多重抗藥結核十年減半成效

臺北市立萬芳醫院　余明治醫師

報告大綱

- 多重抗藥性結核
- 醫療照護體系
- 十年減半成效
- 防治策略
- 醫療照護體系的運作
- 病例分享
- 進展與難題
- 結論

多重抗藥性結核
Multidrug-Resistant Tuberculosis

發現結核菌

◀ *Fig. 18*
This picture of Koch (fig 18), in a real-life situation amidst the relative disorder of a busy laboratory, conveys an idea of the large frame and resolute air of the discoverer of the tubercle bacillus who was capable of holding his own and imposing his views on the august and solemn assembly of the Berlin Society, as imagined in the drawing below (fig 19).

▲ *Fig. 19*
On 24 March, 1882, KOCH announced his discovery of the tubercle bacillus during the monthly meeting of the Physiological Society of BERLIN - not of the Pathology Society, as VIRCHOW, with whom he was in conflict of opinion, was a prominent figure in that association. The session is represented here in the library of the laboratory of Profes-

人類未來與這致命的疾病奮戰時，面臨的
不再是未知的敵人，而是真實的細菌。 Robert Koch

抗結核藥物

1944年

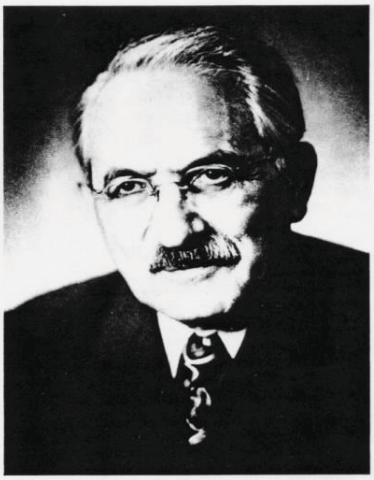


Fig. 1. Selman Waksman. Signed personal photograph presented to the author (1954)

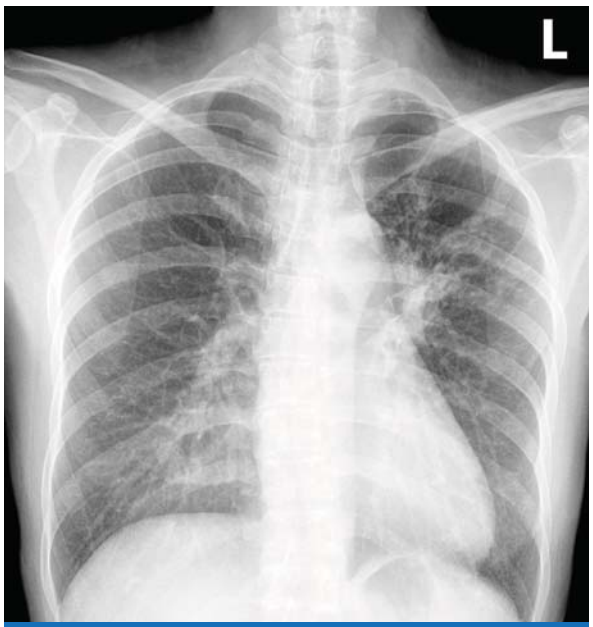
Table 1.–Landmarks in tuberculosis (TB) therapy

Date	Landmark
1944	SM and PAS
1948	Randomised trial, SM *versus* PAS *versus* SM/PAS
1952	Triple therapy, isoniazid/SM/PAS, 24 months
1960s	EMB replaces PAS, 18 months
1970s	RIF added to INH/EMB/SM, 9 months
1980s	PZA added to INH/RIF, 6 months

SM: streptomycin; PAS: para-amino salt of salicylic acid; RIF: rifampicin; EMB: ethambutol; INH: isonicotinic acid hydrazide; PZA: pyrazinamide.

Eur Respir J 2002; 20: 87s-94s

結核病診治指引



M(+), C(+), DST: all susceptible
2HERZ/4HR

防疫學苑系列

結核病診治指引

Taiwan Guidelines for TB Diagnosis & Treatment

第六版

衛生福利部疾病管制署 編

主 編 江振源

編輯委員群

（依姓氏筆畫排序）

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臺灣家庭醫學醫學會 臺灣兒科醫學會 臺灣感染症醫學會

臺灣胸腔暨重症加護醫學會 臺灣內科醫學會 臺灣結核暨肺部疾病醫學會

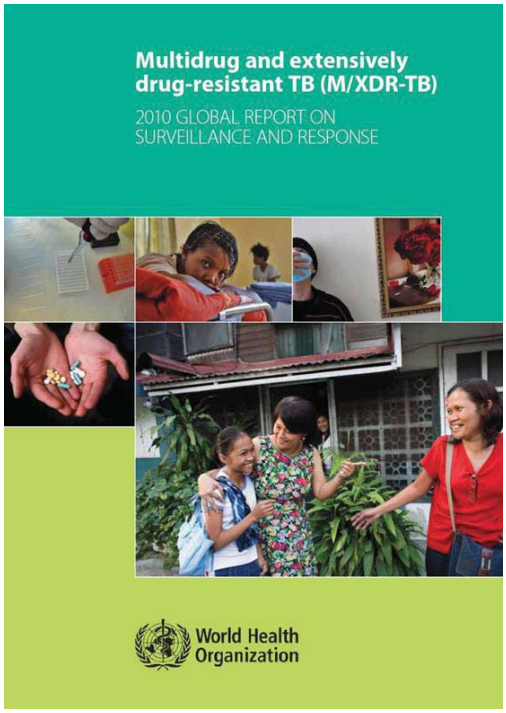
衛生福利部疾病管制署 出版

2017 年 7 月

當其他來源(非本署)之指引與本署全球資訊網有出入時，請以本署全球資訊網版本為主

Multidrug-resistant TB (MDR-TB)

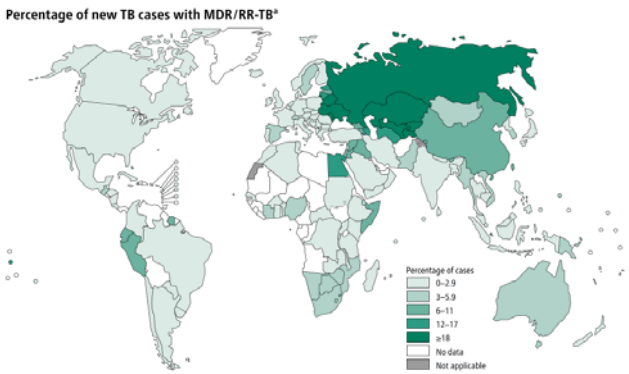
Resistant to Isoniazid and Rifampin

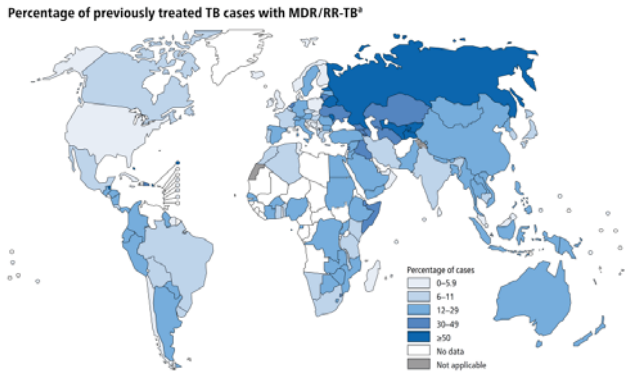


- MDR-TB
  - Primary infection with resistant bacteria
  - Develop in the course of a patient's treatment
- Not respond to the standard six month treatment with first-line anti-TB drugs
  - Can take up to two years or more to treat with drugs
    - Less potent
    - More toxic
    - Much more expensive

Multidrug-resistant/Rifampicin-resistant TB

- Globally in 2016, an estimated 4.1% of new cases and 19% of previously treated cases had MDR/RR-TB.
- There were an estimated 600,000 incident cases of MDR/RR-TB in 2016, with cases of MDR-TB accounting for 82% (490,000) of the total.

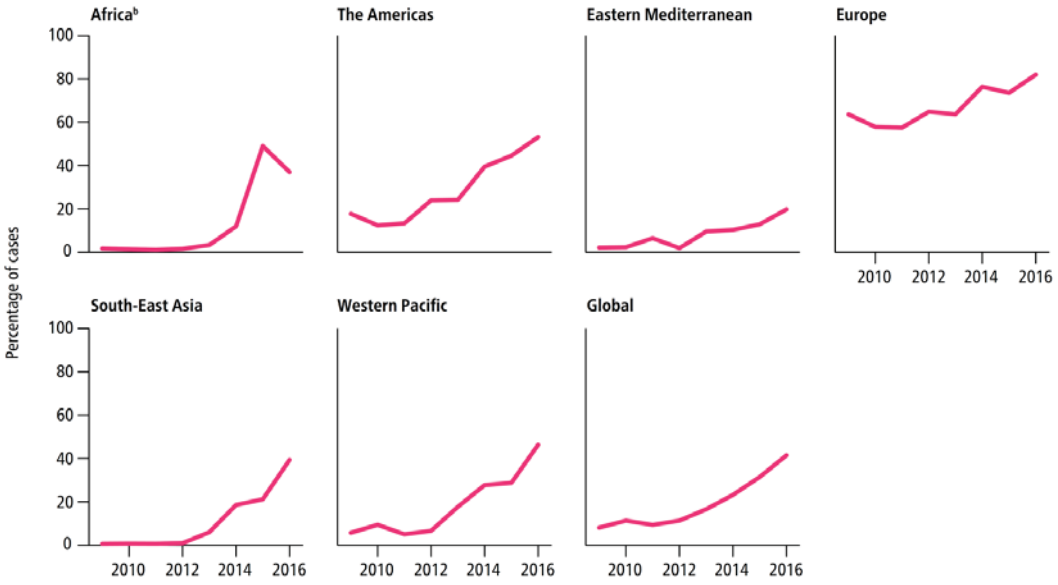




GLOBAL TUBERCULOSIS REPORT 2017, P46

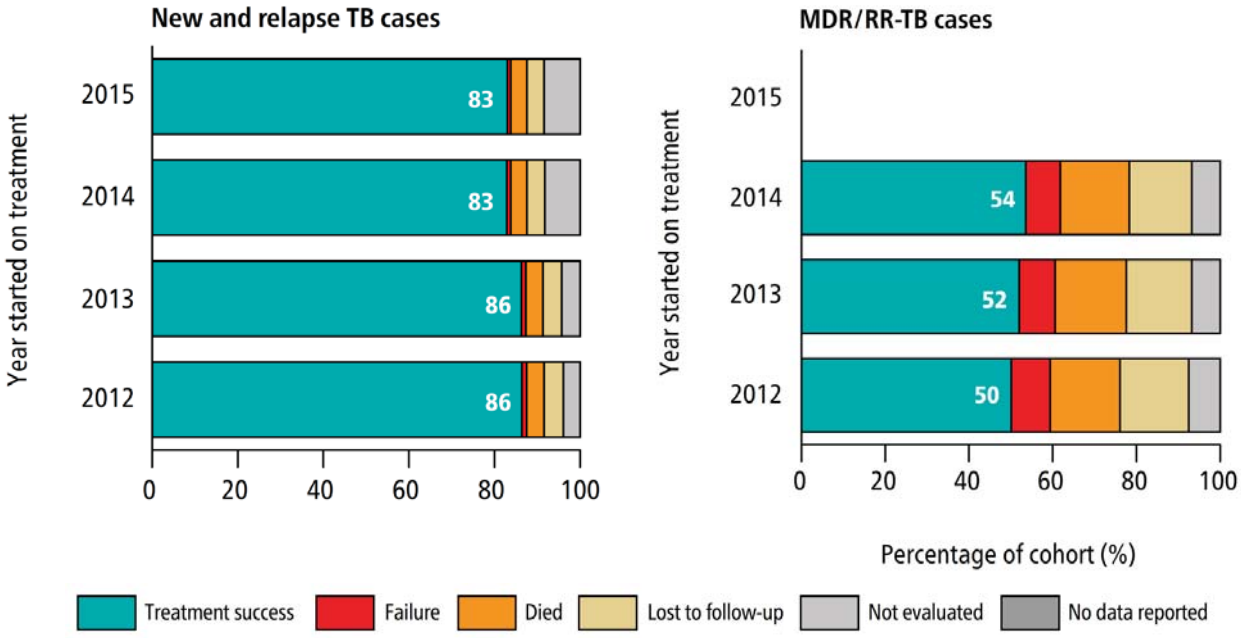
Percentage of Bacteriologically Confirmed TB Cases Tested for RR-TB, 2009–2016

- In 2016, coverage of testing for rifampicin resistance was 33% for new TB patients and 60% for previously treated TB patients, and 41% overall



