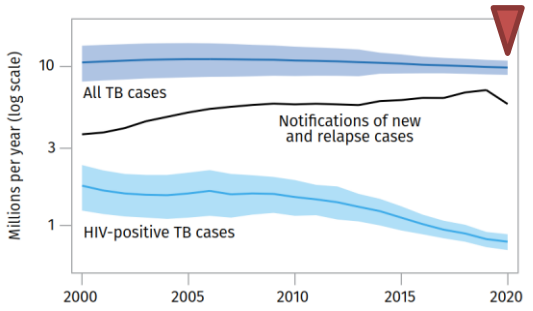
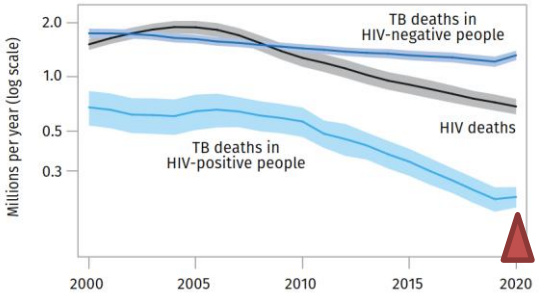
臺北醫學大學
TAIPEI MEDICAL UNIVERSITY

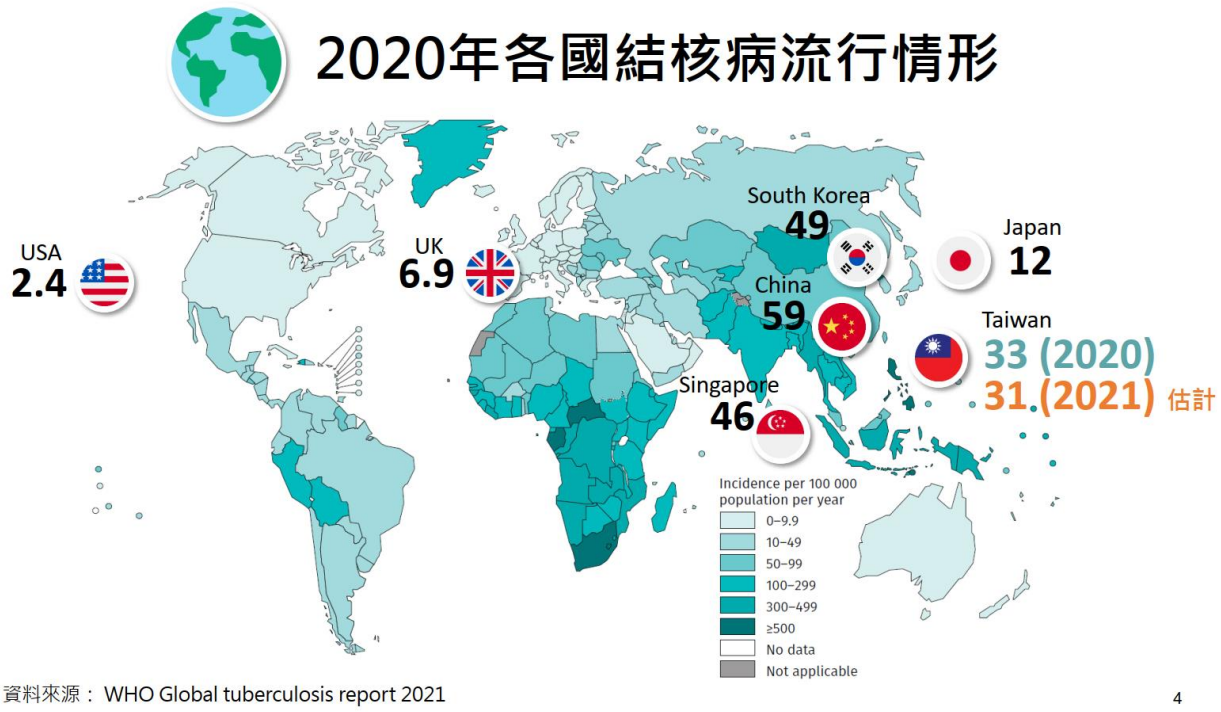
MDRTB治療的大改變和藥物毒性監測

李枝新醫師
台北市立萬芳醫院 結核病中心

全球結核病疫情現況



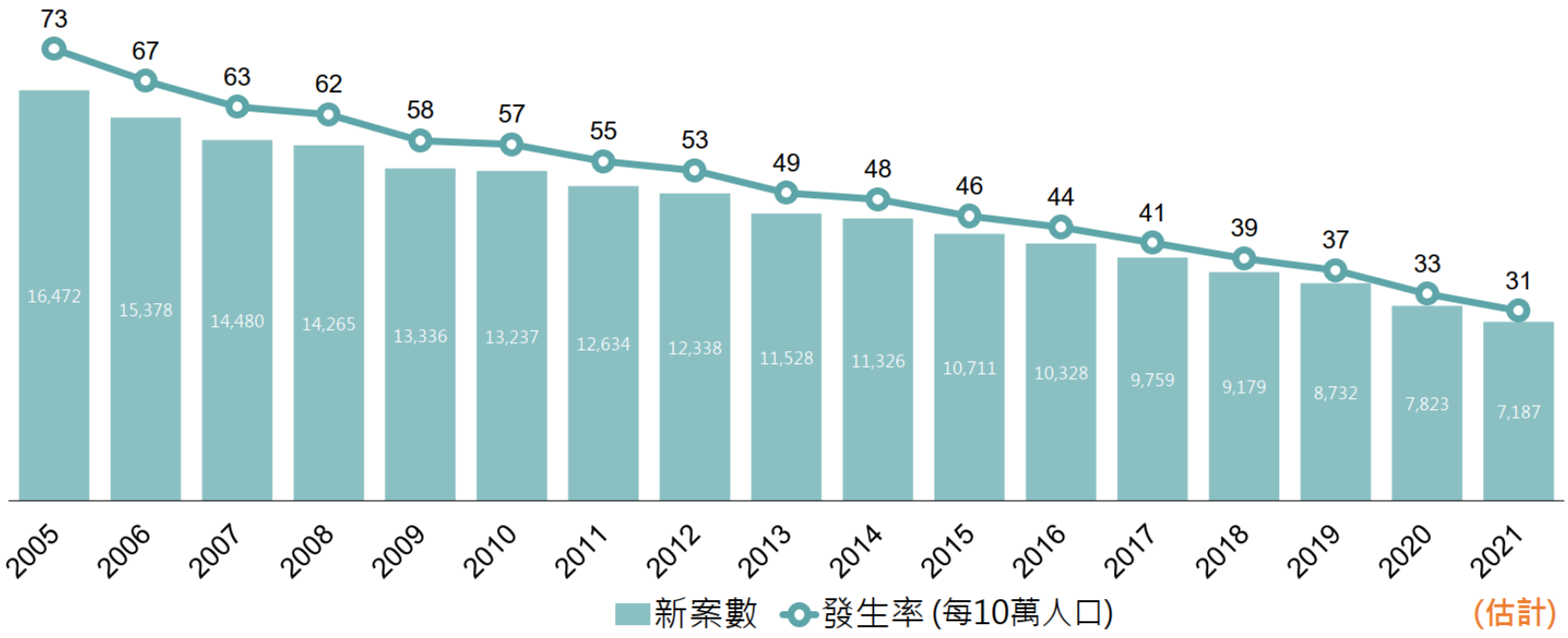




資料來源： WHO Global tuberculosis report 2021

- 2020年，全球新發生990萬個結核病個案，造成約150萬人死亡，抗藥結核病(RR-TB/MDR-TB)佔約46.5萬人(2019)。
- 2020年，因為COVID-19疫情的影響，全球結核病的**通報人數下降**，但是**死亡率上升**。

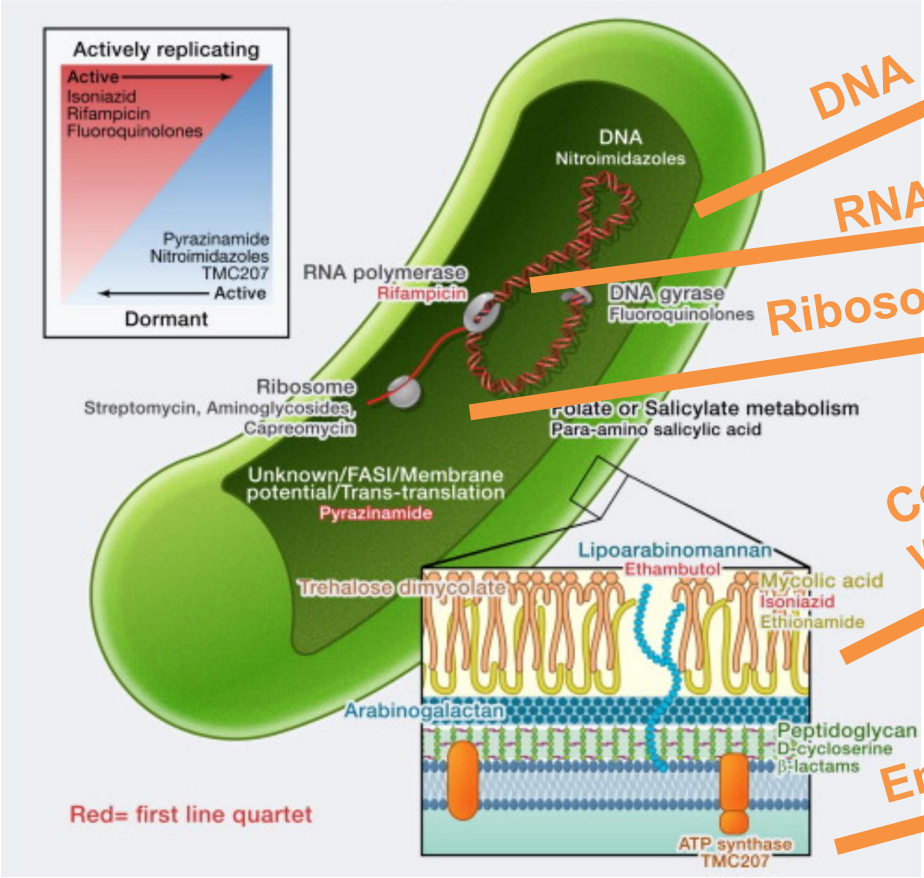
台灣結核病發生率持續改善



台灣的結核病現況


2021結核病監測
預估 新案發生率31每十萬人口
結核病通報
8,258
(含疑似及確診)
結核病確診新案
7,187 (估計)
塗片或培養陽性
80%
塗片陽性
40%
多重抗藥結核
82

Anti-TB Agents, Mechanisms of Action



1. Fluoroquinolones, pretomanid
2. **Rifampicin** (1944)
3. Streptomycin, linezolid
4. **Isoniazid**, **ethambutol**, cycloserine, ethionamide
5. **Pyrazinamide**, bedaquiline, clofazimine

Goldberg DE, Cell 2012 https://doi.org/10.1016/j.cell.2012.02.021

Bhat ZS, Biomedicine & Pharmacotherapy 2018 https://doi.org/10.1016/j.biopha.2018.04.176

MDR-TB (多重抗藥性結核病)

Active replicating | **Dormant**

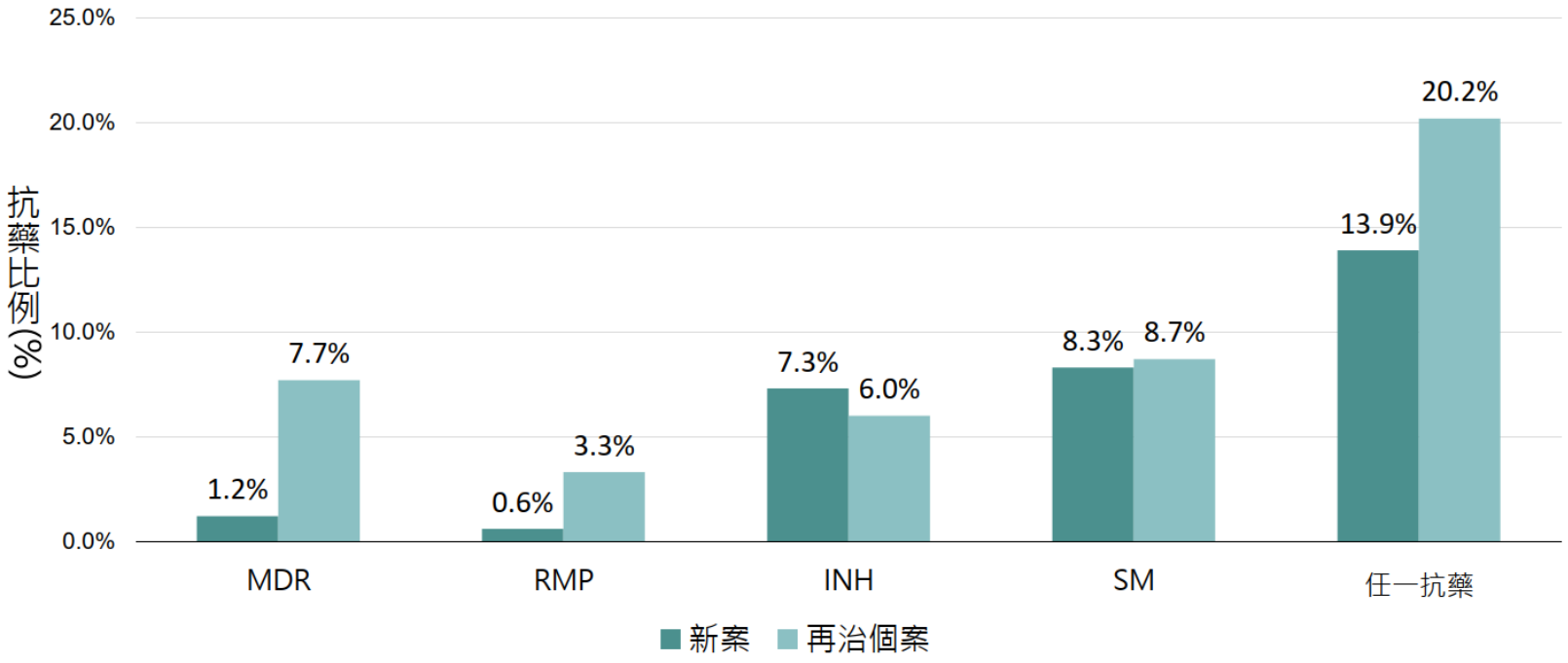
Bactericidal Effect — **Sterilizing Activity**

