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※ Biological, Epidemiological and Economical Evaluation of Tuberculosis (TB) ※

※ Re-visit to Natural History, Prevention and Economic Evaluation of TB in Taiwan ※

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- □赴國外出差或研習心得報告一份
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- □國際合作研究計畫國外研究報告書一份

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壹、中文摘要

第一部份、成人結核菌素反應與卡介苗接種：社區結核菌素測驗篩檢計劃（Adult Tuberculin Reactivity and BCG Vaccination: A Community-based Screening Project for TB with Tuberculin Test in Malin and Yuri, Keelung, Taiwan）

本研究於基隆市瑪陵、友蚋地區複合式篩檢計劃中，針對參與篩檢 739 名居民進行結核菌素測驗。並以結構式問卷取得結核病史、結核病接觸史等基本資料。結核病過去史部分資料得自結核病登記系統。結核菌素測驗使用一單位 RT23 結核菌素，以 Mantoux test 實施。運用歷年結核年感染率資料，本研究以 time-dependent proportional hazard model (Cox regression model)估計卡介苗接種對結核菌素反應的影響及結核感染的危險因子。結果發現：非典型結核感染的交互反應比率低。10mm 可作為結核菌素測驗的陽性判準。Cox regression model 估計結果顯示：卡介苗接種與結核菌素反應的交互作用隨年齡增加而減少。同樣經結核感染，20-30 歲年齡組的卡介苗接種者在結核菌素測驗上的陽性機率為無接種者的二倍（相對危險性 Odds Ratio=2.11）；30-40 歲與 60-70 歲年齡組則分別為 1.53 和 1.12 倍。在控制了卡介苗與結核菌素反應相互干擾的影響之後，Cox regression model 顯示結核病接觸者對結核感染俱顯著意義。本研究結果表示：成人卡介苗接種者的陽性結核菌素反應不可單獨歸因於卡介苗接種造成的偽陽性。在高卡介苗接種率地區，結核菌素測驗仍可用來檢測結核感染。配合結核感染的風險評估，結核菌素測驗仍可在在中結核盛行、高卡介苗接種地區，扮演有用的防治工具。

第二部份、台灣結核病傳染模式的分子流行病學分析：內因性和外因性結核病的角色（Epidemiological investigation of transmission mode of TB using RFLP analysis: Re-infection or reactivation）

本研究目的在區分內因性和外因性結核病在山地鄉及周邊地區的結核病傳染模式中的角色。透過痰檢體代檢系統，取得 87 個檢體樣本，分別來自南投、彰化、台中等縣市。所有取得檢體以 IS6110-based RFLP analysis 進行分析。結果發現：24 樣本檢體（30.4%）分布在 10 個聚集中。每一聚集個案數從 2 至 5。8 個聚集的個案數為 2，1 個聚集的個案數為 3，1 個為 5。檢體來源的醫院有 6 家（54.5%）出現聚集個案。60% 的聚集個案為跨縣市。大部分的聚集個案來自不同村里。以縣市分析，南投縣和台中縣有三分之一以上的個案出現聚集。本研究發現與西方國家類似研究結果接近。外因性的新感染肺結核在山地鄉及周邊地區的結核病傳染模式中扮演重要的角色。大多數的聚集個案發生在家庭之外，顯示對於接觸者的追蹤必須考量其他的社會接觸。

