APEC CONFERENCE ON PREVENTION, CONTROL AND CARE FOR MDR-TB AND SUPPLY OF 2nd-LINE ANTI-TB DRUG

CONFERENCE HANDBOOK

CHINESE TAIPEI

June 29-30, 2016

APEC CONFERENCE ON PREVENTION, CONTROL AND CARE FOR

MDR-TB AND SUPPLY OF 2nd-LINE ANTI-TB DRUG

Asia-Pacific Economic Cooperation

Centers for Disease Control

Table of Contents

Welcome Message

Welcome to the "APEC Conference on Prevention, Control and Care for Multi-Drug Resistant Tuberculosis (MDR-TB), and Supply of Second-Line Anti-Tuberculosis Drug".

As we know the rising MDR-TB cases are a growing global health security concern. In the APEC region, the significant healthcare costs for MDR-TB treatment has resulted in a serious economic impact for many APEC members. Considering the urgent need for APEC members to take appropriate actions against the growing MDR-TB epidemic, Chinese Taipei proposed this conference to provide APEC developing economies with a platform to share and discuss preparedness efforts for effective management of MDR-TB.

This conference will provide a good opportunity for APEC member to exchange and share experience and information on the current MDR-TB situation and the control strategies. Furthermore, it will introduce the programmatic management MDR-TB, latest surveillance systems, laboratory diagnosis and supply chain of second-line anti-TB drugs in order to enhance APEC developing economies' capacity building for the prevention, care and control of MDR-TB. .

On behalf of the Conference Organizer, we hope you will find this Conference stimulating, enjoyable and productive. Thank you for your participation and contributions to this event, and we wish you a wonderful time in Taipei.

Steve H.S. Kuo, M.D., M.P.H., Ph.D.
Director-General
Centers for Disease Control, Chinese Taipei

Conference Information

Date

June 29-30, 2016

Venue

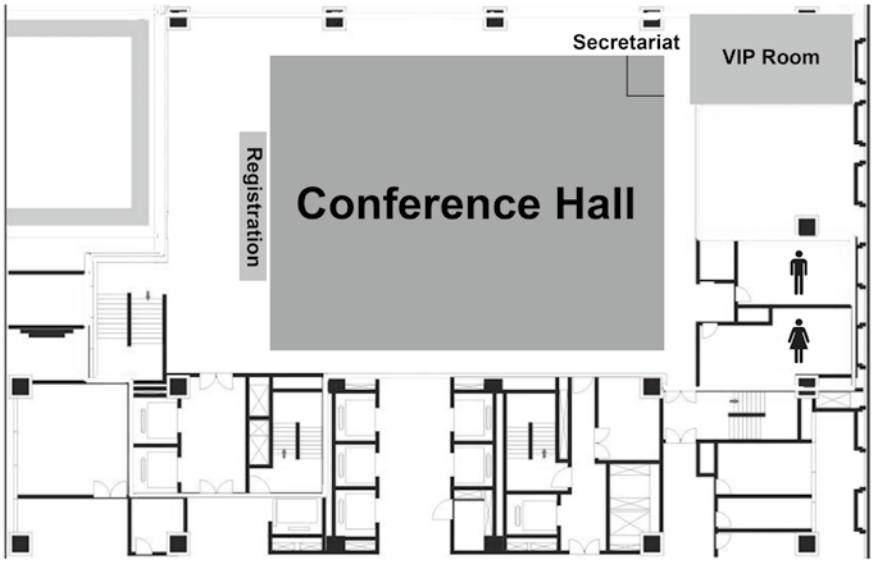
3rd Floor, International Conference Hall, GIS MOTC Convention Center
(No.24, Sec. 1, Hangzhou S. Rd., Zhongzheng Dist., Taipei City 100, Taiwan)

Organizer

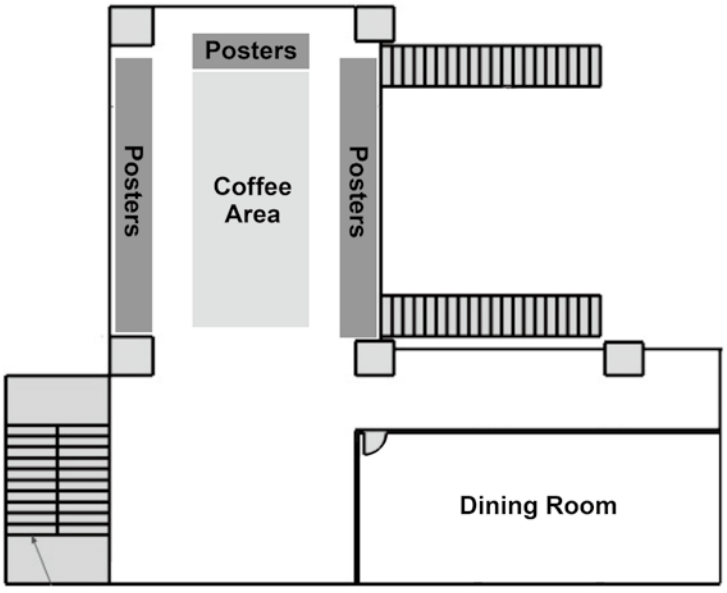
Centers for Disease Control, Chinese Taipei

Floor Plans

3rd Floor, International Conference Hall



2nd Floor, Foyer



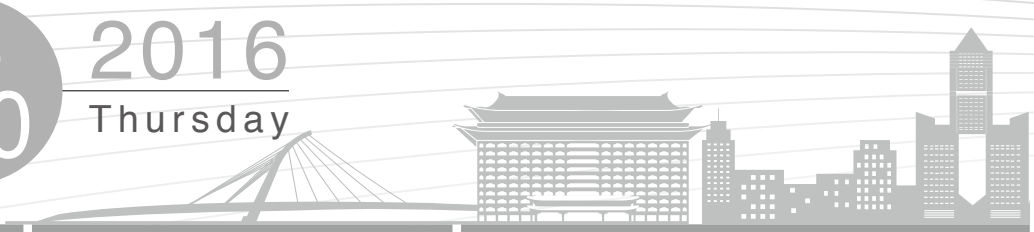
June 29 2016 Wednesday

Conference Information

Time	Subject	Moderator /Speaker
08:30-09:30	**Registration**	
09:30-09:40	**Opening Remarks**	**Tzou-Yien Lin** Minister, Ministry of Health and Welfare, Chinese Taipei
09:40-09:50	**Group Photo** (Invited Guests)	
09:50-10:20	**Keynote Speech** **The Way Ahead to End DR-TB**	**Moderator** **Steve Hsu-Sung Kuo** Director-General, Centers for Disease Control, Chinese Taipei **Speaker** **Susan Maloney** Chief, Global TB Branch, Division of Global HIV and TB, Center for Global Health, Centers for Disease Control and Prevention, the United States
10:20-10:40	**Coffee Break**	
Session I	**Sharing APEC Members Experiences on Programmatic Management of DR-TB**	**Moderator** **Chen-Yuan Chiang** Consultant, Department of Tuberculosis and HIV, International Union Against Tuberculosis and Lung Disease
10:40-11:00	**PMDT in China Economy**	**Yunzhou Ruan** Vice Director, Drug-resistant TB Control, Chinese Center for Disease Control and Prevention, China
11:00-11:20	**Addressing MDR-TB: The Philippine Experience**	**Rosalind G. Vianzon** Division Chief, Disease Prevention and Control Bureau, Department of Health, the Philippines
11:20-11:40	**PMDT in Japan**	**Takashi Yoshiyama** Deputy Head, Respiratory Diseases Center, Fukujuji Hospital, Japan
11:40-12:00	**PMDT in Chinese Taipei Economy**	**Anita Pei-Chun Chan** Medical Officer, Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
12:00-12:30	**Panel Discussion**	
12:30-13:50	**Lunch Break**	

Time	Subject	Moderator /Speaker
Session II	**Deepening Understanding of DR-TB Prevention, Control and Care Measures**	**Moderator** **Yi-Wen Huang** President, Taiwan Society of Tuberculosis and Lung Disease, Chinese Taipei **Rosalind G. Vianzon** Division Chief, Disease Prevention and Control Bureau, Department of Health, the Philippines
13:50-14:10	**DRS and Molecular Epidemiological Study in Mainland China**	**Yanlin Zhao** Vice Director, Chinese Center for TB Control and Prevention, Chinese Center for Disease Control and Prevention, China
14:10-14:30	**Introducing Novel Diagnostic Tools to Fortify Laboratory Capacity: Experience from Chinese Taipei Economy**	**Ruwen Jou** Director, Tuberculosis Research Center, Centers for Disease Control, Chinese Taipei
14:30-15:10	**Reinforcing Surveillance System of Drug-Resistant Tuberculosis**	**Peter Cegielski** Team Leader, Global TB Branch, Division of Global HIV and TB, Centers for Disease Control and Prevention, the United States **Chawetsan Namwat** Director, Bureau of Tuberculosis, Department of Disease Control, Thailand
15:10-15:30	**Coffee Break**	
15:30-16:30	**Promising Specialized and Friendly Patient-Centered Care**	**Hoang Thi Thanh Thuy** Focal Person, Programmatic Management of Drug-Resistant Tuberculosis, National TB Programme, Vietnam **Hyungseok Kang** Director, Department of Chest Medicine, Masan National Hospital, Republic of Korea **Chou-Jui Lin** Attending Physician, Taoyuan General Hospital, Ministry of Health and Welfare, Chinese Taipei
16:30-17:00	**Panel Discussion**	
17:00-17:20	**Group Photo** (All Participants)	
18:00-20:00	**Welcome Party** (Invited Only)	

June 30 2016 Thursday



Time	Subject	Moderator /Speaker
08:30-09:30	Registration	
Session III	Taking Action to Secure Supply of Second Line Drugs	**Moderator** **Jen Suo** Physician, Taiwan Anti-Tuberculosis Association, Chinese Taipei **Peter Cegielski** Team Leader, Global TB Branch, Division of Global HIV and TB, Centers for Disease Control and Prevention, the United States
09:30-10:00	Access to Quality and Affordable Drugs through the Global Drug Facility	**Kaspars Lunte** Team Leader, Global Drug Facility, Stop TB Partnership
10:00-10:30	Supply Chain Management: Tackling Challenges to Secure Second Line Drugs at Regional and Country Levels	
10:30-10:50	Coffee Break	
10:50-11:20	Supply Chain Management of Second Line Drugs: Russian Example	**Vadim Testov** Leading Researcher, Central TB Research Institute, Russian Federal Agency of Scientific Organizations, Russia
11:20-11:50	Novel Regimen Options for DR-TB Treatment	**Chen-Yuan Chiang** Consultant, Department of Tuberculosis and HIV, International Union Against Tuberculosis and Lung Disease
11:50-12:20	Panel Discussion	
12:20-12:30	Closing Remarks	**Steve Hsu-Sung Kuo** Director-General, Centers for Disease Control, Chinese Taipei
12:30-13:30	Lunch Break	
Session IV	Site Visit to Taiwan MDR-TB Consortium (Invited Only)	**Place: Taipei Municipal Wan Fang Hospital**
14:00-14:30	Patient Centered Care of DR-TB Cases - TMTC experiences	**Kuan-Jen Bai** Vice Director, Taipei Municipal Wan Fang Hospital, Chinese Taipei
14:30-15:30	Visiting Negative Pressure Isolation Wards	**Ming-Chih Yu** Vice Director, Taipei Municipal Wan Fang Hospital, Chinese Taipei
15:30-16:00	Panel Discussion	

Opening Remarks Speaker

Tzou-Yien Lin

Position: Minister
Department/Organisation: Ministry of Health and Welfare
Economy: Chinese Taipei

Educational Background

- Fellow, Pediatric Infectious Diseases, Children's Medical Center, Dallas University of Texas Health Science Center at Dallas, 1982-1984
- Fellow, Pediatric Infectious Diseases, Buffalo Children's Hospital, State University of New York at Buffalo, 1981-1982
- M.D., Taipei Medical College, 1966-1973

Professional Experience

- Distinguished Professor, Chang Gung University, College of Medicine, 2015 Dec. to Now
- Emeritus Superintendent, Chang Gung Children's Medical Center, 2015 Dec. to Now
- Political Deputy Minister, Ministry of Health and Welfare, 2013-2015
- Deputy Minister, Department of Health, Executive Yuan, 2011-2013
- Professor, Chang Gung University Medical College, 2003-2011
- Superintendent, Chang Gung Children's Hospital, 1997-2011
- Deputy Superintendent, Chang Gung Children's Hospital, 1993-1997
- Associate Professor, Chang Gung University Medical College, 1989-2003
- Attending Pediatrician, Chang Gung Memorial Hospital & Chang Gung Children's Hospital, 1984-2011

Recent Publications

- Chang SC, Li WC, Huang KY, Huang YC, Chiu CH, Chen CJ, Hsieh YC. Kuo CY, Shih SR, Lin TY*. Efficacy of alcohols and alcohol-based hand disinfectants against human enterovirus 71. J Hosp Infect 2013;83:288-93. (Corresponding author)
- Chen CJ, Lee PI, Chang SC, Huang YC, Chiu CH, Hsieh YC, Chang SC, Chang FY, Lee JJ, Su SC, Shen GH, Chuang YC, Chen YS, Liu JW, Lin TY*. Seroprevalence and severity of 2009 pandemic influenza A H1N1 in Taiwan. PLoS One 2011;6(9):e24440. (Corresponding author)
- Chen CC, Kong MS, Lai MW, Chao HC, Chang KW, Chen SY, Huang YC, Chiu CH, Li WC, Lin PY, Chen CJ, Lin TY*. Probiotics have clinical, microbiologic, and immunologic efficacy in acute infectious Diarrhea. Pediatr Infect Dis J 2010;29(2):135-8. (Corresponding author)
- Hsieh YC, Lin PY, Chiu CH, Huang YC, Chang KY, Liao CH, Chiu NC, Chuang YC, Chen PY, Chang SC, Liu JW, Yen MY, Wang JH, Liu CY, Lin TY*. National survey of invasive pneumococcal diseases in Taiwan under partial PCV7 vaccination in 2007: Emergence of serotype 19A with high invasive potential. Vaccine 2009;27:5513-8. (Corresponding author)
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Over 308 monographs

Keynote Speech

Moderator:

Steve Hsu-Sung Kuo

Director-General, Centers for Disease Control, Chinese Taipei

Speaker:

Susan Maloney

Chief, Global TB Branch, Division of Global HIV and TB, Center for Global Health, Centers for Disease Control and Prevention, the United States

Moderator

Steve Hsu-Sung Kuo

Position: Director-General
Department/Organisation: Centers for Disease Control
Economy: Chinese Taipei

Educational Background

- SEF. 2002 John F. Kennedy School of Government, Harvard University, U.S.A.
- Ph.D. 1987-91 Department of Epidemiology and Public Health, School of Medicine, Yale University, U.S.A.
- M.P.H.1982-84 College of Public Health, National Taiwan University, Chinese Taipei
- M.D. 1975-82 National Yang-Ming Medical College, Chinese Taipei

Professional Experience

- 2014-present Director-General, Centers for Disease Control, Ministry of Health and Welfare, Chinese Taipei
- 2010-2014 Senior Advisor, Taipei Economic and Cultural Representative Office (TECRO), Washington, D.C., U.S.A.
- 2004-2010 Director-General, Centers for Disease Control, Department of Health (currently known as Ministry of Health and Welfare), Chinese Taipei
- 2003 Chief Coordination Officer and Spokesman of the Taiwan SARS Task Force
- 1998-2002 Director-General, Bureau of Health Planning and Evaluation, Department of Health (currently known as Ministry of Health and Welfare), Chinese Taipei
- 1991-1998
  Secretary General, National Yang-Ming University, Chinese Taipei
  Associate Dean, Faculty of Medicine, National Yang-Ming University, Chinese Taipei
  Associate Professor, Epidemiology and Medicine, National Yang-Ming University, Chinese Taipei

Recent Publications

- Lu CY, Ni YH, Chiang BL, Chen PJ, Chang MH, Chang LY, Su IJ, Kuo HS. Humoral and cellular immune responses to a hepatitis B vaccine booster 15-18 years after neonatal immunization. J Infect Dis. 2008, 197(10):1419-26.
- Chan PC, Huang LM, Kuo HS. Is neonatal bacillus calmette-guerin vaccination protective in Taiwan? J Formos Med Assoc. 2008, 107(3):195-7. No abstract available.
- Chang CM, Lin WC, Kuo HS. Estimation and prediction system for multi-state disease process: application to analysis of organized screening regime. J Eval Clin Pract. 2007, 13(6):867-81.
- Wang TH, Wei KC, Hsiung CA, Maloney SA, Eidex RB, Posey DL, Chou WH, Shih WY, Kuo HS. Optimizing severe acute respiratory syndrome response strategies: lessons learned from quarantine. Am J Public Health. 2007, 97 Suppl 1:S98-100.
- Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev. 2006;28:126-35.

Speaker

Susan Maloney

Position: Chief
Department/Organisation: Global TB Branch, Division of Global HIV and TB, Center for Global Health, US Centers for Disease Control and Prevention
Economy: the United States

Educational Background

- BS, MD, MHSc.

Professional Experience

- Chief, Global TB Branch, CDC
- Global TB Coordinator, CDC
- Director, Global Disease Detection Centers for Disease Control and Prevention, US CDC, Bangkok, Thailand

Recent Publications

- Chuke SO, Yen NTN, Laserson KF, Phuoc NH, Trinh NA, Nhung DTC, Mai VTC, Qui AD, Hai HH, Loan LTH, Jones WG, Whitworth WC, Shah JJ, Painter JA, Mazurek GH, Maloney SA. Tuberculin Skin Tests versus Interferon-Gamma Release Assays in Tuberculosis Screening among Immigrant Visa Applicants. Tuberculosis Research and Treatment; vol 2014, Article ID 217969, 11 pages, http://dx.doi.org/10.11155/2014/217969 (published March 7, 2014).
- Watt G, Pachirat O, Baggett HC, Maloney SA, Lulitanond V, Raolt D, Bhengsri S, Thamthitiwat S, Paupairoj A, Kosoy M, Ad-Ai N, Sukwicha Q, Whistler T, Fournier PE. Infective Endocarditis in Northeastern Thailand. Emerging Infectious Diseases, Vol 20, No. 3, March 2014. DOI: http://dx.doi.org/10.3201/eid2003.131059
- Hasan R, Rhodes J, Thamthitiwat S, Olsen SJ, Prapasiri P, Naorot S, Chittaganpitch N, Henchaichon S, Dejsirilert S, Srisaengchai P, Sawatwong P, Jorakate P, Kaewpwan A, Fry A, Erdman D, Chuananon S, Amorintapicket T, Maloney SA, Baggett HC. Incidence and Etiology of Acute Lower Respiratory Tract Infections in Hospitalized Children Younger Than 5 Years in Rural Thailand. The Pediatric Infectious Disease Journal, Vol 32, November 2013.
- Porter KA, Rhodes J, Dejsirilert S, Henchaichon S, Siludjai D, Thamthitiwat S, Prapariri P, Jorakate P, Kaewpan A, Peruski LF, Maloney SA, Baggett HC. Acinetobacter Bacteremia in Thailand: Evidence for infections outside the hospital setting. Epidemiol Infect 201 Jun;142 (6): 1317-27. Doi: 10. 1017/S0950268813002082. Epub 2013 Sep 4.
- Painter JA, Graviss EA, Hai HH, Nhung DTC, Nga TT, Ha NP, Wall J, , Reeves R, TBESC TO20 Workgroup (Loan LTH, Parker M, Manangan L, Nga TTT, O'Brein R, Maloney SA, Hoekstra RM). Tuberculosis screening by tuberculosis skin tests or Quantiferon –TB Gold In-Tube Assay among an immigrant population with a high prevalence of tuberculosis and BCG vaccination. PLoS One. 2013;8;e82727.
- Naorot S, Chittaganpitch M, Thamthitiwat S, Henchaichon S, Sawatwong P, Srisaengchai P, Lu Y, Chuananon S, Amornintapichet T, Chantra S, Erdman D, Maloney SA, Akarasewi P, Baggett HC. Hospitalizations for Acute Lower Respiratory Tract Infection Due to Respiratory Syncytial Virus in Thailand. The Journal of Infectious Diseases 2013:208(S3):S238-45).

