

多重抗藥結核病人的照護

衛福部桃園醫院 胸腔科
林倬睿醫師

名詞定義

- ❑ **Drug-susceptible TB (DSTB):** 對第一線抗結核藥物皆敏感
- ❑ **Drug-resistant TB (DRTB):**
 - **Isoniazid-resistant TB (Hr-TB):** resistant to **isoniazid**, but not to rifampin
 - **Rifampin-resistant TB (RR-TB):** resistant to **rifampin**
 - **Multidrug-resistant TB (MDR-TB):** resistant to **isoniazid** and **rifampin**
 - **Pre-XDR-TB:** MDRTB plus resistant to **any fluoroquinolone** (moxifloxacin, levofloxacin)
 - **Extensively drug-resistant TB (XDR-TB):** pre-XDR-TB plus resistant to additional **one group A drug** (bedaquiline, linezolid)

大綱

- 背景介紹
 - 全球及台灣的流病現況
 - TB治療的原則
- 近期發展
 - 診斷方法
 - 藥物
 - 處方
- 抗藥結核照護體系
 - 台灣的照護模式
 - 案例分享

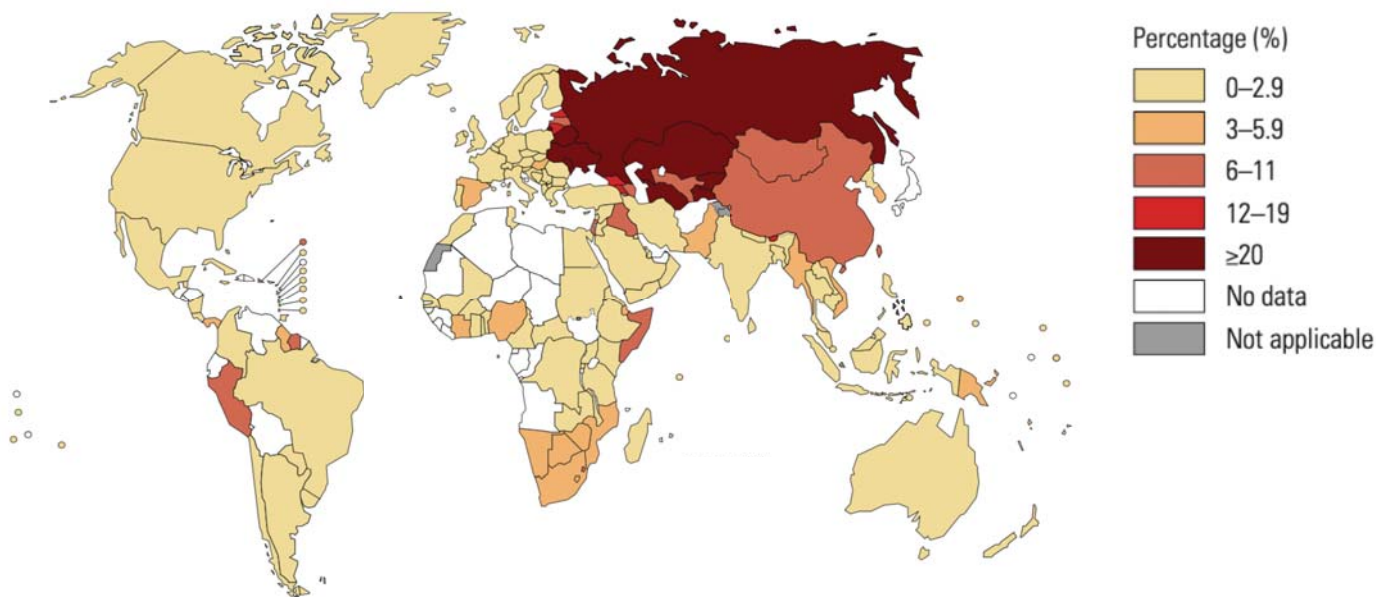


背景介紹

全球及台灣的流病現況

MDR/RR-TB 在新病人中的比率

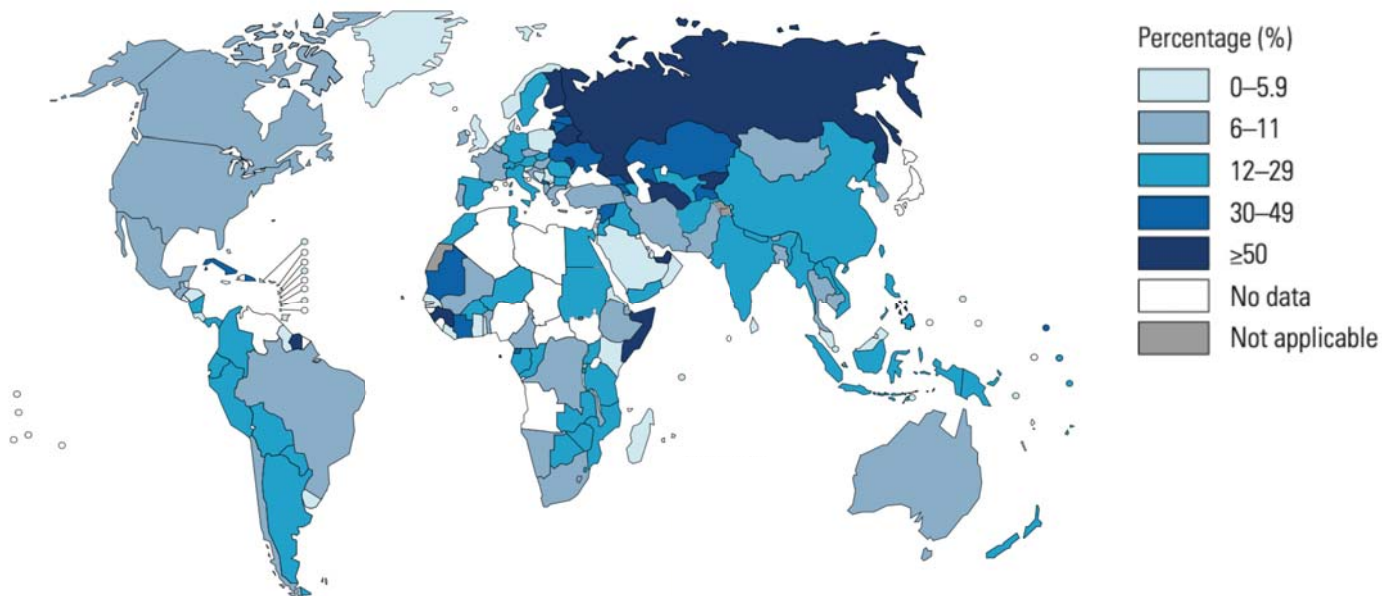
Percentage of new TB cases with MDR/RR-TB^a



