分子診斷，能幫結核病做甚麼？

臺北市立萬芳醫院　余明治醫師

報告大綱

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- 分子檢驗，就這樣嗎?
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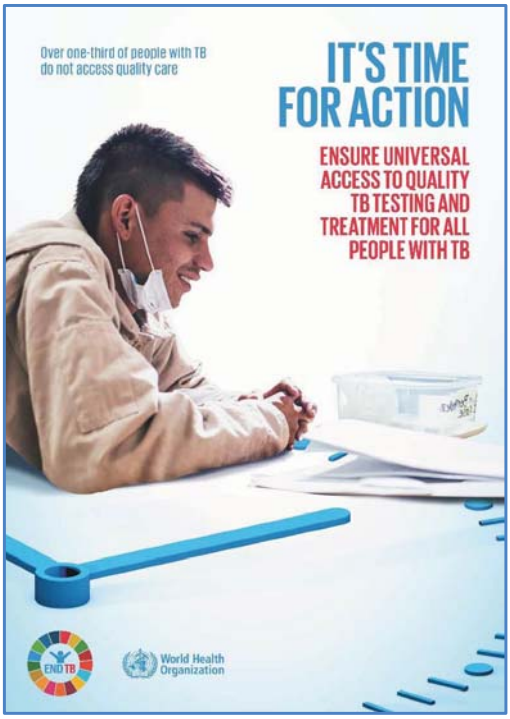
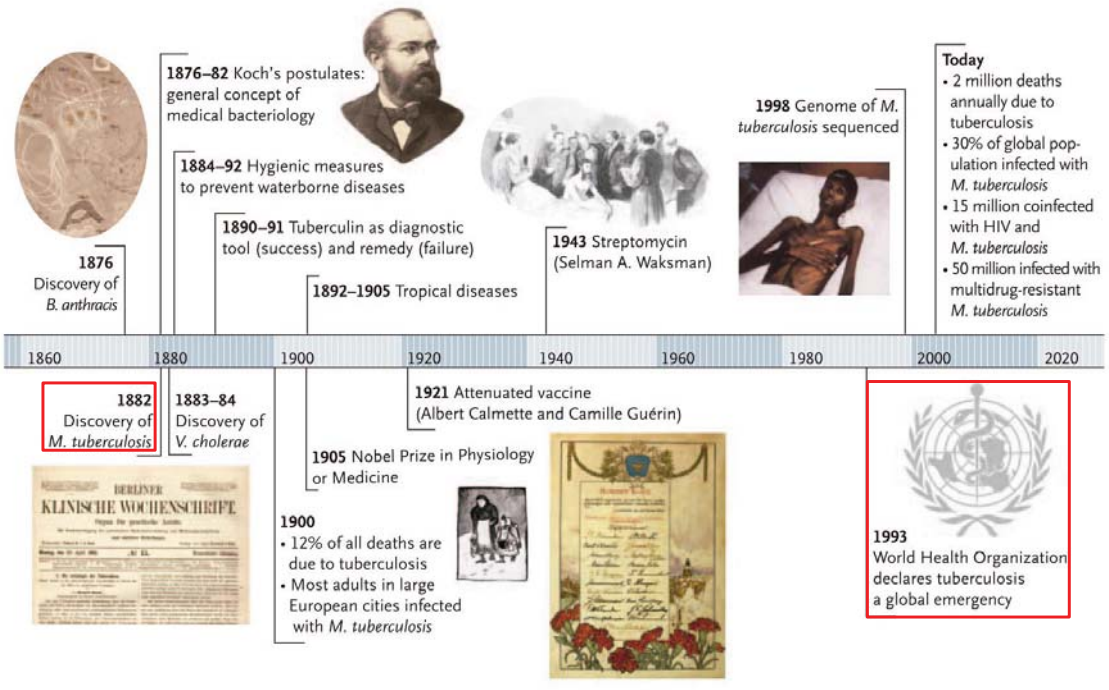


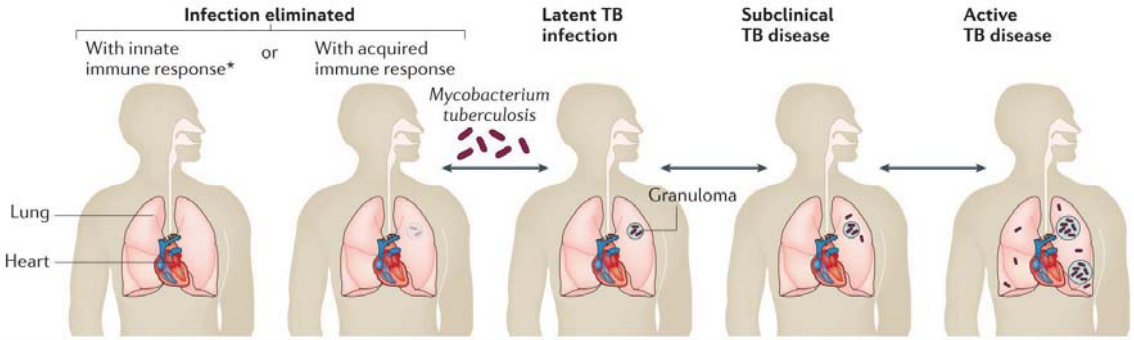
前言

Timeline Showing Highlights of Robert Koch's Work and the Ongoing Threat Posed by Tuberculosis



N Engl J Med 353;23:2423-2426

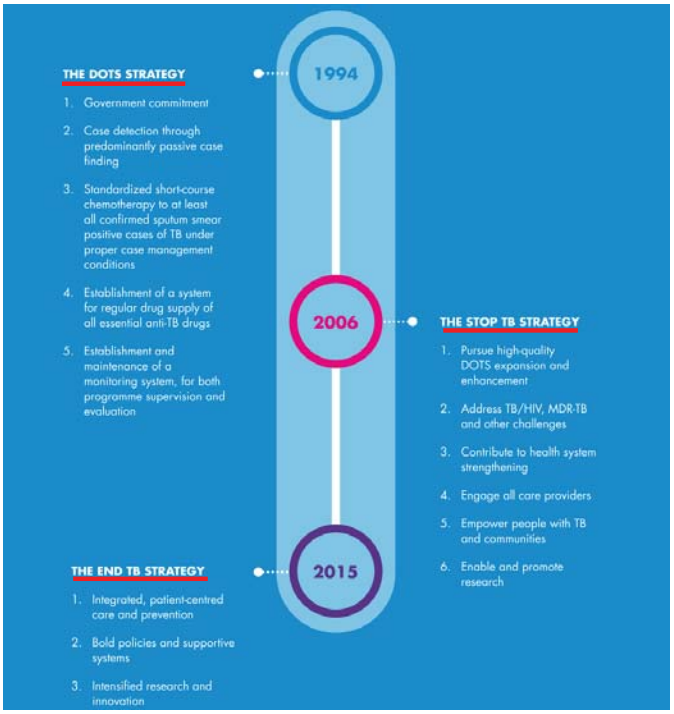
The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Nature Reviews Disease Primers 2016 (2), Article number: 16077

Evolution of WHO Global TB Strategies



WHO 2015: Implementing the end TB strategy: the essentials

Integrated, Patient-Centered Care and Prevention

A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups

B. Treatment of all people with TB including drug-resistant TB, and patient support

D. Preventive treatment of persons at high risk; and vaccination against TB

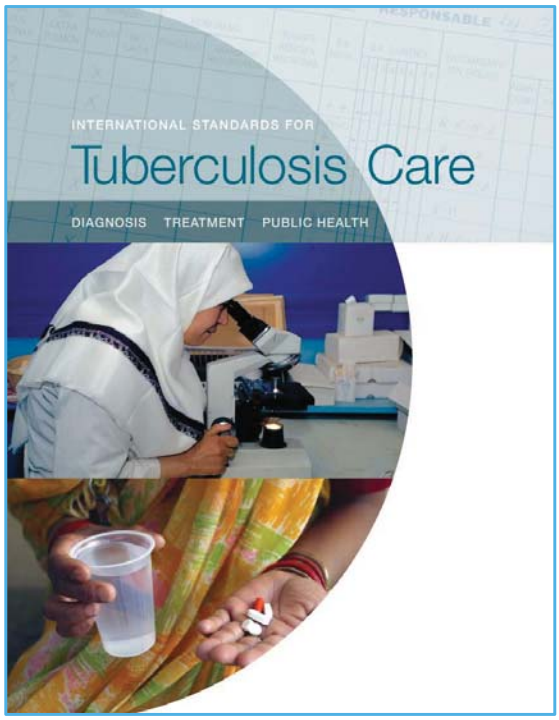
C. Collaborative TB/HIV activities; and management of comorbidities

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

結核病國際照護標準
International Standards for TB Care

International Standards for Tuberculosis Care

2006



Developed by the Tuberculosis Coalition for Technical Assistance (TBCTA)

TBCTA

TBCTA Partners:

CDC ATS KNCV World Health Organization

Funded by the United States Agency for International Development (USAID)

USAID

Endorsements:

For an updated list of endorsers, see the Francis J. Curry National Tuberculosis Center website at http://www.nationaltbcenter.edu/international/ or the Stop TB Partnership website at http://www.stoptb.org/.

Disclaimer:

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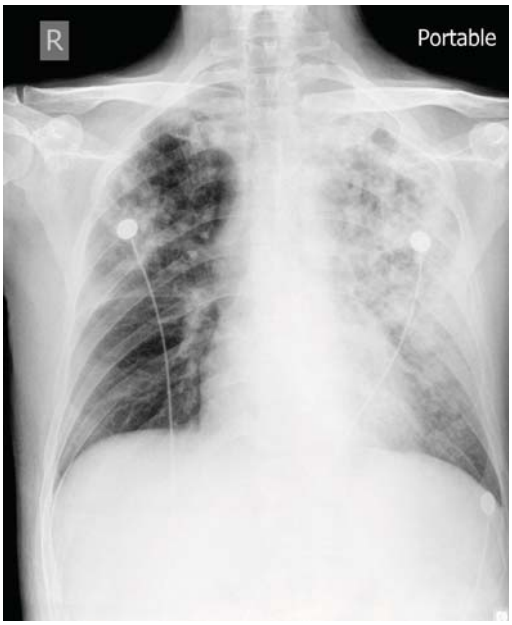
Standard 1

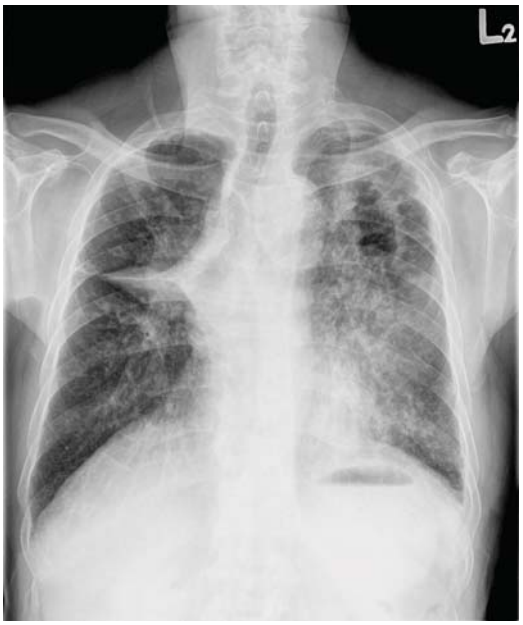
All Persons with otherwise Unexplained Productive Cough Lasting Two–three Weeks or more Should be Evaluated for TB

Taiwan ?