Speech Abstract

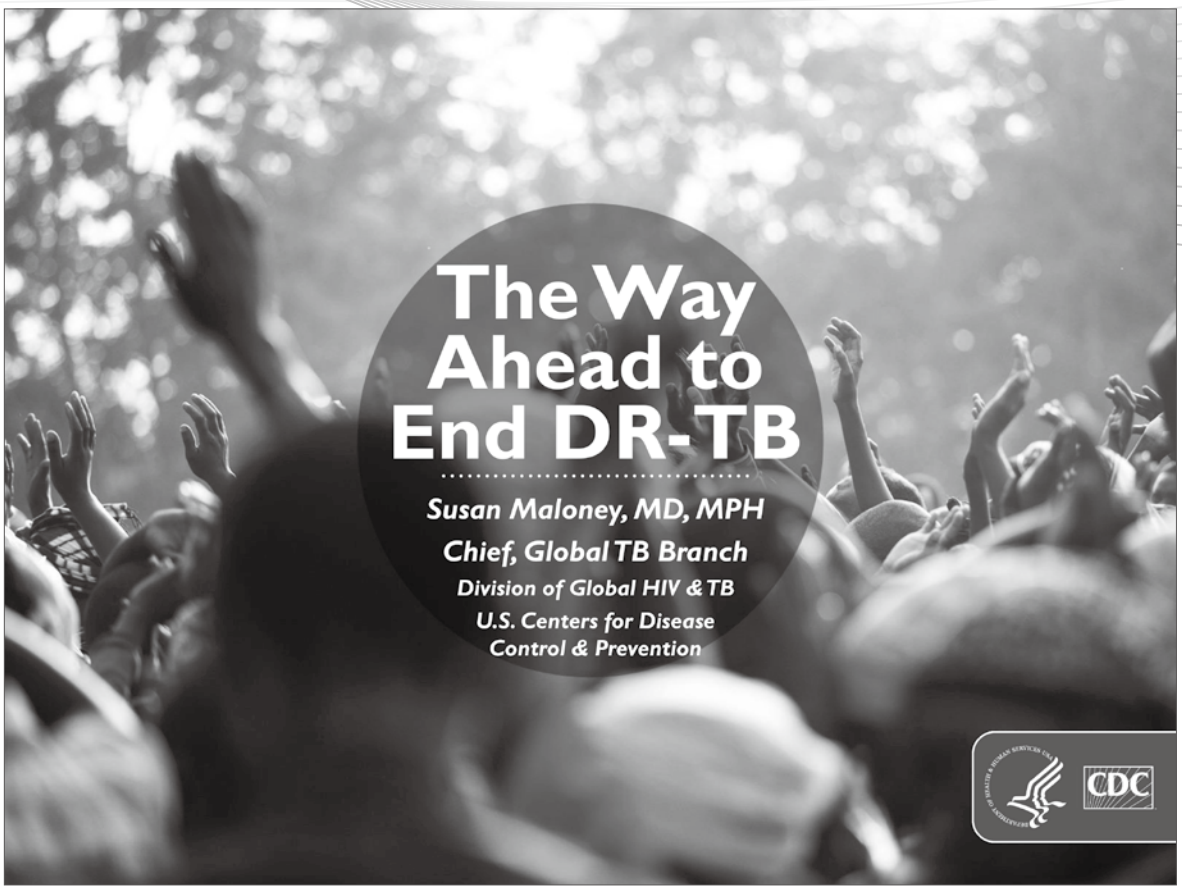
The Way Ahead to End DR-TB

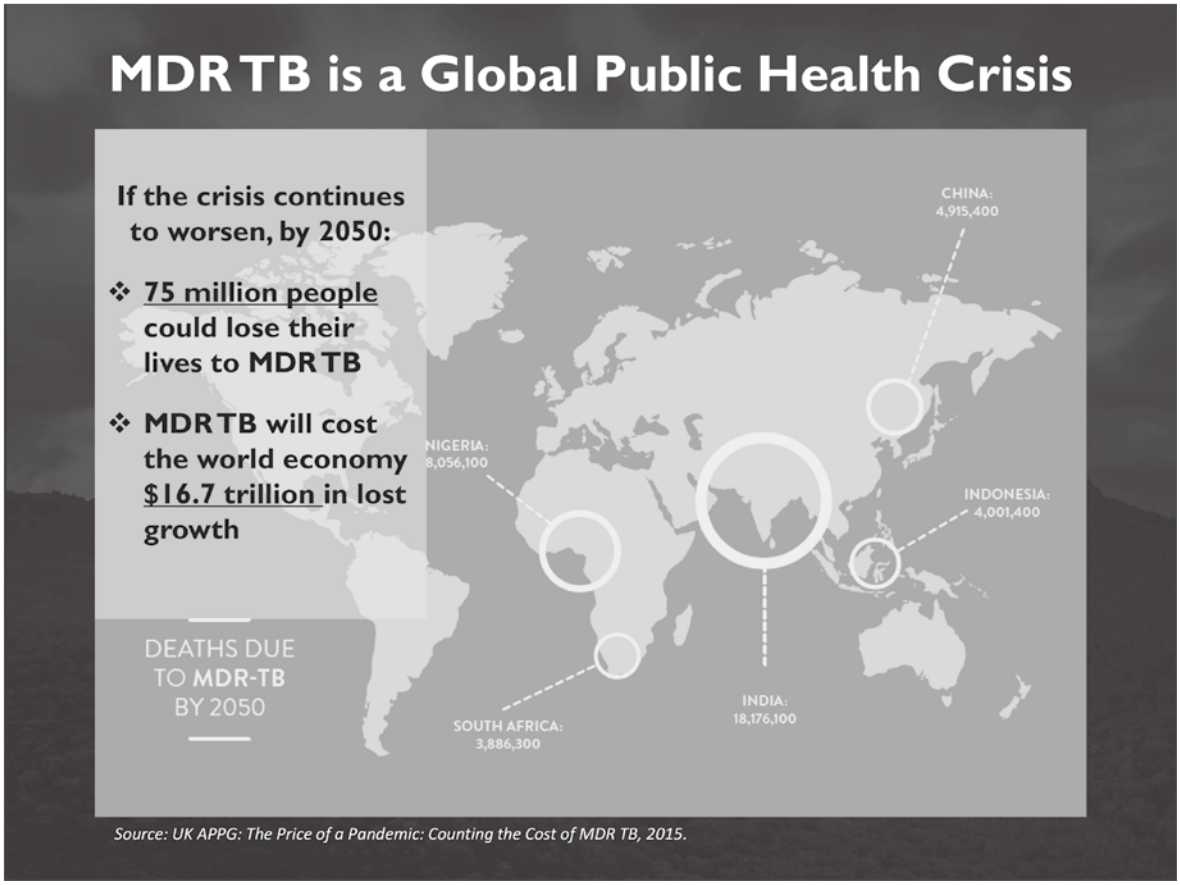
Susan Maloney, MD, MHSc

Chief

Global TB Branch, Division of Global HIV and TB, U.S. Centers for Disease Control and Prevention

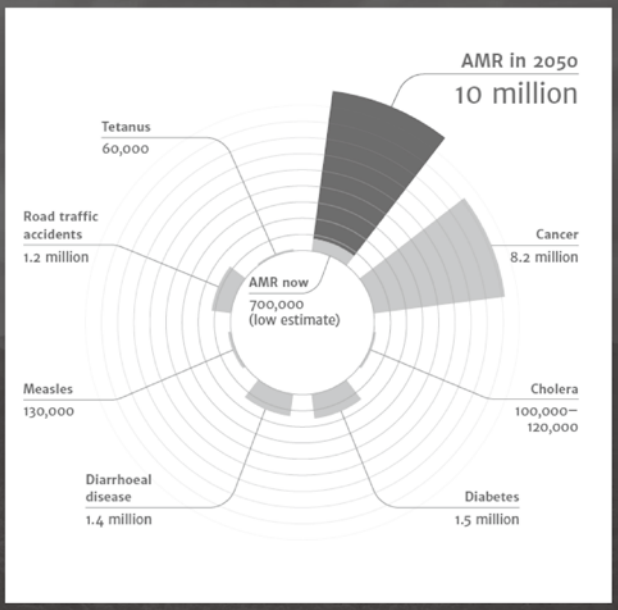
What is the scope of MDR TB? What are its costs – to the health system, to our economy, and in human lives? How did we get here? This presentation will discuss the global burden of TB and MDR TB. It will explore how weak health systems and inadequate oversight can breed drug resistance, and why MDR TB is such an alarming global health threat. While there has been much progress in recent years, this talk will discuss what's next and what the global health community can do to combat TB in all its forms.


The Way Ahead to End DR-TB
Susan Maloney, MD, MPH
Chief, Global TB Branch
Division of Global HIV & TB
U.S. Centers for Disease Control & Prevention
CDC


MDR TB is a Global Public Health Crisis
If the crisis continues to worsen, by 2050:
75 million people could lose their lives to MDR TB
MDR TB will cost the world economy $16.7 trillion in lost growth
DEATHS DUE TO MDR-TB BY 2050
CHINA: 4,915,400
NIGERIA: 8,056,100
INDONESIA: 4,001,400
INDIA: 18,176,100
SOUTH AFRICA: 3,886,300
Source: UK APPG: The Price of a Pandemic: Counting the Cost of MDR TB, 2015.

The Global Health Security Threat of Antimicrobial Resistance

- Modeling suggests that all AMR infections will outstrip all other major diseases by 2050 if left unchecked
- Drug-resistant TB accounts for nearly 30% of projected AMR disease and death – more than diabetes and diarrheal disease combined
- As strains grow more resistant, we have fewer and much older, more toxic drugs effective against them
- MDR TB is a primary AMR and global health security threat



Sources: UK Review on Antimicrobial Resistance: Tackling Drug-Resistant Infections Globally: Final Report and Recommendations, May 2016. Diabetes: www.whi.int/mediacentre/factsheets/fs312/en/ Cancer: www.whi.int/mediacentre/factsheets/fs297/en/ Cholera: www.whi.int/mediacentre/factsheets/fs107/en/ Diarrhoeal disease: www.sciencedirect.com/science/article/pii/So140673612617280 Measles: www.sciencedirect.com/science/article/pii/So140673612617280 Road traffic accidents: www.whi.int/mediacentre/factsheets/fs358/en/ Tetanus: www.sciencedirect.com/science/article/pii/So140673612617280

Outline

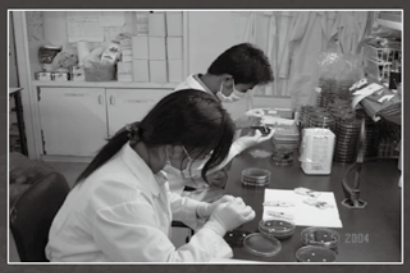
- **Global TB & MDR TB: What, Where, & Why**
- **MDR TB: Progress & Challenges to Date**
- **What's Needed to Reach Global Goals?**
  - Invest in global TB control
    - Scale-up what works
    - Engage all providers
    - Develop innovative new tools and strategies
- **Ending TB & MDR TB Together**

The Global Burden of TB

- **2 billion infected**
  - 1/3 of the world's population
- **9.6 million new TB cases/year**
  - >3 million cases missed each year
  - >80% of this burden concentrated in 30 highest burden countries
  - 1 million cases among children;
  - 10 million children orphaned
- **1.5 million deaths from TB**
  - **Leading cause of death from infectious disease**
  - Leading cause of death among PLHIV

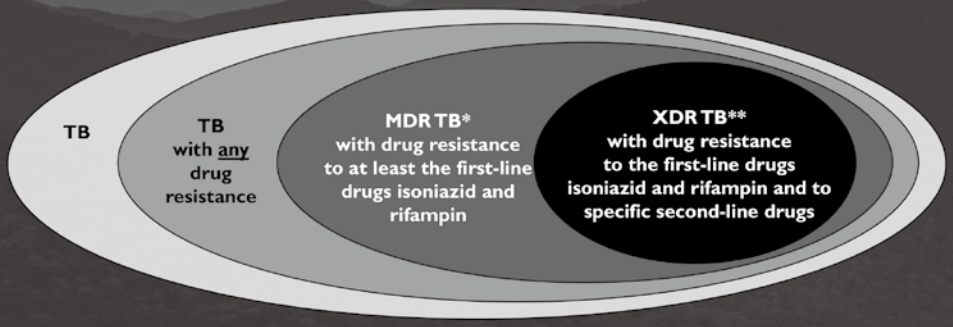
The Global Burden of MDR TB

- **480,00 cases of multidrug-resistant (MDR) TB**
  - 190,000 deaths
- **Extensively drug-resistant (XDR) TB identified in 105 countries**
  - An estimated 50,000 XDR TB cases worldwide
- **Diagnostic and treatment gaps are dramatic**
  - 1 in 4 MDR TB cases were diagnosed in 2014
  - 1 in 5 MDR TB cases were on treatment in 2014
  - **1 in 10 MDR TB** cases were successfully treated



What You Should Know about MDR and XDR TB

- Naturally evolves in a small number of cases but amplified by inadequate therapy of drug-susceptible TB
- Both are more common if the initial treatment regimen is inadequate or adherence is poor, but they can also be transmitted.
- MDR and XDR TB often thrive where health systems are weak.



*Often resistant to additional drugs

**Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin

The Challenges of MDR TB Diagnosis & Treatment

- MDR TB takes weeks to months to diagnose
  - Diagnostic delays lead to inappropriate therapy which breeds further resistance and treatment failures
- Traditional treatment for MDR and XDR TB involves
  - Treatment for up to 24 months
  - 15,000 pills and hundreds of injections
  - Long-term side effects (e.g. hearing loss)
  - $150-500,000 per patient in the U.S.; 17-20x as expensive as drug-susceptible TB around the world
  - Patients may require prolonged isolation and hospitalization

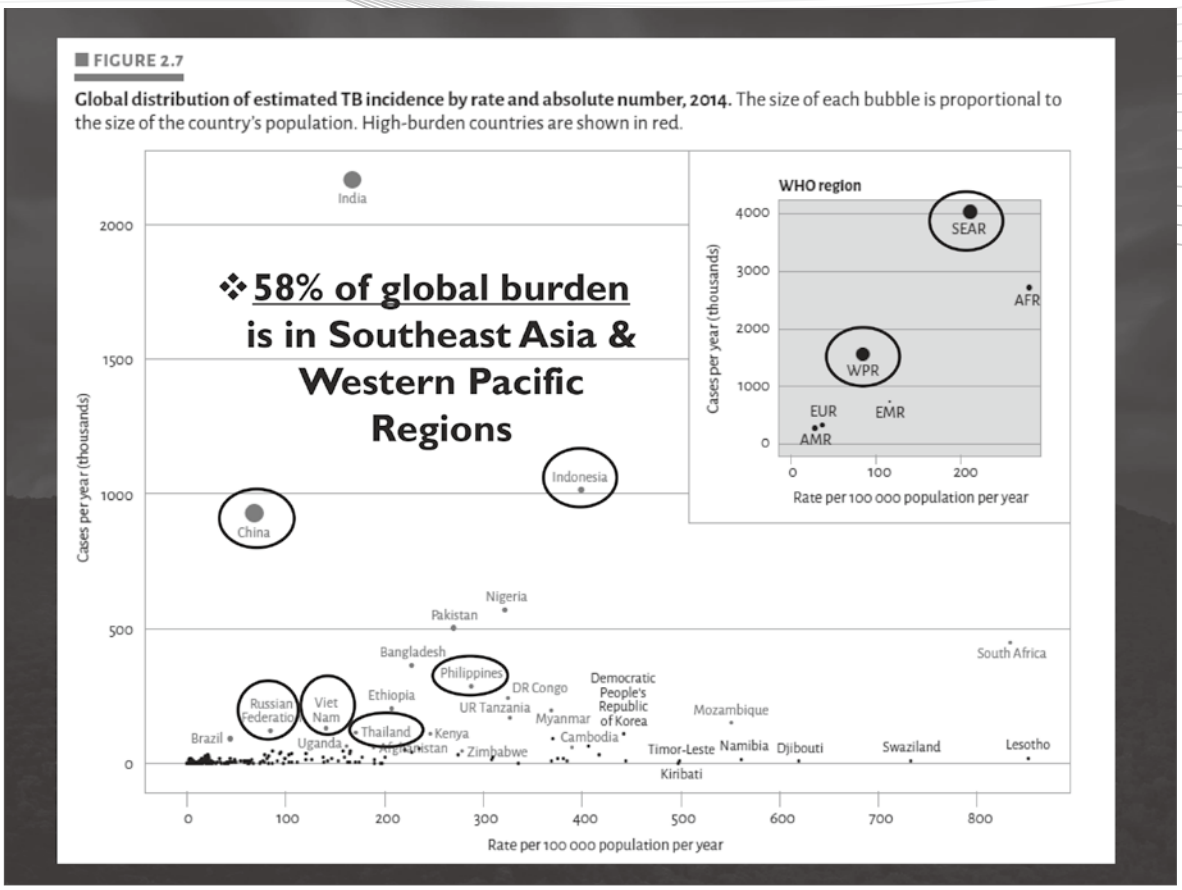
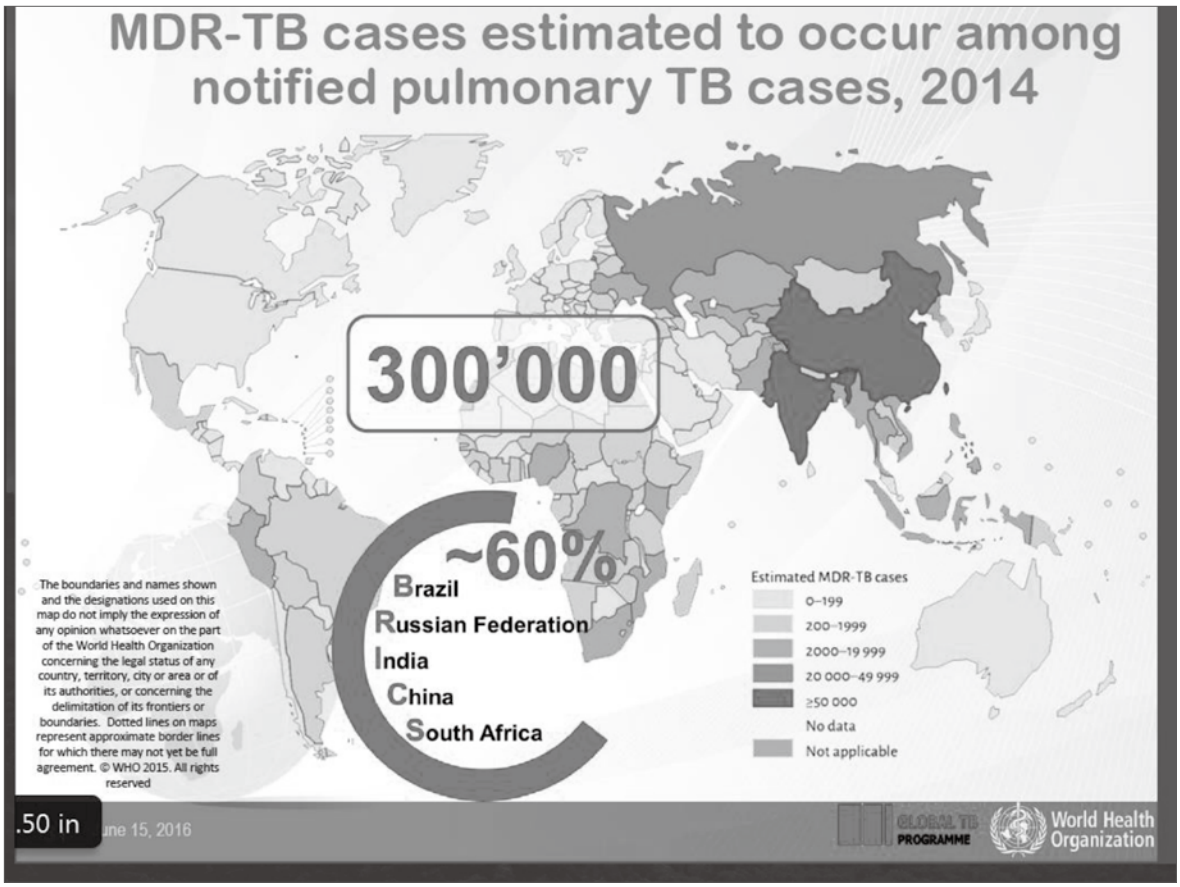