GLOBAL TUBERCULOSIS REPORT 2017, P75

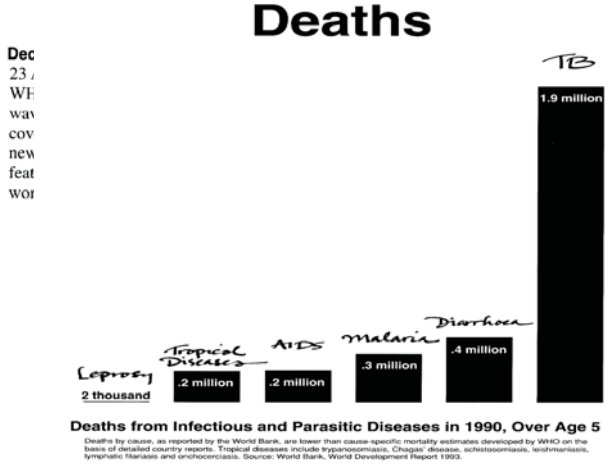
Treatment Outcomes for New and Relapse TB Cases and MDR/RR-TB Cases 2012–2015 Globally

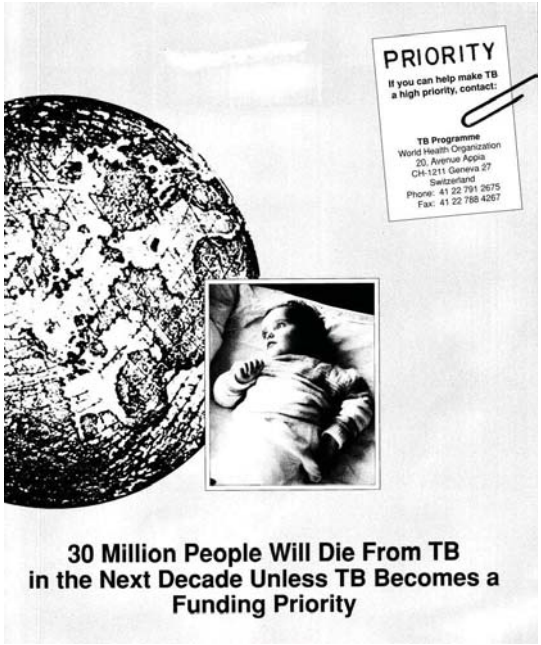


GLOBAL TUBERCULOSIS REPORT 2017, P88

多重抗藥結核病醫療照護體系

Global TB Emergency 1993





Directly Observed Treatment, Short-course

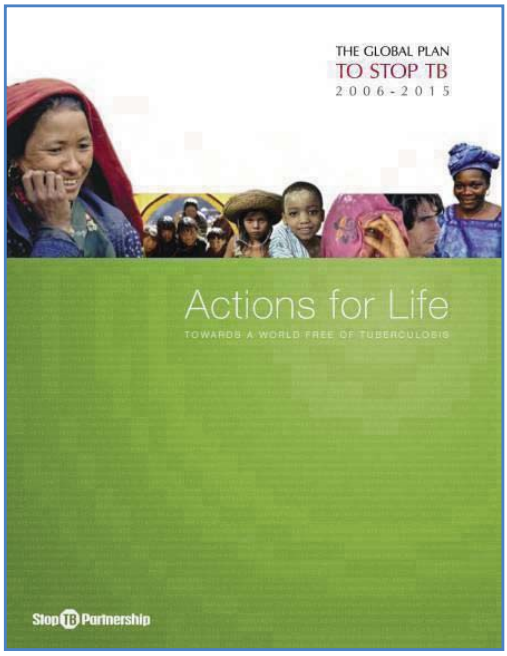
DOTS

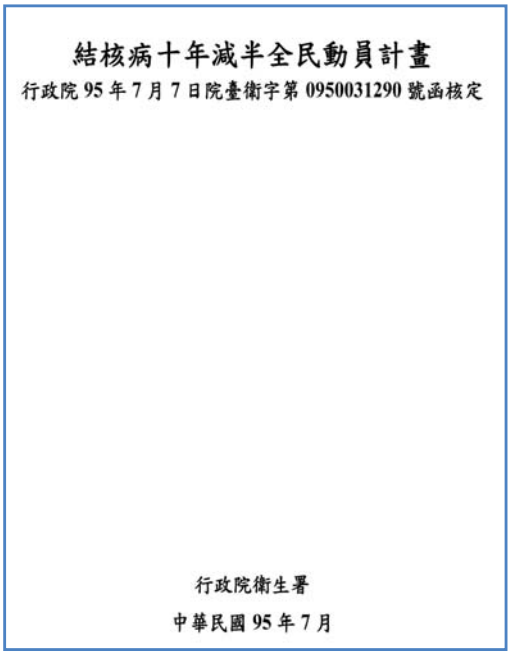
Since 1990, the World Health Organization Global Tuberculosis Programme has promoted the planning and organization of national tuberculosis control programmes focused on a "five-point policy package" comprising:

- Government commitment.
- Case detection by microscopy through predominantly passive case finding.
- Direct observed standardized short-course chemotherapy to all confirmed smear positive cases of pulmonary tuberculosis.
- Regular drug supply of all essential antituberculosis drugs.
- Monitoring of case detection and treatment outcomes based on recording individual patient information in district registers and a system of quarterly reporting and analysis.

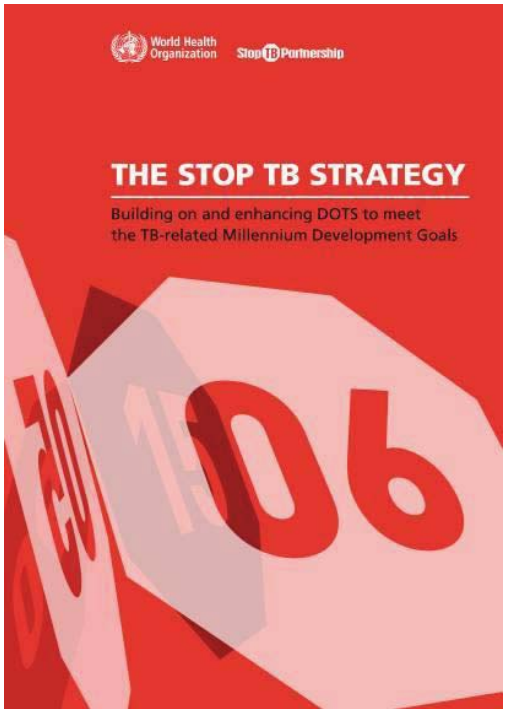
By the end of 1995, there were over 80 national programmes which had adopted the current WHO technical and managerial policies for tuberculosis control and were implementing the planned activities in the whole country or in some regions. Most national efforts have been supported by WHO, other international agencies and non-governmental organizations, in particular the International Union against Tuberculosis and Lung Disease (IUATLD).

結核病：十年減半





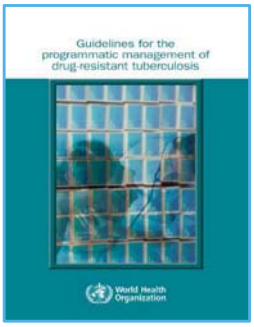
The Stop TB Strategy



- Pursue high-quality DOTS expansion and enhancement
- Address TB/HIV, MDR-TB and other challenges
- Contribute to health system strengthening
- Engage all care providers
  - Public–Public and Public–Private Mix (PPM) approaches
  - International Standards for Tuberculosis Care
- Empower people with TB, and communities
- Enable and promote research

Prevent and Control Multidrug-resistant TB

- Management of MDR-TB under programmatic conditions is feasible, effective and cost-effective when implemented in the context of a well-functioning DOTS program and based on WHO's DOTS-Plus policy guidelines



- The key actions for preventing and controlling drug-resistant TB include
  - Use of recommended treatment regimens
  - A reliable supply of quality-assured first- and second-line anti-TB drugs
  - Adherence to treatment by patients

都治(DOTS)

疫情報導 184　　2008 年 3 月 25 日

台灣都治（DOTS）執行經驗及成效初探

許建邦[1]、羅秀雲[2]、李政益[2]、楊祥麟[2]、王貴鳳[1]、楊世仰[3]

1. 衛生署疾病管制局第三組
2. 衛生署疾病管制局第五組
3. 衛生署疾病管制局第二分局

摘要

台灣自 2006 年 4 月起在結核病十年減半的目標及長程計畫下，全面落實推動都治，2007 年 12 月之資料顯示管理中之痰塗片陽性納入都治之執行率達 92.6%，除了量的提升外，在執行品質的部份亦透過落實督導考核來加強。初步的世代追蹤資料顯示：比較 2006 年參加都治及非都治之痰塗片陽性個案治療成功率、三個月之痰陰轉率、失落率均有顯著差異，2006 年之資料與實施都治前之 2005 年個案追蹤資料相較亦有相當進步，顯示台灣執行都治已有一定的成效。

都治之執行應有整體的配套策略，尤其世界衛生組織所建議的五要素，過程中亦需要透過不斷地實證研究，發現缺失並持續修正，俾以提升都治執行的品質及績效。

MDR-TB人數

公開徵求「建構 MDR 結核病醫療照護體系」計畫需求說明書

壹、背景說明及計畫目的：

結核病一直是台灣最嚴重的傳染病，不但危害民眾健康、耗損社會生產力，更嚴重影響國家競爭力及國際形象。有鑑於此，本局於 95 年 7 月 7 日奉行政院核定「結核病十年減半全民動員計畫」，期以更積極主動之防治作為，達成結核病十年減半之目標。

我國初發病患多重抗藥性結核之比率，已由 1990 年代的 0.2%，十年間增加十倍，目前約有 600-800 人，且分散於 60 多家醫療院所治療，而這些醫療院所卻大都未具備治療此類病患之能力，如果此問題無法解決，勢將影響結核病防治工作成效，所以本局期藉由此計畫之推行，提供資源建立一專門的、集中的醫療照護體系，以有效控制 MDR 結核病疫情。

