國立臺灣大學公共衛生學院流行病學與預防醫學研究所

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潛伏性結核感染的研究: HIV 陰性病人

Study on Latent Tuberculosis (TB) Infection in non-HIV patients

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口試委員會審定書

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本論文係 **詹珮君** 君（學號 D98842003 ）在國立臺灣大學流行病學與預防醫學研究所完成之博士學位論文，於民國 102 年 7 月 17 日承下列考試委員審查通過及口試及格，特此證明。

口試委員：

方啓泰（簽名）

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[illegible]

目錄

致謝

在學校學習的時光中，感謝方啟泰老師無私地教誨，體諒珮君的工作型態和身兼母親及職業婦女的身分，讓珮君可以如期完成學業，順利畢業；本論文的第二章獲選優秀論文獎，要歸功於老師的提醒和推薦。從住院醫師時代，黃立民老師鼓勵我進入本所碩士班在職進修，台大醫院對進修開放包容的態度，讓我進入流行病學與預防醫學研究所這個大家庭裡面，學習公共衛生的思維以及流行病學評估的方法論。期間經歷了進入疾病管制局工作，結婚、生了兩個古靈精怪的女兒，從 H1N1 走到 H7N9，從結核病都治計畫走到推動潛伏結核感染治療。四年來的博士研究生涯，最最要感謝我的先生和我的父母公婆，百分百的支持和包容; 工作上，同事和長官，持續的鼓勵和支援。也謝謝所內的老師們，對於疾病管制局業務計畫大力支持及給予指教! 我畢業了，也是該回饋的時候了! 未來希望有更多機會，將疾病控制的實務經驗，持續帶回校園，激勵在校學弟妹對於公共衛生實務的認知，提高投入實務工作的動力及量能；也期待珮君可以像台大公衛學院過去的傑出校友，投身國內或國外公共衛生的行列，將學校所學，結合實務，持續有亮眼的發展。願以此致謝文獻給親愛的師長及家人分享。

中文摘要

1. 卡介苗接種者潛伏結核感染率較低: 一監獄收容人之橫斷面研究

目的: 探討卡介苗接種對結核感染的保護效用是否持續到成年。

方法: 於一所位於北臺灣收容超過 3000 人的監獄，在愛滋病毒檢測陰性的收容人進行潛伏結核感染的橫斷面研究。本研究使用剋肺勞結核菌感染檢驗 (QuantiFERON gold in tube，QFT-IT) 檢查，潛伏結核感染的定義為 QFT-IT ≥0.35 IU/ml。近期潛伏結核感染 (Recent LTBI) 定義則為 QFT-IT ≥0.7 IU/ml。分析時以年齡分層來分析卡介苗疤痕數與潛伏結核感染與近期潛伏結核感染風險之間是否有顯著負相關。本研究經過倫理委員會事前審查通過，所有參與者瞭解研究內容且簽署同意書。

結果: 在 2385 位參加者中，25% QFT-IT ≥0.35 IU/ml。隨著年齡越大，潛伏結核感染 (14%, 32% and 50%) 的盛行率就越高 (18-34 歲、35-54 歲和≥55 歲) (Cochran–Mantel–Haenszel method, $p<0.001$)。而在上述三個年齡層中，卡介苗疤痕數與潛伏結核感染與近期潛伏結核感染風險均呈現顯著負相關 (Cochran–Mantel–Haenszel method, $p<0.001$)。

結論: 近期潛伏結核感染風險與卡介苗疤痕數間的顯著負相關意味：在卡介苗接種後的數十年，接種仍然對結核感染有保護作用。這發現可供各國新生兒卡介苗政策的參考。並且值得進一步進行前瞻性世代研究，以證實卡介苗對成人的保護力。

2. 監獄收容人潛伏結核感染治療：一隨機對照試驗

場所： 台灣北部一監獄

研究目的： 比較每日服用 rifampin 四個月 (4R) 或每日服用 isoniazid 六個月 (6H) 兩種治療潛伏結核感染的處方在監獄收容人的安全性與完成率。

設計： 這是一個在 HIV 陰性監獄收容人之非盲隨機對照試驗。收案對象為沒有活動性結核病，且皮膚結核菌素測試及剋肺勞結核菌感染檢驗 (QuantiFERON gold in tube，QFT-IT) 結果均陽性之受檢收容人。排除條件則為肝功能基礎值 (麩丙酮酸轉胺, glutamic pyruvic transaminase,GPT) ≥ 120 U/L，黃膽指數≥ 2.4 U/L，或血小板 <150 k/mm^3。研究的主要終點為因為任何不良事件造成潛伏結核感染治療之中斷。

結果： 參加者 (373 位，14%為 B 型肝炎表面抗原陽性，21%為 C 型肝炎表面抗原陽性) 在都治關懷之下，依照分層(B 型肝炎、C 型肝炎及兩年刑期) 隨機分派接受 4R 或 6H 的處方治療。接受 4R 治療者 (190 人) 與 6H 治療者(183 人)比較，碰到因為任何不良事件造成潛伏結核感染治療之中斷的機會較低 (所有的不良反應 2% vs. 12%, p< 0.001; 及肝毒性 0% vs. 8%, p<0.001)，且完成潛伏結核感染治療的機會較高 (86% vs. 78%, p=0.041)。

結論： 對於監獄收容人來說，相較於每日 isoniazid 六個月 (6H)，每日 rifampin 四個月 (4R) 的安全性及完成率皆較高。

3. 兒童接觸者的結核病發病風險: 預測評分表之發展及驗證

背景: 結核病接觸者檢查及追蹤耗時費力，迄今仍無接觸者發病風險預測指標可作為追蹤優先次序的參考。

目標: 以例行接觸者檢查登錄資料發展及驗證一簡單實用的結核病發病風險預測評分表。

方法: 發展世代是由 2008-2009 年間，全國十二歲及以下 9411 位接觸者兒童組成；我們使用多變項考克斯迴歸模式來預測活動性結核病發病的風險。驗證世代則是由 2005 年全國的 2405 位兒童接觸者組成。我們計算模式的接受者操作曲線下面積 (area under the receiver operating characteristic curves，AUROC)，以及不同評分所預測的接觸者發病風險。

測量及主要結果: 我們發展了一個八分評分系統，包括接觸者皮膚結核菌素測試、指標個案的痰塗片陽性、居住在高發生地區及性別。由發展世代計算出來的 AUROC 為 0.872 (95% CI: 0.810–0.935)而驗證世代則為 0.900 (95% CI: 0.830–0.969)。預估評分為 7, 6, 5, 4, 3 及 2 分者，其三年內活動性結核病發病風險分別為 100%, 7.8%, 4.3%, 1.0%, 0.7% 及 0.2%。

結論: 我們成功地發展及驗證一個結核病接觸者發病風險預估評分系統，能夠從十二歲及以下接觸者兒童中辨認出高發病風險個案，優先予以安排主動胸部 X 光追蹤或潛伏結核感染治療。

Abstracts

1. Lower prevalence of tuberculosis infection in BCG vaccinees: a cross-sectional study in adult prison inmates

Objectives To address whether the effect of the Bacillus Calmette-Guérin (BCG) vaccination against tuberculosis (TB) infection lasts to adulthood.

Methods A cross-sectional study on the prevalence of LTBI among HIV-negative men, using QuantiFERON® -TB Gold In-tube (QFT-IT), was conducted at a prison with >3,000 inmates in northern Taiwan. A QFT-IT ≥ 0.35 IU/ml was defined as LTBI. A QFT-IT ≥ 0.7 IU/ml was defined as recent LTBI. The association between the number of BCG scars and LTBI stratified by age was analysed. The study procedure was approved by institutional review board and all participants gave written informed consent before receiving screening tests.

Results Among the 2385 participants, 25% had a QFT-IT ≥ 0.35 IU/ml. Increasing LTBI (14%, 32% and 50%) was observed with increased age (18-35 years, 35-54 years and ≥ 55 years) ($p<0.001$ by the Cochran-Armitage Trend Test). The number of BCG scars were found to be inversely correlated with QFT-IT results for both LTBI and recent LTBI in all three age groups ($p<0.001$ by Cochran-Mantel-Haenszel statistics).

Conclusions Our results suggest that the BCG vaccine seems to have a protective effect in adults decades after vaccination according to the number of recent infections (QFT-IT ≥ 0.7 IU/ml). This finding has important implications for national policy of BCG vaccination. Further prospective cohort studies on the protective effect of the BCG vaccination against TB infection in adults are warranted.

2. Latent tuberculosis infection treatment for prison inmates: a randomised controlled trial

Setting A prison in northern Taiwan

Objective To compare safety and completion rate of the 4-month daily rifampin regimen (4R) versus standard 6-month daily isoniazid regimen (6H) for latent tuberculosis infection (LTBI) in prison inmates

Design This was an open-label randomised trial among HIV-negative male inmates. Inmates without active tuberculosis but tested positive for both tuberculin skin test and QuantiFERON® -TB Gold In-tube were eligible, but those with baseline glutamic pyruvic transaminase (GPT) levels ≥ 120 U/L, bilirubin levels ≥ 2.4 U/L, or a platelet count <150 k/mm^3 were excluded. The primary endpoint was any adverse event that resulted in discontinuation of LTBI therapy.

Results Participants (*n*=373, 14% HBsAg-positive; 21% anti-HCV-positive) were randomised (stratified by HBV, HCV status, and 2-year prison term) to receive either 4R or 6H by directly observed therapy. 4R group (n=190) were less likely to experience an adverse event leading to discontinued therapy (2% vs. 12%, p< 0.001, for all adverse event; and 0% vs. 8%, p<0.001, for hepatotoxicity), and more likely to complete the LTBI treatment (86% vs. 78%, p=0.041), compared with 6H group (n=183).

Conclusions 4R is safer and has a higher completion rate than 6H as LTBI treatment for male prison inmates.

3. Risk for Tuberculosis in Child Contacts: Development and Validation of a Predictive Score

Rationale: Contact investigation of persons exposed to tuberculosis (TB) is resource intensive. To date, no clinical prediction rule for tuberculosis risk exists for use as a guide during contact investigation.

Objectives: We sought to develop and validate a simple and easy-to-use predictive score for TB risk, using data routinely available during contact investigation.

Methods: The development cohort consisted of 9411 children aged 0-12 years from 2008-2009 national contacts cohort. We used a multivariate Cox proportional hazards model to predict the risk of developing active TB. The validation cohort consisted of 2405 children from 2005 national contacts cohort. We calculated area under the receiver operating characteristic curves (AUROC) of the model, as well as the predicted risk of TB for contacts with different score.

Measurements and Main Results: An 8-point scoring system was developed, including reaction to tuberculin skin test of the contacts, as well as smear-positivity, residence in high incidence areas and gender of the index cases. AUROC was 0.872 (95% CI: 0.810–0.935) for the development cohort and 0.900 (95% CI: 0.830–0.969) for the validation cohort. The risk of developing active TB within 3 years is 100%, 7.8%, 4.3%, 1.0%, 0.7% and 0.2% for contacts with risk scores of 7, 6, 5, 4, 3 and 2, respectively.

Conclusions: A risk predictive score was developed and validated to identify child contacts aged 0-12 years at increased risk for active TB. This predictive score can help to prioritize active case-finding or latent TB infection treatments among children exposed to TB.

Chapter 1 Lower prevalence of tuberculosis infection in BCG vaccinees: a cross-sectional study in adult prison inmates

1.1 Introduction

The Bacillus Calmette-Guerin (BCG) vaccine was developed 90 years ago.[1] The BCG vaccine has a documented protective effect against tuberculosis (TB) meningitis and disseminated TB in children and is used as a complementary strategy for TB control.[2,3] Greater than 80% of neonates and infants are covered by BCG in countries where the vaccine is part of the national childhood immunization programme.[4]

However, the protective effect of BCG against pulmonary TB in previous studies remains controversial. A long-term follow-up study in Native Americans and two studies of cohorts in Brazil and the UK demonstrated 48-59% protection against TB from the BCG vaccine 10-50 years after vaccination in newborns, schoolchildren and the community.[5,6,7] Nevertheless, no evidence of substantial protection against TB from the BCG vaccine was observed among schoolchildren and young adults in several randomized, controlled trials in the U.S. state of Georgia and Madras, India.[8,9] Environmental mycobacteria exposure, differences between the BCG strains used, genetic susceptibility and several other factors have been proposed as possible reasons for variable efficacy.[1,10]

In immunocompetent individuals, TB infection often has an initial latent phase, in which the spread of TB bacilli is contained by the immune system and the subjects remain asymptomatic.[11] In these patients, progression to symptomatic TB disease occurs only after the breakdown of this containment.[12] Measuring the BCG impact on latent TB infection (LTBI) may provide insight on the protective effect of BCG against the initial stage of TB pathogenesis.

Before the development of the interferon gamma release assay (IGRA) in early 2000, the tuberculin skin test (TST) was the only diagnostic tool for LTBI. Nevertheless, the BCG vaccine *per se* can yield a false positive TST that complicates interpretations as evidenced by the discordance between TST and IGRA in persons who had received BCG.[13] The arrival of IGRA provides a specific diagnostic tool for LTBI in BCG vaccinees. [14] IGRA was used as an indicator for LTBI in children in Turkey in a 2005 study that demonstrated a 40% efficacy of BCG against LTBI. [15] One outbreak investigation in a nursery for 2- to 5-year-old children in the UK revealed that BCG vaccination provided 66% protection from infection.[16] Does the same protective effect against LTBI from BCG vaccination also hold true in adults who received the BCG vaccine after infancy? How long can BCG protect vaccinated individuals from LTBI? There are currently no answers for these questions.

The first BCG used in Taiwan was a liquid vaccine from an old Pasteur strain, which was certified by the World Health Organization (WHO) and provided to TST-negative schoolchildren after 1953.[17] The BCG vaccine was subsequently changed, first to a new Pasteur strain in 1956 and then to a freeze-dried vaccine manufactured from the Japan Tokyo 172 strain in 1979. Since 1965, BCG has been provided to all infants and TST-negative schoolchildren.[17] Re-vaccination of schoolchildren was halted in 1997 per WHO recommendation.[18]

To survey the prevalence of LTBI and its risk factors in adult prison inmates, a group vulnerable to TB transmission, the Centers for Disease Control, Taiwan (Taiwan CDC) provided a voluntary and free LTBI screening program (including both TST and IGRA) to inmates at a prison in northern Taiwan.[19] Among the inmates who agreed to participate, we analysed the effects of BCG vaccination on the prevalence of LTBI. We hypothesize that if BCG protects vaccinated individuals from TB infection, then in a cross-sectional LTBI survey stratified by age groups, we should observe an inverse association between the

number of BCG inoculations and the prevalence of LTBI as determined by IGRA.

1.2 Materials and Methods

1.2.1 Study setting

Participants were enrolled from a prison near Taipei, Taiwan that is capable of accommodating 3,000 adult male inmates, from April to October, 2008. The turnover of inmates in and out of the prison is high. Up to 300 new inmates arrive at this prison every 4 weeks.

1.2.2 Ethics

The Institutional Review Board of the National Taiwan University Hospital reviewed and approved the study protocol (No. 200707047M). The screening was not compulsory. All participants gave written informed consent before receiving screening tests. Any active TB cases identified in this study were offered appropriate anti-tuberculosis drug therapy. Participants found to have LTBI by this study were also offered the option to receive LTBI treatment. [19]

1.2.3 Eligibility

HIV-negative inmates without active tuberculosis who understood the screening program and who gave informed consent were enrolled. HIV-positive inmates were enrolled in another study. The exclusion criteria were as follows: inmates who had a prison term less than six months, who had received complete treatment for tuberculosis, or who had evidence based on

a chest radiograph suggesting active tuberculosis.

1.2.4 Evaluation for active TB disease

All inmates were routinely offered a chest radiography evaluation and HIV testing upon their arrival at the prison. The frequency of chest radiography screening for new inmates was once per month.[20] Inmates who had not yet completed screening radiographies were isolated from the other inmates. Sputum cultures for mycobacteria were used to exclude active TB when there were suspicious chest radiography findings or symptoms. Chest radiography was provided to all participants who decided to receive the screening in our study and the procedure of excluding active TB diseases was the same as the above process of sputum collections.

1.2.5 Evaluation for latent TB infection

The TST with purified protein derivative (RT 23 2 TU, Statens Serum Institute, Copenhagen, Denmark) and the QuantiFERON® -TB Gold In-tube test (QFT-IT, Cellestis Ltd., Carnegie, Victoria, Australia) were done with the flow of drawing blood first followed by performance of TST. The transverse induration size of the TST was read by the nurses who administered the test between 48 and 72 hours after administration. Experts from the TST training committee double-checked the reading result of both the BCG scars and the TST as a part of a bi-annual training program. A TST $\geq$ 10 mm (according to the Taiwan guidelines of TB diagnosis and treatment) and a QFT-IT $\geq$ 0.35 IU/ml (according to the rules of the manufacturers) were defined as positive.[21] When analysing the association between the number of BCG scars and the TB infection risk, we further defined cases of recently acquired LTBI (recent LTBI) using a cut-off point of QFT-IT $\geq$ 0.7 IU/ml. After acquisition of LTBI,

the risk for progression to active TB is the highest in the first two years.[22] In parallel, a higher level of IFN-γ response corresponds to a higher risk for progression to active TB,[23,24] which indicates that a high IFN-γ response may be used as a marker for recent LTBI in immunocompetent persons. We chose 0.7 IU/ml as the cut-off value for recent LTBI because studies on serial testing of health care workers showed 0.35-0.7 IU/ml to be an uncertainty zone for recent TB infection.[25,26]

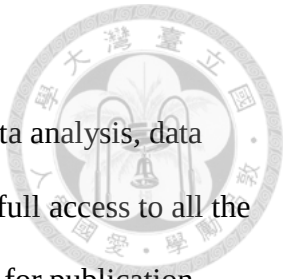
1.2.6 Number of BCG inoculations

The number of BCG scars was counted immediately prior to administration of the TST by trained public health nurses. Because there was no record of BCG immunization in this study, we used the BCG number as a proxy for previous BCG vaccination.