FIGURE 2.7
Global distribution of estimated TB incidence by rate and absolute number, 2014. The size of each bubble is proportional to the size of the country's population. High-burden countries are shown in red.
❖58% of global burden is in Southeast Asia & Western Pacific Regions
WHO region
SEAR
AFR
WPR
EMR
EUR
AMR
Cases per year (thousands)
Rate per 100 000 population per year
India
Indonesia
China
Nigeria
Pakistan
Bangladesh
Philippines
Ethiopia
DR Congo
UR Tanzania
Myanmar
Democratic People's Republic of Korea
Cambodia
Russian Federation
Viet Nam
Thailand
Kenya
Uganda
Zimbabwe
Brazil
Mozambique
South Africa
Timor-Leste
Namibia
Djibouti
Swaziland
Lesotho
Kiribati


MDR-TB cases estimated to occur among notified pulmonary TB cases, 2014
300'000
~60%
Brazil
Russian Federation
India
China
South Africa
Estimated MDR-TB cases
0–199
200–1999
2000–19 999
20 000–49 999
≥50 000
No data
Not applicable
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2015. All rights reserved
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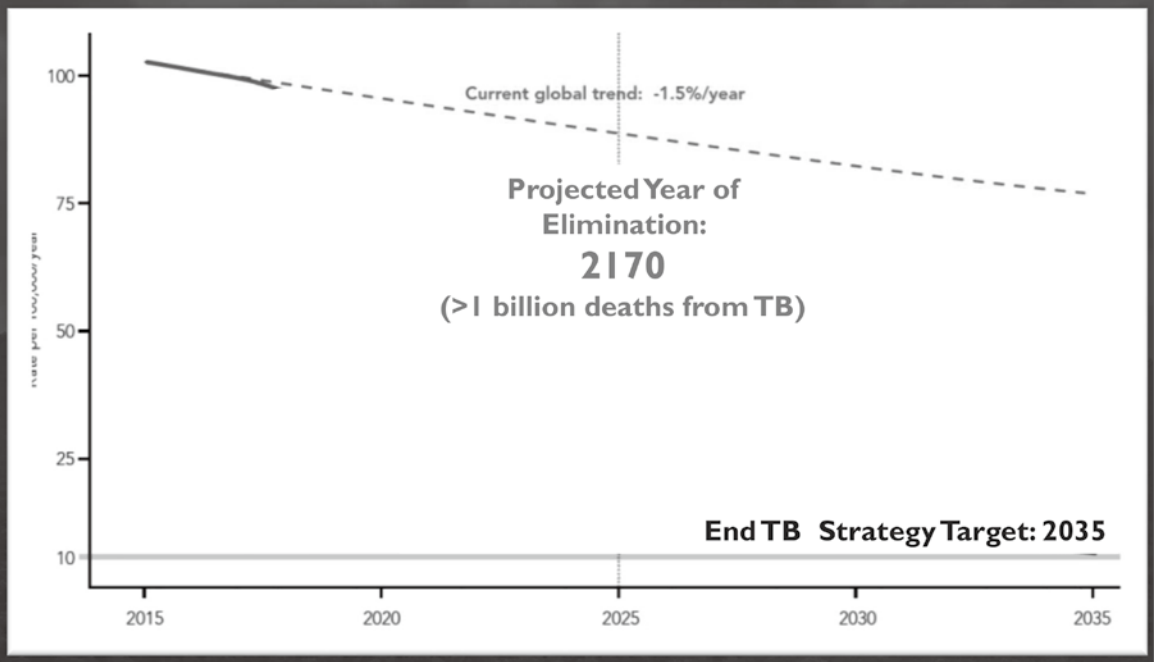
une 15, 2016
GLOBAL TB PROGRAMME
World Health Organization

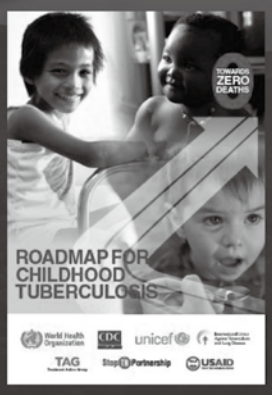
Progress Toward Ending TB:
Current Global TB Trend?

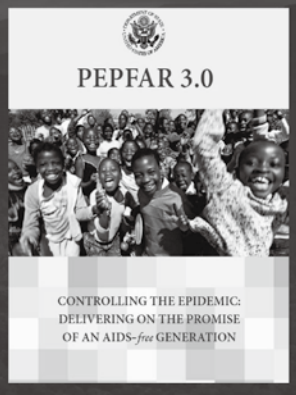


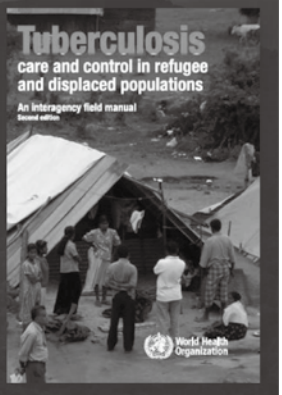
Source: WHO End TB Strategy & Stop TB Partnership Global Plan to End TB

How Did We Get Here: Key Challenges to Global TB Exacerbate the MDR TB Crisis

- Weak core TB programs and health systems
- The "missing" 3M
- HIV-associated TB
- Inadequate investment in new tools, technologies, and approaches



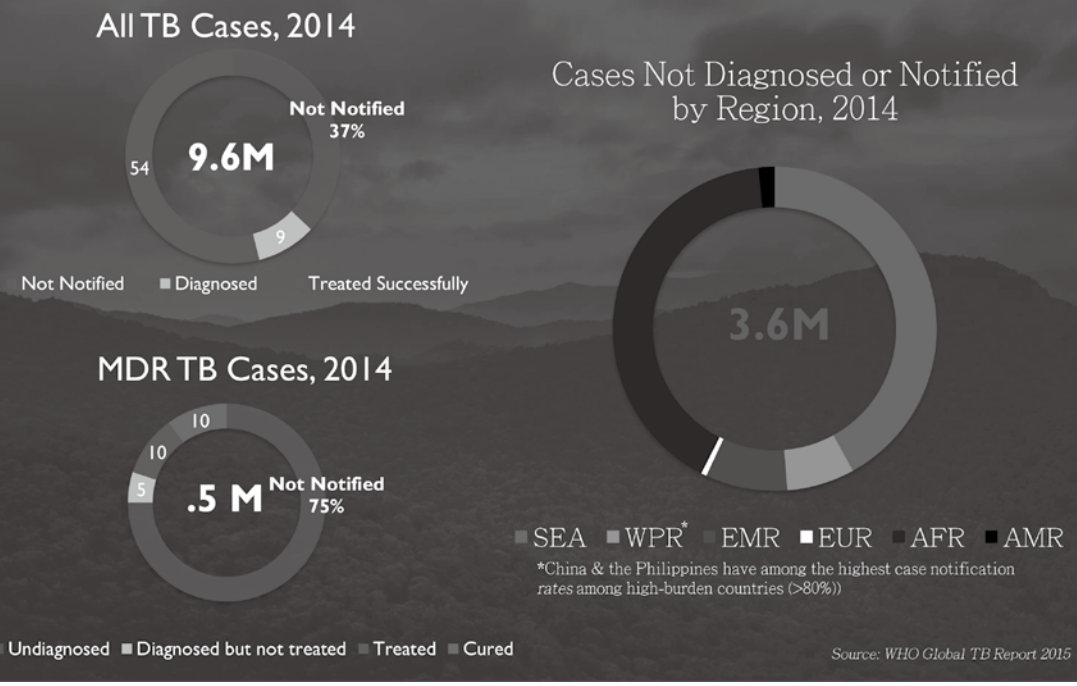




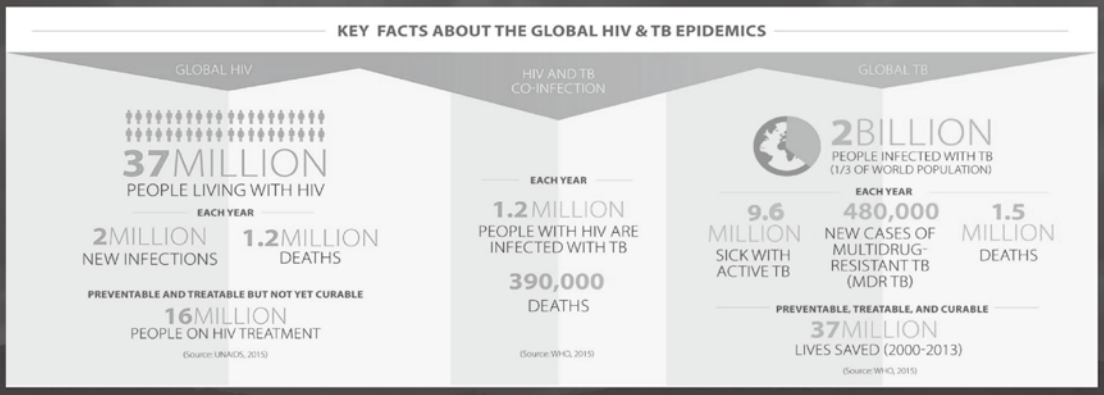
The Dual Threat: Weak Health Systems & Greater Transmission Routes

- **We can't treat MDR TB cases faster than poorly functioning health systems create it**
  - Inadequate, interrupted, or incomplete therapy breeds resistant strains
    - Drug supply chain causes interruptions in treatment
    - Inadequate oversight of private sector leads to mismanagement
    - Patients are unable to complete treatment course
- **Conditions are ripe for greater transmission**
  - Missed TB and MDR TB cases continue chain of transmission
  - Poor infection control in health facilities leads to transmission
  - Greater travel and migration leads more easily to cross-border transmission

Missed and Inadequately Treated Cases Lead to Transmission and Resistance

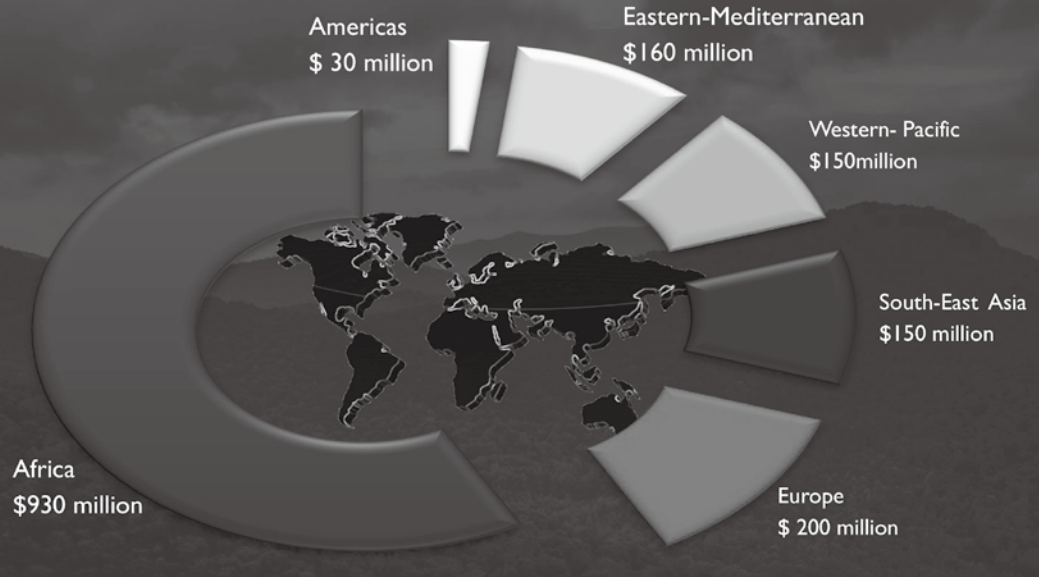


HIV-associated TB (TB/HIV)



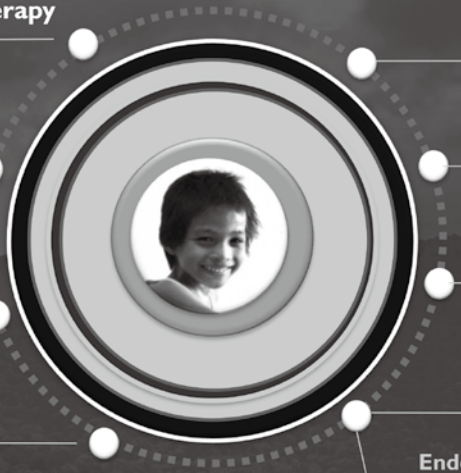
- In countries with high burdens of both diseases, HIV fuels transmission of TB and MDR TB and further complicates diagnosis while TB remains the #1 cause of death among PLHIV

Funding Gaps by Region per year, 2014-16



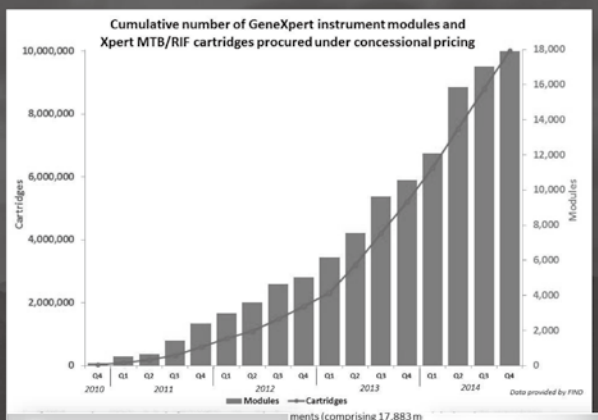
Reason to Hope: Progress & Momentum

- 43 million lives saved 2000-2014 through TB and TB/HIV therapy
- 8.4 million lives saved since 2000 through TB/HIV activities
- 66 M patients successfully treated, 1995-2014
- Incidence falling slowly (1.5%/yr)
- Xpert Rollout: 10 million cartridges delivered
- Doubling MDR TB Case Notifications since 2010
- Two New Anti-TB Drugs Approved for MDR TB
- WHO endorses shortened 9-12 mo. MDR regimen
- Endorsement of SL-LPA for rapid detection of second-line drug resistance



Xpert MTB/RIF®
A Revolution in TB Diagnosis?

- Automated molecular diagnostic test for TB and resistance to rifampicin
- Produces results in hours vs. weeks
- Performs better among PLHA
- 10M cartridges & 18,000 modules by 2015
- Case notifications doubled
- Xpert Omni & Ultra



Xpert: Promise & Reality

Articles

Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF

Summary

Introduction

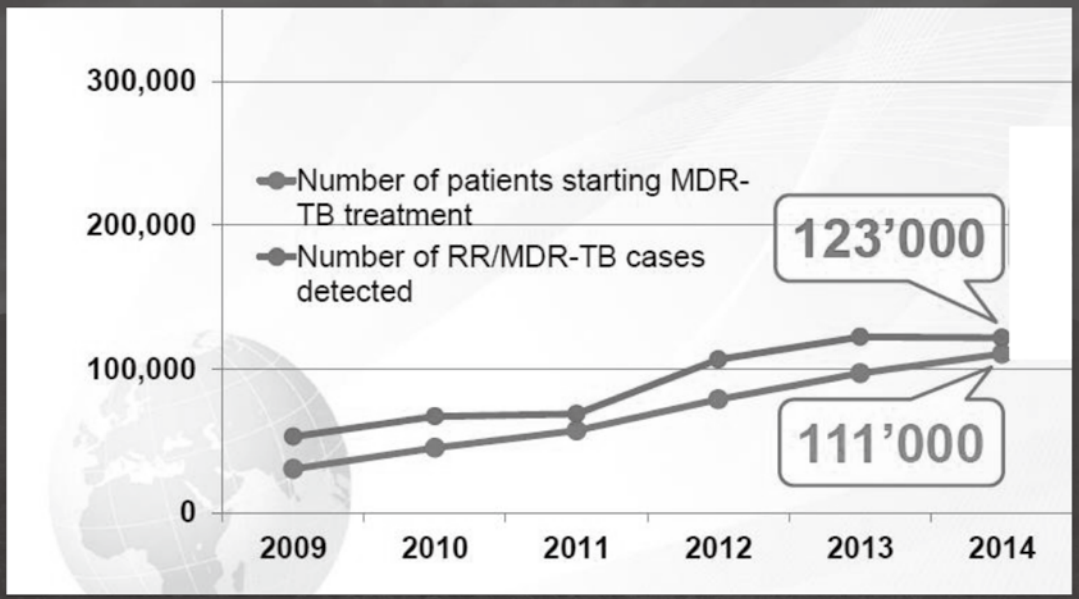
Methods

Study design

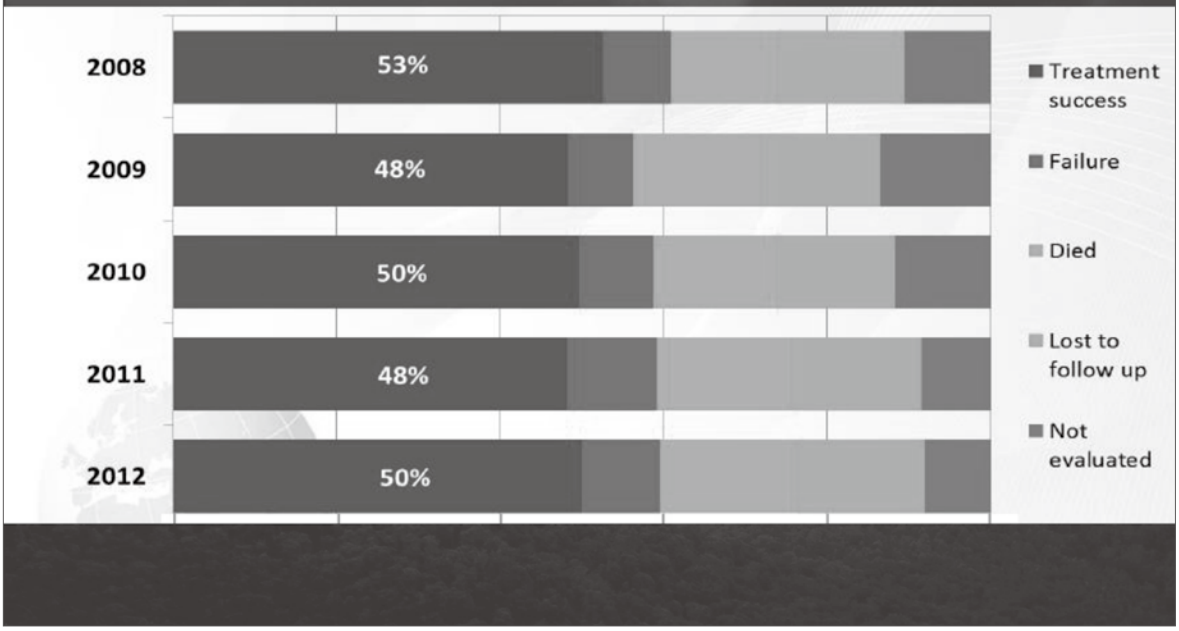
"Xpert did not reduce mortality at 6 months compared with sputum microscopy. Improving outcomes in drug-sensitive tuberculosis programmes might require not only better diagnostic tests but also better linkage to care."

- **Promise of new diagnostics must be paired with strong systems:**
  - Clinician education and outreach
  - Expanded patient access to diagnosis
    - Located at most-accessed facilities
    - Case finding for hard-to-reach populations
    - Strong specimen referral and transport
  - Faster, reliable results reporting mechanisms
  - Ensuring linkage to care and treatment
  - Supply chain systems for forecasting, shipping, monitoring first and second-line drugs

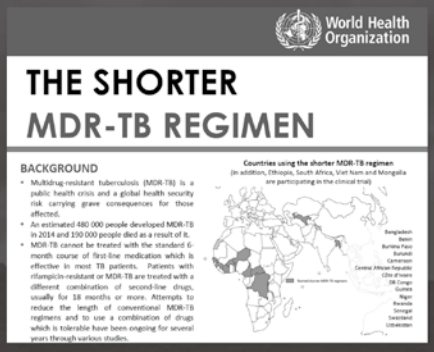
DR-TB Notification and Treatment Initiation, 2009-2014



Outcomes of MDR TB Treatment 2008-2012



New Anti-TB Drugs & Treatment Regimens


World Health Organization

THE SHORTER MDR-TB REGIMEN

BACKGROUND

- Multidrug-resistant tuberculosis (MDR-TB) is a public health crisis and a global health security risk carrying grave consequences for those affected.
- An estimated 480 000 people developed MDR-TB in 2014 and 190 000 people died as a result of it.
- MDR-TB cannot be treated with the standard 6-month course of first-line medication which is effective in most TB patients. Patients with rifampicin-resistant or MDR-TB are treated with a different combination of second-line drugs, usually for 18 months or more. Attempts to reduce the length of conventional MDR-TB regimens and to use a combination of drugs which is tolerable have been ongoing for several years through various studies.