第三部份、台灣地區山地鄉結核病之流行病學探討（TB Epidemiology in Taiwan Mountain Areas）

台灣地區結核病發生率最高地區發生在山地鄉，本研究主要目的在針對結核病流行病學特徵進行山地鄉與非山地鄉結核病之比較，並評估以山地鄉為中心點其周圍非山地鄉區域結核病發生率是否隨著距離增加而減少，進而了解山地鄉外因性新感染結核病及內因性潛伏後發結核病之相對重要性。主要資料來源包括台灣地區結核病登記系統、台灣地區死亡檔、山地鄉人口結構資料。以山地鄉為中心將其鄰近非山地鄉依<20 公里、20-40 公里及>40 公里分為三層，除比較年齡標準化發生率外，利用 Generalized Linear Model 考慮時間自我相關及調整年齡及性別之下，各山地鄉相較於非山地鄉其結核病發生之危險性。結果發現：山地鄉發生率與致死率均較非山地鄉高，在調整年齡及性別後其發生率最高之地區相較於非山地鄉可高至 15 倍。非山地鄉結核病個案增加大部份是在老年人，山地鄉男性曲線呈現直線上升，且以 25-44 歲結核病個案較非山地鄉多。以山地鄉為中心點，隨著鄰近非山地鄉距離增加結核病發生隨之降低，呈現劑量效應，鄰近山地鄉之非山地鄉大多較全國非山地鄉為高。本研究顯示：山地鄉男性結核病個案發生主要來自新近感染或再感染。山地鄉與鄰近非山地鄉之間具有結核病傳染動力學上的關係，擬定結核病防治策略時應加以考慮。

貳、英文摘要

A. Adult Tuberculin Reactivity and BCG Vaccination: A Community-based Screening Project for TB with Tuberculin Test in Malin and Yuri, Keelung, Taiwan

A community-based TST survey was incorporated into KCIS in Malin and Yuri. We invited those adults older then 18 years old for TST. Structured questionnaires were used for collecting information including age, sex, occupation, transportation, BCG vaccination history, TB history, TB contact history

and TB family history etc. Clinical TB information came from TB registration system. The Mantoux test, with 1TU RT23, was conducted by a well-trained public nurse of TPCDCB who has been trained by direction of the Bureau. The nurse was also responsible for inspecting the BCG scar imprinted on the arm of each TST recipient. Approximately 2-3 well-trained public nurses read the indurations 48-72 hours after the test by the palpation method. Chest X ray were read by one specialist of chest medicine in TPCDCB, recorded according to the TPCDCB guideline.

The effect of BCG vaccination on TST induration is contingent on three major factors, the age when vaccination, the time since vaccination, and the probability of TB infection. The interaction of BCG vaccination and TB infection could result in overestimation of the BCG effect on TST induration. Thanks to lacking BCG vaccination registration in early 1950s-1970s, the age when vaccination be approximately estimated by the BCG vaccine policy. The time since vaccination was then determined. Historical data of annual risk of infection (ARI) demonstrated that the probability of TB infection of each age group was approximately linear by age.

Based on above observations and assumptions, a time-dependent proportional hazard model (Cox regression model) is applied to estimate the BCG effect. The model also included related risk factors to quantify their effects on tuberculin reactivity after taking the BCG-vaccination-interference into account.

The frequency distribution of induration sizes showed a pattern of low frequency of atypical mycobacterial cross-reactivity, with a clear mode and anti-mode. Two convergent points (at 10mm and 15 mm) were found on plotted curves of cumulative proportion of induration size by age group. Taking 10mm as the cut-off point for TST positivity is therefore justified. The total positive rate of TST was around 50%. The highest rate (61.9%) occurred in 50-60 years old age group, the lowest (26.7%) in 80-90. Induration size $\geqq$ 15mm might be a characteristic of other kind, which would be revealed in the Cox model.

The interaction of BCG vaccination and TB infection on TST reactivity decreases with age. For the twenties age group, BCG vaccination confers twice (OR=2.11) the probability of TST positivity for the TB infected as those not vaccinated. The numbers for the thirties and the sixties were 1.53 and 1.12 respectively. The positive tuberculin reactions in BCG-vaccinated young adults could not be naively attributed to the independent false-positive-effects of BCG.

Contacts with TB cases (OR=1.7) was found to be a significant independent effects on TB infection Only 1.6% of the population need to be treated or further investigated when the target group was defined as being both TB contacts and with induration size larger then 15mm. These independent effects demonstrated the feasibility that even in median-prevalence high-BCG-coverage areas, combined with the knowledge of risks of TB infection, under limited resources, TST could still play a role in targeted active case-detection strategies.

BCG effects on TST induration might be over-estimated. In high BCG- vaccination-overage areas, TST could still be used to measure TB infection. Targeting risk groups for preventive therapy or further investigations need the knowledge of risk factors of TB infection. Community-based TST survey could identify some risks. However, other studies of TB transmission modes, for example, DNA fingerprinting studies, should be encouraged to help reveal more comprehensively the risks of TB transmission.