Male, 53 y/o



Male, 82 y/o

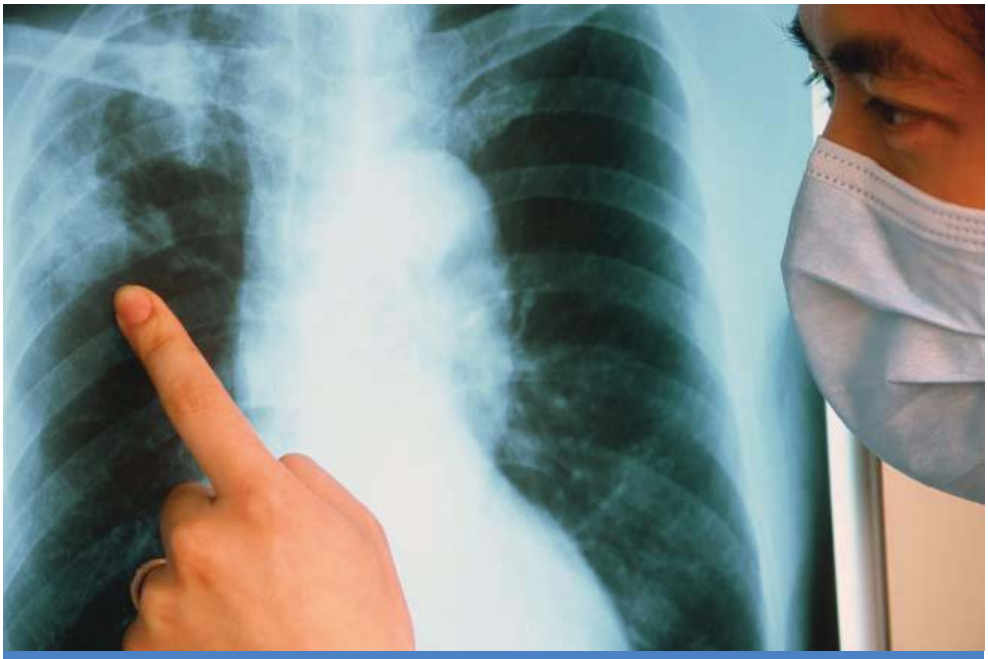


Standard 2

All Patients Suspected of Having Pulmonary TB Should Have Sputum Specimens Obtained for Microscopic Examination

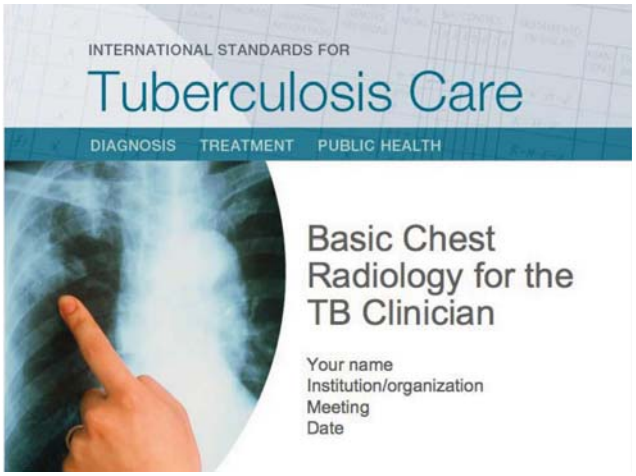
Standard 4

All Persons with Chest Radiographic Findings Suggestive of TB Should Have Sputum Specimens Submitted for Microbiological Examination



A diagnosis of tuberculosis cannot be established by radiography alone

CXR

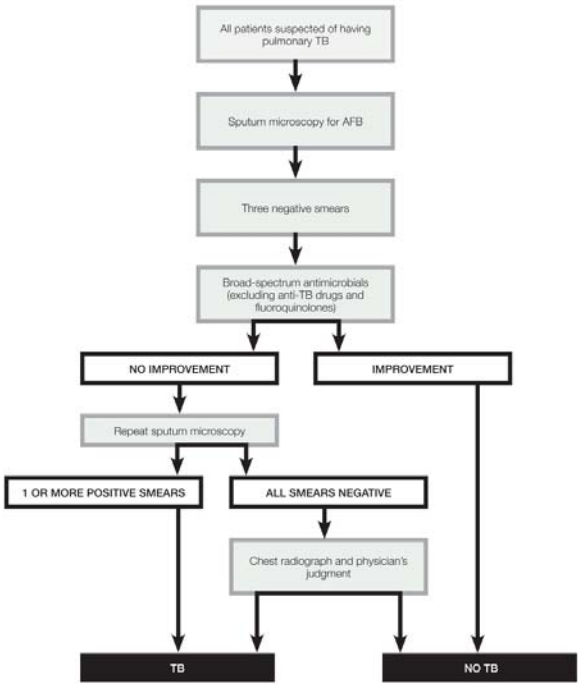


Radiographic Finding (modified from Ref 1)

	Pooled Sensitivity (%)	Pooled Specificity (%)
Any abnormality compatible with TB (active or inactive)	98 (95–100)	75 (72–79)
Abnormalities suggestive of active TB	87 (79–95)	89 (87–92)
After positive screening for symptoms (one study)	90 (81–96)	56 (54–58)
Chest radiography scoring systems[81]	96 (93–98)	46 (35–50)

Standard 5

The diagnosis of Sputum Smear-negative Pulmonary TB: at Least Three Negative Sputum Smears; CXR consistent with TB; and Lack of Response to a Trial of Broad-spectrum Antimicrobial Agents



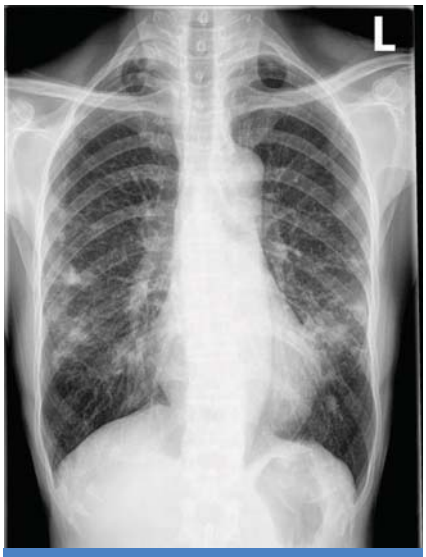
- If facilities for culture are available, sputum cultures should be obtained

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

挑戰(1)

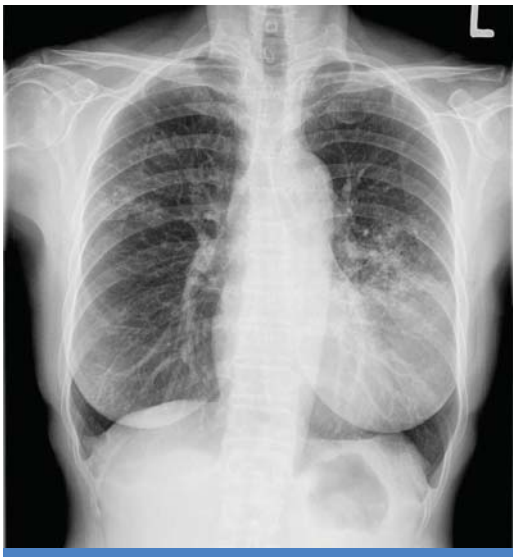
Sputum Acid-fast Stain (+)

Female, 58 y/o



M. avium complex

Female, 64 y/o

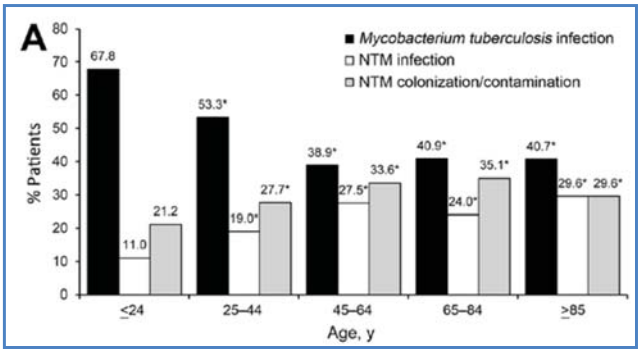


M. tuberculosis

1. *Mycobacterium tuberculosis* (TB) vs. Nontuberculous Mycobacteria (NTM)

- NTUH, 2000–2012
- 13,652 respiratory isolates
  - *M. tuberculosis*: 5,878 (43.1%)
  - NTM: 7,774 (56.9%)

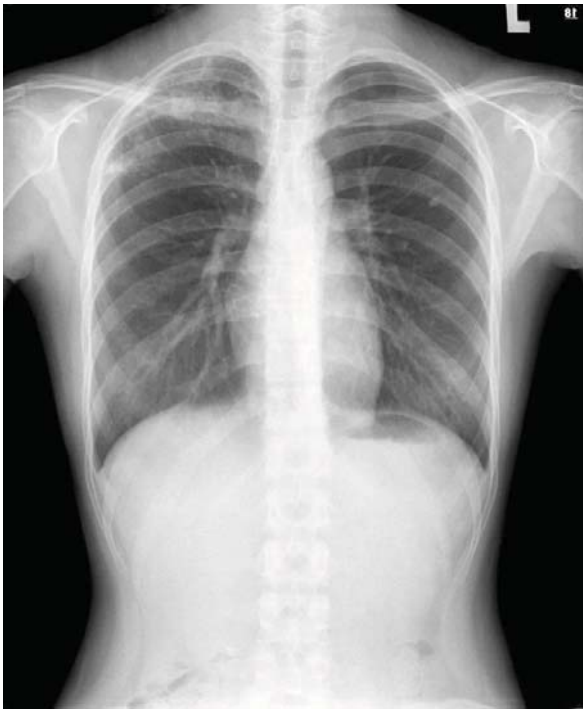
Positive Acid-fast stain =TB (?)

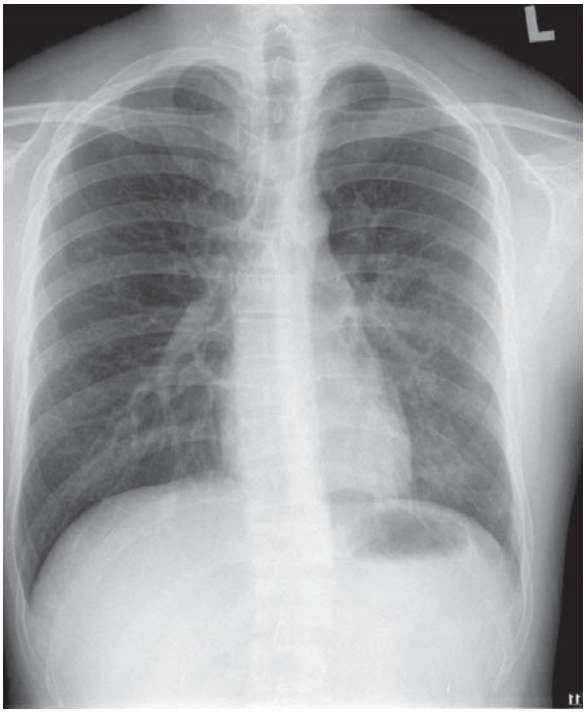


Rates of MTB infection, NTM infection, and NTM colonization/contamination

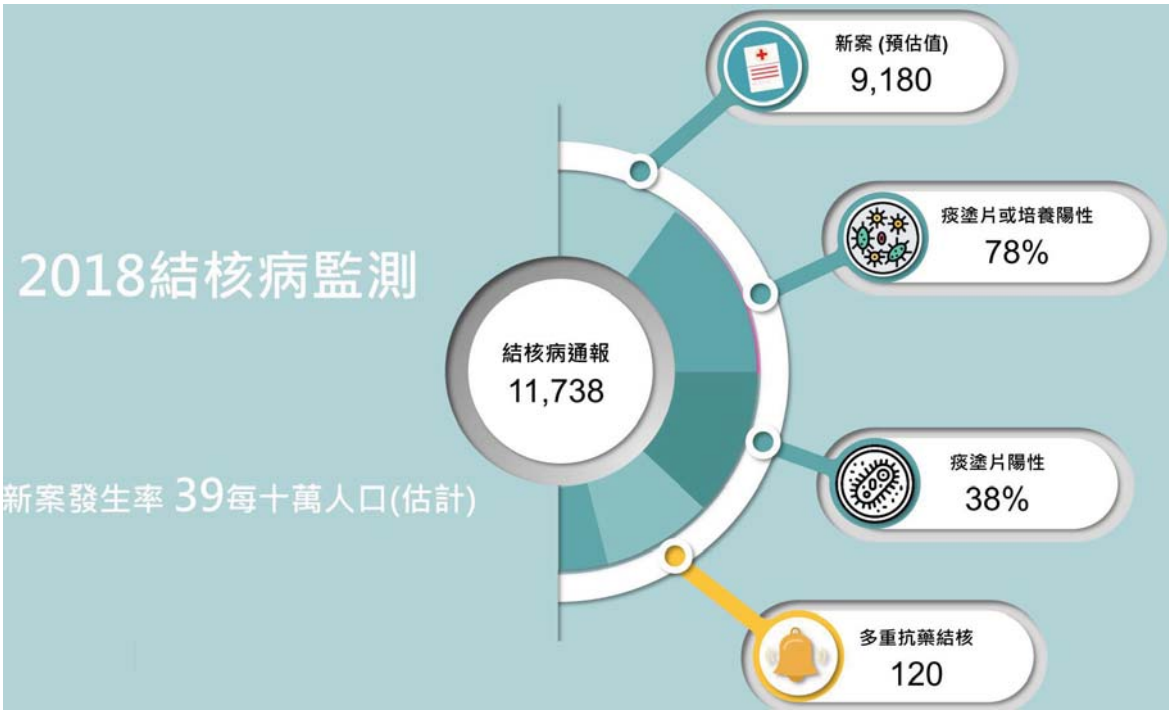
Pulmonary Infection and Colonization with Nontuberculous Mycobacteria, Taiwan, 2000–2012. *Emerg Infect Dis* 2014; 20:1382-5

Sputum Acid-fast Stain (-)





2. Smear-negative Pulmonary TB



Taiwan CDC 2019.5.8

Comparative Evaluation of the BACTEC MGIT 960 System with Solid Medium for Isolation of Mycobacteria

