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行政院衛生署疾病管制局九十五年度科技研究發展計畫

預防接種過卡介苗一般兒童與開放性肺結核病患之兒童接觸者之結核菌素測試之分布

研 究 報 告

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Abstract

Objective: to obtain the distribution of reaction of tuberculin skin test (TST) in Bacillus Calmette-Guérin (BCG) vaccinated children aged from 3 months to 3 years and in children with close contact of sputum positive confirmed TB cases (2002 to 2005).

Methods: A cross-sectional study of TST with purified protein derivative (PPD RT 23 2TU) was conducted among those children who had received BCG as schedule, and no known immuno-compromised status. The distribution of reaction of TST grouping by different age groups were compared with the standard curve composed by annual risk of infection from pre-vaccination TST evaluation. Goodness of fit was used to check the best cutoff points and were further accessed the sensitivity by a dataset of TST from house-hold contact children with sputum positive confirmed tuberculosis (TB) cases.

Results: 850 eligible data was analyzed. According to distribution of positivity of TST, the effect of BCG on TST decreased after vaccination and the positivity reversed after 7 year-old. The cutoff points fitted the standard curve best were 21mm for 0 to 2 year-old, 15mm for 3 to 7 year-old, and 12 mm for 8 to 14 year-old, said cutoff211512. This cutoff points provided a sensitivity of 44.5% in children with house-hold TB

contact, and a specificity of 89.5% in children without known risk of TB infection. Sensitivity could be up to 90% if 10 mm was the cutoff point for children with house-hold TB contact. Cutoff used in different standards were compared for sensitivity and specificity in these two cohorts.

Conclusions: The study provided a normal distribution of TST size for BCG vaccinated children in a country with moderate risk of TB. Since it was a bi-modal distribution of TST reaction, using age specific cut-off value for children was mandatory. Our cutoff points provided high specificity but more restrictive cutoff point for high risk children was necessary to gain enough sensitivity.

Keywords: tuberculin skin test, infant and children, tuberculosis

中文摘要

目標： 欲得知施打過卡介苗之三個月到三歲兒童，以及曝露於痰抹片陽性結核病患之家庭內接觸者孩童（2002~2005）的其皮膚結核菌素測試反應的分布。

方法： 對按規接種卡介苗且無免疫不全的孩童以結核菌素 PPD RT 23 進行橫斷面研究。利用學童補接種前所建立的標準曲線推算出的年感染率，來對照不同年齡的受試者的反應分布。兩者之間利用 goodness of fit 找出最佳的臨界值，且利用曝露於痰抹片陽性結核病患之家庭內接觸者孩童的皮膚結核菌素測試反應，算出此臨界值的敏感度。

結果： 由八百五十位兒童的皮膚結核菌素測試反應分析顯示，卡介苗對皮膚結核菌素測試反應的影響，在接種後逐年降低且陽性率在七歲之後不降反升。對於零到兩歲的兒童，21 公釐與標準曲線推算出的年感染率差異最小，而對於三到七歲的兒童則是 15 公釐，八到十四歲的兒童則是 12 公釐。曝露於痰抹片陽性結核病患之家庭內接觸者孩童若使用這組臨界值，敏感度為 44.5%，用於沒有已知得結核危險的孩子則特異性為 89.5%。若欲將敏感性提高到 90%，必須使用 10 公釐當作判斷家庭內接觸者孩童陽性的標準。對於不同標準的臨界值，也利用這兩組資料，來比較各個臨界值的敏感度及特異度。

結論：本研究提供在一個中度結核病盛行國家，施打過卡介苗之兒童，皮膚結核菌素測試反應的分布。由於這個反應的分布是雙峰型的，有必要在不同年齡的兒童有不同的臨界值。文中建議的臨界值提供相當高的特異度，但對於高危險群

的孩童，使用更嚴格的臨界值才會提供足夠的敏感性。

中文關鍵詞：皮膚結核菌素測試，幼童及兒童，結核病

Introduction

Tuberculosis (TB) is still a very important burden in many developing countries and some developed countries. With emerging of extensive drug resistance *Mycobactrium tuberculosis*, persistent open TB became an even worse problem for public health systems to face in the coming 10 years.[1] In areas with high prevalence, primary infection occurred in early childhood. Clinicians have to identify the symptomatic children with undiagnosed TB after exposure of TB adult cases. However, it is not easy to identify one in early stage of disease.[2] Children with TB disease are usually suspected after the presentation with unremitting cough for weeks, prolonged fever for unknown origin, weight loss or failure to thrive. Bacteriological or pathological diagnosis from sputum, gastric juice or extra-pulmonary sites are valuable for diagnosis confirmed.[3] Latent TB infection (LTBI) is much more difficult to confirm diagnosis. Nowadays, tuberculin skin test (TST) is still the tool for LTBI diagnosis[4] though it maybe influenced by vaccination of Bacillus Calmette-Guérin (BCG), exposure of Mycobacteria other than *Mycobacterium tuberculosis* and immune status.[5] In areas with low prevalence, aggressive treatment of patient with LTBI is a strategy for TB elimination. Improvements in treatment coverage or effectiveness alone are unlikely to reach the goal of elimination of TB. The goal can be achieved through a combination of improvements of targeted preventive therapy and

vaccination programs. [6-7] In areas with moderate burden of TB, national vaccination program usually includes BCG at birth. WHO estimated that BCG coverage rate reached >80% of neonates and infants in countries where it was part of the national childhood immunization program.[8] How to use TST to identify LTBI, and provide preventive therapy to children who have had risk of exposure is a daily encounter problem. More accurate diagnosis, early preventive therapy for high risk children will prevent the development of disease for the patient, and decrease the prevalence of TB in next decade.

