出國報告（出國類別：出國開會、考察）

針對 MDR 結核病個案以專屬車隊都治之成效

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摘要

國際抗癆與肺病聯盟(IUATLD)爲召集全世界的專家共同研討關於結核病、愛滋病、肺疾病、煙草控制與研究的組織。每年舉辦世界會議讓各地的專家與學者進行新學術交流。今年我們台灣醫師、學者熱烈參與，共有 30 篇文獻發表，包括口頭報告、壁報討論與壁報發表。

此次參與會議的目的爲瞭解目前全球結核病的新政策、治療、診斷和成果，吸收新的知識，並發表結核病相關之研究成果。印象較爲深刻的重點可供我們參考的爲「定點照護」的構想、新的檢驗儀器的開發和多重抗藥性結核病的用藥。

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目的

參加 2010 年第 41 屆國際抗癆與肺病聯盟 (IUATLD)年會，於德國柏林 11 月 11 日至 15 日舉行。瞭解目前全球結核病的新政策、治療、診斷和成果，吸收新的知識。另外，並發表結核病相關之研究成果。

前言

國際抗癆與肺病聯盟(IUATLD)爲召集全世界的專家共同研討關於結核病、愛滋病、肺疾病、煙草控制與研究的組織。每年舉辦世界會議讓各地的專家與學者進行新學術交流。而在此所發表的學術研究，通常爲全世界抗癆政策的指引，是從事結核病相關工作的醫師和醫事人員非常重要的會議。此聯盟的總部於法國巴黎，地區性與聯盟國家分佈包括非洲、亞太地區、歐洲、拉丁美洲、中東、北美與東南亞地區。而今年是發現結核菌的德國學者 Robert Koch 逝世 100 年，特別在他所出生的國家德國舉行國際抗癆與肺病年會，以示對他的尊敬。並慶祝 IUATLD 創辦 90 週年紀念，特別命名 2010 年爲「肺之年 Year of the Lung」。今年年會主題爲「從研究和新發現到解決方案來探討結核病, HIV 和肺之健康 Tuberculosis, HIV and lung health: from research and innovation to solutions」。

這次的年會，我們台灣熱烈參與，共有 30 篇文獻發表，包括口頭報告、壁報討論與壁報發表。有此可鑑台灣在結核病的防疫治療、監測與政策方面，占有重要的一席。

會議內容摘要

第 41 屆國際抗癆與肺病聯盟 (IUATLD)年會，會議共分成 5 天舉辦，主要討論議題包括了對結核病診斷治療與預防的回顧與新知、結核病與愛滋病的關係、肺的疾病、肺病與煙草和結核病的治療。因身爲「多重抗藥性結核病醫療照護體系」中區的領導醫院主持人，此次參與會議重點注重於多重抗藥性結核病的治療與診斷。

1. 回顧結核病的診斷與發展 – 從柯霍到 2010

結核病治療的發展，開始於德國學者柯霍 (Robert Koch)細菌學之父，在 1882 年 3 月 24 日發現了**結核桿菌** (*Mycobacterium tuberculosis*)，並確認它是引致結核病的原因，應而解決十九世紀十大死因之謎題。不只如此，柯霍對結核病的貢獻還包括了發明染色和純化技術、細菌培養介質，以及培養皿和顯微照影，這些技術至今仍廣泛應用於生物研究。他還發現炭疽桿菌和霍亂弧菌並發展出柯霍氏法則，用以判斷疾病病原體的原則，對世人細菌學上的發展是一大突破。他於 1905 年獲得諾貝爾生理學與醫學獎。

由於結核桿菌的發現，潛伏性結核病的偵測和治療結核病的抗生素也紛紛產

生，使得結核病的治療從放置於療養院修養到積極治療並預防結核病，甚至在 1970 年代，Karel Styblo 發動了都治關懷 (DOTs - 確保病患確實服藥的監測行動)，一度把結核病控制住。但是，於 1990 年美國發現嚴重的多重抗藥性結核病的爆發，並發現患有結核病與愛滋病合併症的患者會增加死亡率。世界衛生組織開始從新檢討結核病的政策，投入大量心血召集世界各國的專家一起研究新的結核病診斷與治療。