Acquired Resistance — **Disease Relapse**

Failure

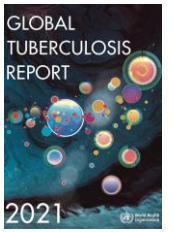
再治病人有較高的抗藥結核風險

2021年本國籍結核病初痰抗藥性監測



備註：本國人初痰檢出MTBC抗藥比例。INH、RMP抗藥，不含MDR抗藥者。

MDR-TB治療成功率僅59%



Eur Respir J 2006; 28: 980–985
DOI: 10.1183/09031936.06.00125705
Copyright©ERS Journals Ltd 2006

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"

ABSTRACT: **A retrospective study was performed to determine factors associated with the outcome of pulmonary multidrug-resistant tuberculosis (MDR-TB) in Taipei, Taiwan.**

All patients newly diagnosed with pulmonary MDR-TB in a referral centre from 1992–1996 were enrolled and their outcome over the subsequent 6 yrs was determined.

A total of 299 patients were identified, comprising 215 (71.9%) males and 84 (28.1%) females with a mean age of 47.3 yrs. The patients received a mean of 3.7 effective drugs. Out of the 299 patients, 153 (51.2%) were cured, 31 (10.4%) failed, 28 (9.4%) died and 87 (29.1%) defaulted. Of the 125 patients receiving second-line drugs with ofloxacin, 74 (59.2%) were cured. Those who received ofloxacin had a lower risk of relapse than those receiving only first-line drugs (hazard ratio (HR) 0.16, 95% confidence interval (CI) 0.03–0.81) and a lower risk of TB-related death than those receiving second-line drugs but not ofloxacin (adjusted HR 0.50, 95% CI 0.31–0.82).

In conclusion, multidrug-resistant tuberculosis patients who received ofloxacin were more likely to be cured, and were less likely to die, fail or relapse. The utility of new-generation fluoroquinolones, such as moxifloxacin, in the treatment of multidrug-resistant tuberculosis needs to be evaluated. Default from treatment is a major challenge in the treatment of multidrug-resistant tuberculosis.

KEYWORDS: **Death, follow-up, multidrug resistant, relapse, tuberculosis**

Multidrug-resistant tuberculosis (MDR-TB), which is defined as a disease with isolates resistant to at least isoniazid and rifampin, compromises response to anti-TB treatment [1–3]. MDR-TB is prevalent in a number of countries [4].

Recommended treatment of MDR-TB includes the use of second-line anti-TB drugs [5]. To date, there have been no randomised controlled trials to evaluate the treatment of MDR-TB. Treatment regimens are determined individually for each patient, taking into account the results of susceptibility testing [6–12], or are standardised regimens [13–15] depending on the local situation.

The management of MDR-TB in Taipei, northern Taiwan, has been highly specialised in a referral centre, the Chronic Disease Control Bureau (CDCB), which was the headquarters of a TB control system functioning for >40 yrs (until 2002), with a network of public health nurses distributed in all townships and villages, responsible for TB services [16]. The majority of MDR-TB patients identified in general hospitals were referred to the CDCB for further management. Treatment of MDR-TB has increasingly included the use of ofloxacin in the second-line treatment regimen [17]. To understand the long-term outcome of MDR-TB, a consecutive series of MDR-TB cases were reviewed and followed up over time, with specific attention paid to the results of the use of ofloxacin for treatment. The results of this follow-up study are reported here.

METHODS

Case ascertainment

Patients with MDR-TB were identified from the Mycobacteriology Laboratory of the CDCB (Taipei, Taiwan). Patients who were newly diagnosed with pulmonary MDR-TB from 1992–1996 were enrolled in this study in 2000, and their outcome over the subsequent 6 yrs after commencing treatment determined. All drug-susceptibility testing was performed in the CDCB [18]. Medical records were reviewed and information was collected on age, sex, history of TB treatment, drug susceptibility, HIV status, medications used for treatment, adverse reactions occurring during treatment for which medications had to be stopped, and outcome of treatment.

AFFILIATIONS
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SUPPORT STATEMENT
C-Y. Chiang and D.A. Enarson proposed the original idea and designed the study. C-Y. Chiang, M-C. Yu, K-J. Bai, R-M Huang, C-J. Hsu, J. Suo, and T-P. Lin collected information and followed up patients. C-Y. Chiang and D.A. Enarson analysed and interpreted the data. All authors were involved in drafting the manuscript and gave final approval of the manuscript

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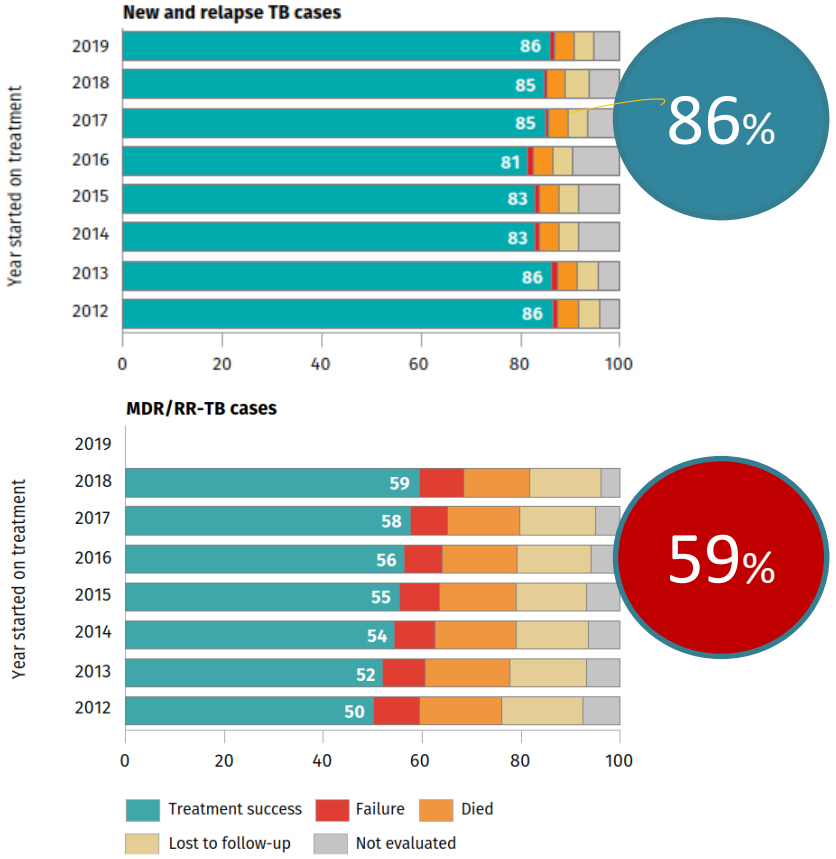


Chiang CY, 2006 ERJ

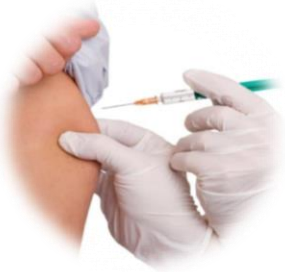
台灣MDR-TB治療成功率**51.2%**，引進新藥處方，成功率僅提高到**59.2%**

失落率達29.1%，應改善**管理模式**

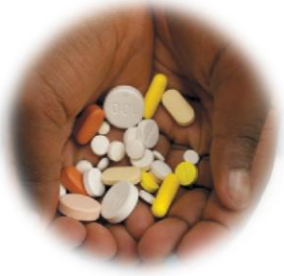
抗藥性結核病防治的困境

Physical, mental, economical distress

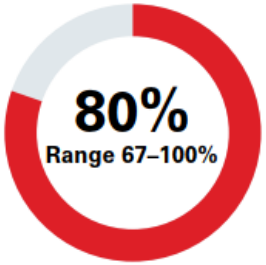
Injectables 6 – 8 mo



Enormous pill burden



80% Catastrophic economical distress



WHO, 2021, Global TB Report

Adverse Events

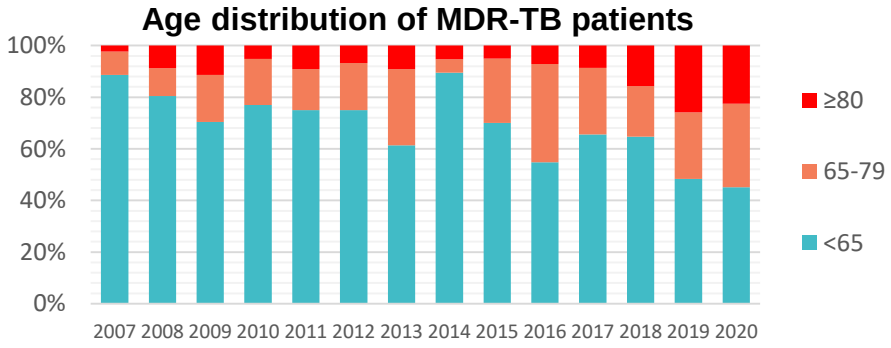
Hearing loss

Permanent numbness

Required regimen adjustment

Lead to admission or death

Ageing and Comorbidities



Social Stigma

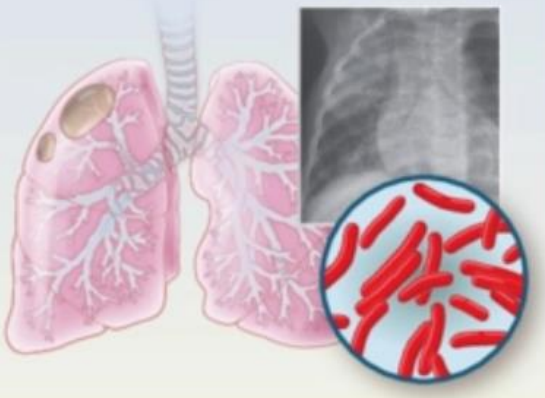
Comorbidities 69.3%, DM 27.2%, Cancer 6.7%

Novel Regimen with Shorter Treatment Course

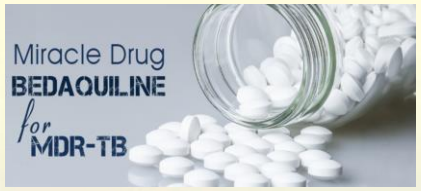
Treatment of Highly Drug-Resistant Pulmonary TB

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

109 Patients
with confirmed tuberculosis



Three-drug regimen (26 wk)



Pretomanid
(recently approved)

Linezolid

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
95% CI, 83–95

89%
95% CI, 79–95

92%
95% CI, 79–98

以病人為中心

1. 進階都治無縫銜接住院與社區 (觀察→關懷)
2. 視訊都治 (避免傳染病污名化壓力)
3. 主動藥物安全監測 (藥物安全)
4. 藥物血中濃度監測 (個人化劑量調整)
5. 全面快速分子藥敏檢測 (即時的個人化處方)

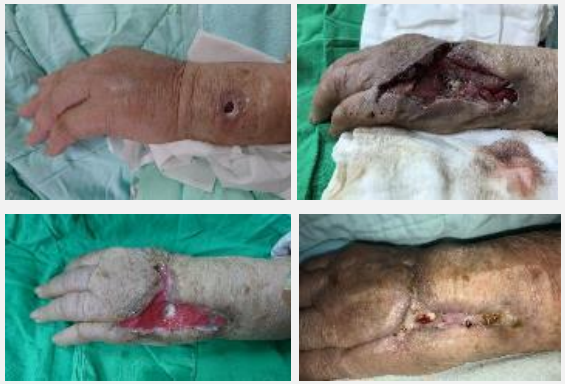
多重抗藥結核病防治策略及患者管理

Taiwan MDR-TB Treatment Consortium (TMTC)