1.2.7 Statistical analysis

We compared categorical data by using the Pearson $\chi 2$ or Fisher exact tests, as appropriate. When analysing the association between the number of BCG scars and the TB infection risk, 2 x N tables were analysed by the Cochran-Armitage trend test. Age-stratified analysis for the number of BCG scars and the TB infection risk was summarized by Cochran-Mantel-Haenszel statistics. The kappa value and agreement were calculated to compare the concordance of TST (3 cut-off values) and QFT-IT (LTBI and recent LTBI). All analyses were conducted by using SAS, version 9.1 software (SAS Institute, Cary, North Carolina, USA).

1.2.8 Role of the funding source



The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors have full access to all the data in the study and have final responsibility for the decision to submit for publication.

1.3 Results

A total of 4,136 inmates were invited to complete the questionnaires for enrolment. Of a total of 3,312 (80%) inmates who agreed to be enrolled in our study, 2,425 received at least one LTBI screening test, and 2,385 had QFT-IT, TST and BCG data available for analysis (see Fig. 1 and Table 1 for details). The characteristics of the participants and non-participants are compared in Appendix Tables 1 and 2.

Overall, the QFT-IT was ≥ 0.35 IU/ml (LTBI) in 25% of the subjects and ≥ 0.7 IU/ml (recent LTBI) in 19% of the 2,385 subjects included in the analysis. The TST was positive in 82% of the subjects with a cut-off point of 10 mm, 45% of the subjects with a cut-off of 15 mm, and 17% of the subjects with a cut-off of 18 mm. The concordance of these two tests was analysed according to different cut-offs for both the TST and QFT-IT (Table 2). The kappa values were 0.09 for a TST ≥ 10 mm and a QFT-IT ≥ 0.35 IU/ml, indicating a poor concordance between the two tests. The kappa values were up to 0.243 for a TST ≥ 18 mm and a QFT-IT ≥ 0.7 IU/ml.

Tables 3 and 4 show the positive rate of QFT-IT and TST, stratified by age groups and the number of BCG scars. Increasing positivity of QFT-IT was observed with increased age ($p<0.001$ by the Cochran-Armitage Trend Test). QFT-IT results were found to be inversely correlated with the number of BCG scars when two different cut-offs were used (LTBI or

recent LTBI) in all three age groups (p<0.001 by Cochran-Mantel-Haenszel statistics) (Table 3). In contrast, the TST positivity increased with the number of BCG scars when a cut-off of 10 mm was used (p <0.001), but the trend was not observed when cut-offs of 15 mm or 18 mm were used (Appendix Table 2).

The evaluation for active TB disease identified only one case. The individual was asymptomatic at the time of arrival, but the chest radiograph showed a suspicious pulmonary lesion during the entry screening. However, two months later, the individual was determined to not have active TB because his cultures were negative and his chest radiography was stable. He therefore received a LTBI test, and the double-positive result was confirmed. He did not receive LTBI treatment. Two years later, bacteriology determined that the individual had active TB.

1.4 Discussion

Our results showed that after stratification by age, there was an inverse correlation between the number of BCG scars and the prevalence of positive QFT-IT, which indicates a protective effect of BCG against TB infection. Because the association was significant in all age groups (18–35 years, 35–54 years, and >55 years), our results suggest that the BCG vaccine seems to have a protective effect in adults decades after vaccination.

Our observation that BCG vaccination may provide protection against TB infection in adults is consistent with the previously reported findings in Turkey and the UK that there is a higher LTBI rate in unvaccinated children compared with those who were vaccinated.[15,16] Diel et al. also reported some evidence supporting a protective effect from BGC vaccination in 104 children aged younger than 16 years in a cohort in Hamburg, Germany.[24] The QFT-IT

positive rate was higher in unvaccinated children (26.5%) than in those who were vaccinated (13.9%), although this difference did not reach statistical significance due to the small sample size.

Whether revaccination in adolescents or adults is beneficial or useless in TB control has long been a subject of debate. A double-blind, randomized, placebo-controlled trial conducted in Karonga, Malawi, between 1986 and 1987 showed that revaccination with BCG did not provide any protection against TB but that primary vaccination or revaccination did provide protection against leprosy.[27] WHO officially recommended to not revaccinate with BCG in 1995,[18] and Taiwan followed the recommendation and stopped the revaccination program in 1997.[17] However, we should note that the Karonga trial in Malawi that documented the failed BCG revaccination strategy also failed to find primary BCG vaccination protective against TB.[10] A retrospective cohort consisting of 303,692 children born between 1978 and 1982 in Hong Kong who received the primary BCG in infancy and a booster at 6-9 years of age also failed to demonstrate any significant difference in the TB rate between participants and non-participants in a school revaccination programme.[28] An open-label, no placebo, clustered, randomized, controlled trial was conducted among 200,805 schoolchildren aged 7-14 years in Salvador and Manaus, Brazil 5 years later.[29] In the initial follow-up for 3-4 years, no substantial additional protection from BCG revaccination in schoolchildren was found. However, after 9 years of follow-up, a 33% (3-54%) vaccine efficacy in children aged <11 years was reported recently in Salvador, a location with a lower non-tuberculous mycobacteria (NTM) prevalence.[30] This finding was comparable to the 30% (3-52%) protective effect from BCG revaccination observed in nonreactors to NTM, 15 years after a double-blind, randomized, controlled trial conducted in South India.[31] The inverse dose response of the BCG vaccine over the TB infection risk noted in our study further supports the possibility that revaccination may have some protective effect.

The inconsistent protective effect from either BCG vaccination or revaccination has caused a number of debates over the past two decades.[1,10] The difference in antigenicity between the BCG strains and the epidemic strains prevalent in some regions could be factors behind the discrepancies between studies conducted in different geographical regions. Theoretically, the heavy use of BCG in high-burden regions could also drive the evolution of prevalent *M. tuberculosis* strains. This hypothesis was proposed because of a case-control study of TB patients conducted in Vietnam, Hong Kong, China and the Netherlands, which revealed that a higher proportion of BCG-vaccinated TB cases were infected with the modern Beijing strain of *M. tuberculosis* after age stratification.[32] Further studies using cohort or randomized control trial designs to compare the protective efficacy of BCG against Beijing strains versus non-Beijing strains are required to clarify these important issues.

Consistent with previous reports from Korea, which has 95.7% BCG coverage and moderate LTBI risk,[33] our results showed only an unsatisfactory concordance between TST and QFT. Similarly, discordance between TSTs and IGRAs was observed in Japanese health workers who had predominately undergone multiple BCG vaccinations.[34] The concordance between the TST and QFT was also low in BCG-vaccinated Korean health care workers (kappa=0·31, agreement 67.5%).[35] The high false positive rates of the TST after BCG vaccination has raised concerns of un-necessary LTBI diagnosis and treatment,[36, 37] and can explain why the inverse correlation between BCG vaccination and LTBI could not be discovered by previous TST-based studies.

Similar to many previous studies,[15,38] we used the number of BCG scars as a proxy for the BCG vaccination record. The proportion of vaccinated people who develop and retain a recognizable scar following vaccination has been reported to vary from 98.9%, in a vaccine trial in South India 4 years after vaccination,[38] to 60%, in Swedish children assessed 14 years after vaccination at birth.[39] In the present study, nurses did not know the result of LTBI when

they counted the number of BCG scars. Therefore, any misclassification of a BCG scar would very likely be non-differential and yield a bias toward to null. Our estimate for the correlation of more BCG scars with a lower rate of LTBI is therefore a conservative one.

In the present study, the lower prevalence of LTBI in BCG vaccinees is unlikely to be confounded by social economic status in early life because: (1) BCG vaccination is free in Taiwan; and (2) BCG vaccination is universally provided through public health stations (newborn and school children), hospitals (new born), and schools (school children) in Taiwan. So families from all social classes have the same access to BCG vaccination.

Our study has some limitations. Although up to eighty percent (3312/4136) of inmates were willing to be enrolled, 13% (440/3312) of them could not receive the test due to transfer or parole. As the age categories in stratification are broad (spanning 20 years), the relationship between BCG vaccination and LTBI could be confounded by a birth cohort effect if the TB trends changed rapidly over time. However, the nationwide TB registry data in Taiwan over the past half century (Appendix Table 1) show no such change, which makes confounding by birth cohort effect unlikely. Because of the limitations in the design of the cross-sectional study, the temporality between a lack of BCG vaccination and the occurrence of LTBI in participants is unclear. Furthermore, we were not informed of the reasons for the different numbers of vaccinations (or the lack of vaccination) among the participants. Therefore, factors influencing whether BCG has been received during infancy or childhood could confound our results. Nevertheless, analysis using QFT-IT $\geq$ 0.7 IU/ml as a cut-off value, a marker of recently acquired LTBI, also yielded the same result, indicating that the observed effect is genuine rather than confounded or a coincidence. Therefore, our results justify further prospective cohort studies to clarify the causal relationship between the BCG vaccine and protection against LTBI.

In conclusion, our results suggest that the BCG vaccine seems to have a protective effect in adults decades after vaccination according to the number of recent infections (QFT-IT ≥ 0.7 IU/ml). This finding has important implications for the continuation of a national policy of BCG vaccination. Further prospective cohort studies on the protective effect of the BCG vaccination against TB infection in adults are warranted.

1.5 References

1. Fine PEM, Carneiro IAM, Milstein JB, Clements CJ. Issues relating to the use of BCG in immunization programs. Geneva: World Health Organization, 1999.
2. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *Int J Epidemiol* 1993; **22**: 1154-8.
3. Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, et al. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics* 1995; **96**: 29-35.
4. World Health Organization. BCG vaccine WHO positional paper. *Weekly Epidemiology Record* 2004; **79**: 25-40.
5. Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska natives A 60-year follow-up study. *JAMA* 2004; **291**: 2086-91.
6. Barreto ML, Cunha SS, Pereira SM, Genser B, Hijjar MA, Yury Ichihara M, et al. Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil. *Int J Tuberc Lung Dis* 2005; **9**: 1171-3.
7. Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *BMJ* 1977; **2**: 293-5.
8. Comstock GW, Webster RG. Tuberculosis studies in Muscogee County, Georgia, VII. A twenty year evaluation of BCG vaccination in school population. *Am Rev Respir Dis* 1969; **100**: 839-45.
9. Tuberculosis Prevention Trial, Madras. Trial of BCG vaccines in south India for

tuberculosis prevention: first report. *Bull World Health Organ* 1979; **57**: 819–27.

10. Smith D, Wiegeshaus E, Balasubramanian V. An analysis of some hypotheses related to the Chingelput bacille Calmette-Guérin trial. *Clin Infect Dis* 2000; **31**(Suppl 3): S77-80.

11. Dietrich J, Doherty TM. Interaction of Mycobacterium tuberculosis with the host: consequences for vaccine development. *APMIS* 2009;**117**:440-57.

12. Russell DG, Barry CE, Flynn JL. Tuberculosis: what we don't know can, and does, hurt us. *Science* 2010; **328**: 852-6.

13. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, et al. Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. *Eur Respir J* 2011; **37**: 88–99.

14. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008; **149**: 177-84.

15. Soysal A, Millington KA, Bakir M, Dosanjh D, Aslan Y, Deeks JJ, et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005; **366**: 1443-51.

16. Eriksen J, Chow JY, Mellis V, Whipp B, Walters S, Abrahamson E, Abubakar I. Protective effect of BCG vaccination in a nursery outbreak in 2009: time to reconsider the vaccination threshold? *Thorax* 2010; **65**: 1067-71.

17. Provincial Chronic Disease Control Bureau. A review of the tuberculosis control program in Taiwan, 1949-1989: Chronological Development of the Program, BCG vaccination. Taipei, Taiwan: Provincial Chronic Disease Control Bureau; 1991: 4-37.

18. World Health Organization. Statement on BCG revaccination for the prevention of tuberculosis. *Weekly Epidemiological Record* 1995; **70**: 229-36.

19. Chan PC, Yang CH, Chang LY, KF Wang, BY Lu, CY Lu, et al. Latent Tuberculosis Infection Treatment for Prison Inmates: A Randomised Controlled Trial. *Int J Tuberc Lung Dis* 2012; **16**: 633-8.

20. Chiang CY, Hsu CJ, Hsu PK, Suo J, Lin TP. Pulmonary tuberculosis in the Taiwanese prison population. *J Formos Med Assoc* 2002; **101**: 537-41.

21. Centers for Disease Control, Department of Health. *Taiwan Guidelines for TB Diagnosis & Treatment*. 2nd edition. Taipei, Taiwan: CDC, 2006.

22. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004; **350**: 2060–7.

23. Yoshiyama T, Harada N, Higuchi K, Sekiya Y, Uchimura K. Use of the QuantiFERON-TB Gold test for screening tuberculosis contacts and predicting active disease. *Int J Tuberc Lung Dis* 2010;**14**:819-27.

24. Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. Negative and Positive Predictive Value of a Whole-Blood Interferon-gamma Release Assay for Developing Active Tuberculosis: An Update. *Am J Respir Crit Care Med* 2011; **183**: 88-95.

25. Costa JT, Silva Rui, Sa Raul, Cardoso MJ, Nienhaus A. Serial testing with the interferon-gamma release assay in Portuguese healthcare workers. I*nt Arch Occup Environ Health* 2011; **84**: 461–9.

26. Ringshausen FC, Schablon A, Nienhaus A. Interferon-gamma release assays for the tuberculosis serial testing of health care workers: a systematic review. *J Occup Med Toxicol* 2012;**7**:6.

27. Karonga Prevention Trial Group. Randomized controlled trial of single BCG, repeated

BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet* 1996; **348**: 17–24.

28. Leung CC, Tam CM, Chan SL, Chan-Yeung M, Chan CK, Chang KC. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. *Int J Tuberc Lung Dis* 2001; **5**: 717-23.

29. Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, de Brito SC, et al. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet* 2005; **366**: 1290-5.

30. Barreto ML, Pereira SM, Pilger D, Cruz AA, Cunha SS, Sant'Anna C, et al. Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: second report of the BCG-REVAC cluster-randomised trial. *Vaccine* 2011; **29**: 4875-7.

31. Narayanan PR. Influence of sex, age & nontuberculous infection at intake on the efficacy of BCG: re-analysis of 15-year data from a double-blind randomized control trial in South India. *Indian J Med Res* 2006; **123**: 119-24.

32. Kremer K, van-der-Werf MJ, Au BK, Anh DD, Kam KM, van-Doorn HR, et al. Vaccine induced immunity circumvented by typical mycobacterium tuberculosis Beijing strains. *Emerg Infect Dis* 2009; **15**: 335-9.

33. Kang YA, Lee HW, Yoon HI, Cho B, Han SK, Shim YS, et al. Discrepancy between the tuberculin skin test and the whole-blood interferon gamma assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. *JAMA* 2005; **293**: 2756-61.

34. Harada N, Nakajima Y, Higuchi K, Sekiya Y, Rothel J, Mori T. Screening for

tuberculosis infection using whole-blood interferon-gamma and Mantoux testing among Japanese healthcare workers. *Infect Control Hosp Epidemiol* 2006; **27**: 442-8.

35. Choi JC, Shin JW, Kim JY, Park IW, Choi BW, Lee MK. The effect of previous tuberculin skin test on the follow-up examination of whole-blood interferon-gamma assay in the screening for latent tuberculosis infection. *Chest* 2008; **133**: 1415-20.

36. Nienhaus A, Schablon A, Diel R. Interferon-gamma release assay for the diagnosis of latent TB infection—analysis of discordant results, when compared to the tuberculin skin test. *PLoS ONE* 2008; **3**: e2665.