多重抗藥結核病防治策略及患者管理

2007 年5 月成立「多重抗藥結核病醫療照護體系」

疾病管制局提供資源，要求全臺灣5個醫療團隊依世界衛生組織所訂診治指引進行診治，並執行社區進階都治(DOTS-Plus)，給予病人完整且持續之照護。

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

多重抗藥結核十年減半成效

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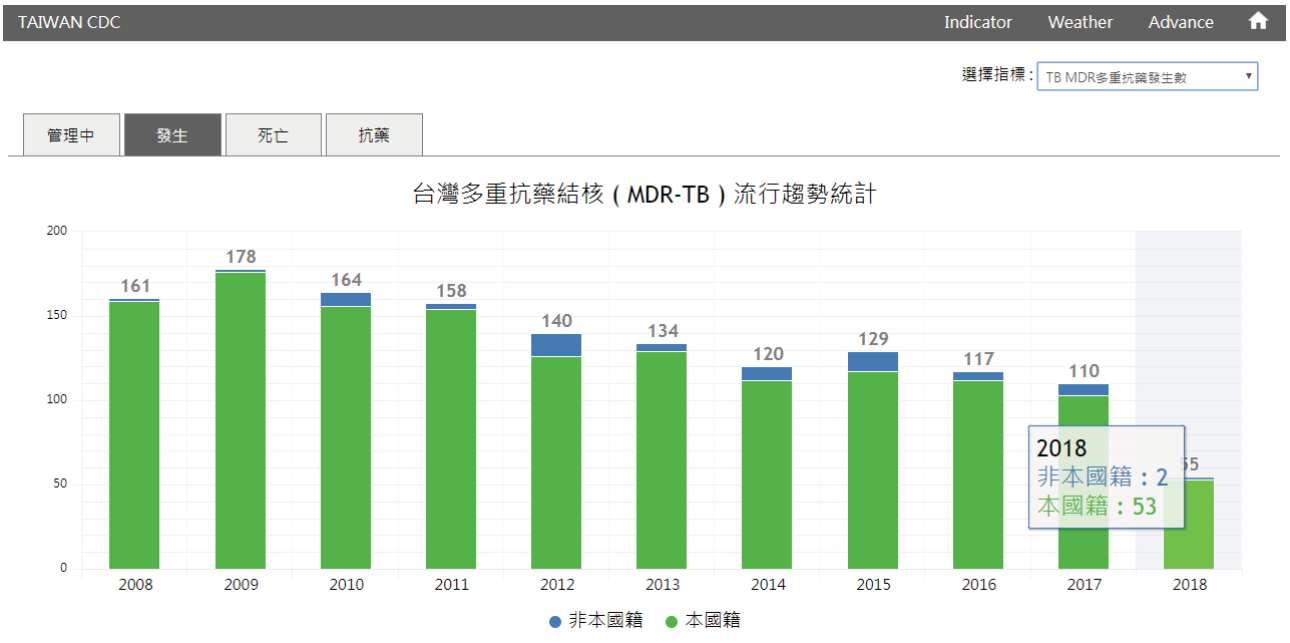
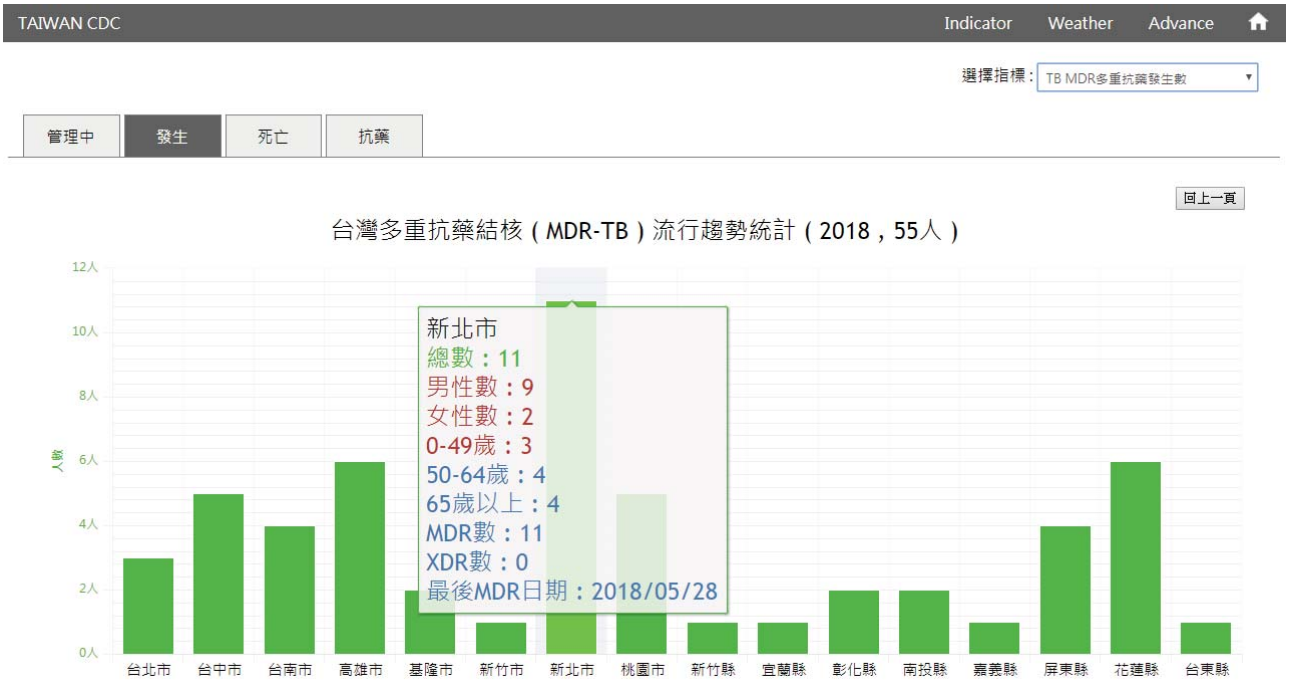
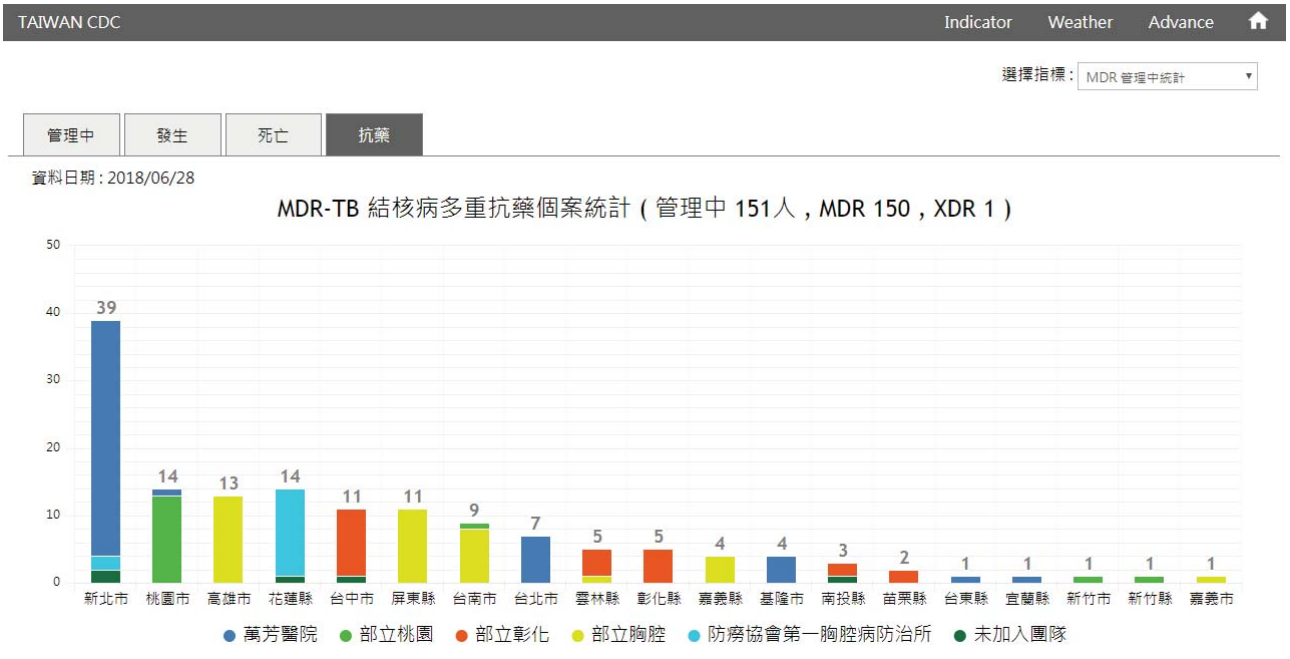
CDC Monitoring (1)



CDC Monitoring (2)



CDC Monitoring (3)



多重抗藥結核十年減半成效

END TB終結結核，各界領袖一起攜手邁向零結核 (2018-05-09)

世界衛生組織（WHO）訂定每年3月24日為世界結核病日，今（2018）年主題是「Wanted: Leaders for a TB-free world. You can make history. End TB」，希望各界都能發揮領導力，一起終結結核病。疾病管制署於3月23日晚間舉辦「END TB 終結結核」記者會，由衛生福利部陳時中部長、疾病管制署周志浩署長、社會福利及環境衛生委員會立法委員吳玉琴委員、陳曼麗委員、國際抗痨聯盟江振源顧問及其他國際專家、團體代表等各界領袖一同簽名，象徵將為「終結結核」行動努力，並於疾管署外牆首度點亮巨型「→ | END TB」標誌及標語燈飾，喚起民眾對結核病防治的重視。

會中陳部長表示，政府將持續提升結核病防治之廣度及深度，讓民眾免於結核病威脅，期望在政府、醫界、學界及民眾的攜手努力下，達到終結結核的目標。江顧問特別分享對抗結核在國際上的成果，並提醒民眾有結核症狀應儘速就醫，配合醫囑接受治療。另潛伏結核個案「林同學」，分享親身的經歷，同時呼籲，過去總以為結核病是老年人的疾病，經過這次經驗，他發現年輕人也不可輕忽，所以如果被通知可能感染，不管是自己，還要提醒同學、好友或家中長輩，配合治療，就可治癒，降低未來發病的可能性。

在各衛生及醫療單位的努力下，我國結核病新案發生數從2005年的16,472人降至2017年的9,754人，首次破萬人以下，死亡率也下降40%，即使是多重抗藥性結核病照護個案數亦由2007年的440人降至2017年的152人，治療成功率約達八成，遠超過全球治療成功率之五成。

結核病是可預防可治療的疾病，若民眾被通知為結核病接觸者，請務必配合衛生單位進行相關檢查及潛伏結核感染治療評估，如確定為潛伏結核感染者，及早接受治療可降低發病風險。但若已出現咳嗽有痰、咳嗽超過2-3週、胸痛、食慾不振、體重減輕、發燒等症狀，請儘速就醫檢查，以及早發現及早治療，保護自己與家人的健康。

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

多重抗藥結核防治策略

疫情報導 Taiwan EB
2012年9月18日 第28卷 第18期

原著文章

我國多重抗藥性結核病防治策略演進

黃淑華、王貴鳳、詹珮君、楊靖慧、陳昶勳

衛生署疾病管制局第三組

摘要

結核病是我國最嚴重的傳染病，每年有將近 1 萬 3 千名新發個案產生。由於治療期程較長及藥物副作用等因素，常造成病人不規則服藥，是引發後續轉為抗藥性結核病的原因。

世界衛生組織於 2007 年提出警告，指出「抗藥性肺結核蔓延」是一個威脅全球的重大公衛問題，建議世界各國推動進階都治（Directly Observed Treatment, Short-course, plus, DOTS-plus）以防治多重抗藥性結核病疫情。

多重抗藥性結核病防治策略

- 2006年12月：抗藥種類及抗結核二線藥使用之監測
- 2007年5月：成立「多重抗藥性結核病醫療照護體系」
  - 由疾病管制局提供資源，要求5 個團隊依WHO 所訂診治指引進行診治，並執行社區進階都治工作，給予病患完整且持續之照護
- 2007年7月：多重抗藥性結核病納入第二類法定傳染病
- 2007年8月：與中央健康保險局合作，進行 Fluoroquinolone 類藥物管控
- 2008年5月：凡通報多重抗藥性結核病之個案，均需將菌株送疾病管制局實驗室進行確認
- 2009年9月：提供高危險族群進行基因型別(GenoType)快速檢驗

抗藥種類及抗結核二線藥使用之監測

2006年12月

公開徵求「建構 MDR 結核病醫療照護體系」計畫需求說明書

壹、背景說明及計畫目的：

結核病一直是台灣最嚴重的傳染病，不但危害民眾健康、耗損社會生產力，更嚴重影響國家競爭力及國際形象。有鑑於此，本局於 95 年 7 月 7 日奉行政院核定「結核病十年減半全民動員計畫」，期以更積極主動之防治作為，達成結核病十年減半之目標。

我國初發病患多重抗藥性結核之比率，已由 1990 年代的 0.2%，十年間增加十倍，目前約有 600-800 人，且分散於 60 多家醫療院所治療，而這些醫療院所卻大都未具備治療此類病患之能力，如果此問題無法解決，勢將影響結核病防治工作成效，所以本局期藉由此計畫之推行，提供資源建立一專門的、集中的醫療照護體系，以有效控制 MDR 結核病疫情。

成立多重抗藥性結核病醫療照護體系

2007年5月

多重抗藥性結核病納入第二類法定傳染病

2007年7 月

- 醫師診治病人或醫師、法醫師檢驗、解剖屍體，發現傳染病或疑似傳染病時，應立即採行必要之感染控制措施，並報告當地主管機關
  - 第二類傳染病，應於二十四小時內完成
    - 多重抗藥性結核病
  - 第三類傳染病應於一週內完成
    - 結核病（除多重抗藥性結核病外）


Weekend 生活新聞 A8

結核男落跑 疾管局點名通緝

他回電護士：在花東山區吃草藥

Fluoroquinolone 類藥物管控

2007年8月

494 MDR isolates: 28.9% resistant to ofloxacin

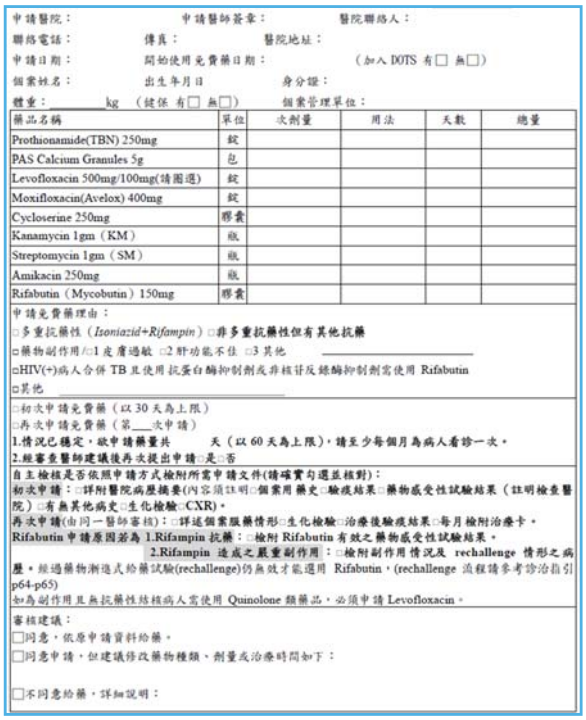
A population-based study was performed to characterize the genotype and drug-resistant patterns of multidrug-resistant tuberculosis (MDR-TB) in Taiwan. From 2007 to 2008, we analyzed 494 MDR *Mycobacterium tuberculosis* complex isolates using spacer oligonucleotide typing and drug susceptibility testing. The majority of cases occurred in the age groups of 45–54 (24.3%) and ≥65 (23.1%). Of the 494 MDR isolates, 25.1% were resistant to ethambutol, 15.6% were resistant to streptomycin, 27.1% were resistant to all four first-line anti-tuberculosis drugs, 28.9% were resistant to ofloxacin, and 8.7% were extensively drug-resistant (XDR). Compared with the SpolDB4, 86 spoligotypes were identified in 492 isolates. We observed 427 (86.8%) isolates belonging to 49 known spoligotypes and 65 isolates (13.2%) in 37 undesignated spoligotypes. Beijing lineages (50.0%) were the predominant genotype, followed by Haarlem (18.2%) and East-African-Indian (EAI) (5.7%). Geographically, Beijing lineages were predominant in all regions, whereas Haarlem lineages were predominant only in the east (28.1%) and EAI (11.3%) only in the south. Beijing lineages are statistically associated with MDR in younger age groups and eastern Taiwan. Furthermore, we found that Beijing ST1 (46.1%), Haarlem3 ST50 (7.1%) and ST742 (4.7%), and EAI2_MANILA ST19 (3.9%) were the prevalent groups. Thus, continuous surveillance with more thorough genotyping and epidemiological investigation is crucial for the prevention of further dissemination, the determination of the temporal and spatial trends of multi-drug resistance, and the emergence of XDR-TB in Taiwan.