目前，在這多元化的醫療體系，我們可用的檢查儀器可分成三大類：Real-Time PCR, Microfluidics 和 TB DNA sequence。但是在不同的實驗室可使用的儀器不同，時間也相對的會延誤診斷。例如當一個抹片陰性的患者在培養未出來前的 6 個月之間，他的病情可能加重並傳染給其他的家人朋友。所以，演講者 Dr. Roscigno (FIND 組織的主席) 呼籲我們的策略應從提早檢查，防止傳播爲主。檢驗的進化，從顯微鏡、螢光顯微鏡 (Fluorescent microscope)、Rapid speciation、Liquid culture、藥敏檢驗、Line-probes assay、LED Fluorescent microscope(檢驗敏感度增加 10%)和現在最新的卡匣式 NAAT (cartridge-based automated NAAT –檢驗敏感度增加 40%，並且結果報告可在 2 小時後出來)，這些都是可以增加我們在防禦方面的工具。

Dr. Roscigno 還強調我們已經從被動的等待患者 disease-centered approach 到主動的思考尋找病患 patient-centered approach，現在應該以預防性 people-centered approach 爲主，結核病的防治需要加強在「定點照護 point of care」，以患者在第一時刻進到診間開始，就能隨時處理病患的症狀，並提供全方位的檢驗（如 TB, HIV, malaria 等）不需要轉出或需要長時間的等待。FIND 組織積極研發新的儀器來偵測感染疾病（包括：愛滋、結核、瘧疾等)，來預防與提早治療，希望可以降低死亡率和提高完治率。

另外，在非洲服務的學者表示，雖然檢驗的時間從 2005 年時的 72 天到 2009 年所需 35 天，但是對於非洲地區去年的治療結果還是有 53%的患者因而死亡。而現在新的分子診斷儀器，可共用於檢驗 TB 和 HIV 的功能。目前檢驗結果所需時間 Indirect Line Probe Assay 爲 22 天、Direct Line Probe Assay 爲 8 天，而新的 NAAT 分子診斷儀器 GeneXpert 則爲 0.5 天。今年 GeneXpert 已在非洲 Cape Town 做實驗，敏感度爲 99%特異性爲 96%。預定在 2015 年時，NAAT 系統可用在 Point of Care 上，增加檢驗的速度。

GeneXpert MTB 是以 PCR 爲原理，用法簡單，不需要專門技術人員的培訓，任何人只要經過短期的訓練都可使用。它的敏感度與特異性，不論是有無 HIV 的患者，都達到高等級，並且可可分辨出 TB 和 NTB。而結果可在可在 90 分鐘內完成檢驗結果。台灣昆陽實驗室，據聞也以引進做初部試驗。

2. 多重抗藥性結核病(MDR-TB)的治療

至從 1980 年 fluoroquinolone 類抗生素的發明，就成爲治療多重抗藥性結核病不可或缺的主要藥物。Fluoroquinolone 類包括了：ciprofloxacin, ofloxacin, levofloxacin,

sparfloxacin, gatifloxacin 和 moxifloxacin。由動物實驗中發現，新一代的 fluroroquinolone 比前一代在殺菌方面更佳，尤其是 moxi-和 gati-與現在抑制結核菌最有效的 isoniazid 效果相當。另外，許多的治療成果都顯示含有 fluoroquinolone 的結核病治療處方，可改善治療結果，甚至對於廣泛抗藥性結核(XDR-TB)患者的成功率也有顯著的增加。但是，ciprofloxacin 就不建議使用在治療 TB 上了，有研究報告指出，ciprofloxacin 會延遲痰培養陰轉的時間，並增加復發的機率。