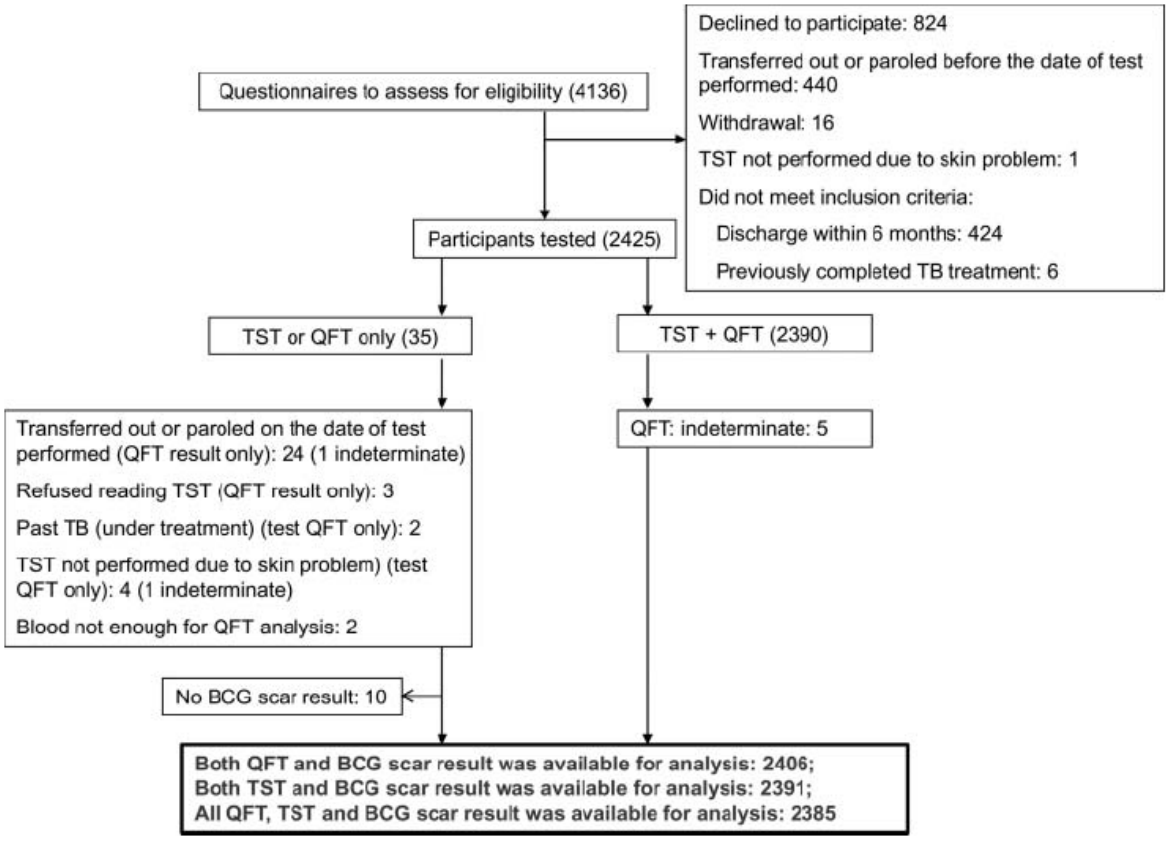
37. O'Neal S, Hedberg K, Markum A, Schafer S. Discordant tuberculin skin and interferon-gamma tests during contact investigations: a dilemma for tuberculosis controllers. *Int J Tuberc Lung Dis* 2009; **13**: 662–4.

38. Tuberculosis Prevention Trial, Madras. Trial of BCG vaccines in south India for tuberculosis prevention. *Indian J Med Res* 1980; **72**: S1-74.

39. Beskow R, Bleiker M, Dahlstrom G, Mellbin T, Sjogren I, Styblo K. Sensitivity to tuberculin in Swedish schoolboys vaccinated with BCG at birth. *Bull Int Union Tuberc* 1980; 55: 101-6.1.6 Figures

1.6 Figures

Fig 1 The flowchart of enrollment.



1.7 Tables

Table 1 Characteristics of participants who received at least one test in this study.

Variables	Number of persons	Both results available	Only one result available	P value*
		N (%)		
Age (years)				
18-24	178 (8)	177 (7)	1 (3)	0.029
25-34	960 (40)	949 (40)	11 (28)	
35-44	754 (31)	741 (31)	13 (33)	
45-54	389 (16)	381 (16)	8 (20)	
55-64	107 (4)	102 (4)	5 (13)	
≥65	37 (2)	35 (1)	2 (5)	
Total	2425 (100)	2385 (100)	40 (100)	
Age (years)				
18-35	1138 (47)	1126 (47)	12 (30)	0.003
35-54	1143 (47)	1122(47)	21 (53)	
≥55	144 (6)	137 (6)	7 (18)	
	2425 (100)	2385 (100)	40 (100)	
Body weight				
≥70 kg	1229 (51)	1206 (51)	23 (58)	0.384
Prison term				
> 6 months	2423 (100)	2383 (100)	40 (100)	1.0
Education				
≥13 years	1101 (45)	1079 (45)	22 (55)	0.219
BCG scar no				
No inoculation	218 (9)	212(9)	17(43)	<0.001
Inoculation once	1065 (44)	1053 (44)	12 (30)	
Booster	1131 (47)	1120 (47)	11 (28)	
	2414 (100)			

BCG= Bacillus Calmette-Guérin

* Pearson χ^2 for 2 × N tables or Fisher's exact test for 2 × 2 tables with small sample sizes.

Table 2 Summary statistics for the double positive results (QuantiFERON® -TB Gold In-tube and tuberculin skin test) and the analysis for concordance between the two tests.

	Age			P value
	18-35 years	**35-54 years**	**≥ 55 years**	
	1126	1122	137	
TST≥ 10mm and QFT-IT ≥ 0.35 IU/ml	Kappa value: 0.090 Agreement: 40%			
		N (%)		
Positive	142 (13)	344 (31)	64 (47)	<0.001†
No inoculation	9 (14)	53 (54)	27 (55)	<0.001*
Inoculation once	84 (15)	144 (33)	25 (48)	
Booster	49 (10)	147 (25)	12 (33)	
TST≥ 15mm and QFT-IT ≥ 0.35 IU/ml	Kappa value: 0.202 Agreement: 62%			
Positive	100 (9)	244 (22)	35 (26)	<0.001†
No inoculation	7 (11)	41 (42)	19 (39)	<0.001*
Inoculation once	64 (11)	103 (23)	9 (17)	
Booster	29 (6)	100 (17)	7 (19)	
TST≥ 18mm and QFT-IT ≥ 0.35 IU/ml	Kappa value: 0.224 Agreement: 74%			
Positive	42 (4)	125 (11)	21 (15)	<0.001†
No inoculation	3 (5)	26 (27)	9 (18)	<0.001*
Inoculation once	26 (5)	49 (11)	8 (15)	
Booster	13 (3)	50 (9)	4 (11)	
TST≥ 10mm and QFT-IT ≥ 0.7 IU/ml	Kappa value: 0.070 Agreement: 35%			
Positive	101 (9)	273 (24)	54 (39)	<0.001†
No inoculation	9 (14)	43 (44)	25 (51)	<0.001*
Inoculation once	59 (11)	124 (28)	19 (37)	
Booster	33 (7)	106 (18)	10 (28)	
TST≥ 15mm and QFT-IT ≥ 0.7 IU/ml	Kappa value: 0.197 Agreement: 62%			
Positive	79 (7)	202 (18)	33 (24)	<0.001†
No inoculation	7 (11)	35 (36)	19 (39)	<0.001*
Inoculation once	47 (8)	92 (21)	7 (13)	
Booster	25 (5)	75 (13)	7 (19)	
TST≥ 18mm and QFT-IT ≥ 0.7 IU/ml	Kappa value: 0.243 Agreement: 78%			
Positive	37 (3)	106 (9)	19 (14)	<0.001†
No inoculation	3 (5)	22 (22)	9 (18)	<0.001*
Inoculation once	21 (4)	44 (10)	6 (12)	

Booster	13 (3)	40 (7)	4 (11)

* Cochran-Mantel-Haenszel statistics for stratification analysis

† Pearson χ^2 for N × N tables

Table 3 Summary statistics for results of QuantiFERON® -TB Gold In-tube.

Stratification	Number of persons	Cutoff for positivity (%)	Cutoff for positivity (%)
	2416	**LTBI (QFT-IT ≥ 0.35 IU/ml)**	**Recent LTBI (QFT-IT ≥ 0.7 IU/ml)**
Age (years)		**N (%)**	
18-24	178	15 (8)	12 (7)
25-34	955	141 (15)	98 (10)
35-44	753	205 (27)	161 (21)
45-54	389	163 (42)	130 (33)
55-64	105	50 (48)	41 (39)
≥ 65	36	20 (56)	18 (50)
Chi-square P value		<0.001	<0.001
Age (years)			
18-35	1133	156 (14)	110 (10)
35-54	1142	368 (32)	291 (25)
≥55	141	70 (50)	59 (42)
		<0.001†	<0.001†
BCG scar number	**2406**	**N (%)**	
No inoculation	216	102 (47)	86 (40)
Inoculation once	1062	271 (26)	216 (20)
Booster	1128	218 (19)	155 (14)
		<0.001†	<0.001†
Controlling for age		<0.001*****	<0.001*****
18-35 years		**N (%)**	
No inoculation	65	12 (18)	10 (15)
Inoculation once	563	93 (17)	66 (12)
Booster	504	51 (10)	34 (7)
		P=0.002†	P=0.002†
35-54			
No inoculation	101	60 (59)	48 (48)
Inoculation once	446	150 (34)	129 (29)
Booster	587	155 (26)	111 (19)
		P<0.001†	P<0.001†
≥ 55			
No inoculation	50	30 (60)	28 (56)
Inoculation once	53	28 (53)	21 (40)
Booster	37	12 (32)	10 (27)
		P=0.013†	P=0.006†

BCG= Bacillus Calmette-Guérin
* Cochran-Mantel-Haenszel statistics for stratification analysis
† Cochran-Armitage trend test

1.8 Appendix Table

Appendix Table 1 Cases notified and centrally registered in Taiwan since 1957 with TB notification incidence

Remark	Year	Annual Numbers of TB Cases	Incidence (/100,000)
Only smear-positive pulmonary TB was required for registry during 1957-1968			
	1953-1956	-	-
	1957	2457	25.4
	1958	4569	45.5
	1959	7012	67.2
	1960	5975	55.4
	1961	5987	53.7
	1962-1964	-	-
	1965	5602	53.7
	1966	-	-
	1967	5376	53.7
Cavitary pulmonary TB was included in the registry since 1969			
	1968-1969	-	-
	1970	6563	53.7
Cases with extensive parenchyma involvement was included in the registry since 1974			
	1971-1974	-	-
	1975	6212	53.7
	1976	7193	53.7
	1977	6855	40.6
Pleural TB cases included in the registry since 1978			
	1978	6851	39.8
	1979	5531	31.5
	1980	5829	32.6
Bacteriology- or pathology-proved extrapulmonary TB was included in the registry since 1981			
	1981	6297	34.6
	1982-1984	-	-
	1985	5782	34.6
	1986-1987	-	-
	1988	5774	34.6
All forms of TB were reported and included in registry since 1991			
	1989-1996	-	-
	1997	15386	70.8
	1998	14169	64.6
	1999	13496	61.1
	2000	13910	62.4
	2001	14486	64.7
	2002	16758	74.4
	2003	15042	66.5
	2004	16784	74.0

2005	16472	72.3
2006	15378	67.2
2007	14480	63.1
2008	14265	61.9
2009	13336	57.7
2010	13237	57.1

Note: There were no documented official statistics on annual numbers of reported TB cases during 1962-1964, 1966, 1968-1969, 1971-1974, 1982-1984, 1986-1987, and 1989-1996.

References

1. Yu MC, Bai KJ, Chang JH, Lee CN. Age transition of tuberculosis patients in Taiwan, 1957-2001. *J Formos Med Assoc* 2006;**105**:25-30.
2. Provincial Chronic Disease Control Bureau. A review of the tuberculosis control program in Taiwan, 1949-1989: Chronological Development of the Program, BCG vaccination. Taipei, Taiwan: Provincial Chronic Disease Control Bureau; 1991: 4-37.
3. Centers for Disease Control, Department of Health. Taiwan Tuberculosis Control Report 2001. Taipei, Taiwan: CDC 2001.
4. Centers for Disease Control, Department of Health. Taiwan Tuberculosis Control Report 2007. Taipei, Taiwan: CDC 2007. Available at: http://www.cdc.gov.tw/uploads/files/362cccde-59ac-4fd5-b12f-0af6d54555bd.pdf
5. Centers for Disease Control, Department of Health. Taiwan Tuberculosis Control Report 2011. Taipei, Taiwan: CDC 2011. Available at: http://www2.cdc.gov.tw/public/data/219124871.pdf

Appendix Table 2 Summary statistics for results of tuberculin skin test.

Stratification	Number of persons	Cutoff for positivity (%)	Cutoff for positivity (%)	Cutoff for positivity (%)
TST	**2391**	**10mm**	**15mm**	**18mm**
Age (years)			**N (%)**	
18-24	177	115 (65)	34 (19)	12 (7)
25-34	953	761 (80)	399 (42)	133 (14)
35-44	741	647 (87)	397 (54)	154 (21)
45-54	381	325 (85)	191 (50)	79 (21)
55-64	103	84 (82)	43 (42)	20 (19)
≥65	36	26 (72)	16 (44)	7 (19)
BCG scar number			**N (%)**	
No inoculation	213	160 (75)	100 (47)	45 (21)
Inoculation once	1056	848 (80)	477 (45)	181 (17)
Booster	1122	950 (85)	503 (45)	179 (16)
Controlling for age				
18-35 years			**N (%)**	
No inoculation	65	38 (58)	20 (31)	6 (9)
Inoculation once	564	430 (76)	226 (40)	79 (14)
Booster	501	408 (81)	187 (37)	60 (12)
35-54 years				
No inoculation	98	84 (86)	54 (52)	28 (29)
Inoculation once	440	376 (85)	233 (53)	91 (21)
Booster	584	512 (88)	301 (55)	114 (20)
≥55 years				
No inoculation	50	38 (76)	26 (52)	11 (22)
Inoculation once	52	42 (81)	18 (35)	11 (21)
Booster	37	30 (81)	15 (41)	5 (14)

BCG= Bacillus Calmette-Guérin

Chapter 2 Latent tuberculosis infection treatment for prison inmates: a randomised controlled trial

2.1 INTRODUCTION

People exposed to contagious tuberculosis (TB) are at risk for acquiring latent tuberculosis infection (LTBI), defined by a positive reaction to tuberculin skin test (TST) and/or interferon gamma release assay. People with LTBI have a 10% lifetime risk of developing active TB, one half of which would occur within two years after exposure.[1] Fortunately, randomised controlled trials have demonstrated that 6–12 months isoniazid preventive therapy (IPT) can reduce the incidence of subsequent active TB by 65–90% among patients with LTBI.[2,3] In countries with a decreasing incidence of active TB after the implementation of a directly observed therapy (DOT) program, treatment for LTBI may further reduce the incidence and transmission of tuberculosis.[4-6]

Epidemiologic studies in many countries have shown that incidences of LTBI are much higher in prison than that in general population, indicating the difficulty in preventing TB transmission at such facilities.[7] Screening LTBI and providing IPT in this vulnerable population is an important strategy in TB control.[8] Providing IPT for prison inmates with LTBI, nevertheless, has been hampered by potential risk of hepatotoxicity, due to the high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in this population.[8,9] Suboptimal completion rate is another concern, since prison inmates are often lost to follow-up after parole. A safer and shorter LTBI treatment regimen that can be completed during stay in prison will be an important advance in TB control.

A 2-month regimen of rifampin and pyrazinamide (2RZ) has been investigated as an alternative to 6–12 month isoniazid.[10] However, after one prison inmate died from

hepatotoxicity,[11] 2RZ was no longer recommended. Regimens of rifampin monotherapy appear to be safer. Three months of rifampin has been compared with 6 months of isoniazid in silicosis patients.[12] There was no significant difference in hepatotoxicity, but the overall completion rate was better for 3 months of rifampin. In another randomised clinical trial conducted at university hospitals, treatment with 4 months of daily rifampin was associated with less hepatotoxicity and a better adherence than 9 months of daily isoniazid.[13]

The safety and the completion rate of the 4-month daily rifampin regimen (4R) as an alternative to standard 6-month daily isoniazid regimen (6H) for LTBI have not yet been compared in prison inmates. This study was an open-label randomised controlled trial aimed to examine the hypothesis that the 4R is less likely to cause hepatotoxicity, and more likely to be completed than the standard 6H for LTBI treatment in this vulnerable population with a high HBV and HCV prevalence.

2.2 SUBJECTS AND METHODS

The study protocol was approved by Department of Health, Executive Yuan, Taiwan, and the Institution Review Board of National Taiwan University Hospital. All participants gave written informed consent.

2.2.1 Setting

Participants were enrolled from a prison that can accommodate 3,000 male adult inmates near Taipei in Taiwan. Upon their arrival, all inmates routinely received physical check-ups, including chest radiography evaluation and human immunodeficiency virus (HIV) testing.

