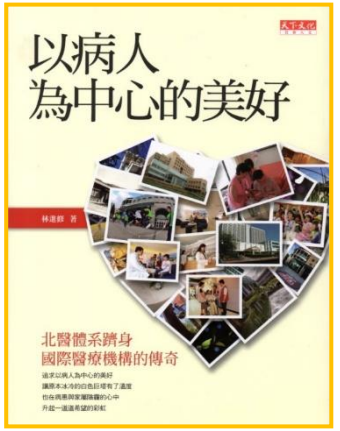

Patient-Centered Treatment for Multidrug-Resistant Tuberculosis

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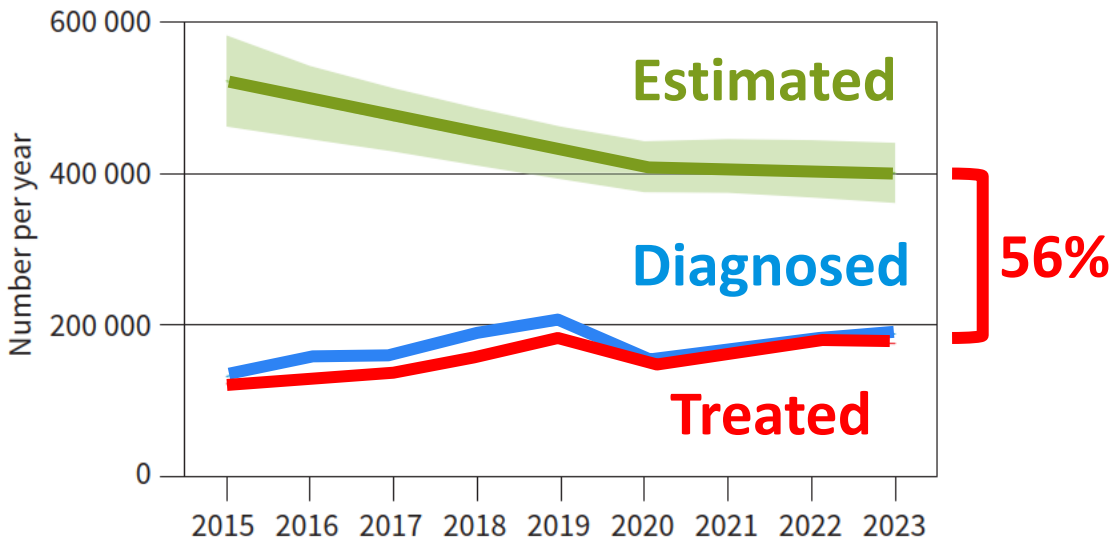
Taipei Medical University

Outlines

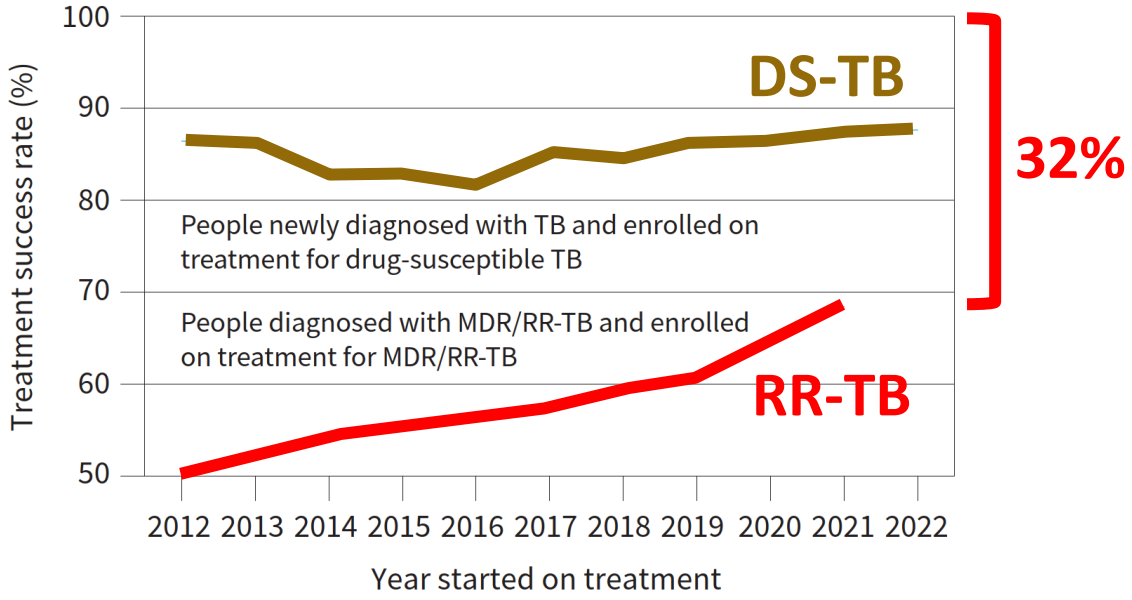
1. Background
2. Holistic care for DR-TB
3. Active Drug Safety Monitoring
4. Therapeutic Drug Monitoring