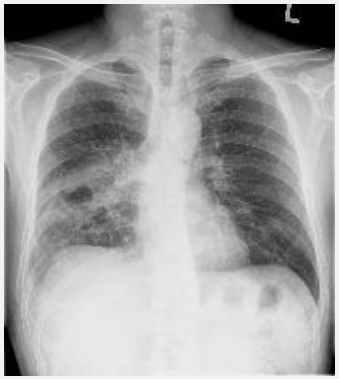
跨領域的全人關懷

衛教 → 生理評估 → 心理評估 → 家庭及社經支持評估

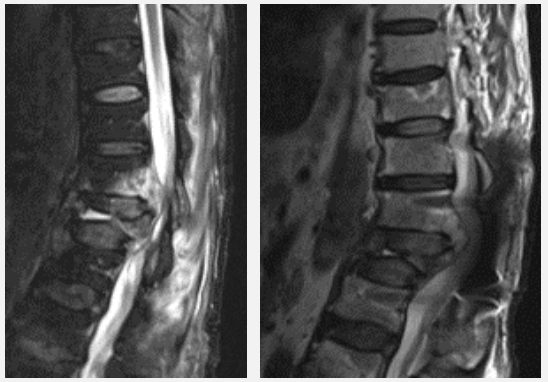
跨領域團隊合作



85歲女性，庫欣式症候群
多重抗藥結核骨髓炎
與整型外科團隊合作

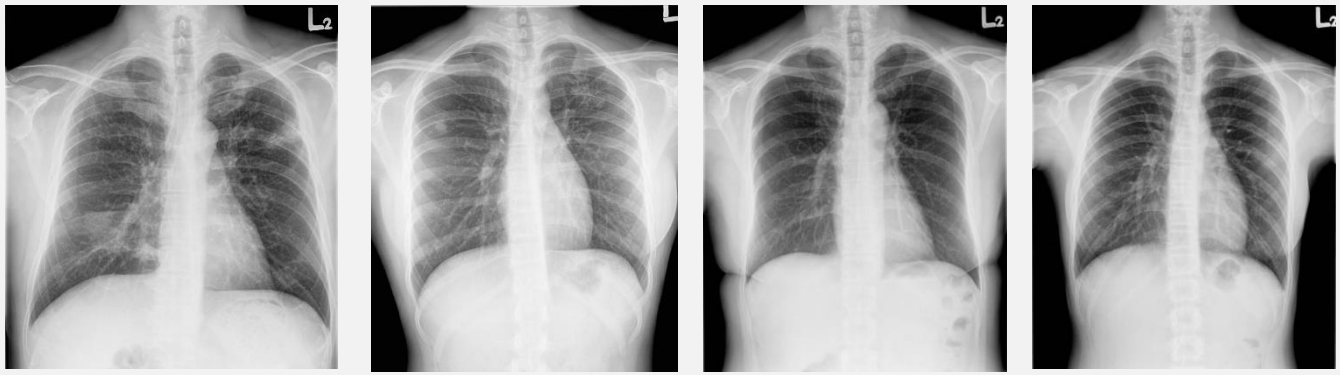


48歲男性，糖尿病
肺部大面積開洞病灶
與胸腔外科團隊合作



72歲男性，冠心症+心衰竭，抗藥結核腰椎感染，下肢無力臥床，小便滯留，與心臟科、骨科及復健團隊合作

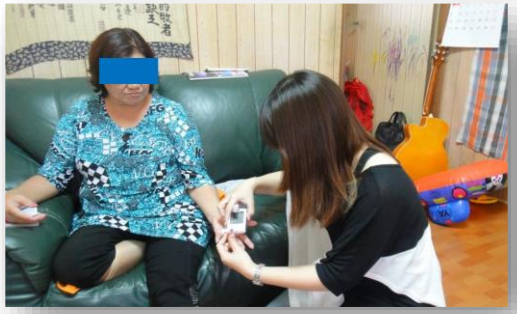
家戶接觸者評估及衛教



55歲男性，糖尿病，於團隊診治抗藥結核病，案長女經接觸者評估後診斷為抗藥結核病
案妻及案次女為抗藥結核潛伏結核感染，均由團隊治療，並緩和父母對傳播給家人的負罪感

無縫銜接住院與社區全人照護

Outreach the patient-centered care to the community
Timely response for adverse event management



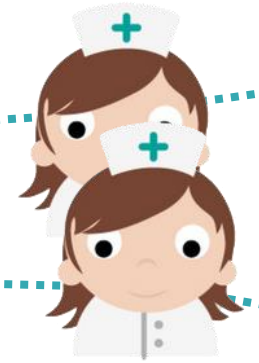
Attending physicians

Nursing specialists

DOT supporters

Patients

Social
Network
Software



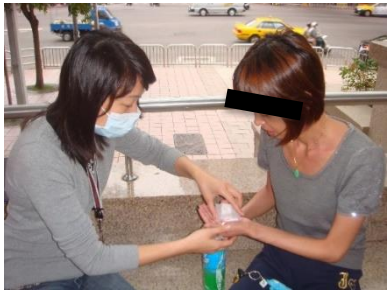
有路，咱沿路唱歌；無路，咱蹚溪過嶺

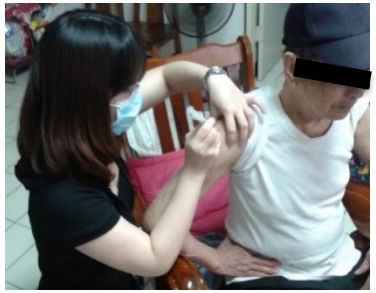
DOTS-Plus, Much More Than Just DOTS

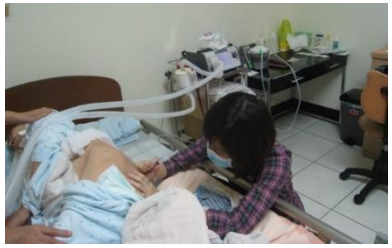
Anywhere: either rural or urban, even far in the mountains

Omnipotent: wound care, injection, adverse events monitoring …

Nonstop: throughout the course of treatment







臺北醫抗藥性結核病個案經濟困難程度評分表

姓名：_____ 評估日期： 年 月 日

項 目	結 果
一、補助個案為弱勢族群家庭	
1. 身心障礙	□是(1) □否(0)
2. 原住民	□是(1) □否(0)
3. 清寒證明	□是(1) □否(0)
4. 中低收入戶	□是(1) □否(0)
二、個案家戶中未有穩定的經濟來源	□是(1) □否(0)
三、家戶中無工作能力人口數(以人數計分)	_____ 人(1)
四、特殊困難狀況	
1. 負家庭主要生計責任者無法工作致生活陷入困境。	□是(1) □否(0)
2. 財產或存款帳戶因遭強制執行、凍結或其他原因未能及時運用，致生活陷於困境。	□是(1) □否(0)
五、其他狀況：	(1 分)
總分	0

總評：

□2 分以下，不需補助

□3 分以上，予以每月補助

評估人員：_____ 主管核章：_____

Emergency Allowance

有溫度的都治關懷服務

Directly Observed Treatment, DOT

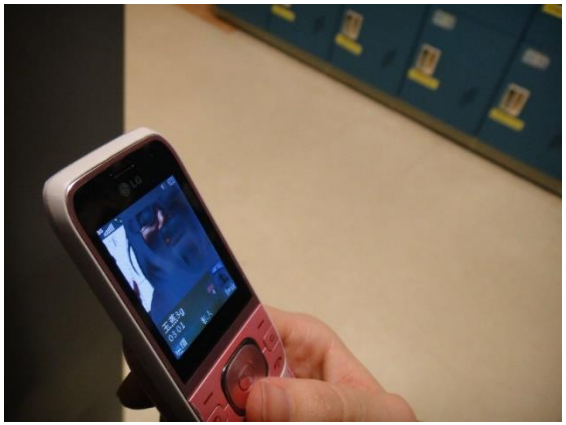
DOT Station → At Home → Remote DOT

Improve convenience

Protect Privacy

遠端視訊都治

Education and preparation

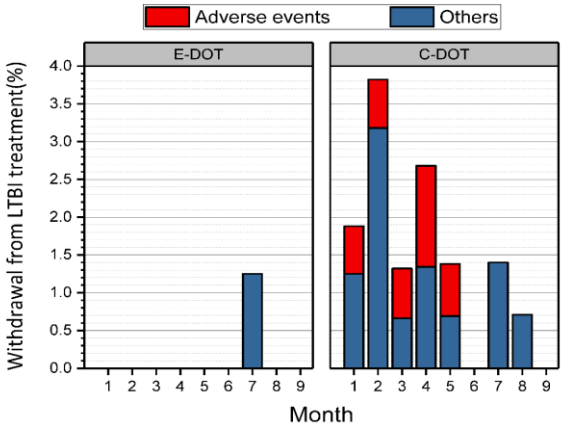


Free cell phones and data plans

User-friendly

All-in-one package

International video DOT



Lower drop-out rate by video-DOT

Lee C. J Inf Pub Health 2020

不良反應的風險管控

治療不良反應是病人退出治療或治療失敗的最重要因素

Active surveillance for adverse events in patients on longer treatment regimens for multidrug-resistant tuberculosis in Viet Nam

Nguyen Bao Ngoc[1,2,3], Hoa Vu Dinh[3]*, Nguyen Thi Thuy[1,2], Duong Van Quang[3], Cao Thi Thu Huyen[3], Nguyen Mai Hoa[3], Nguyen Hoang Anh[3], Phan Thuong Dat[1], Nguyen Binh Hoa[1], Edine Tiemersma[4], Nguyen Viet Nhung[1]

Vietnam: 659 (Age 41) MDR-TB

71% AE, 17.5% SAE

Ngoc NB. 2021 PLoS ONE 16(9): e0255357

Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis

*Zhiyi Lan, Nafees Ahmad, Parvaneh Baghaei, Linda Barkane, Andrea Benedetti, Sarah K Brode, James C M Brust, Jonathon R Campbell, Vicky Wai Lai Chang, Dennis Falzon, Lorenzo Guglielmetti, Petros Isaakidis, Russell R Kempker, Maia Kipiani, Liga Kuksa, Christoph Lange, Rafael Laniado-Laborín, Payam Nahid, Denise Rodrigues, Rupak Singla, Zarir F Udwadia, Dick Menzies, and The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017**

Global: 9178 MDR-TB, (Age 37)

Permanent interruption: Lev 1.3%, Mox 2.9%, Bedaq 1.7%, Clofaz 1.6%

Amk 10.2%, Kana 7.5%, Capre 8.2% PAS 11.6%, Linezolid 14.1%

Lan Z. 2020 Lancet Resp Med

Putting in harm to cure: Drug related adverse events do not affect outcome of patients receiving treatment for multidrug-resistant Tuberculosis. Experience from a tertiary hospital in Italy

Gina Gualano[1], Paola Mencarini[1]*, Maria Musso[1], Silvia Mosti[1], Laura Santangelo[2], Silvia Murachelli[2], Angela Cannas[3], Antonino Di Caro[3], Assunta Navarra[4], Delia Goletti[5], Enrico Girardi[4], Fabrizio Palmieri[1]

Italy: 74 MDR-TB (Age 32)

