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Contact Investigations With a Single Tuberculin Skin Test on Infants Exposed to Tuberculosis in a Postpartum Care Center During the Neonatal Period

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ABSTRACT

Background: Tuberculosis (TB) exposure in congregate settings related to neonates is a serious medical and social issue. TB exposure happens during the neonatal period, but contact investigations for exposed infants are usually conducted after the neonatal period. Generally, recommendations for screening and managing close contact are different for neonates and children. Thus, there are challenges in contact investigations. We aimed to report contact investigations with a single tuberculin skin test (TST) on infants exposed to infectious TB in a postpartum care center.
Methods: The index case was a healthcare worker with active pulmonary TB: sputum acid-fast bacilli smear negative, culture positive, and no cavitary lesion. All exposed infants underwent medical examinations and chest X-ray. After TB disease was ruled out, contacts received window period prophylaxis with isoniazid (INH) until three months after the last exposure. TST was performed only once after completing the prophylaxis.
Results: A total of 288 infants were selected as high-priority contacts. At the initial contact investigation, the age of infants ranged from 8 to 114 days. None of these exposed infants had TB disease. The prevalence of latent TB infection (LTBI) was 25.3% (73/288; 95% confidence interval [CI], 20.7–30.7). There were no serious adverse events related to the window period prophylaxis or LTBI treatment with INH. During the 1-year follow-up period, no infants progressed to overt TB disease. The size of TST induration in infants vaccinated with percutaneous Bacillus Calmette-Guérin (BCG) vaccine was significantly larger than that of infants vaccinated with intradermal BCG vaccine (median, 8 mm vs. 5 mm; $P = 0.002$). In multiple logistic regression analysis, independent factors associated with TST positivity (≥ 10 mm induration) were male (adjusted odds ratio [aOR], 2.98; 95% CI, 1.6–5.64), percutaneous BCG vaccination (aOR, 3.30; 95% CI, 1.75–6.48), TST reading between 60 and 72 hours after injecting purified protein derivative (aOR, 2.87; 95% CI, 1.53–5.49), and INH prophylaxis

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Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Choi SH, Park SE. Data curation: Choi SH, Oh CE, Park SE. Formal analysis: Choi SH, Oh CE. Investigation: Choi SH, Oh CE, Lee JM, Cho YY, Kwon Y, Kim J, Lee H. Park SE. Methodology: Choi SH, Oh CE, Park SE. Validation: Choi SH, Park SE. Visualization: Choi SH. Writing - original draft: Choi SH. Writing - review & editing: Choi SH, Oh CE, Park SE.

more than four weeks (aOR, 0.49; 95% CI, 0.25–0.94).
Conclusion: A single TST at three months after the last TB exposure with INH prophylaxis could be used as a main protocol in contact investigations for infants exposed to infectious TB during the neonatal period in congregate settings in Korea.

Keywords: Tuberculosis; Contact Tracing; Tuberculin Test; Infant, Newborn; Isoniazid Prophylaxis

INTRODUCTION

Although the incidence and prevalence rates of tuberculosis (TB) in Korea have steadily decreased over the past decade, the notification rate of new TB cases with 35.7 per 100,000 populations as of 2021 was still high among high-income countries. In addition, continued TB outbreaks at various congregate settings have become important problems.[1] According to national TB control programs in Korea, the TB epidemic investigation team has conducted contact investigations in congregate settings at the national level since 2013.[2,3] During 2017–2021, the rate of latent TB infection (LTBI) in congregate setting contacts ranged from 18.1% to 25.7%.[4] Compared to the incidence of TB in 2021 in Korea, the risk of TB transmission was 2.6 times higher in congregate setting contacts.[5]

TB exposure in congregate settings related to neonates, such as neonatal intensive care units (NICUs), nurseries, or postpartum care centers, is a serious medical and social issue.[3,4] Young children exposed to people with active TB are at high risk of TB infection and progression to active TB disease.[6,7] The risk of developing TB disease is the highest during the 12 months after TB infection. It remains high for two years.[6] In a meta-analysis,[7] 2-year cumulative TB incidence among children aged 0–5 years with untreated TB infection was 19%. In particular, infants aged 0–1 year had 17.9% risk of developing TB disease within two years.[7] Early diagnosis and treatment of TB infection is crucial to prevent the development of TB disease and secondary transmission.[8] However, there are confusion and challenges in contact investigations on infants temporarily exposed to active TB at NICU, nursery, or postpartum care center. TB exposure happens during the period of newborns who have stayed in congregate settings related to neonates, but contact investigations for exposed infants are usually conducted after the neonatal period. Generally, recommendations for screening and managing close contacts with infectious TB are age-specific. They are different for neonates and children.[8-13]

This study aimed to outline a protocol based on a single tuberculin skin test (TST) and report results of contact investigations on infants who were exposed to infectious TB at a postpartum care center during the neonatal period. In addition, factors associated with TST positivity were analyzed.