B. Epidemiological investigation of transmission mode of TB using RFLP analysis: Re-infection or reactivation

This study used RFLP analysis method to reveal the relative contribution of exogenous TB and endogenous TB in TB epidemics in middle Taiwan. 87 sputum samples were collected from 11 hospitals/clinics in Nanto County, Changhua County, Taichung City and Taichung County. 79 samples were eligible for IS-6100 RFLP analysis after excluding those with double samples. 24 samples (30.4%) were found in 10 clusters. The size of clusters ranged from 2 (8 clusters), 3 (1 clusters) to 5 (1 clusters). Among the 11 hospitals/clinics, 6 (54.5%) presented clustered cases. 60% of the clustered cases came from different counties/cities. Besides, most of the clustered cases within the same counties came from different townships. In Nanto and Taichung counties, more than one third of the cases were clustered. The result was in accordance with those of studies in western countries. Exogenous TB played an important role in TB epidemics in middle Taiwan. Most of the clustered cases occurred beyond household contacts. The empirical studies of other countries had stressed the importance of social contacts in TB transmission. The study indicated that further researches were needed to reveal the social networks of TB transmission.

C. TB Epidemiology in Taiwan Mountain Areas

Residents living in townships adjacent to mountains were disadvantaged at level of economic status and high prevalence of TB may be ascribed to recently transmitted infection. To make a clear understanding of transmission mode of TB in these areas the aims of this study are (1) to make the comparison of morbidity, mortality and prognosis on Tuberculosis (TB) between residents living in townships adjacent to mountains and those in other townships near the horizon; (2) and to examine whether the incidence of TB is negatively associated with the distance from foci of transmission i.e. townships adjacent to mountains.

Target population consists of subjects residing in thirty townships adjacent to mountains. Archival data on incident cases of TB from 1991 to 1997 were collected from TB Taiwan TB Disease Registry. This information was linked with Taiwan Mortality Registry to ascertain deaths. Four areas of foci transmission in respect of townships adjacent to mountains were also identified to demarcate three levels of townships adjacent to foci of transmission, e.g. <20 Km, 20-40 Km, > 40Km. A variety of statistical methods were adopted to assess the above objectives.

Morbidity and mortality of TB in residents in townships adjacent to mountains are much higher than those in other townships. A linear relationship of age-specific curve and the comparison of age distribution in two distinct groups suggest that recently infection or infection rather than reactivation may account for the increase of TB incident cases in young people. In contrast, reactivation may be responsible for the increased TB for residents living in townships near the horizon. The incidence of TB is inversely related to the distance from foci of transmission. Approximately 20-32% reduction of TB cases due to subsidized program on inpatient of TB. Both findings support the hypothesis that TB cases in young people are attributed to recently transmitted infection or re-infection.

The present study demonstrates recent infection or re-infection accounts for young TB cases. This result addresses the importance of elucidating transmission mode of TB between townships adjacent to mountains and the neighborhood of townships.