WHO, Global report, 2020

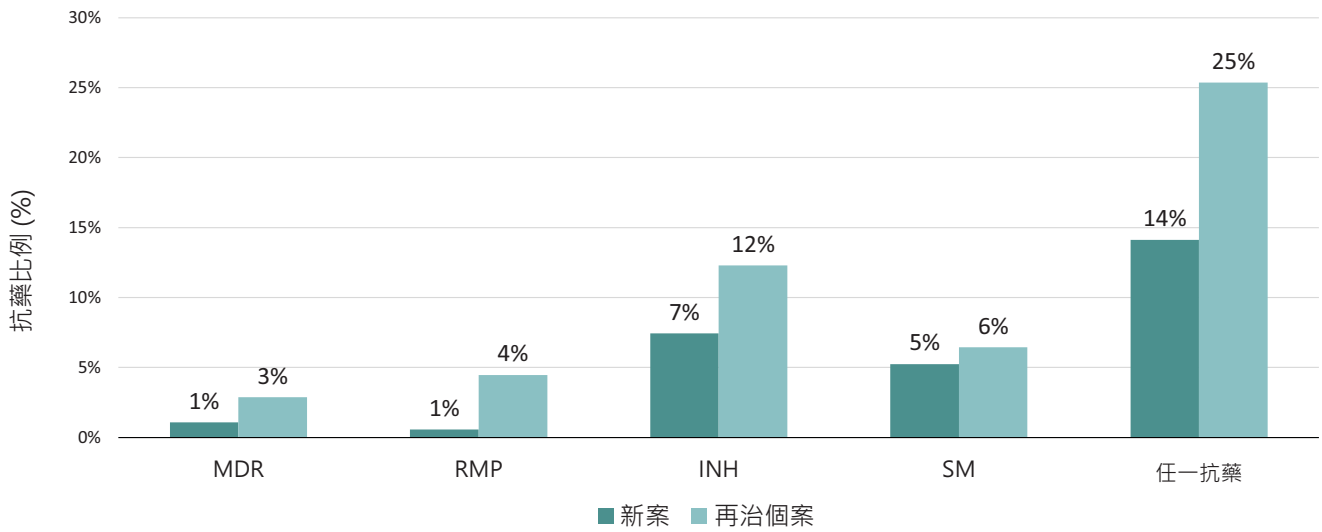
MDR/RR-TB 在再治病人中的比率

Percentage of previously treated TB cases with MDR/RR-TB^a



WHO, Global report, 2020

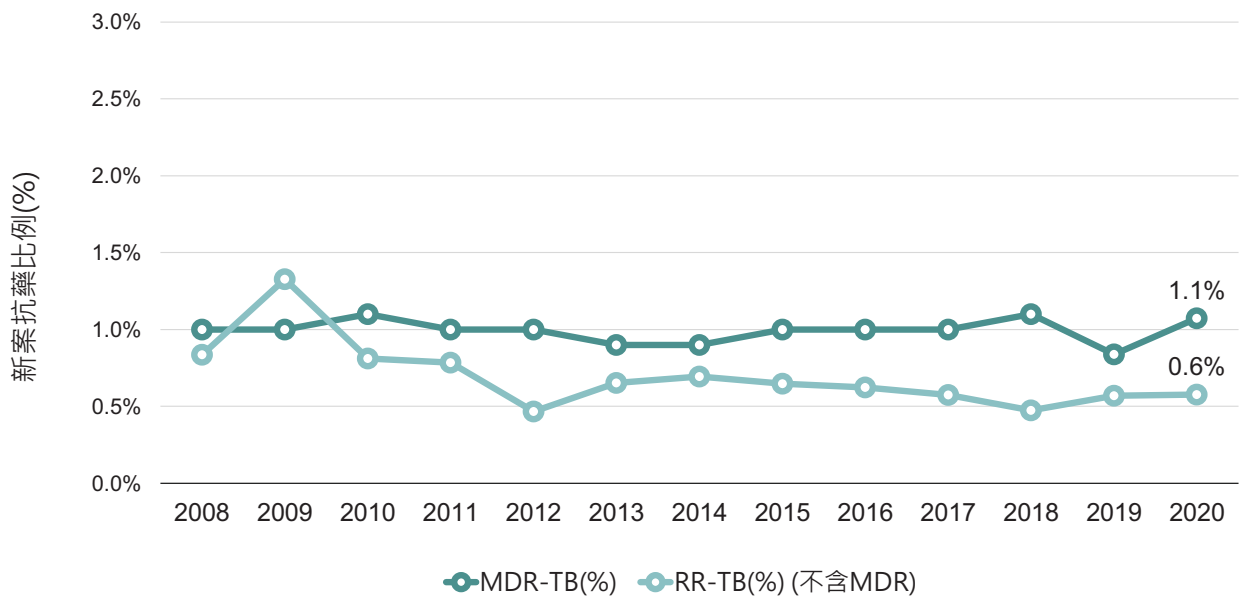
2020年本國籍結核病初發抗藥性監測



備註：本國人抗藥比例。INH、RMP、SM抗藥，不含MDR抗藥者。

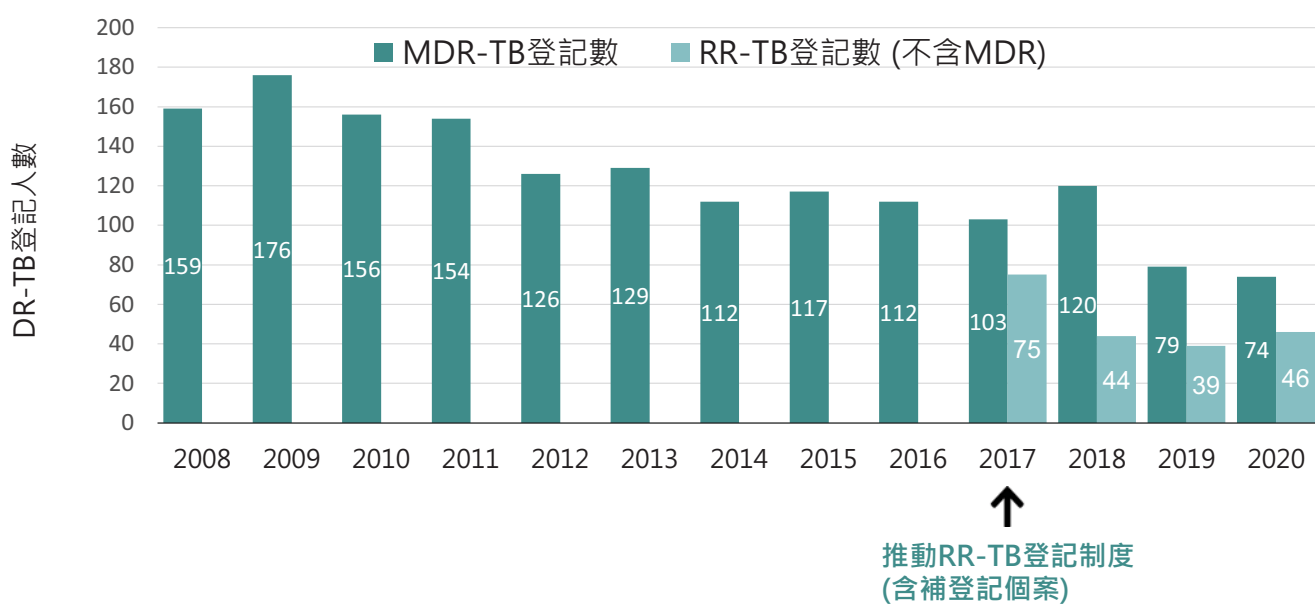
Taiwan CDC, TB report, 2021

歷年本國籍結核病新案MDR/RR-TB監測



Taiwan CDC, TB report, 2021

歷年本國籍RR-TB及MDR-TB登記數



Taiwan CDC, TB report, 2021

背景介紹

TB治療的原則

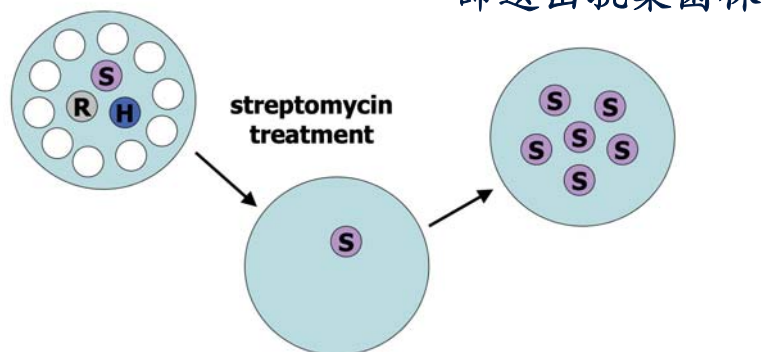