Unmet Need for Management of RR-TB

Globally, 56% of RR-TB is left untreated.



The treatment is unsuccessful in 32%.



Lost-to-follow-up in MDR-TB Treatment

- Before 2000, the treatment success rate in Taiwan was only 51.2%.
- Despite the inclusion of Fluoroquinolones, the treatment success was still unsatisfactory (59.2%).
- Lost-to-follow-up as high as 29.1%.
- Not only the regimen but also the management matters.

Eur Respir J 2006; 28: 980–985
DOI: 10.1183/09031936.06.00125705

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.

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Received:
October 27 2005
Accepted after revision:
June 23 2006

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

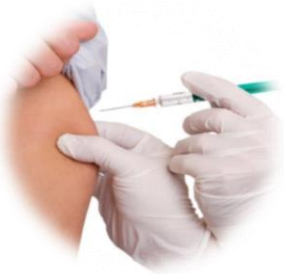
European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

CY Chiang, 2006 ERJ

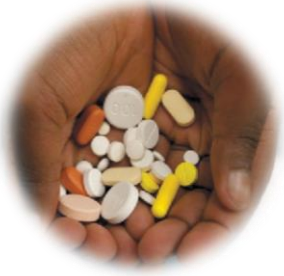
Obstacles to Successful MDR-TB Treatment