Int J Tuberc Lung Dis 2003;7:569-74

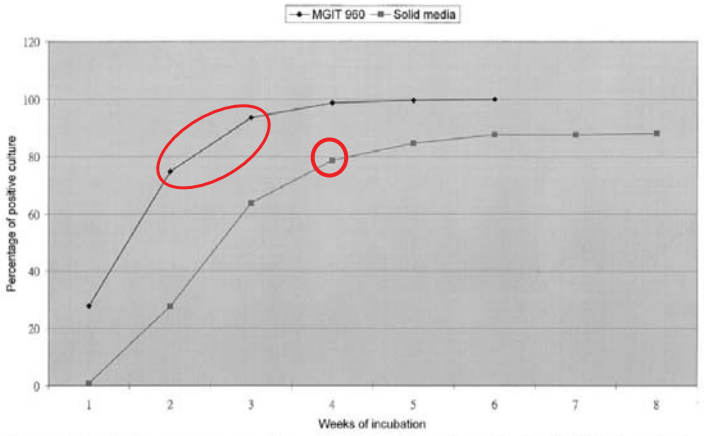
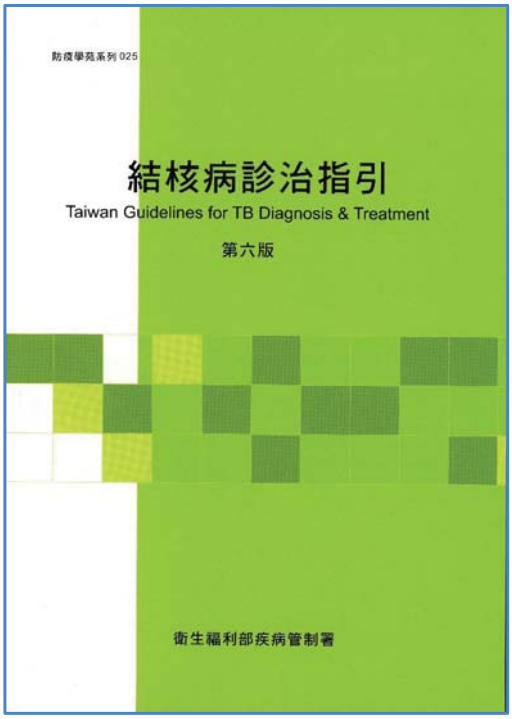


Figure Cumulative percentages of mycobacteria detected weekly by individual methods. BACTEC MGIT 960 system and solid media (Löwenstein-Jensen plus 7H11).

Table 2 Time to detection (TTD) of all mycobacteria and *M. tuberculosis* complex in different systems

	TTD of all mycobacteria (days)			TTD of *M. tuberculosis* (days)		
Medium	Total	Smear (+)	Smear (−)	Total	Smear (+)	Smear (−)
MGIT 960	11.6	9.0	15.5	11.6	9.1	16.2
LJ	20.3	17.6	25.1	20.1	17.6	25.2
7H11	18.9	16.1	23.8	18.7	16.1	23.5

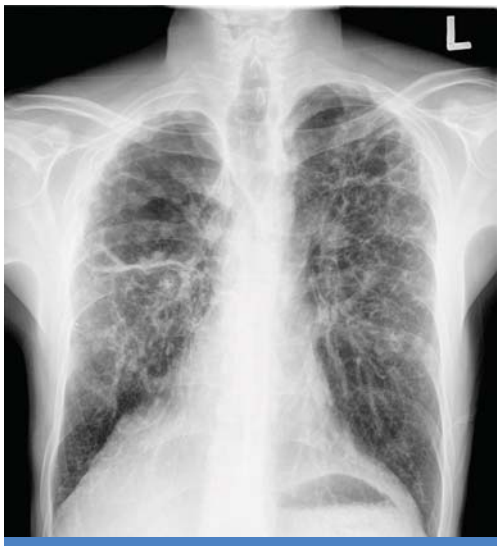
台灣結核病診治指引



- **所有檢體必須同時進行塗片檢驗及分枝桿菌培養**
  - 培養比塗片更敏感
    - 每mL 標本10 至100 隻細菌
  - 菌株之鑑定
  - 藥物感受性試驗
  - 提供基因分析
    - 流行病學及院內感染、實驗室交叉污染之比對
- **必須使用固體及液體培養基培養**

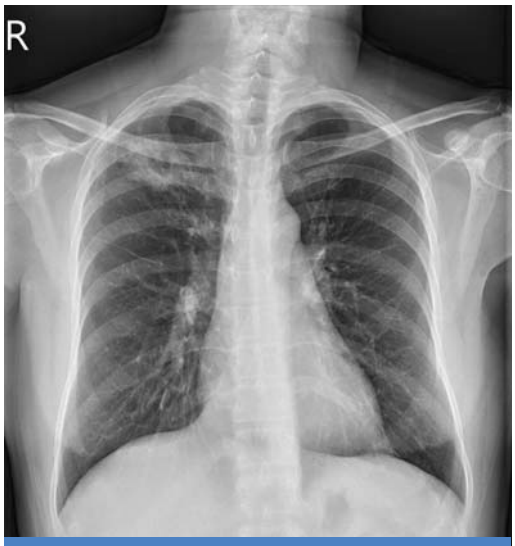
診斷的時效，滿意嗎？

Male, 40 y/o



Sputum AFS (+) x III
Sputum culture (+) 18, 16, 16 days

Female, 50 y/o



Sputum AFS(-) x III
Sputum Culture (+) 19 days

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

分子檢驗，能幫些甚麼呢？

◀ *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 Professor DU BOIS-RAYMOND, Chairman of the Society, where

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

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Tuberculosis Diagnosis — Time for a Game Change

Peter M. Small, M.D., and Madhukar Pai, M.D., Ph.D.

N Engl J Med 2010:363; 1070-1071

Nucleic Acid Amplification Methods

TABLE 2 Sensitivity and specificity of nucleic acid amplification methods in different samples[#]

	Amplicor[¶]		AMTD		Real-time PCR		BDProbeTec[+]	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Smear positive pulmonary	97	>95	92–100	>95	78	100	90–100	92
Smear negative pulmonary	40–73	>95	40–93	>95	78	100	33–100	83–97
Extrapulmonary	27–98	>95	93	>95	80	100	76	>90

Data are presented as %. AMTD: amplified *Mycobacterium tuberculosis* direct test. [#]: adapted from references [22] and [91]; [¶]: Amplicor *M. tuberculosis* test; [+]: amplified *M. tuberculosis* direct test.

Eur Respir J 2005; 26: 339–350

Reduction in Turnaround Time for Laboratory Diagnosis of Pulmonary TB by Routine Use of a Nucleic Acid Amplification Test

Diagn Microbiol Infect Dis 2005; 52: 247–54

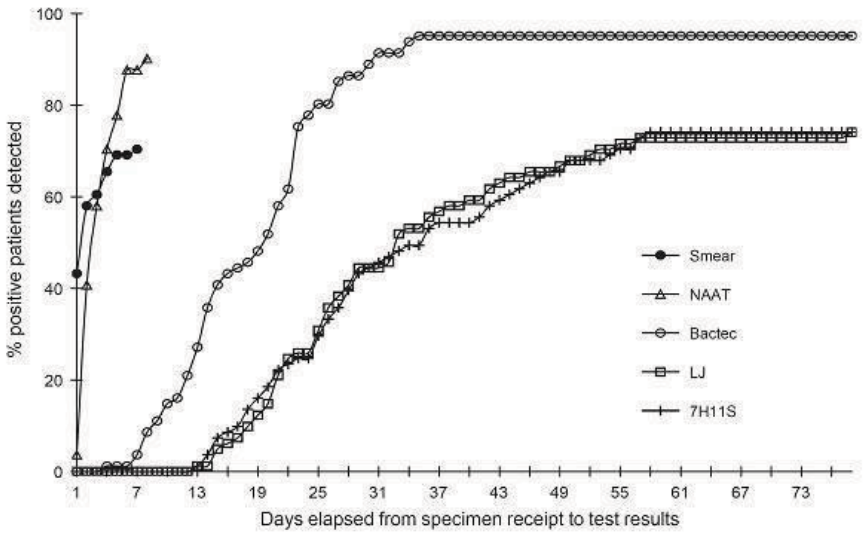
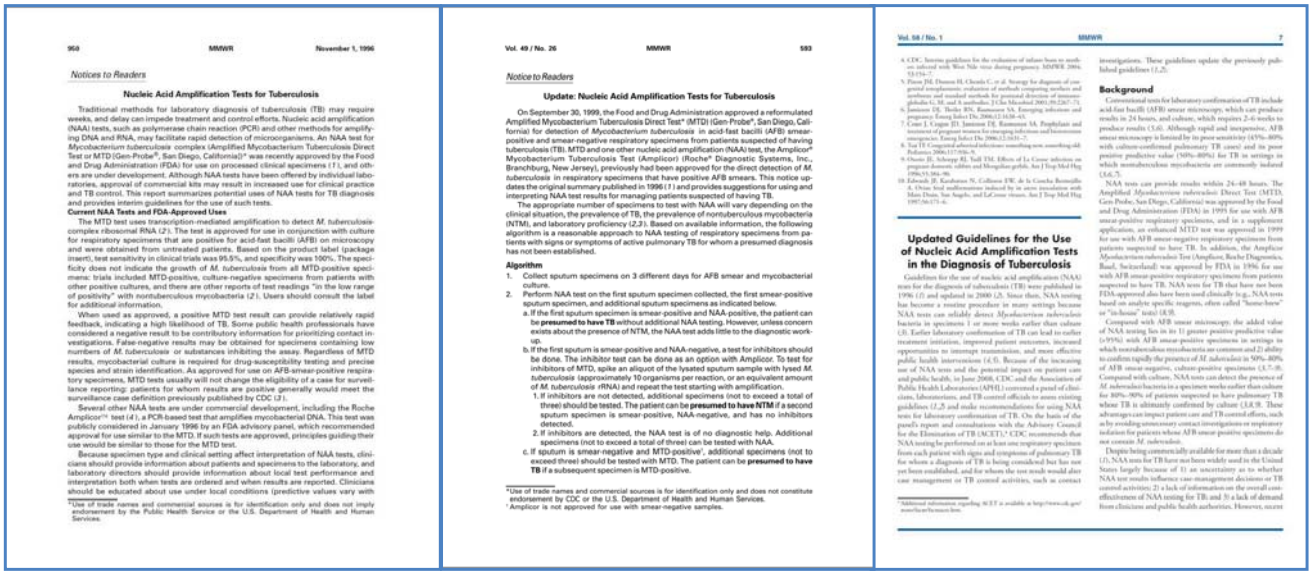


Fig. 2. TAT to report TB-positive patients. The elapsed time from specimen receipt to assay results was evaluated under normal working conditions in the laboratory. The results are expressed as the percentage of TB-positive patients that were reported as positive by the day indicated. The results include all 3 specimens for AFB smear and culture techniques and the first specimen for NAAT.

Identification and testing every first diagnostic specimen by NAAT has the potential to reduce the overall TAT for laboratory TB diagnosis by approximately 2 weeks

Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis



950 MMWR November 1, 1996

Notices to Readers

Nucleic Acid Amplification Tests for Tuberculosis

Traditional methods for laboratory diagnosis of tuberculosis (TB) may require weeks, and delay can impede treatment and control efforts. Nucleic acid amplification (NAA) tests, such as polymerase chain reaction (PCR) and other methods for amplifying DNA and RNA, may facilitate rapid detection of microorganisms. An NAA test for *Mycobacterium tuberculosis* complex (Amplified Mycobacterium Tuberculosis Direct Test or MTD [Gen-Probe®, San Diego, California][1]* was recently approved by the Food and Drug Administration (FDA) for use on processed clinical specimens (1), and others are under development. Although NAA tests have been offered by individual laboratories, approval of commercial kits may result in increased use for clinical practice and TB control. This report summarizes potential uses of NAA tests for TB diagnosis and provides interim guidelines for the use of such tests.

Current NAA Tests and FDA-Approved Uses

The MTD test uses transcription-mediated amplification to detect *M. tuberculosis*-complex ribosomal RNA (2). The test is approved for use in conjunction with culture for respiratory specimens that are positive for acid-fast bacilli (AFB) on microscopy and were obtained from untreated patients. Based on the product label (package insert), test sensitivity in clinical trials was 95.5%, and specificity was 100%. The specificity does not indicate the growth of *M. tuberculosis* from all MTD-positive specimens: trials included MTD-positive, culture-negative specimens from patients with other positive cultures, and there are other reports of test readings "in the low range of positivity" with nontuberculous mycobacteria (2). Users should consult the label for additional information.

When used as approved, a positive MTD test result can provide relatively rapid feedback, indicating a high likelihood of TB. Some public health professionals have considered a negative result to be contributory information for prioritizing contact investigations. False-negative results may be obtained for specimens containing low numbers of *M. tuberculosis* or substances inhibiting the assay. Regardless of MTD results, mycobacterial culture is required for drug-susceptibility testing and precise species and strain identification. As approved for use on AFB-smear-positive respiratory specimens, MTD tests usually will not change the eligibility of a case for surveillance reporting; patients for whom results are positive generally would meet the surveillance case definition previously published by CDC (3).

Several other NAA tests are under commercial development, including the Roche Amplicor™ test (4), a PCR-based test that amplifies mycobacterial DNA. This test was publicly considered in January 1996 by an FDA advisory panel, which recommended approval for use similar to the MTD. If such tests are approved, principles guiding their use would be similar to those for the MTD test.