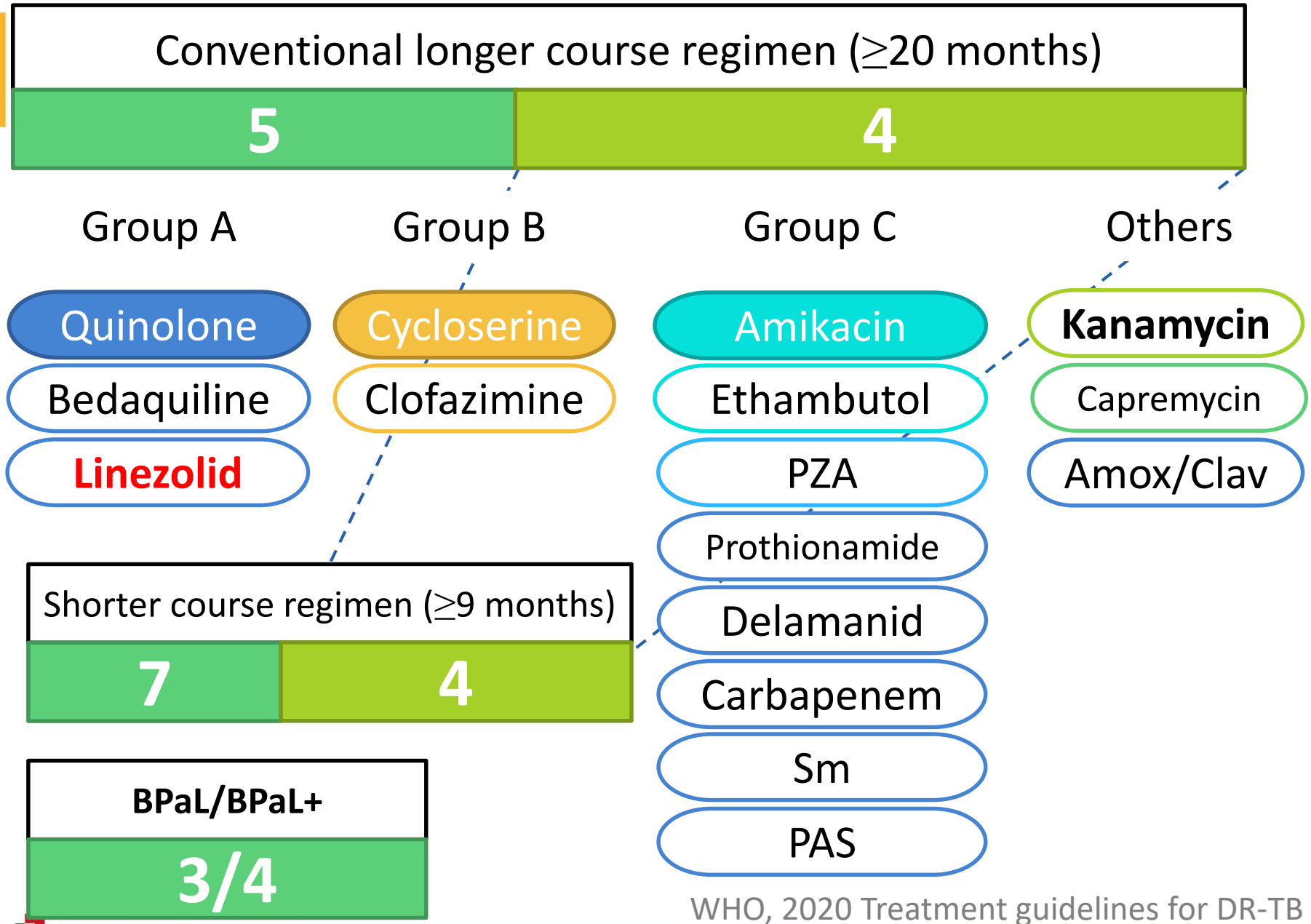
84% AE, 15.4% SAE

Gualano G. 2019 PLoS ONE 14(2): e0212948

Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis in China: An Ambispective Cohort Study

China: 751 MDR-TB (Age 44) **90.7%** AE, 55.2% Regimen adjustment, 6.8% Discontinuation of offending drug

Chang Y. 2017 Medical Science Monitor

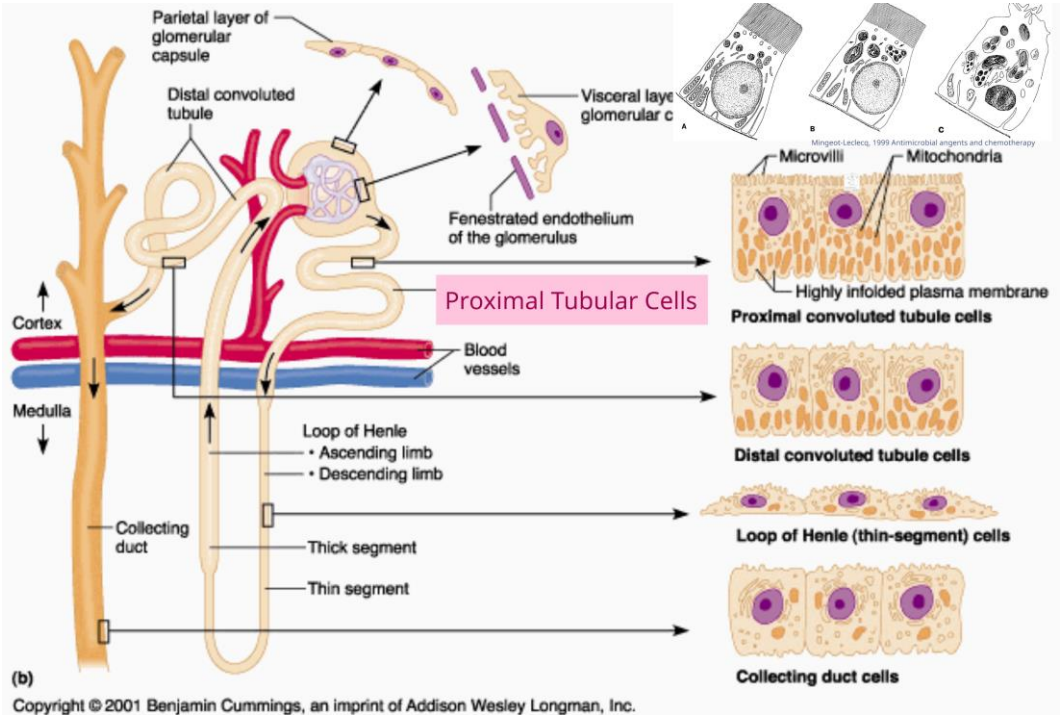


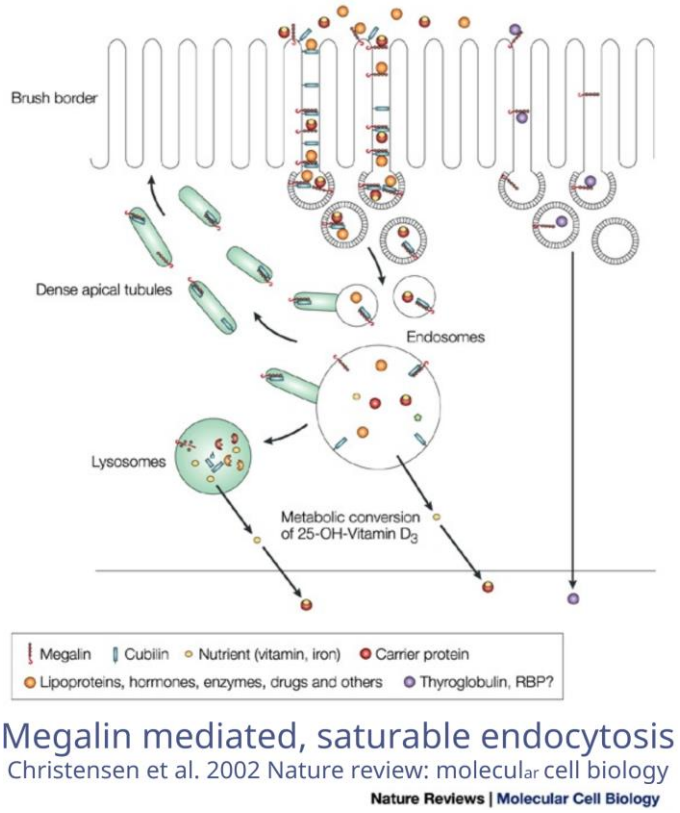
WHO, 2020 Treatment guidelines for DR-TB