可是，在 Dr. Sterling (Vanderbilt University, USA)的演講中指出因爲 fluoroquinolone 的濫用(不論是已開發或開發中國家)，fluoroquinolone 的抗藥性持續增加中。許多國家都把 fluoroquinolone 以治療結核病一線藥在使用或當作細菌感染時(如: pneumonia)用藥。他擔心目前並不是所有 TB 或 MDR-TB 的治療都有在做二線藥敏的檢查，有許多患者可能在藥敏報告出來前，都只是以 fluoroquinolone 的單一治療！以他收集的數據顯示新結核病患 isoniazid (INH)抗藥比率爲 10%、rifampin (RIF) 4%、ethambutol (EMB) 3%、streptomycin (SM)11%；再治病人 INH 抗藥比率爲 28%、RIF 18%、EMB 10%、SM 20%。而 Fluoroquinolone 的結果，令人驚訝的，新病人比率居然高達 0.15-4%，而再治病人則是 15%！另外，Dr. Sterling 還說曾使用過 fluoroquinolone 10 天以上的抗藥性比率爲 2%，20 天以上則高達 9%。所以，他呼籲 fluoroquinolone 在結核病的治療是有一定的效果，但前提是需要斟酌是否以前已使用過 fluoroquinolone 超過 10 天以上及注意 2 線藥藥敏的結果。

Dr. Cegielski 也提到不適當的 MDR-TB 治療，造成了更多的 XDR-TB 病患的產生。在三年前的統計指出 MDR-TB 的治療數量與 XDR-TB 的病人是成正比。從綠光委員會 Green Light Committee（GLC）所引導的計畫在過去的 9 年內有近 115 件，合作國家有 72 國，治療患者有 64, 447 人。目前所執行的「保存結核病二線藥的有效藥效研究 Preserve Effective TB Treatment Study (PETTs)」。目的在於了解治療過程中，後天性二線藥抗藥的情況，包含：（1）GLC 可預防的極限；（2）發生的比率；（3）形成抗藥的速度；（4）用藥的改變；和（5）是否會影響治療結果。研究分爲加入 GLC 的國家（Estonia、Latvia、Russia, Peru, Philippines）也就是依照 WHO 結核藥用指引，由他們 GLC 委員會監督並提供二線藥物治療和非 GLC 國家(S.Africa, S. Korea, Thailand, 和 Taiwan)由各國家自行管理治療病患。共包含了 9 個國家一起參與研究。所有參與之地區在確定 MDRTB 後收案，取得受試者收案後治療 30 天內的第一套痰治療和每月的痰檢追蹤持續 2 年直到完治。實驗室培養陽性結核菌株、基因型別資料及個案病歷資料收集統計後傳回美國 CDC。以現在所收集到的結果顯示 (只有 2/3 的資料統計)，收入 PETTs 計畫裏的後天性二線藥抗藥患者，在治療結束時，產生：（1）**後天性 fluoroquinolone (FQN)抗藥**的有 9.4%非 GLC 組則有 15.1%；GLC 組的抗藥比率比不加入的低；（2）**後天性二線注射用藥抗藥**比率也是 6.6%和 10.7%，相對的也比較低；（3）**後天性 PreXDR-TB**(對 FQN 或 3 種 2 線針劑抗藥)的比率是 26.5%和 46.9%，明顯的減少；（4）**後天性 XDR-TB**(對 FQN 和≥ 1 種 2 線針劑抗藥) 的比率則是 0.94%和 4.4%。經過仔細的評估後，小心用藥還是

可以保有我們現有的一些可用二線抗結核病藥。

另外，Linezolid 的用藥也是這次大會討論的另一個重要議題。許多醫師表示這類藥物的副作用難以控制，安全使用劑量以還未確切保握，但是以現在抗藥性的增加，使用此類的藥物實驗是必須的。Dr. Dravniece 在「MDRTB 藥物毒性副作用處理」演講中提到 Linezolid 是“most dangerous and difficult drug”，她所面臨到的困境是醫護人員用藥與副作用的資料並不完善尤其是非英語系的國家文獻與資料的收集有限，還有，診斷的缺乏和藥物的供給，都是導致她們在治療結核病障礙。

