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Cost-Effectiveness of Age-Expanding Strategy of Latent Tuberculosis Infection Treatment in Household Contacts in South Korea

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Purpose: The strategy of latent tuberculosis infection (LTBI) treatment in household tuberculosis (TB) contacts has been expanding in South Korea. However, there is little evidence of the cost-effectiveness of LTBI treatment in patients over 35 years of age. This study aimed to evaluate the cost-effectiveness of LTBI treatment among household TB contacts in different age groups in South Korea.

Materials and Methods: An age-structured model of TB was developed based on the reports from the Korea Disease Control and Prevention Agency and the National Health Insurance Service. Quality-adjusted life-years (QALY) and the averted number of TB-related deaths were estimated along with discounted costs for a measure of incremental cost-effectiveness ratios.

Results: The number of cumulative active TB cases would decrease by 1564 and 7450 under the scenario of LTBI treatment for those aged <35 years and <70 years, respectively, relative to the no-treatment scenario. The treatment strategies for patients aged 0 to <35 years, <55 years, <65 years, and <70 years would add 397, 1482, 3782, and 8491 QALYs at a cost of $660, $5930, $4560, and $2530, respectively, per QALY. For the averted TB-related deaths, LTBI treatment targeting those aged 0 to <35 years, <55 years, <65 years, and <70 years would avert 7, 89, 155, and 186 deaths at a cost of $35900, $99200, $111100, and $115700 per deaths, respectively, in 20 years.

Conclusion: The age-specific expansion policy of LTBI treatment not only for those under 35 years of age but also for those under 65 years of age among household contacts was cost-effective in terms of QALYs and averted TB deaths.

Key Words: Cost-effectiveness analysis, mathematical model, tuberculosis, latent tuberculosis infection

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INTRODUCTION

Tuberculosis (TB) is a communicable disease, a major cause of ill health, and one of the leading causes of infectious diseases worldwide. According to the World Health Organization (WHO), TB affected 10.6 million people and caused 1.6 million deaths in 2021.[1] The WHO End TB Strategy, in line with the 2030 Agenda for Sustainable Development Goals,[2] set ambitious targets to end the epidemic by reducing its incidence and mortality by 80% and 90% in 2030, respectively, from those reported in 2015.[3] An integrated and multi-sectoral approach is necessary to reach these TB targets globally.

To achieve end-TB targets, preventive treatment of persons at high risk for TB is one of the key interventions in integrated and patient-centered care. The WHO recommends scaling up latent tuberculosis infection (LTBI) testing and TB preventive treatment (TPT) under programmatic management of preventive treatment (PMTPT).[4] However, the efficacy of the currently available TPT is not perfect,[5] and there is a high risk of drug-related adverse events. Therefore, the potential benefits of LTBI treatment should be carefully balanced against the risk of adverse drug reactions and costs. The WHO guidelines for TPT strongly recommend preventive treatment for children aged <5 years in household contacts, but conditionally recommend preventive treatment for other age groups among household contacts, following national and local guidelines,[4] as well as clinical judgement on the harms and benefits. In addition, regarding the feasibility of PMTPT, the cost-effectiveness of TPT is a main consideration in TB control policy in each country.

South Korea has a considerable TB burden, with an incidence rate of 44.6/100000 in 2021.[6] Active screening and management of LTBI in households is one of the key policies in the Korean national TB control program,[7] conducted since 1962 for family members under 5 years of age. The LTBI management program was gradually expanded, and the age of LTBI treatment was extended to under 35 years in 2014 and then to 65 years in 2017 to strengthen the TB control program in South Korea.[8]

However, there is a lack of evidence addressing the policy expansion of LTBI treatment in household contacts in South Korea, particularly regarding cost-effectiveness. Building and implementing the TB control policy based on various pieces of evidence supporting the policy is important. This study aimed to develop an age-structured mathematical model of TB to evaluate the cost-effectiveness of LTBI treatment by considering different age groups in Korean household contacts.

MATERIALS AND METHODS

Study design and data sources

This study was designed to evaluate the cost-effectiveness of TPT in household contacts of TB by age. Different scenarios for treating patients aged <35 years, <55 years, <65 years, and <70 years were compared to the baseline scenario of not treating any family member. The incidence of TB and cost-effectiveness of each scenario were predicted for the next 20 years.