Minimizing Nephrotoxicity of Aminoglycosides

Accumulation in **Proximal Tubular Cells**

Megalin mediated endocytosis



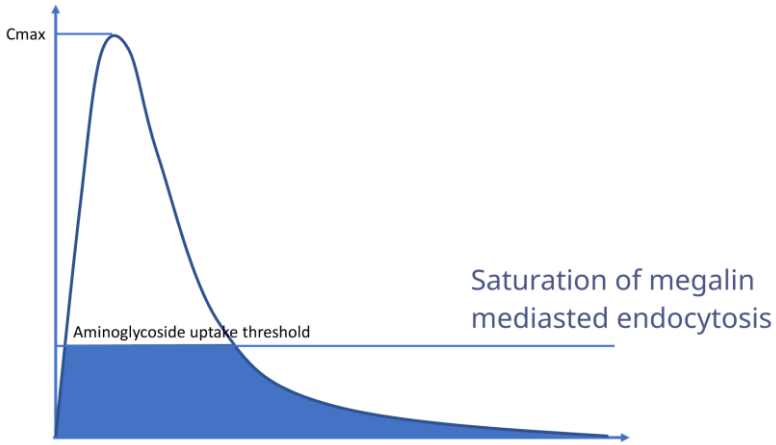


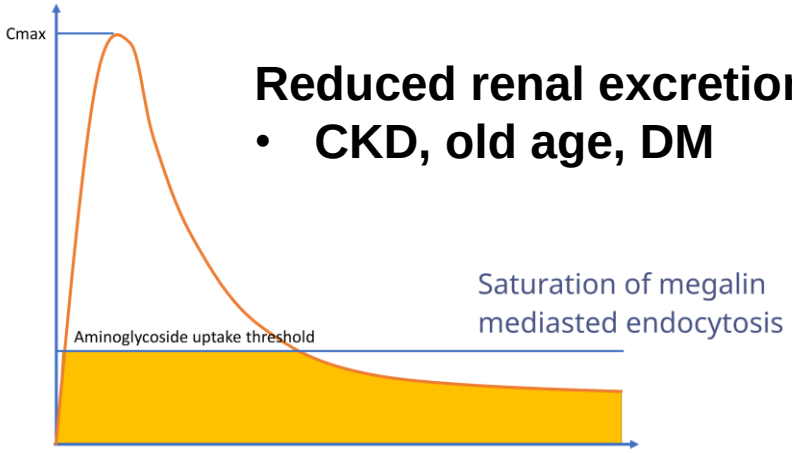
Megalin mediated, saturable endocytosis

Christensen et al. 2002 Nature review: molecular cell biology

Nature Reviews | Molecular Cell Biology

Risk factors for nephrotoxicity of aminoglycosides

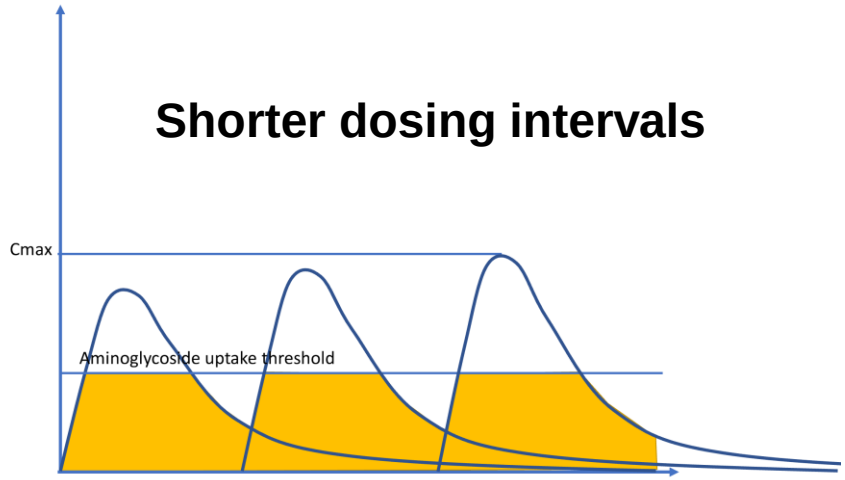




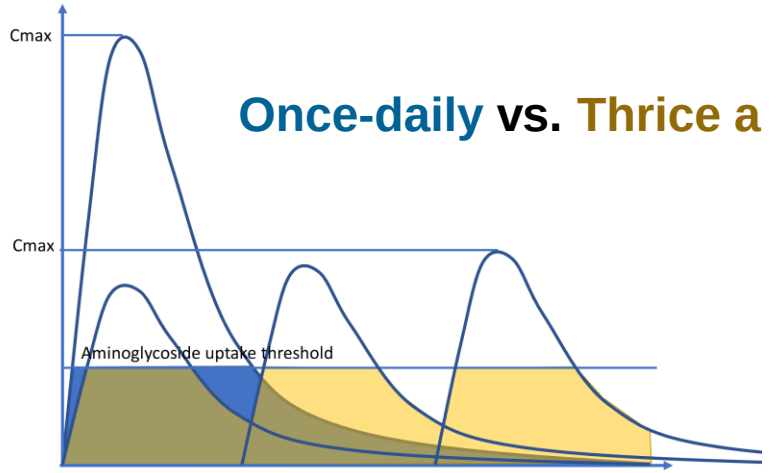
Reduced renal excretion

- **CKD, old age, DM**

Shorter dosing intervals

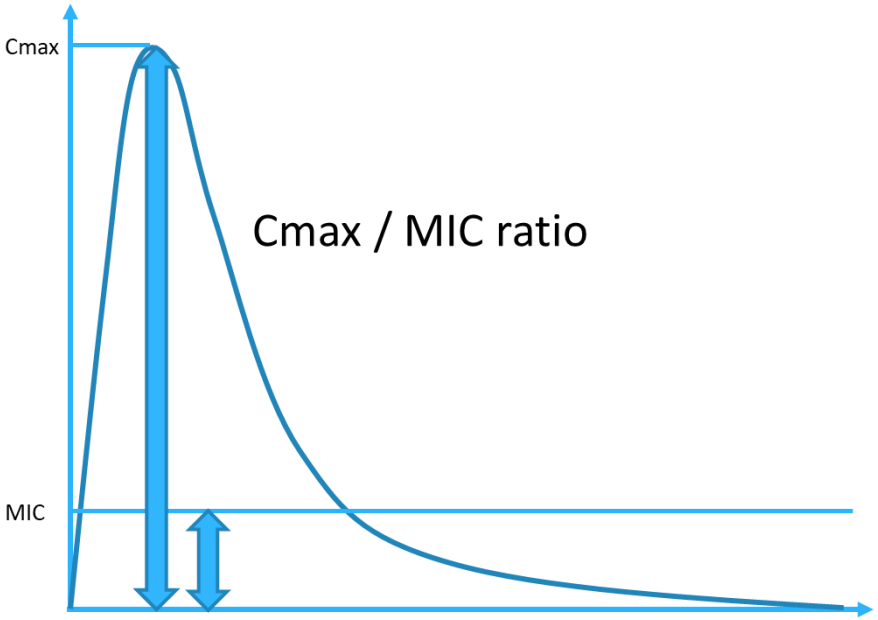


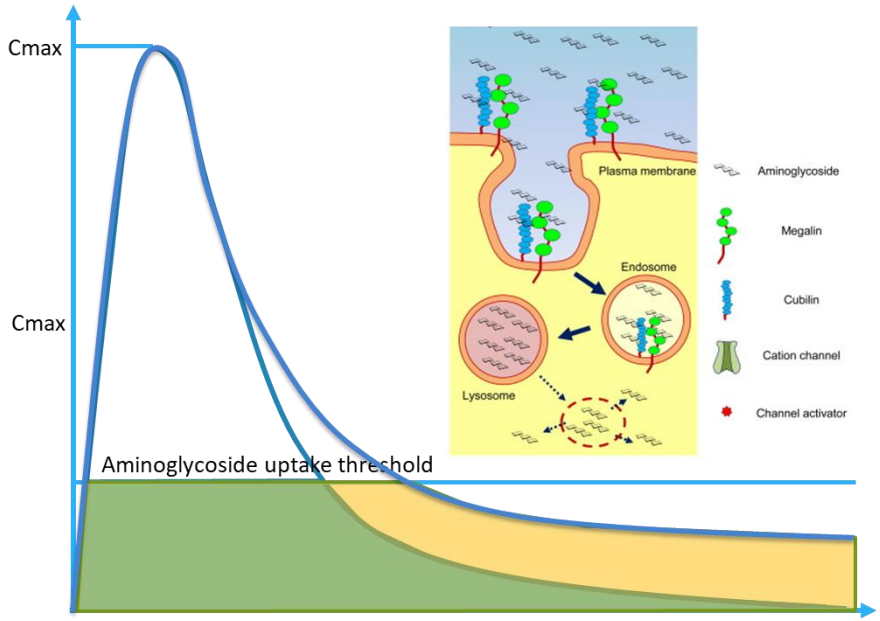
Once-daily vs. Thrice a day



逐步延長二線針劑投藥間距

減低毒性卻不影響藥物療效





High Cmax/MIC ratio → Maximize bactericidal efficacy

Initial daily administration of AMG ensures **maximal bactericidal efficacy** → **78.4% SCC within 2 months**, without acquired drug resistance

Tubular necrosis due to Megalin-mediated endocytosis in renal proximal tubular cells (**Saturable**)

Extend dosing intervals after SCC → **Longer duration to eliminate** ↓Nephrotoxicity

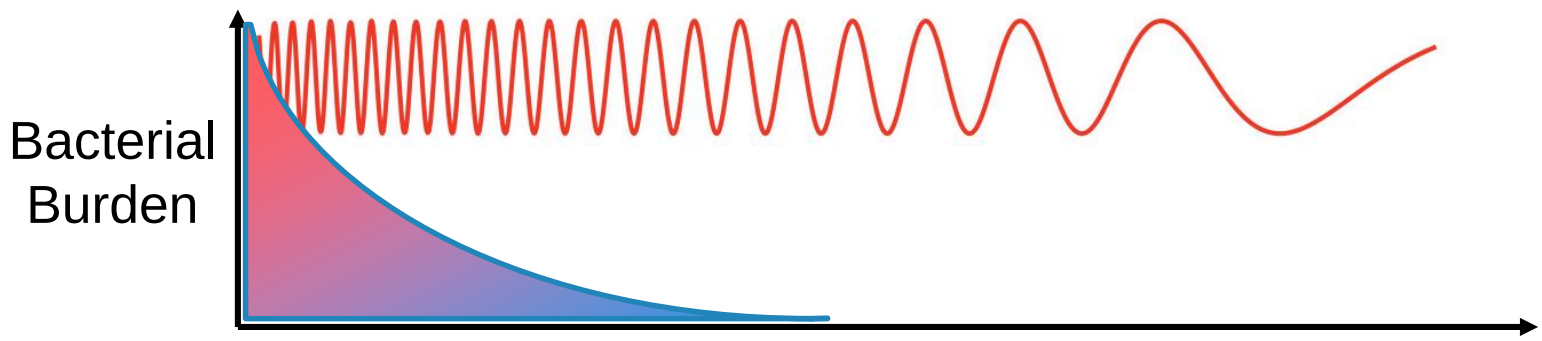
Tolerate higher accumulative dose

Stepwise De-escalation of Dosing Interval for aminoglycosides

- **Aminoglycosides (AMG)** are inexpensive and highly potent for treating multidrug-resistant tuberculosis (**MDR-TB**).
- **Stepwise de-escalation** of AMG dosing intervals was implemented to **minimize** the **nephrotoxicity**

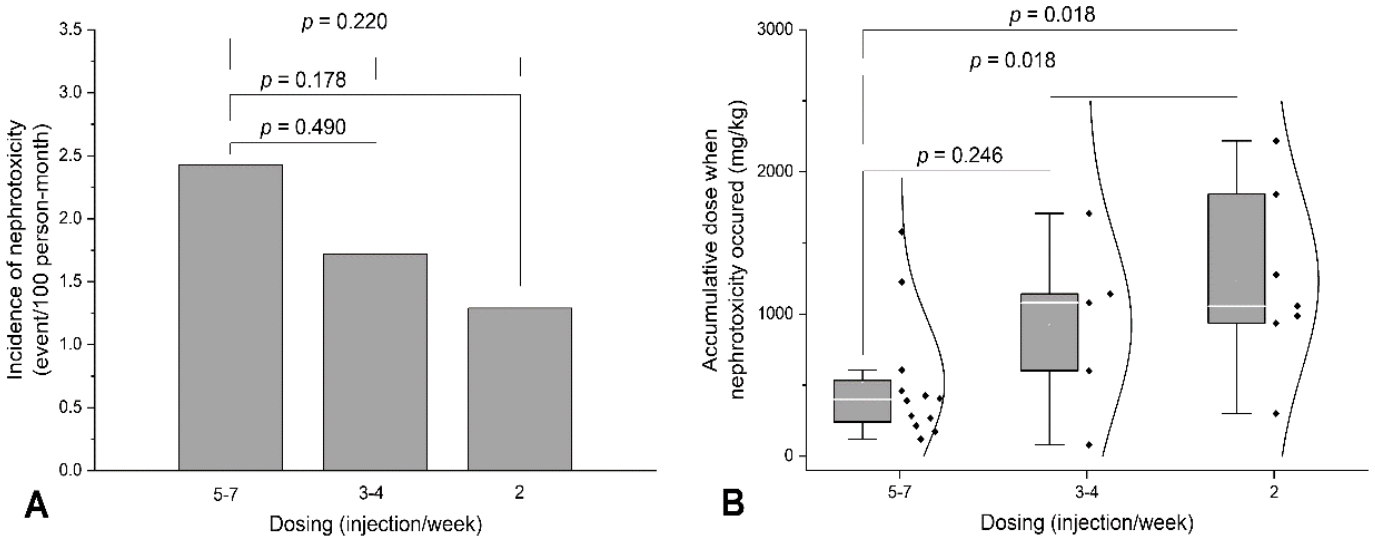
Dosing Interval De-escalation Protocol

- Once daily during admission
- 5 times weekly after discharge
- Thrice weekly after documented sputum culture conversion (SCC) for a further 2 months and later
- Twice weekly for a minimum of 6 months after SCC



投藥間距最佳化成效

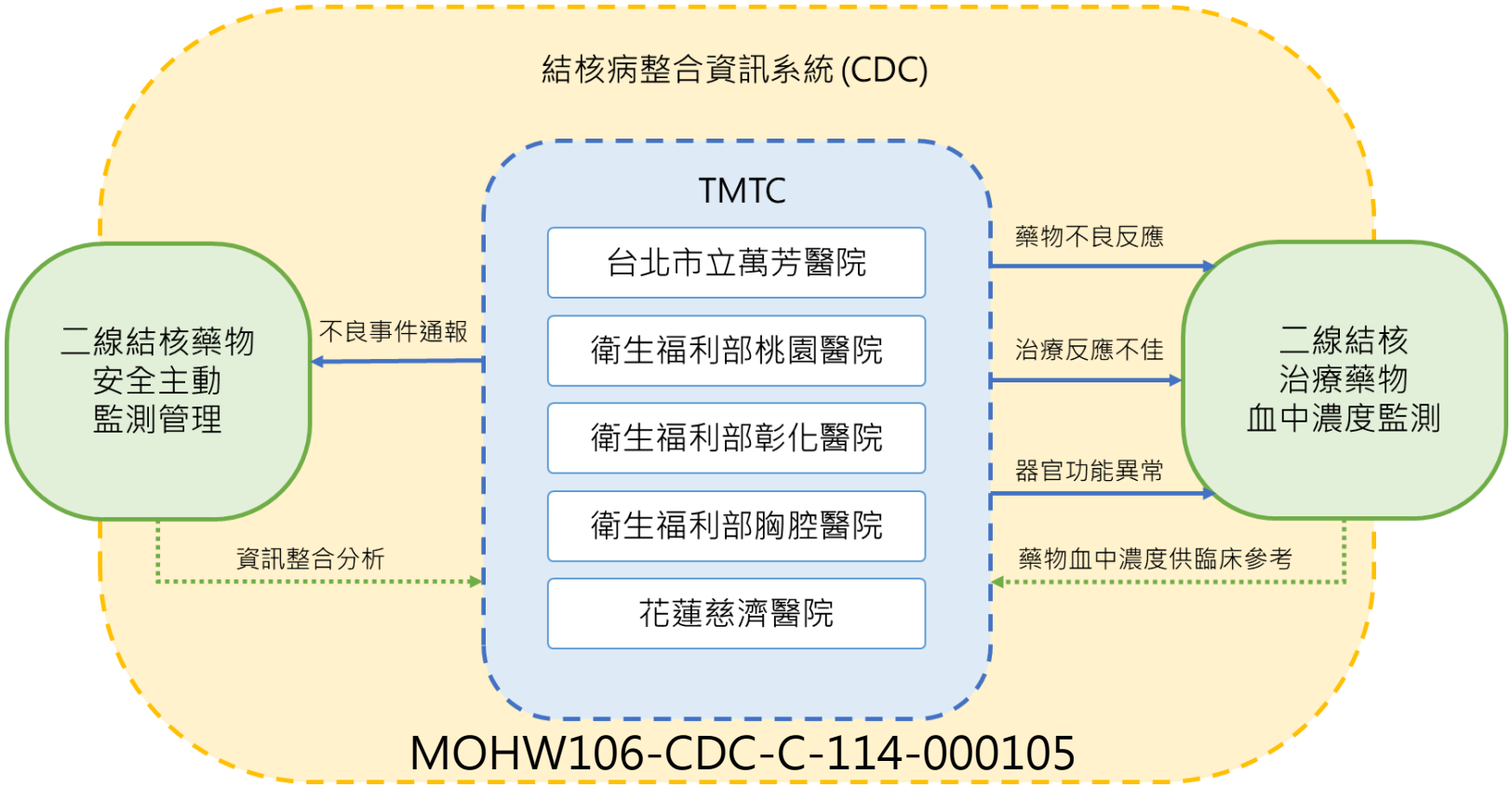
- 185名MDR-TB病人，24(**13%**)發生腎毒性，其中21(87.5%)完全恢復。
- 89%完成治療，兩個月痰培養陰轉率達78.4%。
- 延長給藥間距可以增加累積劑量耐受力。



林賢君/余明治 Clin Microb Inf 2022

主動藥物安全

106-108 年疾病管制署委託科技研究計畫：(**江振源醫師**)



Hepatotoxicity, **Nephrotoxicity**, Hypothyroidism, **QTc prolongation**, **Ototoxicity**
Bone marrow suppression, Peripheral neuropathy, Optic neuropathy, Mood disorder