TB 治療的原則

併用多種有效藥物

- 避免產生續發性抗藥

規則治療足夠時間

自發性染色體突變



不適當的治療

TB 治療的原則

併用多種有效藥物

- 避免產生續發性抗藥

規則治療足夠時間

- 減少完治後復發

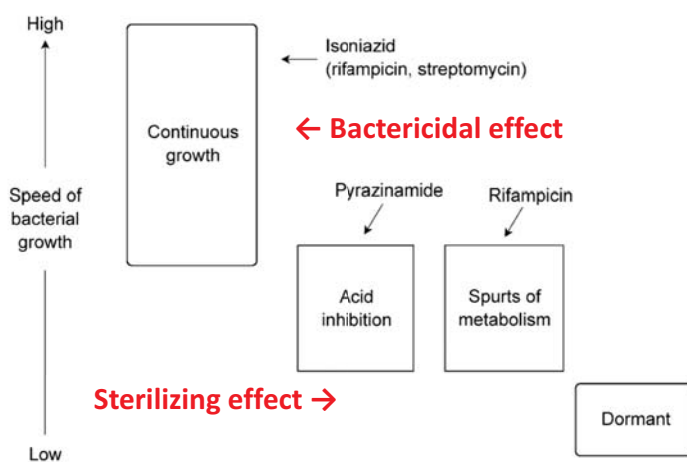


Figure 3.1 Hypothesis: Specific populations of the bacterial population in certain lesions are killed by different drugs. (Adapted from Mitchison, Treatment of tuberculosis, page 93.)

TB 治療的原則

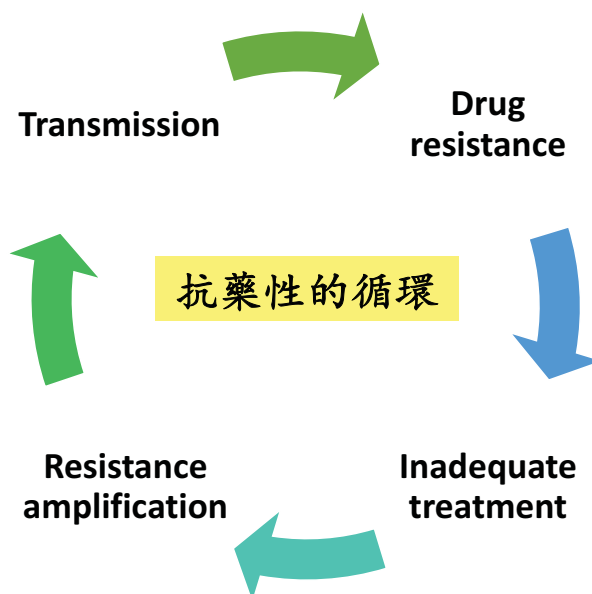
併用多種有效藥物

- DSTB: start with 4 drugs
- MDRTB: start with 4-7 drugs
- challenge: **timely DST**