Because specimen type and clinical setting affect interpretation of NAA tests, clinicians should provide information about patients and specimens to the laboratory, and laboratory directors should provide information about local test performance and interpretation both when tests are ordered and when results are reported. Clinicians should be educated about use under local conditions (predictive values vary with

*Use of trade names and commercial sources is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Vol. 49 / No. 26 MMWR 593

Notice to Readers

Update: Nucleic Acid Amplification Tests for Tuberculosis

On September 30, 1999, the Food and Drug Administration approved a reformulated Amplified Mycobacterium Tuberculosis Direct Test* (MTD) (Gen-Probe®, San Diego, California) for detection of *Mycobacterium tuberculosis* in acid-fast bacilli (AFB) smear-positive and smear-negative respiratory specimens from patients suspected of having tuberculosis (TB). MTD and one other nucleic acid amplification (NAA) test, the Amplicor® Mycobacterium Tuberculosis Test (Amplicor) (Roche® Diagnostic Systems, Inc., Branchburg, New Jersey), previously had been approved for the direct detection of *M. tuberculosis* in respiratory specimens that have positive AFB smears. This notice updates the original summary published in 1996 (1) and provides suggestions for using and interpreting NAA test results for managing patients suspected of having TB.

The appropriate number of specimens to test with NAA will vary depending on the clinical situation, the prevalence of TB, the prevalence of nontuberculous mycobacteria (NTM), and laboratory proficiency (2,3). Based on available information, the following algorithm is a reasonable approach to NAA testing of respiratory specimens from patients with signs or symptoms of active pulmonary TB for whom a presumed diagnosis has not been established.

Algorithm

1. Collect sputum specimens on 3 different days for AFB smear and mycobacterial culture.
2. Perform NAA test on the first sputum specimen collected, the first smear-positive sputum specimen, and additional sputum specimens as indicated below.
   a. If the first sputum specimen is smear-positive and NAA-positive, the patient can be **presumed to have TB** without additional NAA testing. However, unless concern exists about the presence of NTM, the NAA test adds little to the diagnostic workup.
   b. If the first sputum is smear-positive and NAA-negative, a test for inhibitors should be done. The inhibitor test can be done as an option with Amplicor. To test for inhibitors of MTD, spike an aliquot of the lysated sputum sample with lysed *M. tuberculosis* (approximately 10 organisms per reaction, or an equivalent amount of *M. tuberculosis* rRNA) and repeat the test starting with amplification.
      1. If inhibitors are not detected, additional specimens (not to exceed a total of three) should be tested. The patient can be **presumed to have NTM** if a second sputum specimen is smear-positive, NAA-negative, and has no inhibitors detected.
      2. If inhibitors are detected, the NAA test is of no diagnostic help. Additional specimens (not to exceed a total of three) can be tested with NAA.
   c. If sputum is smear-negative and MTD-positive†, additional specimens (not to exceed three) should be tested with MTD. The patient can be **presumed to have TB** if a subsequent specimen is MTD-positive.

*Use of trade names and commercial sources is for identification only and does not constitute endorsement by CDC or the U.S. Department of Health and Human Services.
†Amplicor is not approved for use with smear-negative samples.

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Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis

Background

Individualized Decisions **Reasonable** Approach **Standard** Practice

Performance of Nucleic Acid Amplification Tests for Diagnosis of Tuberculosis in a Large Urban Setting

Clin Infect Dis 2009; 49:46–54

Table 2. Data on the performance of nucleic acid amplification testing of respiratory tract specimens for the *Mycobacterium tuberculosis* complex in New York City during 2000–2004.

Type of patient, performance measure	Patients who received a TB diagnosis on the basis of either a positive culture result or clinical criteria (n = 2418)	Patients who received a TB diagnosis solely on the basis of a positive culture result (n = 2021)
All patients		
Sensitivity, %	92.4	95.0
Specificity, %	97.3	97.3
PPV, %	98.1	97.1
NPV, %	89.5	89.4
Patients whose specimens tested positive for AFB on smear[a]		
Sensitivity, %	94.3	96.0
Specificity, %	98.1	98.1
PPV, %	98.7	98.7
NPV, %	92.0	94.5
Patients whose specimens tested negative for AFB on smear[b]		
Sensitivity, %	70.8	79.3
Specificity, %	85.9	85.9
PPV, %	89.3	88.3
NPV, %	64.0	75.3

NOTE. AFB, acid-fast bacilli; NPV, negative predictive value; PPV, positive predictive value.

[a] There were 2241 patients who received a diagnosis on the basis of either a positive culture result or clinical criteria and 1861 patients who received a diagnosis of TB solely on the basis of a positive culture result.

[b] There were 170 patients who received a diagnosis on the basis of either a positive culture result or clinical criteria and 158 patients who received a diagnosis of TB solely on the basis of a positive culture result.

Table 3. Data on the performance of nucleic acid amplification testing of specimens obtained from patients who also had specimens that tested positive for acid-fast bacilli (AFB) on smear in New York City during 2000–2004, by smear grade.

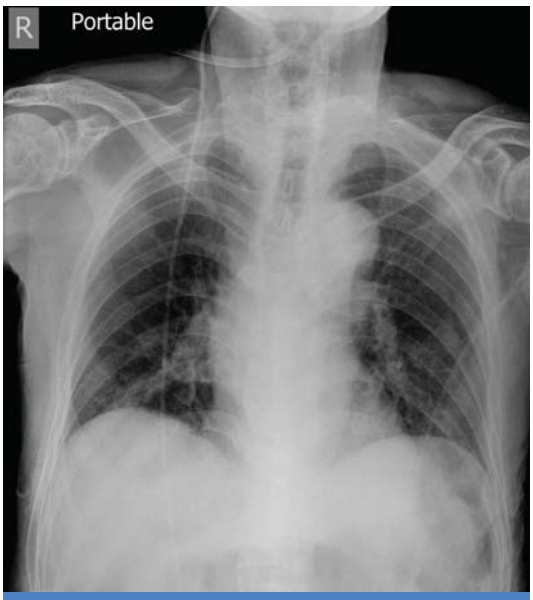
Type of patient, performance measure	Patients whose specimens had a high-grade smear (n = 900)	Patients whose specimens had a low-grade smear (n = 848)
All Patients		
Sensitivity, %	97.6	92.2
Specificity, %	98.1	97.2
PPV, %	99.6	97.4
NPV, %	90.0	91.7
Patients whose specimens tested positive for *M. tuberculosis* on culture[a]		
Sensitivity, %	98.2	94.4
Specificity, %	94.0	92.8
PPV, %	99.4	96.0
NPV, %	82.9	90.1

NOTE. NPV, negative predictive value; PPV, positive predictive value.

[a] There were 800 patients whose specimens tested positive for AFB and had high-grade smear and 668 patients whose specimens tested positive for AFB and had low-grade smear (for details about smear grades, see Methods).

The sensitivity, specificity and predictive values of the test in a real-life situation were high for patients who had a specimen that tested positive for AFB on smear, and they were at a cceptable levels for patients who had a specimen that tested negative for AFB on smear.

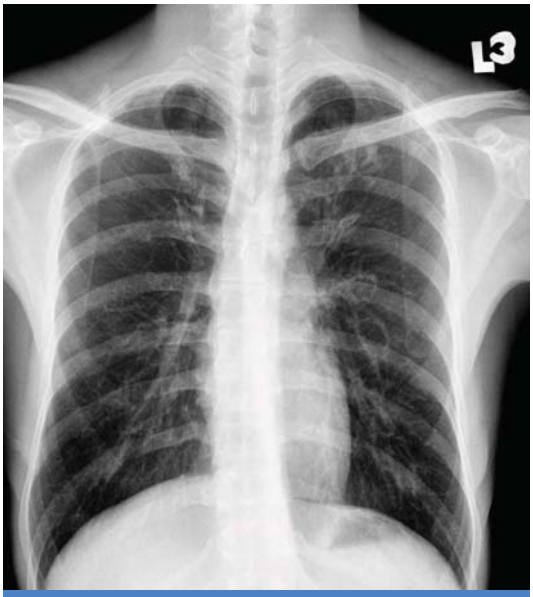
TB vs. NTM (1)



Male, 78 y/o

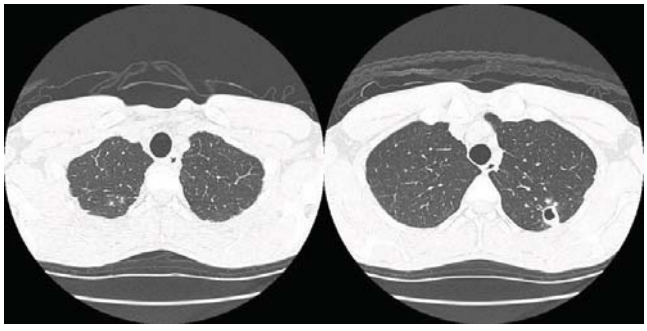
- Sputum acid-fast stain(+)
- NAA test (-)
- Sputum acid-fast culture
  - Nontuberculous Mycobacteria

TB vs. NTM (2)

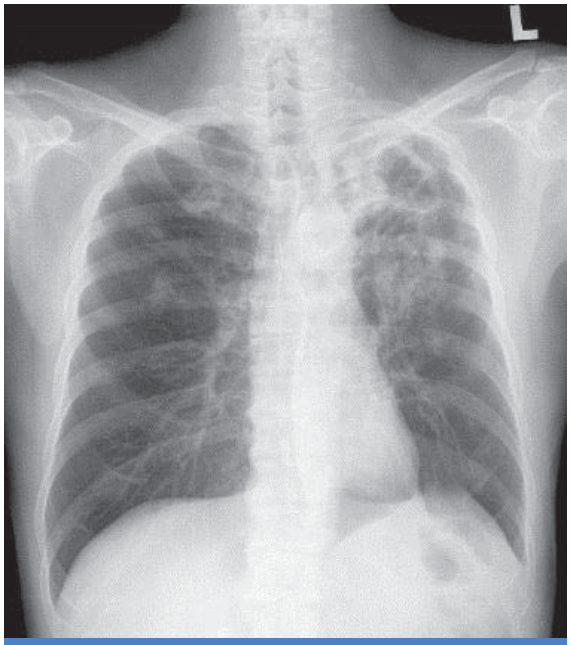


Male, 35 y/o

- Sputum acid-fast stain (+)
- NAA test (-)
- Sputum acid-fast culture
  - *M. kansasii*



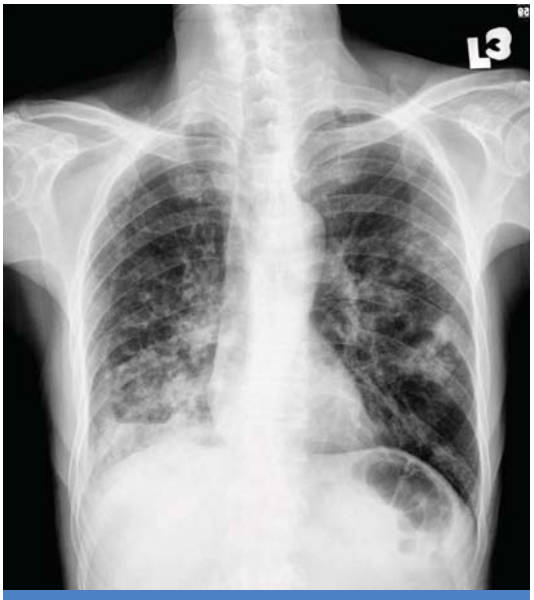
TB vs. NTM (3)



Male, 52 y/o

- Sputum acid-fast stain (+)
- NAA test (+)
- Sputum acid-fast culture
  - *M. tuberculosis*

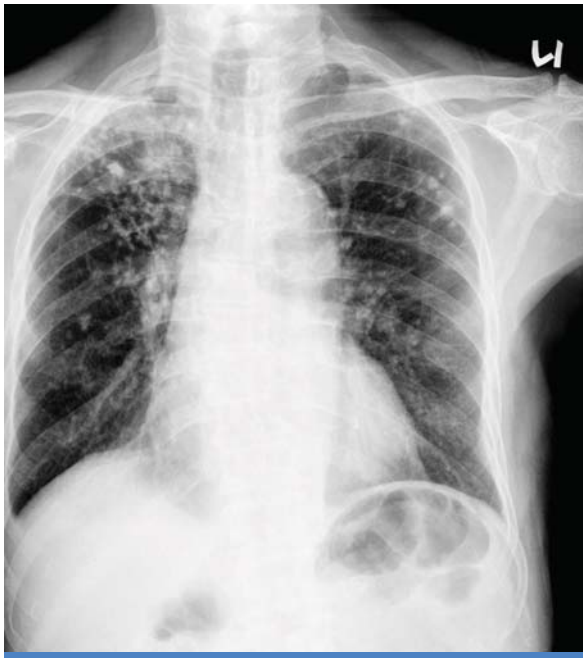
TB vs. NTM (4)



Male, 68 y/o

- Sputum acid-fast stain (+)
- NAA test (+)
- Sputum acid-fast culture
  - *M. tuberculosis*