Professor Lange 則在演講中與大家分享他在德國使用 Linezolid 的用藥成果。在 85 個個案中 41.2%有副作用反應，其中貧血、血小板低下症、噁心嘔吐、神經病變爲主要副作用表現，但是這些症狀都是可逆性的。從他研究結果他並不能清楚的標示 Linezolid 治療療效，但是發現 Linezolid 在對 7 種以上的抗結核藥抗藥的患者有明顯的效果，不論是抹片或痰培養的陰轉時間都有顯著的縮短。他認爲 Linezolid 是有效的，但是目前建議只用在 MDR 或 XDR 的病患中。

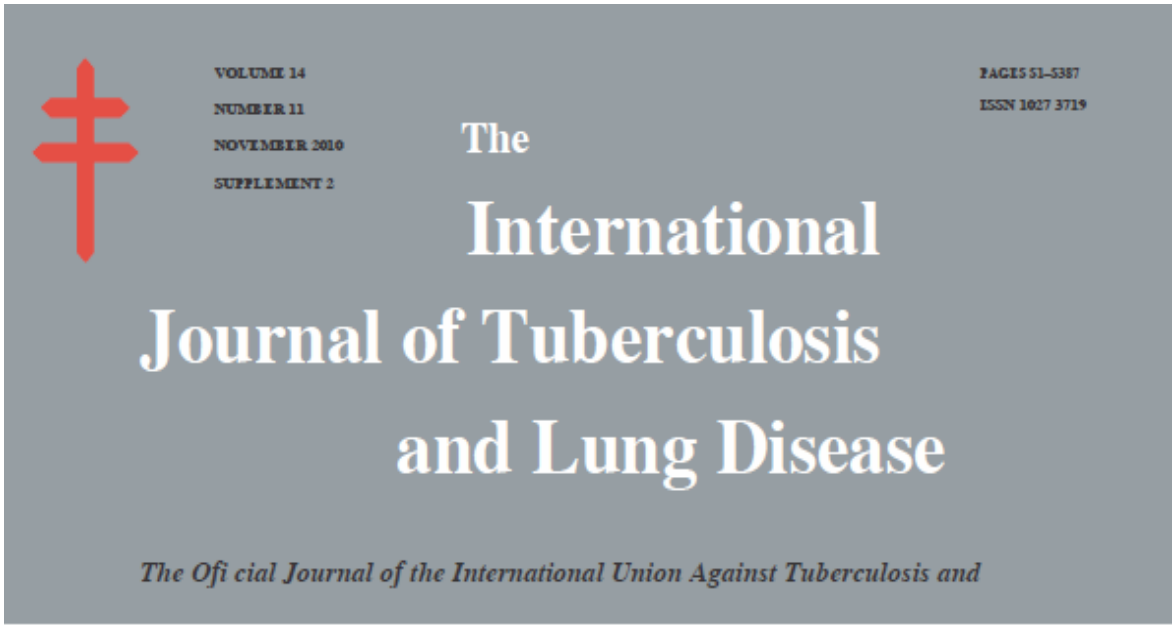
心得及建議

在經過這幾天的會議演講，可以結論台灣在結核病的診斷、治療、防禦方面並不亞於其他國家。台灣從民國 50 年防癆體系到現在的結核病醫療照護體系，我們所累積的經驗與研究，比起許多國家有過之而無不及，尤其是近幾年，台灣積極參與國際的學術交流，並發表了無數的文獻，更可以顯示出我們在結核病方面的投入與重視。