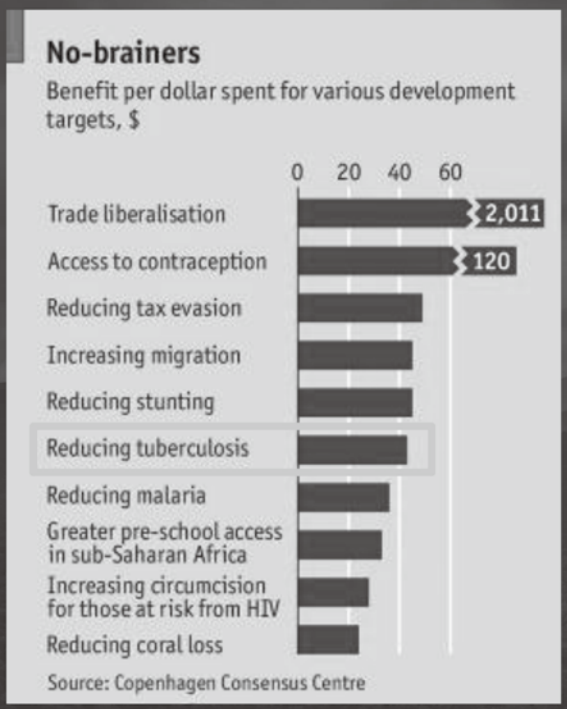
Countries using the shorter MDR-TB regimen (in addition, Ethiopia, South Africa, Viet Nam and Mongolia are participating in the clinical trial)

- **Shorter MDR TB Regimens, 2016**
  - 9-12 months for some patients; <$1,000/course
- **First Pediatric Formulations, 2016**
- **Bedaquiline & Delaminid, 2013-2014**
  - First new anti-TB drugs in nearly 40 years;
  - CDC/WHO developed domestic and international guidance on rational use
- **Shorter LTBI Treatment Regimens, 2011**
  - CDC-led study: once weekly, 12-dose with INH and Rifapentine was as effective and more often completed than 9-mo. traditional therapy; Now regimen recommended as equal alternate

WHERE DO WE GO FROM HERE?

Ending TB and MDR TB

Investment in TB is a "No Brainer"



An Expert panel including 2 Nobel Laureates identified 19/169 Sustainable Development Targets representing the best value for money for 2016-2030

- Focus on these first would effectively quadruple the aid budget without extra spending
- Reducing TB deaths by 95% would result in a $43 gain in environmental, economic and social benefits per $ spent

Sources: Copenhagen Consensus Center; The Economist- Jan 24 2015

Ambitious Global Targets & Milestones

THE END TB STRATEGY

World Health Organization

Global strategy and targets for tuberculosis prevention, care and control after 2015

Reach at least **90%** OF ALL PEOPLE WITH TB and place all of them on appropriate therapy—first-line, second-line and preventive therapy as required

As a part of this approach, reach at least **(90)%** OF THE KEY POPULATIONS the most vulnerable, underserved, at-risk populations

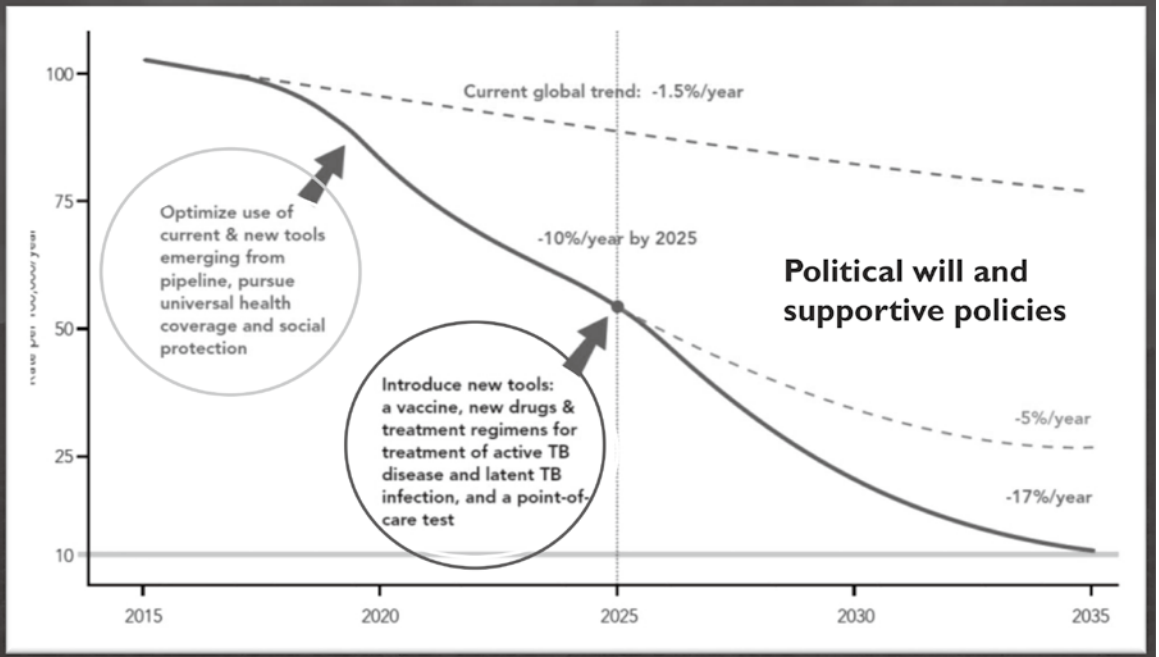
Achieve at least **90%** TREATMENT SUCCESS for all people diagnosed with TB through affordable treatment services, adherence to complete and correct treatment, and social support.

VISION	A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis			
GOAL	End the global tuberculosis epidemic			
INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

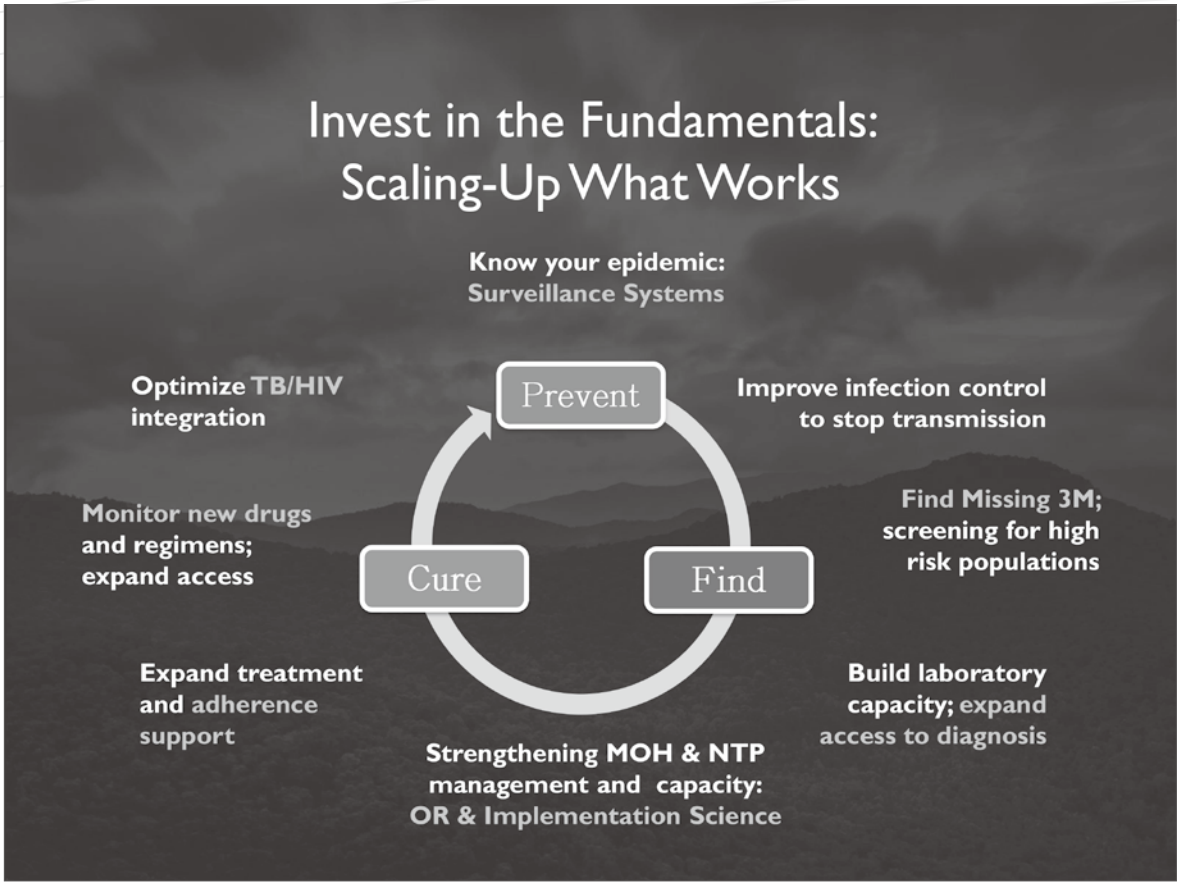
THE GLOBAL STRATEGY AND TARGETS FOR TUBERCULOSIS PREVENTION, CARE AND CONTROL AFTER 2015, WERE ENDORSED BY ALL MEMBER STATES AT THE 2014 WORLD HEALTH ASSEMBLY.

Accelerate Impact to End TB & MDR TB by 2035:

Scale-up What Works & Invest in Innovations



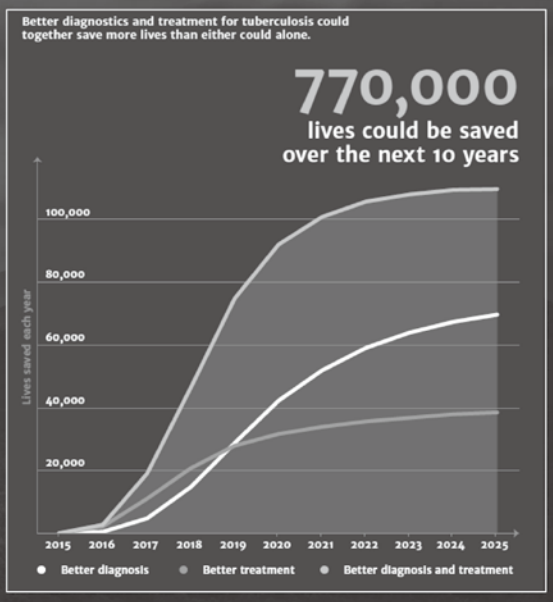
Source: WHO End TB Strategy & Stop TB Partnership Global Plan to End TB


Invest in the Fundamentals:
Scaling-Up What Works
Know your epidemic:
Surveillance Systems
Optimize TB/HIV integration
Prevent
Improve infection control to stop transmission
Monitor new drugs and regimens; expand access
Cure
Find
Find Missing 3M; screening for high risk populations
Expand treatment and adherence support
Build laboratory capacity; expand access to diagnosis
Strengthening MOH & NTP management and capacity:
OR & Implementation Science


Engaging All Sectors
Framework for the engagement of all health care providers in the management of drug resistant tuberculosis
THE END TB STRATEGY
World Health Organization
• We must put effective tools and strategies in the hands of all providers and link them with the public sector:
– Private physicians
– Private pharmacies
– Traditional healers and health workers
– Lay health workers

Investing in Innovations to Bend the Curve

- Rapid, mobile, POC diagnostics
  - Urine, blood, breath, sweat
- New treatments
  - New therapies and drugs for all forms of TB
  - Novel treatment regimens for adults and children
  - Alternative treatment delivery (e.g. depo, transdermal)
- An effective vaccine



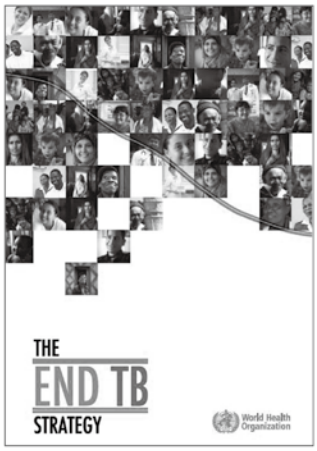
Source: Arinaminpathy N, 2016, www.amr-review.org

A Reminder of What it Takes to Innovate

- **Greatest R&D leaps in past ten years:**
  - Novel drugs
  - Novel treatment regimens
  - Novel drug formulations
  - Novel diagnostic tests

… but without core health systems, implementation science, and technical support, the impact is variable or non-existent

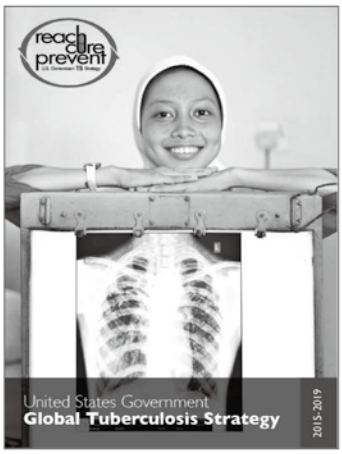
USG Efforts Build Upon Existing Strategies & Plans



World Health Organization

Stop TB Partnership

International Union Against Tuberculosis and Lung Disease



CDC USAID NIH

CDC USAID NIH

Many Nations. One Mission.

DEATHS DUE TO **MDR-TB** BY 2050

Session I

Sharing APEC Members Experiences on Programmatic Management of DR-TB

Moderator

Chen-Yuan Chiang
Consultant, Department of Tuberculosis and HIV, International Union Against Tuberculosis and Lung Disease

Moderator

Chen-Yuan Chiang

Position: Consultant

Department/Organisation: Department of Tuberculosis and HIV, International Union Agaihts, International Union Against Tuberculosis and Lung Disease, Paris, France

Educational Background

- Doctor Philosophiae (DrPhilos), University of Bergen, Norway
- Master of Public Health (MPH), School of Public Health, University of California, Berkeley, USA
- MD, Kaohsiung Medical University, Chinese Taipei

Professional Experience

- Consultant, Department of Tuberculosis and HIV, The Union, Paris, France
- Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Chinese Taipei
- Associate Professor, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Chinese Taipei

Recent Publications

- Chiang C-Y, Van Deun A, Rieder HL. Gatifloxacin for short and effective treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2016 (in press).
- Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y, Keshavjee S, Koh W-J, Shiraishi Y, Viiklepp P, Yim J-J, Pasvol G, Robert J, Shim YT, Shin SS, Menzies D, on behalf of "The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB". Surgery as an adjunctive treatment for multi-drug resistant tuberculosis: an individual patient data meta-analysis. Clin Infect Dis. (2016) doi: 10.1093/cid/ciw002.
- Lo H-Y, Yang S-L, Lin H-H, Bai K-J, Lee J-J, Lee T-I, Chiang C-Y. Does enhanced diabetic management reduce the risk and improve the outcome of tuberculosis? Int J Tuberc Lung Dis 2016; 20(3):376–382.
- Lai T-C, Chiang C-Y, Wu C-F, Yang S-L, Liu D-P, Chan C-C, Lin H-H. Ambient air pollution and risk of tuberculosis: a cohort study. Occup Environ Med 2016;73(1):56-61.
- Chiang C-Y, Yu M-C, Yang S-L, Yen M-Y, Bai K-J. Surveillance of tuberculosis in Taipei: the influence of nontuberculous mycobacteria. PLoS One 10(11): e0142324. doi:10.1371/journal.pone.0142324.

APEC CONFERENCE ON PREVENTION, CONTROL AND CARE FOR

MDR-TB AND SUPPLY OF 2nd-LINE ANTI-TB DRUG

Speaker

Yunzhou Ruan
Vice Director, Drug-resistant TB Control, Chinese Center for Disease Control and Prevention, China

Rosalind G. Vianzon
Division Chief, Disease Prevention and Control Bureau, Department of Health, the Philippines

Takashi Yoshiyama
Deputy Head, Respiratory Diseases Center, Fukujuji Hospital, Japan

Anita Pei-Chun Chan
Medical Officer, Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei

Speaker

Yunzhou Ruan

Position: Vice Director
Department/Organisation: Drug-resistant TB Control, Chinese Center for Disease Control and Prevention
Economy: China

Educational Background

- 2001-2007 Peking University, major in Public Health, Master & Phd
- 1992-1997 Zhejiang University, major in Public Health, Bachelor

Professional Experience

- 2009-now
  work in National Centers for TB Control and Prevention of Chinese Center for Disease Control and Prevention
- 2007-2009
  work in Hospital Management of China Health Economics Institute
- 1997-2001
  Public Health Doctor, work in Wenzhou Center for Disease Control and Prevention, ZheJiang Province

Recent Publications

- Y-Z. Ruan, R-Z. Li, L-X. Wang, et al. The affordability for patients of a new universal MDR-TB coverage model in China. INT J TUBERC LUNG DIS 2016, 20(5):638–644.
- R Li, Y Ruan, Q Sun, et al. Effect of a comprehensive programme to provide universal access to care for sputum-smear-positive multidrug resistant tuberculosis in China: a before-and-after study. Lancet Glob Health 2015, 3: e217–228.
- Lixia Wang, Hui Zhang, Yunzhou Ruan, et. Tuberculosis prevalence in China, 1990—2010; a longitudinal analysis of national survey data. The Lancet, 2014,383(9934):2057-2064.
- RUAN Yun-zhou, LI Ren-zhong, HAO Yang, et. The analysis of 119 cases of multidrug-resistant tuberculosis patients not enrolling for proper treatment in different financing models. Chinese Journal of Antituberculosis, 2014,36(5): 308-312.
- RUAN Yun-zhou, HE Guang-xue, WANG Li-xia, et. Analysis of the socio-economic status of 1301 tuberculosis cases. Chinese Journal of Antituberculosis, 2012, 34(9): 572-575.

Speaker

Rosalind Vianzon

Position: Division Chief
Department/Organisation: Disease Prevention and Control Bureau, Department of Health
Economy: the Philippines

Educational Background

- Doctor of Medicine (MD) and Masters in Public Health (MPH)

Professional Experience

- Rural Health Physician/ Municipal Health Officer
- DOH Representative
- Medical Specialist II – as TB Technical Staff
- Medical Specialist III – as TB Technical Staff
- Medical Specialist IV – as NTP Manager
- Division Chief – as Chief of Infectious Disease Prevention and Control Programs

Recent Publications

- Manual of Procedures, Philippine NTP, 5th edition.
- Philippine Plan of Action to Control TB, 2010-2016.
- Updated PhilPACT, 2013-2016.
- Jointr Program Review of the Philippine NTP, 2012-2013.

Speech Abstract

Addressing MDR-TB: The Philippine Experience

Rosaling G. Vianzon, Md, Mph

Division Chief

National TB Program, Disease Prevention and Control Bureau, Department of Health – Manila, the Philippines

Background:

With the upcoming change in the Philippine national leadership, the Department of Health is facing new directions in addressing the health issues of the country. This is also timely since the globe is transitioning from MDGs to SDGs; and specifically for TB Control Programs, a robust change is occurring with the implementation of the END TB Strategy. In the Philippines, the National Tuberculosis Control Program (NTP) is currently undertaking preparatory steps to adapt all these shifts; and addressing MDR-TB is a major task that the Program needs to uphold in the coming years.

Discussion:

Based on the latest Philippine drug resistance survey done in 2012, drug resistance is noted at 2% and 21% amongst the New and Retreatment cases respectively. While this shows a decline for the New cases as compared to the 2004 figure, no change is seen amongst the Retreatment ones. As of 2015, the total estimated number of MDR-TB cases is about 11,384 and only 4,788 (42%) have been detected by the NTP. There exist 120 Xpert facilities. But still, the challenge of the NTP is on finding the missing cases and thus, efforts should be focus on searching for them. Nonetheless, 85% of the detected are currently enrolled to MDRTB treatment. This is so because treatment services are already available and accessible across the country. A total of 121 Treatment and Satellite facilities have been established by the NTP from 2003 to 2015. While treatment is made available, there's utmost concern of a high Lost to Follow-up rate (40-45%) and consequently, a low Treatment Success. Primary causes are patient-related such as adverse drug reactions and financial difficulties.

The country's strategic plan, the Philippine Plan of Action or PhilPACT has defined targets to guide the stakeholders on how the Program needs to address MDRTB given the current accomplishments. The plan is ending this year and a new one for 2017-2022 is being developed. The recently concluded Joint Program Review (JPR) provides essential findings on MDRTB management that will be incorporated in the plan development.