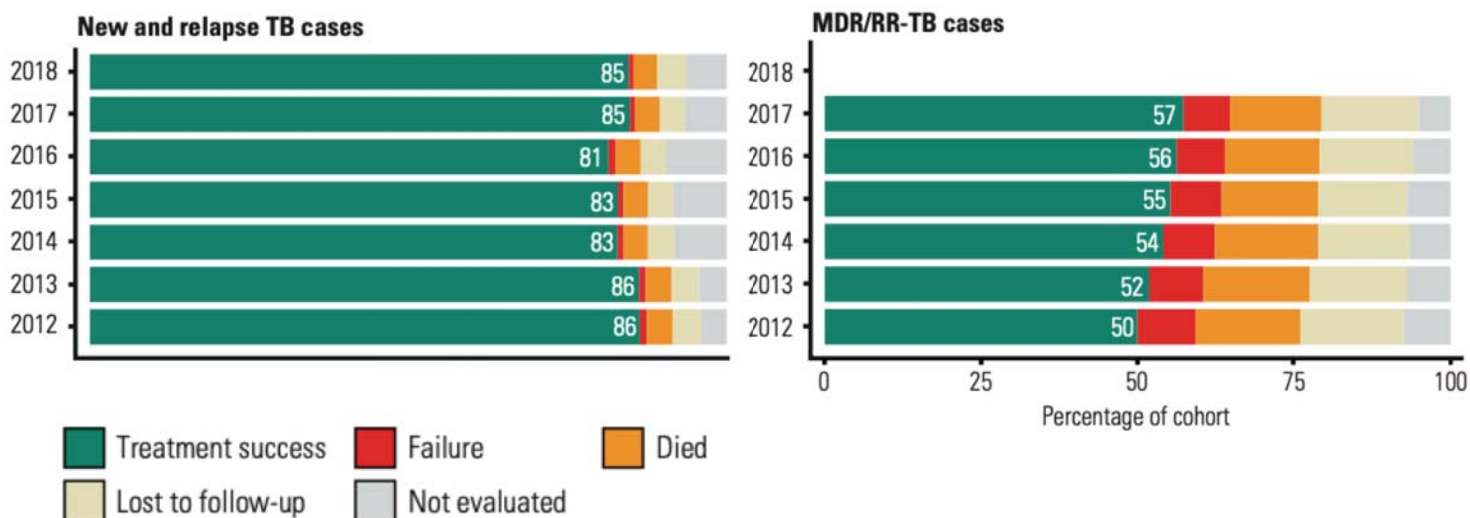
規則治療足夠時間

- DSTB: 6 – 9 months
- MDRTB: 18 -20 months
- challenge: **adherence and ADR**

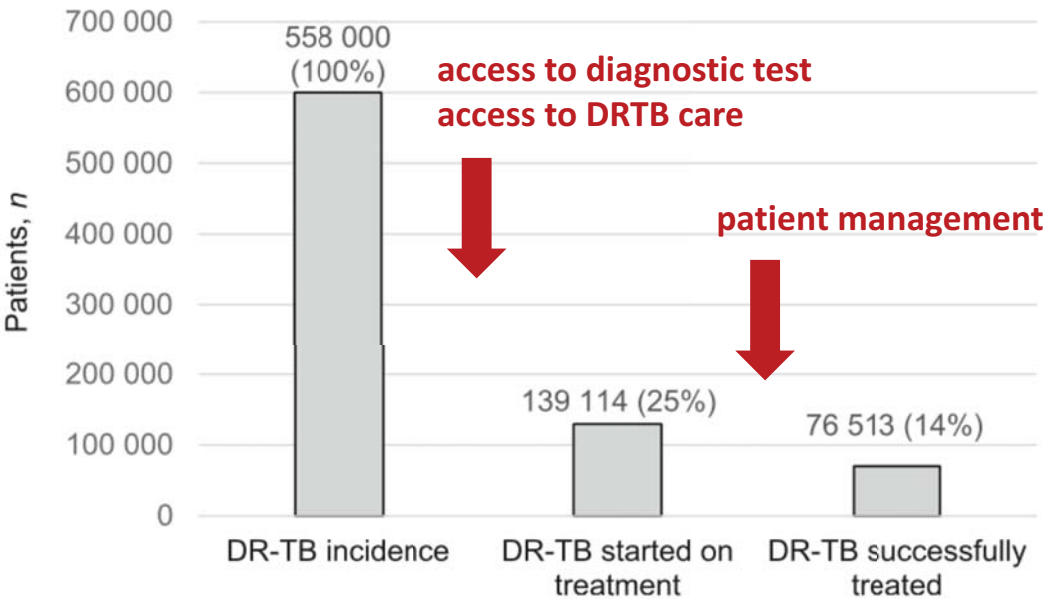
* DST: drug susceptibility test; ADR: adverse drug reaction



全球TB治療結果, 2012-2018



全球DR-TB 病人的照護序列(care cascade)



INT J TUBERC LUNG DIS 23(2):125-135



近期發展

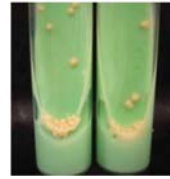
診斷方法

TB實驗室各項結果時序

Delivery
Specimen received in the lab.



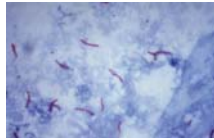
21 Days
Expect a culture identification.
(Is it TB or not?)



At 6-8 Weeks
Expect the culture to be finalized if negative.



At 24 Hours
Expect smear results.



At 28 Days (17 days after +MTBC culture)
Expect 1st line susceptibility results. Expect 2nd line susceptibility results 4 weeks after requested.

Heartland National TB Center

TB實驗室各項結果時序

Delivery
Specimen received in the lab.

21 Days
Expect a culture identification.
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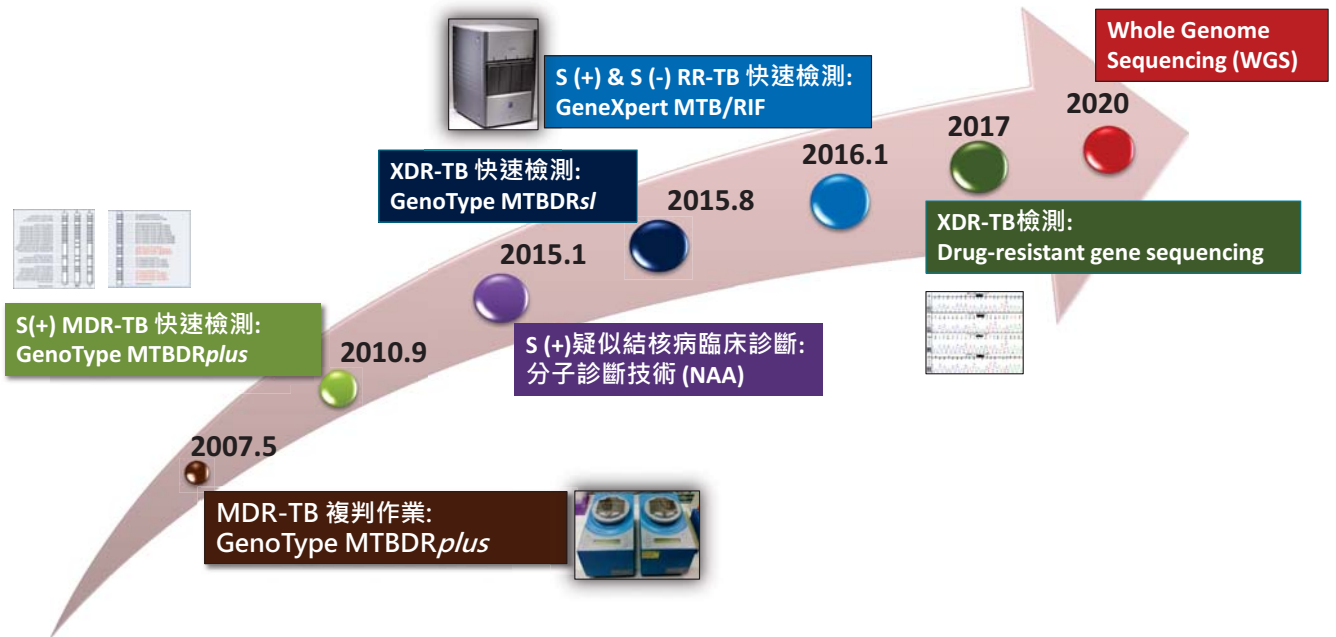


At 24 Hours
Expect smear results.