Characteristics of Multidrug-Resistant *Mycobacterium tuberculosis* in Taiwan: A Population-based Study. *Infect Genet Evol* 2011;11:633–9

健康保險局規定Fluoroquinolone類使用於結核病不給付

充足的第二線抗結核藥物供應及管理

- Streptomycin/Kanamycin/Amikacin
- Capreomycin
- Levofloxacin/Moxifloxacin
- Prothionamide
- Cycloserine/Terizidone
- *p*-aminosalicylic acid (PAS)
- Clofazimine
- Linezolid
- Bedaquiline
- Delamanid



申請醫院：　　申請醫師簽章：　　醫院聯絡人：
聯絡電話：　　傳真：　　醫院地址：
申請日期：　　開始使用免費藥日期：　　（加入 DOTS 有□ 無□）
個案姓名：　　出生年月日　　身分證：
體重：　　kg　（統保 有□ 無□）　　個案管理單位：

藥品名稱	單位	次劑量	用法	天數	總量
Prothionamide(TBN) 250mg	錠				
PAS Calcium Granules 5g	包				
Levofloxacin 500mg/100mg(請圈選)	錠				
Moxifloxacin(Avelox) 400mg	錠				
Cycloserine 250mg	膠囊				
Kanamycin 1gm（KM）	瓶				
Streptomycin 1gm（SM）	瓶				
Amikacin 250mg	瓶				
Rifabutin（Mycobutin）150mg	膠囊				

申請免費藥理由：
□多重抗藥性（*Isoniazid+Rifampin*）□非多重抗藥性但有其他抗藥
□藥物副作用/□1.皮膚過敏 □2.肝功能不佳 □3.其他 _____
□HIV(+)病人合併 TB 且使用抗蛋白酶抑制劑或非核苷反錄酶抑制劑需使用 Rifabutin
□其他 _____

□初次申請免費藥（以 30 天為上限）
□再次申請免費藥（第___次申請）
1.情況已穩定，缺申請藥量共　　天（以 60 天為上限），請至少每個月為病人看診一次。
2.經審查醫師建議後再次提出申請□是□否

自主檢核是否依照申請方式檢附所需申請文件(請確實勾選並核對)：
初次申請：□詳附醫院病歷摘要(內容須註明□個案用藥史□驗痰結果□藥物感受性試驗結果（註明檢查醫院）□有無其他病史□生化檢驗□CXR)。
再次申請(由同一醫師審核)：□詳述個案服藥情形□生化檢驗□治療後驗痰結果□每月檢附治療卡。
Rifabutin 申請原因若為 1.Rifampin 抗藥：□檢附 Rifabutin 有效之藥物感受性試驗結果。
2.Rifampin 造成之嚴重副作用：□檢附副作用情況及 rechallenge 情形之病歷。經過藥物漸進式給藥試驗(rechallenge)仍無效才能選用 Rifabutin。(rechallenge 流程請參考診治指引 p64-p65)
如為副作用且無抗藥性結核病人需使用 Quinolone 類藥品，必須申請 Levofloxacin。

審核建議：
□同意，依原申請資料給藥。
□同意申請，但建議修改藥物種類、劑量或治療時間如下：

□不同意給藥，詳細說明：

多重抗藥性菌株送疾病管制局實驗室確認

2008年5月

Drug-susceptibility testing in tuberculosis: methods and reliability of results

S.J. Kim

ABSTRACT: The demand for reliable drug-susceptibility testing (DST) increases with the expansion of antituberculosis drug-resistance surveillance, and with the need for an appropriate treatment of multidrug-resistant tuberculosis, whose incidence gradually increases in many parts of the world. However, the reliability of DST results obtained through widely used methods does not meet acceptable levels, except for DST to isoniazid and rifampicin.

In general, susceptibility results are highly predictable, while resistance results show low predictive values when the resistance prevalence is <10%. Poor reliability stems from a weak correlation with clinical response and a low reproducibility due to the poor standardisation of the complex and fragile test procedures. Therefore, *in vitro* criteria of resistance for susceptibility testing should be carefully determined with representative clinical samples of *Mycobacterium tuberculosis* isolated from patients never treated with any antituberculosis drug, and from patients having failed treatment with a regimen containing the tested drug; DST should then be carefully standardised to obtain reproducible results.

The critical concentration of some drugs is close to the minimal inhibitory concentration for wild susceptible strains and, thus, drug-susceptibility testing is prone to yield poorly reproducible results. These issues call for physicians' attention when using the results from drug-susceptibility testing for case management.

Eur Respir J 2005; 25: 564–9

Resistance results show low predictive values when the resistance prevalence is <10%

INT J TUBERC LUNG DIS 13(9):1142–1147

Proficiency of drug susceptibility testing for *Mycobacterium tuberculosis* in Taiwan

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SUMMARY

OBJECTIVE: To evaluate the impact of external quality assessment on the quality of drug susceptibility testing (DST) in clinical mycobacteriology laboratories.

DESIGN: A pilot evaluation of DST proficiency was conducted in 2006 and scaled up in 2007. A panel consisting of 20 *Mycobacterium tuberculosis* isolates was used. Accuracy of 95% in detecting resistance to both isoniazid (INH) and rifampicin (RMP), and 90% to both ethambutol (EMB) and streptomycin (SM), was used to define a competent laboratory.

RESULTS: Nine laboratories participated in 2006 and 30 in 2007. In 2006, the mean accuracy in detecting resistance to INH was 91.6%, for RMP it was 96.1%, for EMB it was 90.5% and for SM it was 93.9%. In 2007, the mean accuracy in detecting resistance to INH increased to 95.7% and that for RMP to 97.2%, while the accuracy of EMB resistance detection decreased to 82.0% and that for SM resistance to 86.8%. Quality improvement was observed in those laboratories that had adopted standardised methods. Overall, only five (17%) laboratories fulfilled the competency criteria for all four drugs in 2007.

CONCLUSION: The majority of the laboratories that participated in 2006 demonstrated an improvement in DST performance in 2007. It is essential to continue external quality assessment to strengthen the quality of DST.

KEY WORDS: tuberculosis; proficiency; drug susceptibility testing

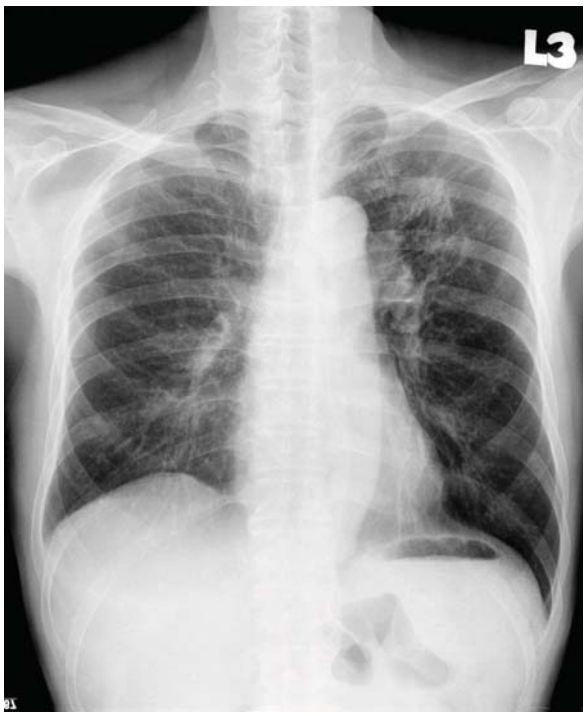
Essential to continue proficiency evaluation of DST to ensure that all laboratories meet the criteria of competency

多重抗藥性菌株送疾病管制局實驗室確認

2008年5月

- 藥物感受性試驗
  - 所有結核病人第一次培養陽性菌株
  - 病人接受治療 4 個月後仍為培養陽性的菌株
  - 陰轉後再度培養陽性的菌株
- 健保制度的配合

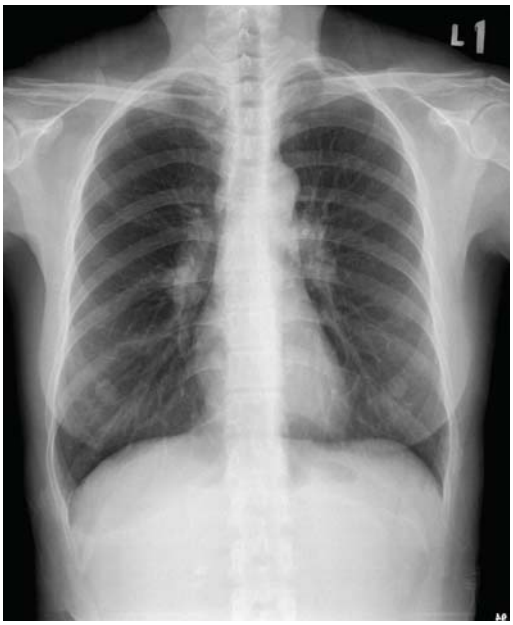
64歲男性



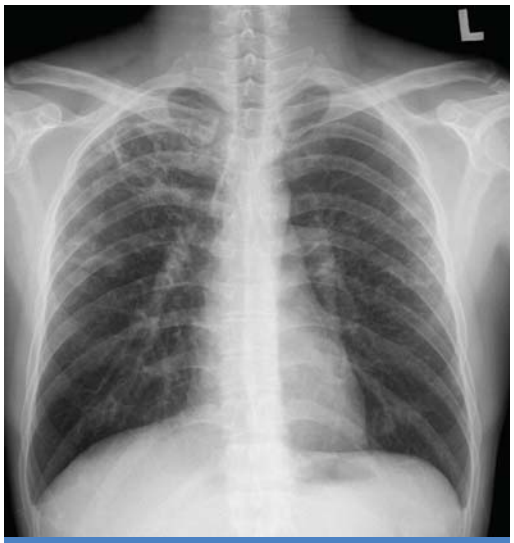
高危險族群進行快速檢驗服務

2009年9月

MDR-TB



親密接觸者



MDR-TB:46天

Performance Assessment of the GenoType MTBDR*plus* Test and DNA Sequencing in Detection of Multidrug-Resistant *Mycobacterium tuberculosis*

To facilitate the management of multidrug-resistant (MDR) tuberculosis, two nucleic acid sequence-based methods, the GenoType MTBDR*plus* test and DNA sequencing, were assessed for the rapid detection of drug-resistant *Mycobacterium tuberculosis* for the first time in the Asia-Pacific region. The performances of these two assays in detecting the presence of rifampin (rifampicin) (RIF) and isoniazid (INH) resistance-associated mutations in the *rpoB*, *katG*, *inhA* regulatory region, *inhA*, and *oxyR-ahpC* genes were compared to that of a conventional agar proportion drug susceptibility test. A total of 242 MDR and 30 pansusceptible *M. tuberculosis* isolates were evaluated in this study. The sensitivities obtained for RIF-resistant detection by the GenoType MTBDR*plus* test and by resistance gene sequencing were 95.5% and 97.9%, respectively. The sensitivities for INH resistance detection by the GenoType MTBDR*plus* test and by resistance gene sequencing were 81.8% and 93.4%, respectively. Together, the sensitivity for MDR tuberculosis detection was 78.5% with the GenoType MTBDR*plus* test and 91.3% by resistance gene sequencing. The specificity for RIF resistance, INH resistance, and MDR detection was 100% by both methods. The GenoType MTBDR*plus* test has the advantage of a short turnaround time for drug-resistant *M. tuberculosis* detection. Overall, the two assays performed equally well in detecting RIF resistance ($P = 0.13$). However, DNA sequencing demonstrated superior performance in detecting INH resistance ($P < 0.001$) and MDR tuberculosis ($P < 0.001$). We suggest that new alleles of INH resistance genes should be evaluated to improve the sensitivity of the GenoType MTBDR*plus* test, especially for different geographic areas with genetically diverse *M. tuberculosis* strains.