2.2.2 Eligibility

The investigators provided tuberculin skin test (TST, with purified protein derivative RT 23 2 TU, Statens Serum Institute, Copenhagen, Denmark, ≥ 10 mm was considered positive) and QuantiFERON® -TB Gold In-tube (QFT-IT, Cellestis Ltd., Carnegie, Victoria, Australia) screenings for all HIV-negative inmates without active TB. Two waves of screening in June and October, 2008, were conducted to achieve enough LTBI patients enrolled for randomised LTBI treatment. By study protocol, all identified LTBI patients in the screenings were offered to join this study. LTBI patients who were positive for both tests were referred for eligibility evaluation including medical history review, chest radiography, baseline blood screening for complete blood cell counts, liver enzymes, bilirubin, hepatitis B surface antigen (HBsAg), and antibody against hepatitis C virus (anti-HCV). Patients were excluded from this study if they had active TB, were taking concomitant medications that may cause potential drug interactions, or had elevated glutamic pyruvic transaminase (GPT) levels ≥ 3 times the upper limit of normal values (ULN=40 U/L), bilirubin levels ≥ 2 times the ULN (ULN=1.2 U/L), or a platelet count <150 k/mm^3 at baseline, or had a prison term less than 6 months. Sputum cultures for mycobacterium were used to exclude active TB when chest radiography or symptoms were suspicious.

2.2.3 Randomisation

Eligible LTBI patients were randomly allocated to receive 6H (5 mg/kg, up to 300 mg/d) or 4R (10 mg/kg, up to 600 mg/d) after signing informed consent. To ensure the comparability between both arms,[14] the randomisation was stratified separately by HBsAg, anti-HCV, and a prison term longer than 2 years. The random allocation sequence within each stratum was

generated with random digit generator of Microsoft Excel 2003.

2.2.4 Follow-up procedures

All participants had at least three blood tests, one before treatment to assay platelet count, liver aminotransferase and bilirubin levels, and two after initiation of treatment to assay aminotransferase and bilirubin levels. Prison Health Services gave the LTBI treatment to participants with DOT. Daily log of medication administration was recorded. Participants were instructed that they should report any discomfort at the time of DOT. Every participant was evaluated by physicians at the time of blood tests and those who reported AE were evaluated on a weekly basis. Because the expected duration of treatment is different in the two arms, blood tests were carried out at 1 and 2 months after the start of therapy for participants receiving 6H, and at 2 weeks and 1 month after the start of therapy for participants receiving 4R, in proportional to the respective duration of treatment. Paroled patients were actively pursued by study nurses who arranged either referrals to a designated clinic or deliveries of medication. Expense for medical care and transportation was reimbursed as an incentive.

2.2.5 Outcome measures

The primary endpoint was any adverse event that resulted in discontinuation of LTBI therapy. Adverse events (AE) were graded by a modified version of National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0 (see the Appendix Table 1).[15] The GPT level was graded as the recommended grading of the American Thoracic Society.[16] Pre-specified criteria for stopping LTBI treatment were as below: (1) The LTBI therapy was

permanently stopped when any grade 3 to 4 adverse event occurred; (2) The LTBI therapy was temporally suspended when a GPT level ≥ 3 times the ULN or a bilirubin level ≥ 2 times the ULN was detected by scheduled blood tests. One more blood test was then performed 2 weeks later, and the therapy was resumed if GPT and bilirubin levels were below the suspension criteria. Another blood test was performed again 2 weeks after resuming therapy. If subjects developed impaired liver function again, they were withdrawn from LTBI therapy permanently. (3) The LTBI therapy was also temporally suspended when other type AE occurred and did not respond to symptomatic treatment, necessitating treatment suspension as judged by the attending physician. The LTBI therapy was resumed after the resolution of AE, and permanently withdrawn if AE recurred after resuming therapy.

2.2.6 Statistical analysis

Based on AE rates reported in literature,[12,13,17,18] assuming 10% of participants would reach the primary endpoint as the control rate, 154 participants in each group were estimated to be able to provide 80% power to detect an absolute risk reduction of 7% , using a fixed sample design (2-sided alpha=0.05). Data were analyzed by intention-to-treat principle. The primary outcome and treatment completion rate were compared using chi-square tests (Fisher's exact test was used when sample sizes were small) Logistic regression was used to adjust for the effects of other variables. Sample size calculations were computed using StatCalc, EpiInfo version 6 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA). Other analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, North Carolina, USA).

2.3 RESULTS

2.3.1 Participants

Screenings identified 550 inmates with LTBI. After chart review and baseline blood test screening, 61 of them were transferred out or paroled before the completion of assessment for eligibility, 73 subjects were ineligible, while 43 (10%) declined to participate (Appendix Table 2). There were 373 patients entered randomisation. The flow of participants was shown in Figure 1.

2.3.2 Baseline data

The 373 participants were randomly assigned to 6H (n=183) or 4R (n=190). Baseline participant characteristics were similar between the two groups, including age, HBV and HCV status, prison term, pretreatment GPT levels, underlying diseases, and concomitantly used medication (Table 1).

2.3.3 Outcomes

Four patients (2%) in the 4R group and 22 patients (12%) in the 6H group had an adverse event resulting in discontinuation of LTBI therapy ($p<0.001$) (Table 2) (Fig 2). Analyses by different types of AE of the primary endpoint revealed that participants in the 6H group were more likely to develop grade 3–4 hepatotoxicity that resulted in discontinuation of LTBI therapy than participants in the 4R group (Table 2). All of these 15 hepatotoxic events were identified at scheduled blood tests according to study protocol, and none of the participants manifested symptomatic hepatotoxicity. Subjects in 4R group were also significantly less

likely to develop grade 1 hepatotoxicity which did not interfere with LTBI therapy than the 6H group (16/190 [8%], vs. 61/183 [33%], p<0.001). There were no differences in the occurrence of other types of AE that resulted in discontinuation of LTBI therapy (Table 2). 4R group was still less likely to reach the primary endpoint and more likely to complete treatment after adjusting for effects of covariates (p<0.001) (Table 3). HCV infection was another independent risk factor for the primary endpoint (p=0.02), and a prison term longer than 2 years was another independent predictor for completing the treatment (p=0.002) (Table 4).

2.3.4 Risk factors for hepatotoxicity

To delineate interactions between effects of LTBI treatment, HBV/HCV status, and age ≥35 years, we conducted an exploratory analysis on risk of hepatotoxicity that resulted in therapy discontinuation. None of the 4R group developed this outcome. Among the 6H group, those positive for both HBsAg and anti-HCV and those positive for anti-HCV alone had an 8.5-fold and 6.4-fold increase in the risk, respectively, compared to those negative for both. Further stratifying data by age ≥35 years (Table 5) showed that HCV infection increased the risk of hepatotoxicity in both age ≥35 years and age <35 years groups.

2.3.5 Dropout after parole

A prison term shorter than 2 years was associated with a higher probability of parole (19/88 vs. 5/285, p<0.001). Nine patients (5%) in the 4R group and 15 patients (8%) in the 6H group were paroled during the treatment course (p=0.173). Eight paroled patients (8/9) in the 4R group and 9 paroled patients (9/15) in the 6H group dropped out before the completion of

LTBI treatment (p=0.191). Participants who were paroled before the completion of LTBI treatment were 10 times more likely to drop out, in comparison with participants who were neither paroled nor relocated (17/24 [71%] vs. 22/329 [7%], p<0.001). In contrast, there was no significant difference in dropout rate between participants who were relocated to another prison and those who were neither paroled nor relocated (3/20 [15%] vs. 22/329 [7%], p=0.164).

2.4 DISCUSSION

The results demonstrated that subjects who were receiving 4R were significantly less likely to have an adverse event resulting in discontinuation of LTBI therapy and more likely to complete the LTBI treatment than those receiving 6H. For LTBI treatment in male prison, a population with a high prevalence of HBV and HCV infection, 4R is significantly safer and has a better completion rate than 6H.

The findings in our study could be limited by the open-label design. With physician and participant aware of the assignment during follow-up, biases might occur for the decision to order the laboratory test, report the symptoms or stop treatments. To minimize this possible source of biases, all of the laboratory test follow-ups in this study were conducted according to pre-specified protocols. For hepatotoxicity, the decision to stop the treatment was based on the same pre-specified criteria for all participants in both arms.

Despite the good intention of the LTBI screening and treatment programs, the coercive nature of the prison setting can obstruct the reporting of AE by inmates.[19] To minimize the potential risk of neglected AE, we arranged physician visit every week for self-reported AE. Nevertheless, this reliance on self-report may still limit the ascertainment of AE. Therefore,

we arranged physicians visiting at the time of blood tests, in order to actively identify AE other than hepatotoxicity.

Because 6H is two months longer than 4R, we scheduled the timing of follow-up blood tests in proportional to the respective duration of treatment. The interpretation of results from time interval-based statistical methods, such as Kaplan-Meier analyses, could be limited by this difference in both treatment duration and follow-up intervals. For this reason, the primary analysis of this study was conducted using chi-square test or Fisher's exact test.

The frequency of hepatotoxicity observed in the 6H group of the present study (8% for hepatotoxicity that resulted in treatment discontinuation) was higher than that observed in non-prison settings where LTBI treatment is provided to TB contacts and immigrants in communities.[13,17] There are two probable reasons. First, our study monitored the liver function by a standardized protocol, and therefore was able to identify all subclinical hepatotoxicity.[11] Second, participants in our study had a high HBV and HCV prevalence. Prior studies conducted in intravenous drug users also showed that 9% (≥ 5 times the ULN) and 8% (≥ 3 times the ULN) hepatotoxicity found during isoniazid treatment with a HCV prevalence of 96% and 51%, respectively.[18,20]

For participants in the 6H group of the present study, those positive for anti-HCV were significantly more likely to develop hepatotoxicity that resulted in the discontinuation of LTBI therapy. Therefore, these patients could benefit most from the safer 4R regimen.

Previous studies showed that age is an important determinant for hepatotoxicity risk during isoniazid treatment, with people aged >35 at higher risk than younger people.[21] More over, a recent study showed that people aged >65 had a significantly higher risk of admission for hepatic events during LTBI treatment (95% isoniazid).[22] Among participants assigned to 6H in the present study, those aged ≥35 years did have a higher risk of hepatotoxicity (4% vs.

3% in HBV/HCV-negative group; 28% vs. 21% in HCV-positive group, see Table 5). However, the logistic regression analysis showed that age was not a statistically significant predictor for either primary or secondary outcome (Table 4).

Previous studies showed that a longer duration of treatment, such as 9 months course of isoniazid, can compromise the patient adherence compared with 4R.[17,23] For 6H, only 2 months longer than 4R, we observed no significant difference in the non-adherence dropout rate between the 6H and the 4R group (Table 2). The 4R advantage appeared to be limited to tolerability and not partly attributable to compliance. Nevertheless, parole before treatment completion was still found to be associated with non-adherence significantly in our study. For prison inmates, a shorter course for LTBI is particularly important for a high completion rate because the compliance is difficult to maintain after the parole.[24] This was illustrated by the immediate drop out of 9 participants receiving 6H and 8 receiving 4R at the time of parole in our study, despite the provision of incentives for them to return for follow-up. Our experience was in keeping with the very low completion rate in people released from jails in the literature.[25]

The efficacy of rifampin-based LTBI treatment has been demonstrated in a double blinded placebo-controlled randomised trial conducted in silicosis patients with four arms, three month of rifampin (3R), 6H, 3 month of isoniazid and rifampin (3HR) and placebo control,[12] which showed that all three regimens were superior to placebo. 4R, with a treatment course one month longer than 3R, should be an effective LTBI treatment, although there is still lack of data on its efficacy in comparison with isoniazid-based regimens.[26] Since the present study was not designed for examining the comparative effectiveness between 4R versus 6H, further studies with a larger sample size and longer follow-up time might be required to provide a definite answer to this important question.

All of the eligible LTBI patients identified in the prison where this study was conducted were offered to join this study. Furthermore, 373 (90%) of the 416 eligible patients participated this study. There was no significant difference in characteristics between eligible people who agreed or declined to participate the present study (Appendix Table 2). This indicates that the results of the present trial should be generalizable to other male inmates in similar settings who met the eligible criteria of this study.

In conclusion, our study added to the evidence that 4 months daily rifampin has fewer AE than the standard 6 months daily isoniazid as treatment regimen for LTBI, even in a population with a high prevalence of HBV and HCV infections, such as prison inmates.

2.5 REFERENCES

1. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med 2004; 350: 2060–2067.
2. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. Adv Tuberc Res 1970; 26: 28–106.
3. International Union Against Tuberculosis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bulletin of the World Health Organization 1982; 60: 555–564.
4. Blumberg HM, Leonard MK Jr, Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis infection. JAMA 2005; 293: 2776–2784.
5. Chee CBE, Teleman MD, Boudville IC, Do SE, Wang YT. Treatment of latent TB infection for close contacts as a complementary TB control strategy in Singapore. Int J Tuberc Lung Dis 2004; 8: 226–231.
6. Chan PC, Huang LM, Suo JS. It is time to deal with latent tuberculosis infection in Taiwan. J Formos Med Assoc 2009; 108: 901–903.
7. Baussano I, Williams BG, Nunn P, et al. Tuberculosis incidence in prisons: a systematic review. PLoS Med 2010; 7: e1000381.
8. Centers for Disease Control and Prevention (CDC), National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Prevention and control of tuberculosis in correctional and detention facilities: recommendations from CDC. Endorsed by the Advisory Council for the Elimination of Tuberculosis, the National Commission on Correctional Health Care, and the American Correctional Association. MMWR Recomm Rep 2006; 55(RR-9): 1–44.

9. Spaulding AC, Weinbaum CM, Lau DT, et al. A framework for management of hepatitis C in prisons. Ann Intern Med 2006; 144: 762–769.

10. Jasmer RM, Saukkonen JJ, Blumberg HM, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 2002; 137: 640–647.

11. Lobato MN, Reves RR, Jasmer RM, et al. 2RZ Study Group. Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. Chest 2005; 127: 1296-1303.

12. Hong Kong Chest Service/British Medical Research Council. A double-blind placebo controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Am Rev Respir Dis 1992; 145: 36–41.

13. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med 2008; 149: 689–697.

14. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999; 52: 19–26.

15. National Cancer Institute. Common Terminology Criteria for Adverse Events, version 2.0. Accessed at http://ctep.info.nih.gov/reporting/ctc.html on 5 May 2011.

16. American Thoracic Society Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935–952.

17. Page KR, Sifakis F, Montes de Oca R, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. Arch

Intern Med 2006; 166: 1863–1870.

18. Sadaphal P, Astemborski J, Graham NM, et al. Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with Mycobacterium tuberculosis. Clin Infect Dis 2001;33: 1687–1691.

19. Crzemska DM, Coninx R, Reyes H. Guidelines for the control of tuberculosis in prisons. WHO/TB/98.250. Geneva: World Health Organization, 1998.

20. Fernández-Villar A, Sopeña B, Vázquez R, et al. Isoniazid hepatotoxicity among drug users: the role of hepatitis C. Clin Infect Dis 2003;36: 293–298.

21. Kunst H, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. Int J Tuberc Lung Dis 2010; 14:1374-1381.

22. Smith BM, Schwartzman K, Bartlett G, Menzies D. Adverse events associated with treatment of latent tuberculosis in the general population. CMAJ 2011;183:E173-179.

23. Trajman A, Long R, Zylberberg D, et al. Factors associated with treatment adherence in a randomised trial of latent tuberculosis infection treatment. Int J Tuberc Lung Dis 2010; 14: 551–559.

24. White MC, Tulsky JP, Reilly P, McIntosh HW, Hoynes TM, Goldenson J. A clinical trial of a financial incentive to go to the tuberculosis clinic for isoniazid after release from jail. Int J Tuberc Lung Dis 1998; 2: 506–512.

25. Nolan CM, Roll L, Goldberg SV, Elarth AM. Directly observed isoniazid preventive therapy for released jail inmates. Am. J. Respir. Crit. Care Med. 1997; 155**:** 583-586.

26. Ziakas PD, Karsaliakos P, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. Clin Infect Dis.

2009;49:1883-9.

2.6 FIGURES

Fig 1 Enrollment and outcomes.

4R: 4 months of daily rifampin therapy; 6H: 6 months of daily isoniazid therapy. "Not default, but patients stopped LTBI therapy before completion of the course" included "no adverse event, but patient stopped LTBI therapy before completion of the course", and "adverse event, physicians did not discontinue therapy, but patient stopped LTBI therapy before completion of the course". TST, tuberculin skin test; QFT-IT, QuantiFERON® -TB Gold In-tube.