Much of the support of NTP's scale-up efforts on MDRTB management is externally-funded. Support for diagnostics, treatment, ancillary services, technical assistances, human resources, operations are provided by international partners. On the other hand, domestic funding mainly goes for the management of drug susceptible TB. With transitions taking place at present, the NTP has started to take-on some of the costs as well as strategizing the scale-up to a more sustainable level. Local opportunities to increase NTP's budget are integrated into the development of the annual plan. Integration to related general health services are being explored, e.g. on infection control. However, provision for 2nd line drugs remains a big challenge for the Program and perhaps for the country. This concern should be addressed to ensure continuity of services that is critical in reducing the burden of MDRTB in the Philippines.

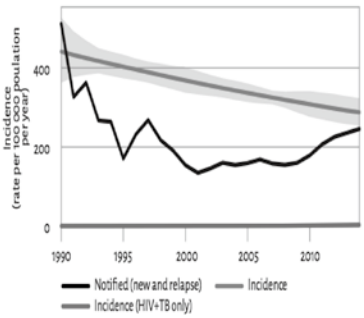
ADDRESSING MDR-TB:
The PHILIPPINE EXPERIENCE

For the APEC Conference on
Prevention, Control and Care of MDR-TB
And Supply of 2nd Line Anti-TB Drugs
Taiwan, June 29, 2016

ROSALIND G. VIANZON, MD, MPH
Division Chief, IDPCD
Disease Prevention and Control Bureau
Department of Health
Philippines

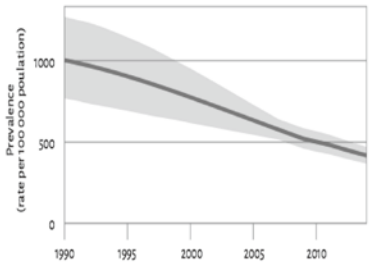
Philippines 2014 - Impact Indicators

Incidence



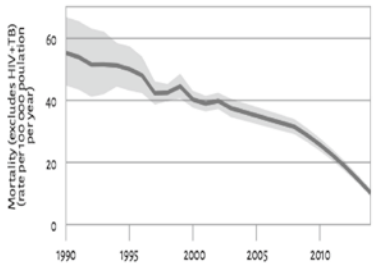
288/100,000
290,000 Filipinos

Prevalence



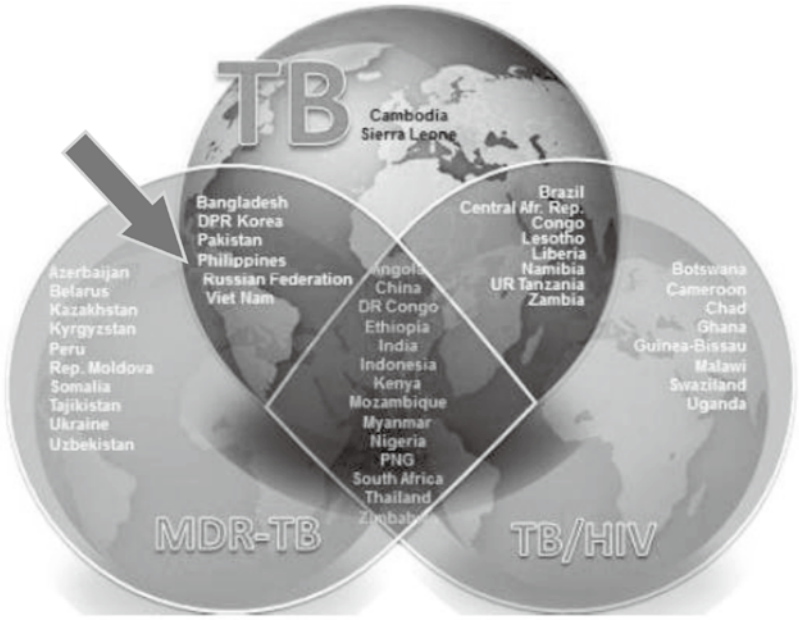
417/100,000
410,000 Filipinos

Mortality

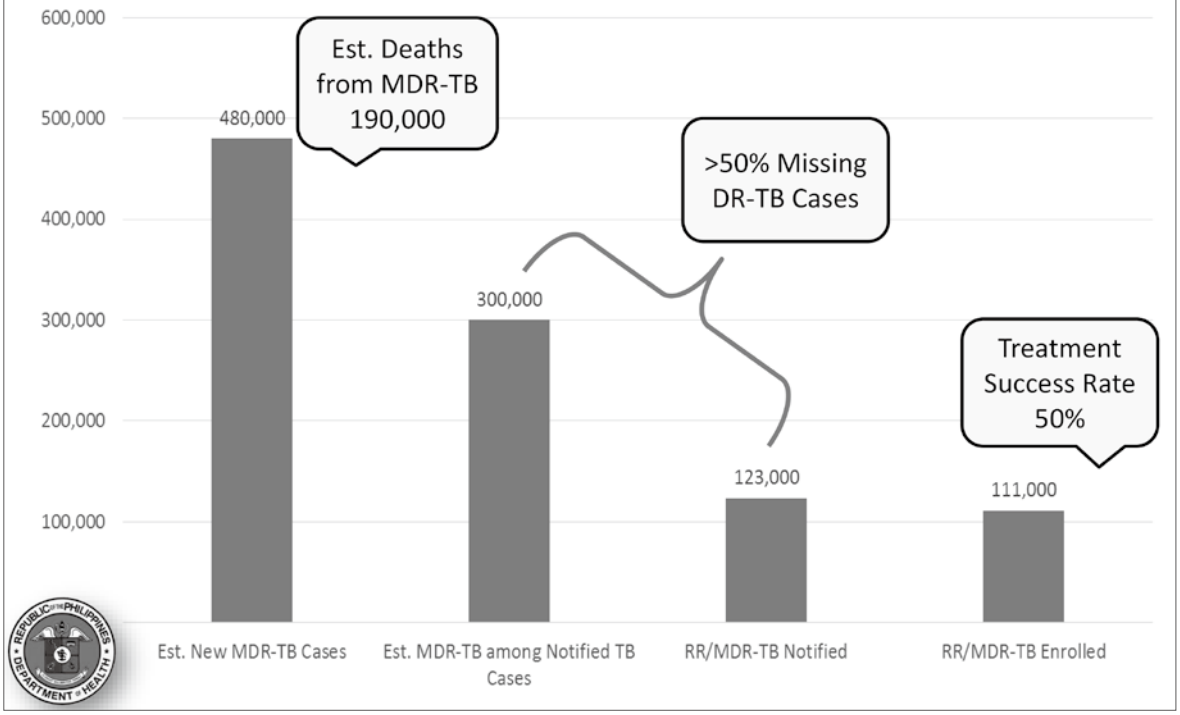


10/100,000
10,000 Filipinos

30 countries with High TB Burden



Global Burden of MDR-TB



Global Burden of MDR-TB

Estimated MDR-TB Cases	New TB Cases: 3.3% Previously Treated TB Cases: 20%
Estimated New MDR-TB Cases Worldwide	480,000
Mortality	190,000
Estimated MDR-TB Cases among Notified TB Cases	300,000
RR/MDR-TB Notified	123,000 (41%)
RR/MDR-TB Enrolled	111,000
Treatment Success Rate	50%

Source: WHO Global TB Report 2015

How Big is the MDR TB Burden in the Philippines?

Drug Resistance Survey		
% of Notified Cases with MDR-TB	2004	2012
Among New TB cases	4%	2%
Among Re-treatment TB cases	21%	21%

How Big is the MDR TB Burden?

Drug Resistance Survey		
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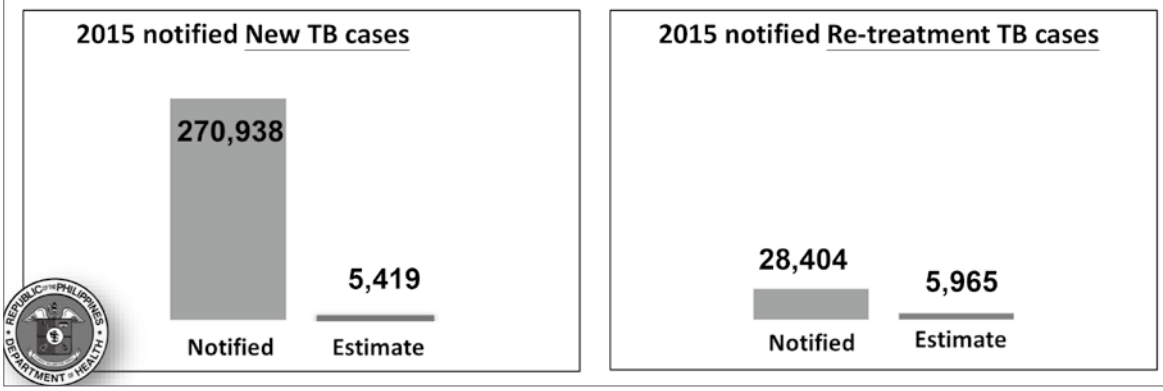

How Big is the MDR TB Burden?

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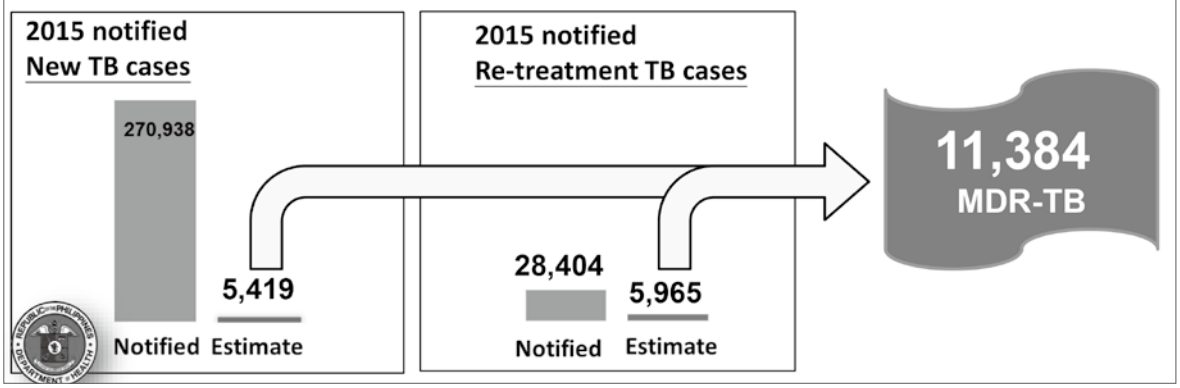
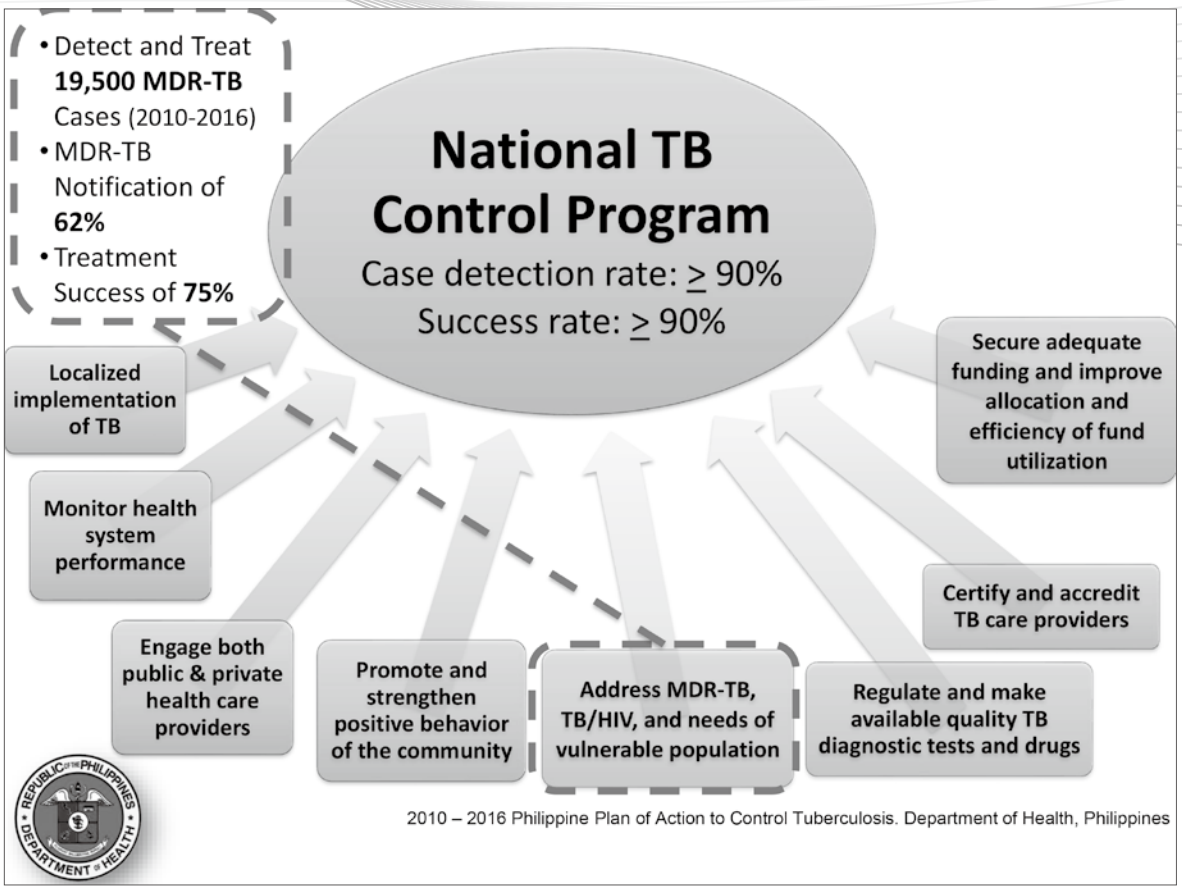
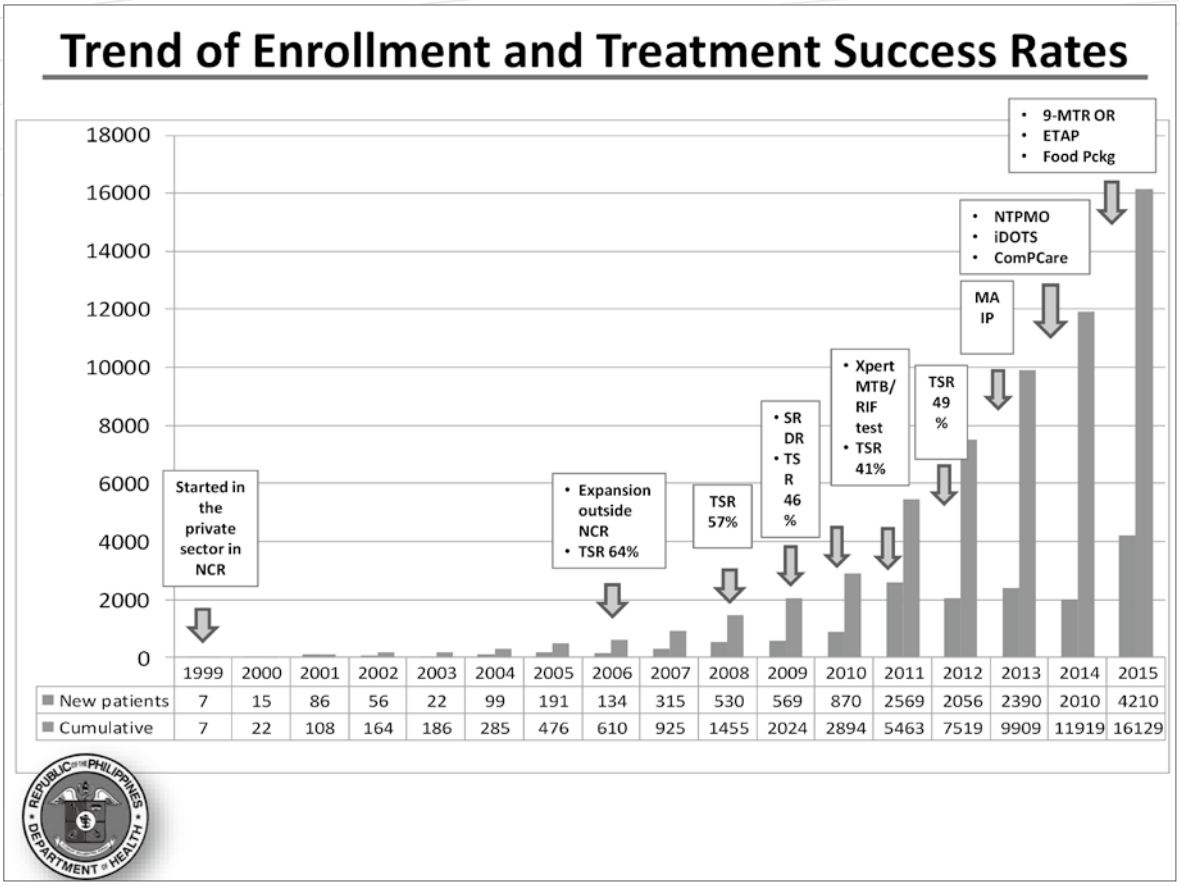
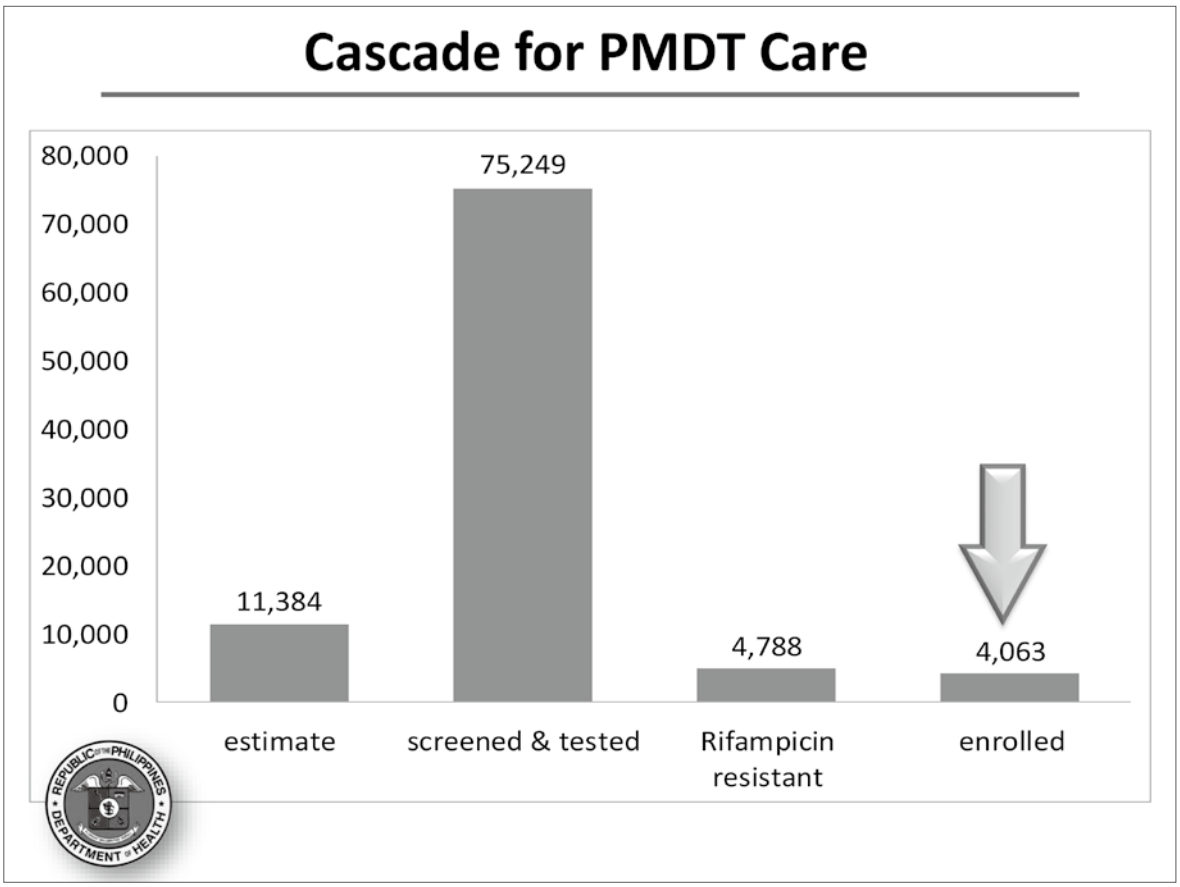