METHODS

Index case

A female nurse aide in her mid-40s who had worked at a postpartum care center was diagnosed with active pulmonary TB on November 6, 2020. Her main task was taking care of neonates at the nursery, such as feeding, bathing, and changing nappies. She had a dry

cough with blood-tinged sputum on October 15, 2020, three weeks before TB diagnosis. Chest X-ray (CXR) showed no specific lung lesions. Chest computer tomography (CT) showed broncholithiasis and atelectasis. However, cavitary lesions were lacking. Her sputum specimen for acid-fast bacilli was smear negative. She continued to work until the diagnosis of TB because she had no more symptoms since her first onset. However, sputum culture was reported positive for *Mycobacterium tuberculosis* on November 6, 2020. A rapid molecular test for rifampin resistance was negative. The isolate was eventually found to be all susceptible in the phenotypic drug susceptibility testing of *M. tuberculosis*.

Conducting contact investigations

Shortly after the active TB case was reported to the local public health center under the jurisdiction of the postpartum care center, contact investigations were immediately conducted by the local infectious diseases (ID) control team and the Korea Disease Control and Prevention Agency. Three pediatric ID specialists attended the planning meeting and contact investigations.

Due to the coronavirus disease 2019 (COVID-19) pandemic, it was mandatory to wear a mask while working at the postpartum care center. The index case had no more symptoms after the first onset, no cavitary lesions on chest images, and sputum smear-negative results. Thus, her infectiousness was estimated to be not high.[8] However, the index case worked in a congregate setting with many contacts, especially those who were at a high risk for rapid development of TB disease if infected with *M. tuberculosis*. The start of the infectious period was estimated to be three months before symptoms onset.[8] We considered that all newborn infants who had been in the postpartum care center during the infectious period were exposed to TB. Infants who were in the postpartum care center from July 15, 2020, to November 6, 2020, were selected as high-priority contacts for investigation. Depending on identifying secondary cases of TB disease in any contacts or the prevalence of TB infection in high-priority contacts, we considered expanding the investigation to other low-priority contacts.

Assessment and management of exposed infants

Infants' age at the initial investigation ranged from 8 to 114 days. However, all infants were exposed to TB during the neonatal period (age less than four weeks). Ages of the last TB exposure (the day of discharge from the postpartum care center) were between 2 and 22 days. Therefore, regardless the age at contact investigation, we decided to conduct a single TST at three months after the last exposure to the index case. The window period prophylaxis was implemented according to the period after the last TB exposure. Infants were distributed to three designated hospitals in the jurisdiction, and one pediatric ID specialist was in charge at each hospital. In the first step, pediatric ID physicians performed physical examinations and reviewed exposed infants' medical history and CXR results. If there were abnormal findings in the first step, evaluation for TB diseases was conducted. Once TB disease was ruled out, exposed infants received the window period prophylaxis until three months after the last exposure. TST was performed only once after completing the window period prophylaxis. At the initial investigation, infants whose last exposure to the index case had passed more than three months underwent TST without the window period prophylaxis (**Supplementary Fig. 1**). Symptom reassessment and follow-up CXRs were performed at the time of TST. If the duration of the window period prophylaxis was less than four weeks, a CXR was not repeated at the judgment of the pediatric ID specialist.

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TST was performed using two tuberculin units of purified protein derivative (PPD) RT 23 (Statens Serum Institut, Copenhagen, Denmark). The criteria for positive TST were induration of diameter ≥ 5 mm in Bacillus Calmette-Guérin (BCG) unvaccinated infants and ≥ 10 mm in BCG vaccinated infants. TST readings were performed by pediatric ID specialists between 48 and 72 hours after injecting PPD. Isoniazid (INH) was used for the window period prophylaxis and LTBI treatment (10–15 mg/kg, once a day). Infants diagnosed with LTBI received a total of nine months of INH therapy.

Monitoring and follow-up of exposed infants

For infants diagnosed with LTBI, careful monthly monitoring was performed at least until treatment completion. Liver function tests were not routinely monitored unless infants receiving LTBI treatment developed symptoms suggestive of hepatotoxicity. Infants without evidence of TB infection in contact investigations were planned for additional follow-ups at least one year after the last TB exposure. Medical examinations with a CXR were performed for these infants.

Data analysis

The prevalence of TB infection among exposed infants who had completed contact investigations was calculated. Adherence to treatment and completion rate were evaluated for infants diagnosed with TB infection. Follow-up data of infants without evidence of TB infection were investigated.