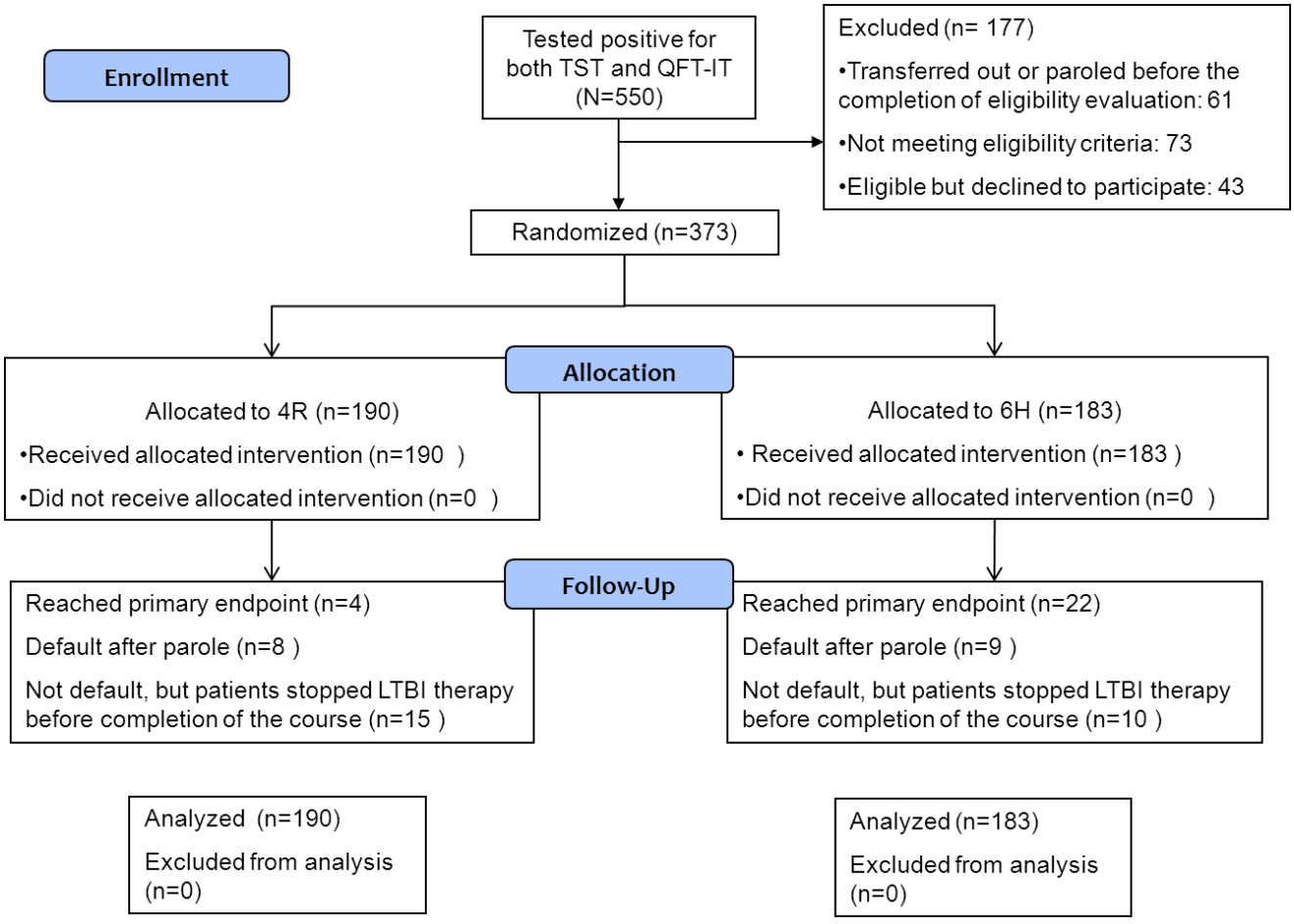
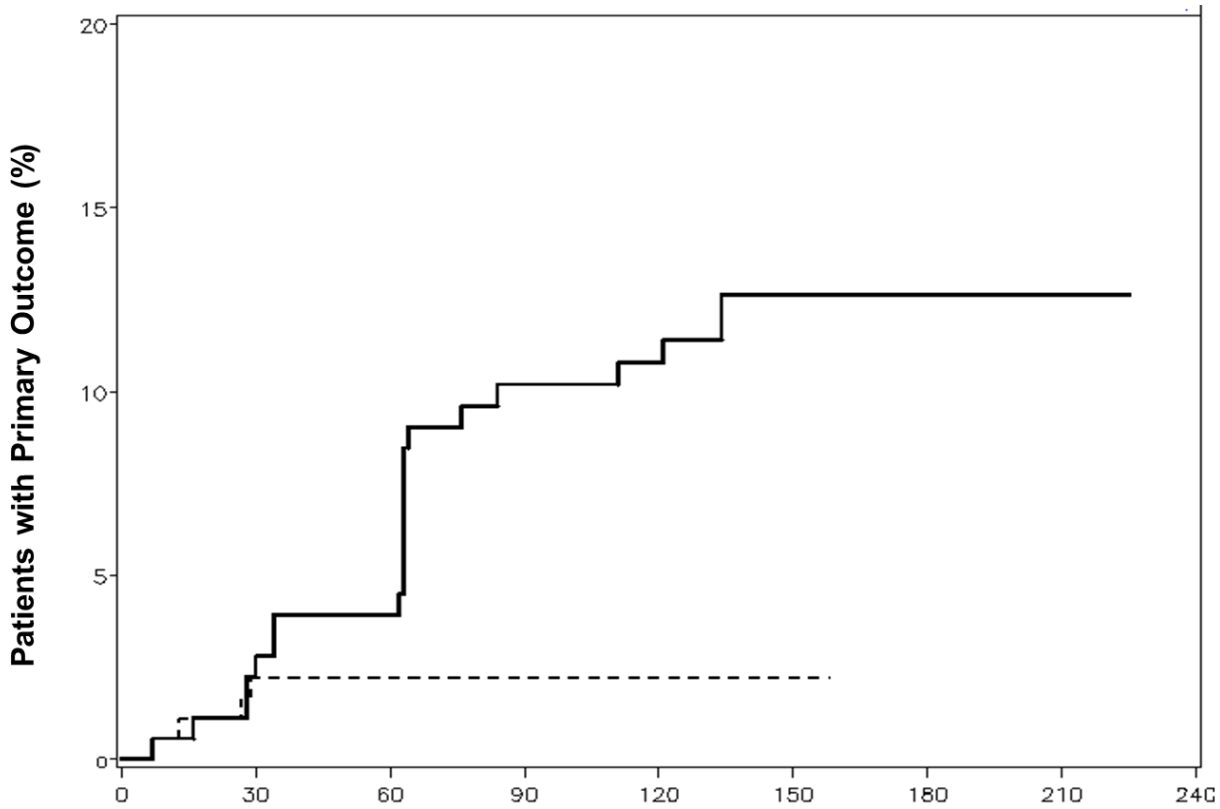


Fig 2 Kaplan-Meier analysis for the primary endpoint (any adverse event that resulted in discontinuation of LTBI therapy).

Dash line, 4 months of daily rifampin therapy; Solid line, 6 months of daily isoniazid therapy (p=0.001 by log-rank test; hazard ratio for 4R vs. 6H: 0.2 [0.1-0.6], p=0.003, by Cox regression model).



2.7 TABLES

Table 1 Baseline characteristics of 373 male inmates in Taiwan

Characteristics	4R group (n=190) n (%)	6H group (n=183) n (%)
Age		
18–24 years	4 (2)	10 (5)
25–34 years	42 (22)	47 (26)
35–44 years	73 (38)	59 (32)
45–65 years	64 (34)	60 (33)
> 65 years	7 (4)	7 (4)
Education		
< 13 years	107 (56)	114 (62)
≥ 13 years	83 (44)	69 (38)
Prison term		
6 months to 2 years	46(24)	42(23)
> 2 years	144(76)	141(77)
TST size		
10–14 mm	60 (31)	55 (30)
15–19 mm	98 (52)	102 (56)
≥ 20 mm	32 (17)	26 (14)
Chronic hepatitis virus infection		
HBsAg-positive	28 (15)	24 (13)
Anti-HCV-positive	42 (22)	38 (21)
Elevated baseline GPT *	39 (21)	39 (21)
Taking other medications	35 (18)	40 (22)

Diabetes mellitus	4 (2)	7 (4)
Medical problems other than diabetes	39 (21)	44 (24)
CXR calcification/problems other than TB	14 (7)	19 (10)

Abbreviations: 4R, 4 months of rifampin therapy; 6H, 6 months of isoniazid therapy; TST, tuberculin skin test; GPT: glutamic pyruvic transaminase; TB: tuberculosis; CXR: chest radiograph

* Baseline GPT > the upper limit of normal values (40 U/L).

Table 2 Causes of discontinuation and final outcomes in male inmates in Taiwan: 4R vs. 6H for treatment of latent tuberculosis infection

Categories	4R group (n=190) n (%)	6H group (n=183) n (%)	P value*
Reached primary endpoint (did not complete therapy, protocol-adherent)	4 (2)	22 (12)	<0.001
Grade 3 or 4 AE†			
Hepatotoxicity	0 (0)	11 (6)	<0.001
Numbness	0 (0)	2 (1)	0.240
Rash	2 (1)	2 (1)	1.000
Drug interaction	2 (1)	0(0)	0.499
Grade 2 AE‡			
Hepatotoxicity	0 (0)	4 (2)	0.057
Rash	0 (0)	2 (1)	0.240
Gastrointestinal intolerance	0 (0)	1 (1)	0.496
Did not complete therapy, not adherent to protocol	23 (12)	19 (10)	0.599
Default after parole	8 (4)	9 (5)	0.807
No AE, but patient stopped LTBI therapy before completion of the course	8 (4)	6 (3)	0.787
AE, physicians did not discontinue therapy, but patient stopped LTBI therapy before completion of the course	7 (4)	4 (2)	0.544
Complete therapy	163 (86)	142 (78)	0.041
No AE	102(54)	52 (28)	<0.001
AE, but never stopped therapy	58 (31)	81 (44)	0.006
AE, discontinued therapy temporarily and restarted			

Grade 2 hepatotoxicity	0(0)	6 (3)	0.013
AE other than hepatotoxicity	3 (2)	3 (2)	1.000

Abbreviations: 4R, 4 months of rifampin therapy; 6H, 6 months of isoniazid therapy; AE: adverse events.

* Pearson χ^2 for 2 × N tables or Fisher's exact test for 2 × 2 tables with small sample sizes.

† Classified by the type of AE that lead to permanent discontinuation of therapy

‡ Classified by the type of AE that recurred after temporary suspension and therefore lead to permanent discontinuation of therapy

Table 3 Comparison of treatment outcome between 4R vs. 6H for treatment of latent tuberculosis infection

Outcomes	4R group (n=190) n (%)	6H group (n=183) n (%)	P value*	Odds ratio (95% CI)	
				Unadjusted	Adjusted†
Primary outcome (any adverse event led to permanent discontinuation of therapy)	4 (2)	22 (12)	<0.001	0.16 (0.05-0.47)‡	0.15 (0.05-0.46)‡
Secondary outcome (any cause led to permanent discontinuation of therapy)	27 (14)	41 (22)	0.041	0.57 (0.34-0.98)‡	0.56 (0.32-0.97)‡

Abbreviations: 4R, 4 months of daily rifampin therapy; 6H, 6 months of daily isoniazid therapy.

* Pearson χ^2 for 2 × 2 tables or Fisher's exact test for 2 × 2 tables with small sample sizes. ‡ Statistically significant ($p<0.05$)

†Adjusting for the effects of HBsAg, anti-HCV, age ≥35 years, and prison term >2 year with logistic regression models.

Table 4. Logistic regression analysis for risk factors of primary and secondary endpoints

Covariates	Primary outcome (any adverse event led to permanent discontinuation of therapy)		Secondary outcome (any cause led to permanent discontinuation of therapy)	
	Univariate Analysis Unadjusted OR (95%CI)	Multiple Regression Analysis Adjusted OR (95%CI)	Univariate Analysis Unadjusted OR (95%CI)	Multiple Regression Analysis Adjusted OR (95%CI)
4R group†	0.16 (0.05-0.47) *	0.15 (0.05-0.46) *	0.57 (0.34-0.98) *	0.56 (0.32-0.97) *
HBsAg(+)	0.50 (0.11-2.16)	0.48 (0.11-2.18)	0.79 (0.35-1.77)	0.72 (0.31-1.66)
anti-HCV(+)	2.47 (1.08-5.69) *	2.90 (1.18-7.10) *	2.04 (1.14-3.65) *	1.81 (0.98-3.34)
age ≥35 years	0.59 (0.26-1.34)	0.78 (0.33-1.85)	0.76 (0.43-1.34)	0.86 (0.48-1.55)
prison term >2 year	1.32 (0.48-3.61)	1.62 (0.56-4.68)	0.38 (0.22-0.67) *	0.40 (0.22-0.70) *

Abbreviations: 4R, 4 months of daily rifampin therapy; 6H, 6 months of daily isoniazid therapy; OR: odds ratio

* Statistically significant ($p<0.05$)

†The reference is 6H group.

Table 5. Risk of hepatotoxicity that resulted in discontinuation of LTBI therapy among subgroups in male inmates in Taiwan

	4R (n=190)	6H (n=183)
HBsAg- and anti-HCV-negative		
Age <35 years	0/31	1/38 (3%)
Age ≥ 35 years	0/97	4/89 (4%)
HBsAg-positive alone		
Age <35 years	0/3	0/2
Age ≥ 35 years	0/17	0/16
Anti-HCV-positive alone		
Age <35 years	0/10	3/14 (21%)
Age ≥ 35 years	0/24	5/18 (28%)
Anti-HCV- and HBsAg-positive		
Age <35 years	0/2	1/3 (33%)
Age ≥ 35 years	0/6	1/3 (33%)

Abbreviations: 4R, 4 months of rifampin therapy; 6H, 6 months of isoniazid therapy

2.8 APPENDIX TABLES

Appendix Table 1 Grading system for adverse events†

Grading based on different types of adverse events

Hepatotoxicity*	
Grade 0	GPT levels within normal limits
Grade 1	GPT levels increased from within normal limits to 1–3 times the upper limit of normal values
Grade 2	GPT levels 3–5 times the upper limit of normal values without symptoms
Grade 3	GPT levels 3–10 times the upper limit of normal values with hepatitis-related symptoms or GPT levels 5–10 times the upper limit of normal values without symptoms
Grade 4	GPT levels >10 times the upper limit of normal values
Rash	
Grade 1	Itching only or limited to limbs, trunk, or face only; no abnormality of vital signs and no mucosal or conjunctival involvement
Grade 2	Rash affects limbs and trunk or more than 50% of total body surface area or rash is confluent in areas
Grade 3	Rash affects 100% of body surface area or mucus membranes, conjunctivae are affected, vital signs are abnormal (fever or low blood pressure), or there is wheezing
Gastrointestinal discomfort	
Grade 1	Some stomach upset with nausea or loss of appetite, but no vomiting and no change in bowel habits
Grade 2	Nausea with some vomiting, abdominal pain that is severe enough to disturb daily routine, or persistent diarrhea
Grade 3	Protracted nausea and vomiting or severe abdominal pain that disrupts daily life, severe diarrhea (≥ 5 times bowel movements per day)

Drug interaction	
Grade 0	No potential drug interactions (or no other medications)
Grade 1	Potential drug interaction noted, but no change in therapy required and neither short- nor long-term effect detected
Grade 2	Potential drug interaction is noted, but after an initial change in therapy, no further problems and therapy does not have to be changed
Grade 3	Drug interaction noted and therapy has to be modified repeatedly; LTBI therapy must be discontinued.

*Abbreviations: GPT, glutamic pyruvic transaminase. LTBI, latent tuberculosis infection

† Modified from the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0.[15]

* The GPT level was graded as the recommended grading of the American Thoracic Society.[16]

Appendix Table 2 Baseline characteristics of the 43 eligible male inmates who refused to participate, in compared with 373 eligible male inmates who participated the randomised control trial.

Characteristics	Non-participants (n=43) n (%)	Participants (n=373) n (%)	P value
Age			0.827
18–24 years	1 (2)	14 (4)	
25–34 years	10 (23)	77 (21)	
35–44 years	16 (37)	117 (31)	
45–65 years	13 (30)	123 (33)	
> 65 years	3 (7)	42 (11)	
Prison term shorter than 9 months	2(5)	24(6)	1
Education			
≥ 13 years	23(53)	152 (41)	0.1091
Chronic hepatitis virus infection			
HBsAg-positive	10(23)	52 (14)	0.104
Anti-HCV-positive	12(28)	80 (21)	0.335
Diabetes mellitus	0(0)	11 (3)	0.614
CXR calcification/problems other than TB	3(7)	32 (9)	1

* Non-participants vs. Participants. Pearson χ^2 for 2 × N tables or Fisher's exact test for 2 × 2 tables with small sample sizes.

Chapter 3 Risk for Tuberculosis in Child Contacts: Development and Validation of a Predictive Score

3.1 INTRODUCTION

Persons exposed to infectious tuberculosis (TB) are at risk for subsequent development of active TB disease (1). Contact investigation has a pivotal role in TB control through the identification and treatment of linked active TB cases to interrupt the chain of TB transmission, as well as the identification and the provision of isoniazid preventive therapy (IPT) for people that have latent TB infection (LTBI) to avert the subsequent development of active TB diseases (2).

Contact investigation is resource intensive. Because of limited resources, investigators need to assign priorities by weighting many index cases and contact characteristics that are associated with an increased risk for TB infection or diseases, at times in the absence of complete data (3,4). Until now, there is no evidence-based clinical prediction rules that can help to stratify contacts at different risks for active TB and to ensure the timely identification of those at high risk for whom vigorous radiologic follow-ups or LTBI diagnosis and treatment are most urgently needed (5). Such a prediction rule would be especially useful in settings with large numbers of contacts who need to be assessed simultaneously.