Physical, mental, and economic distress

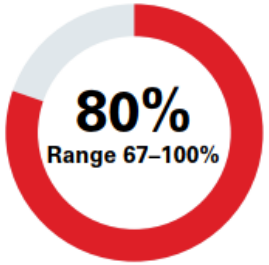
Injectables
6 – 8 mo



High pill burden



80% Catastrophic economical distress



WHO, 2020, Global TB Report

Adverse Events

Permanent Hearing loss

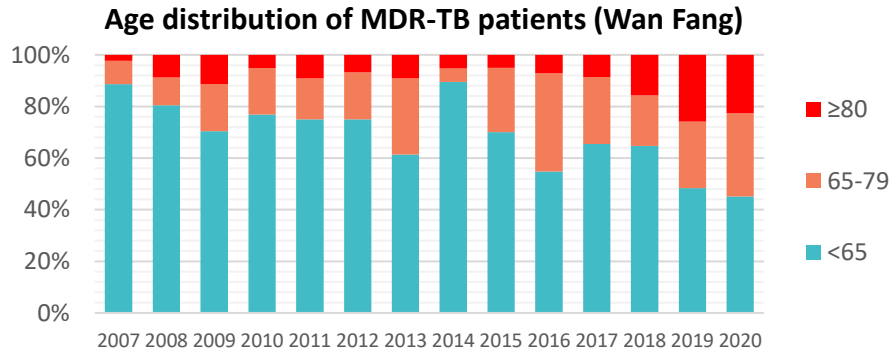
Permanent numbness

Required regimen adjustment 80%

Led to admission or life-threatening 50%

Ageing and Comorbidities

Comorbidities 69.3%
DM 27.2%
Cancer 6.7%

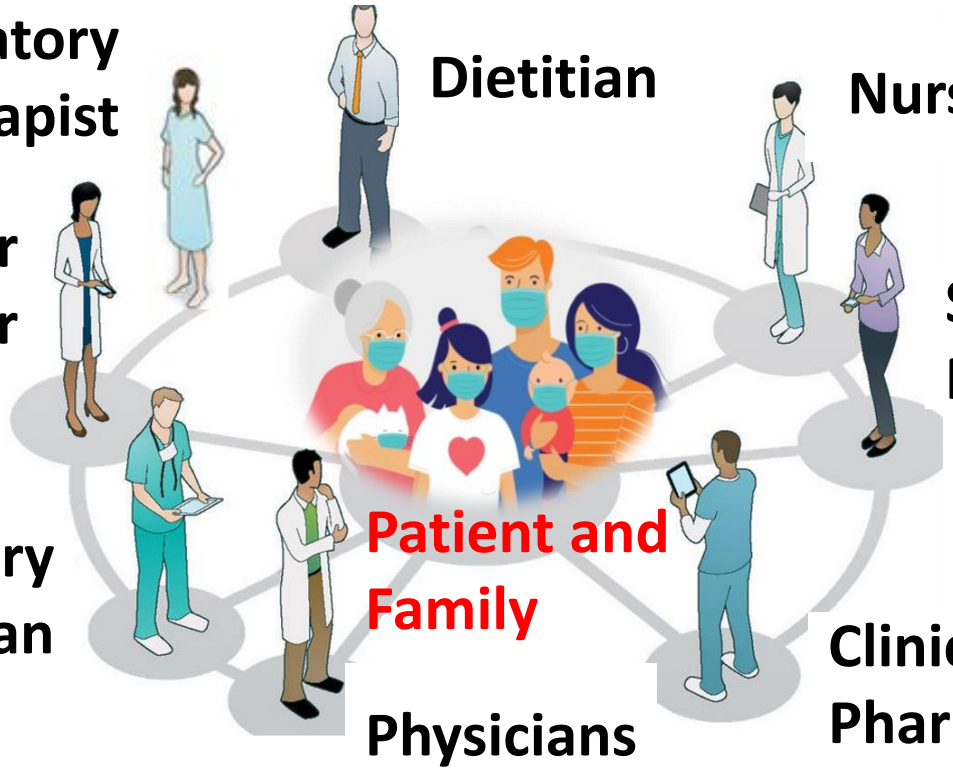


Social Stigma

HOLISTIC CARE FOR DR-TB
ACTIVE DRUG SAFETY MONITORING

Holistic Care for DR-TB

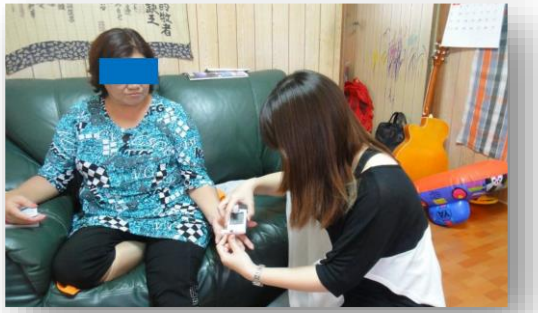
Education → Physical Evaluation → Psychological Assessment → Family and Socioeconomic Support