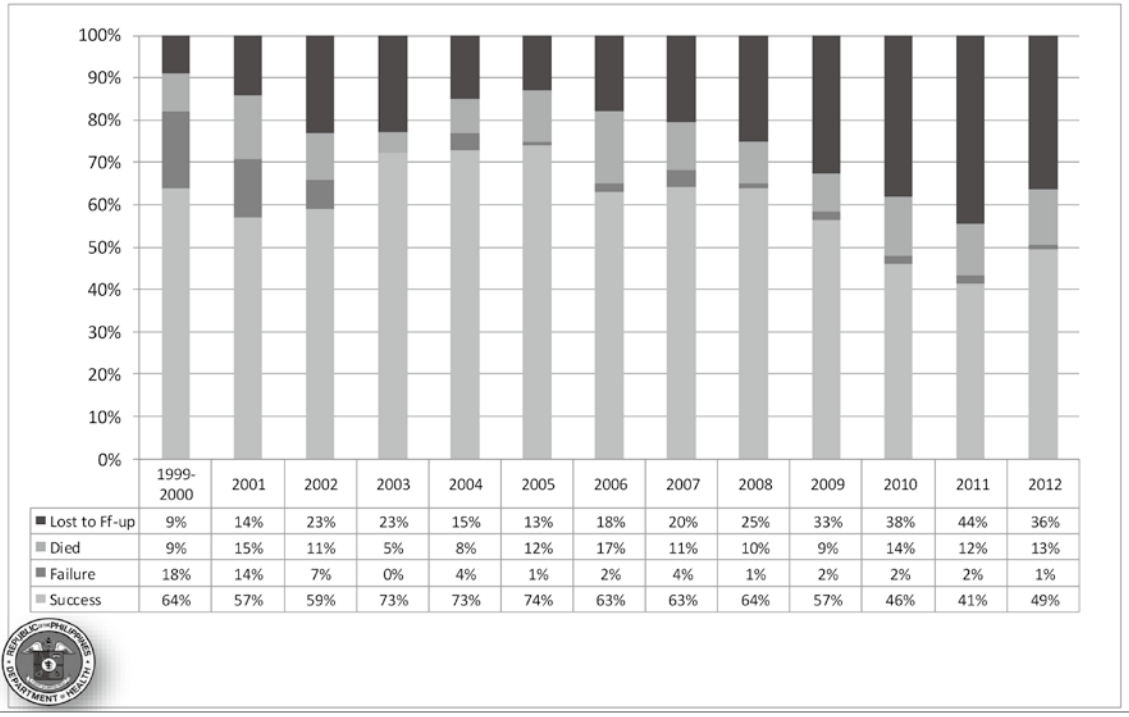


PhilPACT Objectives	Strategies
Reduce local variation in TB control program performance	1. Localize implementation of TB control 2. Monitor health system performance
Scale u of DOTS im	3. Engage both public and private health care providers 4. Promote and strengthen positive behaviour of the communities 5. Address MDR-TB, TB/HIV, and needs of vulnerable population
Ensure provis services	Regulate and make available quality TB diagnostic tests and drugs 7. Certify and accredit TB care providers
Re ut-of-pocket expenses TB care	8. Secure adequate funding and improve allocation and efficiency of fund utilization


Trend of Enrollment and Treatment Success Rates
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
Started in the private sector in NCR
• Expansion outside NCR
• TSR 64%
TSR 57%
• SR DR
• TS R 46 %
• Xpert MTB/ RIF test
• TSR 41%
TSR 49 %
MA IP
• NTPMO
• iDOTS
• ComPCare
• 9-MTR OR
• ETAP
• Food Pckg
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
New patients 7 15 86 56 22 99 191 134 315 530 569 870 2569 2056 2390 2010 4210
Cumulative 7 22 108 164 186 285 476 610 925 1455 2024 2894 5463 7519 9909 11919 16129


Cascade for PMDT Care
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
11,384
75,249
4,788
4,063
estimate
screened & tested
Rifampicin resistant
enrolled

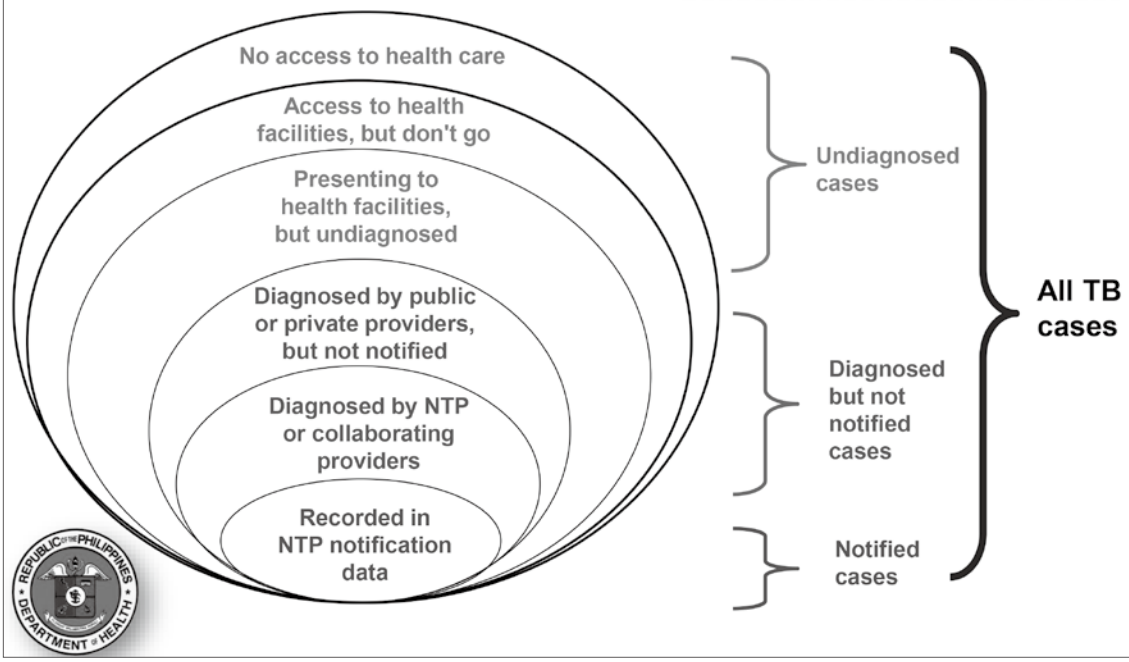
Trend of Treatment Outcome of Patients under PMDT, 1999 to 2012



	1999-2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Lost to Ff-up	9%	14%	23%	23%	15%	13%	18%	20%	25%	33%	38%	44%	36%
Died	9%	15%	11%	5%	8%	12%	17%	11%	10%	9%	14%	12%	13%
Failure	18%	14%	7%	0%	4%	1%	2%	4%	1%	2%	2%	2%	1%
Success	64%	57%	59%	73%	73%	74%	63%	63%	64%	57%	46%	41%	49%

Analyzing Case Notification

PhilPACT Target: 62%



Findings (Joint Program Review March 2016)

- Implementation and scaling-up of PMDT depends heavily on external funding and project-hired staff
- Gap between diagnosis *v.s.* notified *v.s.* treatment cohorts are wide
- Low Treatment Success on MDRTB is due to High Lost to follow-up
- Current regimen for pre-XDR-TB and XDR-TB do not include new anti-TB drugs
  (Bedaquiline and Delamanid)

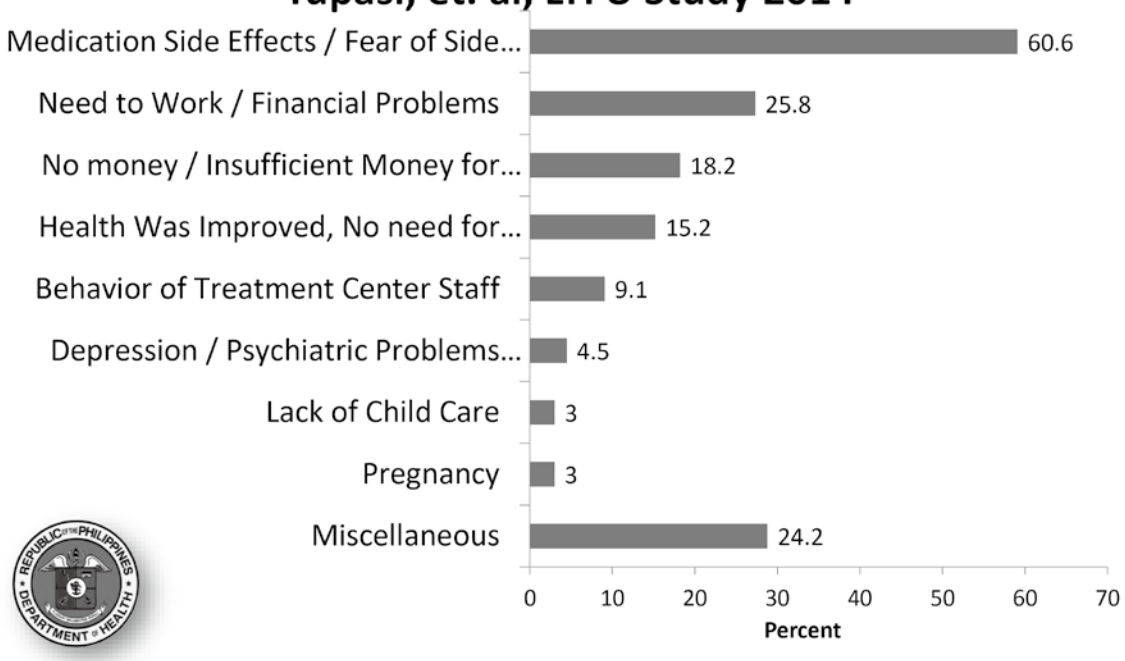
Burdens of MDR-TB

- **On Service Delivery:**
  - Complexity on the needed preparations and high cost of expanding PMDT services
  - Limiting the capacity of DOTS facilities; capable only for basic TB services
- **On Health Systems:**
  - More expensive
  - More workload for the health workforce

Burdens of MDR-TB

- **On Patients:**
  - Onset of ADRs
  - Long treatment duration
  - Absence from work
  - Far from the family

Most frequent self-reported reasons for stopping treatment among LTFU patients (based on qualitative analysis)
Tupasi, et. al, LTFU Study 2014



Tropical Disease Foundation

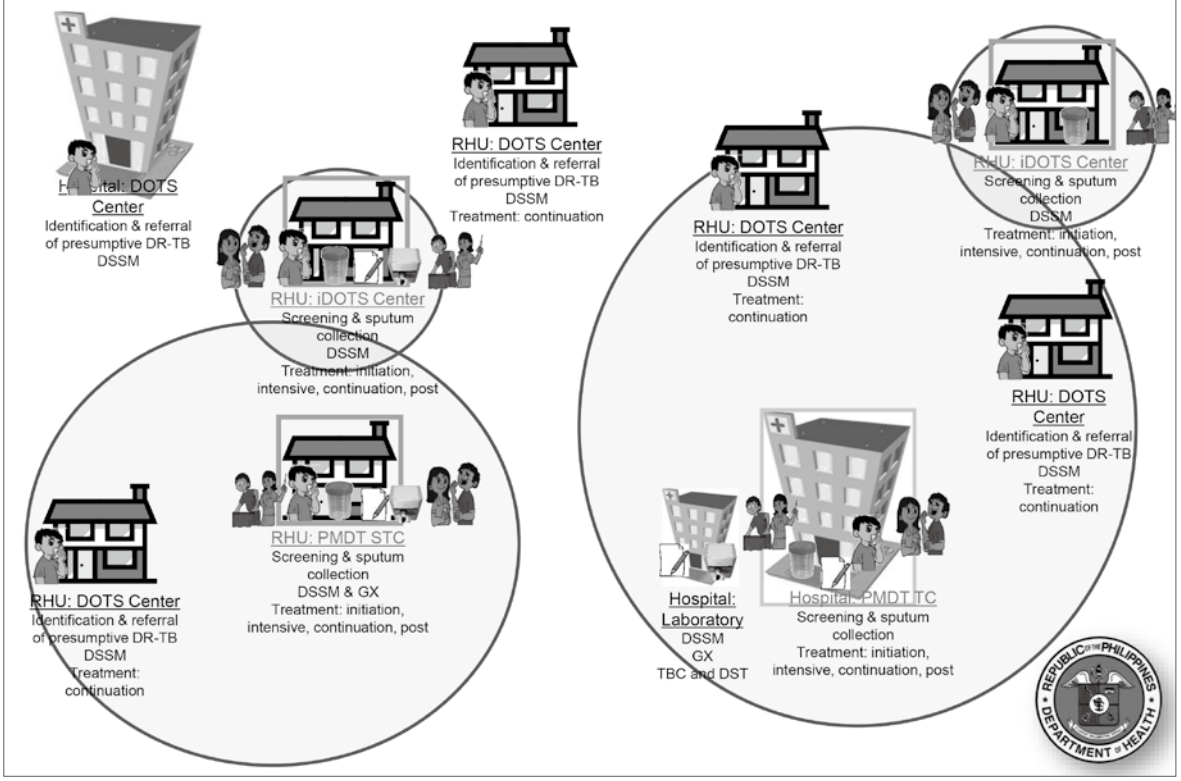
NTP's Actions to "Unburden" MDR-TB

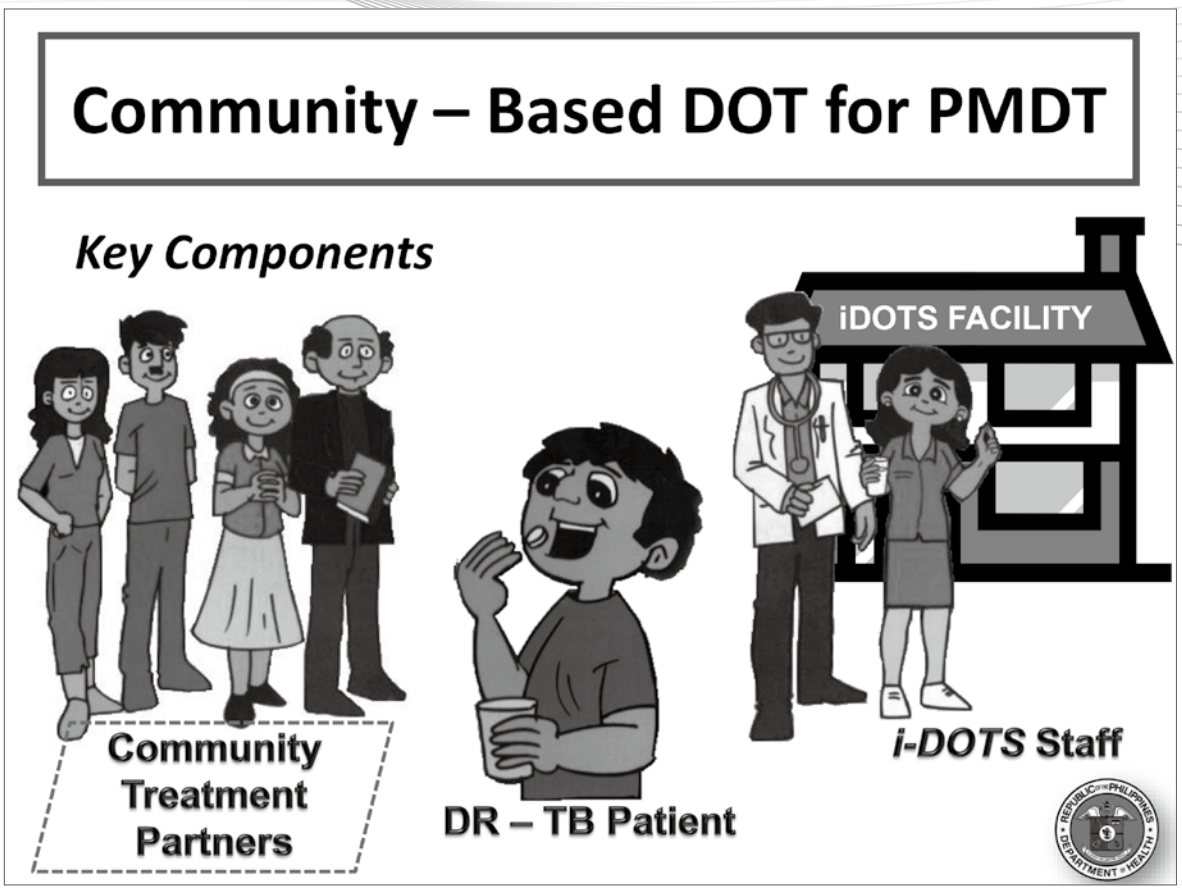
Pillar 1: Integrated, Patient-Centered Care and Prevention

Service Delivery :

- Expand PMDT services: *i-DOTS with CompCare*
- Decentralize services -closer to patients and family
  - *Lessen travel time; no need for re-location*
- Strengthen capability of HCWs; upgraded facilities
- Provide Nurses "*AIDERs"* based at GIDA areas
- Patient Support Group (KAP) per Satellite/Tx Center
- Use RMDT (Xpert MTB/RIF test); includes Sm-CXR+
- Conduct Contact Tracing strategies
- Offer PICT to enrolled DR-TB patients 15y/o &above

Integrated DOTS *(i-DOTS)*





NTP's Actions to "Unburden" PMDT

Pillar 2: Bold Policies and Supportive Systems

Needed Resources (Human and Monetary)

- **TB Law RA.10767** "Comprehensive Tuberculosis Elimination Plan Act"
  - mandatory reporting of TB cases
- PMDT sub-plan under the NSP *(PhilPACT)*
  Includes workforce-specific needs, budget, fund source
- Private Sector support – PMDT policies in CPGs of MDs
- Decentralized TB services to reduce costs (already in 18 reg)
- Priority on available domestic funds for sustainable services
- Initiative to advocate with new National Leadership to expand current insurance financing scheme *(TB OPB Pckge)*

NTP's Actions to "Unburden" PMDT

Pillar 2: Bold Policies and Supportive Systems

DOMESTIC (GOVERNMENT)	EXTERNAL RESOURCE (GFATM)
Consumables Needed; Microscopy supplies, CXR films, Xpert cartridges	Equipment needed: Microscopes, some CXR machines Xpert units
First line anti-TB drugs; IPT for Children and PLHIVs	Second-line anti-TB drugs; Ancillary drugs
Entire drug chain processes	Mainly on procurement; partly on distribution/delivery to periphery
60-70% of Program budget on logistics (primarily drugs)	70-75% of Project budget on PMDT implementation
NTP - biggest budget amongst the Infectious Disease Programs	GF-TB Project has the biggest budget amongst the 3 GF Projects

NTP's Actions to "Unburden" PMDT

Pillar 3: Intensified Research and Innovation

Patient Condition

- Conduct researches to address patient issues:
  - Long treatment duration *(e.g. 9-MTR)*
  - ADRs *(e.g. new treatment regimens?)*
- Assess/Evaluate incentives
  - Milestone Incentive Package

Basic Lessons Learnt

✓ Prevent DR-TB generation
Sustain GOOD basic DOTS

✓ Prevent DR-TB transmission
Expand to
Patient-centered DOTS

TB/DR-TB is a socio economic disease.
It contributes to the country's economic burden
It affects the economically-productive age group;
Our economic workforce.

A well-planned and effective
National TB Program, the NTP,
can help sustain the growing economy
of the country.

Let us all support the NTP;
Let's contribute to the economy!

Thank You...

