, 3HR = 3 months of isoniazid plus rifampicin.

^aFor age, the mean ages of the two regimen groups were compared. For other variables, the proportion of 3HR prescriptions was assessed.

^bThe proportion of 3HR prescriptions was compared between primary and general hospitals and between primary hospitals and tertiary referral centers.

regimen. Comparing ages between the 9H and 3HR groups, patients in the 3HR group tended to be older. The proportion of 3HR prescriptions significantly increased during 2018–2020 compared to 2016–2017. Among different types of medical facilities, the proportion of 3HR prescriptions was significantly higher in primary hospitals compared to general hospitals or tertiary referral centers. Additionally, non-pediatric specialties had a significantly higher proportion of 3HR prescriptions compared to pediatric specialties. Hospitals located in metropolitan areas also had a significantly higher proportion of 3HR prescriptions than those in non-metropolitan regions.

Table 3 displays the results of treatment completion. In total, among the 11,362 patients (0–18 years old) who received LTBI treatment from 2016 to 2020, 4,514 cases (39.7%) did not complete treatment. In the analysis by treatment regimen, the treatment incompleteness rate was 46.9% in the 9H group compared to 30.3% in the 3HR group. In the multivariable analysis, the treatment regimen was the most influential factor associated with treatment incompleteness, with the 9H regimen group having the highest aOR (aOR, 2.42; 95% CI, 2.20–2.66; $P < 0.001$). Treatment in a primary hospital (aOR, 1.52; 95% CI, 1.29–1.79; $P < 0.001$), treatment by a non-pediatric specialist (aOR, 1.57; 95% CI, 1.36–1.81; $P < 0.001$), and treatment in a hospital located in a non-metropolitan region (aOR, 1.10; 95% CI, 1.02–1.19; $P = 0.020$) were also significantly associated with treatment incompleteness. Other factors, such as patient age and treatment period, did not significantly influence treatment incompleteness.

DISCUSSION

To the best of our knowledge, this is the first nationwide study utilizing national insurance claim data to analyze the treatment status of LTBI among pediatric patients in Korea. Our findings confirmed that the choice of treatment regimen strongly influences treatment completion. Specifically, the 9H regimen emerged as the most influential factor associated with treatment incompleteness. Additionally, management in primary hospitals, those located in non-metropolitan regions, and under the care of non-pediatric specialists were also

Table 3. Factors associated with latent tuberculosis infection treatment incompleteness

Variables	Total (N = 11,362)	Incompletion, No. (%)	Adjusted OR (95% CI)	P value
Age, yr				
0–6	4,713	1,930 (41.0)	1.03 (0.92–1.16)	0.600
7–12	2,889	1,144 (39.6)	1.02 (0.90–1.16)	0.705
13–18	3,760	1,440 (38.3)	Reference	
Treatment regime				
9H	6,463	3,031 (46.9)	2.42 (2.20–2.66)	< 0.001
3HR	4,899	1,483 (30.3)	Reference	
Treatment period				
2016–2017	6,021	2,519 (41.8)	1.06 (0.98–1.15)	0.136
2018–2020	5,341	1,995 (37.4)	Reference	
Medical facility				
Tertiary referral center	3,321	1,180 (35.5)	Reference	
General hospital	7,074	2,852 (40.3)	1.04 (0.95–1.14)	0.356
Primary hospital	967	482 (49.8)	1.52 (1.29–1.79)	< 0.001
Specialty of clinicians				
Pediatrics	9,150	3,618 (39.5)	Reference	
Non-pediatrics	2,212	896 (40.5)	1.57 (1.36–1.81)	< 0.001
Hospital location				
Metropolitan	5,977	2,233 (37.4)	Reference	
Non-metropolitan	5,385	2,281 (42.4)	1.10 (1.02–1.19)	0.020

OR = odd ratio, CI = confidence interval, 9H = 9 months of isoniazid, 3HR = 3 months of isoniazid plus rifampicin.

identified as significant risk factors for treatment incompleteness. In our analysis of prescribed regimens, the 3HR regimen was more likely prescribed in the later period (2018–2020) than the earlier period (2016–2017), in primary hospitals, by non-pediatric specialists, and in metropolitan regions.

Previous studies consistently show an inverse relationship between treatment length and completion rates. Specifically, 9H regimen groups tend to exhibit around a 50% completion rate, while completion rates for 3HR range from 70% to 90%.¹³ Recent global research has consistently demonstrated that when comparing the 9H regimen to a rifampicin-based 3–4-month regimen, the shorter rifampicin-based regimen not only results in a higher completion rate^{14–17} but also exhibits similar levels of effectiveness (with no difference in progression to TB) and safety (with no difference in reports of adverse events).^{16,18} Recent updates to LTBI treatment guidelines favor the 3HR regimen over the 9H regimen.¹⁸ While direct comparisons between studies can be challenging due to differences in study designs and populations, the findings of this study align with previous research. The completion rate of the 9H group was 53.1%, whereas the completion rate of the 3HR group was 69.7%, indicating that the 9H regimen carries a higher risk of treatment incompleteness. In Korean guidelines, the 9H regimen is considered the standard, while the 3HR regimen is viewed as an alternative.⁹ The findings of this study suggest that adopting shorter regimens can enhance treatment completion.