Data extracted from the Annual Reports on Notified Tuberculosis cases in South Korea from the Korea Disease Control and Prevention Agency were used for model calibration. The medical fee table of the Health Insurance Review & Assessment Service (HIRA) data in 2020[9] helped determine the diagnostic cost of active TB and LTBI for each age group, and the therapeutic cost for active TB and LTBI was based on the claims data of the National Health Insurance Service (NHIS).[10]

Model and parameters

A deterministic compartment model of pulmonary TB transmission dynamics was developed, incorporating age structure, to assess the effect of LTBI treatment on different age groups. The model population was classified by disease status as susceptible (S), recently infected (E_S), at-risk of relapse, reinfection or reactivation (E_L), infectious (I), long-term latent (L), and LTBI treated (T). Each compartment was subdivided into 15 groups at 5-year increments from 0 to 74 years and one additional group over 75 years of age. The flow diagram of the age-structured TB transmission model is displayed in Fig. 1.

The susceptible individuals, upon effective contact with infectious individuals, progresses to recent infection with transmission rate W. A proportion q of recently infected individuals move to the infectious compartment at rate ν, where 1/ν represents the average pre-infectious period. The rest of the recently infected individuals (1-q) become long-term latent at the same rate, ν. The infectious individuals die from TB with a death rate (d), remain in I in proportion to treatment failure (p) of active TB, or transit to long-term latent if the treatment is successful (1-p-d), all at the rate γ, which denotes the reciprocal of the infectious period. The long-term latent may progress to E_L by relapse, reinfection, or reactivation at rate τ. When individuals in E_S, E_L, and L groups are treated for LTBI, they move to the treated group by the number of preventive treatments m_{ESi}, m_{ELi}, and m_{Li} respectively. Treated individuals are

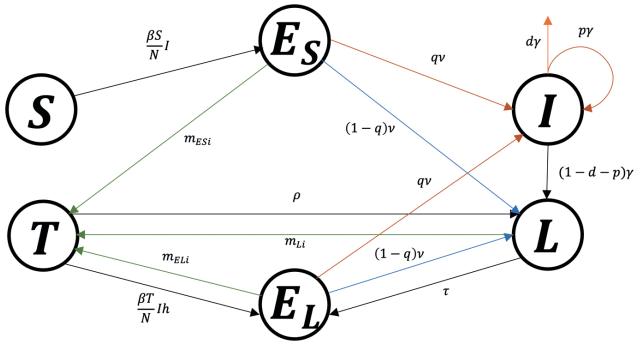

Fig. 1. Age-structured tuberculosis transmission model.

Table 1. Summary of Parameters Used in the Model Simulation

Parameter	Description	Value and reference
W	Transmission matrix	$W=\hat{\beta} \cdot C$
C	Contact matrix	Supplementary Fig. 5 (only online)[14]
$\hat{\beta}$	Proportionality factor of transmission rate in force of infection	Estimated
$1/\nu$	Average pre-infectious period	1.5 years[12]
q	Proportion of active tuberculosis progression	5%[27,28]
$1/\gamma$	Average infectious period	1 year[29-33]
d	Death rate due to tuberculosis	Supplementary Table 12 (only online)[14]
p	Proportion of treatment failure	6%[15]
τ	Rate of relapse, reactivation, or reinfection	Estimated
m	Number of latent tuberculosis infection treatments	Supplementary Table 13 (only online)[16,17]
h	Reduced factor of transmission for preventive therapy	65%[18]
$1/\rho$	Duration of treatment waning	10 years

assumed to have partial immunity to reinfection, and the reduced factor is denoted by h. Individuals in the treatment compartment may return to long-term latent with waning rate ρ. Table 1 provides descriptions and values of the parameters used in the simulations.

The parameter values were based on different reference materials, including literature reviews, annual TB reports, investigator derivations, and estimations. The parameters for the TB model were classified according to domestic demographics, infection, disease progression, and treatment. Demographic parameters included population size, birth, natural death, and aging rate, incorporated from the annual Korean census data.[11] A dynamic population was considered for the long-term perspective owing to the nature of TB, to predict its effect during the 2020–2040 period.