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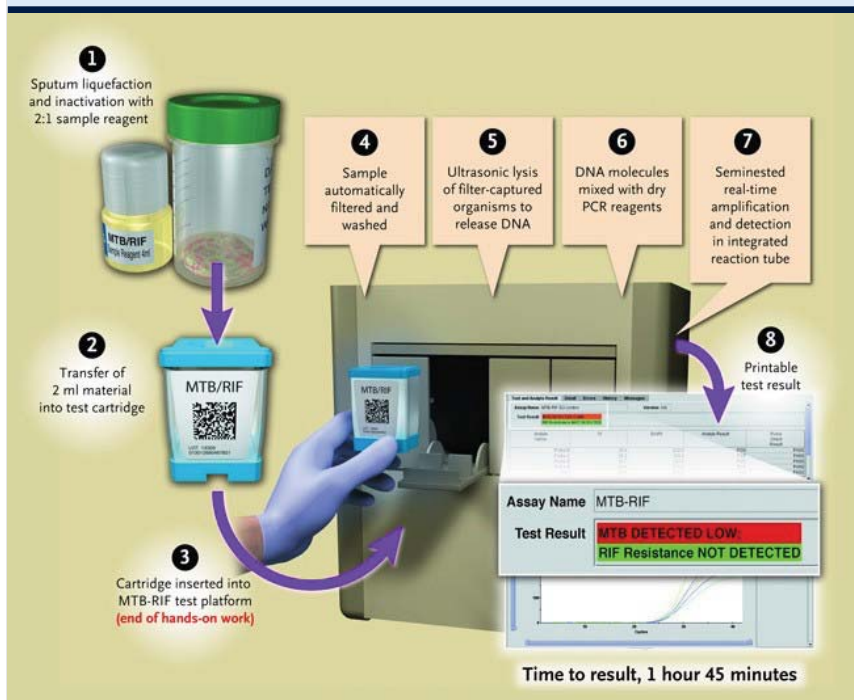
Heartland National TB Center

WHO推薦新檢驗技術之引進



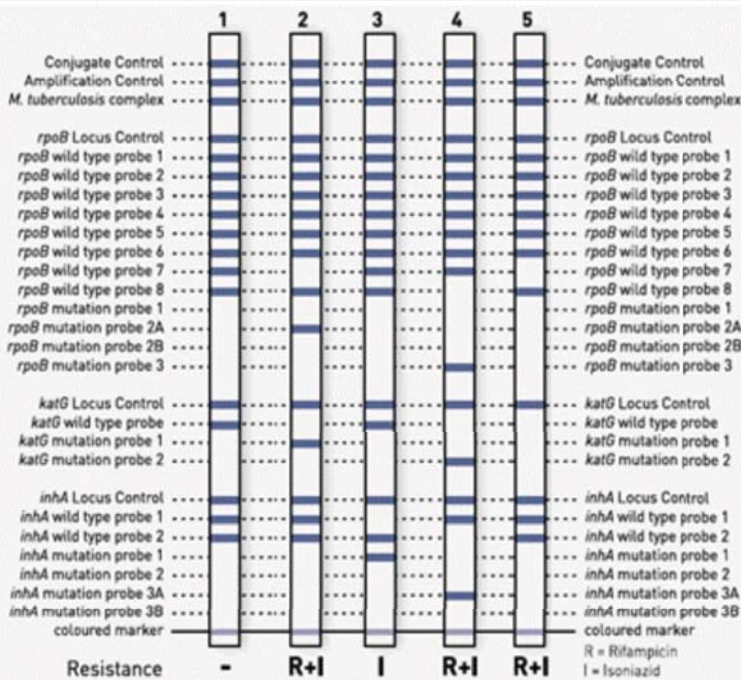
Taiwan CDC, TB report, 2021

GeneXpert® MTB/RIF



- 可偵測TB核酸及 Rifampin 抗藥基因突變
- 約兩小時有結果
- 技術與人力需求低
- 硬體需求:
 - 基礎生物安全設施
 - 穩定的電力供應和電腦
 - 不適合在高溫的環境

Genotype[®] MTBDRplus & Genotype[®] MTBDRsl



- 可偵測TB核酸及突變基因
- **MTBDRplus**: INH, RIF
- **MTBDRsl**: FQ, injectable
- 約1-2天內有結果
- 技術需求高，適合在參考實驗室操作

NAAT

優點

- 同時鑑定TB並得到重點藥物的DST (genotypic)
- 檢驗時間快速
- 不易受到NTM的影響
- 具有在基層定點使用(point-of-care use)的潛力