參、計劃緣由

自從結核病疫情於1990年代前後在西方國家出現反撲之後，結核病的傳染已被視為全球性的危機（Raviglione 等人，1997）。結核病疫情的主要影響因素包括：HIV、多重抗藥性結核、人口移動、公共衛生下層結構（infrastructure）以及結核病防治體系的重建等。最近的估計顯示，結核病是全世界傳染病死因的第一位（Murry 等人，1993；Murry，1994）。以 1997 與 1990 比較，全球結核病發生率雖從每十萬人口 143 為下降至每十萬人口 136，但每年的新病例仍然增加了 5.6%。1997 年全球結核病盛行率為千分之 2.8，結核感染盛行率為 32%（Raviglione 等人，1995；Dye 等人，1999）。1998 台灣地區結核病發生率男性為每十萬人口 89.75，女性為每十萬人口 38.69，與 1991 年比較（男性 59.07，女性 24.23），男女性分別增加了 52%和 60%（Chou，1998；Chronic Disease Control Bureau，1998）。1998 年台灣地區有 1513 人死於結核病，其死亡率為每十萬人口 6.93，佔十大死因的第十二位。顯示結核病仍為一重要的健康問題。不同國家的結核病流行顯示極大差異，此差異不僅與結核病的傳染動力學有關，也影響到結核病的防治策略。結核病依其流行可區分為高盛行（high-prevalent）地區，例如第三世界國家（結核病發生率約在每十萬人口 75 至 500 以上），與低盛行（low-prevalent）地區，例如美國、加拿大（結核病發生率約在每十萬人口 6-7 之間）等西方已開發國家。傳統的假說認為高盛行地區的結核病主要來自外因性（exogeneuos）的新感染或再感染（re-infection），而高盛行地區的結核病主要來自內因性（endogeneous）的舊感染續發（re-activation）（Smith 等人，1994）。外因性與內因性之爭，是結核病流行病學與疾病自然史最核心的課題之一（Fine，1999）。如果結核病的流行以外因性為主，則防治策略就必須加強對地區結核病傳染的追蹤；相對的，如果以內因性為主，則可考慮續發高危險群的結核菌素測驗（tuberculin skin test）篩檢。近十年來，藉由 DNA fingerprinting（RFLP, Restriction fragment length polymorphism analysis）的研究，發現結核再感染可以發生在免疫功能正常或缺損（immuno-competent or immuno-compromised）的病人（van Rie A 等人，1999；Fine，1999）。美國的經驗研究發現，40%至 60%的結核病例具有相同的 DNA fingerprinting 類型（Alland，1994；Small，1994；Barnes，1997），因而可能來自最近共同的感染。以上證據表示，在結核病低盛行地區，外因性結核病仍可能扮演重要角色。近十年來，對結核病防治策略的觀念也產生若干進展。第一、短程直接觀察治療法（directly observed short-course therapy, DOTS）可以有效提高治愈率（China Tuberculosis Control Collaboration，1996）。第二、在臨床監控（monitoring）下，以 isoniazid

治療結核病感染可使藥物性肝炎死亡率降低至每十萬人口 1-2（Salpeter，1997）。對續發高危險群的結核感染病例施予預防性治療（chemoprophylaxis）具成本效益（Salpeter，1997）。其中，必須考慮的重點是結核感染群體進展（progress）成結核病的危險性，而不是感染者的年齡（American Thoracic Society，2000）。第三、藉由 DNA fingerprinting 對結核病傳染模式的研究發現，結核病傳染可以在多次、短暫的接觸（mutiple, transient contacts）下發生。傳統的家戶接觸者（household contacts）追蹤效益不高，接觸者追蹤應考慮患者的社會接觸（social contacts）（Hopwell，2000；Small，1994）。結核病傳染模式的研究也指出，結核病防治策略必須針對不同危險群、不同地區特性多管齊下。

1998 台灣地區結核病發生率為每十萬人口 64.89，屬於結核病中度盛行（median-prevalent）地區，且面臨近年來結核病流行趨勢上升的威脅。台灣地區結核病流行病學具有以下特性：(1) 卡介苗於 1950 年引進台灣，自 1965 年後，80%以上的嬰幼兒均接種過卡介苗（索任等人，1998）。卡介苗全面施打影響了族群的免疫力。除此之外，卡介苗也會干擾結核菌素測驗的特異性（specificity）。晚近的觀念認為，卡介苗施打史並不構成結核菌素測驗的禁忌（American Thoracic Society，2000）。考量受測者的年齡、卡介苗接種史的時間因素、結節反應（induration）的大小以及結核感染的危險性等因素，結核菌素測驗仍可用來測量結核菌感染。惟對於以上因素，目前的研究仍不夠量化。在卡介苗全面接種地區，以結核菌素測驗作為結核菌感染篩檢工具，其陽性反應之界定標準（cut-off point）及檢驗的效度仍有待進一步的研究。唯有在這類研究的基礎上，才能更清楚的評估於台灣地區實施結核感染篩檢策略，其成本效益上的適切性。(2) 山地鄉的結核病發生率和死亡率均較其他地區高。以 1997 年為例，山地鄉的結核病發生率較台灣地區發生率約高出三倍。近年來，山地鄉結核病發生率不僅顯示上升的趨勢，其上升的幅度也較其他地區高。1997 年山地鄉結核病發生率較 1991 年增加了近 90%。山地鄉與鄰近地區的可能傳染模式（transmission mode）值得進一步深入探討。除了以上所述的流行病學特性之外，對於近年來台灣結核病發生率上升的現象，也有必要尋求解釋。在結核病疫情的主要影響因素當中，究竟「何者」（what）「如何」（how）發生？除了這些因素之外，是否仍有其他原因？這些相關因素在傳染動力學裡的角色為何？此外，台灣地區的結核病流行究竟是外因性或內因性？釐清其中緣由，不僅有助於台灣結核病流行病學的了解，亦可應用於預測未來結核病流行的趨勢，評估不同防治策略的成本效益，進而對結核病防治策略的擬定有所幫助。