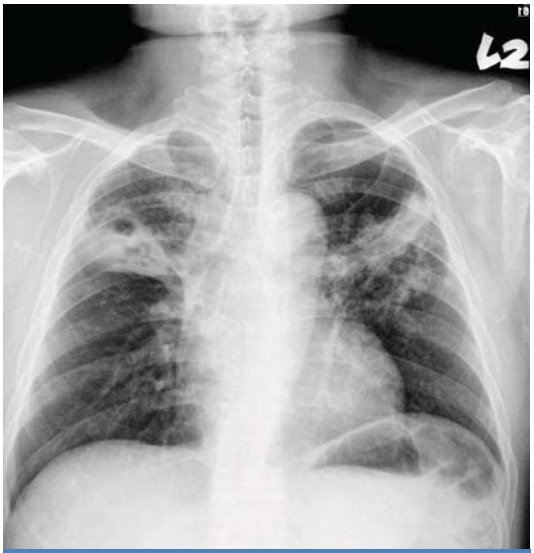
TB vs. NTM (5)



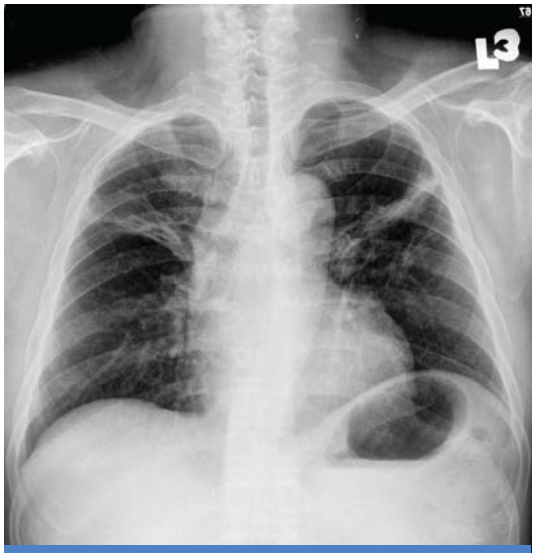
Male, 93 y/o

- Sputum acid-fast stain (+)
- NAA test (+)
- Sputum acid-fast culture
  - *M. tuberculosis*

TB vs. NTM (6)

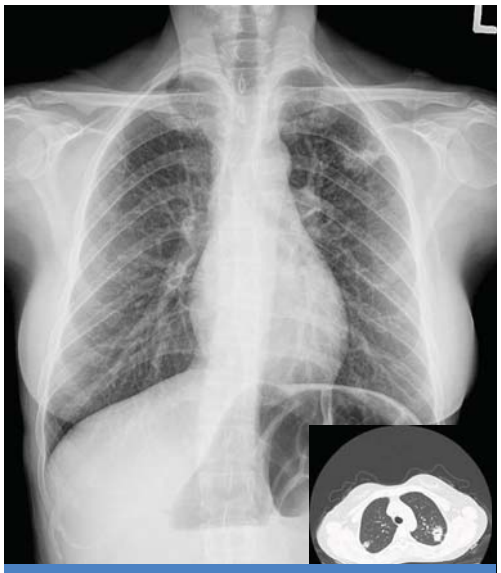


55 y/o, MDR-TB
Sputum AFS (4+), Culture (+)



Sputum AFS (+), NAA test (-)
Sputum culture: *M. abscessus*

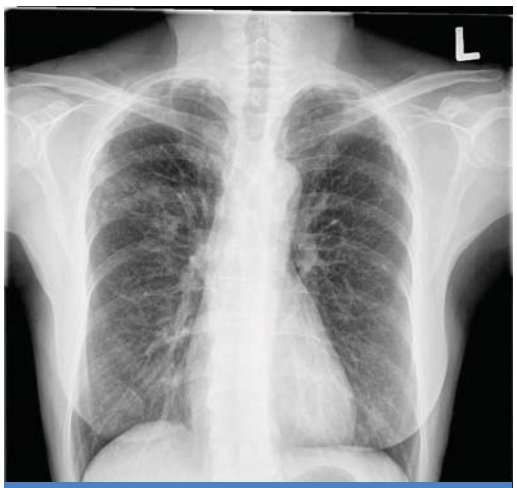
TB vs. NTM (7)



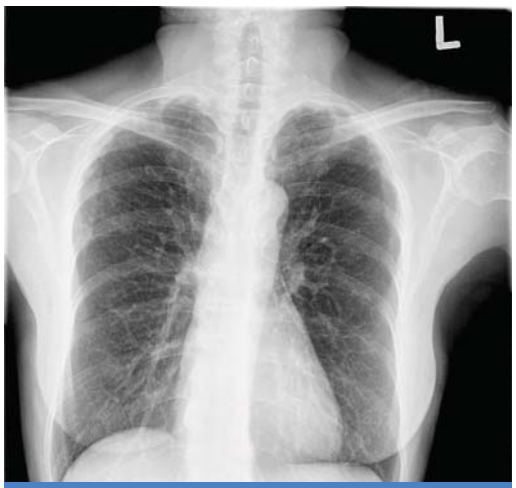
Female, 35 y/o

- Sputum acid-fast stain (-)
- Nucleic acid amplification test (+)
- Sputum acid-fast culture
  - *M. tuberculosis*
- **疑似結核病人皆建議應進行NAA檢驗**
  - 50%至 80%的塗片陰性而培養陽性的檢體，可提早數星期偵測到結核菌

TB vs. NTM (8)

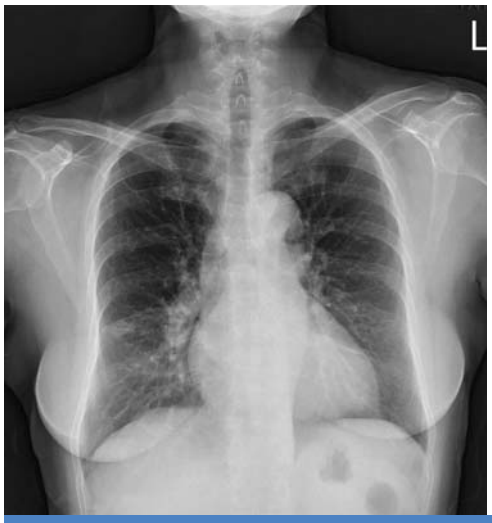


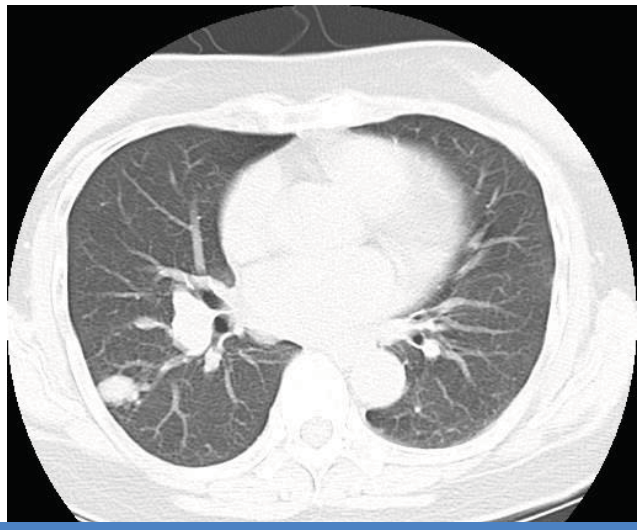
Acid-fast stain (-) x III,
NAAT (-)
Culture: MTB



58 y/o, Female
Anti-TB treatment for 2 months
CXR with improvement

TB vs. NTM (9)

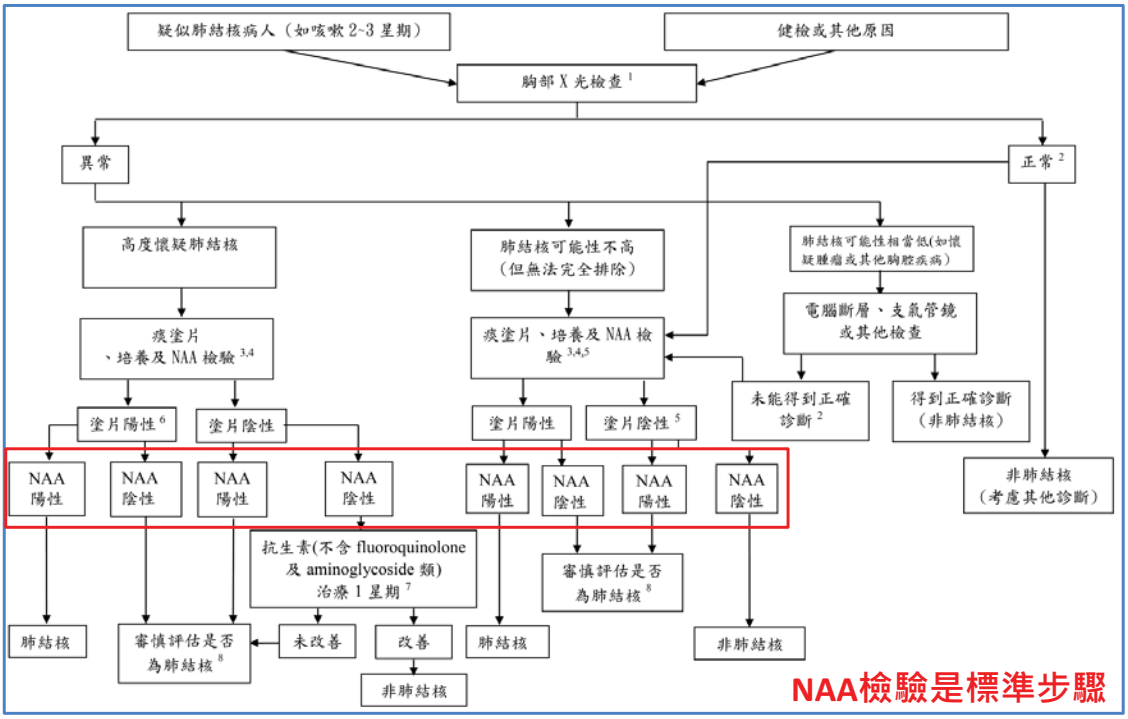




胸腔內視鏡輔助手術(Video-Assisted Thoracoscopic Surgery, VATS)
Granulomatous inflammation with caseous necrosis
Tissue culture: MTB
切片的組織除做病理檢查外，也應當做耐酸性染色及結核分枝桿菌培養

台灣結核病診治指引

第六版(2017)



台灣結核病診治指引

第六版(2017)

疑似肺結核病人	• 儘可能取得細菌學檢驗陽性的證據
核酸增幅檢驗	• 疑似結核病人皆應進行核酸增幅檢驗 • 胸部X光不符合肺結核典型變化但塗片陽性者，務必進行核酸增幅檢驗
細菌學檢驗陰性的疑似病人	• 典型的肺結核臨床表現及胸部X光變化 • 完整的檢查與評估後，再投予抗結核藥物治療 • 觀察其治療後的反應，仍足夠作為診斷之依據

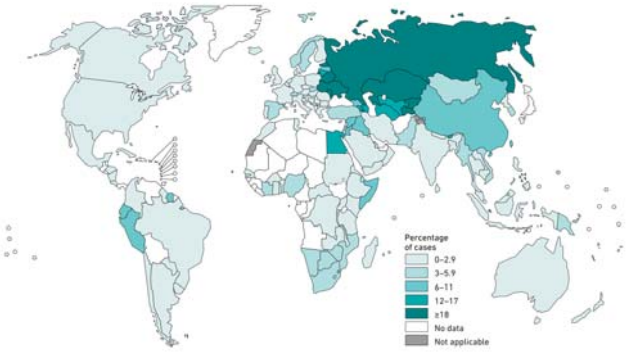
臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

分子檢驗，就這樣嗎?