Taiwan MDR-TB Treatment Consortium Since 2007

Outreach patient-centered care to the community

Fundamental framework for timely adverse event management

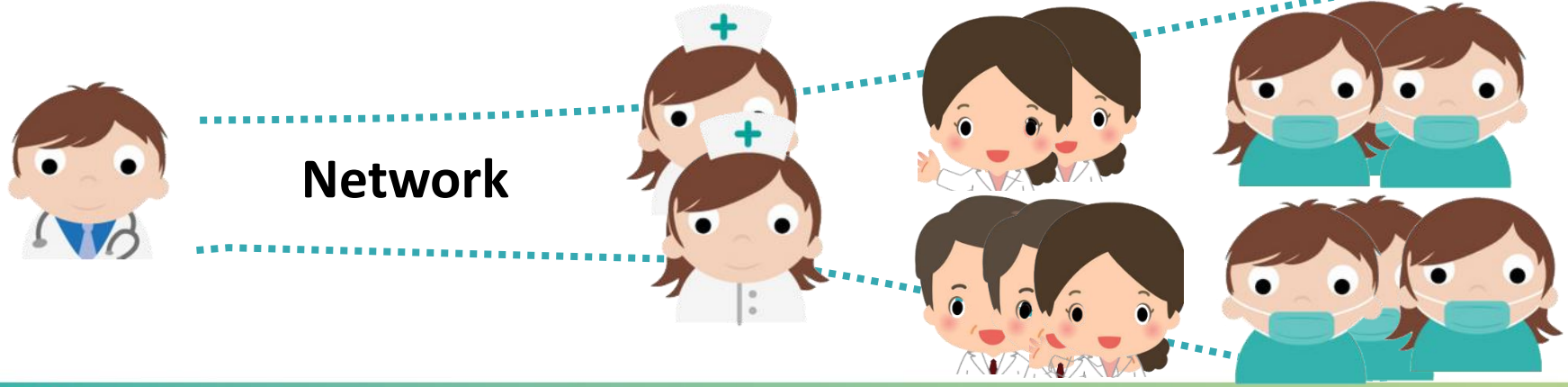


Attending Physicians

Nursing Specialists

DOT Supporters

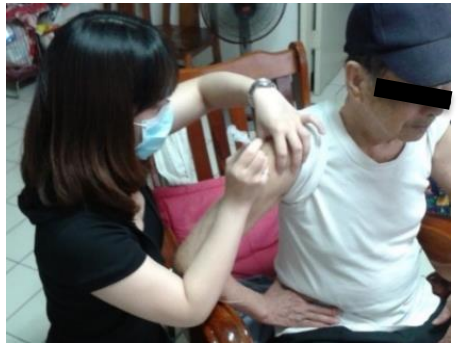
Patients

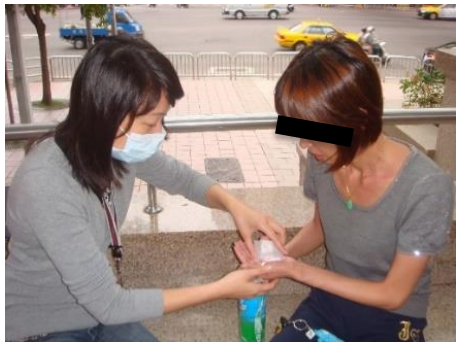
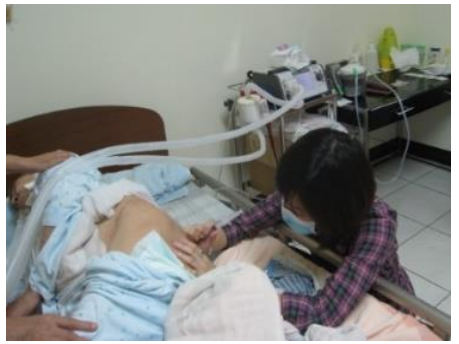


DOTS-Plus, More than DOT

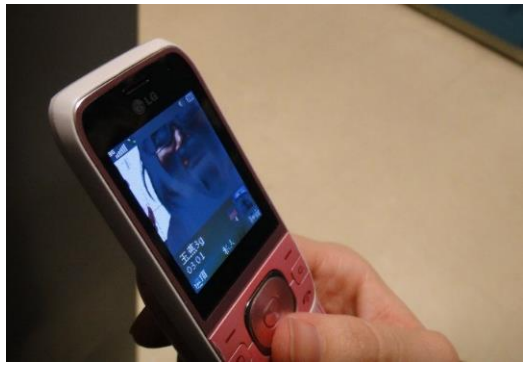
Anywhere: either rural or urban, even far away in the mountains
Omnipotent: wound care, injection, **Active Drug Safety Monitoring**
Nonstop: every day throughout the course of treatment