主動藥物安全的執行層級

- 核心 (Core package):
  - All serious adverse events, SAE
- 進階 (Intermediate package):
  - All SAE
  - AE of special interest
- 高階 (Advanced package):
  - All AE of clinical significance

Clinical Features of **Hypothyroidism**

- A 40-year-old woman developed fatigue, weight gain, constipation, dry skin, myalgia, dyspnea, and menstrual irregularities during the MDR-TB treatment
- Pericardial effusion, pleural effusion

https://www.uptodate.com

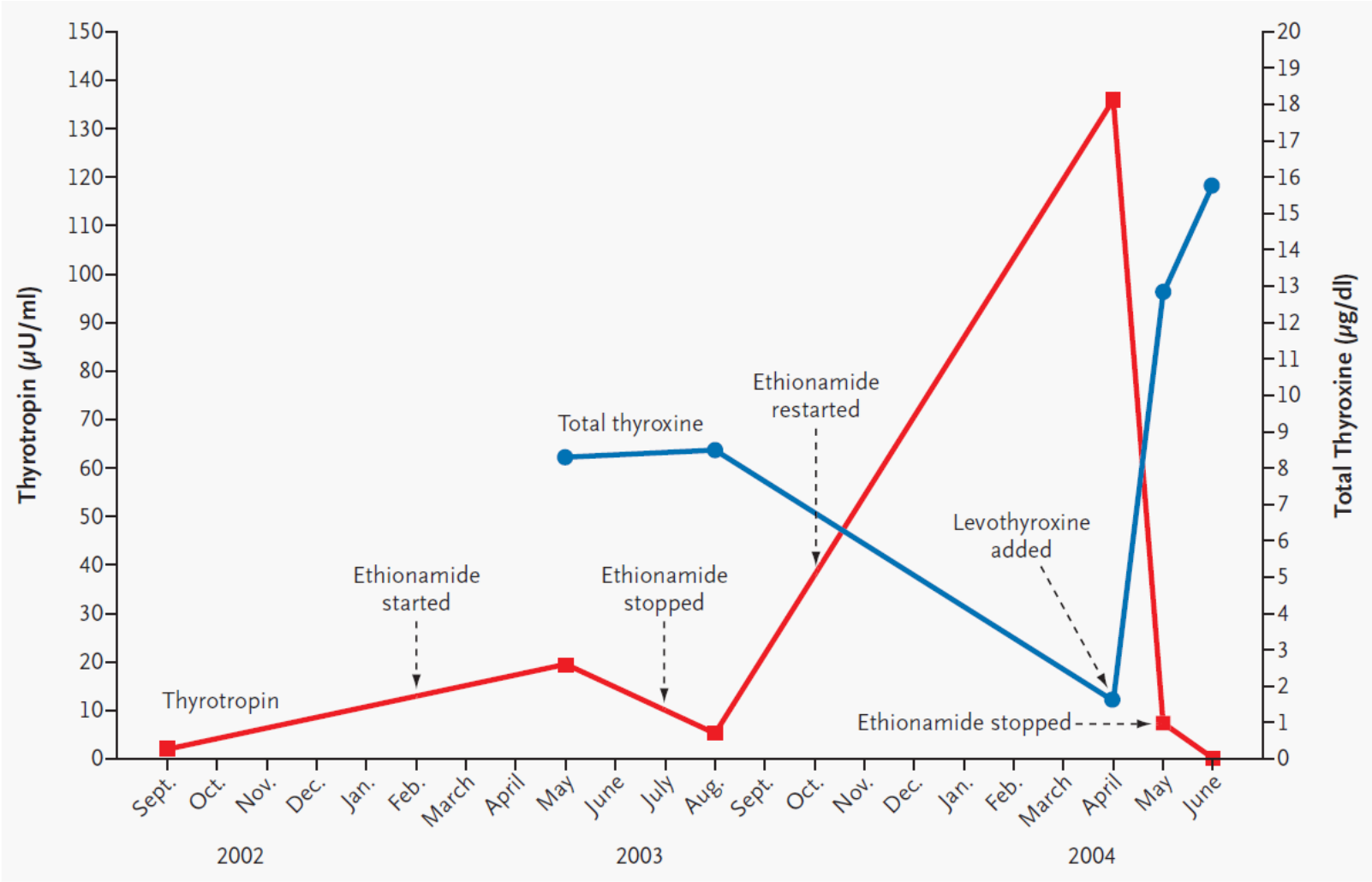
Adverse Events in MDR-TB Treatment

ADVERSE EVENT	N (%)
Nausea/vomiting	268 (32.8)
Diarrhea	173 (21.1)
Arthralgia	134 (16.4)
Dizziness/vertigo	117 (14.3)
Hearing disturbances	98 (12.0)
Electrolyte disturbances	94 (11.5)
Abdominal pain	88 (10.8)
Anorexia	75 (9.2)
Peripheral neuropathy	65 (7.9)

ADVERSE EVENT	N (%)
Depression	51 (6.2)
Tinnitus	42 (5.1)
Allergic reaction	42 (5.1)
Rash	38 (4.6)
Visual disturbances	36 (4.4)
Hypothyroidism	29 (3.5)
Psychosis	28 (3.4)
Hepatitis	18 (2.2)
Nephrotoxicity	9 (1.1)

Nathanson, 2004 IJTLD

A case report of ethionamide associated acquired-hypothyroidism



McDonnell, 2005 NEJM

Hypothyroidism in MDR-TB Treatment

Series	N	%
Lesotho, 2012	186	69%
S. Africa, 2011	137	58%
Botswana, 2012	213	34%
India, 2016	188	23%
India, 2016	52	21%

Satti, 2012 IJTLD; Thee, 2011 IJTLD; Modongo, 2012 IJTLD; Munivenka, 2016 J Tuberc Res; Dutta, 2012 IJTLD

個人化的劑量

Dose-Dependent Bactericidal Effect

- Moxifloxacin
  - AUC/MIC >100 (**MIC 0.5 mcg/ml**)

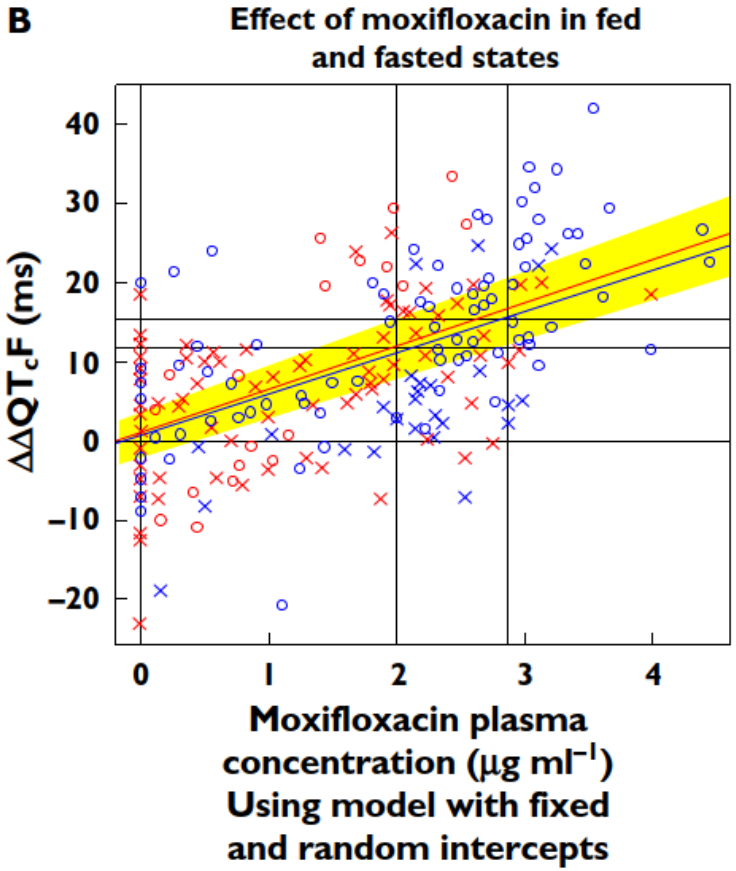
    Predicts bactericidal effect of **log-phase growth** during monotherapy
  - **MSC_{50}=2 mcg/ml**

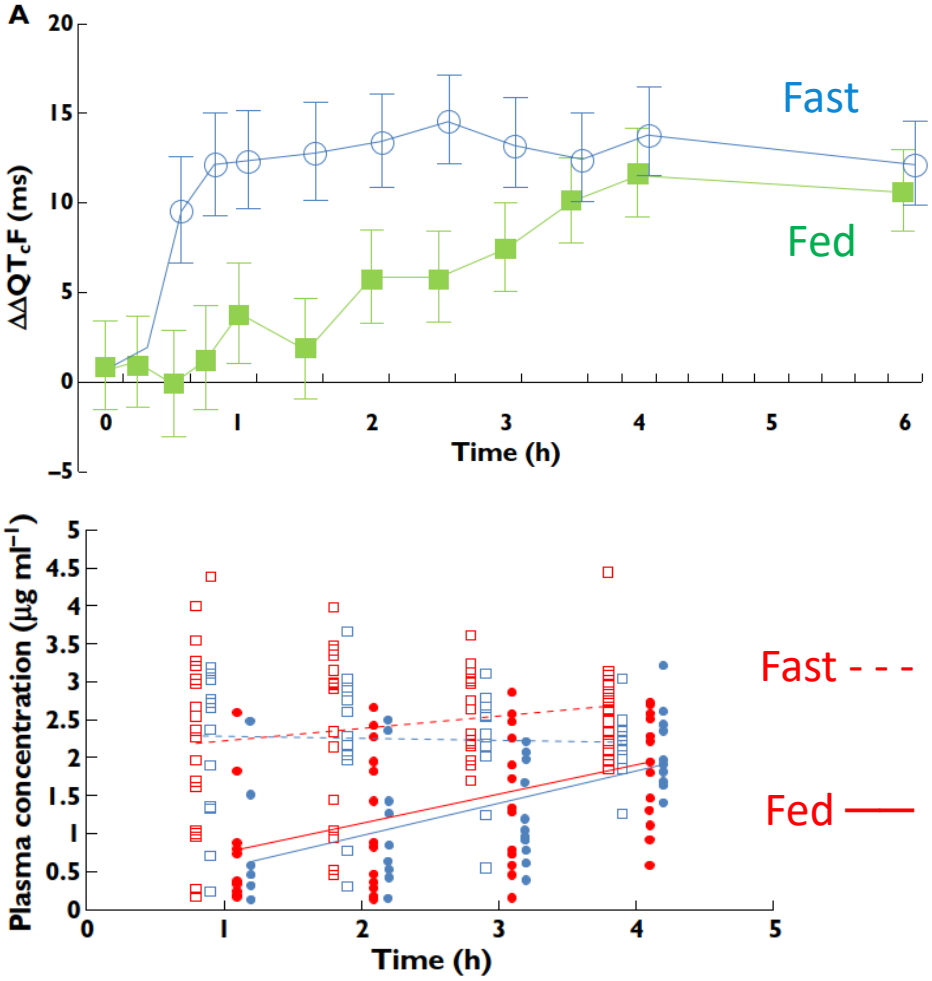
    minimal conc. to kill 50% of bacteria in a stationary (slowly or **infrequently growing) phase**.
  - **MDC_{50}=4 mcg/ml**

    minimal conc. to kill 50% of bacteria in a **dormant phase**.