Global Tuberculosis Report 2018

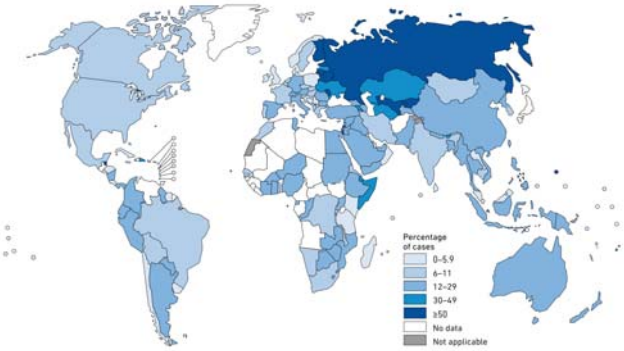
- Globally in 2017, an estimated 3.5% of new cases and 18% of previously treated cases had MDR/RR-TB
- There were an estimated 558,000 incident cases of MDR/RR-TB in 2017
  - The proportion of cases estimated to have MDR-TB was 82%

FIG. 3.20
Percentage of new TB cases with MDR/RR-TB*



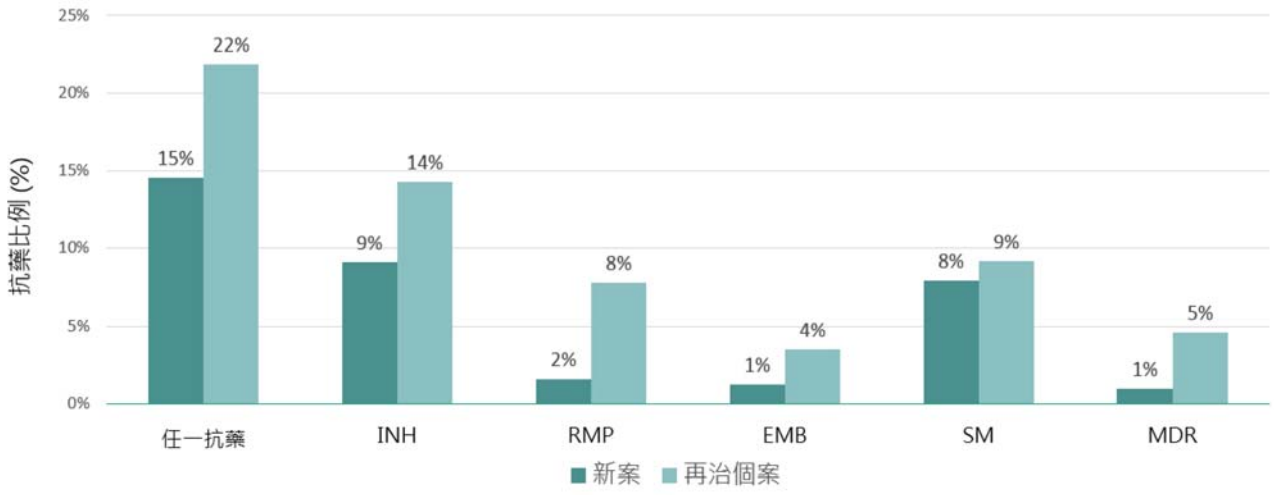
* Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2002–2018.

FIG. 3.21
Percentage of previously treated TB cases with MDR/RR-TB*



* Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2005–2018. The high percentages of previously treated TB cases with RR-TB in Belize, Guam and Sao Tomé and Principe refer to only a small number of notified cases (range: 1–8 notified previously treated TB cases).

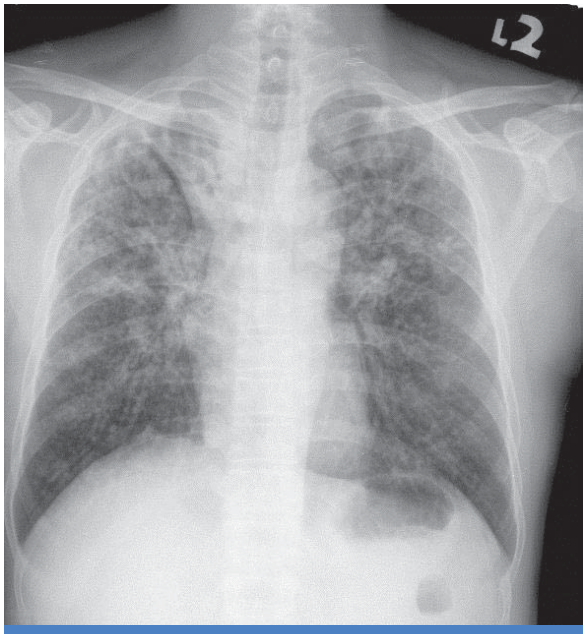
台灣結核病抗藥性監測



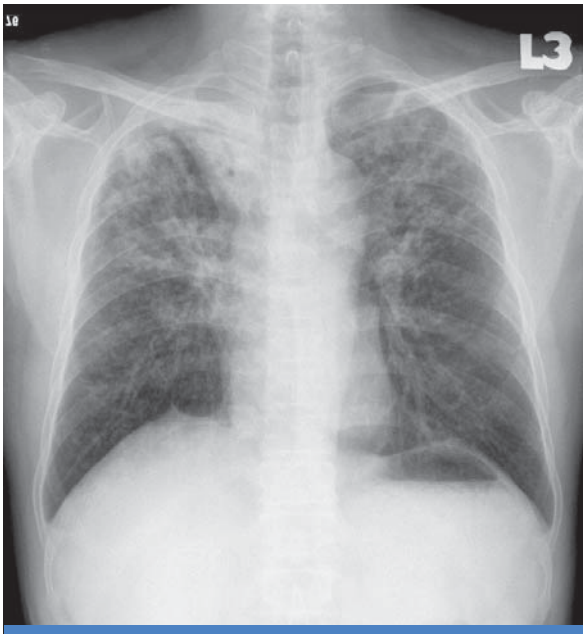
Taiwan CDC 2019.5.8

50歲男性

正確診斷？正確治療？



SHER/Gout

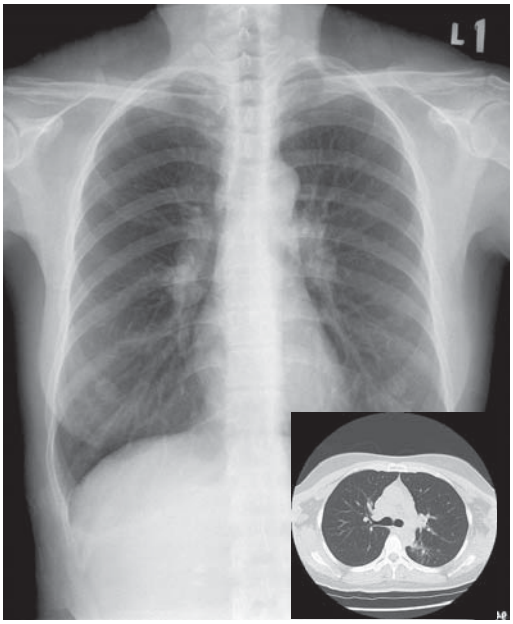


2個月規則治療/MDR-TB

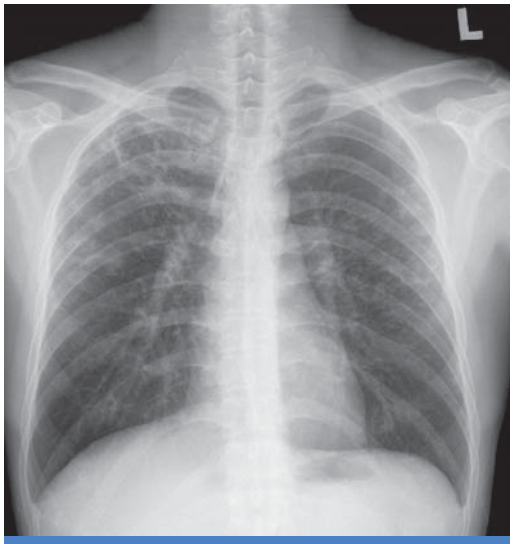
多重抗藥性肺結核

Multidrug-Resistant TB (MDR-TB)

MDR-TB



親密接觸者



MDR-TB:46天

自動化即時分子檢驗

GeneXpert MTB/RIF Assay

TABLE 3. Essential laboratory tests for tuberculosis control

Test	Maximum turnaround time
Microscopy for acid-fast bacilli	≤24 hours from specimen collection or, if test is performed offsite, ≤24 hours from receipt in laboratory; if latter, time from specimen collection to laboratory receipt should be ≤24 hours
Nucleic acid amplification assay	≤48 hours from date of specimen collection

2015 年臺灣認可實驗室

分子檢驗方法	使用家數
羅氏達可結核桿菌測試劑 (COBAS TaqMan MTB Test)	17
賽沛結核分枝桿菌檢測試劑組 GeneXpert MTB/RIF test	11
"飛迅"結核桿菌快速檢驗試劑（未滅菌） FastSure TB Rapid Test	2
晶宇結核分枝桿菌群檢驗試劑套組及生物晶片檢測平臺 DR. MTBC ScreenTM IVD Kit and DR. AimTM Platform	9
亞洲基因結核分枝桿菌核酸探針檢驗試劑 AsiaGen Mycobacterium tuberculosis Detection Kit	2
"必帝"結核桿菌測試劑（未滅菌） "BD"ProbeTec ET Mycobacterium tuberculosis reagents (Non-Sterile)	1
In-house PCR	2

疫情報導 2017 年 第 33 卷 • 第 20 期

- 世界衛生組織推薦於一般實驗室環境使用
  - 2小時知道是否有MTB及Rifampin抗藥
- 塗片耐酸性染色鏡檢陽性
  - 敏感度達98%
  - 特異度達99%
- 塗片耐酸性染色鏡檢陰性
  - 敏感度68%
  - 特異度為99%

Standard 3

All Patients Should Have at Least Two Sputum Specimens Submitted for Smear Microscopy or a Single Sputum Specimen for Xpert® MTB/RIF Testing

- **Xpert MTB/RIF**
  - Excellent performance characteristics for detecting *M. tuberculosis* and rifampicin resistance

- **Should have Xpert MTB/RIF performed as the initial diagnostic test**
  - Risk for drug resistance
  - HIV risks
  - Seriously ill

Standard 5

In Patients Suspected of Having Pulmonary TB Whose Sputum Smears Are Negative, Xpert MTB/RIF and/or Sputum Cultures Should be Performed

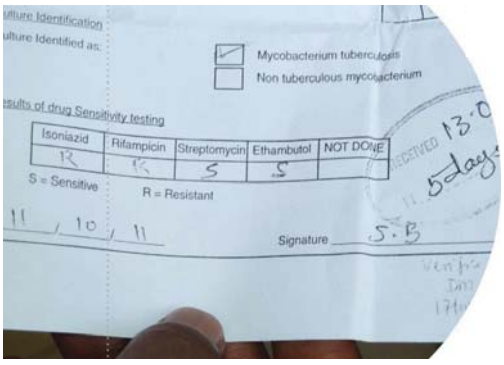
- **WHO recommendations**
  - Use of rapid molecular testing for diagnosis of TB among persons who are suspected of having the disease but have negative sputum smear microscopy are presented

Among patients with sputum that is negative by smear and Xpert MTB/RIF who have clinical evidence strongly suggestive of TB, anti-TB treatment should be initiated after collection of specimens for culture examination

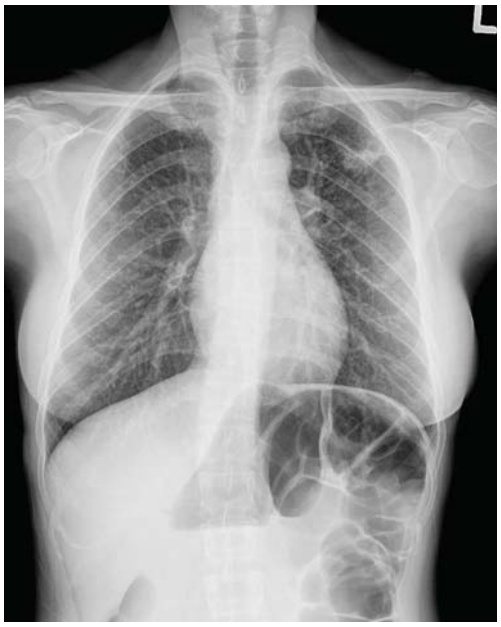
Standard 11

For Patients in Whom Drug Resistance is Considered to be Likely, an Xpert MTB/RIF Should be the Initial Diagnostic Test

- The use of Xpert MTB/RIF in assessing for rifampicin resistance and line probe assay for detecting resistance to both isoniazid and rifampicin



Female, 35 y/o



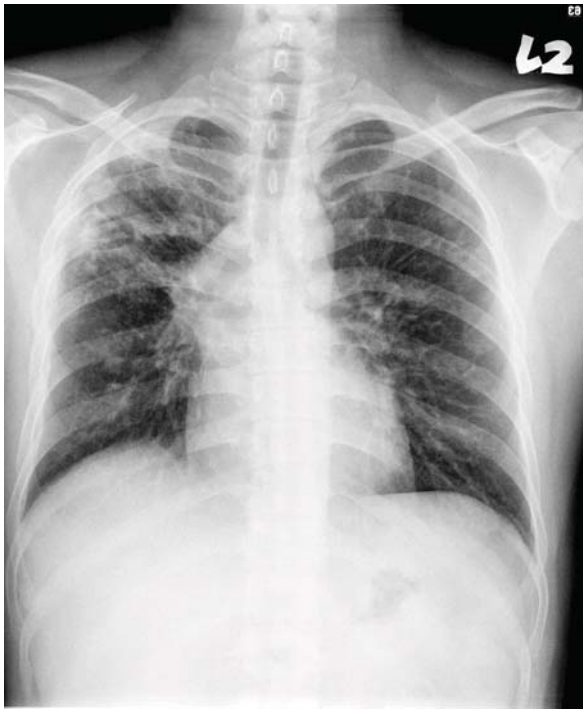
- RMP-resistant TB contact
- Sputum acid-fast stain (-)
- Nucleic acid amplification test (+)
  - MTB
  - Rifampin-resistant TB
- Sputum culture
  - *M. tuberculosis*
  - Rifampin-resistant TB