BCG vaccination program in Taiwan

The BCG strain used in Taiwan is Tokyo 172 strain from Statens Serum Institut, Copenhagen, Denmark since 1965. Infant BCG vaccination program was firstly launched since 1951 in Taiwan, the coverage rates of infant BCG vaccination were 86.54% in 1975 and 98.15% in 2001, respectively.[9-10] Any infant who is healthy and weights over 2400 gram is recommended to receive the immunization of BCG after 24 hour-old. During the initial phase of expanding program of immunization in Taiwan, students at first grade of elementary school without BCG scar received vaccination without preceding TST since 1949. Students at sixth grade without scar received BCG if negative TST. After 1975, children enter elementary school without BCG scar were screened with TST first and received BCG if negative TST. The

program conducted in sixth grade was discontinued since 1987.[10] All children entering elementary school in Taiwan are checked by school nurses for BCG scars and 94% and 97% of all children entering elementary school were found to have BCG scar in 1990 and 1997 respectively.[11] It implies the BCG coverage rate of the cohort in this study (0~14 year-old during year 2005~2006) 94% at least or above.

The epidemiologic characteristics of tuberculin skin test in Taiwan

There were at least 6 times of surveillance of LTBI in 0~5 year-old children with PPD RT23 1TU by national TB program. The surveillance of TST in children without BCG scar showed: 8.29% positive in 2184 children of age four in 1962, 6.91% in 405 children of age four in 1972, and 7.74% of age four in 155 children of age four in 1982.[12] With the increasing coverage of BCG vaccination, the sample size of children without BCG scar became too small. Therefore, the surveillance stopped thereafter. The TST positivity of pre-BCG vaccination program for school children without BCG scar decreased from 8% in 70s to 3% in 90s.[9] The prevalence of TB decreased during the 20 year period rapidly. Annual risk of infection (ARTI) obtained annually from this pre-vaccination TST in elementary school since 1972 and it decreased from 1.5% to 0.43% in 2001 before the shortage of PPD RT 23 1TU.[10] One study conducted in 1974, focused on the TST reaction few months to years after BCG vaccination at birth.[13] The children who received BCG within one month of birth

received TST with Monotest, and 91.66% of the children received test at 3 month-old had positive reaction of TST. 46.6% of the children received test at 1~2 year-old had positive TST and decreased to 20% at 2~3 year-old group. Then the rate increased up to 45.16% at 3~4 year-old. The maximum reaction of TST was peaked at 3 month after BCG vaccination and the effect decreased rapidly within 3 years and then the positivity was up again since 3 year-old.

As to the lately published data from Taiwan,[14] high rate of TST positivity was observed in eastern Taiwan. A very high prevalence of positive TST(≧10 mm) was observed in children elder than 2 year-old (over 20%, and over 30% after 10 year-old). The limitation of this study was case number. Fewer than 200 children (younger than 10 year-old) when they were enrolled for TSTs. The purpose for them to be enrolled was mostly for contact tracing, so the contact history of open TB should be higher than general population in eastern Taiwan. However, despite these shortages, it still gives us a hint that LTBI is a very important issue to be addressed in eastern Taiwan no matter how big the proportion is contributed to NTM. Besides, national tuberculosis program should be enforced in this area to reduce active tuberculosis transmission and treatment completeness.

PPD RT23 1TU (0.02mcg/0.1ml) supplied by Statens Serum Institut, Copenhagen, Denmark, was distributed widely in most of Asia countries. The institute

stopped the production of PPD RT23 1TU since 2000, Sep. and only PPD RT23 2TU (0.04mcg/0.1ml) was available after than. Taiwan CDC started to supply PPD RT23 2TU after an evaluation study for difference of 1TU and 2 TU in 2001.[15] 481 (84 of them without scar of BCG) employees of Division of Chronic disease control and their relatives were enrolled. PPD RT23 1TU and PPD RT23 2TU were tested simultaneously on each arm. Average diameter of TST in people without BCG scar were 10.13 ± 6.8 mm and 13.07 ± 6.9mm with PPD RT23 1TU and PPD RT23 2TU accordingly. Average diameter of TST in people with BCG scar were 9.03 ± 5.8 mm and 12.33 ± 5.7mm accordingly. The increased response of RT 23 1TU to 2TU was 3mm averagely. Five people younger than 29 year-old without scar evaluated in the study showed no difference of RT23 1TU and 2TU when we used 10mm cutoff point for positivity, but the sample size was too small. Therefore, a TST study for RT23 2TU for children is mandatory.

Review of cutoff points to define positive TST in different countries

The USA

Current guidelines from the US CDC, American Thoracic Society (ATS), and American Academy of Pediatrics (AAP) accept 15 mm or greater of induration as a positive TST result for any person.[16] Targeted TST is encouraged and routine TST administration, including programs including populations at low risk is to be

discouraged either a low yield of positive results and a large of false positive results. Definitions of positive TST results in infants, children, and adolescents was classified by the risk of LTBI and progression to tuberculosis disease. Interpretation of 5mm or more or 10 mm or more induration is summarized in Table 1.[17] These definitions apply regardless of previous BCG.

Induration ≥5 mm
Children or adolescents in close contact with a known or suspected infectious case of TB
Children or adolescents with suspected TB disease:
Finding on chest radiograph consistent with active or previously active TB
Clinical evidence of TB disease
Children or adolescents who are immunosuppressed (eg, receiving immunosuppressive therapy or with immunosuppressive conditions [eg, HIV infection])
Induration ≥10 mm
Children or adolescents at increased risk of disseminated disease:
Those <4 y old
Those with concomitant medical conditions (eg, Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition)
Children or adolescents with increased risk of exposure to cases of TB disease:
Those born in a country with a high prevalence of TB cases
Those who travel to a country with a high prevalence of TB cases
Those with parents born in a country with a high prevalence of TB cases
Those frequently exposed to adults with risk factors for TB disease (eg, adults who are HIV-infected or homeless, users of illicit drugs, those who are incarcerated, or migrant farm workers)
Induration ≥15 mm
Children ≥4 y old with no known risk factors

Modified from American Academy of Pediatrics. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:642–660.