We collected information on contacts' demographics, birth history, BCG vaccination status and vaccine types, length of stay at the postpartum care center, and duration of actual exposure to the index case based on her working day. Danish 1331 (intradermal injection) and Tokyo 172 (percutaneous injection) were available BCG vaccine strains in exposed infants. Characteristics of contacts according to the status of TB infection and factors associated with TST positivity were analyzed.

Statistical analysis

We used descriptive statistics, including medians, ranges, interquartile ranges (IQRs), and proportion and prevalence. To compare the two groups, Fisher's exact test and Mann-Whitney *U* test were used for categorical and continuous variables, respectively. Correlations between continuous variables and TST induration size were analyzed using Spearman's correlation analysis. Multiple logistic regression analysis was performed to assess independent factors associated with TST positivity. Adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) were calculated. We tested for multicollinearity with variance inflation factors to control for confounding variables and performed the Hosmer-Lemeshow test for goodness-of-fit. Two-sided *P* values of less than 0.05 were considered statistically significant. Data were analyzed using Prism 9.5.0 (GraphPad Software Inc., San Diego, CA, USA).

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Pusan National University Hospital, and the need for informed consent was waived (approved No. 2205-017-115).

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RESULTS

Contact investigations

A total of 288 infants were selected as high-priority contacts. Of these, all infants participated in contact investigations. Two hundred eighty-three infants underwent contact investigations at designated hospitals in the jurisdiction. However, five infants were examined at other local hospitals because they had moved to other regions. Characteristics of the infants are shown in **Table 1**. The median length of stay at the postnatal care center was 11 days and the median duration of actual exposure to the index case was eight days. More than three-fourths (251, 87.1%) were ≥ 28 days old at the initial investigation. Most infants (90.6%) received BCG vaccination. Among 198 infants eligible for the window period prophylaxis, 189 (95.5%) completed INH prophylaxis (median duration, 56 days; IQR, 34–75.5 days). The median age at TST was 106 days old (range, 88–144 days; IQR, 102–112 days). The overall period of contact investigations was from November 6, 2020, to February 8, 2021. None of the exposed infants had TB disease (**Fig. 1**). A total of 73 infants were eventually diagnosed with LTBI, the prevalence of TB infection was 25.3% (95% CI, 20.7–30.7). Compared to infants without TB infection, male proportion (63.0% vs. 44.2%), BCG vaccination rate (100% vs. 87.4%), and median age at TST (108 days vs. 106 days) were significantly higher in infants with TB infection. The proportion of window period prophylaxis was significantly lower in infants with TB infection than in those without TB infection (50.7% vs. 72.6%). There was no significant difference in the actual duration of exposure to the index case (**Table 2**).

Follow-up

Of 73 infants diagnosed with LTBI, all received LTBI treatment. However, complete data on follow-up were not available in three infants. Seventy (95.9%, 70/73) infants completed LTBI treatment. There were no serious adverse events related to a 9-month INH therapy. The median duration from the last exposure to the index case to the final follow-up was 365 days (IQR, 325–391 days). During the follow-up period, no infants progressed to overt TB disease. Of 215 infants without TB infection at the contact investigations, 181 (84.2%) were followed

Table 1. Characteristics of infants exposed to the index case

Characteristics	Values (N = 288)
Age at the initial investigation, day	69.5 (8–114)
Days from last exposure to initial investigation	56 (5–125)
Sex, male	141 (49.0)
Gestational age, wk[a]	38 (35–40)
35–36	14 (5.1)
37–38	167 (60.7)
39–40	94 (34.2)
Birth weight, g	3,120 (1,800–4,040)[b]
Presence of comorbidities	15 (5.3)[c]
Age at the last exposure, day	15 (2–22)
Length of stay at the postnatal care center, day	11 (1–15)
Duration of actual exposure to the index case, day	8 (1–12)
BCG vaccination	
Unvaccinated	27 (9.4)
Vaccinated, intradermal type	98 (34.0)
Vaccinated, percutaneous type	163 (56.6)

Values are presented as median (range) or number (%).
BCG = Bacillus Calmette-Guérin.
[a]Available data from 275 infants.
[b]Available data from 268 infants.
[c]Available data from 283 infants, including those with congenital heart disease (n = 9), Klinefelter syndrome (n = 1), renal diseases (n = 2), hemangioma (n = 2), and syndactyly (n = 1).