Sensible Directly Observed Treatment, DOT



Application of Third-Generation (3G) Mobile Videophone to the DOTS-Plus Program in Multidrug-Resistant Tuberculosis in Taiwan: Case Report

Veng-Kai Tang, Kuan-Jen Bai, Chin-Yun Wang*, Ming-Chih Yu, Taipei-MDRTB Group

Multidrug-resistant tuberculosis (MDR-TB), caused by the bacterium, *Mycobacterium tuberculosis*, is resistant to both isoniazid and rifampicin and is a phenomenon threatening to destabilize global tuberculosis control. Taiwan's Centers for Disease Control implemented a patient-centered DOTS (directly observed treatment, short-course)-Plus program for MDR-TB patients in May 2007. We report the case of a 71-year-old MDR-TB patient who successfully completed 18 months of MDR-TB treatment under the DOTS-Plus program, beginning October 2007. A third-generation (3G) mobile videophone was used to watch the patient take medicine throughout his course of treatment. His acceptance of the program and compliance with monitoring by videophone DOT (V-DOT) were excellent. We conclude that V-DOT can be an effective approach to case management for MDR-TB patients and can achieve a high level of adherence in selected cooperative cases in Taiwan. ***(Thorac Med 2010; 25: 7-12)***

Innovative video DOT
in 2007 with 3G cell phones

To Door → Remote Video

Journal of Infection and Public Health 13 (2020) 1354–1359

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Original Article

Advantage in privacy protection by using synchronous video observed treatment enhances treatment adherence among patients with latent tuberculosis infection

Szu-Hsuan Chen[a,1], Irene Wang[b,c,1], Han-Lin Hsu[c,d], Chi-Ching Huang[a], Yi-Jun Liu[c], Denise Utami Putri[c], Chih-Hsin Lee[b,c,*]

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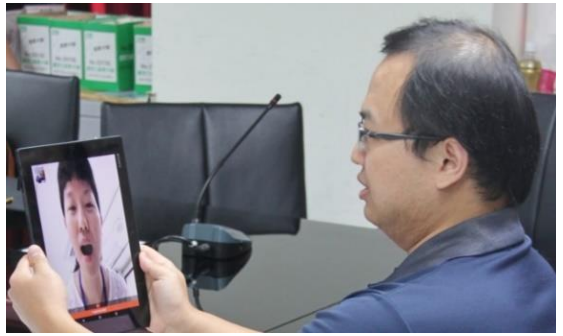
[b] Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan
[c] Pulmonary Research Center, Wan Fang Hospital, Taipei Medical University, Taipei 11696, Taiwan
[d] School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan

Privacy Protection



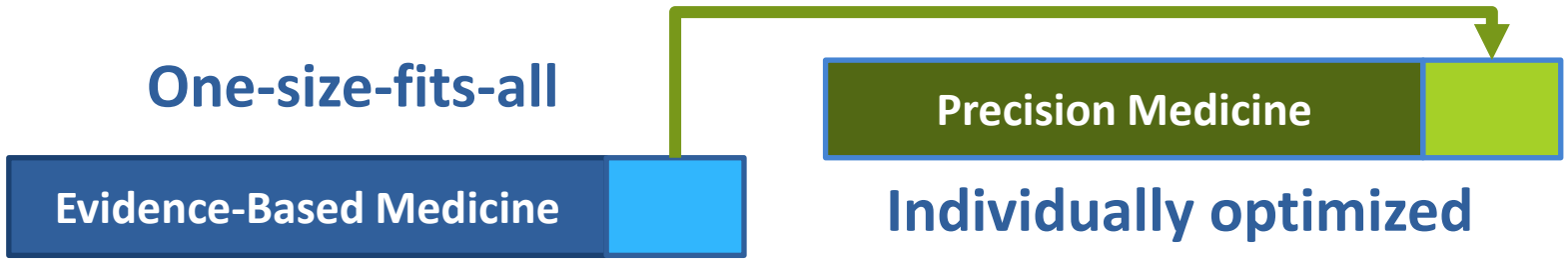
THERAPEUTIC DRUG MONITORING

Optimal Efficacy, Minimal Toxicity

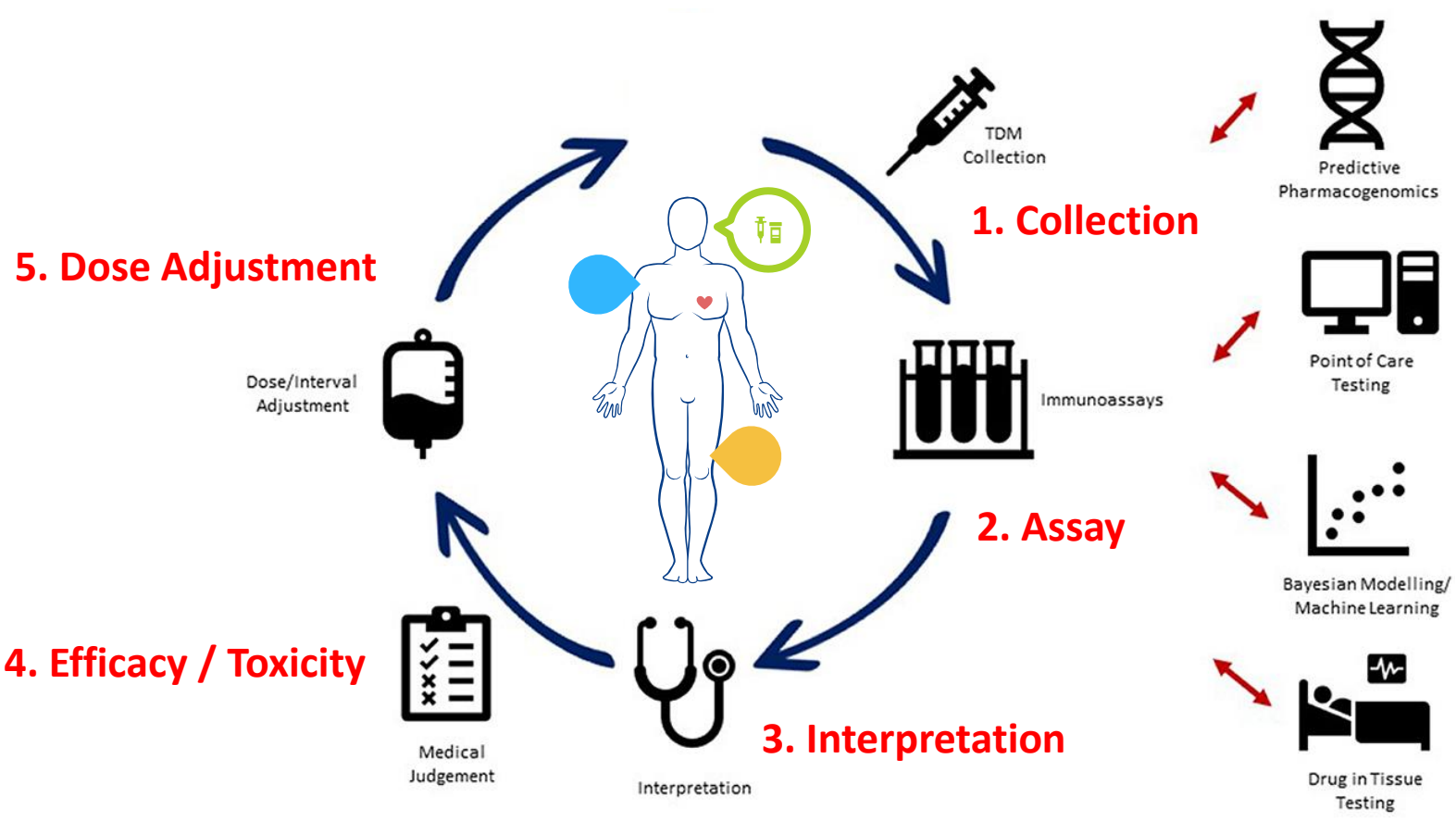
- Absence of PD markers for efficacy and/or toxicity readily assessable. (warfarin)
- Consistent *PD relationships* between drug exposure and efficacy and/or toxicity.
- A **narrow *therapeutic margin*** forbidding very high standard doses in all patients to ensure overall efficacy.