Table 1. Definitions of positive TST results in infants, children, and adolescents

WHO

WHO recommends a TST should be regarded as positive as follows: in high-risk children (includes HIV-infected children and severely malnourished children, i.e. those with clinical evidence of marasmus or kwashiorkor): ≧5 mm diameter of induration; in all other children : ≧10 mm diameter of induration.[3] These

definitions also apply regardless of previous BCG.

Taiwan

With TST RT 23 2TU, the result should be regarded as positive as following recommended by Taiwan CDC: ≧ 10mm for children who had a BCG scar and ≧ 18mm for children with scar.[10]

The Taiwan Academy of Pediatrics (TAP) recommends a risk-based age dependent strategy for TST positivity definition (unpublished data, Treatment guideline for tuberculosis, 2nd edition. Taipei, Taiwan: Center for Disease Control, Taiwan; 2006). A child with immuno-compromised status: ≧5 mm diameter of induration; a child aged elder than 6 year-old and the time lag since BCG vaccination is over 6 year, a child never receives BCG, a child has increased risk of LTBI (ex: closed contact of contagious TB, known family history of TB, failure to thrive, abnormal radiographic image compatible with TB): ≧ 10mm diameter of induration; a child younger than 6 year-old and has received BCG, or the time lag since BCG vaccination is less than 6 year, and no known increased risk of LTBI: ≧ 15mm diameter of induration.

Aim of the research and hypothesis

The agent for TST, PPD RT23 1TU was shifted to 2TU in late 2000 in most Asian countries, where Denmark was the sole supply for PPD. While TST was used mostly in children for diagnosis of LTBI or TB disease, no adequate study has been done for evaluation the TST positivity of PPD RT23 2TU in children. The goals of our study are as follows:

1) The age when the effect of BCG on TST wanes

2) The cut-off value for different age groups for the upper limit of normal value of TST size

3) Evaluation for the sensitivity and specificity of newly developed cut-off value

Subjects and Methods

Study Site and Population

A cross sectional cohort study was conducted in Taipei city, the capital of Taiwan with an estimated population over 2.6 million. The density of population is near 10 thousand/ km^2. A healthy child aged between 3 month to 15 year, who had received BCG as schedule were enrolled during 2005~2006 . Exclusion criteria including: 1) the child had received live vaccines (for example, Measles, Mumps, Rubella, Varicella, Polio) within 6 weeks, 2) the child documented to have the diseases prevented by the above live vaccines within 6 weeks, 3) the child had hospitalized due to viral/bacterial infection with 6 weeks, 4) the child was on therapy of immuno-suppressed regimen (inhalation form of steroid was not included), 5) the child with any known congenital/acquired immunocompromised status, 6) the child aged between 3 month-old to 3 year-old but had received BCG beyond 31 days after birth, 7) the child documented with record of BCG booster (both from the parents or from the database of Taipei city government).

Data Collection

Basic demographic data was obtained from questionnaires done by parents (described previously in DOH 94 -DC-1109).

TST record of children without BCG scar

The BCG strain used in Taiwan is Tokyo 172 from Statens Serum Institut, Copenhagen, Denmark, 1965. The Taiwan vaccination scheme gives a does of BCG at birth. TST is performed in school children without BCG scar at their 2nd grade in Taipei city annually. Those with negative TST (cutoff point 10mm) are suggested to receive BCG vaccination. The records of TST reaction from this pre-vaccination TST surveillance program during 2002~2004 were obtained from 3rd division, Taiwan CDC. Their data was used to construct the standard curve of positivity described later in statistic section.

TST record of possible LTBI

TST and age distribution of children who registered through contact tracing policy for sputum positive confirmed TB cases from 2002 to 2005 were provided by Taiwan TB notification computer system via 5th division, Taiwan CDC. The risk of TST conversion for children with household contact of open TB was around 30% by paper review. Their data was used to evaluate the sensitivity of newly-identified cutoff points of TST.

Procedure of TST

Children who fitted the criteria were planned to be given 0.1 ml of PPD (PPD RT23, 2 units, Statens Serum Institut, Copenhagen, Denmark) intradermally, in accordance with the guidelines recommended by WHO.[3] The tuberculin for the tests was obtained

from Denmark and is used throughout the country. TST indurations was planned to be read 48 and 72 h after administration at 90 degrees from the longest axis of the arm (transversely) and recorded to the nearest millimeter. Indurations size was recorded by one study personal. Since digit preference is a normal behavior (unconsciously prefer even number or numbers ending in digit 0 and 5), we used inversed calipers instead of ruler to reduce this bias. All size of indurations were recorded for further analysis other than arbitrary classification. The maximum size of these 2 results will be analyzed.

Exclusion and Follow-up steps

Clinically, children who had induration size ≧10 mm were invited to be followed up in our clinics according to previous consensus.[18] If LTBI is highly suspected, prophylaxis will be initiated. Closed contact families and care-givers were planned to be required detailed information of TB contact history and asked to take CXR for excluding asymptomatic pulmonary TB.

Sample Size Estimation

Sample size was estimated by epi-info version 6.0. For the purpose of comparing positivity of different age groups, the range of expected positivity was set according to the literature review. The population size was estimated from the possible sampling sources of children for different ages. According to 95% CI

sample size, 45~60 children were planned to be enrolled in the group younger than 1 year-old. We planned to enroll 20~30 children for each year group under 3 year-old from healthy volunteers in well-baby clinics in National Taiwan University Hospital or day care centers**.** For age group of 4 to 6 year-old, cases was planned to be enrolled from volunteered students from kindergarten and 20~ 30 children will be enrolled in each age group. For age group of 7~14 year-old, 20~40 children were planned to be enrolled from volunteered students from elementary school and junior high school in each age group. A total of 325~ 600 children was planned to be enrolled for the study aim.