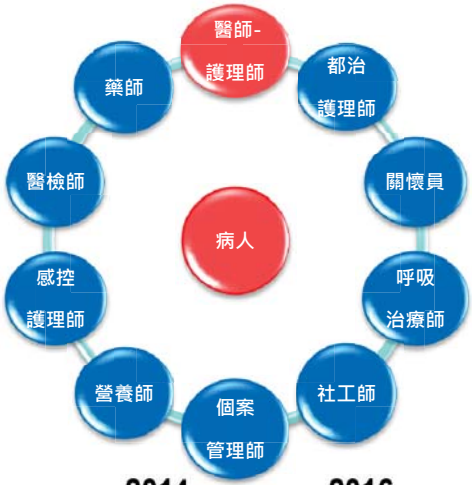
凡發現治療失落、失敗、復發的結核病個案或多重抗藥性結核個案接觸者的痰檢體，應送疾病管制局進行快速分子檢測。

J Clin Microbiol 2009; 47:2520–4

多重抗藥結核病醫療照護體系的運作

多重抗藥結核病醫療照護體系

1. Use of recommended treatment regimens 2. Adherence to treatment



2006 2008 2011 2014 2016

The Union World Conference on Lung Health

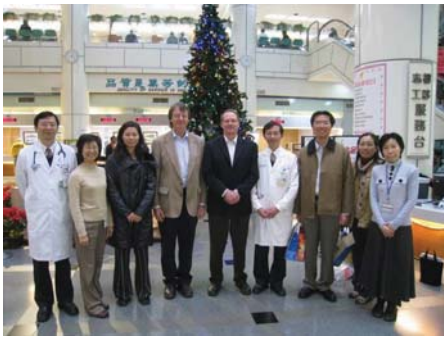
Cape Town, 2007

陸教授親自領隊

站著聆聽Professor Charles Daley演講

多重抗藥結核病醫療照護體系

每3個月舉行專家團隊會議



策略 1

住院/社區照護

Isolation Room

- 初期: 約2 星期至 2 個月
  - 驗痰
  - 治療處方的設計與給予
  - 監控藥物副作用
  - 結核病衛教
  - 呼吸道隔離
- 治療中
  - 疾病惡化或併發症
  - 藥物副作用

策略 2

治療處方的設計：原則

- The intensive phase of MDR-TB treatment should consist of at least four second-line anti-TB drugs that are likely to be effective
  - MDR regimens should include at least pyrazinamide, a fluoroquinolone, an injectable anti-TB drug, ethionamide (or prothionamide) and either cycloserine or PAS
- The intensive phase lasts at least eight months in total
  - At least four months past culture conversion
- Injectable anti-TB drugs should be given once daily
  - The injectable agent may be given three times a week, preferably only after culture conversion
- The total length of treatment
  - At least 20 months in most patients not previously treated for MDR-TB
  - Previously treated for MDR-TB generally receive at least 24 months of therapy

策略 2

治療處方的設計：步驟 (1)

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
	Choose a drug based on DST and treatment history. Streptomycin is generally not used because of high rates of resistance in patients with MDR-TB.	
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Use a later generation fluoroquinolone. If levofloxacin (or ofloxacin) resistance is documented, use moxifloxacin. Avoid moxifloxacin if possible when using bedaquiline or delamanid (see Annexes 4.1–4.2).	
STEP 3	**Add Group 4 drugs**	**Cycloserine/terizidone** **Para-aminosalicylic acid (PAS)** **Ethionamide/prothionamide**
	Add two or more Group 4 drugs until there are at least four second-line anti-TB drugs likely to be effective. Ethionamide/prothionamide is considered the most effective Group 4 drug. Consider treatment history, side-effect profile, and cost. DST is not considered reliable for the drugs in this group.	

策略 2

治療處方的設計：步驟 (2)

STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol can be added if the criteria for an effective drug are met (see Section 5.7.1 for definition of "effective drug"). If isoniazid is unknown or pending it can be added to the regimen until DST results become available, see Section 5.8.	
STEP 5	**Add Group 5 drugs**	**Bedaquiline** **Delamanid** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin plus clavulanate** **Meropenem plus clavulanate** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Consider adding Group 5 drugs if four second-line anti-TB drugs are not likely to be effective from Groups 2–4. If drugs are needed from this group, it is recommended to add two or more. DST is not standardized for the drugs in this group. The drug–drug interactions between bedaquiline and delamanid have not been established and a recommendation about its combined use is not made in the WHO interim policy on these two drugs.	

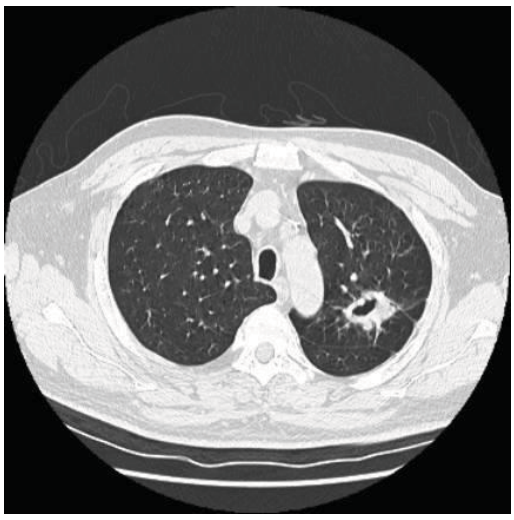
WHO Treatment Guidelines for Drug-resistant TB, 2016

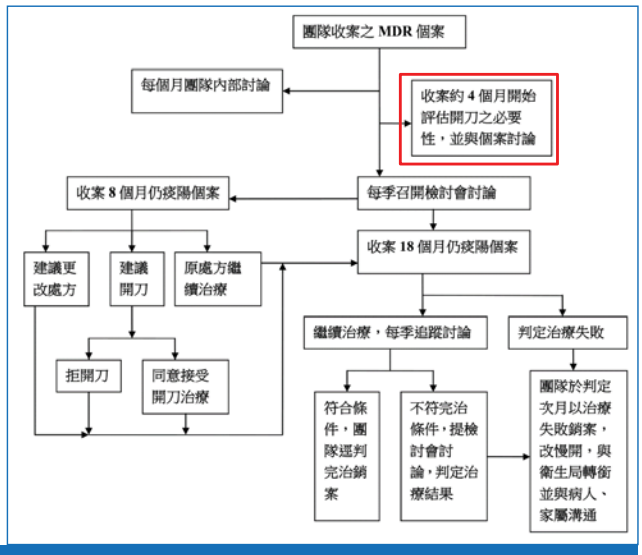
Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[c]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

- At least five effective TB medicines during the intensive phase, including pyrazinamide and four core second-line TB medicines
  - One chosen from Group A
  - One from Group B
  - At least two from Group C
- Clofazimine and linezolid
  - Core second-line medicines
- P-aminosalicylic acid
  - Add-on agent
- Macrolides
  - No longer indicated

策略 3

外科手術





The timing of surgery may be earlier in the course of the disease

- **Generally, at least two months of therapy should be given prior to resection surgery to decrease the bacterial infection in the surrounding lung tissue**

Surgery as an Adjunctive Treatment for Multidrug-Resistant Tuberculosis: An Individual Patient Data Metaanalysis

Gregory J. Fox,[1] Carole D. Mitnick,[2] Andrea Benedetti,[1] Edward D. Chan,[3] Mercedes Becerra,[2] Chen-Yuan Chiang,[4] Salmaan Keshavjee,[2] Won-Jung Koh,[5] Yuji Shiraishi,[6] Piret Viiklepp,[7] Jae-Joon Yim,[8] Geoffrey Pasvol,[9] Jerome Robert,[10] Tae Sun Shim,[11] Sonya S. Shin,[12] and Dick Menzies[1]; for the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB[a]

[1]Montreal Chest Institute, McGill University, Canada; [2]Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts; [3]Departments of Medicine and Academic Affairs, Denver Veterans Affairs Medical Center, Colorado; [4]Wan Fang Hospital, Taipei Medical University, Taiwan; [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [6]Section of Chest Surgery, Fukujuji Hospital, Tokyo, Japan; [7]Estonian Tuberculosis Registry, National Institute for Health Development, Tallinn; [8]Department of Internal Medicine, Seoul National University College of Medicine, South Korea; [9]Department of Infection & Tropical Medicine, Imperial College London, United Kingdom; [10]Laboratoire de Bacteriologie-Hygiene, University Pierre and Marie Curie, Paris, France; [11]Department of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; and [12]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts

Background. Medical treatment for multidrug-resistant (MDR)-tuberculosis is complex, toxic, and associated with poor outcomes. Surgical lung resection may be used as an adjunct to medical therapy, with the intent of reducing bacterial burden and improving cure rates. We conducted an individual patient data metaanalysis to evaluate the effectiveness of surgery as adjunctive therapy for MDR-tuberculosis.

Methods. Individual patient data, was obtained from the authors of 26 cohort studies, identified from 3 systematic reviews of MDR-tuberculosis treatment. Data included the clinical characteristics and medical and surgical therapy of each patient. Primary analyses compared treatment success (cure and completion) to a combined outcome of failure, relapse, or death. The effects of all forms of resection surgery, pneumonectomy, and partial lung resection were evaluated.

Results. A total of 4238 patients from 18 surgical studies and 2193 patients from 8 nonsurgical studies were included. Pulmonary resection surgery was performed on 478 patients. Partial lung resection surgery was associated with improved treatment success (adjusted odds ratio [aOR], 3.0; 95% confidence interval [CI], 1.5–5.9; I^2_R, 11.8%), but pneumonectomy was not (aOR, 1.1; 95% CI, .6–2.3; I^2_R, 13.2%). Treatment success was more likely when surgery was performed after culture conversion than before conversion (aOR, 2.6; 95% CI, 0.9–7.1; I^2_R, 0.2%).

Conclusions. Partial lung resection, but not pneumonectomy, was associated with improved treatment success among patients with MDR-tuberculosis. Although improved outcomes may reflect patient selection, partial lung resection surgery after culture conversion may improve treatment outcomes in patients who receive optimal medical therapy.

Keywords. multidrug resistant tuberculosis; thoracic surgery; pneumonectomy; metaanalysis; individual patient data.

Clin Infect Dis 2016;62:887–95

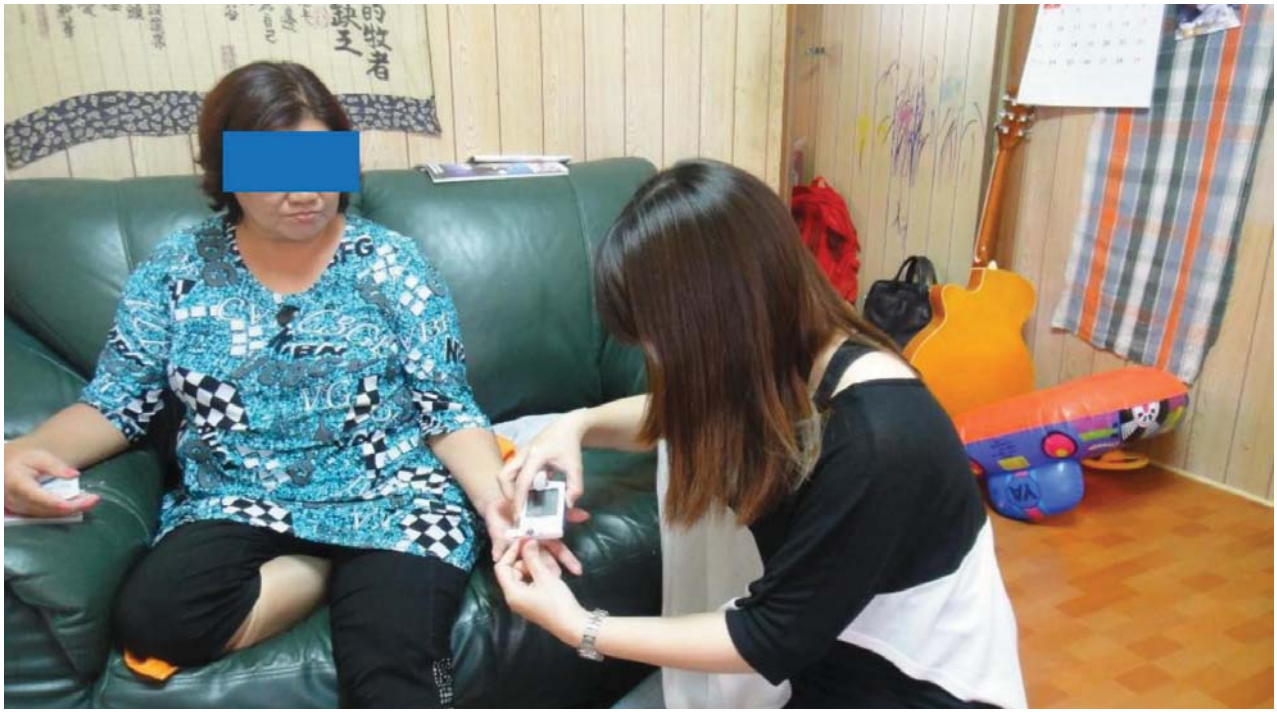
策略 4

Patient-centered DOTS-plus Program(以病人為中心的進階都治)

- **Each dose is given as directly observed therapy (DOT) throughout the treatment**
  - **送藥到手--服藥入口--吃了再走**