這次的會議有幾點是我們可以參考：

1) Dr. Roscigno 所呼籲的加強「定點照護 point of care」，由於台灣的總面積不如美國或非洲的大，他們所面臨的實驗室儀器的缺乏或檢驗檢體運送的延遲，在台灣並不明顯。但是他所提到最新的卡匣式檢驗儀器，CDC 昆陽實驗室已經有在測試中，未來可望在結核菌的檢驗敏感度上可提升 40%，並在 2 小時間可拿到檢驗報告。
2) Fluoroquinolone 的濫用，台灣也是其中之一，根據 Dr.Sterling 的報告，台灣 2007 年 Wang 學者所發表的抗藥比率有 2.5%。這可能是因爲 fluoroquinolone 是肺炎的常用處方用藥。因此，在使用 fluoroquinolone 之前，需要再三考慮病患是否以前用過 fluoroquinolone 類藥物並未超過 10 天以上。另外，藥敏試驗也需要以一線和二線藥敏一起檢查。
3) 由於 MDR 與 XDR 的患者治療越來越艱難，新的藥物是迫切的需要。目前我們中區醫療團與美國 MDR-TB 團隊病審後也開始接觸 Linezolid 的使用，痰檢的培養確實在短期內有陰轉，但是如其他醫師所說 Linezolid 是難以捉摸的藥類，對於它的用法與反應還需要觀察。Linezolid 目前使用建議用於 MDR 或 XDR 病患，特別是在 7 種以上的抗結核藥抗藥的患者上。

附錄



ABSTRACT BOOK

41st World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union)

BERLIN · GERMANY 11–15 NOVEMBER 2010

POSTER DISCUSSION SESSIONS

PC-100787-14 Preliminary report —Taiwan Multiple Drug Resistance Tuberculosis Consortium (TMTC)

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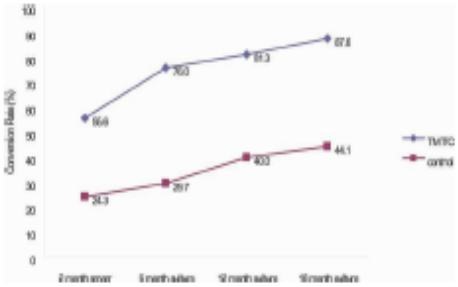
Purpose: In contrary to the conventional model of hospital-treated and government-DOT for MDR-TB patient care, Taiwan CDC launched a hospital-initiated, patient-centered treatment program (Taiwan MDR-TB consortium, TMTC) since May 2007. The aim of this study is to compare the process indicators between MDR-TB patients receiving TMTC care within 6 months of diagnosis of MDR-TB (TMTC group) and those not receiving TMTC care within 6 months of diagnosis of MDR-TB (control group).

Materials and methods: MDR-TB cases in TMTC that were diagnosed before Aug, 2008 with bacteriology evidence after Jan, 2007 were enrolled. The dif-ferences of sputum culture conversion rates were compared between TMTC group and control group by Cochran-Mantel-Haenszel (CMH) method with SAS 9.1 version.

Results: A total of 370 patients received TMTC care during the period were analyzed and 225 (60.8%) were classified as TMTC group. No difference was observed in gender, age, chronic disease and alcohol consumption habit between two groups, except patient classifications ($P < 0.0001$). The crude conversion rates were better in TMTC group than control group and the sputum culture conversion rate at 18 months was up to 87.6% in TMTC group (Figure). After stratification by patient classifications, the sputum culture conversion rate at 6, 12 and 18 months were still signii cantly higher in TMTC group. The probability of culture conversion at 18 months was 64% increment compared to control group (CMH Relative risk = 1.64, 1.38–1.95, $P < 0.0001$).



PC-100979-14 XDR-TB treatment outcome

Figure Crude conversion rates of sputum smear at 2 months, culture conversion at 6 months, 12 months, 18 months between TMTC group and control group

Conclusions: The model of government-organized, hospital-initiated and patient-centered treatment, revealed better process indicators in this preliminary report. Further analysis for treatment outcome in long term follow-up is warranted.