Table 2. Sample size estimation in population survey (random not cluster):

Age group	0~1 (y/o)	1~3(y/o)	4~6 (y/o)	7~12 (y/o)	13~15 (y/o)
Population size (person)	100	100	100	5000	3000
Expected positivity (%)	30	15	5	10	20
Worst positivity (%)	20	10	2	5	10
99%CI sample size	58	77	78	228	103
95%CI sample size	**45**	**66**	**67**	**135**	**60**
80%CI sample size	26	46	46	58	26

Procedure of sampling

Young children in well baby clinics, day care centers and kindergarten were enrolled without sampling as long as the parents agreed to let their children to receive tests. Students in either elementary school and junior high school were sampled

through their seat numbers. 4~8 students out of 30 classmates were randomly sampled for questionnaires and inform consent.

Statistics

Determine how long does the effect of BCG last on TST

We'd firstly draw the figure of distribution of TST size and check the shifting of positivity fraction of different ages to figure out the duration of possible effect from BCG.

Annual risk of tuberculosis infection (ARTI)

We simulated the curve of ARTI from the data of TST positivity obtained from pre-vaccination program in school children during 2002~2004 in Taipei city (Algebraic deviation of the average annual risk of infection from prevalence of these 4 years). At birth, the prevalence of infection is zero or, in other words, the risk of having escaped infection equals 1. Assuming a risk of infection of 10% during the first year of life, the risk of having escaped infection at age 1 year equals 1 * (1 - 0.1) or 0.9. If the risk of infection remains constant at 10%, then the risk of having escaped infection by the end of the second year equals 1 * (1 - 0.1) * (1 - 0.1) = 0.81 or 81%, etc. Thus, the equation for ARTI = 1-(1- positivity rate)^ (1/age). Equal risk of infection of each year after birth is assumed in this approximation. Then the equation is reversed into positive rate= 1-(1- average ARTI)^ age and the percentage

of positive TST in every age is available for composing a standard curve for later analysis. Since the ARI declined slowly, at a rate of 1—3% per year, we assumed the ARI estimate to be constant during each 10-year interval.

The risk of infection that is calculable from the prevalence of infection is thus an average annual risk. It is a proxy for the incidence of TB infection. It differs from the true incidence of infection that led up to the observed prevalence of infection in that it is constant while the true incidence is likely to have varied over time. The calculated risk of infection assumes a constant incidence of infection over the entire lifespan of the individuals in the survey. This is, however, the least likely course over time. The true incidence of infection that led up to the measured prevalence may have declined in the situation of our country.

Using the above ARI estimates, the expected tuberculin conversion rates for individuals in the study population were extrapolated using the following equation, with the age of 10 years used as an example: Expected rate(age 0—10) = 1−(1−ARI(age 0—1)) × (1−ARI(age 1—2)) × (1−ARI(age 2—3)). . . × (1−ARI(age9—10)). The same equation was used for other age groups studied. The formula was developed by Styblo et al.[19-20]

Goodness of fit

TST positivity curve from study population with different cutoff values (5mm, 10mm,

15mm, 18mm etc) are planned to be compared with standard curve.[21] Before BCG effect wanes, we could check the area under curve to fit the ARTI; after the BCG effect wanes, the test for goodness of fit could be used to check the fitness.

Ethical Approval

The study was approved by the Ethical Review Boards of National Taiwan University Hospital. The committee was organized and operated according to good clinical practice GCP and the applicable laws and regulations. The protocol was approved by Department of Health, Taiwan before conduction.

Results

For children younger than 4 year-old, 338 questionnaires were distributed and 183 participated in our study (54.1%). No difference was noted between groups of enrolled and non enrolled, such as parents with a job related to medical care, a babysitter who had foreign nationality, a family who had a foreign nationality, sibling number, and suspicious TB sources. However, the enrolled children lived with more family members (4.3 person/family vs. 3.5 person/family, p=0.0005), and more grand parents (1.00 grand parents/case, 0.58 grand parents/case, p=0.0013).

As a whole, 1757 questionnaires were distributed to 2 junior high school, 3 elementary school, 3 kindergartens, 13 day care centers in Taipei city and volunteers from well-baby clinics in our hospital for children aged from 3 months to 14 years. 48.4% (850) of them signed consent and received the TST screen. The mean age of the enrolled children was 8.9 year-old with 95% confidence interval (CI) 8.6 ~9.2. The ratio of male versus female was 0.99.

Figure 1 revealed the age distribution of the enrolled cases. Figure 2 revealed the distribution of TST size. Half of the reactions were smaller than 5mm, 41.76%, disregard of the age. With RT23 2TU, 27.3% of the children who received BCG during infant period, had TST reaction larger than 10mm. By observing the distribution of positivity of TST at different age groups, the effect of BCG on TST

reaction could be understood much more easily. In figure 3, the larger the cutoff point chosen, the smaller positivity resulted, no matter which age group. Children younger than 1 year (at the age group of "0" year-old) had a highest positivity no matter which cutoff point was chosen to used. The positivity decreased rapidly until 6~7 year-old and then increased again. The BCG effect on TST peaked within months of injection before 1 year-old, and waned rapidly afterwards, the positivity folded back to increase again after 7 year-old.

2504 records of TST size of pre-vaccination TST surveillance program during 2002~2004 were obtained from Taiwan CDC. 9.3% of these children were positive for TST (cutoff point 10mm) and the annual risk of infection was 1.293% in each year under the assumption of equal risk of infection annually. The exponential distribution of annual infection rate was 0.65% to 17.2% for the first year of life till 14^{th} year of life (one for each year of life). This curve was assumed to be the standardized curve for the following evaluation of goodness of fit from population data of 850 children enrolled in the study.

With the above observation according to the figure 4, the sum of square of different age period was calculated by Excel. Since the nadir of positivity was observed at the year of 6~7, the square between 7 points from 8~14 year-old (one point for each year of age) and the respective 7 points from standard curve were

summed. More than ten sets of sum could be calculated with different cutoff points assumed for our population (Here we used 10mm~ 28mm, one mm for each so there were 19 set of sum of square). The one with p value >0.05 implied that there was no difference between the standard curve and the cutoff point chosen for the population at certain age period. The standard curve fitted well with the cutoff point 12mm between 8 year-old to 14 year-old.