肆、計劃目的

本研究包括四部份，其目的分別如下：

第一部份、考量年齡、年代等時間因素及接種政策的影響下，研究卡介苗對結核菌素測驗的影響。

第二部份、運用 DNA fingerprinting 的技術，探討台灣結核病的傳染模式，評估內因性和外因性結核病分別扮演的角色。

第三部份、針對結核病流行病學特徵進行山地鄉與非山地鄉結核病之比較，並評估以山地鄉為中心點其周圍非山地鄉區域結核病發生率是否隨著距離增加而減少，進而了解山地鄉外因性新感染結核病及內因性潛伏後發結核病之相對重要性。

伍、結果

第一部份、成人結核菌素反應與卡介苗接種：社區結核菌素測驗篩檢計劃

1. 卡介苗接種者的結核菌素結節大小分布結果顯示：非典型結核感染的交互反應比率低。以各年齡層各結節尺寸的累積分率由小至大做曲線圖，發現兩聚合點，分別位於 10mm 及 15mm。10mm 可作為結核菌素測驗的陽性判準。以≧10mm 為陽性，640 名受檢者陽性約為 50%，陽性率以 50-60 歲年齡組最高，80-90 歲年齡組最低，分別為 61.9%和 26.7%。

2. Cox regression model 發現：卡介苗接種與結核菌素反應的交互作用隨年齡增加而減少。同樣經結核感染，20-30 歲年齡組的卡介苗接種者在結核菌素測驗上的陽性機率為無接種者的二倍（相對危險性 Odds Ratio=2.11）；30-40 歲與 60-70 歲年齡組則分別為 1.53 和 1.12 倍。成人卡介苗接種者的陽性結核菌素反應不可單獨歸因於卡介苗接種造成的偽陽性。

3. 控制了卡介苗與結核菌素反應相互干擾的影響之後，Cox regression model 顯示結核病接觸者在感染危險性上俱顯著意

義，其相對危險性 1.92(95%信賴區間 1.20-3.06)。以結核病接觸者，且結節≧15mm 者為高危險群，則需治療或介入措施的目標群體只佔受檢人口的為 1.6%。以上結果表示：在中結核盛行、高卡介苗接種地區，配合結核感染的風險評估，結核菌素測驗仍可在有限資源下，扮演有用的防治工具。

第二部份、台灣結核病傳染模式的分子流行病學分析：內因性和外因性結核病的角色

本研究透過痰檢體代檢系統，取得 87 個檢體樣本，分別來自南投、彰化、台中縣、台中市的 11 家醫療院所。其中 8 個案有重複檢體，實際分析樣本數 79。個案居住地涵蓋南投、彰化、台中縣市、花蓮、苗栗、雲林。RFLP 的研究發現 24 樣本（佔所有樣本數 30.4%）出現在 10 個 RFLP 聚集中。6 家（54.5%）院所出現聚集個案。聚集的大小從 2 個案（8 個聚集）、3 個案（1 個聚集）到 5 個案（1 個聚集）。
60% 的聚集個案為跨縣市。大部分的聚集個案來自不同村里。以縣市分析，南投縣和台中縣有三分之一以上的個案出現聚集。本研究發現與西方國家類似研究結果接近。外因性的新感染肺結核在山地鄉及周邊地區的結核病傳染模式中扮演重要的角色。大多數的聚集個案發生在家庭之外，顯示對於接觸者的追蹤必須考量其他的社會接觸。結核病的社會接觸有待進一步的研究。