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PC-100817-14 A retrospective analysis of possible renal toxicity associated with aminiglycoside in MDR-TB patients

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Aim: Aminoglycosides are one of the antibiotics that are often applied to treat the mycobacteria diseases. The main constraints the use of aminoglycosides are risks of nephrotoxicity and ototoxicity. Therefore, the aim of this investigation was to determine factors related to aminoglycoside-associated nephrotoxicity in MDR-TB treatment.

Methods: The clinical data of patients that contained sex, age, weight, height, history of accompanying chronic disease, serum creatinine, uric acid level, body weight adjusted aminoglycoside dose (mg/kg), the total accumulated dose of aminiglycoside before the nephrotoxicity come about and body surface area-adjusted estimated glomerular filtration rate (eGFR) were obtained and calculated from medical records and MDRD2 equation for further analysis. The patients with ESRD (End Stage of Renal Disaese) were excluded. The nephrotoxicity was defined as a 25% decrease in eGFR from baseline. The inference statistics, including Pearson χ^2 test, one-sample K-S test, unpaired t-test and multiple-linear regression.

Results: There were seventy patients with clinical and bacteriological proved MDR-TB cases enrolled. During the course of aminoglycoside therapy in the treatment of MDR-TB, nephrotoxicity were diagnosed in seventeen patients (24.3%). Patients who developed nephrotoxicity were significantly and inversely correlated with baseline eGFR ($P < 0.05$). Additionally, the female gender had higher incidence of aminiglycosides-associated nephrotoxicity than male (43.8% vs. 18.5%; $P < 0.05$). Although the potential nephrotoxicity associated with long-term use of aminoglycoside had been emphasized in the literatures. Fortunately, it was mild and reversible in most of our patients (94.1%).

Conclusion: Felmale gender maybe is a significant factor to enhance aminiglycosides-related nephrotoxicity. Additionally, the nephrotoxicity that associated with aminiglycosides was mild and reversible in long-term MDR-TB treatment.

POSTER DISPLAY SESSIONS

PS-100523-14 Evaluate the isolation rate, drug susceptibility test and clinical features of *M. kansasii*

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Background: The incidence of diseases caused by non-tuberculous mycobacteria (NTM) is increasing worldwide. According to the report of National Taiwan General Hospital, the isolation rate of NTM had also increased from 19.5% in 1997 to 31.9% in 1999 in Taiwan. *M. kansasii* is the most virulent opportunity pathogens among NTM. It can lead to pulmonary or disseminated infections in HIV patients, and noncavitary nodular disease of bronchiectasis and fibrocavitary lung diseases in non-HIV patients. If *M. kansasii* remains untreated, it might cause lung disease. The aim of this research was to investigate the drug resistant problems for *M. kansasii*, potential effect of clarithromycin and the clinical characteristics including radiographic features and treatment outcomes in Taiwan.

Method: All clinical specimens of *M. kansasii* in Taichung Veterans General Hospital (TC-VGH) between January 2004 and December 2006 were col-lected. All specimens were isolated and identified with BDProbeTec, and drug susceptibility tests with agar proportion method and E-test strip were performed. The strains were classified using *hsp*65 PCR-restriction assay. The subjects' clinical and demographic data were collected for analysis.

Results: The isolation rate of *M. kansasii* was only 1.9% (41 isolates). The common comorbidities were chronic respiratory disease (57.7%) and HIV infection (26.9%). Except for the low concentration of isoniazid (0.2 g/mL), all compounds including high level of isoniazid, ethambutol, streptomycin, rifampicin and clarithromycin showed excellent (>85%) results in vitro activity. Genotype I (82.5%) was the most common subtypes found and mostly involved with right upper lobe. 12 patients (46.2%) received antimycobacterial therapy of isoniacid, ethambutol and rifampicin for 6–9 months. The results were 9 success, 1 failed and 2 died.

Conclusion: Clarithromycin is a possible alternative drug for improving the treatment of *M. kansasii* especially when there is drug intolerance.