Approximately 5% of individuals who were exposed to infectious TB progressed to active TB within 1 to 2 years, and the average value was used in the model simulation.[12] The active infectious period was not precisely known and assumed to be 1 year, with the effect investigated through sensitivity analysis.[13] The treatment failure proportion and age-dependent death rate were derived from the literature on treatment success rates and TB death reports.[14,15] The number of close contact treatments was determined from literature reviews.[16,17] A reduced force of infection[18] and waning rate were assumed, and the uncertainty of the outcome was analyzed through sensitivity analysis.

In this model, the force of infection was assumed to be proportional to the number of infectious individuals. The transmission rate of the age-structured model was represented by the Who Acquires Infection From Whom matrix, presumably representing the projected contact patterns of South Korea.[19] Assuming heterogeneous infectiousness of TB by age group, the vector of proportionality factor ($\hat{\beta}$) was estimated with confidence intervals using the maximum likelihood estimation method calibrated based on the annual TB report data from 2008 to 2019.[14]

$$\lambda = W \cdot I = \hat{\beta} \cdot C \cdot$$

Another estimated critical parameter was the reactivation rate. The number of reported TB cases in South Korea has rapidly decreased since 2011, which was incorporated into the age-and time-dependent values of τ. The rates of relapse, reactivation, and reinfection, denoted by τ, were estimated by the maximum likelihood estimation method using the number of TB case per 100000 from 2011 to 2019. In the maximum likelihood estimation, we assumed the data x_j were sampled from a random variable x_j with Poisson distribution. That is, we found the parameter value $\hat{\theta}$ using the following method:

$$\hat{\theta}=\text{argmax}_{\theta}\left[\prod_j \Pr\left(X_j=x_j \mid X_j \sim \text{Poisson}\left(\lambda_j(\theta)\right)\right)\right]$$

where x_j and λ_j represents the data and the mean, respectively.

Supplementary Figs. 1 and 2 (only online) demonstrate the results of model calibration compared with incidence data on the classification of active TB patients from recently infected group and at-risk of relapse, reinfection, or reactivation compartments, respectively.

Scenarios for LTBI treatment strategy and cost-effectiveness analysis

The no-treatment baseline scenario was compared for different preventive strategies for treating patients aged 0 to <35 years, <55 years, <65 years, and <70 years. Supplementary Table 1 (only online) lists the number of individuals with LTBI treated among households as of 2018, under the LTBI management program to treat household contacts from 0 to <35 years of age. According to scenarios for LTBI treatment by age group, the number of individuals with LTBI treatments in 2018 was estimated by age (Supplementary Table 2, only online). The active TB incidence was predicted for each scenario over the next 20 years.

The incremental cost-effectiveness ratio (ICER) for each scenario was also estimated. ICER was defined as the ratio of

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incremental costs to incremental effectiveness introduced by the intervention compared to baseline. Quality-adjusted life year (QALY) values from the literature[20-22] were used as a measure of effectiveness. The values for the active TB with/without treatment and LTBI-treated individuals were 0.76 and 0.99, respectively. However, the untreated LTBI individuals were assigned a utility of one, similar to people in perfect health. The number of TB-related deaths was also an alternative measure of effectiveness.

The cost of diagnosing and treating LTBI and active TB were analyzed. Only direct medical costs for diagnosis and treatment were considered, and the values were extracted from the medical fee table of the HIRA data.[9] The average treatment costs per LTBI and active TB were estimated based on the NHIS data.[10] The costs of diagnosis and treatment were presented in US dollars using the 2020 yearly average exchange rate of $1 per 1088 won (Supplementary Tables 3 and 4, only online).

The QALY of each disease status was applied to the corresponding compartment to estimate the overall value of effectiveness every 5 years from 2020 to 2040. The targeted LTBI diagnosis cost included individuals with negative test results and those who have not received treatment. The costs of LTBI treatment, active TB diagnosis, and treatment for each age group were applied to the number of treated and active TB patients, respectively, to calculate the cumulative medical cost. All costs were discounted annually at 3%. The sensitivity of ICER from 2020 to 2040 was also investigated to model parameters from the perspective of QALY and TB-related deaths.