Anna Diewerke Pranger, Rijksuniversiteit Groningen 2018

Conc.-dependent QT prolongation (Toxicity)





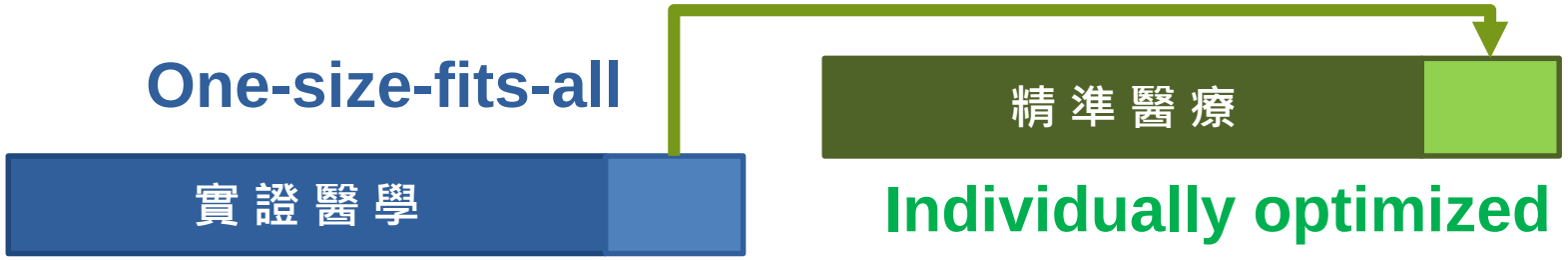
Taubel J, Br J Clin Pharam 2013, doi: 10.1111/bcp.12168

The Gap between Efficacy and Toxicity

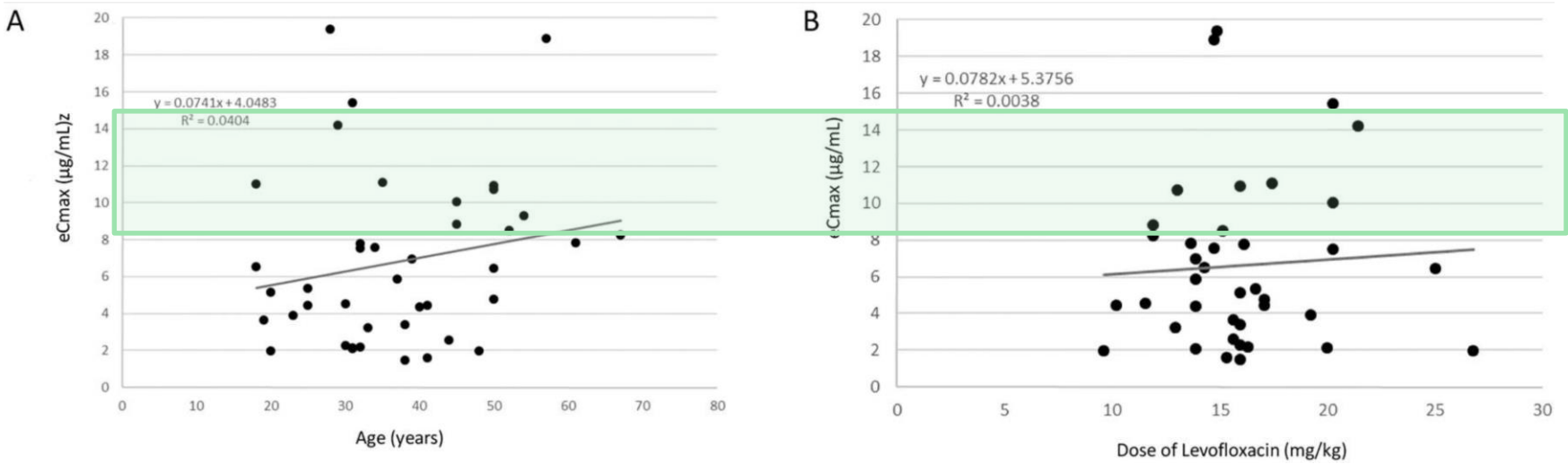
- Shorter Course Needs Higher Dose
  - Conventional > 18-month regimen
    - Moxifloxacin 400 mg
    - Levofloxacin 750 mg
    - Linezolid 600 mg
  - Short-course > 9-month regimen
    - Moxifloxacin 800 mg
  - Nix-TB Trial 6-month BPAL regimen
    - Linezolid 1200 mg
  - NExT study > 6-month regimen
    - Levofloxacin 750-1000 mg

族群的平均值不代表個體的最佳值

- Only a few subjects were eligible for clinical trials.
- Patients with comorbidities, extreme BMI, advanced age, drug-drug interaction are usually not covered during the development of pharmacometrics data in phase I-III stages.



Levofloxacin Cmax in MDR-TB (Tanzania)



Wide variability in Cmax
Only 1/3 reached the target

Inadequate Cmax
- **Later sputum conversion**
- **Acquired resistance**

	eC_{max} < 7.55 µg/ml n = 18	eC_{max} ≥ 7.55 µg/ml n = 15	P value
Time to Sputum Culture Conversion in days	47.8 ± 26.5	38.3 ± 22.7	0.27
Treatment outcome[a]			
Cured	6 (33.3)	10 (66.7)	0.06
Treatment completed	7 (38.9)	3 (20.0)	
Death	4 (22.2)	2 (13.3)	
Development of acquired drug resistance	1 (4.5)	0 (0)	
Favorable[b]	13 (72.2)	13 (86.7)	0.31

Andrew Ebers, PLoS one, 2017 doi: 10.1371/journal.pone.0170663

Therapeutic Drug Monitoring (TDM)

- The clinical laboratory assay of a chemical parameter that, with **appropriate medical interpretation**, will **directly influence drug prescribing** procedures.
- Individualization of drug dosage by keeping plasma (blood) drug conc. within a **targeted therapeutic range**.
- TDM is certainly not suitable for every drug in every patient and every disease.

Kang JS, Korean J Int Med 2009. doi: 10.3904/kjim.2009.24.1.1
Buclin T, Front Phar 2020. doi:10.3389/fphar.2020.00177

Are TB Drugs Suitable Candidates to TDM?

- Significant ***between-subject PK variability***
  - **Absorption**: moxifloxacin, linezolid
  - **Distribution**: clofazimine, bedaquiline, moxifloxacin
  - **Metabolism**: isoniazid, pyrazinamide, moxifloxacin
  - **Excretion**: levofloxacin, ethambutol, 2nd-line Inj
- Poorly predictable from individuals' characteristics
- A standard dosage achieves a wide range of drug exposure

療效最佳化，毒性最小化

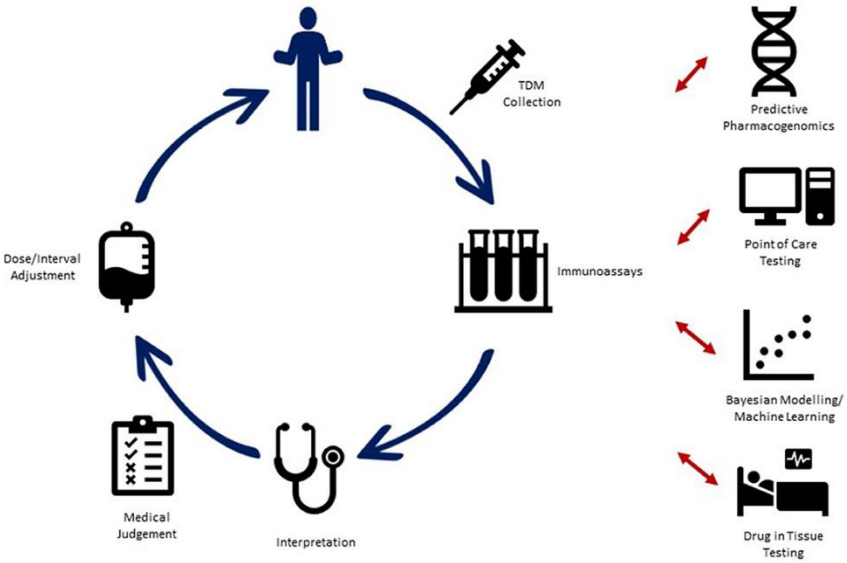
- A **narrow *therapeutic margin*** forbidding the use of very high standard doses in all patients to ensure overall efficacy.
- Absence of PD markers for **efficacy** and/or **toxicity** readily assessable. (warfarin)
- **Consistent *PD relationships*** between drug exposure and efficacy and/or toxicity.

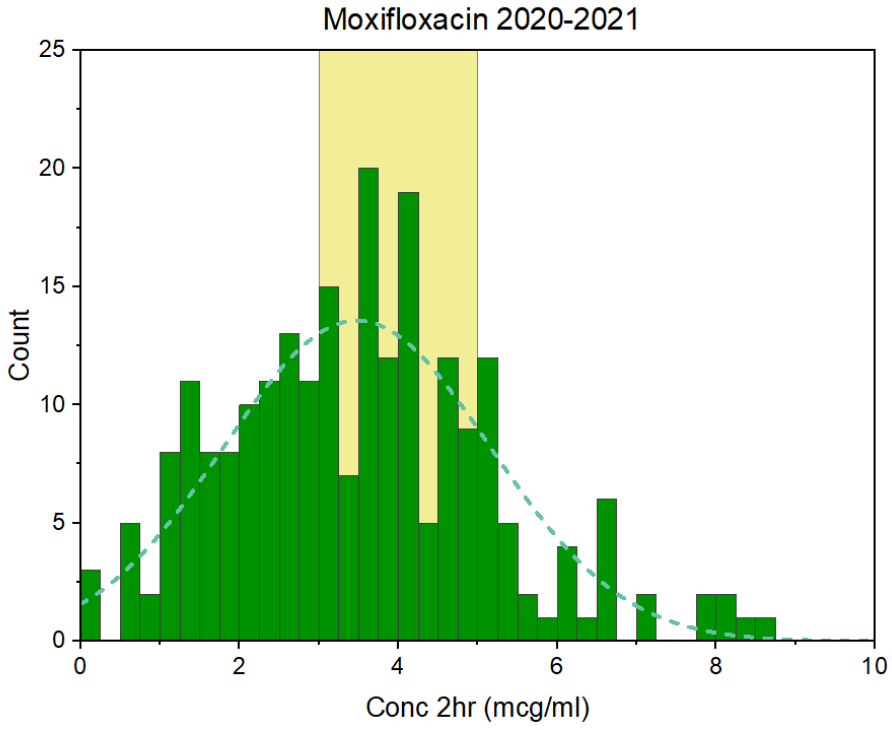
Predictability after Dosage Optimization

- Sufficient *treatment duration* and criticality for patient's condition to justify dosage adjustment efforts
- Acceptable *PK stability*, limited within-subject PK variability over time

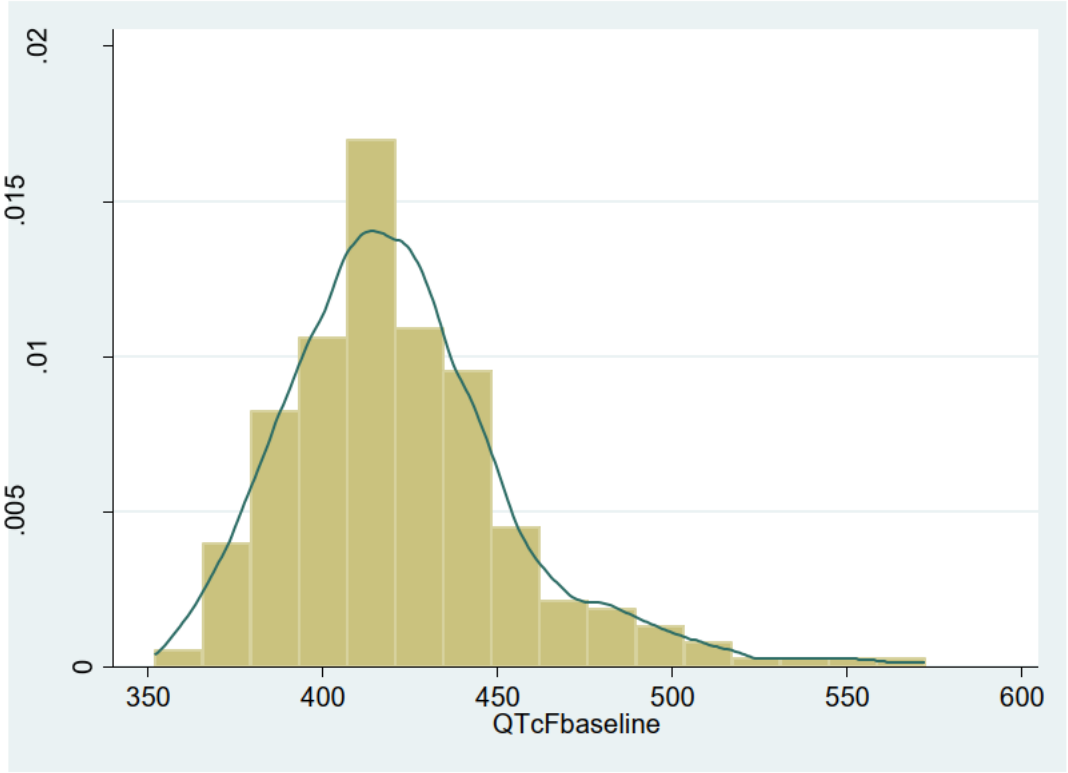
抗結核藥物治療濃度監測

二線抗結核藥物血中濃度代檢實驗室





Baseline QTc of Patients in TMTC



Baseline QTc: 470ms 與500ms 間(5.4%)，大於500ms(2.9%)

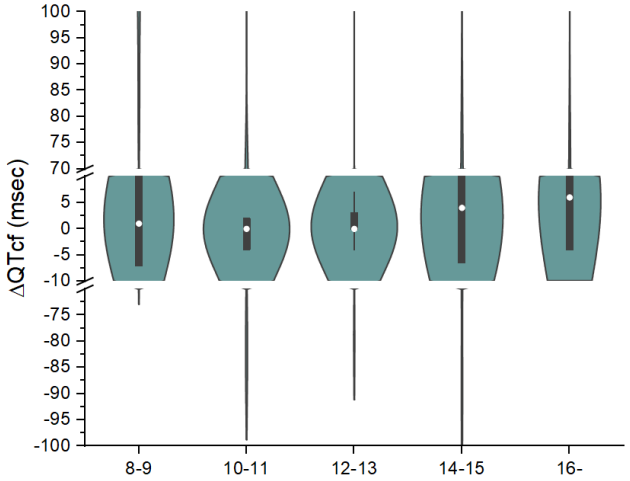
106-108年疾病管制署委託科技研究計畫：MOHW106-CDC-C-114-000105 (**江振源醫師**)