限制

- 無法完全取代培養為主的DST (phenotypic)
- 並非所有抗藥相關的突變都能被檢測出來
- 並非所有檢測出來的突變都會導致抗藥

Genotypic
Result



Phenotypic
Result

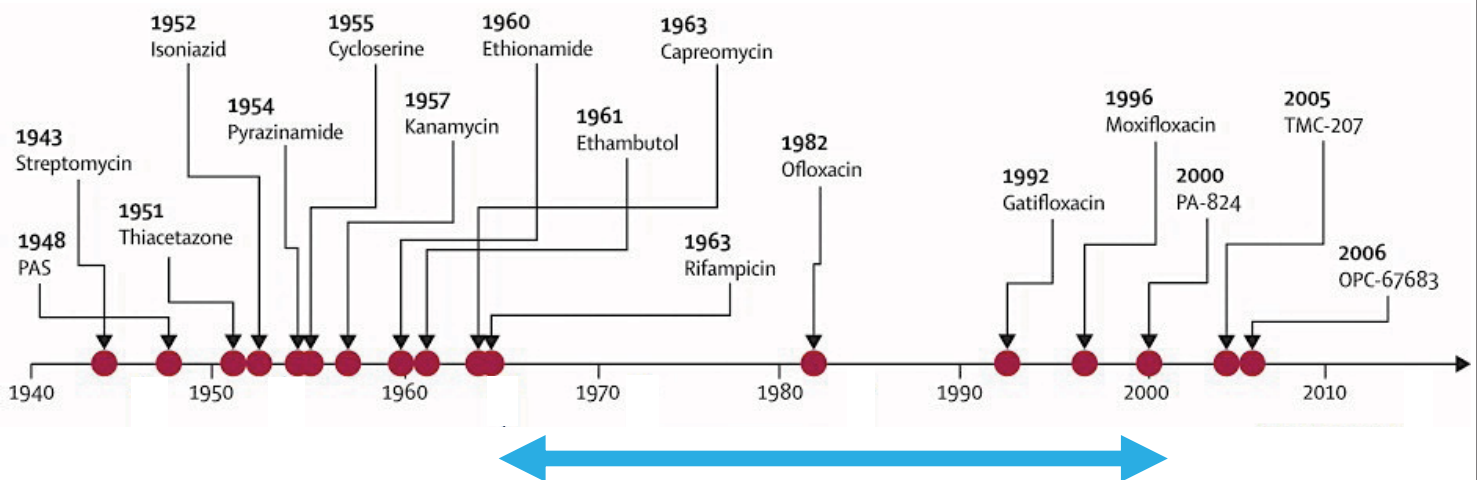


Clinical
Response

近期發展

藥物

TB藥物的發現史



新的抗結核藥物的發展

調整劑量或改變用途

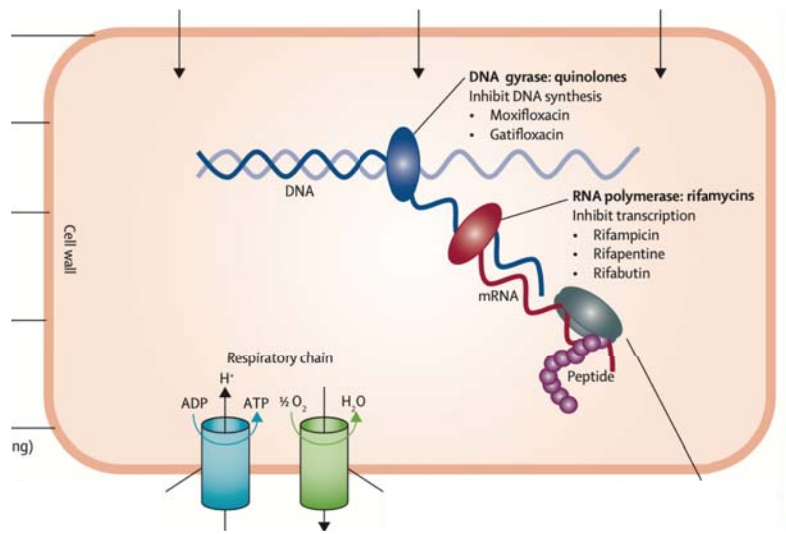
- rifampin, isoniazid
- **moxifloxacin, linezolid, clofazimine**

已知藥物再造

- **delamanid, pretomanid** (nitroimidazole)
- sutezolid, tedizolid(oxazolidinone)

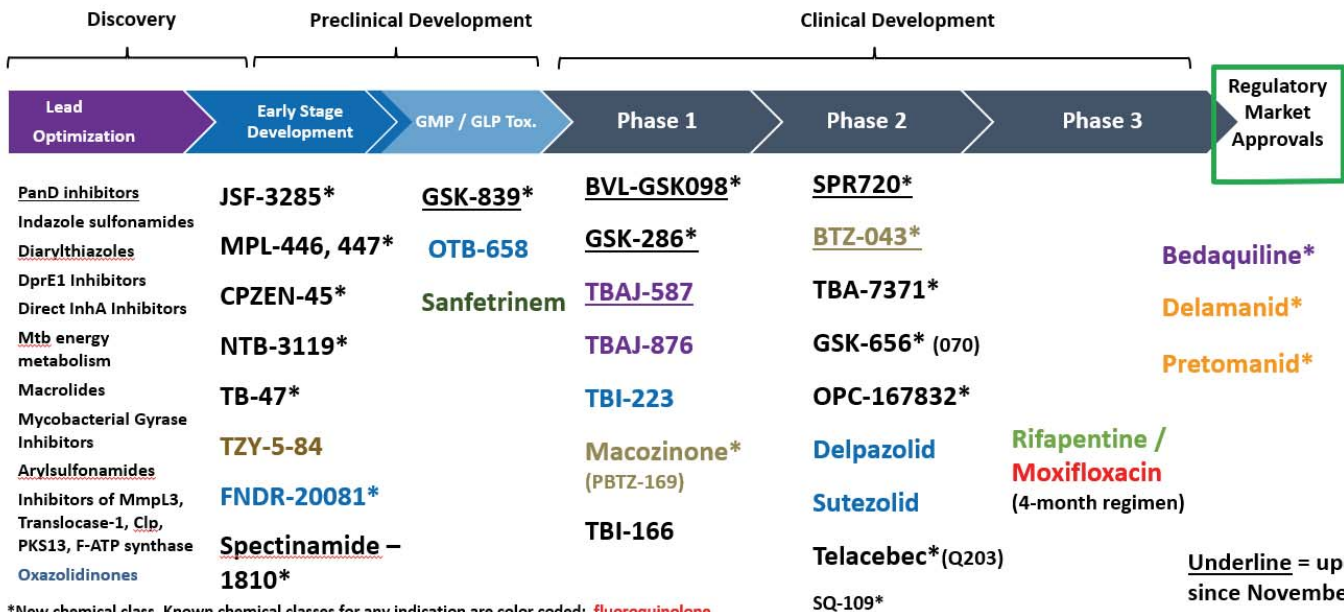
研發新的藥物種類

- **bedaquiline** (diarylquinoline)



Lancet Infect Dis 2014; 14: 327–40

2021 Global New TB Drug Pipeline ¹



*New chemical class. Known chemical classes for any indication are color coded: **fluoroquinolone**, **rifamycin**, **oxazolidinone**, **nitroimidazole**, **diarylquinoline**, **benzothiazinone**, **imidazopyridine amide**, **beta-lactam**.

¹ New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at <http://www.newtbdrugs.org/pipeline/clinical>. Ongoing projects without a lead compound series identified: <http://www.newtbdrugs.org/pipeline/discovery>

Underline = updates since November 2020

WORKING GROUP
ON NEW TB DRUGS
www.newtbdrugs.org

Updated: March 2021

近期發展

處方

WHO treatment guidelines for drug-resistant tuberculosis

2016 update

OCTOBER 2016 REVISION

THE
END TB
STRATEGY



Group A. Fluoroquinolones^b	Levofloxacin Moxifloxacin Gatifloxacin
1	
Group B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin) ^c
1	
Group C. Other core second-line agents^b	Ethionamide / prothionamide Cycloserine / terizidone Linezolid Clofazimine
>=2	
Group D. Add-on agents (not part of the core MDR-TB regimen)	D1 Pyrazinamide Ethambutol High-dose isoniazid
	D2 Bedaquiline Delamanid
	D3 <i>p</i> -aminosalicylic acid Imipenem–cilastatin ^d Meropenem ^d Amoxicillin-clavulanate ^d (Thioacetazone) ^e 28
≧ 5 effective drugs 18 – 22 months	

MDR/RR-TB 處方所面臨的挑戰

- 口服藥顆粒數多
- 藥物費用高昂
- 藥物毒性多
- 針劑使用的困難
- 治療時間冗長



新的MDR/RR-TB處方趨勢

- **All oral-based regimen (全口服處方)**
 - new hierarchy of drugs(新的藥物分類)
 - discourage the use of injectables(不再鼓勵使用針劑)
- **Shorter regimen(短程處方)**
 - 9 – 12 months “**Bangladesh regimen**” (STREAM trial)
 - 6 – 9 months “**BPaL regimen**” (NIX-TB trial)

WHO consolidated guidelines on drug-resistant tuberculosis treatment

THE
END TB
STRATEGY



Groups and steps

Group A:
Include all three medicines

3A

Group B:
Add one or both medicines

1B

Group C:
Add to complete the regimen and when
medicines from Groups A and B cannot be used