RESULTS

TB incidence and deaths

The active TB incidence and TB-related deaths from 2020 to 2040 were estimated for each scenario and compared with the baseline scenario of no treatment strategy. Model simulations projected a gradual decrease in the number of TB cases from 24728 in 2020 to 21096 in 2040, with stagnation over time for the baseline scenario with no LTBI treatment strategy (Fig. 2, Supplementary Table 5, only online).

The cumulative number of TB cases were predicted to be reduced by 1564, 5236, 6921, and 7450 over 20 years under LTBI treatment strategies for patients aged 0 to <35 years, <55 years, <65 years, and <70 years, respectively (Supplementary Table 5, only online). As the target age group of LTBI treatment in household contacts expanded, the number of active TB patients decreased yearly.

The number of TB-related deaths decreased from 1711 in 2020 to 1697 in 2026, and then increased to 2089 in 2040 without LTBI treatment, as a result of demographic changes (Supplementary Table 6, only online). Tuberculosis-related deaths in the general population increased, while decreasing among those aged under 70 years, and increasing among those aged over 70 years (Fig. 3A-C). However, the increase in the number of deaths for patients aged over 70 years was due to an increase in the population in that age group, and the number of deaths per 100000 people in this age group also decreased (Fig. 3D). The cumulative deaths due to TB over 20 years were reduced by 11, 126, 222, and 266 under LTBI treatment strategies for those aged 0 to <35 years, <55 years, <65 years, and <70 years, respectively. The expanded policy of LTBI treatment resulted in a decrease in TB-related deaths as well as a

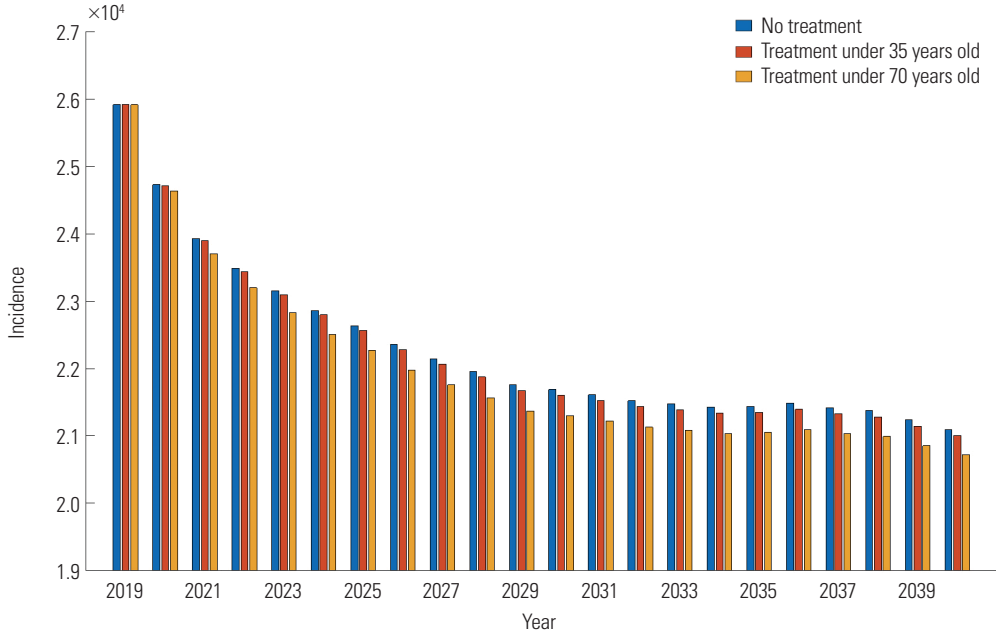

Fig. 2. The number of tuberculosis patients for the latent tuberculosis infection treatment scenario of <35 and <70 years old, compared to baseline.