Before the curve of positivity for population data folded back after 7 year-old, the area under standard curve was the goal for us to set the cutoff point for certain age under 7 year-old. The area, the same, was determined by the curve of positivity for the population for a certain cutoff point. Therefore, the concept was just the reversion as the goodness of fit between the standard curve and the curve of positivity for the population for a certain cutoff point. The standard curve fitted well with the cutoff point 22mm between 0 year-old to 1 year-old, 21mm between 0 year-old to 4 year-old, 15mm~16mm between 2 year-old to 5 year-old, and 12~13mm between 4 year-old to 6 year-old.

The final cutoff points for different age groups were chosen by the best sum of square which were 21mm for 0 to 2 year-old, 15mm for 3 to 7 year-old, and 12 mm for 8 to 14 year-old, said cutoff211512. Figure 5 revealed the relationship between the 3 different cutoff points and the representative positivity of the population we studied

smoothened by moving average method. After excluding the children with a suspicious contact of tuberculosis or a non-contact family history of tuberculosis in our cohort, 783 data was further evaluated for specificity of different cutoff points.

TST distribution and age distribution of children who registered through contact tracing policy for sputum positive confirmed TB cases from 2002 to 2005 were provided by Taiwan TB notification computer system via 5th division, Taiwan CDC. 3523 children younger than 15 year-old were analyzed. Fig 6 and 7 showed the distribution of age and the TST size accordingly. This data was evaluated for sensitivity of different cutoff points. If Cutoff211512 was used for the children who had contact history of cases with sputum positive pulmonary, 13.34% was diagnosed as positive. Approximately, 30% of close contact of cases with sputum positive pulmonary TB could have latent TB infection, depended on the age of exposure, duration of exposure and patient condition.[22] If 30% of children was considered to be infected already, using the cutoff points cutoff211512 would have a sensitivity of 44.5%, and specificity of 89.5% (based on the 783 data). If the cutoff point suggested by AAP[17] (10mm for child < 4-year-old, and 15mm for child >= 4-year-old, but if the child is a case of contact, 5mm should be used) was used, 45.1% was diagnosed as positive. If we still considered 30% of children had already been infected, then we would have a sensitivity over 100%, and specificity of 88.4% (based on 783 cohort).

If the cutoff point suggested by TAP (TAP recently proposed 15mm for child < 6-year-old, and 10mm for child >= 6-year-old, but if contact, 10mm was used) was used, 27.5% was diagnosed as positive in age group 0~2 year-old, and 25.2% in age group 3~7 year-old, 30.9% in age group 8~14 year-old. If we still considered 30% of children had already been infected, then we would have a sensitivity of 90% as TAP suggestion, and specificity of 81.5% (based on 783 cohort). If the cutoff point suggested by Taiwan CDC (18mm for child with scar, and 10mm for child without scar) was used, 7.6% was diagnosed. If we still considered 30% of children had already been infected, then we would have a sensitivity of 25% as TCDC suggestion, and specificity of 98.1% (based on 783 cohort).

Discussion

The value of the TST as a screening test for LTBI is important for prevalence estimation and disease control. The interpretation of the TST in a BCG-vaccinated individual often poses a dilemma for the TB control health worker. Studies have shown postvaccination BCG-induced tuberculin reactivity to range from no induration to reactions of 19 mm. [23-25] Though there are several studies being done to evaluate the effect of BCG on TST, the study population are mainly adult or adolescent,[26] or the main purpose is to compare the blood interferon γ assay and TST.[50-51] It should also be noted that the cutoff TST readings recommended by the ATS/CDC and AAP are based on 5 TU of PPD-S, which is the bioequivalent of 2 TU of PPD RT 23.[29] Therefore, the results vary a lot and are difficult to apply to children.

Some studies support tuberculin reactivity to BCG given in infancy waning rapidly within one year. In Peru, 6 months after BCG vaccine (Pasteur-Me´rieux-Connaught, Lyon, France) at birth, 69 participants received a TST using 0.1 mL of PPD containing 5TU (Tubersol, Connaught Lab. Ltd, Willowdale, Ontario, Canada).[30] Mean TST reaction size 6 months after vaccination was 2.9 ± 0.3 mm. Only 3 children had a TST >10 mm, and the 3 had a TB contact at home. The result was similar with the study in Navajo Indian 40 years ago in the United States, none of the 250 children aged 9 month-old to 4 year had TST≧ 10 mm after BCG at

birth.[43]

In Hong Kong, a mass survey including 21113 schoolchildren aged 6–9 years, were skin tested with 1 TU of tuberculin (PPD RT-23) during a routine BCG revaccination program.[32] The coverage rate of neonatal vaccination was estimated to be universal. The positivity (≧ 10 mm) were 10.22% at age of six, 11.87% for age of seven, and 13.38% for age of eight. Though the ARTI as estimated by the same method like we used was unexpectedly high among BCG vaccinated children and did not agree with that anticipated from the annual incidence of active disease, A significant linear trend was found between the tuberculin positive rates and age at all cut-off points. The author debated that it was in sharp contrast with the reduction in the tuberculin response reported in younger children who had been vaccinated at birth. He proposed that the reduction in the BCG effect has either stopped or been masked by a higher rate of tuberculin conversion due to tuberculous infection/exposure to nontuberculous mycobacteria.

In a study in Singapore, where universal BCG vaccination at birth and revaccination policy in schoolchildren who were nonreactors (TST ≦ 10mm, using 1TU PPD RT23) at 12 and 16 year-old, had a 17.2% positivity at age twelve.[33] They used the TST data of 59 TB cases in the same study birth cohort occurred between age 13~16 year, to calculate the best cutoff point by receiver-operating characteristic

(ROC) curve. A TST reading of 10 mm was the most sensitive (75%) and specific (more than 80%) cutoff for predicting the development of TB disease in this age group.