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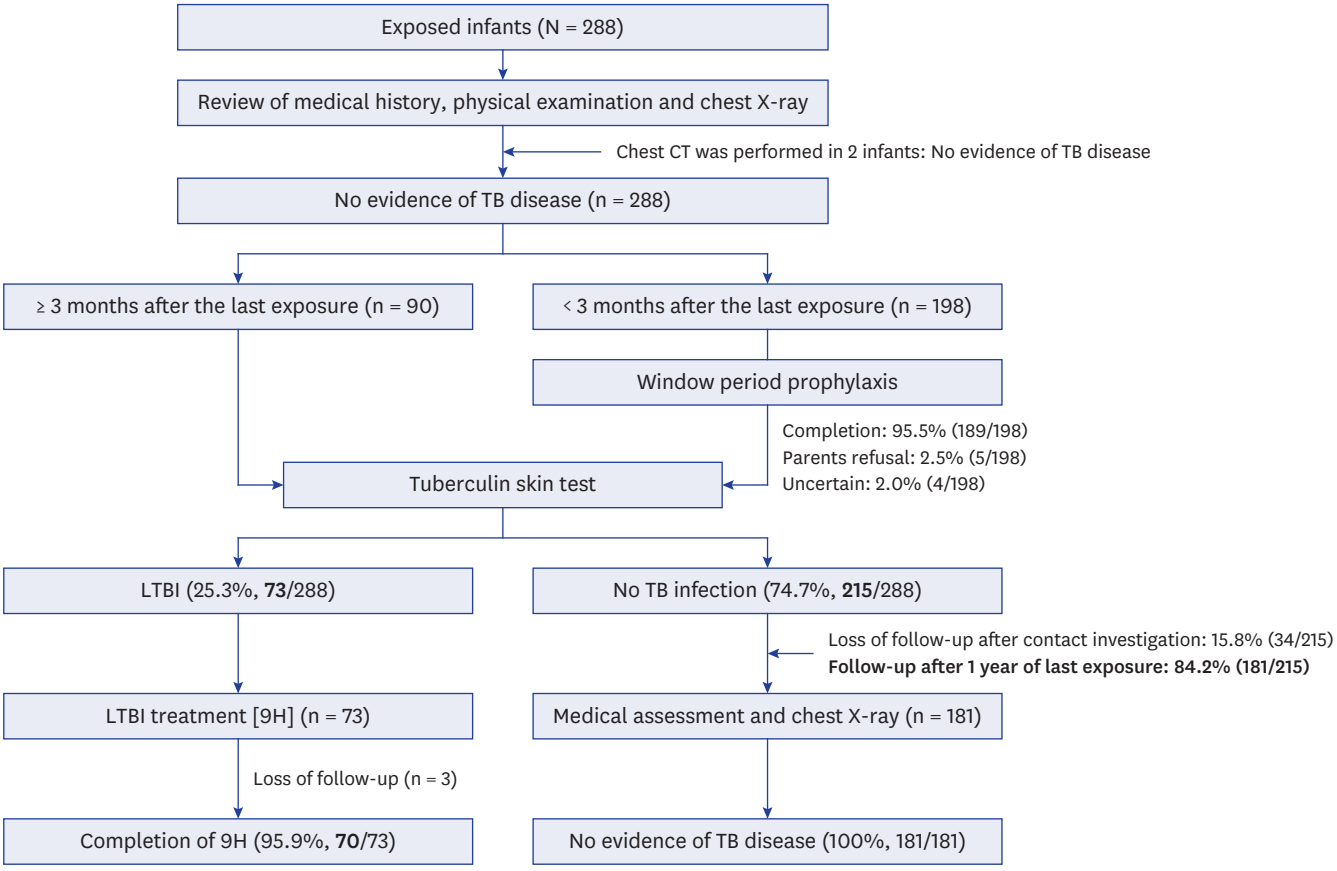

Fig. 1. Overall results of TB contact investigations.
CT = computer tomography, TB = tuberculosis, 9H = 9-month isoniazid therapy, LTBI = latent tuberculosis infection.

Table 2. Comparisons of characteristics of exposed infants by TB infection

Characteristics	TB infection (n = 73)	No TB infection (n = 215)	*P* value
Sex, male	46 (63.0)	95 (44.2)	0.007
Premature	2 (2.9)	12 (6.3)	0.366
Birth weight, g	3,120 (2,100–3,880)	3,140 (1,800–4,040)	0.899
Age at the last exposure, day	15 (7–22)	14 (2–20)	0.473
Length of stay at the postnatal care center, day	13 (3–14)	11 (1–15)	0.202
Duration of actual exposure to the index, day	8 (3–12)	8 (1–12)	0.865
BCG vaccination			0.002
Unvaccinated	0 (0.0)	27 (12.6)	
Vaccinated, intradermal type	22 (30.1)	76 (35.3)	
Vaccinated, percutaneous type	51 (69.9)	112 (52.1)	
Window period prophylaxis before TST	37 (50.7)	156 (72.6)	< 0.001
Age at TST, day	108 (88–136)	106 (91–144)	0.039
Days from the last exposure to TST	93 (73–121)	92 (83–125)	0.091
Days from BCG vaccination to TST	92 (69–121)	91 (56–120)[a]	0.112

Values are presented as median (range) or number (%).
TB = tuberculosis, BCG = Bacillus Calmette-Guérin, TST = tuberculin skin test.
[a]One hundred eighty-eight BCG vaccinated infants.

up at least one year after the last exposure (median, 458 days; IQR, 449–467 days). In the follow-up assessment, no infants had symptoms of TB disease or abnormal findings on CXRs (**Fig. 1**). In addition, there were no newly diagnosed LTBI or active TB cases among 18 healthcare workers at the postpartum care center.