It is worth noting that a larger proportion of 3HR regimens were observed in primary healthcare settings and among non-pediatric specialties (Table 2). However, primary hospitals and non-pediatric specialties were associated with treatment incompleteness. In Korea, designated medical facilities are responsible for conducting TB contact investigations. Among primary hospitals designated for this purpose, most physicians specialize in internal medicine, and those with a pediatric specialty are relatively rare. This may be due to the fact that TB index patients are typically adults who visit internal medicine clinics and bring their family members for contact investigation. Our findings suggest that internal medicine specialists in primary

hospitals may be more inclined to prescribe shorter LTBI treatment regimens, specifically the 3HR regimen, as opposed to the 9H regimen. In contrast, pediatricians tend to lean towards the more established 9H regimens over the 3HR regimens. In this study, we assessed treatment completion by dispensed medication. Treatment incompleteness indicates that the patient either did not return to the hospital or that the physician discontinued the medication, regardless of whether parental refusal was involved. The Korean health authority has put substantial effort into increasing TB treatment completion rates, emphasizing patient management as a core strategy.^{19,20} Effective patient management is also essential in LTBI treatment; healthcare personnel play a critical role in enhancing patient and parental understanding of the disease, motivating better adherence to treatment, and ensuring that patients return for follow-up visits. A lack of knowledge among physicians regarding pediatric LTBI or the treatment guidelines, coupled with insufficient emphasis on the importance of treatment completion, may contribute to treatment incompleteness. Such occurrences may be more common in primary care settings compared to tertiary referral centers, and they are more prevalent in non-pediatric specialties than in pediatric departments.

In Korea, hospitals are primarily concentrated in metropolitan regions, and these regions have benefited from well-developed public transportation networks that make hospital access convenient. In contrast, non-metropolitan regions may show variations from place to place, but generally, they tend to have limited healthcare infrastructure compared to metropolitan areas. This means that accessing hospital facilities is easier in metropolitan regions.^{21,22} It can be hypothesized that the accessibility of medical facilities influences patients' follow-up visits and treatment completion. Consequently, we categorized hospital locations as either metropolitan or non-metropolitan, and the results clearly indicated that the non-metropolitan region was significantly associated with treatment incompleteness. Given that patients with LTBI exhibit no symptoms and parents may not perceive the disease as a serious threat, we presume that the ease of visiting a hospital may have influenced treatment completion.

In our analysis of prescription patterns (**Table 2**), the 3HR regimen was more frequently employed in the later period (2018–2020) compared to the earlier period (2016–2017). This shift might be attributed to the influence of reports published in the late 2010s, which indicated a preference for the 3HR regimen over the 9H regimen. Additionally, the average age was higher in the 3HR group compared to the 9H group, suggesting that physicians may lean towards prescribing regimens with more data supporting their use in younger children. Notably, the 3HR regimen was more likely to be prescribed in metropolitan areas than in non-metropolitan regions, although the exact reasons remain uncertain. Further observation may be necessary to better understand this trend.

While this study did not delve into the underlying reasons for treatment discontinuation, it is important to consider the potential impact of the diagnostic accuracy of the TST on LTBI treatment incompleteness. TST is known for its low specificity. False-positive TST results can be influenced by factors such as prior Bacillus Calmette-Guerin vaccination, errors in TST administration or interpretation, and exposure to non-tuberculous mycobacteria.^{23,24} Physician's uncertainty regarding a positive TST result and their failure to reinforce treatment completion may have possibly occurred. In previous studies, concerns expressed by parents or patients about potential side effects have been reported as potential barriers in LTBI treatment.^{25,26} As a result of these concerns, parents may have discontinued the medication, or physicians may have chosen to halt the treatment, and such situations may have empirically been noted in this study.

Unlike active TB, LTBI is asymptomatic and not contagious, which is why treatment for LTBI has not garnered significant public attention. Pediatric patients with LTBI or their parents may feel that treatment is not needed or they may not observe symptoms and so be unaware of the disease. However, emphasizing the treatment of pediatric patients with LTBI is crucial in preventing morbidity and mortality in this particular population.^{2,3} In addition to merely prescribing medication, ensuring treatment completion is essential, as it plays a pivotal role in reducing the reservoir of future TB cases and mitigating subsequent transmission. The findings of this study suggest that promoting the use of the 3HR regimen for LTBI treatment could substantially improve the treatment completion rate. To enhance the treatment completion rate, particularly for patients in primary hospitals, those located in non-metropolitan regions, and non-pediatric specialties, the implementation of educational programs for physicians may prove to be a valuable strategy.

The present study is the first of its kind, conducting a nationwide investigation into treatment patterns and completion rates among pediatric patients in Korea. It offers crucial insights into the longer treatment duration of the 9H regimen as a significant risk factor for incomplete treatment. However, the study does have limitations due to the nature of administrative data. First, prescription records alone could not confirm whether the dispensed medication was actually taken. Second, the lack of access to clinical data made it challenging to investigate potential adverse effects of medication, which could possibly contribute to treatment discontinuation, as well as other variables, such as diagnostic methods (TST or IGRA), that might influence treatment completion. Further research is necessary to delve into treatment completion and elucidate the contributing factors to treatment discontinuation. Additionally, studies comparing the effectiveness and safety of the 9H and 3HR regimens are warranted. Ongoing observation is also needed to gain a better understanding of the distribution of prescribed regimens and the characteristics of both patients and medical facilities.

In conclusion, this study suggests that to enhance the completion of LTBI treatment among pediatric patients, a greater emphasis should be placed on the 3HR regimen. Furthermore, physicians in primary hospitals, hospitals located in non-metropolitan regions, and non-pediatric physicians need to be more attentive in the management of pediatric patients with LTBI to ensure treatment completion. The findings of this study are anticipated to offer valuable insights for clinical practice and contribute to the improvement of LTBI treatment guidelines in Korea.

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