Speaker

Takashi Yoshiyama

Position: Deputy Head
Department/Organisation: Respiratory Diseases Center, Fukujuji Hospital
Economy: Japan

Educational Background

- 1990 DTMH, Liverpool School of Tropical Medicine and Hygiene
- 1986 MD, Tokyo University

Professional Experience

- 2005-now In charge of TB ward, Fukujuji Hospital
- 2001-2003 Nepal TB control project, JICA
- 1993-1994 Yemen TB control project, JICA
- 1990-2004 Research Institute of Tuberculosis

Recent Publications

- T. Yoshiyama, Nobuyuki Harada, Kazue Higuchi, Masami Saitou, Seiya kato; Use of the QuantiFERON®-TB Gold in tube test for screening TB contacts and predictive value for active TB. Scand. J Infectious Diseases; 2015; Aug;47(8):542-9.
- Yoshiyama T, Morimoto K, Okumura M, Sasaki Y, Shiaishi Y, Ogata H, Kudou S, Long term outcome of MDR TB in Fukujuji hospital in Japan, Tansactions of royal society of tropical medicine and hyginene,2014;108(9):589-590 doi 10.1093/trstmh/tru80
- Yoshiyama T, Shrestha B, Maharajan B. Risk of relapse and failure after CAT2 regimen in Nepal. International journal of tuberculosis and lung diseases, 2010;14:1418-23
- Yoshiyama T, Harada N, Higuchi K, Nakajima Y, Ogata H. Estimation of incidence of tuberculosis infection in health care workers using repeated interferon ganma assays. Epidemiol Infect. 2009;137:1691-98
- Yoshiyama T, Yanai H, Rhiengtong D, Palittapongarnpim P, Nampaisan O, Supawitkul S, Uthaivorawit W, Mori T.:Development of acquired drug resistance in recurrent tuberculosis patients with various previous treatment outcomes (International journal of tuberculosis and lung diseases, 2004;8:31-38

Speech Abstract

PMDT in Japan

Takashi Yoshiyama
Deputy Head
Respiratory Diseases Center, Fukujuji Hospital, Japan

There has been a steady decline of case detection rate of tuberculosis in Japan. Two kind of statistical data of MDR TB in Japan show almost stable proportion of MDR TB cases during the past 40 years. In recent years, around 50 new and retreatment MDR TB cases are diagnosed every year. In addition some cases acquired drug resistance during treatment and some cases without drug susceptibility result at the time of diagnosis of tuberculosis are diagnosed as MDR TB during treatment. Total around 100 MDR TB cases are estimated to occur every year. With the increasing success of treatment, the number of chronic tuberculosis has decreased during the past 25 years. The improvement of referral is the main cause of the reduction of chronic cases in 1990s and 2000s.

Tuberculosis cases are under individualized treatment in Japan upon the information of individual drug susceptibility pattern. Sputum smear positive tuberculosis cases are treated at the health facilities with isolation beds for infectious tuberculosis and around 200 hospitals in Japan are equipped with isolation beds. Any doctor in these health facilities can prescribe anti-TB drugs. However, doctors tend to refer MDR TB cases to more specialized health facilities recently. MDR TB treatment result in Fukujuji hospital has improved from 1980s to 1990s, was almost the same in 1990s and early 2000s, and improvement occurred only after the introduction of Linezolid in 2010s. Delamanid has come to be used only from 2014 and we are not yet sure of its effect on the case management of MDR TB. The use of Delamanid is under very strict control of expert committee and those who want to treat XDR TB with Delamanid without accompanying drugs are advised not to treat.

PMDT in Japan

June 2016

Takashi Yoshiyama

Proportion of drug resistance, Japan (Ryoken sampling survey)

Without treatment	1977	1982	1987	1992	1997	2002	2007
INH0.1(1997=0.2)		5.8%	3.9%	3.7%	4.4%	2.8%	3.1%
INH1	2.2%	2.0%	1.4%	1.6%	2.5%		
RFP	0.4%	0.7%	0.5%	0.8%	1.4%	1.0%	0.7%
SM	3.1%	5.1%	4.7%	3.8%	7.5%	7.0%	5.6%
EB	3.0%	2.4%	0.9%	0.7%	0.4%	1.2%	1.3%
H0.1+R		0.9%	0.5%	0.3%	0.8%	0.7%	0.4%
H1+R	0.3%	0.4%	0.1%	0.1%			
LVFX							3.2%

Proportion of drug resistance, Japan (Ryoken sampling survey)

With TB history	1977	1982	1987	1992	1997	2002	2007	
INH0.1(1997=0.2)	41.4%	31.4%	29.8%	26.5%	33.0%	18.9%	12.3%	
INH1	23.3%	20.1%	17.8%	18.1%	23.9%			
RFP	17.5%	17.4%	16.3%	14.9%	21.6%	11.0%	6.7%	
SM	7.0%	7.2%	9.0%	7.4%	24.6%	14.4%	12.3%	
EB	1.6%	4.2%	2.4%	1.9%	15.2%	10.1%	2.6%	
H0.1+R		13.6%	14.9%	10.7%	19.7%	9.8%	4.1%	
LVFX							6.1%	

Proportion of drug resistance by surveillance (MDR and INH resistance)

	toal			new		retreatment	
	MDR	H res	proportion of exam	MDR	H res	MDR	H res
2007	1.2%	6.2%	41.8%				
2008	1.1%	4.9%	45.7%				
2009	0.8%	5.0%	63.5%				
2010	0.8%	4.7%	72.9%				
2011	0.7%	4.1%	73.7%				
2012	0.7%	4.6%	74.1%	0.5%	4.0%	4.0%	12.1%
2013	0.6%	4.8%	73.2%	0.4%	4.5%	3.7%	8.0%
2014	0.7%	4.6%	74.5%	0.56%	4.1%	3.34%	12.7%

Surveillance

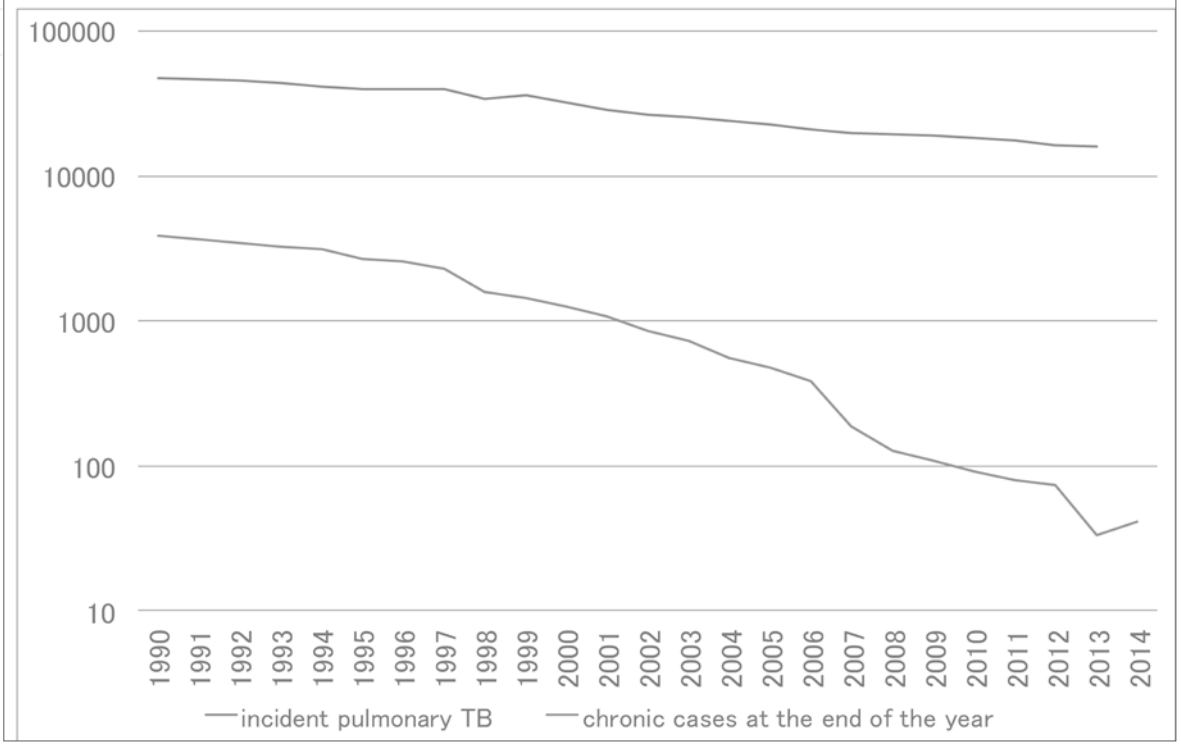
TB surveillance of Japan is not treatment based but disease-activity based. If failure, continue to be registered.

Cohort analysis started only in 2000s and no specific cohort analysis of MDR TB.

Chronic TB in Japan

Year	prevalent chronic TB	TB incidence
1990	3859	51821
1995	2698	43078
2000	1244	39384
2006	387	26384
2007	188	25311
2008	127	24760
2009	109	24170
2010	92	23261
2011	80	22681
2012	74	21283
2013	33	20681
2014	41	

FChronic cases in Japan



Treatment of MDR TB

Treatment upon individual DST to each drug (Japan)

priority drugs 4-5: PZA-EB-FQ-AG-TH-PAS-CS

DLM / LZD: potent drugs but second choice in Japan now

Quality of DST (fist line drugs) was assured by the periodical QC by Japan Tuberculosis Society. (no QC for the DST to second line drugs)

Management

Hospitalization of TB cases are basically done at the TB beds. All sputum smear positive TB cases are basically hospitalized in Japan. (total 6000-7000 cases per year and around 200 hospitals are qualified for the hospitalization of TB cases). All 200 hospitals can hospitalize any kind of TB cases. Around 20 hospitals hospitalize MDR TB cases. Total detected MDR TB cases are around 60-100 and 10-20 cases of these are hospitalized in Fukujuji hospital.

Supervision

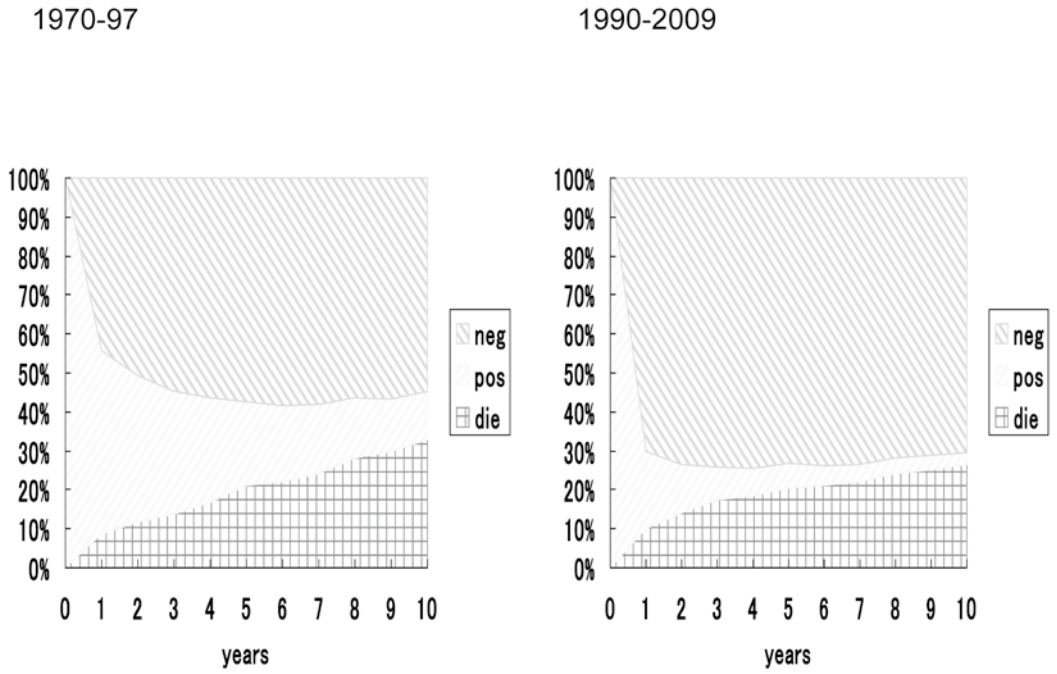
Difficult TB cases are either

referred to specialist hospitals

treated at the local hospital and consulted to specialist hospitals.

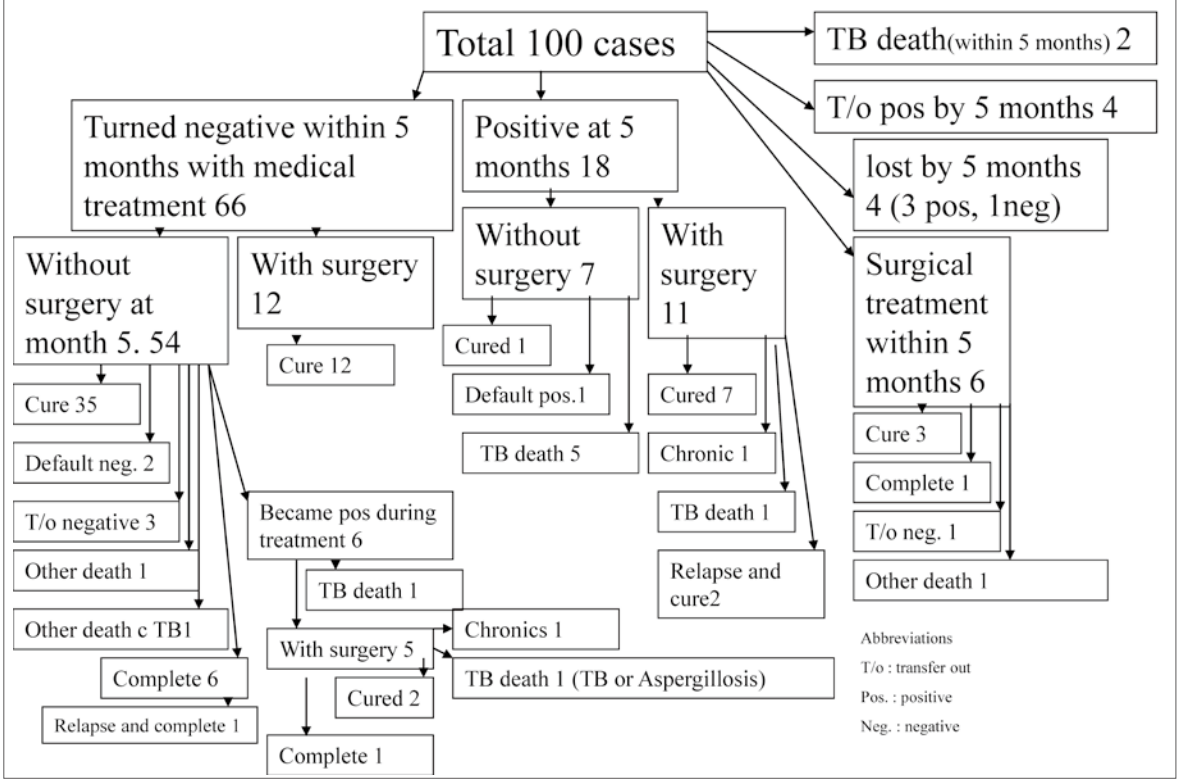
All TB cases are supervised by government (public health centers) and regimen is consulted at the committee in the public health centers.

Fate of MDR TB in F hospital



Treatment result of 100 MDR cases, 1990s,

Fukujuji hospital, this data is confidential as yet



Comparison between 200-05 vs 1990s

		2000-05 (102)	1990s(100)
cure (and negative during 2 year fu)		33	62
cure (without follow up)		26	8
unknown (after conversion)	return to home country	1	0
	die	6	3
	transfer	14	4
	lost	4	3
	without information	1	0
Fail (without Conversion)	chronic	2	2
	die	9	10
	lost	2	4
	transfer out	2	4
Relapse and cure later		2	0

Before and after LZD

	before		afer
	1990-2001	2002-2011	2011-
Resistant drug		5.05	4.85
XDR		21/158(13%)	5/28(18%)
Cure%	65%	54%	39%
Cure+t/o neg.	74%	74%	82%
Fail %	19%	15%	7%

Experiences in Fukujuji hospital

	-1988	1989-2000	2000-2011	2011-2014
Age	48	47	48	48
Resistant drug (without PZA/LVFX)	4.6	3.9	4.4	4.1
(with PZA/LVFX)			4.9	5.0

Treatment result in Fukujuji hp

	-1988	1989-2000	2000-2011	2011-2014
cure	52(relapse1)	77(relapse2)	107(relapse 3)	24
t/o with negative	20(maybe lost)	6	38(relapse1)	23
(total favorable)	52-72(50-69%)	83(73%)	144(75%)	47(76%)
Died with positive	9	11	18	2
t/o positive	0	4	6	2
Lost, positive	0	6	4	0
Failure	16	0	1	2
(total unfavorable)	25(24%)	21(19%)	29(15%)	6(10%)
Died with negative	8	4	9	3
Lost, negative	0	3	8(2 relapse)	1
Turned negative	0	0	0	5
Unknown	1	1	0	0

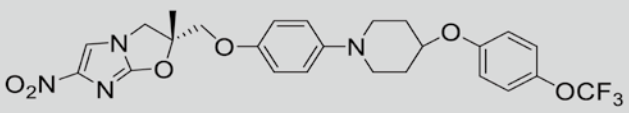
Infection control

Modern TB infection control is based upon US-CDC recommendation in 1994 and in Japan started in 2000s.

All sputum smear positive TB cases are hospitalized and infection control is done to these all. Most of the current infection of TB occur before diagnosis of TB.

1. Delamanid

Drug information

Generic name	Delamanid
剤形	Oral drug
有効成分	Delamanid 50mg/tab
効能・効果	Indication (bacilli) susceptible M. tb indication MDR - TB
Dosage	100mg bid
Structure	
mechanism	Inhibition of mycolic acid synthase

Restrictions for use, Institutional criteria

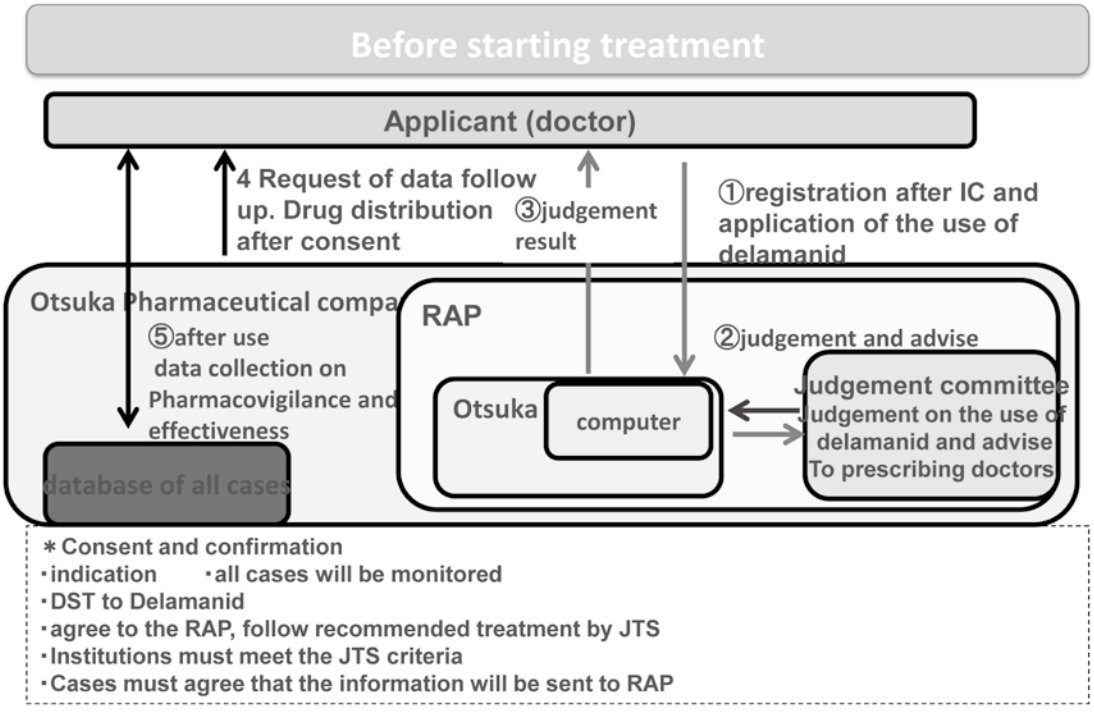
1QC of DST (INH and RIF resistance : sensitivity and specificity >95% by panel testing of Japan TB society QC)

2Japanese DOT is done

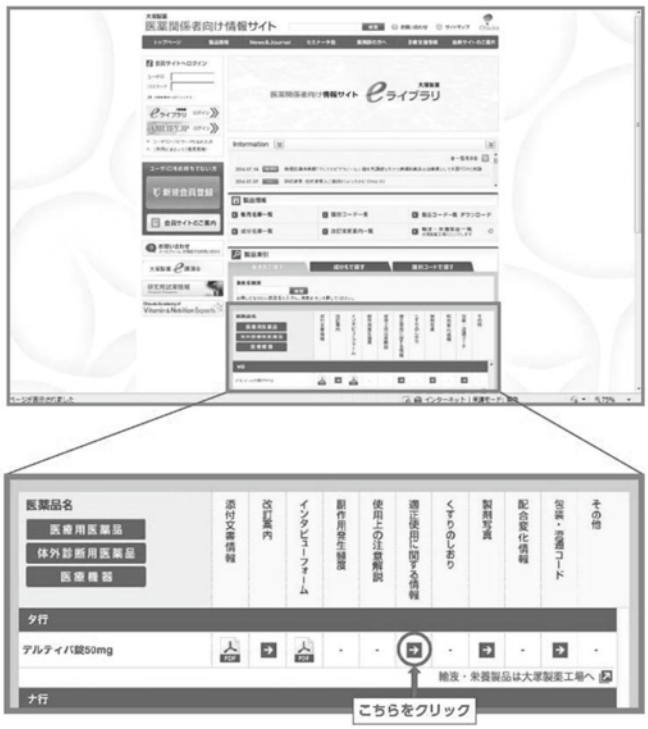
3Air born infection isolation room

4Human resources : with experiences of MDR treatment

4. Responsible access program



Responsible access program



Judgement result, Jan 29, 2016

requested	**59**
appropriate	**46**
inappropriate	**10**
pending	**3**
treated	**?**

10 cases not accepted with RAP

1. Non MDR :2
2. No information of DST
3. extrapulmonary
4. Culture negative for 2 years and not necessary
5. Turned to negative with LSEZ and add DLM
6. Add EVM + DLM to failing regimen
7. Add only LZD+DLM
8 add CS+DLM
9. Add only DLM

Japanese experiences in Fukujuji hospial

SN	sex	age	Nationality	culture at start	resist drugs	regimen with DLM	outcome ADR
1	M	43	Chi	neg	HREZTL(pre)	KLzdCs	
2	M	55	Jap	neg	HRSEZL(pre)	TCsPas	
3	F	32	Afgan	neg	HRSZ	H9KPas	
4	F	29	Jap	pos	HRSEZL(pre)	KTLzdPas	
5	M	72	Jap	neg	HRSEZKTL(X)	HECsPasEvm	
6	M	63	Jap	neg	HREK	ZLLzdCsPas	plt<70T
7	M	57	Jap	neg	HREST	HRbtEKLzdCsPas	
8	M	52	Jap	neg	HR	EZLTPas	
9	M	49	Jap	pos	HR	ZELS	
10	M	49	Jap	pos	HR	ZLPasCs	
11	M	60	Phil	pos	HRSEZT	ZLLzdCsPas	

（all cases turned to negative during treatment）

Monitor

Every 3-6 month, company request information for

- Effectiveness – sputum smear / culture
- ADR – symptom / blood test ECG

Cost of MDR TB treatment

Total TB medical cost in Japan in 2012 was 27 billion Yen (around 250 million US$, 11 thousand US$/person). We have no differentiation between MDR and non MDR TB. The majority of the cost was hospitalization cost.