Taiwan is a middle-burden country with an annual TB incidence at around 70 per 100,000 people from 1997 to 2005 (6). The TB control effort has been intensified since 2006, with the launch of national Directly Observed Therapy (DOT) program for all identified TB patients (7). Since 2008, IPT was freely provided to all child contacts with LTBI discovered during contact investigation (8,9). To facilitate uniformly high-quality contact investigation, the present study aimed to develop and validate a simple and easy-to-use predictive score (10) based on data routinely available during contact investigation for the purpose of prioritizing active case-finding

and IPT among contacts aged 0-12 years.

Some of the results of these studies have been accepted in the form of an abstract in the poster discussion session of the 44th IUATLD annual conference and will be reported to attendees on November 3, 2013 in Paris (11).

3.2 METHODS

3.2.1 Study Design

This was a retrospective cohort study based on nationwide public health surveillance and follow-up data. We first developed a predictive scoring system using a development cohort. The predictive scores were then evaluated using an independent validation cohort. In Taiwan, two national contacts cohorts (Year 2005 [pre-IPT era] and Year 2008-2009 [IPT era]) have been systematically followed for developing active TB disease. The characteristics and follow-up results of the 2005 cohort have been previously described (12, 13). In the present study, we used 2008-2009 contacts cohort to develop the predictive score and used 2005 cohort for validation. This project was reviewed by the Taiwan Centers for Diseases Control (Taipei, Taiwan) and approved as public health surveillance, which is exempt from human subject review and does not require informed consent.

3.2.2 Settings

We obtained data on TB cases and contacts from Taiwan National Surveillance Network of Communicable Disease (NSNCD), which is a centralized, internet-based TB case management system. TB cases must be reported within 7 days of diagnosis, with information registered into NSNCD (14). Contact investigation is also mandatory by law. Since 2008, all contagious index

cases' close child contacts (aged younger than 13 years) were routinely tested for LTBI, using tuberculin skin test (TST) (15), and all identified child LTBI cases were given IPT by directly observed therapy (14). Since April 2012, the IPT-DOT program has been expanded to contacts aged 13 to 25 years in household, school and congregate settings if the index case is smear- and culture-positive for TB (16).

3.2.3 Contact Investigation and LTBI Treatment

he contact investigations are conducted by public health officials at township levels within 30 days of a TB diagnosis (14). The household family members are the main targets. The contact investigations are also routinely conducted in the congregate settings, such as schools, healthcare facilities and prisons (14). The contacts receive clinical and chest radiographic evaluations to rule out active TB at outpatient clinics in hospitals or public health station clinics (14, 17). For contacts under 13 years of age, a TST is performed using a cutoff point of 10 mm (17). Those children with a positive TST without clinical symptoms/signs of TB and with a normal chest radiograph are considered for LTBI treatment after evaluation (17). Prophylaxis was offered to young children less than 5 years regardless of their initial TST reading to cover the window period (14). We did not routinely offer prophylaxis for children aged 5–15 years in whom the initial TST was negative. Those with initial TST <10 mm underwent repeat TST 2-3 months after the last exposure to the infectious index case. Prophylaxis was discontinued if the TST remained <10 mm or continued to 9 months if the TST reading increased to ≥10 mm (17). The medication and dosage for IPT was Isoniazid 10mg/kg once daily (max. 300mg), either for prophylaxis or LTBI treatment (17).

3.2.4 Development Cohort

To develop the risk score, all contact children under 13 years of age who received a TST from April 2008 to September 2009 (a period of 18 months) were included as the development cohort. Figure 1 shows the flowchart of follow-up and IPT, which included 9,411 contacts and their 4,511 index cases. An index case was defined as the latest reported TB case linked to the contacts.

3.2.5 Validation Cohort

To validate the risk score, all child contacts under 13 years of age who received TST from January 2005 to December 2005 were included as the validation cohort, which consisted of 2405 contacts and 1130 index cases (12). The definition of index cases was the same as that for the development cohort. No IPT policy was implemented back to year 2005 when the validation cohort was collected.

3.2.6 Characteristics of the Index Cases and Contacts

Data on the characteristics of the index cases and contacts were obtained from the NSNCD system, including age, gender of both the contacts and index cases, areas where the index cases lived (high incidence areas or not), relationship between the contacts and index cases (household or not), results of an acid-fast stain smear test, mycobacteria culture of the sputum, manifestation of the chest radiograph (cavitation or not) from the index cases and TST results of the contacts (only the first TST was included) (Table 1, 2 and appendix Table). The high incidence areas are the 30 administrative townships serving as protected areas for aboriginal peoples in Taiwan. The incidence of TB in these areas was 277.1 / 100,000 (65.3-435.1) in 2011, which was five times more than the

incidence of Taiwan (54.5/100,000) (18). The Bacillus Calmette-Guérin (BCG) immunization records of the contacts were obtained from the National Immunization Information System.

3.2.7 Follow-up

Since medical and public health interventions could be taken only after the identification of index cases, we used the notification date of the index case related to a contact as the start time point, except for the rare scenario when the contact had a TST performed several days before the notification date of his/her index case. In such scenario, the TST date was designated as the start time point. For the development cohort, the end date of follow-up was October 7, 2011. For the validation cohort, the end date of follow-up was December 31, 2010. The endpoint of event-free time could be earlier than the end date of follow-up, including the following: the date on which the contact was notified as an active TB case (event), the date of the commencement of IPT (for LTBI) in a contact (censored), or the date of mortality due to any cause (censored).

3.2.8 Ascertainment of Outcome

Whether a contact developed active TB during follow-up was ascertained using national TB notification registry till October 7, 2011. All notified TB cases, including smear-negative and extra-pulmonary TB case, were included as the endpoint. The characteristics of those notified were obtained by reviewing medical records. The survival status of the contacts was also ascertained using Department of Health census database. The ascertainment of active TB and survival for the validation cohort was the same as that for the development cohort.

3.2.9 Development of Scores

The development of the risk score comprised two steps. First, a Cox proportional hazards model was used to analyze the risk predictors for developing active TB among the development cohort. Second, the regression coefficient in the final model for each risk predictor was divided by the regression coefficient for the gender of the index case before it was rounded to an integer value to generate the risk score.

3.2.10 Validation of Scores

The sensitivity and the specificity of the predictive scores in identifying those contacts who developed active TB was evaluated using the receiver operating characteristic (ROC) curves. We calculate the area under ROC curves (AUROC). The AUROC of the development cohort and the validation cohort were compared.

3.2.11 Predicted Risk of TB

Because the date of starting IPT was considered as censored in the time-to-event analysis, we can use Kaplan-Meier method to estimate the risk for the contacts in each risk score (range: 0–7) to develop active TB within 3 years if IPT were not given. We then used this predicted risk to estimate the number of active TB cases that would have occurred within 3 years if no IPT had been given to the contacts.

3.2.12 Number Needed to Treat

For each risk score (range: 0–7), we estimated the number of contacts needed to be treated (NNT)

with IPT to avert one active TB case, under the following two assumptions: (1) active TB cases occurred within 3 months were already active at the start time point, and therefore were not avertable; and (2) IPT had an 93% efficacy in averting the progression from LTBI to active TB (19). The NNT for each risk score was therefore calculated by the following formula:[(Predicted number of active TB cases that would have occurred within 3 year if no IPT had been given to the contacts) – (Actual number of active TB cases that occurred within 3 months)] divided by [(Total number of contacts with the risk score) – (Actual number of active TB cases that occurred within 3 months)], then further divided by 0.93 considering with IPT efficacy.

3.2.13 Statistical Analysis

All analyses were conducted using the SAS version 9.2 software package (SAS Institute, Cary, North Carolina). Stepwise procedure was used for model selection during multivariate regression analysis. $P < 0.05$ was considered statistically significant.

3.2.14 Role of the Funding Source

The funding source for this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

3.3 RESULTS

3.3.1 Baseline Demographic data

Table 1 and Table 2 shows the characteristics of the 9411 contacts and 4511 index TB patients in

the development cohort. Ninety-eight percent of the child contacts had received BCG vaccination. The contacts that developed active TB disease (n=27) had a larger TST induration ($P < 0.001$). The index cases (n=17) whose contacts developed active TB disease had a higher proportion of positive sputum smear (76% vs. 50%), cavitation (47% vs. 23%), residence in high incidence area (47% VS. 6%,) and relapse (29% vs. 7%) (all *Ps* <0.05). There was no significant difference in characteristics of contacts and index cases between the development cohort and validation cohort (appendix Table).

3.3.2 Follow-up and Outcome

Twenty-seven contacts in the development cohort and eight contacts in the validation cohort developed active TB during follow-up (27/9411 [0.28%] vs. 8/2405 [0.33%], P =0.676, Fisher's Exact test). All of them completed anti-TB treatment and no mortality was noted. For eight TB cases in the validation cohort which has been partially described before (11), the median age was 6.4 years-old (3.0-10.9) and male to female was 1:7. One of them was diagnosed as bone and joint TB without lung involvement and four with bacteriology confirmation (one smear-positive only, one smear-positive plus culture-positive and the other two with smear-negative and culture confirmation). Among those 4, the only boy was diagnosed with TB meningitis, military TB, peritonitis and mediastinal lymph adenitis. For twenty-seven TB cases in the development cohort, the median age was 10.2 years-old (1.7-14.1) and male to female was 11:16. Four of them were diagnosed extra-pulmonary TB without lung involvement (2 mediastinal lymphadenitis, 1 submandibular lymphadenitis, 1 pleural effusion). Among the 23 pulmonary TB cases, twelve with bacteriology confirmation (all culture-positive confirmation and 3 smear-positive) and three had extra-pulmonary components. Nine contacts in the development cohort died during the follow-up

from the following direct causes of death: 3 from suffocation, 1 from septic shock, 2 from acute respiratory failure, 1 from heart failure, 1 from cardiopulmonary failure and 1 for whom the autopsy result is pending. None of the contacts died with active TB.

3.3.3 Development of Risk Score

Table 3 shows the final model of multivariate Cox regression analysis for risk factors of development of active TB in 9411 contacts of the development cohort (Proportional hazards assumption test, *P*=0.919). The independent risk predictors included TST size of the contacts (risk score 0: < 10 mm; 2: 10-14 mm; 3: 15-19 mm; 4: ≥ 20 mm), as well as smear-positivity of (risk score 1), residence in high incidence areas (risk score 2) and female genders (risk score 1) of the index cases. The overall scores for each contact can range from 0 to 8.

3.3.4 Validation of Risk Score

Figure 2 shows the ROC curves for the overall score in the development cohort (AUROC: 0.872, 95% CI: 0.810-0.935) and each of its items, including TST size (AUROC: 0.803, 95% CI: 0.711–0.894), the smear result of the index TB patient (AUROC: 0.633, 95% CI: 0.549–0.718), the residence of the index TB patient (AUROC: 0.715, 95% CI: 0.619–0.811) and the gender of the index patient (AUROC: 0.601, 95% CI: 0.505–0.696). Figure 3 shows the ROC curves for the overall score in the validation cohort (AUROC: 0.900, 95% CI 0.830 –0.969) and each of its items. There is no significant difference in AUROC of the overall score in the validation cohort and that in the development cohort (*P*=0.841).

3.3.5 Risk of Developing Active TB Disease

Figure 4 shows the predicted risk for developing active TB in contacts in the development cohort if no IPT were given. For example, a contact with a TST induration of 16 mm (score=3) after exposed to a female index case (score=1) who was smear-positive (score=1) and resided in an high incidence area (score=2) would have an overall risk score of 7, with a predicted TB risk of 0.3 at 6 months, 0.3 at 1 to 2 years and 1.0 at 3 years. The predicted score could stratify child contacts at different TB risk in both 0-4 and 5-13 age groups (Figure 5).

3.3.6 Number Needed to Treat

Table 3 shows that a total of 63 active TB cases would have occurred in the development cohort within 3 years if no IPT was given, in contrast to the observed 26 cases within 3 years when IPT was actually provided. The NNT for IPT to avert one active TB case during the 3-year follow-up was 1, 18, 30, 147, 263 and 1765 for contacts with risk scores of 7, 6, 5, 4, 3 and 2, respectively.

3.4 DISCUSSION

We successfully developed a predictive score for TB risk among contacts by analyzing the follow-up data of Year 2008-2009 nationally registered cohort of child contacts. The 8-point score was validated with the follow-up data of Year 2005 national contact cohort. The predictive score integrated routinely collected data in contact investigations by public health nurses, such as TST results of the contacts, smear-positivity of the index cases, and residence and genders of the index cases, in a systematic and ease-to-use way. Based on this simple and basic information, this score can effectively stratify child contacts with different risks of developing active TB, and thus help to identify high-risk child contacts for whom vigorous radiologic follow-ups as well as IPT are most urgently needed.

In the present study, the induration size of TST was an important risk factor for active TB among contacts. The association between TST induration size and TB disease risk among child contacts has been well documented (20). This association is also in agreement with the previous finding that an increased level of interferon-gamma release assays (IGRAs) predicts a higher risk of developing TB disease (21). Compared with TST, IGRA was considered to be more specific for LTBI diagnosis in populations with wider BCG vaccination coverage (22). However, IGRA is currently not routinely used for contact investigation due to many practical issues, including requirement for phlebotomy, laboratory facilities and training, debates about cutoff values and the relatively high cost of using IGRA (30-60 USD) compared to the 1-2 USD cost of using TST (23). Our results highlighted that, even in populations with high BCG vaccination coverage such as Taiwan, the easy-to-perform and inexpensive TST results can be successfully used to predict risk of TB diseases among child contacts when the information on the size of TST induration and other risk factors were combined into a predictive score.

Child contacts aged younger than 5 years had been reported to have a significantly higher risk

of developing active TB (24). Nevertheless, age less than 5 years was not a risk factor for TB in our study. Among the 27 child contacts that developed TB disease during the follow-up, the proportion of those aged younger than 5 years was not higher than those did not develop TB (19% vs. 28%, P=0.258) (Table 1). In Taiwan, the coverage of BCG immunization in infancy is universal. Ninety-eight percent of the child contacts in the present study had received BCG vaccination (Table 2). Furthermore, childhood measles is now nearly eliminated in Taiwan (25). The increased risk of tuberculosis after measles has been observed since 1930s, which was believed to be linked to the measles-induced suppression of cell-mediated immunity (26, 27). The combination of the protective effect of universal BCG and measles elimination may explain the observation that the incidence of developing TB in child contacts aged younger than 5 years was not higher than elder children in our cohort (28).

It has been well documented that populations residing in high incidence areas in Taiwan have a much higher burden of TB than general population of ethnic Han Chinese (29). Indigenous populations comprised up to 34-98% of the population in these high incidence areas. A comparison of TB incidence rates between high incidence areas and non-high incidence area revealed a 2.0-2.8 times higher risk between 1996 and 2006 (30), mainly due to the children living in the high incidence areas bear even higher relative risk compared to children living in non-high incidence areas, with up to 11-17 times the risk among children aged younger than 15 years (31). A study on TST results of aboriginal children in Eastern Taiwan also revealed that exposure to infectious TB continued to increase with age till young adulthood in this population (32). In addition to possible genetic factors, lower socio-economic status, housing, time spent indoors in crowded circumstances in poorly ventilated dwellings, poor access to medical care might also be the reasons (33, 34). Nevertheless, by the Indigenous Peoples Basic Law, utilizing data of indigenous peoples for research required the approval and participation of indigenous peoples (35). Because we did not have the access to the ethnic information of the child contacts and the index cases, we used

addresses in aboriginal areas as a surrogate for aboriginal ethnicities. Our results showed that residence of the index case in high incidence area was indeed an important predictor for active TB disease (risk score = 2) for the child contacts.

Female index cases posed a higher risk of developing TB disease in child contacts in our study. Many studies have investigated demographic factors that influence the risk of LTBI in child contacts, including the number of index patients in the household; proximity to the case patient (i.e., in the same bed vs. in the same room, household vs. not a household); relationship of the index patient as parents to contacts; older ages of the contacts; contacts without a BCG scar; a smaller household size; and a longer cough duration of the index cases (34, 36, 37). In Taiwan, female index cases were most likely the mother, the grandmother or the important caregivers of the child contacts. The higher proximity and even parenting relationship may explain the significantly higher risk of developing active TB for the child contacts whose index cases were of female gender.

It was not surprising for child contacts in developed West-Pacific countries with national DOTS and IPT programs to have a much lower TB rate compared to those in high-burden South-Eastern Asian countries. In contrast to the 3-10% TB rates observed in India, Indonesia and Philippines (38), investigators in Hong Kong reported a merely 0.58% (4/692) TB rate for 5-year follow-up (39), similar to the 0.3% TB rate for 3-year follow-up in our study. It is noteworthy that the public health service in Taiwan routinely actively follow-up all child contacts with yearly CXR for at least one year since 2001. Furthermore, the coverage rate of National Health Insurance in Taiwan reached 98% of total population (92% of people living in high incidence areas), which ensured nearly all child contacts, including those from low socio-economic families and high incidence areas, have free access to medical evaluation and management once they developed symptomatic TB.

No HIV test was routinely provided to contacts in our cohort. Overall, a very low prevalence

of HIV among child bearing mothers (11/100,000 in 2005, peaked in 2006 with rate of 16/100,000 and down to 3/100,000 in 2007 and after) was observed from active surveillance among pregnant women with a coverage of 95%-99% during 2006 to 2008 (40). Preventing mother to child transmission (PMTCT) was conjugated with HIV screening program since 2005.