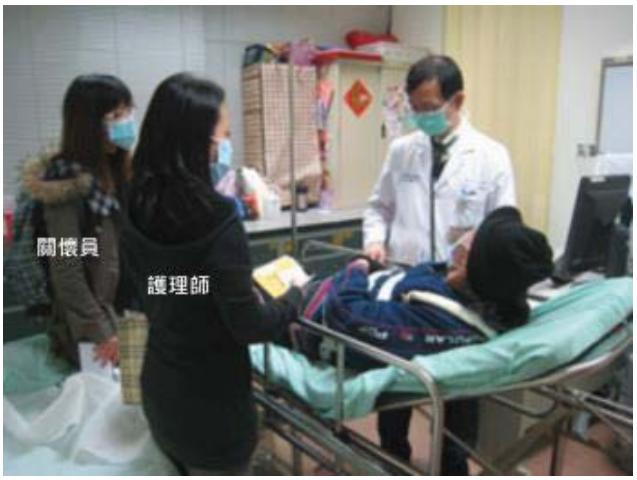
策略 4

Patient-centered DOTS-plus Program:都治不僅僅是都治！



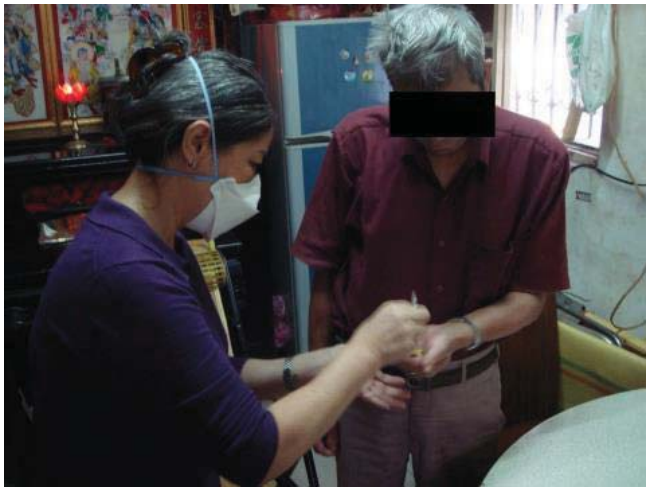
策略 4

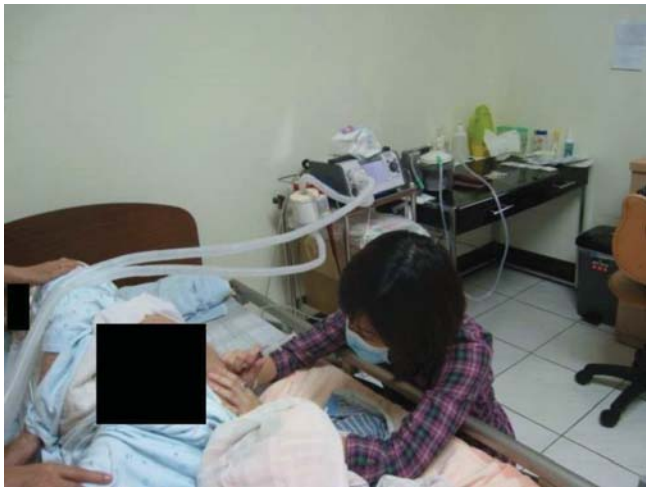
Patient-centered DOTS-plus Program



策略 4

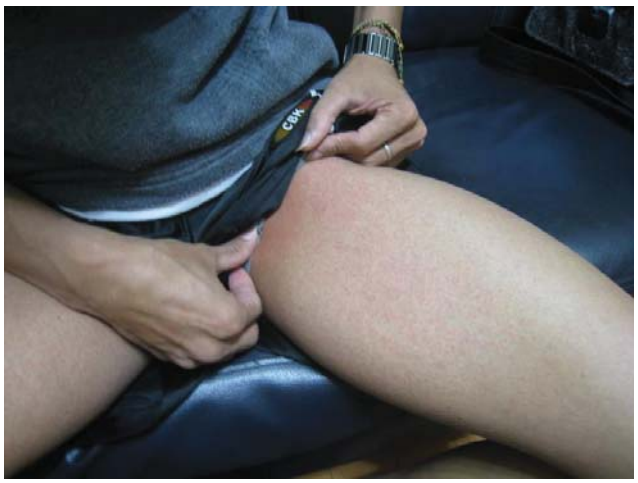
Patient-centered DOTS-plus Program





策略 4

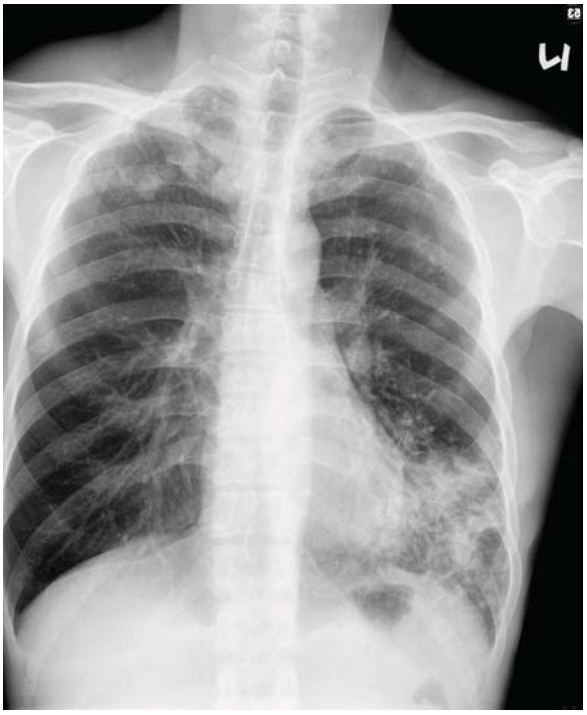
Patient-centered DOTS-plus Program



病例分享

40歲男性(1)

MDR-TB

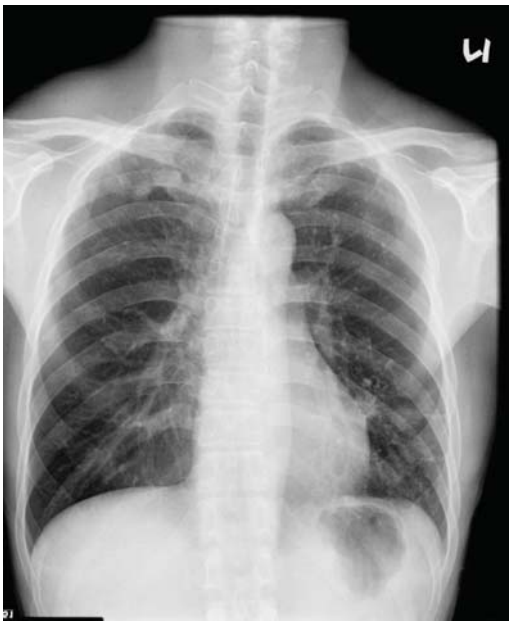


- **藥物敏感性試驗：抗藥**
  - Isoniazid/Ethambutol/Rifampin Streptomycin/Pyrazinamide Rifabutin
- **治療處方**
  - Kanamycin/Moxifloxacin Prothionamide/PAS
    - 2 months
    - PAS—GI upset
  - Kanamycin/Moxifloxacin Prothionamide/Cycloserine
    - 4 months
  - Moxifloxacin/Prothionamide Cycloserine
    - 15 months

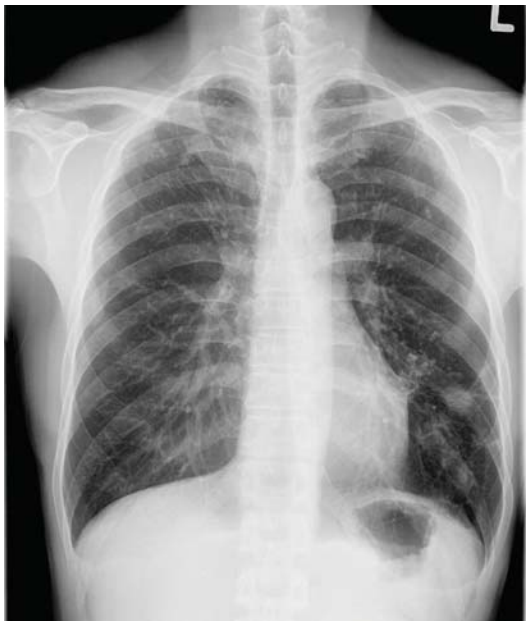
40歲男性(2)

MDR-TB

完成治療



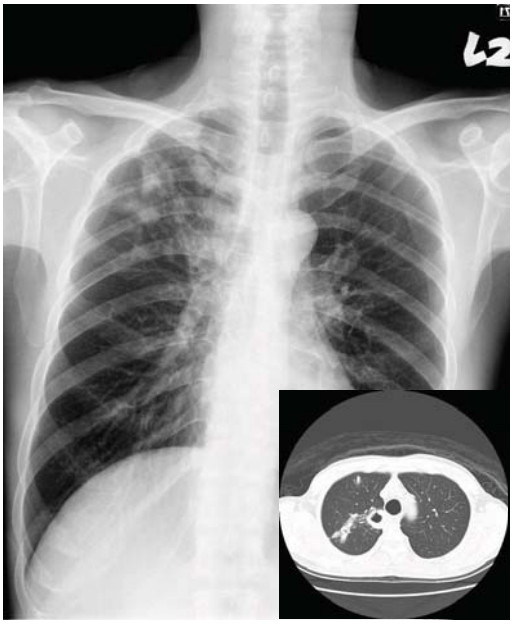
追蹤2年



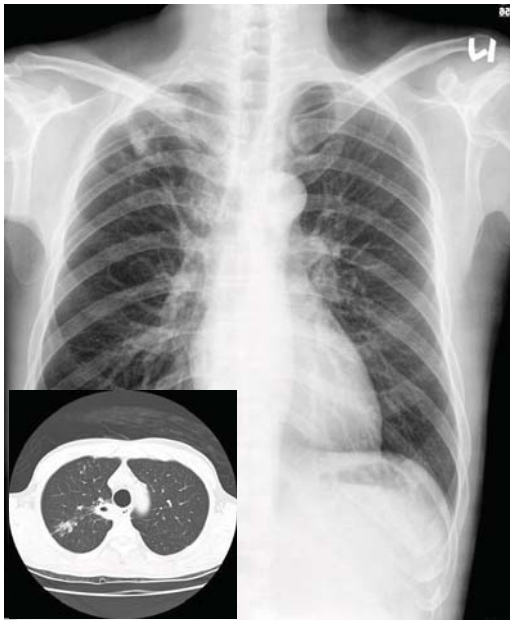
46歲男性

MDR-TB/Poor Sugar Control

Before treatment

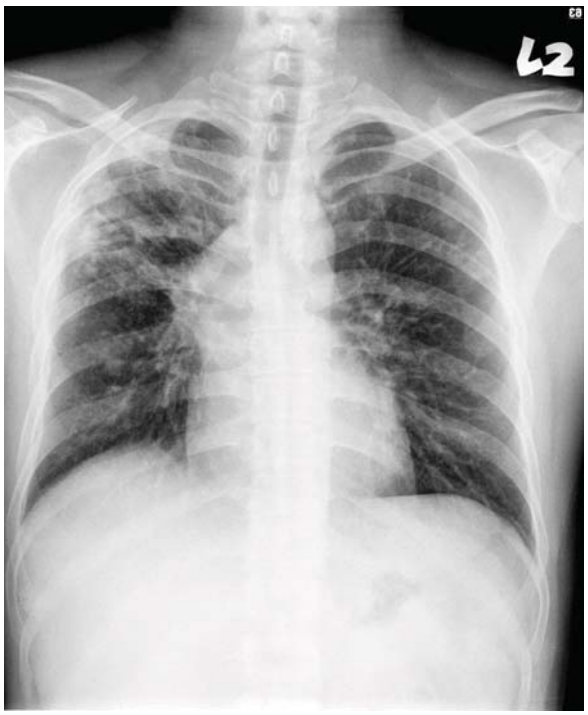


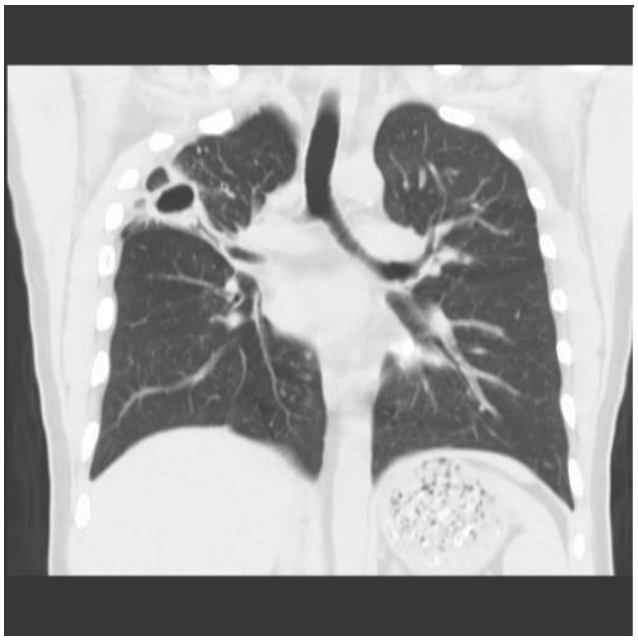
Treatment, 2 months



28歲男性

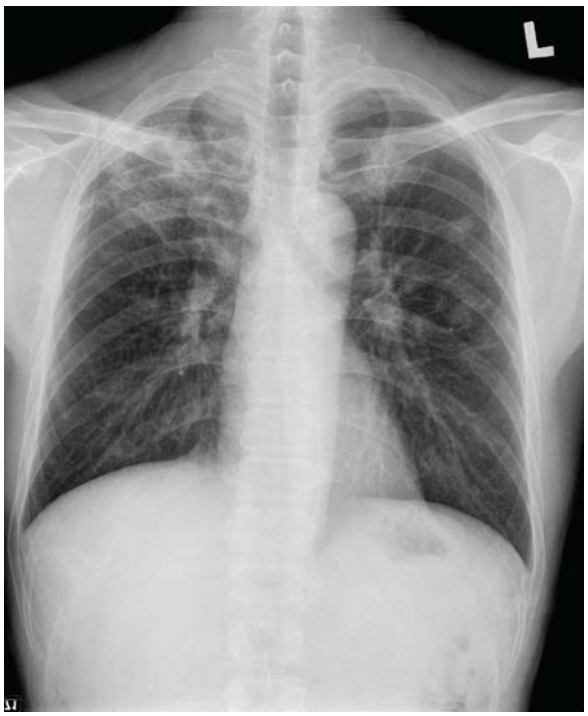
Kanamycin+PAS+Moxifloxacin+Prothionamide+Ethambutol
Hepatitis (AST:476; ALT:1206) (~~Prothionamide~~---Cycloserine)