台灣的現行規定

符合分子快速篩檢對象

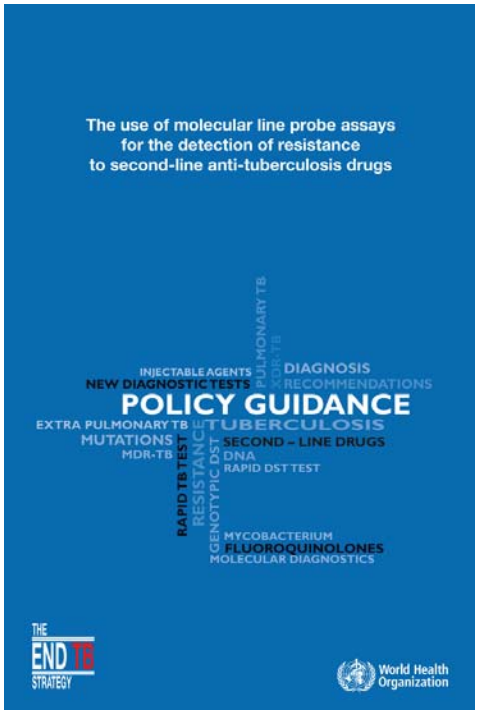
1. 結核病再治個案(失落、失敗、復發，重開非復發曾經使用抗結核藥物 4 週以上)。
2. RR-TB 及 MDR-TB 個案之接觸者轉為個案者。
3. 國內高風險地區之新發生個案。
4. 於民國 80 年後，個案過去曾停留在疾病管制署指定應送分子快速篩檢國家，於 1年內累積達 1 個月以上(即連續任 365 天內，停留時間累積達 30 天以上)。

28歲男性



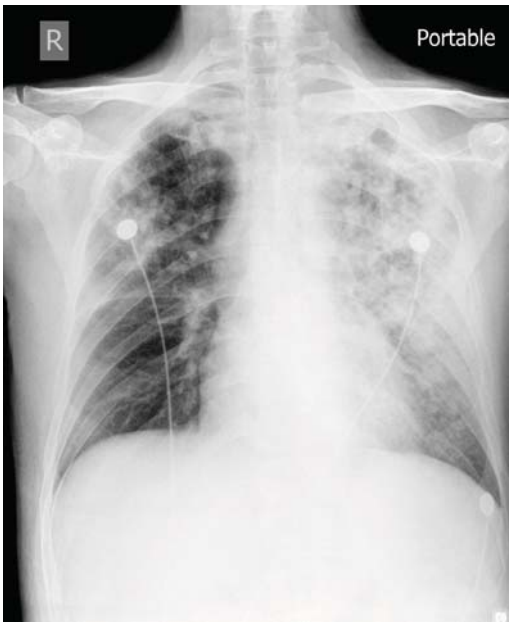
- 2012-4-16
  - 檢體收件
- 2012-4-18
  - 確認MDR-TB
- 2012-5-22
  - 提供第二線抗結核藥物感受性試驗結果

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, 53 y/o



檢體收件日期	民國108年2月21日	檢體不良狀況	
分子鑑定		檢體液化程度/檢體量	
檢體編號	N19-0386	再採檢日期	
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	
LJ 培養報告日期		LJ 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分子檢驗報告日期		MDR分子檢驗結果	
MDR傳統藥敏試驗檢驗報告日期		MDR傳統藥敏試驗檢驗結果	
MDR 備註			
Xpert：			
MTBC 報告日期	民國108年2月21日	MTBC 檢驗結果	本次送驗痰檢體MTBC核酸陽性，敬請臨床醫師進行個案最終判定
RMP 報告日期	民國108年2月21日	RMP 檢驗結果	R，敬請臨床醫師進行個案最終判定
分生一線藥特：			
報告日期	民國108年2月22日		
MTBC 檢驗結果	本次送驗痰檢體MTBC核酸陽性，敬請臨床醫師進行個案最終判定	RMP 檢驗結果	R，敬請臨床醫師進行個案最終判定
INH 檢驗結果	R，敬請臨床醫師進行個案最終判定		
分生二線藥特：			
報告日期	民國108年2月22日		
FLQ 檢驗結果	S，敬請臨床醫師進行個案最終判定	KAN 檢驗結果	S，敬請臨床醫師進行個案最終判定
AMK 檢驗結果	S，敬請臨床醫師進行個案最終判定	CAP 檢驗結果	S，敬請臨床醫師進行個案最終判定
PZA 報告日期		定序 PZA 檢驗結果	
分子快速檢測備註			
痰檢菌株保存編號		分子分型結果	
分子分型結果備註			
一線藥敏報告日期		一線藥敏檢驗結果	
一線藥敏備註			
二線藥敏報告日		二線藥敏檢驗結果	
二線藥敏報告日期	民國108年4月17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. 低濃度Kanamycin：敏感. p-aminosalicylicacid：敏感
二線藥敏備註	Linezolid 敏感；Clofazimine 敏感		

台灣結核病診治指引

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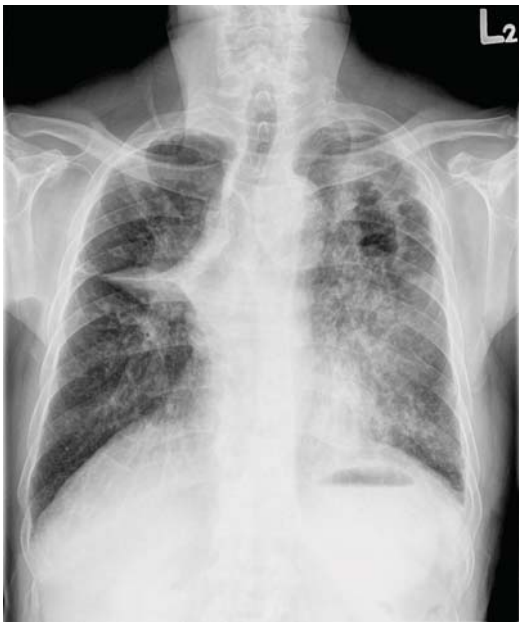
第一線抗結核藥物感受性試驗

- 第一次培養陽性的結核菌株
- 治療第五個月及以後培養陽性
- 陰轉後再度培養陽性

快速分子檢測

- 抗藥性的高危險族群
- 疾病管制署的分枝桿菌實驗室

抗藥基因突變位點



衛生福利部疾病管制署

結核菌藥物分子檢測抗藥位點報告

姓　名

檢體編號

Bar-code

方法學類別　定序(菌株)

檢驗項目　MDR複驗

檢體採檢日　2019/5/2

備　註

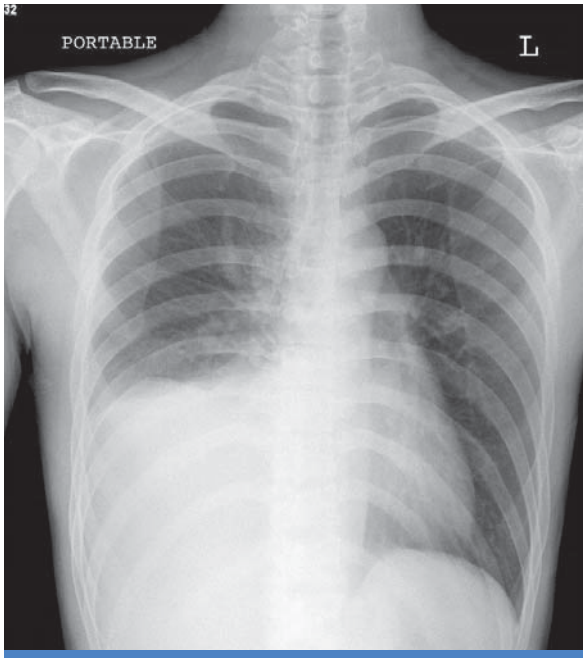
藥物	抗藥基因突變位點	抗藥關聯性
RIF	rpoB S531L	S531L confers high-level resistance to all rifamycins
INH	katG 315, inhA promoter no mutation	
FLQ	gyrA 88-94, gyrB 538/540 no mutation	
SLID	rrs 1401/1402/1484, eis promoter no mutation	
PZA	pncA W68R	pncA mutations associated with PZA resistance

疾病管制署 檢驗及疫苗研製中心 分枝桿菌實驗室

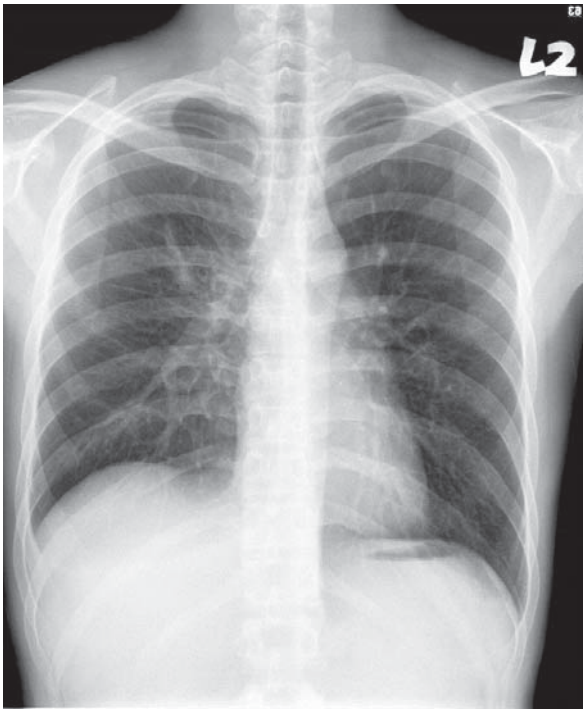
臺北市立萬芳醫院 -委託財團法人臺北醫學大學辦理-

挑戰(2)

Isoniazid-resistant Tuberculosis



Male, 29 y/o



Isoniazid-resistant TB vs. Isoniazid-sensitive TB

- Higher treatment failure (11% vs 1%)
- Relapse (10% vs 5%)
- Higher rates of acquired multidrug resistance (8% vs 0.3%)

Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis

Medea Gegia, Nicholas Winters, Andrea Benedetti, Dick van Soolingen, Dick Menzies

Summary

Background The results of some reports have suggested that treatment of isoniazid-resistant tuberculosis with the recommended regimens of first-line drugs might be suboptimal. We updated a previous systematic review of treatment outcomes associated with use of first-line drugs in patients with tuberculosis resistant to isoniazid but not rifampicin.

Methods In this systematic review, we updated the results of a previous review to include randomised trials and cohort studies published in English, French, or Spanish to March 31, 2015, containing results of standardised treatment of patients with bacteriologically confirmed isoniazid-resistant tuberculosis (but not multidrug-resistant tuberculosis—ie, not resistant to rifampicin) in whom failure and relapse were bacteriologically confirmed. Results in patients with drug-sensitive tuberculosis included in the same studies were also analysed. We pooled treatment outcomes with random-effects meta-analysis.

Findings We identified 19 cohort studies and 33 trials with 3744 patients with isoniazid-resistant tuberculosis and 19 012 patients with drug-sensitive disease. The pooled rates of failure or relapse, or both, and acquired drug resistance with all drug regimens were 15% (95% CI 12–18) and 3·6% (2–5), respectively, in patients with isoniazid-resistant tuberculosis and 4% (3–5) and 0·6% (0·3–0·9) in those with drug-sensitive tuberculosis. Of patients with initial isoniazid-resistant tuberculosis with acquired drug resistance, 96% (93–99) had acquired multidrug-resistant disease. Treatment of isoniazid-resistant tuberculosis with the WHO standard regimen for new patients resulted in treatment failure, relapse, and acquired multidrug resistance in 11% (6–17), 10% (5–15) and 8% (3–13), respectively; treatment with the standard WHO regimen for previously treated patients resulted in treatment failure in 6% (2–10), relapse in 5% (2–8), and acquisition of multidrug resistance in 3% (0–6). For patients with drug-sensitive disease treated with the standard retreatment regimen the rates were 1% (0–2), 5% (4–7), and 0·3% (0–0·6).

Interpretation Treatment of isoniazid-resistant tuberculosis with first-line drugs resulted in suboptimal outcomes, supporting the need for better regimens. Standardised empirical treatment of new cases could be contributing substantially to the multidrug-resistant epidemic, particularly in settings where the prevalence of isoniazid resistance is high.