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TST positivity

According to BCG vaccine types, TST positive rate (≥ 10 mm induration) was 22.4% (95% CI, 15.3–31.7) in intradermal BCG vaccinated infants and 31.3% (95% CI, 24.7–38.8) in percutaneous BCG vaccinated infants. Of 27 BCG unvaccinated infants, 26 were not reactive to TST (0 mm induration), and the remaining one had 3 mm induration of TST. The size of TST induration was significantly related to BCG vaccine types. The size of TST induration in infants vaccinated with percutaneous BCG was significantly larger than that of infants vaccinated with intradermal BCG (**Fig. 2**). Compared to infants without INH prophylaxis, the median size of TST induration was significantly smaller in infants with INH prophylaxis (**Fig. 3A and C**). However, there was no difference in the size of TST induration according to INH prophylaxis among infants vaccinated with intradermal BCG (**Fig. 3B**). Similarly, the size of TST induration and the duration of INH prophylaxis showed a significant negative correlation in only infants

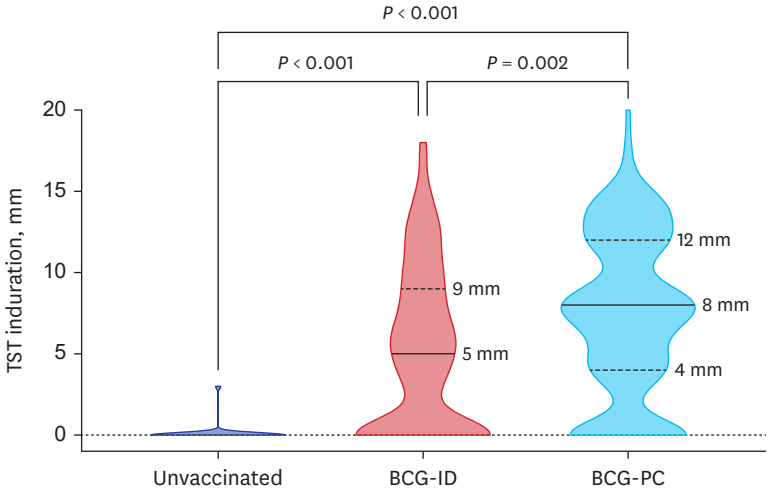

Fig. 2. The size of TST induration by BCG vaccination status. The size of TST induration in infants vaccinated with percutaneous BCG was significantly larger than that of infants vaccinated with intradermal BCG. Horizontal lines and dotted lines indicate median value and quartiles, respectively.
TST = tuberculin skin test, BCG = Bacillus Calmette-Guérin, BCG-ID = intradermal Bacillus Calmette-Guérin vaccination, BCG-PC = percutaneous Bacillus Calmette-Guérin vaccination.