Our study did have certain limitations. Theoretically, the results of the second TST might provide additional information on the risk of subsequent development of active TB. However, since the purpose of the present investigation is to develop a simple and easy-to-use predictive score for prioritizing active case-finding and IPT at the time of initial contact investigation, we therefore only include the first TST in the analyses. Besides, the accuracy of predicting TB risk might be further improved by including clinical presentations of the child contacts during initial contact investigation. However, since clinical data of contacts is not registered to NSNCD (14), we did not have the access to these information. Even so, our results shows that it is feasible to use basic epidemiologic data routinely available for public health nurses to construct a highly effective risk scoring system to guide the contact investigation and the subsequent medical interventions.

In conclusion, an 8-point risk-score for identifying child contacts at increased risk for TB was successfully developed and validated. This predictive score can help to prioritize the active case-finding or LTBI treatment among children exposed to TB.

3.5 REFERENCES

1. Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med* 2012;367:348-361.
2. National Tuberculosis Controllers Association; Centers for Disease Control and Prevention (CDC). Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR Recomm Rep* 2005:16;54(RR-15):1-47.
3. Comstock GW. Frost revisited: the modern epidemiology of tuberculosis. *Am J Epidemiol* 1975;5:363–382.
4. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974;99:131–138.
5. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004; 350: 2060–2067.
6. Lo HY, Chou P, Yang SL, Lee CY, Kuo HS. Trends in tuberculosis in Taiwan, 2002-2008. *J Formos Med Assoc* 2011;110:501-510.
7. Bloss E, Chan PC, Cheng NW, Wang KF, Yang SL, Cegielski P. Increasing directly observed therapy related to improved tuberculosis treatment outcomes in Taiwan. *Int J Tuberc Lung Dis* 2012;16:462-467.
8. Chan PC, Yang CH, Chang FY. Scaling up of latent tuberculosis infection treatment for close contacts of tuberculosis in Taiwan. *J Formos Med Assoc* 2011;110:733-736.
9. Chan PC, Chiou MY, Wang KF, Yang CH, Fang CT. Engaging all TB care providers to implement isoniazid preventive therapy nationwide. *Int J Tuberc Lung Dis* 2011;11:S295-296.
10. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011;12:568-574.

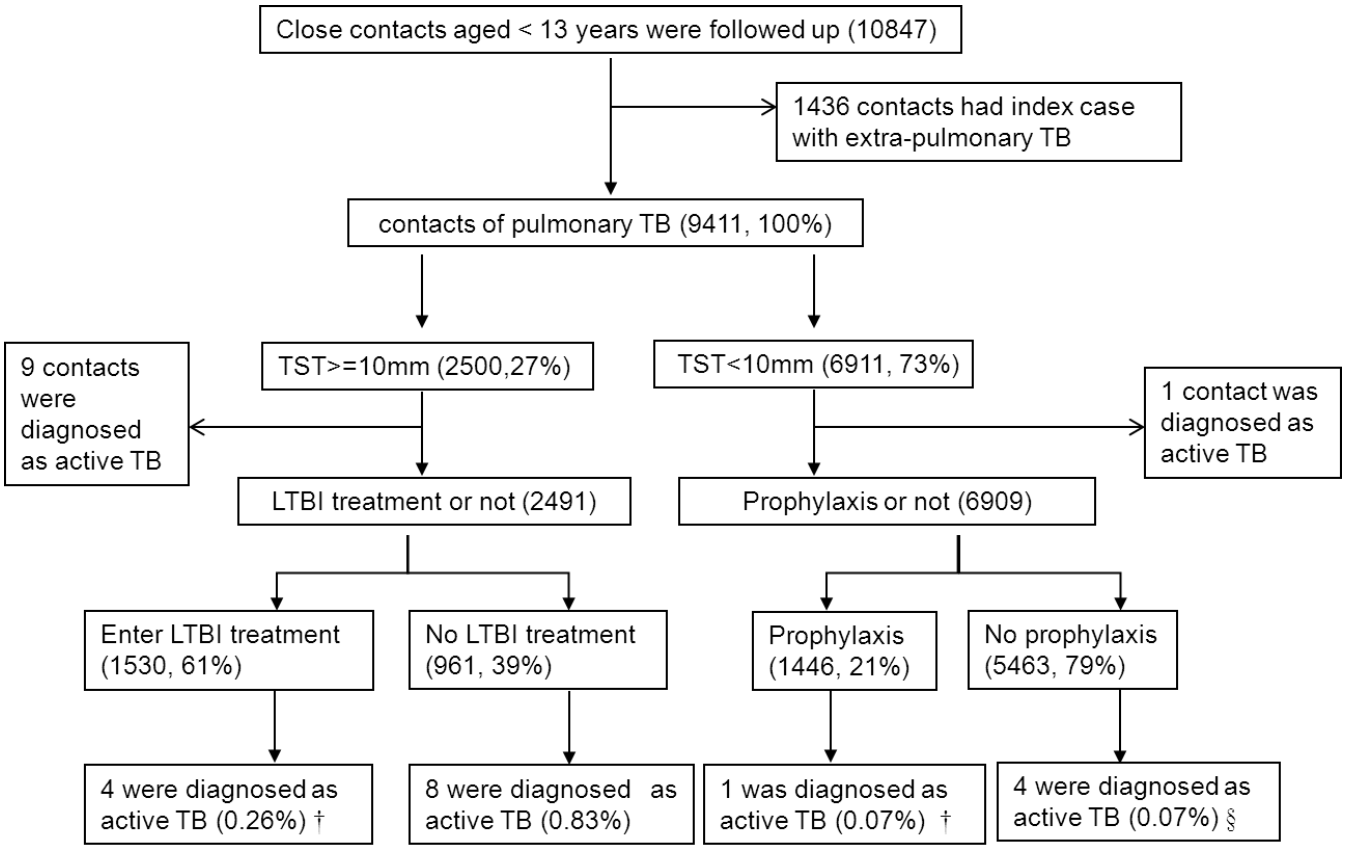
11. Poster discussion PC-824-03 will be presented in the 44th Union World Conference in Paris, France. November 3, 2013.
12. Ling DL, Liaw YP, Lee CY, Lo HY, Yang HL, Chan PC. Contact investigation for tuberculosis in Taiwan contacts aged under 20 years in 2005. *Int J Tuberc Lung Dis* 2011;15:50-55.
13. Ling DL, Liaw YP, Lo HY, Lee CY, Wang KF, Yang HL, Chan PC. Tuberculosis contact investigation in Taiwan: a 5-year follow-up study. Thoracic Med 2011; 26(Suppl):FA04.
14. Centers for Disease Control, Department of Health. Manual for Tuberculosis Control. Taipei, Taiwan: CDC. Available at: http://www2.cdc.gov.tw/ct.asp?xItem=5711&ctNode=1540&mp=230
15. Chan PC, Huang LM, Suo J. It is time to deal with latent tuberculosis infection in Taiwan. *J Formos Med Assoc* 2009;108:901-903.
16. Lee PH, Chang FY. Latent infection treatment to prevent TB transmission in school settings. *J Formos Med Assoc* 2012;111:525-526.
17. Centers for Disease Control, Department of Health. Taiwan Guidelines for TB Diagnosis & Treatment. 3rd edition. Taipei, Taiwan: CDC 2008. Available at: http://www.cdc.gov.tw/infectionreportinfo.aspx?treeid=075874dc882a5bfd&nowtreeid=8dba723ff186fac0&tid=778876767EA9B06C
18. Centers for Disease Control, Department of Health, R.O.C. (Taiwan). Taiwan Tuberculosis Control Report 2012. Taipei, Taiwan: CDC 2012. Available at: http://www.cdc.gov.tw/professional/infectionreportinfo.aspx?treeid=56CA56252A0FA705&nowtreeid=D538638F3B6E9418&tid=2E3ABF0F44B82D24
19. Veening GJJ. Long term isoniazid prophylaxis. Controlled trial on INH prophylaxis after recent tuberculin conversion in young adults. *Bull Int Union Tuberc* 1968; 41: 169-71.
20. Pediatric Tuberculosis Collaborative Group. Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents. Pediatrics 2004;114:1175–1201.

21. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, et al. Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. *Eur Respir J* 2011; 37: 88–99.
22. Chan PC, Yang CH, Chang LY, Wang KF, Kuo YC, Lin CJ, et al. Lower prevalence of tuberculosis infection in BCG vaccinees: a cross-sectional study in adult prison inmates. *Thorax* 2013;68:263-268.
23. Abubakar I, Stagg HR, Whitworth H, Lalvani A. How should I interpret an interferon gamma release assay result for tuberculosis infection? Thorax 2013;68:298-301.
24. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013;41:140-156.
25. Lee MS, Nokes DJ. Predicting and comparing long-term measles antibody profiles of different immunization policies. *Bull World Health Organ* 2001;79: 615-24.
26. Duke T, Mgone CS. Measles: not just another viral exanthem.
27. *Lancet* 2003;361:763-73. Karp CL. Measles: immunosuppression, interleukin-12, and complement receptors. *Immunol Rev* 1999; 168: 91-101.
28. Soysal A, Millington KA, Bakir M, Dosanjh D, Aslan Y, Deeks JJ, et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005; 366: 1443-1451.
29. Yu MC, Bai KJ, Chang JH, Lee CN. Tuberculosis incidence and mortality in aboriginal areas of Taiwan, 1997–2001. *J Formos Med Assoc* 2004;103:817–823.
30. Chang YM, Shen CK, Chiu CH, Chiang HJ, Lu LC, Liou SH. Burden of tuberculosis among aboriginal and non-aboriginal Taiwanese, 1996-2006. *Int J Tuberc Lung Dis* 2011;15:471-477.
31. Chan PC, Huang LM, Wu YC, Yang HL, Chang IS, Lu CY, et al. Tuberculosis in children and adolescents, Taiwan, 1996-2003. *Emerg Infect Dis* 2007;13:1361-1363.

32. Bowerman RJ. Tuberculin skin testing in BCG-vaccinated populations of adults and children at high risk for tuberculosis in Taiwan. *Int J Tuberc Lung Dis* 2004;8:1228-1233.
33. Bloss E, Holtz TH, Jereb J, Redd JT, Podewils LJ, Cheek JE, et al. Tuberculosis in indigenous peoples in the U.S., 2003-2008. *Public Health Rep* 2011;126:677-89.
34. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. *Pulm Med* 2013;2013:828939. Epub 2013 Feb 12.
35. The Indigenous Peoples Basic Law. Available at: http://law.moj.gov.tw/LawClass/LawSingle.aspx?Pcode=D0130003&FLNO=22.
36. Lienhardt C, Sillah J, Fielding K, Donkor S, Manneh K, Warndorff D, et al. Risk factors for tuberculosis infection in children in contact with infectious tuberculosis cases in the Gambia, West Africa. *Pediatrics* 2003;111:e608-614.
37. Roy RB, Sotgiu G, Altet-Gómez N, Tsolia M, Ruga E, Velizarova S, et al. Identifying predictors of interferon-γ release assay results in pediatric latent tuberculosis: a protective role of bacillus Calmette-Guerin?: a pTB-NET collaborative study. *Am J Respir Crit Care Med* 2012;186:378-384.
38. Triasih R, Rutherford M, Lestari T, Utarini A, Robertson CF, Graham SM. Contact investigation of children exposed to tuberculosis in South East Asia: a systematic review. *J Trop Med* 2012;2012:301808. doi: 10.1155/2012/301808. Epub 2011 Nov 15.
39. Lee MSN, Leung CC, Kam KM, Wong MY, Leung MSM, Tam CM, et al. Early and late tuberculosis risks among close contacts in Hong Kong. *Int J Tuberc Lung Dis* 2008;12:281-87.
40. Liu PL, Lai AC, Huang YF, Yang CH. Research on the hidden space of mother-child vertical transmission of HIV－the pregnant women with high risk outside the medical network. *Taiwan Epidemiology Bulletin* 2009;25:754-761.

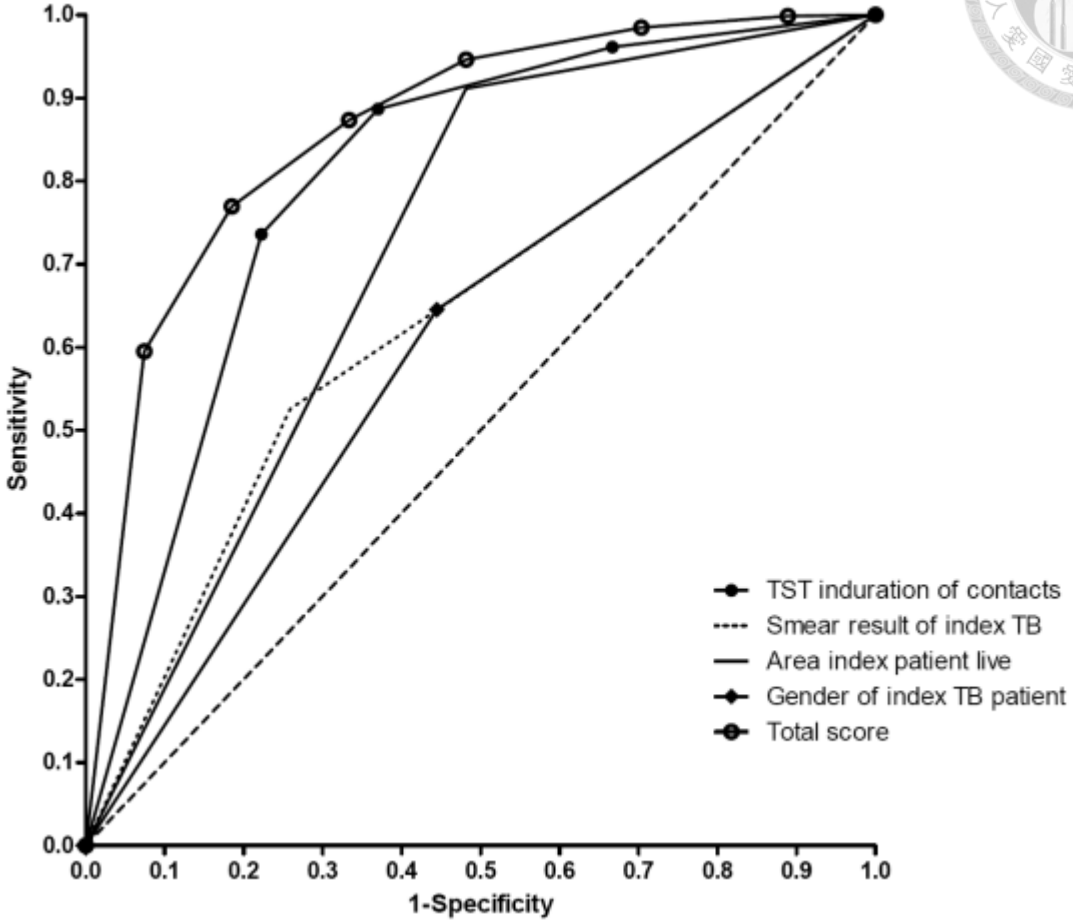
3.6 FIGURES

Fig1 Flowchart of follow-up and LTBI treatment for the 9411 contacts in the development cohort.