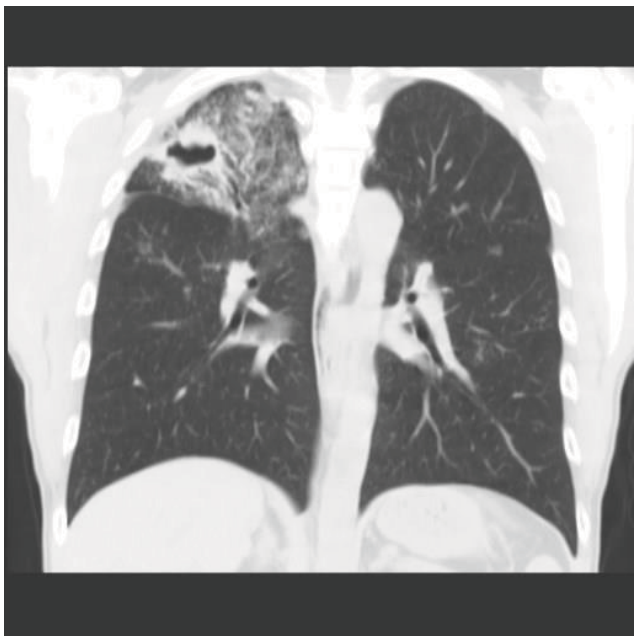




43歲男性(1)

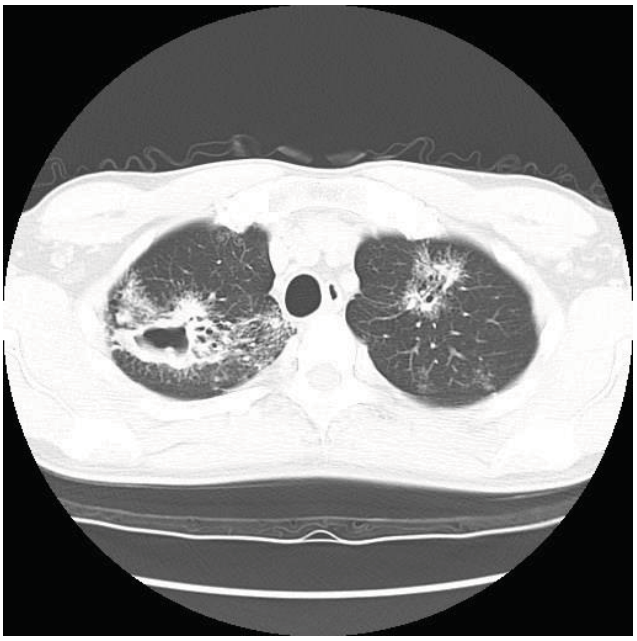
Kanamycin+Moxifloxacin+Pyrazinamide+Prothionamide+PAS

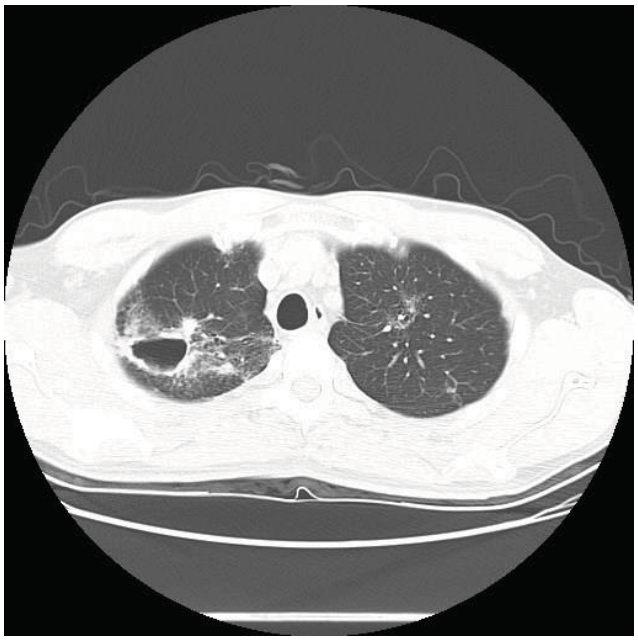




43歲男性(2)

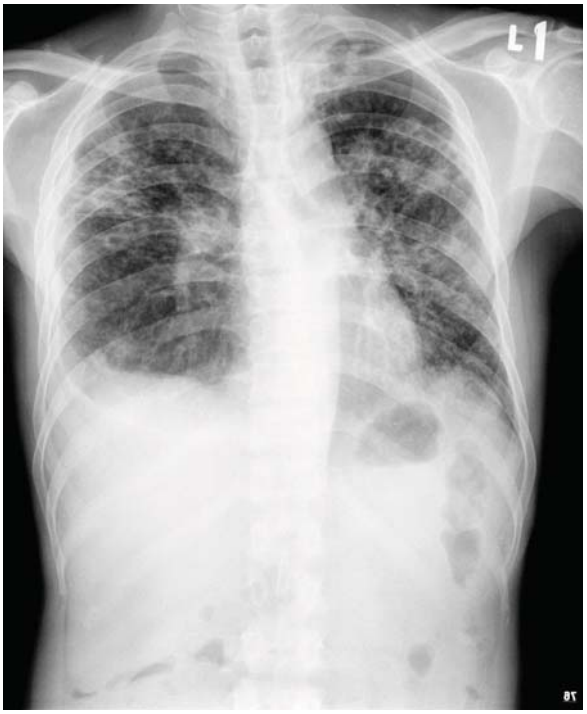
AST: 1607 U/L, ALT: 2239 U/L, HBV DNA: 69,107,408 (normal <20 IU/ml) HBsAg(+)

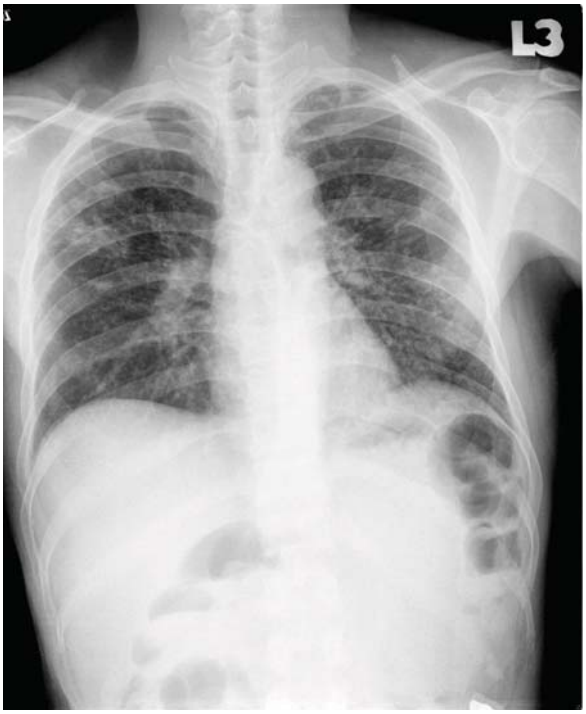




39歲男性

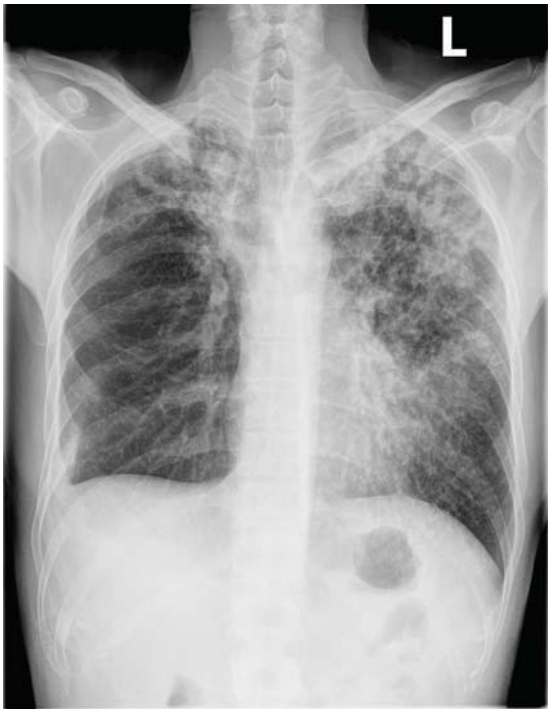
Prothionamide-related Hypothyroidism

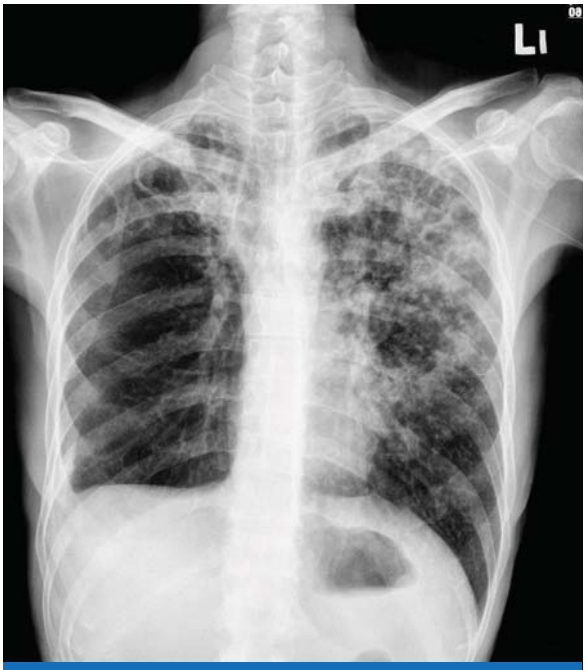




44歲男性

KM+Moxifloxacin+Ethambutol+Pyrazinamide+Cycloserine+Linezolid+Isoniazid
(Rifampin + Low level isoniazid + Prothionamide resistant)





Peripherally Inserted Central Catheter, PICC

Effectiveness of a Government-Organized and Hospital-Initiated Treatment for Multidrug-Resistant Tuberculosis Patients

A Retrospective Cohort Study

2000-2006:治療成功率61%
2007-2008:治療成功率82%

Background: In contrast to the conventional model of hospital-treated and government directly observed treatment (DOT) for multidrug-resistant tuberculosis (MDR-TB) patient care, the Taiwan MDR-TB Consortium (TMTC) was launched in May 2007 with the collaboration of five medical care groups that have provided both care and DOT. This study aimed to determine whether the TMTC provided a better care model for MDR-TB patients than the conventional model.

Methods and Findings: A total of 651 pulmonary MDR-TB patients that were diagnosed nation-wide from January 2000-August 2008 were enrolled. Of those, 290 (45%) MDR-TB patients whose initial sputum sample was taken in January 2007 or later were classified as patients in the TMTC era. All others were classified as patients in the pre-TMTC era. The treatment success rate at 36 months was better in the TMTC era group (82%) than in the pre-TMTC era group (61%) ($p<0.001$). With multiple logistic regressions, diagnosis in the TMTC era (adjusted odds ratio (aOR) 2.8, 95% confidence interval (CI) 1.9–4.2) was an independent predictor of a higher treatment success rate at 36 months. With the time-dependent proportional hazards method, a higher treatment success rate was still observed in the TMTC era group compared to the pre-TMTC era group (adjusted hazard ratio 6.3, 95% CI 4.2–9.5).

Conclusion: The improved treatment success observed in the TMTC era compared to the pre-TMTC era is encouraging. The detailed TMTC components that contribute the most to the improved outcome will need confirmation in follow-up studies with large numbers of MDR-TB patients.

PLoS One 2013;8(2):e57719

Treatment Outcomes of Multidrug-Resistant Tuberculosis in Taiwan: Tackling Loss to Follow-up

2007-2012:治療成功率82.4%

Background. The proportion of treatment success among patients with multidrug-resistant tuberculosis (MDR-TB) enrolled between 1992 and 1996 was 51.2%, and that among patients enrolled between 2000 and April 2007 was 61%. To address the challenge of MDR-TB, the Taiwan MDR-TB Consortium (TMTC) was established in May 2007. To assess the performance of the TMTC, we analyzed the data of patients enrolled in its first 5 years.