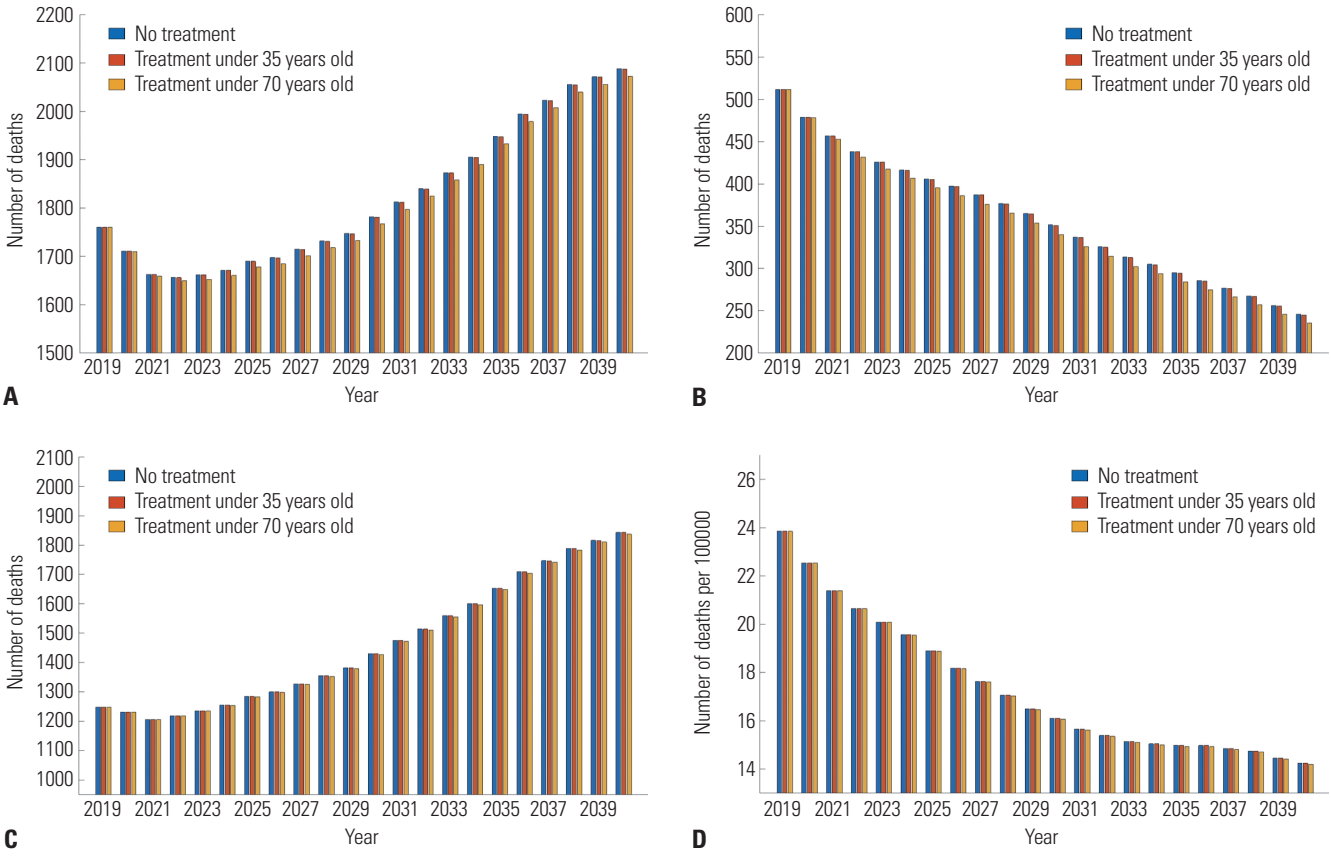

Fig. 3. (A) The number of tuberculosis-related deaths in the general population under the treatment scenario of <35 and <70 years old, compared to baseline. (B) The number of tuberculosis-related deaths among the population <70 years under the treatment scenario of <35 and <70 years old. (C) The number of tuberculosis-related deaths among the population for ≥70 years old under treatment scenario for <35 and <70 years old. (D) The number of tuberculosis-related deaths per 100000 people ≥70 years old under treatment scenario for <35 and <70 years old.

Table 2. Cost-Effectiveness of LTBI Treatment for Patients Aged 0 to <35, <55, <65, and <70 Years among Household Contacts, Over 20 Years

Age group (years)	Incremental costs (thousands $)	Incremental QALYs	ICER (thousands $/QALY)	Deaths averted	ICER (thousands $/death)
0–34	260.1	396.8	0.66	7.2	35.9
0–54	8795.5	1481.9	5.93	88.7	99.2
0–64	17251.7	3782.0	4.56	155.4	111.1
0–69	21511.8	8491.3	2.53	186.0	115.7

LTBI, latent tuberculosis infection; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

decline in TB incidence. Among household contacts, treating individuals with LTBI in the 0 to <35 years of age group had little effect on death reduction since the death rate was very low, of under 30.