Big Gap between Research and Practice

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



Individualized Precision Dosing



01 Predictive Pharmacogenomics

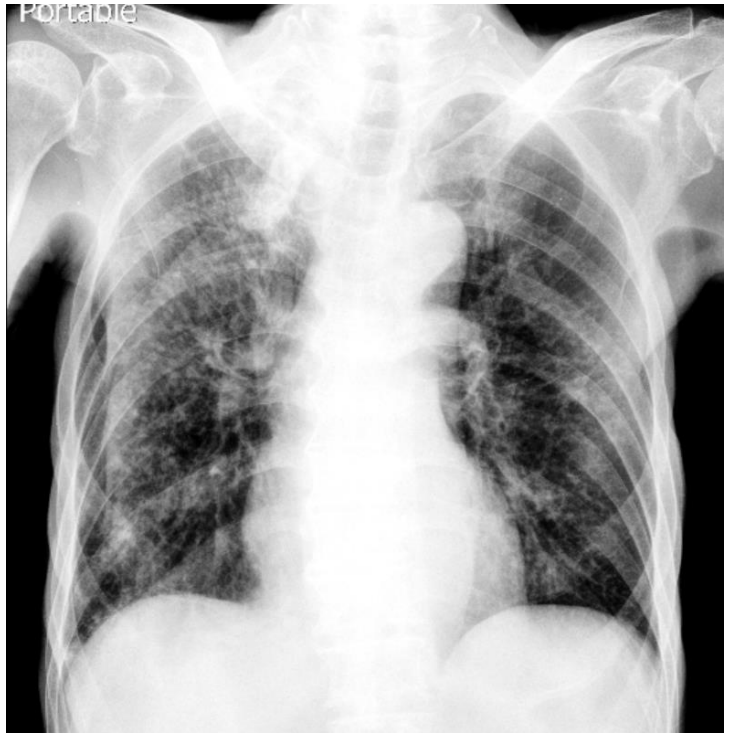
02 Point of Care Testing

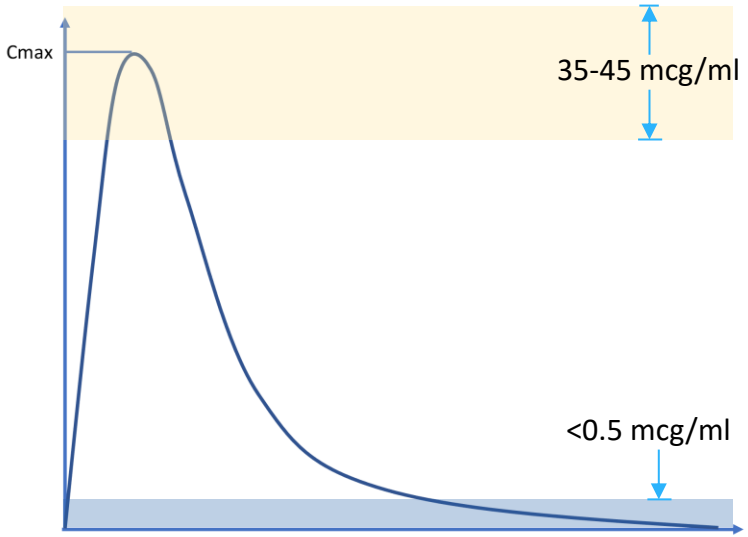
03 Population Modelling

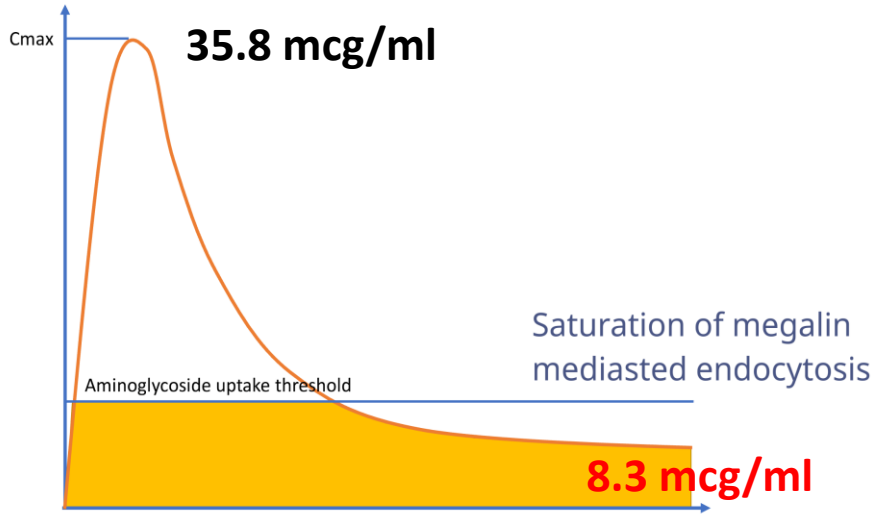
04 In Tissue Drug Concentrations

Kapoor A, Front. Pediatr. 2021. doi: 10.3389/fped.2021.661536

Therapeutic Drug Monitoring for Kanamycin