18 – 20 months

Medicine

Levofloxacin *or*
moxifloxacin

Bedaquiline^{b,c}

Linezolid^d

Clofazimine

Cycloserine *or*
terizidone

Ethambutol

Delamanid^e

Pyrazinamide^f

Imipenem–cilastatin
or meropenem^g

Amikacin
(*or* streptomycin)^h

Ethionamide *or*
prothionamideⁱ

P-aminosalicylic acid^j

STREAM trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 28, 2019

VOL. 380 NO. 13

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

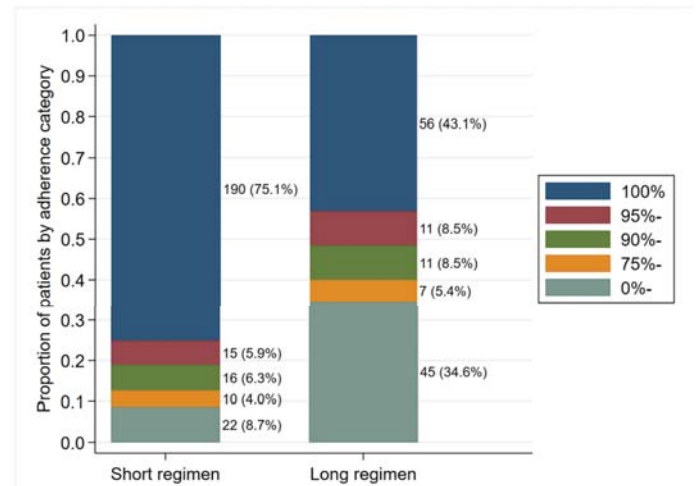
A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*

STREAM trial

- A phase 3 RCT trial, 383 RRTB patients
- “**Bangladesh regimen**” v.s. longer regimen
- H^h, E, Z, Km, Mfx^h, Cfz, Tbn (4-6m) then E, Z, Mfx^h, Cfz (5m)
- Result: a shorter regimen was **non-inferior** to a longer regimen
- WHO further recommend an all-oral shorter regimen (replace Km with bedaquiline) in 2021

Figure S1. Adherence to allocated treatment, mITT analysis population.

Number in each category and percentage of mITT population shown on figure.



N Engl J Med 2019;380:1201-1213

NIX-TB trial

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 5, 2020

VOL. 382 NO. 10

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

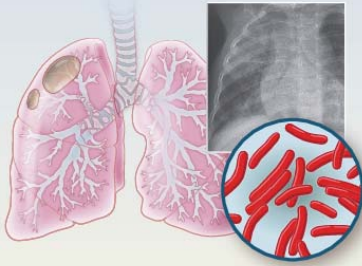
N Engl J Med 2020;382:893-902.

Treatment of Highly Drug-Resistant Pulmonary TB

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients

with confirmed tuberculosis



Three-drug regimen (26 wk)

Bedaquiline **B**



Pretomanid **Pa**
(recently approved)



Linezolid **L**



XDR
tuberculosis

N=71
(65%)

Nonresponsive or
treatment-intolerant
MDR tuberculosis

N=38
(34%)

Clinical resolution at
6 mo after therapy

90% of all patients had favorable outcomes

89%

95% CI, 79–95

95% CI, 83–95

92%

95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

N Engl J Med 2020;382:893-902.

新的MDR/RR-TB處方趨勢

- All oral-based regimen(全口服處方)
 - new hierarchy of drugs
 - discourage the use of injectables
- Shorter regimen(短程處方)
 - 9 – 12 months “Bangladesh regimen” (STREAM trial)
 - 6 – 9 months “BPaL regimen” (NIX-TB trial)
- Caveat
 - 核心藥物(core drug) : 即時且可靠的DST?
 - 新藥(new drug): 未知的副作用? 藥物交互作用?



抗藥結核照護體系

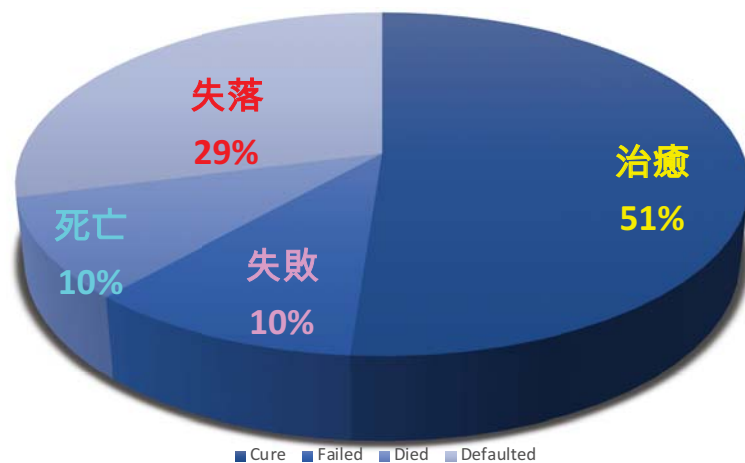
台灣的照護模式

Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study

C-Y. Chiang*, D.A. Enarson*, M-C. Yu#, K-J. Bai#, R-M. Huang[†], C-J. Hsu⁺, J. Suo⁺ and T-P. Lin⁺

Treatment Outcome

- 1992-1996
- 299 pts
 - 215 males (72%)
 - mean age: 47.3



Taiwan MDRTB Consortium (TMTC)

- 成立於2007, 全國分為五個責任區域
- 由醫院同時負責醫療照護和都治 (DOTs)
- 強烈建議開始治療時採住院模式
- 由政府預算支付所有醫療照護費用
- 提升照護品質及推行政策的同步化平台

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團隊核心成員

- MDRTB physician (抗藥結核醫師)
- Case manager(個案管師)
- Nursing staff in isolation ward (病房護理師)
- DOTS provider (都治關懷員)

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情報蒐集

- 細菌學報告及之前的TB治療紀錄
- 流行病學資訊
- 共病狀況
- 身心狀況及社會經濟的負擔

入團隊前

加入團隊

初期住院

社區照護



個案管理師

- 負責串連病人與醫療和公衛體系,以建構完整的照護網
- 確保不同照護階段的銜接及社區都治的品質
- 評估及提供各式補助及情緒支持
- 副作用的持續評估

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形成戰略共識

- 安排家庭會議,提供初步說明及諮詢
- 帶入接觸者篩檢的概念
- 評估治療風險及服藥順從性
- 形成初步共識

入團隊前

加入團隊

初期住院

社區照護



抗藥結核醫師

- 依據治療準則來設計處方
- 處理副作用及提供共病照護(必要時會診相關科別)
- 組織臨床照護團隊提供全方位的照顧
- 持續評估治療反應及治療成果

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全面啟動

- 逐步調整藥物增加劑量
- 副作用及共病處理
- 建立良好信任關係
- 持續衛教

入團隊前

加入團隊

初期住院

社區照護



病房護理師

- 嚴格都治但允許給藥時間的彈性
- 時刻觀察病患的需求, 副作用及身心狀況
- 提供衛教及情緒支持

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馬拉松式的照護

- 關懷型都治
- 持續身心社會支持
- 副作用及共病的持續照護
- 協助去除污名化

入團隊前

加入團隊

初期住院

社區照護



都治關懷員

- 彈性化及關懷型都治
- 迅速偵測並即時反應病人的照護需求
- 深入了解病人的生活型態
- 成為病患在社區的溝通橋樑

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Active tuberculosis
drug-safety monitoring
and management (aDSM)