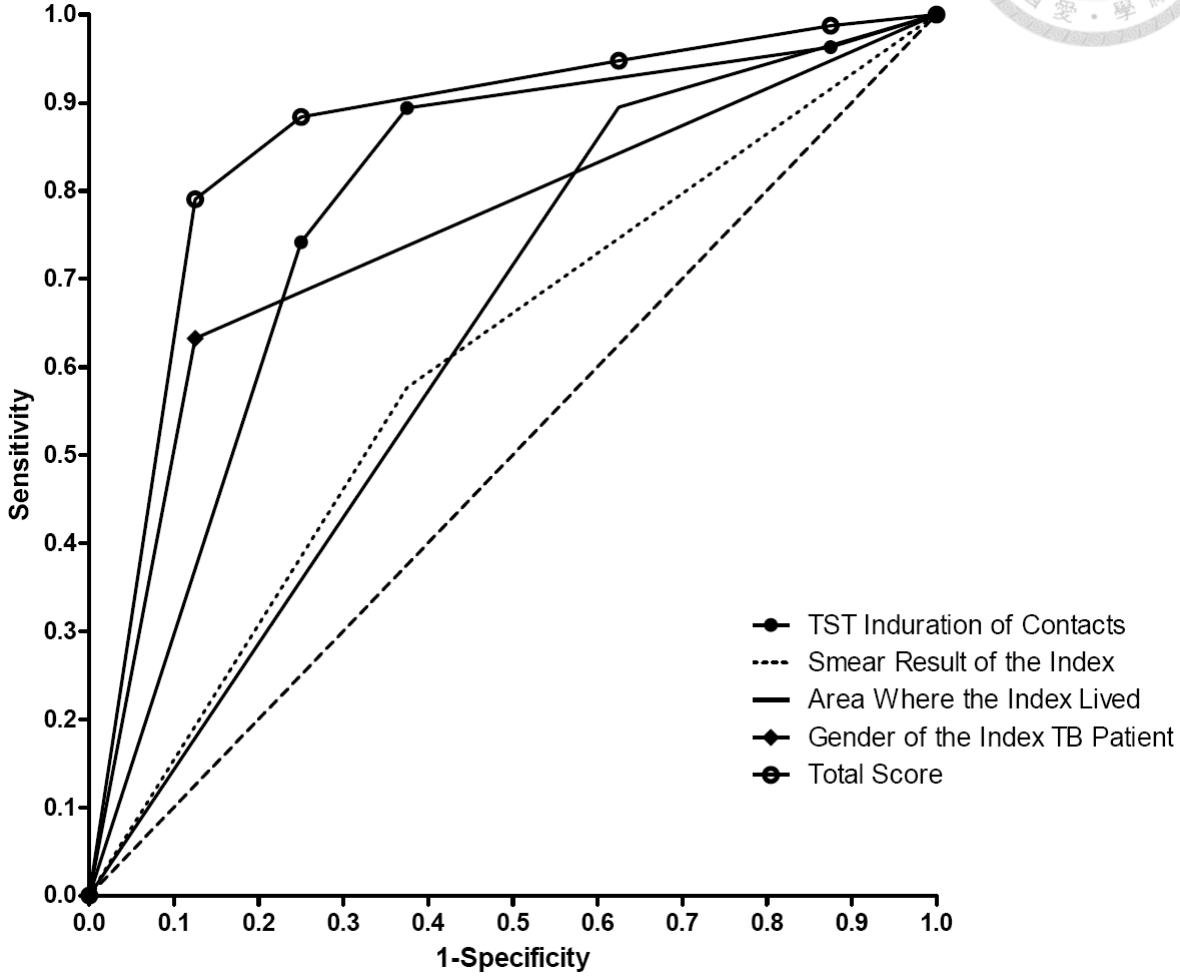
†These contacts were notified to have active TB after the start of isoniazid preventive therapy. Review of serial images by an independent radiologist, however, concluded that active TB was already present before the start of LTBI treatment. The date of TB (event) was rectified accordingly. § Three of these four contacts had received the second TST. Two of them had TST conversion but never received isoniazid preventive therapy. *Definition of abbreviations:* TST = tuberculin skin test; TB = tuberculosis; LTBI = latent TB infection

Fig 2 ROC curves for the predictive score in the development cohort.



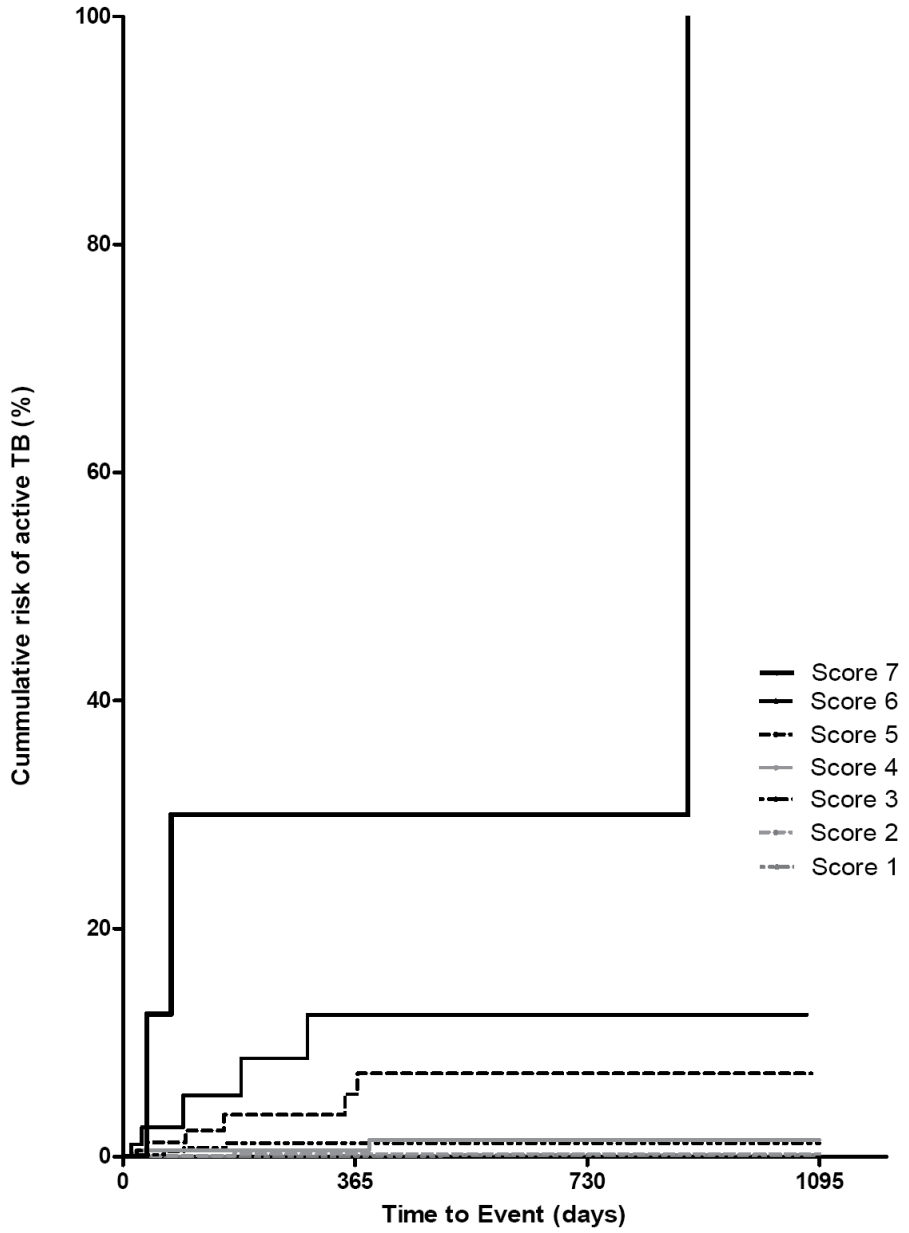
Definition of abbreviations: ROC = receiver operating characteristics; TST = tuberculin skin test; TB = tuberculosis.

Fig 3 ROC curves for the predictive score in the validation cohort.



Definition of abbreviations: ROC = receiver operating characteristics; TST = tuberculin skin test; TB = tuberculosis.

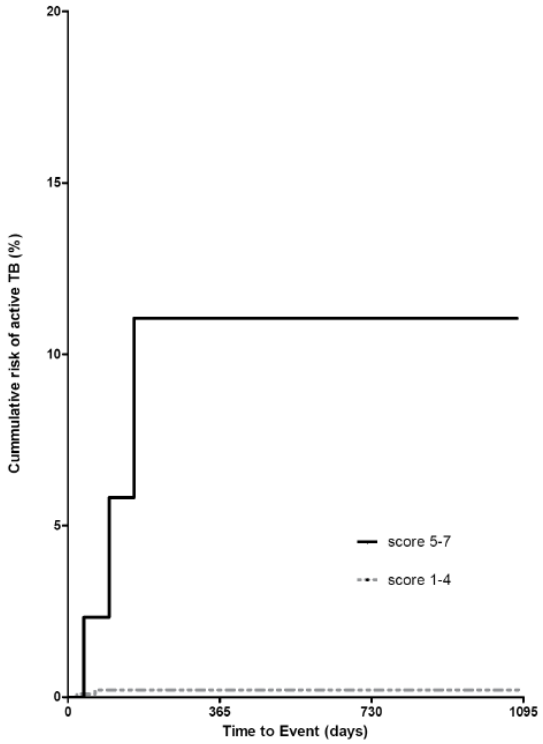
Fig 4 Predicted risk of developing active TB if no isoniazid preventive therapy were given.



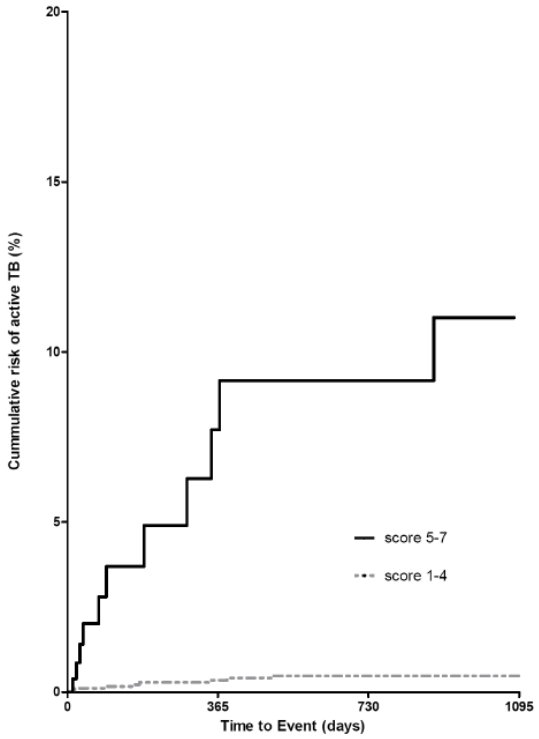
Definition of abbreviations: TB = tuberculosis.

Fig 5 Predicted risk of developing active TB (a) contacts aged <5 year-old and (b) aged >= 5 year-old.

Definition of abbreviations: TB = tuberculosis.



(A)



(B)

3.7 TABLES

TABLE 1 CHARACTERISTICS OF CHILD CONTACTS (A) AND THEIR INDEX PATIENTS (B) IN THE DEVELOPMENT COHORT

	Contacts who developed active TB disease (n=27) n (%)*	Contacts who did not develop active TB disease (n=9384) n (%)*	P value†
Female	16 (59)	4515 (48)	0.247
Age (years)‡			
<5	5 (19)	2660 (28)	0.258
5-9	9 (33)	4172 (44)	
10-12	13 (48)	2552 (27)	
Received BCG vaccination	26 (96)	9215 (98)	0.389
TST induration			
TST <10 mm	6 (22)	6905 (74)	<0.001
TST 10-14 mm	4 (15)	1417 (15)	
TST 15-19 mm	8 (30)	698 (7)	
TST ≥ 20 mm	9 (33)	364 (4)	
Relationship with the index TB patients			
Household	25 (93)	7507 (80)	0.145
Median duration of follow-up# (Day; IQR)	96 (22-342)	925 (110-1166)	<0.001

Definition of abbreviations: TST = tuberculin skin test; BCG = Bacillus Calmette-Guerin; IQR = interquartile range

* Unless otherwise stated.

† Pearson χ^2 for 2 × N tables or Fisher's exact test for 2 × 2 tables with small sample sizes and Mann–Whitney U test for median duration of follow-up.

‡ The age of each contact was the age when the TST was performed.

The end of the follow-up was the endpoint of event-free time.

(B)

	Index patients whose contacts developed active TB disease (n=17) n (%)	Index patients whose contacts did not develop active TB disease (n=4494) n (%)	P value*
Female	8 (47)	2982 (66)	0.121
Age (years) † ≥50	6 (35)	2767 (62)	0.042
Sputum smear positive for Acid Fast Stain	13 (76)	2237 (50)	0.030
Sputum culture positive for *M. tuberculosis*	15 (88)	3678 (82)	0.753
Cavitation over chest radiograph	8 (47)	1020 (23)	0.036
Residence in aboriginal area	8 (47)	288 (6)	<0.001
Relapse	5 (29)	336 (7)	0.007

* Pearson χ^2 for 2 × N tables or Fisher's exact test for 2 × 2 tables with small sample sizes.
†The age of each index case was the age on the TB registry date.

TABLE 2 UNIVARAIATE COX PROPORTIONAL HAZARDS MODEL FOR TUBERCULSOSIS RISK IN DEVELOPMENT COHORT

	Number of contacts (n=9411) n (%)	Non-adjusted Hazard Ratio (95% CI) *
Gender of contacts		
Male	4880 (52)	1
Female	4531 (48)	1.6 (0.7-3.4)
Age of contacts (years) †		
<5	2665 (28)	1
5-12	6746 (72)	1.6 (0.6-4.3)
BCG vaccination		
Not received BCG	170 (2)	1
Received BCG	9241 (98)	0.5 (0.1-3.7)
TST induration		
TST <10 mm	6911 (73)	1
TST 10-14 mm	1421 (15)	1.3 (0.5-3.9)
TST 15-19 mm	706 (8)	8.9 (3.9-20.5) *
TST ≥ 20 mm	373 (4)	20.4 (9.1-45.8) *
Relationship with the index TB patients		
Outside-household	1879 (20)	1
Household	7532 (80)	3.7 (0.9-15.8)
Gender of the index TB patient		
Male	6068 (64)	1
Female	3343 (36)	2.3 (1.1-4.8) *
Age of the index TB patient (years) †		
<50	4381 (47)	1
≥50	5030 (53)	0.5 (0.2-1.0)
Sputum smear for Acid Fast Stain		

Negative	4939 (52)	1
Positive	4472 (48)	3.8 (1.6-8.9) *
Sputum culture for *M. tuberculosis*		
Negative	1943 (21)	1
Positive	7468 (79)	3.9 (0.9-16.4)
Cavitation over chest radiograph		
No	7362 (78)	1
Yes	2049 (22)	3.2 (1.5-6.9) *
Residence in high incidence area		
No	8565 (91)	1
Yes	846 (9)	10.9 (5.1-23.3) *
Relapse		
No	8754 (93)	1
Yes	657 (7)	4.9 (2.1-11.7) *

Definition of abbreviations: CI= confidence interval; HR=hazard ratio; TST= tuberculin skin test

* $p<0.05$

† The age of each contact was the age when the TST was performed; the age of each index case was the age on the TB registry date.

TABLE 3 MULTIVARIATE COX PROPORTIONAL HAZARDS MODEL FOR TUBERCULSOSIS RISK AMONG CONTACTS IN DEVELOPMENT COHORT

Predictor variable	Adjusted hazard ratio (95% CI)	β coefficient	*P* value	Risk score
TST induration of contacts				
TST < 10 mm	1.0	0.0000	-	0
TST 10-14 mm	5.7 (1.6-20.3)	1.7385	0.008	2
TST 15-19 mm	16.7 (5.6-49.1)	2.8125	<0.001	3
TST ≥ 20 mm	31.0 (10.8-89.4)	3.4345	<0.001	4
Smear result of the index TB patient				
Negative	1.0	0.0000	-	0
Positive	3.3 (1.4-7.9)	1.1921	0.008	1
Area where the index TB patient lived				

Non-high incidence area	1.0	0.0000	-	0
High incidence area	8.2 (3.8-18.0)	2.1085	<0.001	2
Gender of the index TB patient				
Male	1.0	0.0000	-	0
Female	2.3 (1.1-4.9)	0.8183	0.035	1

Definition of abbreviations: CI= confidence interval; HR=hazard ratio; TST= tuberculin skin test

TABLE 4 PREDICTED RISK FOR TUBERCULOSIS WITHIN 3 YEARS AND THE NUMBER NEEDED TO TREAT

Score	No. of contacts with each score	Predicted risk of developing active TB within 3 year	Predicted No. of TB cases if no IPT was given†	Observed No. of TB cases which occurred within 3 years	No. of active TB cases assumed to be present at baseline *	Potentially avertable No. of TB cases†	No. needed to treat†
8	0	-	-	-	-	-	-
7	16	1.0000	16	3	2	14	1
6	135	0.0779	11	5	3	8	19
5	369	0.0432	16	6	3	13	30
4	685	0.0098	7	4	3	4	197
3	980	0.0070	7	4	3	4	271
2	1642	0.0015	2	2	1	1	1206
1	3382	0.0008	3	2	0	3	1344
0	2202	0.0000	0	0	0	0	-
Total	9411	-	63	26	15	47	-

Definition of abbreviations: CI=contact investigation; No. = number; TB= tuberculosis; IPT=isoniazid preventive therapy
*Observed number of active cases that occurred within 3 months, which was considered already present at the start time and therefore was not avertable by IPT. †Round to an integral

3.8 APPENDIX TABLES

TABLE CHARACTERISTICS OF DEVELPOMENT AND VALIDATION COHORTS

	Development cohort n (%)*	Validation cohort n (%)*
Children contacts	n=9411	n=2405
Male	4880(52)	1241(52)
Age (years)		
<5	2665(28)	664(28)
5-9	4181(44)	1211(50)
10-12	2565(27)	530(22)
BCG vaccination	9241(98)	-
TST induration		
TST ≥10 mm	2500(27)	625(26)
TST ≥15 mm	1079(11)	259(11)
TST ≥20 mm	373(4)	89 (4)
Relationship with the index TB patients		
Household	7532(80)	2079(86)
Median duration of follow-up (Day; IQR)	924(108-1165)	2016(1914-2096)
Index patients	n=4511	n=1130
Male	2990 (66)	734(65)
Age (years)		
≥50	2773(61)	676(60)
Sputum smear positive for Acid Fast Stain	2250(50)	454(40)
Sputum culture positive for *M. tuberculosis*	3693(82)	710(63)
Cavitation over chest radiograph	1028(23)	240(21)
Living in Mountainous area	296(7)	107(9)
Relapse	341(8)	-

Definition of abbreviations: TST= tuberculin skin test; BCG = bacillus Calmette-Gue´rin; IQR= interquartile range;
* Unless otherwise stated.