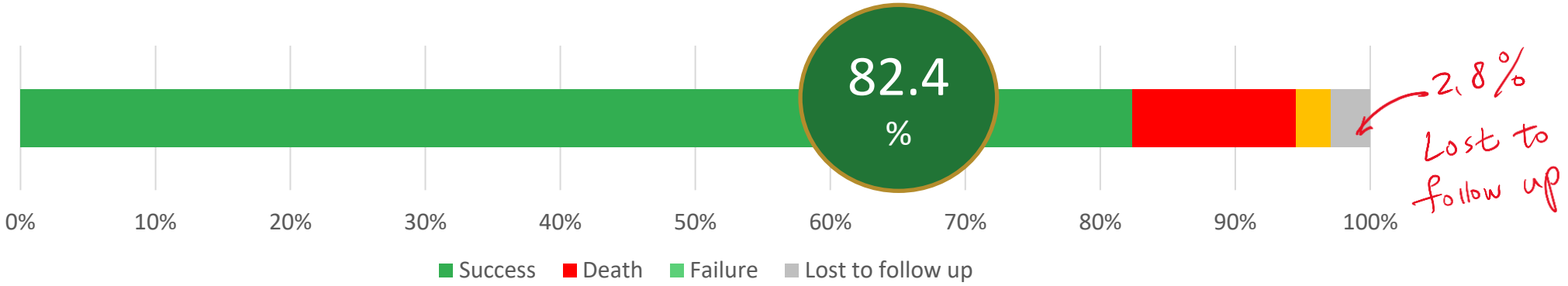




74-year-old man, Cr 0.83 mg/dl
35 kg

Kanamycin 500 mg qd

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.

Summary

- We successfully supported MDR-TB patients in safely and effectively completing anti-TB treatment with these strategies:
  1. Comprehensive team care in the community.
  2. Active monitoring and management of treatment-associated adverse events.
  3. Individualized, precise dosing to minimize toxicity and ensure treatment efficacy.