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See Comment page 127

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Treatment outcome of patients with isoniazid mono-resistant tuberculosis

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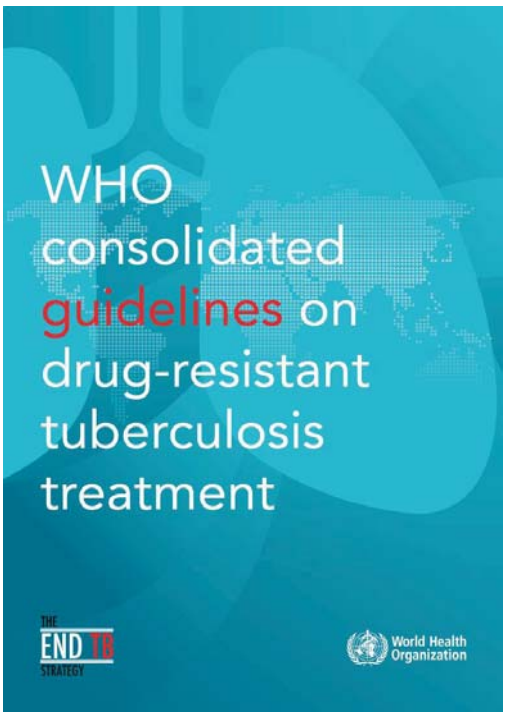
Abstract

Isoniazid mono-resistance is the most common first-line drug resistance in tuberculosis (TB), but its treatment outcome remains unclear. From January 2004 to October 2011, 425 (5.1%) of 8414 patients with culture-confirmed pulmonary TB from four hospitals in Taiwan were identified as having isoniazid mono-resistant TB. Among them, 395 (92.9%) were included and followed up for 2 years after complete treatment. Although 328 (83.0%) patients were successfully treated, 67 (17.0%) had unfavourable outcomes, including death in 56 (14.2%) and treatment failure in 11 (2.8%). The treatment success rate was similar in patients with high-level and low-level isoniazid-resistant TB (82.2% versus 83.4%, p 0.785) and among those taking anti-TB treatment with and without isoniazid (83.1% versus 83.0%, p 1.000). Patients without rifampicin interruption had lower risk of unfavourable outcome (14.3% versus 37.0%, p <0.001), especially those with low-level isoniazid resistance (11.5% versus 56.5%, p <0.001). Supplementation with a new-generation fluoroquinolone improved treatment success (60.0% versus 12.5%, p 0.003). The presence of cavitary lesions was significantly associated with a higher relapse rate (4.1% versus 0.0%, p 0.006) and extended treatment of 7–9, 10–12 and >12 months had less relapse than 6-month treatment (3.2%, 0%, 3.7% and 25.0%, respectively, p 0.037). Multivariate Cox proportional hazards analysis revealed that co-morbidity with cancer (hazard ratio, 2.43) and rifampicin interruption (hazard ratio 1.91) were independent factors associated with unfavourable outcomes. Treatment throughout with rifampicin and extended treatment for cavitary disease are crucial for improving outcomes in patients with isoniazid mono-resistant TB.

Clin Microbiol Infect 2015; 21: 59–68

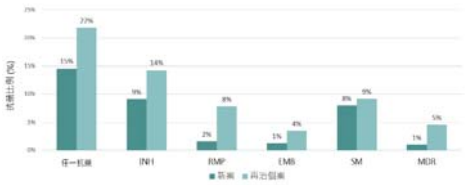
Isoniazid-resistant Tuberculosis

About 8% of TB cases worldwide are estimated to have confirmed rifampicin-susceptible, isoniazid-resistant TB (Hr-TB), ranging from 5 to 11% between the WHO regions



Recommendations

- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis
  - Treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months
- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis
  - Not recommended to add streptomycin or other injectable agents to the treatment regimen



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The Fourth National Anti-Tuberculosis Drug Resistance Survey in Viet Nam

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SUMMARY

SETTING: Viet Nam's Fourth National Anti-Tuberculosis Drug Resistance Survey was conducted in 2011.

OBJECTIVE: To determine the prevalence of resistance to the four main first-line anti-tuberculosis drugs in Viet Nam.

METHODS: Eighty clusters were selected using a probability proportion to size approach. Drug susceptibility testing (DST) against the four main first-line anti-tuberculosis drugs was performed.

RESULTS: A total of 1629 smear-positive tuberculosis (TB) patients were eligible for culture. Of these, DST results were available for 1312 patients, including 1105 new TB cases, 195 previously treated TB cases and 12 cases with an unknown treatment history. The proportion of cases with resistance to any drug was 32.7% (95%CI 29.1–36.5) among new cases and 54.2% (95%CI 44.3–63.7) among previously treated cases. The proportion of multidrug-resistant TB (MDR-TB) cases was 4.0% (95%CI 2.5–5.4) in new cases and 23.3 (95%CI 16.7–29.9) in previously treated cases.

CONCLUSIONS: The fourth drug resistance survey in Viet Nam found that the proportion of MDR-TB among new and previously treated cases was not significantly different from that in the 2005 survey. The National TB Programme should prioritise the detection and treatment of MDR-TB to reduce transmission of MDR-TB in the community.

KEY WORDS: Viet Nam; MDR-TB; drug resistance survey; tuberculosis

Resistance to SM, INH, RMP and EMB

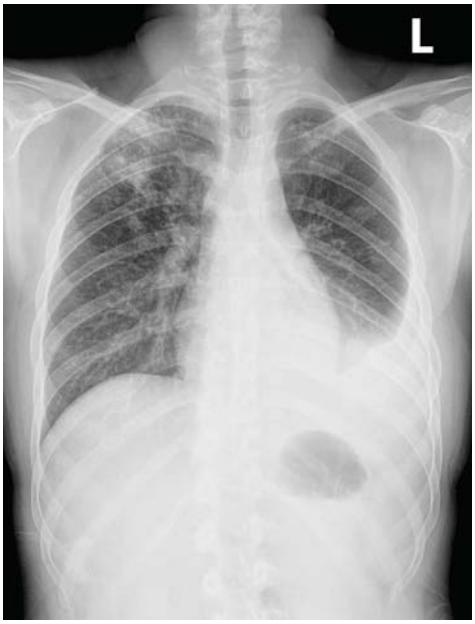
by Treatment History

	New		Previously treated		Total*		
	n (%)	95%CI	*n* (%)	95%CI	*n* (%)	95%CI	*P* value
Total patients with available DST results	1105		195		1312		
Susceptibility to all SM, INH, RMP, EMB	763 (67.3)	63.5–70.9	95 (45.9)	36.3–55.7	863 (63.8)	59.9–67.6	
Any resistance							
SM	284 (27.4)	23.9–31.1	81 (42.2)	33.1–51.8	370 (30.0)	26.7–33.5	0.005
INH	204 (18.9)	16.0–22.2	79 (44.7)	35.4–54.3	286 (22.4)	19.5–25.6	<0.001
RMP	47 (4.1)	2.7–6.2	47 (23.1)	15.9–32.3	94 (6.7)	5.1–8.7	<0.001
EMB	33 (3.4)	1.9–6.0	25 (11.9)	6.7–20.2	58 (4.5)	3.0–6.7	0.002
Total	342 (32.7)	29.1–36.5	100 (54.2)	44.3–63.7	449 (36.2)	32.4–40.1	<0.001
Monoresistance							
SM	137 (13.7)	11.3–16.6	19 (8.3)	4.6–14.6	160 (13.6)	10.9–16.8	0.116
INH	54 (5.0)	3.5–7.1	14 (10.4)	4.0–24.2	70 (5.8)	4.5–7.4	0.118
RMP	0		0		0		
EMB	0		0		0		
Total	191 (18.7)	16.2–21.6	33 (18.7)	10.7–30.5	230 (19.4)	16.1–23.1	0.990

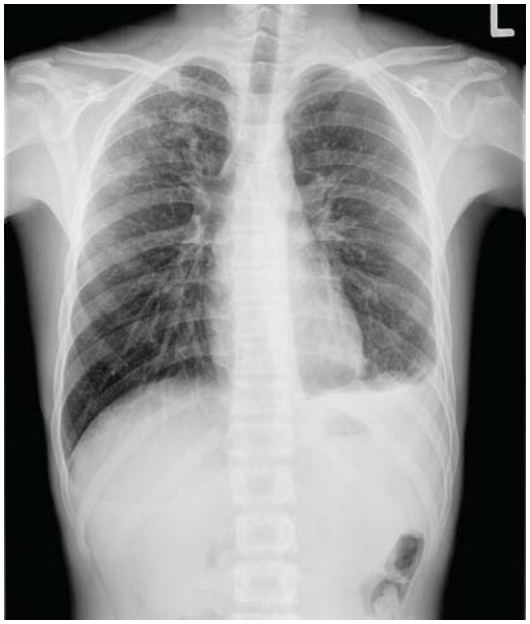
* Includes 12 cases with unknown treatment history.
SM = streptomycin; INH = isoniazid; RMP = rifampicin; EMB = ethambutol; CI = confidence interval; DST = drug susceptibility testing.

GeneXpert MTB/RIF: Rifampin-resistant ?

Female, 16 y/o

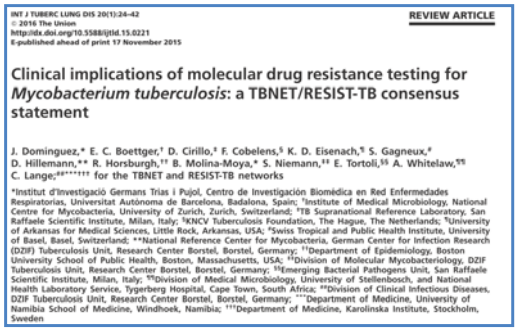


Male, 14 y/o



Discordance

Phenotypic and Molecular Methods for Drug Susceptibility Testing



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Clinical implications of molecular drug resistance testing for *Mycobacterium tuberculosis*: a TBNET/RESIST-TB consensus statement

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- If the results of molecular and culture-based drug susceptibility testing differ, what is the gold standard?
  - Despite the fact that results of phenotypic methods do not always correspond to response to clinical treatment, culture-based methods are still regarded by most experts involved in this document as the gold standard for DST.
  - Agreed: 13; disagreed: 0; abstained: 0.

衛生福利部疾病管制署
結核菌藥物分子檢測抗藥位點報告

姓　名
檢體編號
Bar-code
方法學類別　定序(菌株)
送驗項目　RIF單抗
檢體採檢日　2017/05/20
備　註

藥物	抗藥基因突變位點	抗藥關聯性
RIF	rpoB P520P	CCG/CCA silent mutation
INH	katG 315, inhA promoter no mutation	
FLQ	gyrA 88-94, gyrB 538/540 no mutation	
SLID	rrs 1401/1402/1484, eis promoter no mutation	
PZA	pncA no mutation	

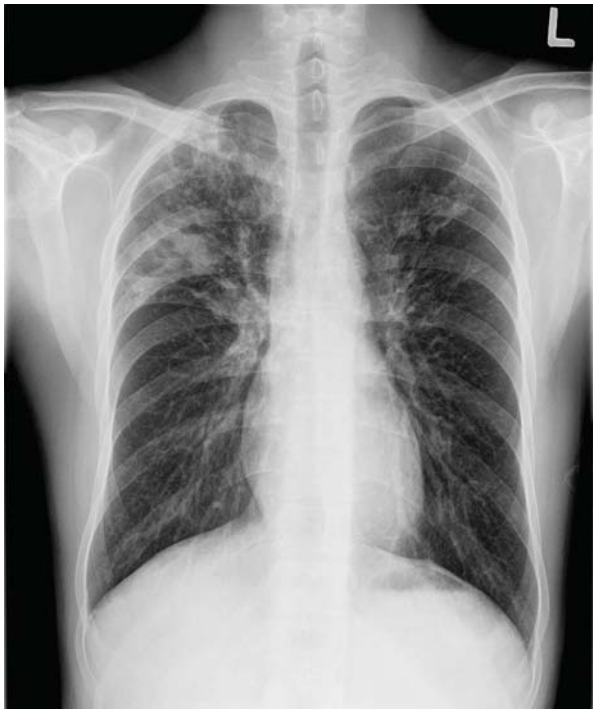
The NEW ENGLAND JOURNAL of MEDICINE

Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing

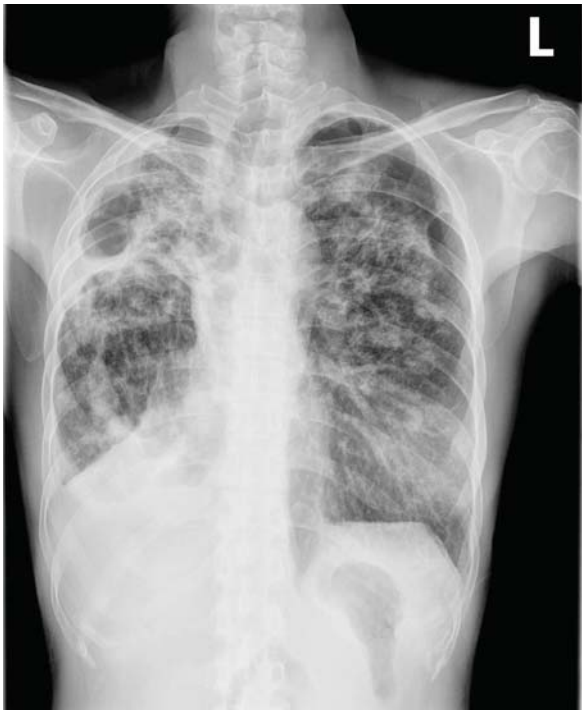
臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

結論

Male, 19 y/o



Female, 44 y/o



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EDITORIALS

Tuberculosis Diagnosis — Time for a Game Change

Peter M. Small, M.D., and Madhukar Pai, M.D., Ph.D.

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EDITORIAL

The Coming of Age of Drug-Susceptibility Testing for Tuberculosis

Helen Cox, Ph.D., and Valerie Mizrahi, Ph.D.

Thanks for Listening!