Cost-effectiveness analysis

The scenario of LTBI treatment for patients aged 0 to <35 years was associated with additional 396.8 QALYs at a cost of $660 per QALY over 20 years relative to the no-treatment strategy (Supplementary Tables 7 and 8, only online, Table 2). Each scenario of LTBI treatment strategies for patients under 55, 65, and 70 years of age would add 1481.9, 3782.0, and 8491.3 QALYs at a cost of $5930, $4560, and $2530 per QALY, respectively. The cost-effectiveness improved as the target age group for LTBI treatment among household contacts expanded (Fig. 4, Supplementary Table 9, only online).

Considering the averted deaths, the LTBI treatment scenarios targeting patients under 35, 55, 65, and 70 years of age would reduce deaths by 7.2, 88.7, 155.4, and 186.0 at a cost of $35900, $99200, $111100, and $115700 per death, respectively, over 20 years (Supplementary Tables 10 and 11, only online, Table 2). The scenario treating individuals with LTBI aged 0 to 35 years achieved the smallest ICER value for averted TB-related deaths. The cost-effectiveness results for other scenarios were quite similar (Fig. 5).

Sensitivity analysis

Sensitivity analysis was performed to investigate the effect of

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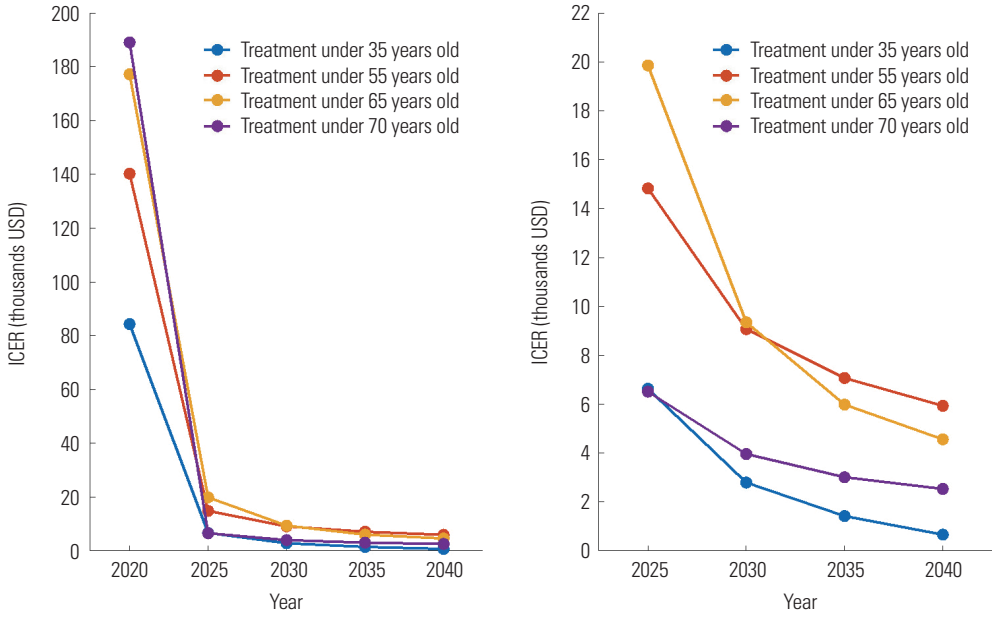

Fig. 4. The incremental cost-effectiveness ratio (ICER) of latent tuberculosis infection treatment for 0 to <35, <55, <65, and <70 years old, over 20 years with quality-adjusted life years (QALY) as measure of effectiveness (thousands $/QALY).