According to studies in Asian countries, schoolchildren seemed to have a positivity approaching 10% when they entered elementary school, however, the BCG effect on TST was not described clearly. In our study, the distribution of TST along with different age groups helped to get a more clear picture from early childhood to adolescents. Over half of the children receive BCG at birth had a positive TST in the first year of life with cutoff point of 10 mm. The rate decreased gradually to 8.7% at 6 year-old, much more slowly than the condition described in Peru and Navajo Indian. The cause of slow waning for the BCG effect on TST was unknown, but the distribution gave us a hint that we had to choose higher TST cutoff points at this age period than that recommended by the ATS/CDC and AAP to guide our decision for treatment of LTBI in different risk groups.

After age of seven, the positive rate climbed up to 13.3% slowly and reached 30% positive at age of fourteen with cutoff point of 10mm. Since 9.3% of the children without BCG scar at 2nd grade of elementary school were positive for TST (cutoff point 10mm), which reflected the tuberculin conversion without BCG effect in our community, we used goodness of fit to find out the best fitted cutoff point for the

ongoing ages. 12 mm was the best fitted cutoff with the minimal sum of square compared to the standard curve composed by children without BCG scar.

We did not have a sense data for cohort analysis between TST record in school and subsequent hospitalization for TB disease to get an ROC curve for the best cutoff to distinguish the disease from low risk children.[33] So we chose to get the registration record of children through contact tracing policy for sputum positive confirmed TB cases. It was not a direct way but it simply provided a method for evaluating the value of cutoff in high risk children. The result was not surprising. If we want to use the same cutoff for screening in general population, like schoolchildren or in high risk group, like children closed contact with open TB, the sensitivity was lower than 50%. Therefore, we recommended a risk based and age specific strategy. For children with closed contact of open TB, 10 mm should be used for any age of children to ensure the protection from LTBI treatment. For children without known contact of open TB and immunocompromised status, age specific cutoffs should be used: 21 mm for 0-2 year old, 15mm for 3 -7 year old, and 12 mm for 8-14 year-old. It might be a concern in countries with moderate prevalence of TB. Children born in these countries are viewed to have an increasing risk of exposure of TB since the incidence of adult is around 50~100/100000 person year. Very so often, TST would have to be used as a screening tool in school for LTBI or in hospital for diagnosis of TB without known

contact history.[2-3] The age specific cutoffs is practical if the strategy for stop TB including LTBI treatment, or too many children with false positive results will be treated, which is not cost-effectiveness.

結論與建議

In conclusion, the study provided a normal distribution of TST size for BCG vaccinated children in a country with moderate risk of TB. Since it was a bi-modal distribution of TST reaction, using age specific cut-off value for children was mandatory. Our cutoff points provided high specificity but more restrictive cutoff point for high risk children was necessary to gain enough sensitivity. Risk based, age specific cutoffs can be helpful to select children who need closely follow up or LTBI treatment as a strategy for TB control.

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Figure 1. The age distribution of 850 children.

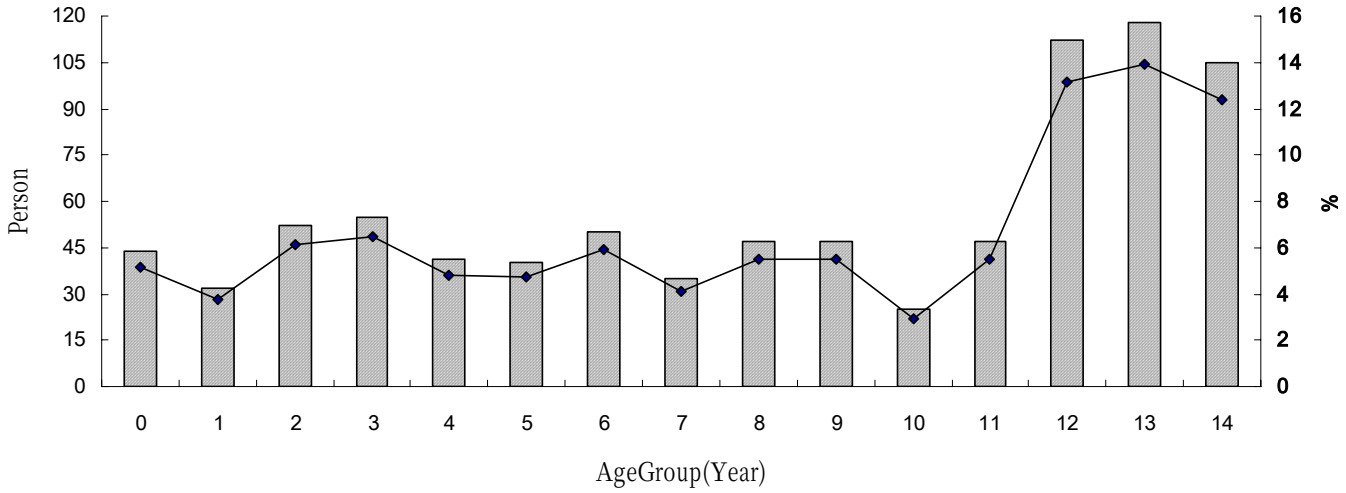

Figure 2. The distribution of TST size of 850 children.