第三部份、台灣地區山地鄉結核病之流行病學探討

1. 本研究結果發現山地鄉發生率與致死率均較非山地鄉高，在調整年齡及性別後其發生率最高之地區相較於非山地鄉可高至 15 倍，除了蘭嶼之外，其發生率較低區域相較於非山地鄉大約為 2 倍。

2. 由年齡別曲線及年齡分佈來看非山地鄉其結核病個案增加大部份是在老年人，因此可能屬於潛伏性結核病感染而被再活化(Reactivation)之內因性結核病，而在山地鄉方面男女性不同，男性曲線呈現直線上升，而且 25-44 歲結核病個案較非山地鄉多，表示山地鄉除了年老個案可能被再活化變成內因性結核病之外，男性結核病年輕個案極有可能來自新近感染或再感染之後變成外因性結核病，至於女性則沒有這樣的現象。若以山地鄉為中心點，本研究發現隨著鄰近非山地鄉距離增加結核病發生隨之降低，呈現劑量效應，而且幾乎鄰近山地鄉之非山地鄉均較全國非山地鄉為高。

陸、討論

一、 經由本計劃第一部分的研究發現卡介苗接種與結核菌素反應的交互作用常使卡介苗對結核菌素反應的影響被高估。在高卡介苗接種率地區，結核菌素測驗仍可用來檢測結核感染。近來，美國胸腔病學會（American Thoracic Society, ATS）和疾病管制中心（Centers for Disease Control and Prevention, CDC）已將傳統所稱的結核病預防性治療（Chemoprophylaxis）重新命名為結核感染治療法（Treatment of Latent TB Infection）。而針對特定結核病高危險群進行結核菌素測驗並給予結核感染治療（Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection）已廣泛運用於疫情調查、接觸者追蹤、結核感染篩檢等結核病的防治策略中。台灣地區的結核病防治策略歷年均以個案發現（Case Finding）、臨床治療及個案管理等被動策略（Passive Strategies）為主。除了社區胸部 X 光篩檢之外，並無計劃性地採用其他主動策略（Active Strategies）。本研究發現證明在台灣地區仍可將結核菌素測驗有效地運用在成人結核病防治上，不受卡介苗接種史的影響。如何彈性有效地運用結核菌素測驗及結核病高危險群結核感染治療策略是未來值得思考的方向。

二、 本研究第二部分及第三部份分別以 RFLP 分析和流行病學研究發現：外因性結核病在台灣地區結核病疫情中扮演重要的角色。此外，山地鄉與鄰近非山地鄉之間具有結核病傳染動力學上的關係。以上發現對台灣地區的結核病防治策略具有兩點重要意義：

1. 山地鄉結核病防治不僅是地區性疾病防治問題，也是台灣地區結核病防治的整體問題。

2. 對於外因性結核病經由社會接觸的傳染途徑應該進一步深入探討；結核病防治可考慮適度運用 RFLP 等分子流行病學的工具，擬定場所導向（location-oriented）的防治策略（Barnes,1997）。

柒、成果自評

一、 本計劃原屬三年計劃，第一年完成之RFLP分析仍需後續計劃，進一步配合田野流行病學的探討以釐清其社會接觸的傳染途徑。按審核通過之計劃及預算，本研究計畫均已依照原訂進度完成預期成果。

二、 本計劃完成之三項研究，依目前所知的文獻，均屬台灣地區首次進行的相關探討，對於本土結核病流行病學研究及公共衛生政策上都極具意義。此外，以台灣地區獨特的卡介苗接種政策變遷經驗，本計劃對於不同卡介苗接種政策對成人結核菌素測驗的影響所做的探討及發現，對於國際上卡介苗與結核菌素測驗之間關係的學術探討，亦富參考價值。而在山地鄉結核病流行與周遭非山地鄉之間傳染動力學的探討方面，國際上不論山地鄉或原住民結核病流行病學的研究仍然少見，因此，對於國際學界，本計劃相關研究，亦頗富台灣地區的獨特性。

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