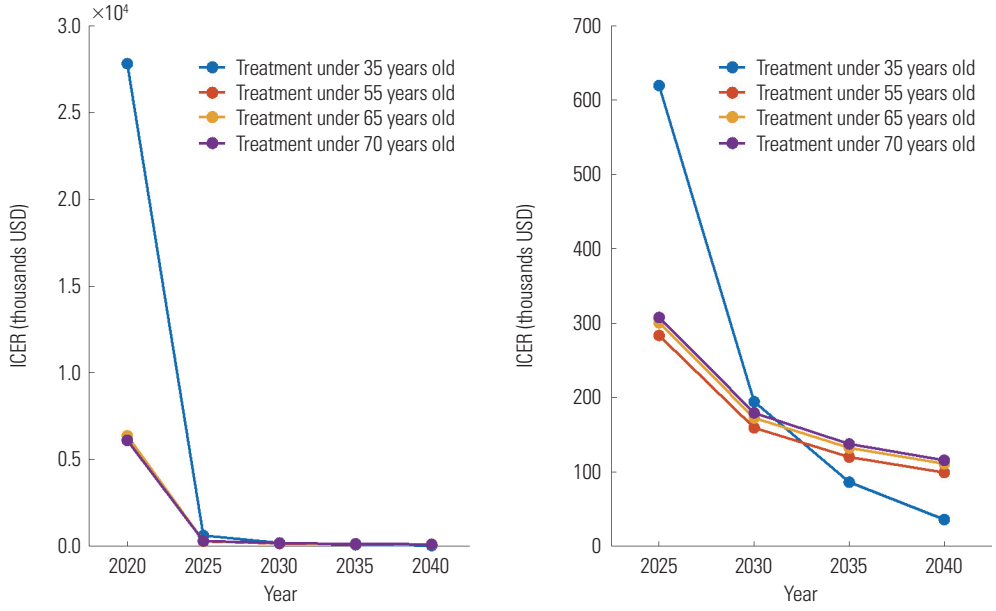

Fig. 5. The incremental cost-effectiveness ratio (ICER) of latent tuberculosis infection treatment for 0 to <35, <55, <65, and <70 years old, over 20 years with averted number of death as measure of effectiveness (thousands $/death).

uncertainty in the parameter values on the output of model simulation. The sensitivity analysis was performed for ICER values in 2040 for the two LTBI treatment scenarios, treating individuals with LTBI in the 0 to <35 years of age group and the 0 to <70 years of age group. All model parameters were perturbed by ±5% to compute the relative impact on ICER, and the sensitivity of the six most influential parameters was displayed in tornado diagrams (Supplementary Figs. 3 and 4, only online). The ICER with QALY of LTBI treatment scenario was highly sensitive to the proportion of progression (q) to active TB, average infectious period ($1/\gamma$), and transmission rate in patients aged 20–30 years (β_4,β_5) (Supplementary Fig. 3, only online). With averted TB-related deaths as a measure of effectiveness, ICER was very sensitive to TB death rate (d) in the treatment scenario of the 0 to <70 years of age group (Supplementary Fig. 4, only online).

DISCUSSION

This model-based analysis describes the cost-effectiveness of age-specific interventions for LTBI in household contacts in

South Korea. In particular, the scenario of treating individuals with LTBI aged 0 to <35 years among household contacts showed the lowest ICER (i.e., the most cost-effective). However, the differences in cost-effectiveness were small for each scenario treating different age range in terms of ICERs for QALY and death; all strategies were similarly cost-effective. Therefore, the strategy of LTBI treatment for those aged under 65 years in Korean household contacts was cost-effective in reducing TB.

Screening and treatment of LTBI is one of the main strategies for the elimination of TB in South Korea, and support for this policy is actively being promoted. Household contacts are a priority group for screening and treatment of LTBI in South Korea, and the age of treatment has been continuously expanding from <35 years in the 2014 guidelines to <65 years in the 2017 guidelines.[8]

Prioritizing candidates for LTBI treatment is an important challenge, as public health programs compete for resources. In this context, the cost-effectiveness of expanding the treatment age for LTBI in South Korea has not been clear. Through this mathematical model, based on domestic data, we could find that a reduction in TB incidence by the treatment of LTBI for household TB contacts was cost-effective. Among household contacts, the current WHO guidelines prioritize children aged <5 years for the treatment of LTBI.[4] Our results endorse this recommendation, and the expanded age group policy is also cost-effective in the Korean situation.