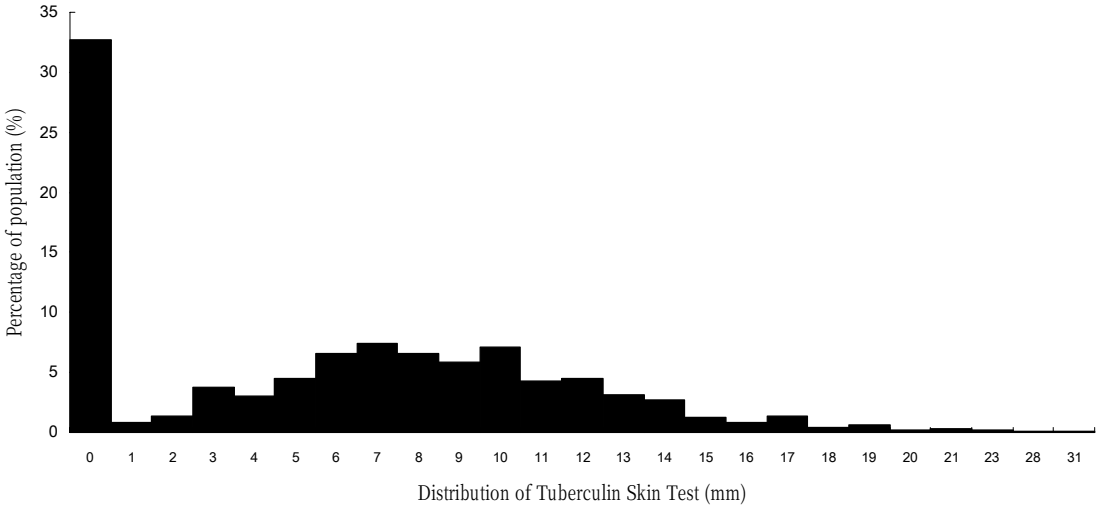

Figure 3. The positivity was stronger right after BCG vaccination in age group of 0 year-old, 56.8% of them were positive with 10 mm as the cutoff point. The positivity decreased gradually with age increased and only 8.7% was positive at 6 year-old group. After this age, the positivity again increased back no matter with any kind of cutoff points.

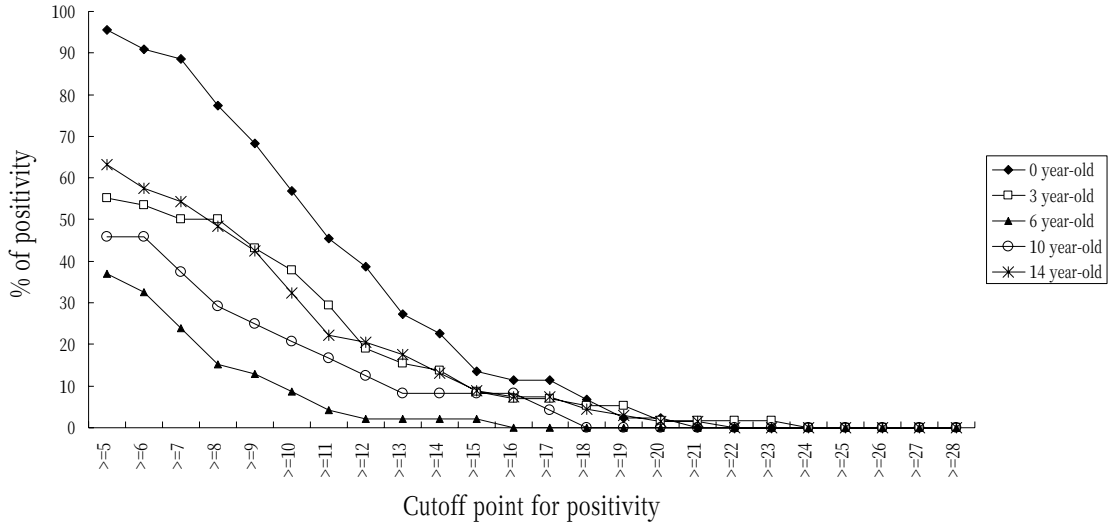

Figure 4**.** The positivity curve from population data with 3 different cutoff points to fit the stander curve of infection estimated from children without BCG scar.

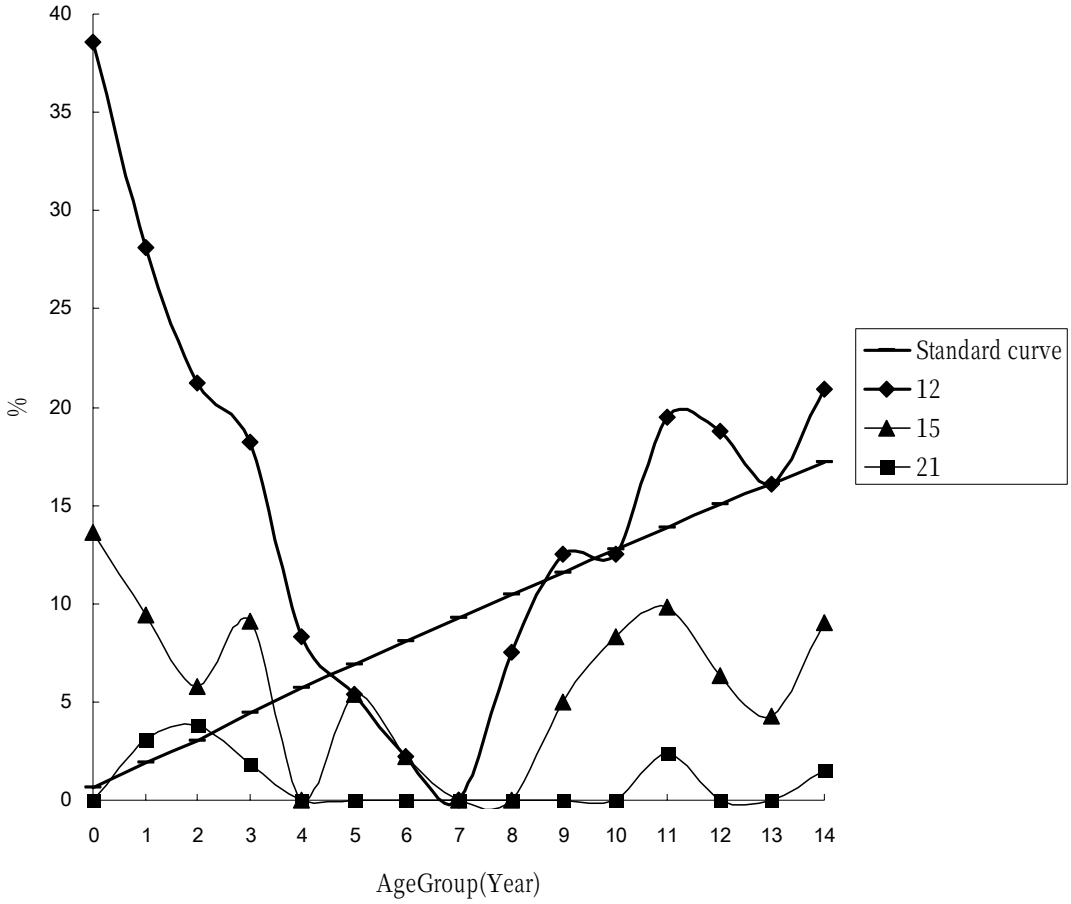

Figure 5. Moving average for the positivity curve from population data with 3 different cutoff points to fit the stander curve of infection estimated from children without BCG scar.