Methods. Comprehensive care was provided at no cost to patients, who were usually hospitalized for 1 month initially. Treatment regimens consisted of 4–5 drugs and the duration of treatment was 18–24 months. A case manager and a directly observed therapy provider were assigned to each patient. Psychosocial support was provided to address emotional stress and stigma. Financial support was offered to avoid the financial hardship faced by patients and their families. We assessed treatment outcomes at 30 months using internationally recommended outcome definitions.

Results. Of the 692 MDR-TB patients, 570 (82.4%) were successfully treated, 84 (12.1%) died, 18 (2.6%) had treatment failure, and 20 (2.9%) were lost to follow-up. Age ≥65 years (adjusted odds ratio [aOR], 6.78 [95% confidence interval {CI}, 3.14–14.63]), cancer (aOR, 11.82 [95% CI, 5.55–25.18]), and chronic kidney disease (aOR, 3.62 [95% CI, 1.70–7.71]) were significantly associated with death. Resistance to fluoroquinolone (aOR, 10.89 [95% CI, 3.97–29.88]) was significantly associated with treatment failure.

Conclusions. The TMTC, which operates under a strong collaboration between the public health authority and clinical teams, has been a highly effective model of care in the management of MDR-TB.

Keywords. tuberculosis; multidrug resistance; MDR; outcome.

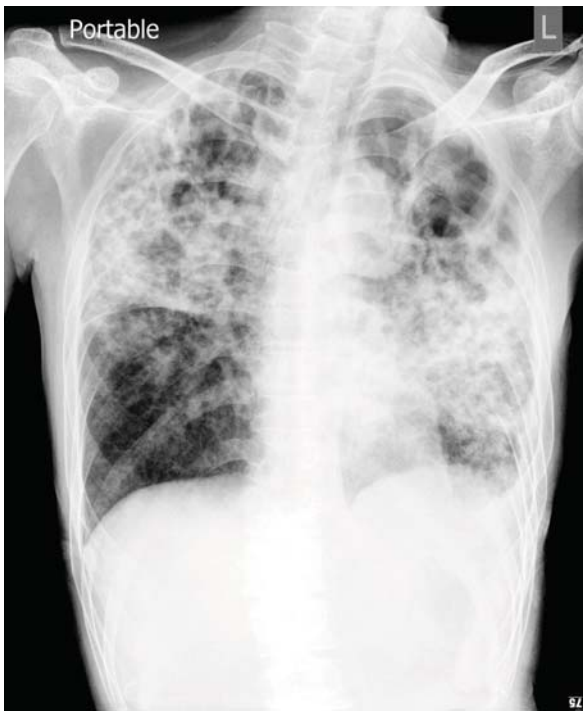
Clin Infect Dis 2018;67(2):202–210

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

進展與難題

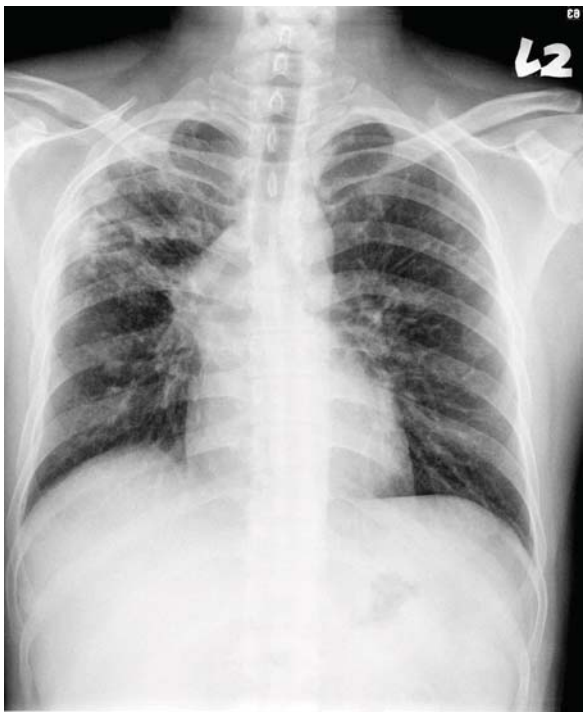
自動化即時分子檢驗

GeneXpert MTB/RIF Assay



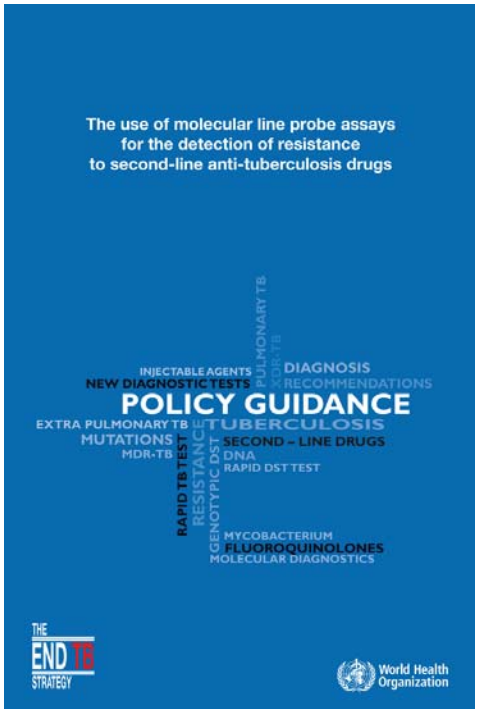
- 失落再治肺結核病人
- 快速知道是否有MTB及Rifampin抗藥

28歲男性



- 2012-4-16
  - 檢體收件
- 2012-4-18
  - 確認MDR-TB
- 2012-5-22
  - 提供第二線抗結核藥物感受性試驗結果

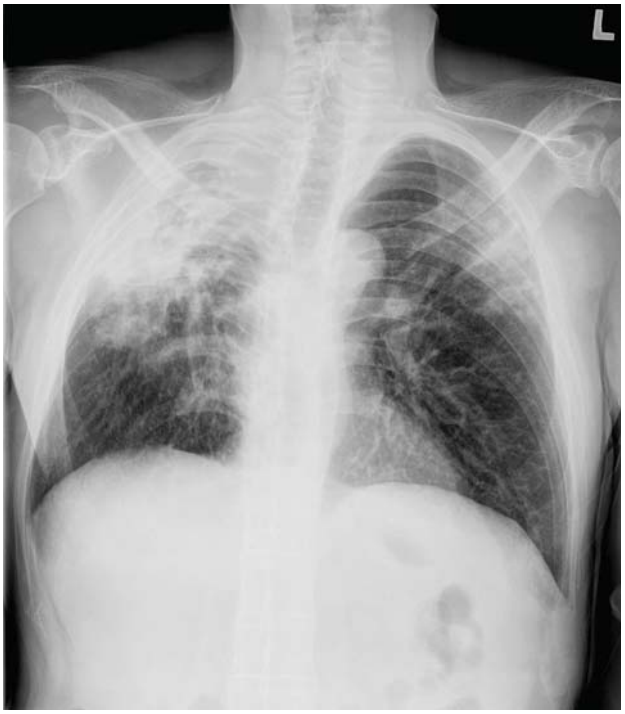
WHO's Policy Recommendations 2016



- For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to **fluoroquinolones**
- For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to **the second-line injectable drugs**

MDR-TB

快速分子檢驗的時代



檢體收件日期	民國106年1月26日	檢體不良狀況	
分子鑑定		檢體濃化酸度/檢體量	
檢體編號		丙反應日期	
塗片報告日期		塗片方法/結果	
痰檢體病原體分生檢測報告日期		痰檢體病原體分生檢測結果	
MGIT 培養報告日期		MGIT 培養結果	
L-J 培養報告日期		L-J 培養結果	
培養報告備註			
菌種鑑定日期		菌種鑑定方法/結果/菌種	
菌種鑑定備註			
IGRA 報告日		IGRA 檢驗結果	
IGRA QFT NIL:		IGRA TB antigen	
IGRA Mitogen			
IGRA 備註			
MDR分子複驗報告日期	民國106年2月6日	MDR分子複驗結果	是
MDR傳統藥敏試驗複驗報告日期		MDR傳統藥敏試驗複驗結果	
MDR 備註			
	Xpert：		
MTBC 報告日期		MTBC 檢驗結果	
RMP 報告日期		RMP 檢驗結果	
	分生一線藥物：		
報告日期			
MTBC 檢驗結果		RMP 檢驗結果	
INH 檢驗結果			
	分生二線藥物：		
報告日期		民國106年2月6日	
FLQ 檢驗結果	S：敏感臨床醫師進行個案最終判定	KAN 檢驗結果	S：敏感臨床醫師進行個案最終判定
AMK 檢驗結果	S：敏感臨床醫師進行個案最終判定	CAP 檢驗結果	S：敏感臨床醫師進行個案最終判定
PZA 報告日期	民國106年2月8日	定序 PZA 檢驗結果	S：敏感臨床醫師進行個案最終判定
分子快速檢測備註	(20170206)二線藥物分子檢測報告(20170208)PZA分子檢測報告		
疑似群聚事件編號		分子分型結果	
分子分型結果備註			
一線藥敏報告日期	民國106年4月11日	一線藥敏檢驗結果	Pyrazinamide：敏感
一線藥敏備註			
二線藥敏報告日	民國106年4月11日	二線藥敏檢驗結果	Levofloxacin：敏感 Amikacin：敏感 Cycloserine：敏感 Moxifloxacin：敏感 Capreomycin：敏感 Rifabutin：抗藥 Ethionamide：敏感 任選其Kanamycin：敏感 p-aminosalicylicacid：敏感
二線藥敏備註	Linezolid 敏感 (20170411)Clofazimine 敏感		

Bedaquiline and Delamanid

Combining bedaquiline and delamanid to treat multidrug-resistant tuberculosis

Clinicians recognise how difficult it is to manage multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: the treatment is lengthy, expensive, and most patients have severe adverse events.[1-4]

The recent availability of two new drugs, bedaquiline and delamanid, offers hope in treating patients previously considered incurable. When four active drugs are insufficient either because of the extensive pattern of drug resistance or intolerance, the combined use of bedaquiline and delamanid is a possible life-saving option.[5-10]

Given the potential cardiotoxicity of both drugs, leading to prolongation of the QT interval and subsequent possible arrhythmias, WHO has not recommended their combined use until sufficient evidence is made available.[5] Although two clinical trials will provide experimental evidence 3 years from now and criteria have been suggested to ensure patients' safety,[6] initial evidence is accumulating on the combined use of bedaquiline and delamanid.

Only reports on six cases undergoing combined treatment have been published;[7-10] no serious adverse events were reported, although one case needed temporary discontinuation of bedaquiline (because of QT corrected for heart rate frequency of >500 ms) followed by its reintroduction in combination with verapamil.[7,9,10]

In *The Lancet Infectious Diseases*, Gabriella Ferlazzo and colleagues[11] report early safety and efficacy information on the largest available cohort of patients having combined treatment with delamanid and bedaquiline.

The study offers several additional elements of interest. First, combined treatment was implemented at the programmatic level[1] in three different settings, using an outpatient approach in India and South Africa, although in Armenia some cases were admitted to hospital. Second, the patients with MDR-tuberculosis were young (median age 32·5 years), had severe presentation (50% with XDR-tuberculosis), and 39% were co-infected with HIV. A median of seven drugs were prescribed to ensure at least four were

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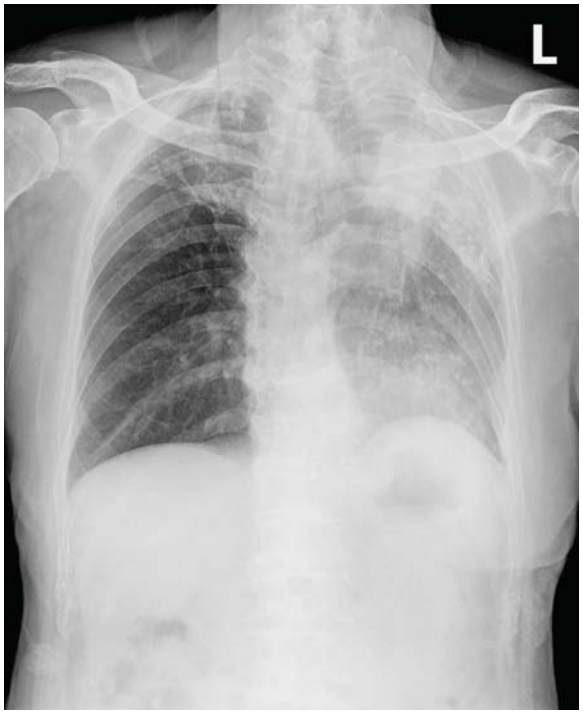
77歲男性

MDR-TB
≧65 y/o: 24.5%



- Parkinsonism
- Pneumonia with acute respiratory failure
- Drug susceptibility test
  - Resistant to HERS + Rifabutin
- Treatment with
  - Kanamycin
  - Moxifloxacin
  - Prothionamide
  - Cycloserine
  - Pyrazinamide

結論

謝謝聆聽！

- Cure the TB patient the first time around
- Provide access to diagnosis
- Ensure adequate infection control in facilities where patients are treated
- Ensure the appropriate use of recommended second-line drugs

Leave No One Behind