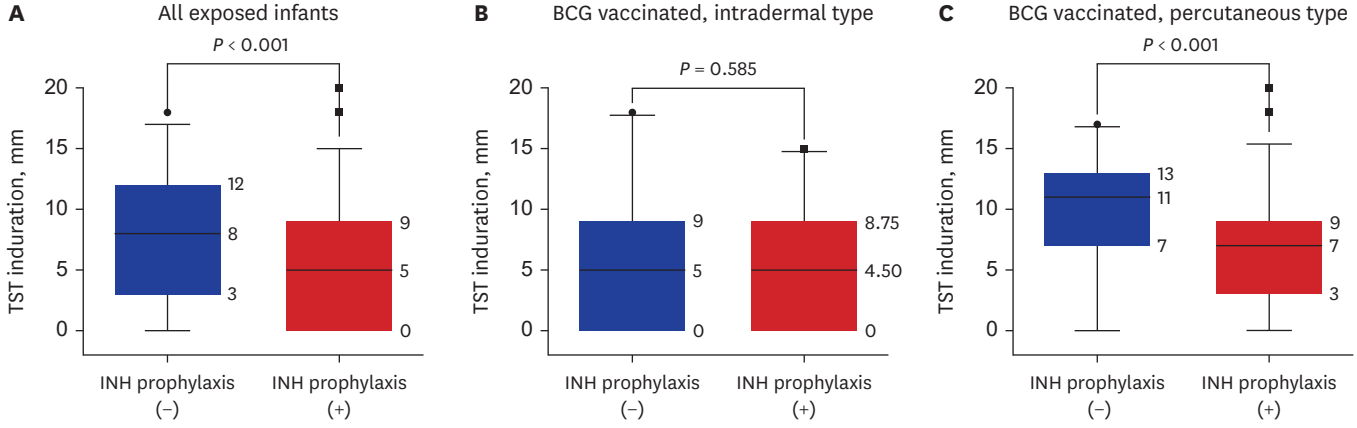

Fig. 3. The size of TST induration by window period prophylaxis and BCG vaccination status. (**A**) All exposed infants. (**B**) BCG vaccinated, intradermal type. (**C**) BCG vaccinated, percutaneous type Compared to infants without INH prophylaxis, the median size of TST induration was significantly smaller in infants with INH prophylaxis (**A**, **C**). However, there was no difference in the size of TST induration according to INH prophylaxis among infants vaccinated with intradermal BCG (**B**). Box indicates median value and quartiles. Whiskers indicate 2.5–97.5 percentiles.
TST = tuberculin skin test, BCG = Bacillus Calmette-Guérin, INH = isoniazid.

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Table 3. Correlation coefficient related to TST induration size

Characteristics	Spearman ρ	95% confidence interval	*P* value
Any status of BCG vaccination			
Age at TST	0.1502	0.0318 to 0.2644	0.011
Days from the last exposure to TST	0.0906	−0.0287 to 0.2073	0.125
Days from BCG vaccination to TST	0.1075	−0.0177 to 0.2294	0.083
Duration of INH prophylaxis	−0.3325	−0.4349 to −0.2215	< 0.001
Unvaccinated			
Age at TST	−0.0633	−0.4425 to 0.3351	0.754
Days from the last exposure to TST	0.0133	−0.3788 to 0.4013	0.948
Duration of INH prophylaxis	−0.1146	−0.4831 to 0.2884	0.569
BCG, intradermal type			
Age at TST	−0.0223	−0.2254 to 0.1826	0.827
Days from the last exposure to TST	0.0826	−0.1236 to 0.2819	0.419
Days from BCG vaccination to TST	−0.0323	−0.2349 to 0.1730	0.752
Duration of INH prophylaxis	−0.1019	−0.3018 to 0.1066	0.323
BCG, percutaneous type			
Age at TST	0.1542	−0.0041 to 0.3049	0.049
Days from the last exposure to TST	0.0646	−0.0945 to 0.2206	0.412
Days from BCG vaccination to TST	0.0751	−0.0841 to 0.2306	0.340
Duration of INH prophylaxis	−0.3191	−0.4552 to −0.1685	< 0.001

TST = tuberculin skin test, BCG = Bacillus Calmette-Guérin, INH = isoniazid.

Table 4. Factors associated with TST positivity

Characteristics	Positive TST[a] (n = 73)	Negative TST (n = 215)	Univariable		Multiple logistic	
			OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Male	46 (63.0)	95 (44.2)	2.15 (1.26–3.65)	0.007	2.98 (1.62–5.64)	< 0.001
From the last exposure to TST ≥ 90 day	55 (75.3)	182 (84.6)	0.55 (0.29–1.06)	0.078	0.49 (0.23–1.04)	0.059
Age at TST > 120 day	16 (21.9)	19 (8.8)	2.90 (1.40–5.76)	0.006	1.80 (0.70–4.61)	0.218
BCG vaccinated, percutaneous type	51 (69.9)	112 (52.1)	2.13 (1.22–3.68)	0.009	3.30 (1.75–6.48)	< 0.001
TST reading between 60 and 72 hr after the injection of PPD	45 (61.6)	77 (35.8)	2.88 (1.69–4.89)	< 0.001	2.87 (1.53–5.49)	0.001
INH prophylaxis > 4 wk	28 (38.4)	130 (60.5)	0.41 (0.24–0.69)	0.002	0.49 (0.25–0.94)	0.031

TST = tuberculin skin test, OR = odds ratio, aOR = adjusted odds ratio, CI = confidence interval, BCG = Bacillus Calmette-Guérin, INH = isoniazid.
[a]≥ 5 mm induration in BCG vaccinated infants and ≥ 10 mm induration in BCG unvaccinated infants.

vaccinated with percutaneous BCG (**Table 3**, **Supplementary Fig. 2**). In multiple logistic regression analysis (**Table 4**), independent factors associated with TST positivity were male (aOR, 2.98), percutaneous BCG vaccination (aOR, 3.30), TST reading between 60 and 72 hours after injecting PPD (aOR, 2.87), and INH prophylaxis for more than four weeks (aOR, 0.49).