PS-100441-15 Initial outcome of MDR-TB treatment in central Taiwan

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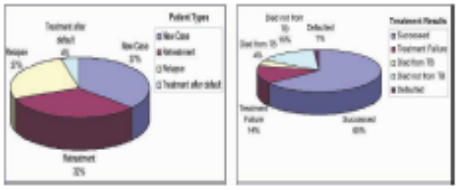
Background: Around 1% of the newly reported TB cases in Taiwan are MDR-TB. The Taiwan CDC provides a budget of NT$400 millions each year on the DOTs-plus program. They allow NT$800 000 per patient annually for the anti-TB treatment. Chang-hua Hospital conducted hospitals surrounding the central Taiwan and supervised their DOTs-plus work. This report reviewed our initial outcome of the DOTs-plus program and aimed to establish a professional medical system of treating MDR-TB and control prevalence of MDR-TB.

Methods: Any subjects from May 2007 to January 2010 resistant to isoniazid and rifampin as coni rmed by the Reference Laboratory of Mycobacteriology were included in the study. Medications for all subjects were delivered by our DOTs-plus car team workers in twice daily door to door basis to ensure the compliance, and any adverse effects were monitored and reported back to the hospital immediately. If the subjects were difficult to be reached, 3G visual mobile phones were provided to the workers to ensure drug intake by the subjects, but no more than 4 days per month. This program was managed by a supervisor who randomly would visit the subjects to find out feedback of the DOTs-plus program and the health workers. In order to increase the patient compliance, a financial support of NT$6000 monthly was provided for those who needed.

Results: 145 MDR-TB subjects in the program with 71 subjects who had completed the two year treatment —32% were retreatment, 27% were relapsed, 4% were defaulted and 37% were new cases. Forty-six subjects (65%) were successfully treated, 10 (14%) failed, 3 (4%) died from TB, 11 (16%) died from non-TB and 1 (1%) defaulted. This indicated the implement of the intensive follow-up and monitoring improved the patients' compliance and increased the cure rate and reduced the default rate.



Conclusions: The initial outcome of MDR-TB DOS-plus program showed an impressive result especially in the defaulted rate that only 1 patient was defaulted.

PS-101344-15 Investigation of a tuberculosis cluster in a college

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Background: Tuberculosis (TB) remained an endemic infectious disease in Taiwan with the incidence of 63.2 per 100 000 persons in 2007. TB cluster in school setting poses a major public health challenge. A cluster of TB in a college, with most patients related to the wrestle team, was reported in 2008.

Methods: Contact investigation was conducted to identify close contacts and potential transmission routes. Information of case patients were collected from medical records and the National TB Registry. *Mycobacterium tuberculosis* isolates were genotyped with IS*6110* restriction fragment length polymorphism (RFLP), mycobacterial interspersed repetitive-unit-variable-number tandem-repeat (MIRU-VNTR) and spoligotyping. Annual chest radiographic examination was implemented in the college to find new TB patients. Any latent infected member in the wrestle team, identified by tuberculin skin test, was under direct observed prophylaxis.

Results: From May 2006 to Oct 2009, nineteen TB patients were notii ed. Of the nineteen patients, seven were diagnosed with respiratory symptoms at health care facilities, eight through annual chest radiographic examination campaign, two through contact tracing and two through health examination. Twelve were culture-positive cases. Of these 12 *M. tuberculosis* isolates from respective 12 wrestlers, eleven isolates had identical spoligotypes, RFLP and MIRU-VNTR patterns. Among the 53 wrestlers, 24 had a diameter of tuberculin induration > 10 mm. Wrestlers recruited after 2006 had significant higher risk of tuberculin induration > 10 mm than those before 2006 (OR, 14.40; 95%CI, 3.24–68.48; $P < 0.001$).

Conclusion: Due to close contact with an active TB case during sport training, TB transmission was identified in a wrestler team.