In general, health intervention has been considered as cost-effective if ICER is below a predetermined threshold. In the United Kingdom, £20000–£30000 per QALY have been accepted as the threshold by the National Institute for Health and Clinical Excellence for recommending the use of new healthcare technology.[23] A threshold of US $50000–$100000 per QALY is often mentioned in the medical literature of the United States.[24] In South Korea, there is no consensus regarding the cost-effectiveness threshold. A previous report suggested that the willingness to pay for one additional QALY was US $74000 in South Korea.[24] Thus, the policy for the treatment of LTBI for individuals under 65 years of age among household contacts could be cost-effective based on our results. However, to achieve this cost-effectiveness in real practice, the cascade of care for LTBI should be operated effectively in the healthcare system.[25] In the model, we assumed that all individuals in each age group with LTBI underwent treatment for LTBI and completed the treatment in each scenario. However, in real practice, there are major losses at several steps in the weak care cascade for LTBI, which weakens the cost-effectiveness of the LTBI treatment strategy for household contacts.[25,26]

Limitations and suggestions for follow-up studies

This study not only built a dynamic mathematical model for TB incidence until 2040, considering changes in the age structure, but also examined actual LTBI treatment costs through claims data from the NHIS; however, the study still had several limitations.

First, in the dynamic mathematical model of this study, a contact matrix was applied to estimate the age structure and infectiousness between the age groups. The contact matrix was constructed based on the POLYMOD[19] contact survey conducted in European countries, which can be different from the contact patterns in South Korea. Therefore, a mathematical model based on a new contact survey is required to predict not only TB, but also the outbreak of infectious diseases due to close contact.

Second, in calculating the direct medical cost within the healthcare system, the cost of treatment for LTBI and active TB could be analyzed through health insurance claims data. However, for the diagnostic cost, we used the medical fee table from HIRA and calculated the hypothetical costs. In practice, the diagnostic costs for LTBI and active TB will likely be higher than the hypothetical costs calculated in this study. Thus, policies to treat LTBI among household contacts may be more cost-effective. Therefore, it is necessary to calculate and apply the actual medical costs incurred during the diagnosis of LTBI and active TB. In addition, the indirect medical cost was not considered in our model.

Third, the diagnosis and treatment of drug-resistant (DR) TB were not included in the mathematical model of this study. In South Korea, about 500 to 1000 multidrug-resistant (MDR) TB patients have been reported annually[6] since 2011, and the diagnosis and treatment of DR-TB are more expensive than those of drug-susceptible TB. For household contacts with MDR-TB, the treatment of LTBI is not recommended in South Korea. Therefore, to simplify our mathematical model, we did not include the DR-TB status in this study.

Fourth, annual reports on the notified TB and local epidemiological data were used to stabilize the mathematical model. We should consider the difference between the number of reported TB patients and the actual number of TB incidences, affected by the gap between diagnosis and notification.

Finally, this cost-effectiveness analysis was limited to household TB contacts; therefore, we cannot generalize our results to other groups or the general population.

Conclusions

In this study, the cost-effectiveness of the age expansion policy for LTBI treatments among household contacts was investigated using a dynamic mathematical model. The results demonstrated the cost-effectiveness of the age-specific expansion policy of LTBI treatment not only for patients under 35 years of age, but also for those under 65 years, among household contracts. The study is meaningful in providing a scientific basis for LTBI treatment policy in household contacts in South Korea.

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Conceptualization: Hee Jin Kim, Young Ae Kang, and Jeehyun Lee. Data curation: Youngmok Park, Eun Hye Lee, Hee Jin Kim, and Young Ae Kang. Formal analysis: Hyunwoo Cho and Jeongjoo Seok. Funding acquisition: Jungeun Park, Dong Ah Park, and Young Ae Kang. Investigation: Youngmok Park, Eun Hye Lee, and Hee Jin Kim. Methodology: Young Ae Kang and Jeehyun Lee. Project administration: Jungeun Park, Dong Ah Park, Young Ae Kang, and Jeehyun Lee. Resources: Youngmok Park and Eun Hye Lee. Software: Hyunwoo Cho and Jeongjoo Seok. Supervision: Young Ae Kang and Jeehyun Lee. Validation: Young Ae Kang and Jeehyun Lee. Visualization: Hyunwoo Cho and Jeongjoo Seok. Writing—original draft: Hyunwoo Cho and Young Ae Kang. Writing—review & editing: Hyunwoo Cho, Jeongjoo Seok, Hee Jin Kim, Young Ae Kang, and Jeehyun Lee. Approval of final manuscript: all authors.

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