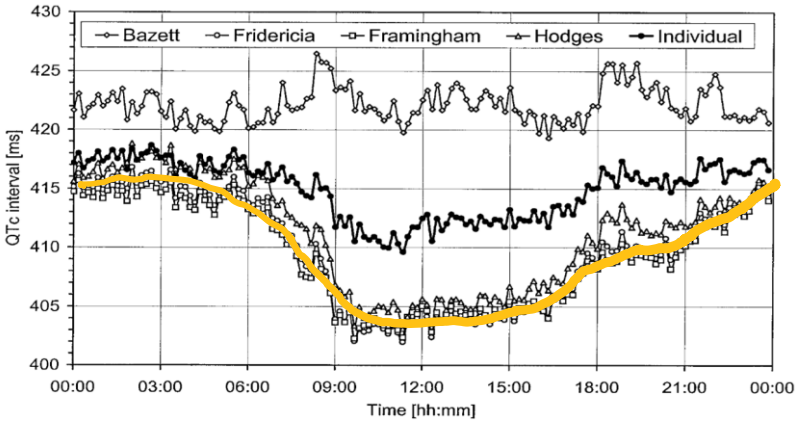
QTc Prolongation during Treatment

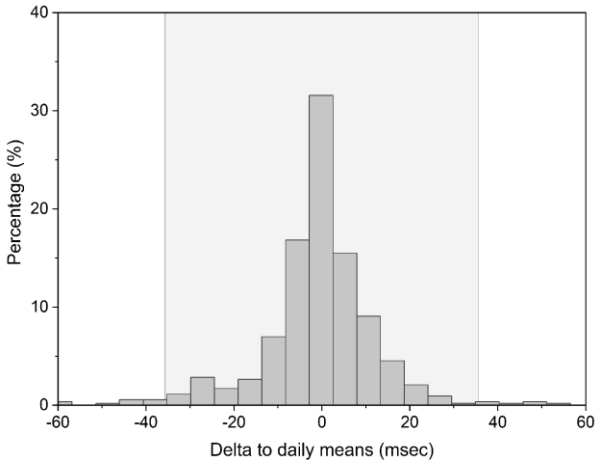
- 治療滿八個月共 248 名，37 (17.6%)位QTcF 增加值大於等於60ms。
- 發生QTcF >500ms
  - Normal dose Moxifloxacin 172位，11.3%
  - High dose Moxifloxacin 17 位，41.1%
  - Levofloxacin 48 位，18.7 %
  - Clofazimine 120 位，25.8%

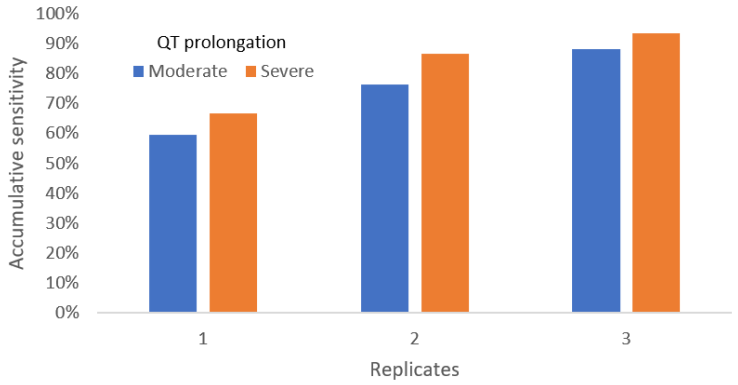
106-108年疾病管制署委託科技研究計畫：MOHW106-CDC-C-114-000105 (江振源醫師)

Circadian Rhythm + Fluoroquinolones









Smetana P, Pacing Clin Electrophysiol 2003. doi: 10.1046/j.1460-9592.2003.00054.x.

2015 Aug

二線藥物快速分子檢測

2015 Jan

分子檢測納入常規診斷流程
快速Rifampicin抗藥分子檢測

2014 Jan

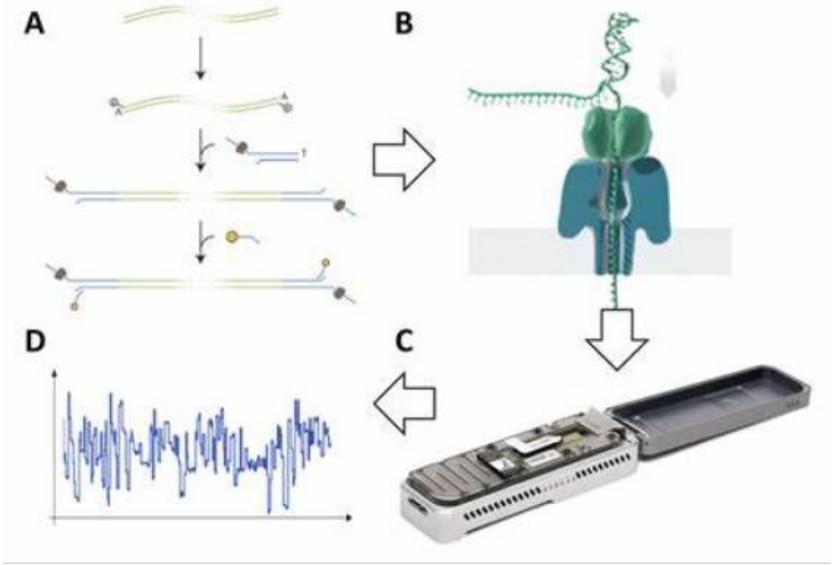
抗藥結核全面二線藥敏

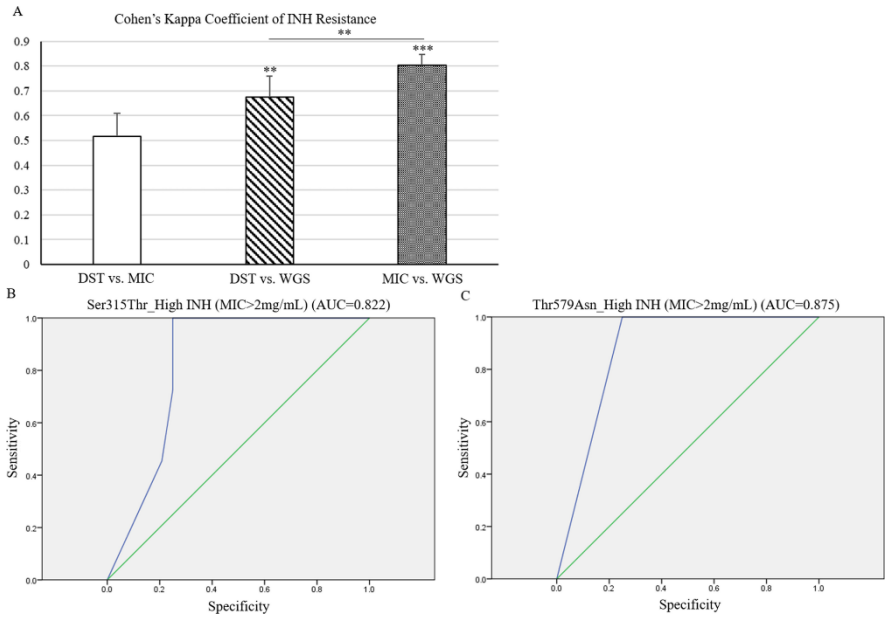
2009 Sep

MDR-TB 快速分子檢測

應用全面性分子快速藥物敏感性檢測
即時量身訂作的個人化的處方

結核菌長基因片斷全基因定序

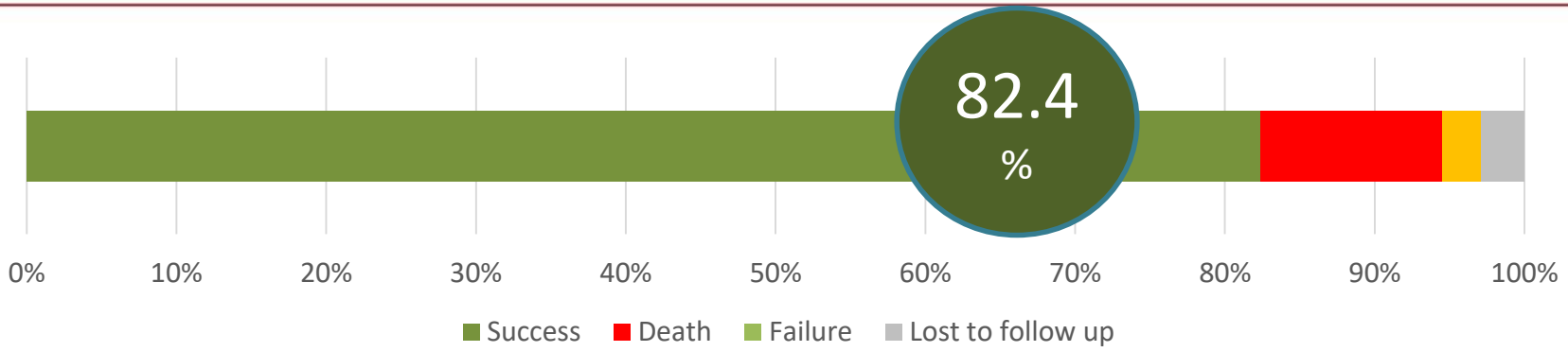




以Nanopore系統，對結核菌進行長基因片所全基因定序，預測結核菌的藥物MIC。
優勢：裝置簡單，透過雲端進行資料分析，發揮Point-of-Care的潛力

Ming-Chih Yu J Biomed Sci 2021 doi: 10.1186/s12929-021-00783-x

Treatment Outcomes of MDR-TB in Taiwan Tackling Loss to Follow-up

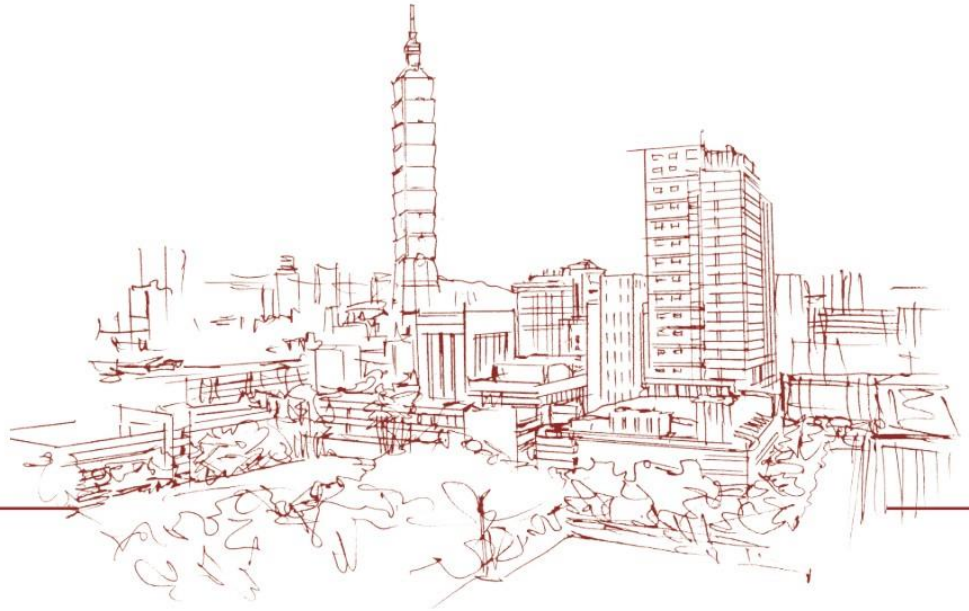


Predictor	Total No.	Univariate		Multivariate	
		OR	(95% CI)	aOR	(95% CI)
Age, year					
<45	224	Reference		Reference	
45–64	294	0.55	(.31–.99)	0.71	(.37–1.35)
≥65	168	0.16	(.09–.28)	0.19	(.10–.35)
FQ resistance	121	0.64	(.40–1.03)	0.49	(.29–.85)
Cancer	41	0.12	(.06–.23)	0.11	(.05–.24)
Chronic kidney disease	46	0.25	(.14–.47)	0.28	(.14–.55)

Ming-Chih Yu. Clin Infect Dis. 2018 Jul 15; 67(2): 202–210.

MDR-TB的全人醫療

- 以病人為中心，滿足臨床需求。
- 主動藥物安全，及時控制毒性。
- 實證醫學出發，朝向精準醫療。



謝謝指教

臺北醫學大學
TAIPEI MEDICAL UNIVERSITY