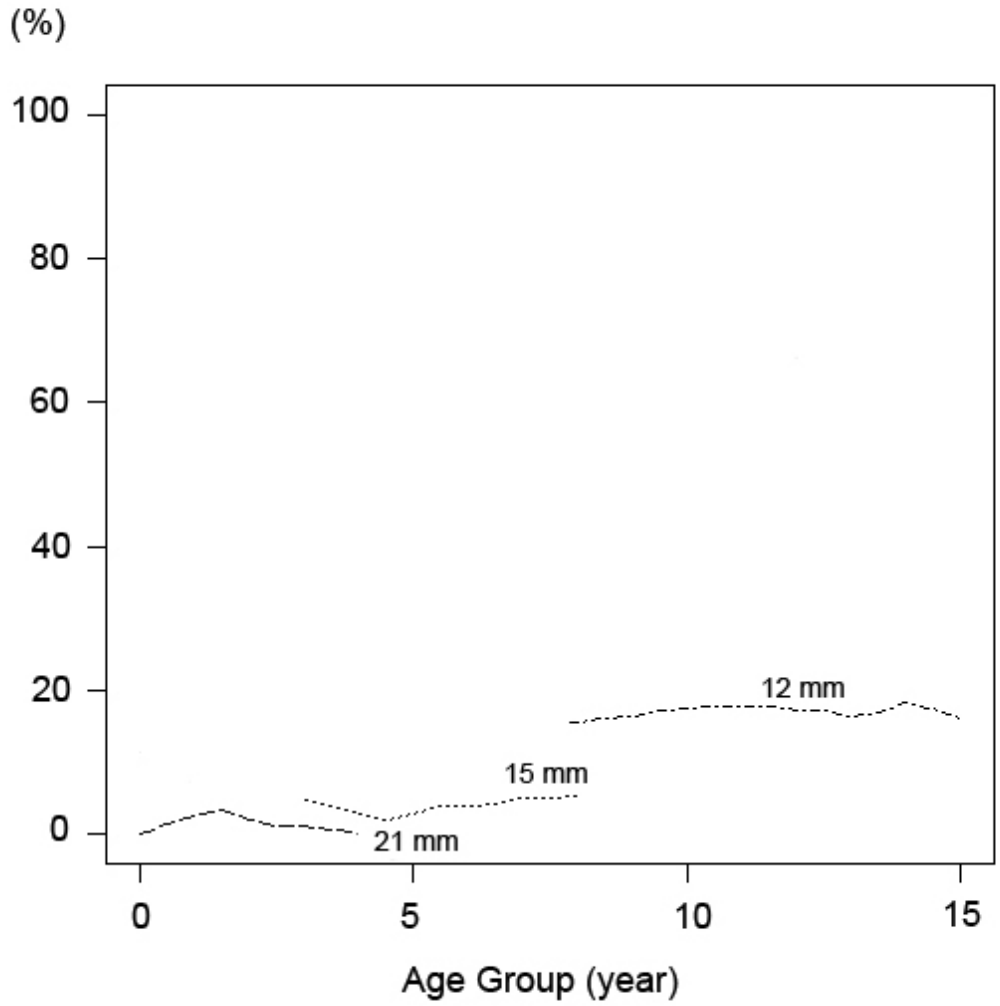

Figure 6. The age distribution of 3523 children with household contact of sputum positive cases.

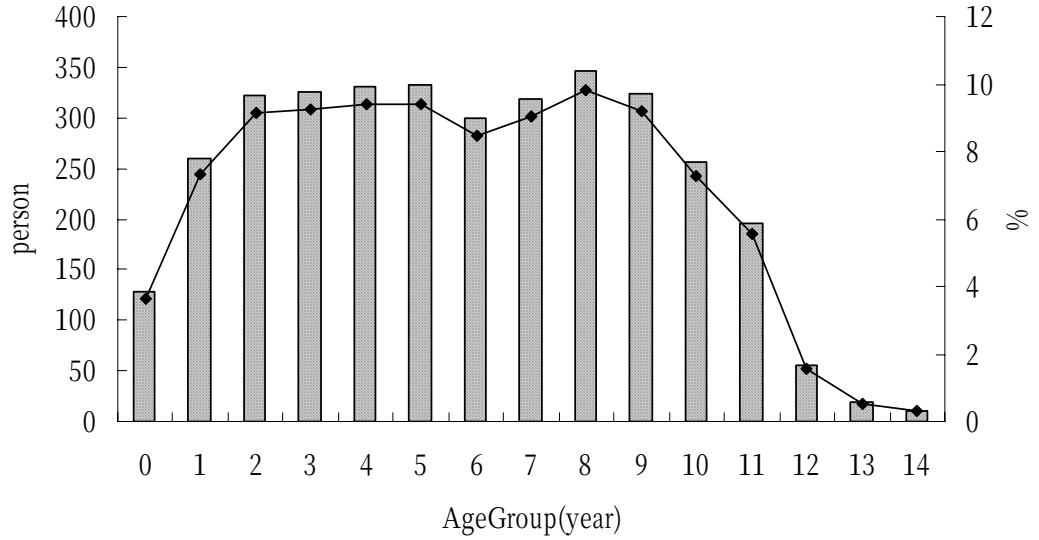

Figure 7. The distribution of TST size of 3523 children with household contact of sputum positive cases.