Framework for implementation



ADSM

主動且系統性地
針對治療中病人
進行臨床及實驗室評估
以偵測, 處理並通報
疑似或確定的藥物毒性

Active tuberculosis
drug-safety monitoring
and management (aDSM)

Framework for implementation



ADSM in Taiwan

- 2017-2019: 研究計畫
- 監測對象: RR-/MDR-TB patients on
 - longer regimen
 - shorter regimen
 - new drugs (linezolid, bedaquiline, delamanid, meropenem)
- 建立常規:
 - ECG
 - Audiogram
 - adverse event report

Adverse event	Event		patient	
	N	%	N	%
No			48	19.3
Yes	431		200	80.6
Serious adverse event				
No	291	77.6	105	60.0
Yes	84	22.4	70	40.0
Death	28	7.4	28	16.0
Life-threatening	10	2.6	9	5.1
Leads to hospitalization	33	8.8	25	14.2
Prolong hospitalization	11	2.9	10	5.7
Permanent disability	2	0.5	2	1.1
Congenital anomaly	0	0.0	0	0.0
Severe adverse event				
No	148	39.4	37	21.1
Yes	227	60.5	138	78.8
Leads to discontinuation of TB drugs				
No	49	13.0	6	3.4
Yes	326	86.9	169	96.5

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公告

- 有關帳號申請事宜，如有疑慮可洽結核病追蹤管理系統窗口：張小姐(Nancy)，Tel：(02)2395-9825#3104，單一窗口信箱：cdctb2035@cdc.gov.tw ...more
- 有關【智慧關懷卡功能】與【卡片安裝元件】問題反應窗口
Tel：(02)2382-2984，E-mail：
help@changingtec.com ...more
- TB系統於每週四中午進行系統維護作業。

- 自然人憑證
- 醫事人員卡
- 晶片健保卡

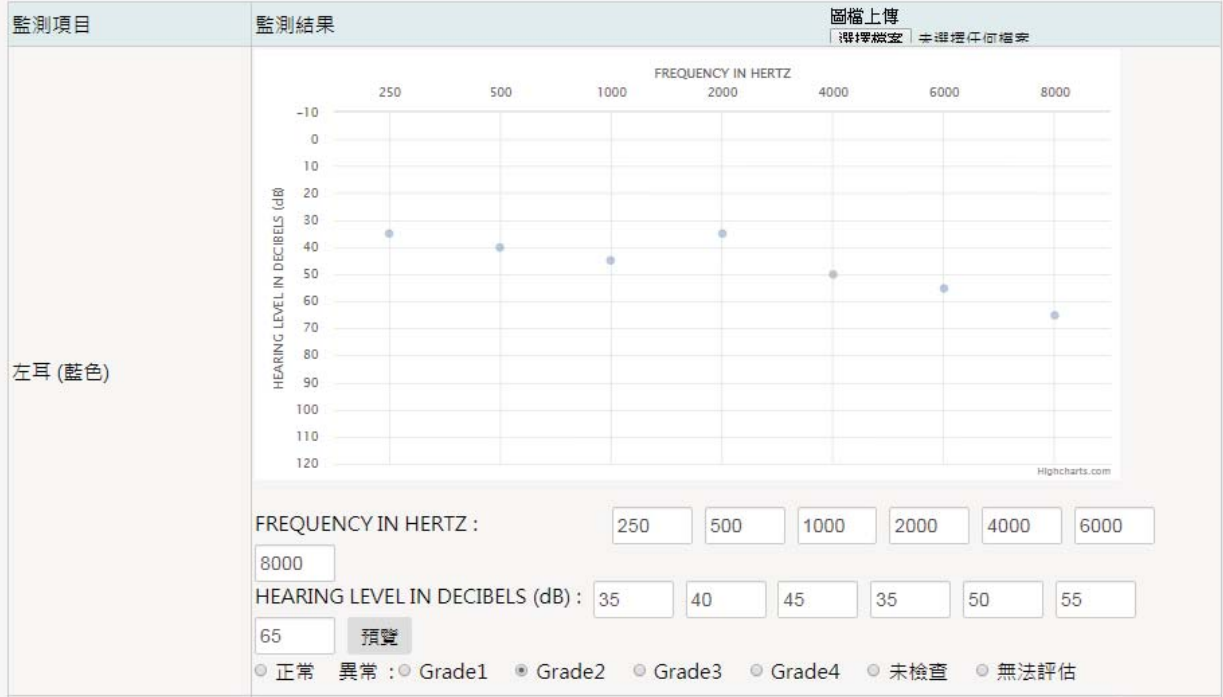
LOGIN



TAIWAN CDC
結核病追蹤管理系統



Audiogram



ECG

檢驗項目	檢驗結果	檢驗判讀
檢查日期	2018/6/20 小時 12-15	<input type="button" value="選擇"/> <input type="button" value="清除"/>
Heart rate	<input type="text" value="94"/> /分鐘	
QT	<input type="text" value="388"/>	
QTcF	<input type="text" value="450.634"/>	<input checked="" type="radio"/> 正常 <input type="radio"/> 異常 <input type="radio"/> 未檢查
檢驗項目	檢驗結果	檢驗判讀
檢查日期	小時 請選擇	<input type="button" value="選擇"/> <input type="button" value="清除"/>
Heart rate	<input type="text"/> /分鐘	
QT	<input type="text"/>	
QTcF	<input type="text"/>	<input type="radio"/> 正常 <input type="radio"/> 異常 <input type="radio"/> 未檢查
檢驗項目	檢驗結果	檢驗判讀
檢查日期	小時 請選擇	<input type="button" value="選擇"/> <input type="button" value="清除"/>
Heart rate	<input type="text"/> /分鐘	
QT	<input type="text"/>	
QTcF	<input type="text"/>	<input type="radio"/> 正常 <input type="radio"/> 異常 <input type="radio"/> 未檢查

Patient-centered care



入團隊前

加入團隊

初期住院

社區照護

- Seamless transition (無縫接軌)
- Holistic approach (全人/全隊/全家/全程)
- Individualized support (客製化的照護)

51

抗藥性結核病照護成效

2020.12

97%

多重抗藥性結核病
個案納入團隊接受
照護

2019

90%

團隊個案6個月痰培
養陰轉



2018

0%

團隊個案24個月追蹤
失落比率

2018

76%

團隊個案24個月治
療成功率

58

結論



- 和公衛體系保持合作
- 和病人建立關係
- 和團隊成員互相支持
- 善用現有資源
- 清楚每個階段的目標
- 保持全程規劃的視野



Thank You!