If TST positive cutoff value was ≥ 15 mm induration, TST positive rate was 4.1% (95% CI, 1.6–10.0) in intradermal BCG vaccinated infants and 6.1% (95% CI, 3.1–10.9) in percutaneous BCG vaccinated infants (**Supplementary Fig. 3**, **Supplementary Table 1**). TST reading between 60 and 72 hours after injecting PPD was the only independent factor associated with TST positivity (aOR, 5.29; 95% CI, 1.43–25.76; *P* = 0.020) (**Supplementary Table 2**).

DISCUSSION

This study is the first report of TB contact investigation with a single TST to all infant contacts who were temporarily exposed to active pulmonary TB at a congregate setting during the neonatal period. We performed TST only once at three months after the last TB exposure. The prevalence of TB infection was 25.3% (73/288) among infant contacts. There were no serious adverse events related to the window period prophylaxis or LTBI treatment. About 90% of exposed infants were followed up until at least one year after their last exposure

to the index case, and there was no secondary case of TB disease. However, in our study, TST positivity was significantly associated with BCG vaccine type, INH prophylaxis, and TST reading date.

Contact investigations are important to successfully cease TB transmission and to prevent future cases and outbreaks of TB.[8,13] Several guidelines provide direction regarding contact investigations and management.[8,10-13] For neonates or young children who have been exposed to infectious TB but have no evidence of TB disease, protocols regarding testing for infection with *M. tuberculosis* and the window period prophylaxis vary according to guidelines. The US Centers for Disease Control and Prevention[8] and the Canadian[12] guidelines recommend the window period prophylaxis for all children younger than five years of age once TB disease has been ruled out. The window period prophylaxis can be discontinued if contact reaches six months of age and repeated TST or interferon-gamma release assay (IGRA) done 8 to 10 weeks after the last exposure is negative. The UK National Institute for Health and Care Excellence guidelines[9,10] recommend an immediate start of INH prophylaxis for children younger than two years old. TST is performed at 6 weeks after INH prophylaxis in neonates. In children aged 4 weeks to 2 years, TST is performed at baseline and after six weeks. In Korea,[11] the window period prophylaxis is recommended for children younger than two years old. Korean guidelines recommend performing a TST after completing 3-month INH prophylaxis in neonates. In infants aged 4 weeks to 24 months old, serial TST is performed at baseline and 8 weeks after the last exposure. However, previous studies on contact investigation in congregate settings related to neonates showed that protocols were modified according to expert opinions or epidemiologic circumstances, as in our study.[14-20]

Previous studies on TB exposure at NICUs or nurseries in low TB burden countries have reported rare secondary attack rates (0–0.32%).[14-16,19-21] However, in a Thai study of nosocomial TB exposure in two NICUs, the overall incidence of TB disease in exposed infants up to one-year follow-up was 10.2% (24/236). Contact investigation beginning > 111 days after exposure was an independent risk factor for TB.[18]

Ahn et al.[17] noted that 3.7% (4/108) of infants exposed to a nurse with active pulmonary TB developed LTBI at a NICU in a tertiary referral hospital in Korea in 2009. Oh et al.[22] reported a high TB transmission rate among young children exposed to a healthcare worker with undetected pulmonary TB at a nursery of an obstetrics clinic in Korea during 2014–2015. Because a secondary case with TB meningitis was identified among children with low priority for assessment at the initial investigation, contact investigation was expanded to children born at the clinic who were less than 24 months old at the start of the investigation. The rate of LTBI was 42.5% (134/315; mean age, 66.3 days) in the first investigation and 18.7% (249/1,334; mean age, 17.6 months) in the second investigation. A recent national report on TB epidemiological investigations noted six contact investigations in congregate settings related to neonates from 2017 to 2021 (2 in 2017, 3 in 2020, and 3 in 2021).[4] Index patients included two cases of neonates and four cases of healthcare workers. There was no secondary TB case. The rate of LTBI in neonates or infants, excluding those found in this study, ranged from 3.5% to 25.0%.[4]

TST is mainly used to investigate young children exposed to TB.[23] There is a hesitancy to use IGRAs in young children less than 5 years old due to the lack of data and concerns about a low sensitivity of IGRA.[23-28] However, there is no reference standard or gold-standard test for TB infection since TST and IGRA are indirect tests that measure the immunological response to

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previous infection with *M. tuberculosis*.[23] An observational cohort study to assess test agreement between IGRAs (QuantiFERON and T-SPOT.TB) and TST in the US showed that US-born children younger than 5 years had similar proportions of positive TST (10.3%) and IGRAs (13.9% in QuantiFERON and 8.2% in T-SPOT.TB).[28] However, single test positivity was 24.7% (224/868) in TST, 3.5% (31/874) in QuantiFERON and 1.5% (13/866) in T-SPOT.TB among non-US-born children younger than five years. Discordance between TST and IGRAs with TST-positive and IGRA-negative was 87.2% among non-US-born children younger than five years, probably indicating false-positive TST due to BCG vaccination rather than true infection.[28]

TST reactivity among BCG-vaccinated population is affected by multiple factors such as the strain and dose of BCG vaccine,[29,30] the method of vaccination,[31] the number of BCG doses,[32,33] age at vaccination,[34] and the time interval since BCG vaccination.[34-37] Kurtz et al.[37] assessed the effect of neonatal BCG on TST reaction in the first 2 years of life in children without TB exposure. There was a significant decrease in mean TST reaction with an increase in age. A greater induration reaction was observed in infants aged 3–9 months. After the age of 10 months, no children had a TST reaction of > 5 mm. Although all participants were close contacts of infectious TB in our study, factors associated with TST reactivity were compatible with results of previous studies. Percutaneous BCG (Tokyo 172 stain) vaccination was a significant independent factor of TST reactivity in this study. We also found that TST reactivity was significantly affected by INH prophylaxis and the time interval of TST reading (48–60 hours vs. 60–72 hours after the injection). However, there was no significant difference in the size of TST induration among intradermal BCG-vaccinated infants regardless of INH prophylaxis (**Fig. 3B**) or the time at TST reading (median, 4 mm vs. 6.5 mm; $P = 0.166$; data not shown in results). There are few previous studies on the influence of INH on the size of TST.[38-40] A randomized controlled trial study conducted before 1970 showed that in persons vaccinated with BCG, INH given simultaneously resulted in significantly less increase in the size of post-vaccination tuberculin reactions after two months of medication compared with the placebo group.[39] A significant difference was still in TST conducted 4.5 months after INH discontinuation.[39]

There is no consensus about the appropriate TST cutoff value by age or BCG vaccination status. World Health Organization (WHO) guidelines[13] note that there are no correlations between the size of TST induration and the likelihood of current TB disease or future risk of developing TB disease or between the size of TST reactions post-BCG vaccination and protection against TB disease. WHO guidelines[13] recommend that results of TST should be interpreted carefully considering individual clinical risk factors before determining TST positivity. In our contact investigations, although BCG vaccination had some impact on the high positive rate of TST, we prioritized the risk of developing serious TB disease in exposed infants and the social problem of TB exposure in the postpartum care center.

This investigation has several limitations. First, TST reading was performed by more than one person, which could lead to variations between readers. However, experienced pediatric ID physicians read TST results of almost all exposed infants. Second, about 15% of contacts without TB infection were lost to follow-up after the investigation. However, the risk of developing TB disease among infants with negative baseline TST and/or IGRA results is low.[7] Moreover, there was no secondary case of TB disease among exposed infants who were followed up until one year after their last exposure to the index case in this investigation. Third, we could not evaluate false positives of TST related to BCG vaccination. There is no gold-standard test to confirm TB infection. Although IGRAs are

unaffected by BCG vaccination, it is practically difficult to collect blood samples from large numbers of exposed infants and implement IGRA in large contact investigations. Despite these limitations, we quickly identified contacts and planned assessment for TB infection. Screening of high-priority contacts began at four days after the index case notification. Appropriate management was provided to all contacts. In addition, close communication between public health authorities and pediatric ID experts took place, from establishing a contact investigation plan to evaluating the investigation results. Our protocol eliminated unnecessary additional TST and shortened the overall contact investigation period. The national TB management guidelines have been revised to the same protocol as this study since 2021.[41]

In conclusion, a single TST at three months after the last TB exposure with INH prophylaxis could be used as a useful protocol in contact investigations for infants temporarily exposed to infectious TB during the neonatal period in congregate settings in Korea.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
TST positive rate according to BCG vaccine type

Click here to view

Supplementary Table 2
Independent factors associated with positive TST according to the cutoff value of TST induration

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Supplementary Fig. 1
Algorithm of TB contact investigations.

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Supplementary Fig. 2
Distribution of TST induration size and duration of INH medication by the status of BCG vaccination. (**A**) All exposed infants. (**B**) BCG vaccinated, intradermal type. (**C**) BCG vaccinated, percutaneous type. There was a significant negative correlation between the duration of INH medication and TST induration size (**A**). However, a significant correlation was found only in the infants vaccinated with the percutaneous type of BCG vaccine (**C**).

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Supplementary Fig. 3

TST positive rate by cutoff value of TST induration. The black, purple, and blue line indicate any types of BCG vaccine, intradermal BCG, and percutaneous BCG, respectively.

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