The proportion of MDRTB among newly diagnosed cases is around 0.7% and the average duration of hospitalization of MDR TB is around 3 times higher than non MDR TB. There are around 40 chronic cases that are hospitalized. Roughly speaking, the medical cost of MDR TB will be around 4% of all TB cost, that is around 1 Billion Yen (around 9 million US$).

Cost of MDR TB treatment

There is a threat of increase of drug cost.

Linezolid : 7000 Yen / 600mg. 1 260 000 Yen with 6 months treatment.

Delamanid : 26000 Yen / 200mg. 4 680 000 Yen with 6 months treatment.

If both drugs are used, 6 million Yen = 50-60 000 US$

If 30 cases are treated with this regimen, total amount will be 180 million Yen with these drugs only. (around 0.7% of all TB cost). With the introduction of Linezolid, the proportion of failure decreased by 5%. To avoid one failure case, the cost will be 20-40 million Yen? (admission of one chronic case will cost around 7 million Yen / year)

Speaker

Anita Pei-Chun Chan

Position: Medical Officer
Department/Organisation: Division of Chronic Infectious Diseases , Centers for Disease Control
Economy: Chinese Taipei

Educational Background

- 2009-2013 PhD, Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University
- 2005-2007 MSc, Institute of Epidemiology, College of Public Health, National Taiwan University
- 1993-2000 MD, Department of Medicine, National Cheng-Kung University

Professional Experience

- Associated Director: 2016/1~, Tuberculosis Research Center, Centers for Disease Control, Ministry of Health and Welfare
- Adjunct Assistant Professor: 2015/7~, Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University
- Adjunct Attending Physician: 2005/7~, Department of Pediatrics, National Taiwan University Children's Hospital, National Taiwan University, College of Medicine

Recent Publications

- Lin WL, Chiu NC, Lee PH, Huang AS, Huang FY, Chi H, Huang DT, Chan PC*. Management of Bacillus Calmette-Guérin osteomyelitis/osteitis in immunocompetent children-A systematic review. Vaccine. 2015; 33(36):4391-7.
- Huang YH*, Chan PC, Lu MJ, Liao YT, Hsu CB, Chen CH. The Effectiveness of Chest Radiographic Screening Among Tuberculosis Contacts. Taiwan Epidemiology Bulletin 2015;31:140-151.
- Chan PC, Peng SS, Chiou MY, Ling DL, Chang LY, Wang KF, Fang CT*, Huang LM*. Risk for tuberculosis in child contacts: development and validation of a predictive score. Am J Respir Crit Care Med. 2014;189(2):203-213.
- Chan PC, Chen CH*, Chang FY. External review of the National Tuberculosis Program and the development of strategy and targets post 2015 in Taiwan. J Formos Med Assoc. 2014;113(11):757-777.
- Chan PC*, Huang SH, Yu MC, Lee SW, Huang YW, Chien ST, Lee JJ; Taiwan Multidrug-Resistant Tuberculosis Consortium-TMTC. Effectiveness of a government-organized and hospital-initiated treatment for multidrug-resistant tuberculosis patients-a retrospective cohort study. PLoS One. 2013;8(2):e57719.

Speech Abstract

Programmatic Management of Drug-resistant TB (PMDT) in Chinese Taipei Economy

Anita Pei-Chun Chan

Medical Officer

Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei

The emergence of resistance to anti-tuberculosis (TB) drugs—particularly resistance associated with multidrug-resistant TB (MDR-TB)—has become a major public health problem worldwide and an obstacle to effective global TB control. In 2015, Chinese Taipei Economy had a moderate incidence of TB with 45.8 cases per 100,000 people and a 2% rate of MDR-TB among new TB patients. Today we will present our experience with Programmatic Management of Drug-resistant TB (PMDT).

Chinese Taipei Economy has implemented DOTS (Directly Observed Treatment, Short-Course) strategies since 2006. These strategies decreased relapse rates among TB patients to less than 2% in 2-year follow-ups after completion of treatment. In contrast, the development of MDR-TB, highlighted the shortcomings of previously existing treatment practices and failures to adopt international guidelines. Therefore, patient-centered management promoting adherence to lengthy treatment regimens is the cornerstone of PMDT in Chinese Taipei. The Taiwan MDR-TB Consortium (TMTC), a government-funded, hospital-based PMDT, was established in 2007 to deliver high quality care for all reported pulmonary MDR-TB patients.

Any National TB Program (NTP) should provide key components for supporting PMDT including laboratory services, technical/clinical support for case management, and timely administration of appropriate second-line drugs. In Chinese Taipei, successful implementation of these three key services led to a 50% decline in prevalent MDR-TB patients from 2008 to 2014, with an overall treatment success rate of 74.5%.

There are still challenges ahead of us. Increasing international travel and immigration could lead to the transmission of MDR-TB to APEC member economies. In addition, although many PMDT programs in APEC member economics are making progress, mobilization of domestic sources is usually insufficient and gaps in funding are often pronounced. Regional collaboration is needed to find the most cost-effective PMDT model; one that links patients to the best diagnoses and care.

MDR-TB

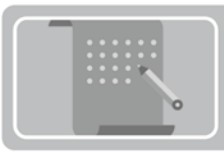
Anita Pei-Chun Chan, MD, PhD
Medical Officer, TCDC
Associated Director, TB Research Center, TCDC
Assistant Professor, Institute of Epidemiology and Preventive Medicine, NTU
Adjunct Physician, Children's Hospital, NTU

PMDT IN CHINESE TAIPEI ECONOMY

Nai-Ming Ou
1958- 2007

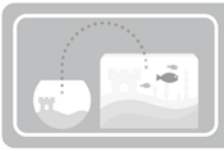
Former Chief Secretary Dr. Ou Nai-Ming (pictured above) devoted himself to communicable disease control. One of his most important contributions was the establishment of the Taiwan MDR-TB Consortium (TMTC) in 2007.

Programmatic Management of Drug-resistant TB



Epidemiology and Policy

- Transition of epidemiology
- Policy for detection and prevention



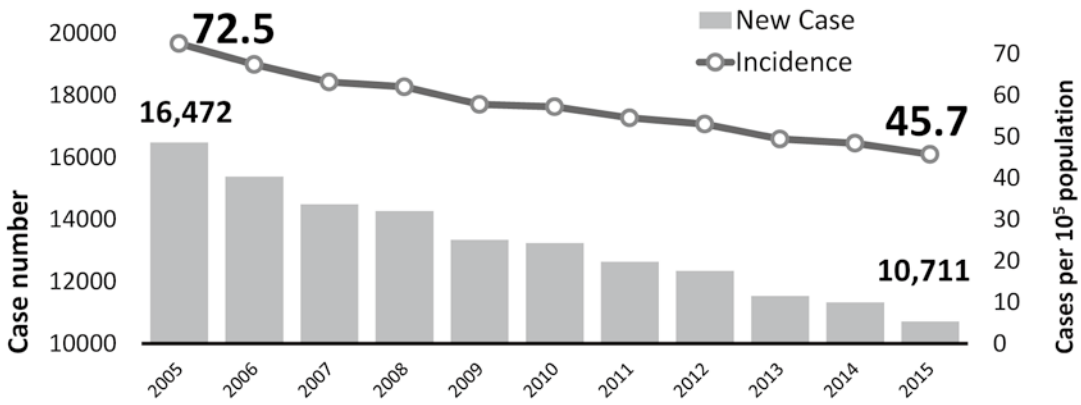
Care System

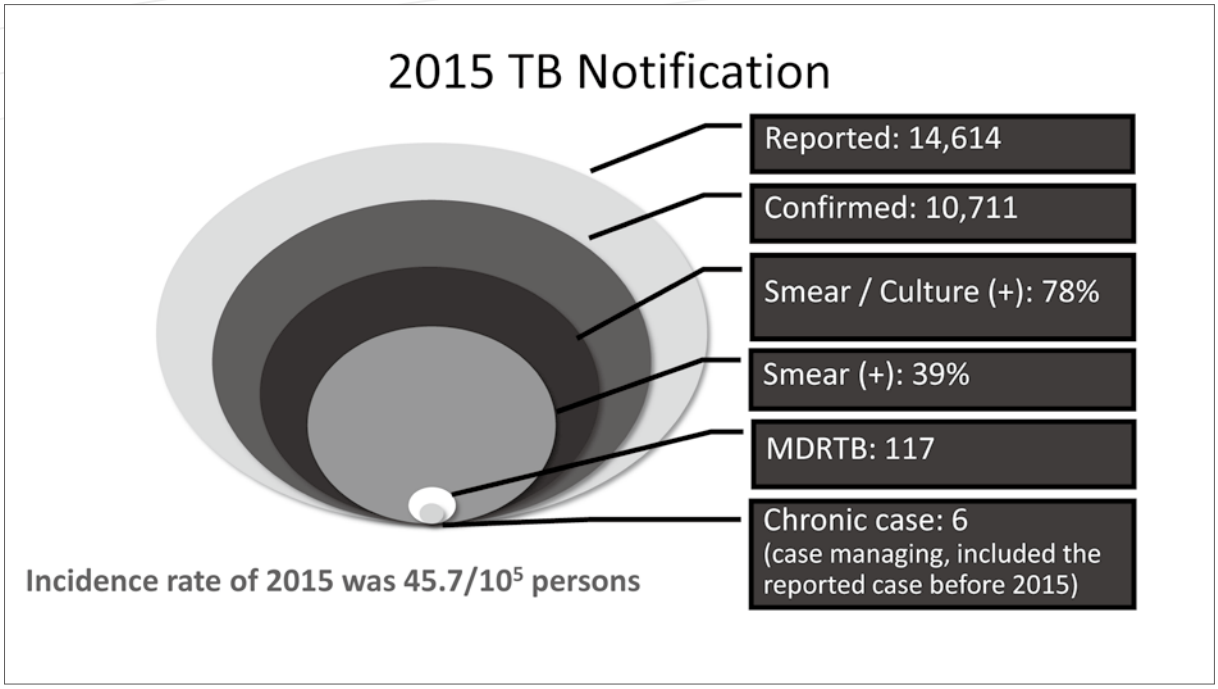
- Patient-centered
- Effective delivery

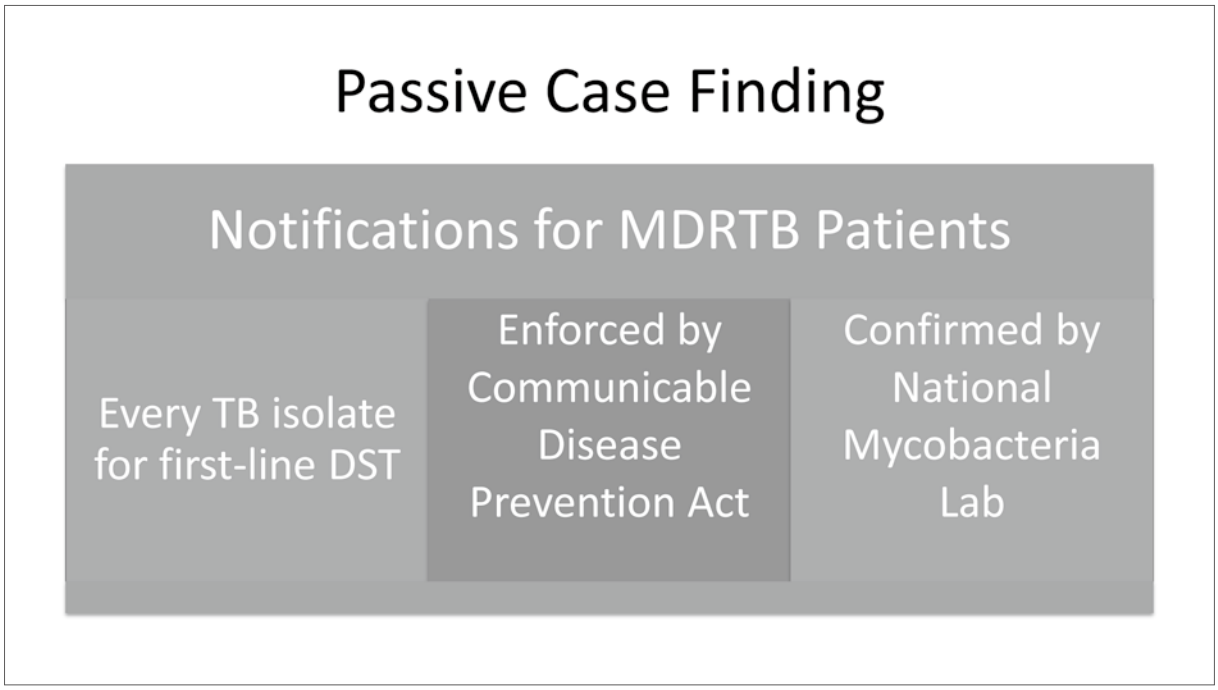
Challenges

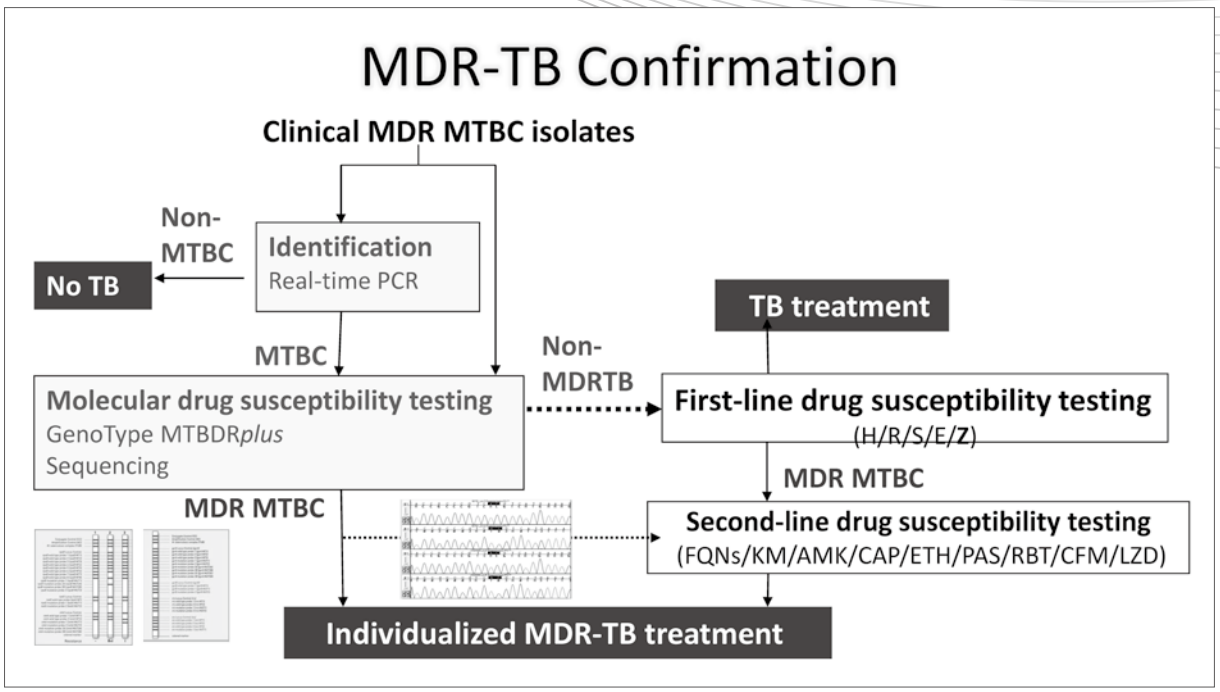
- Domestic issues
- International collaboration

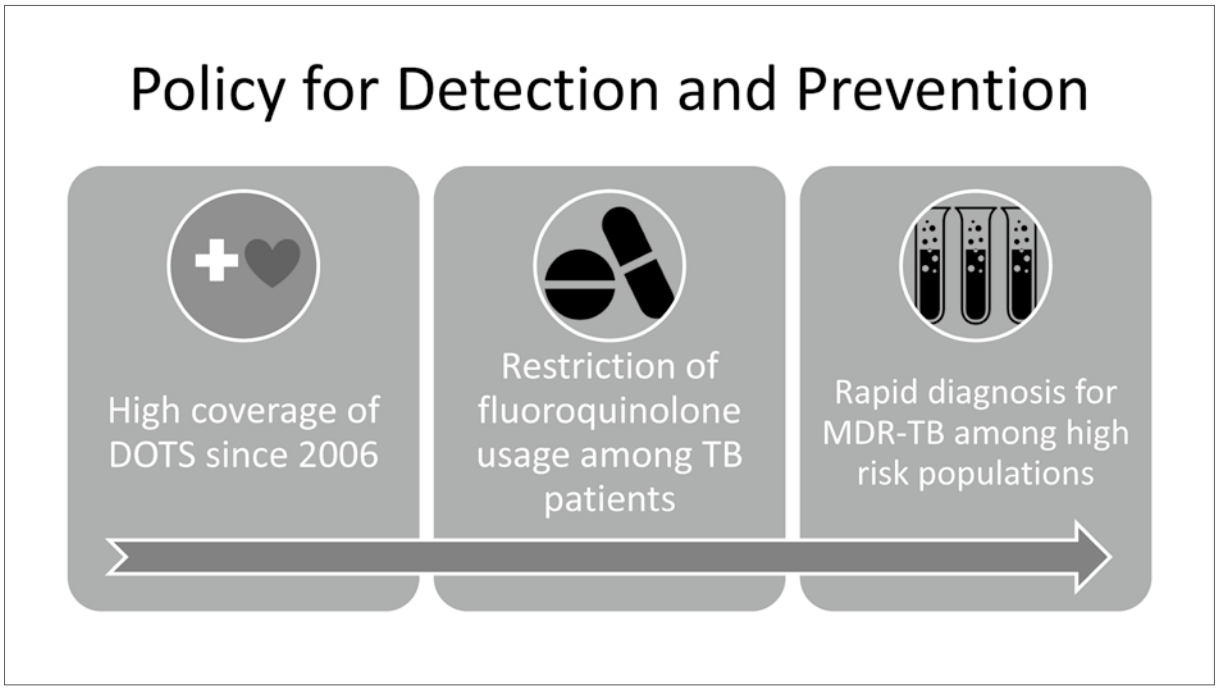

Epidemiology and Policy
• Transition of epidemiology
• Policy for detection and prevention

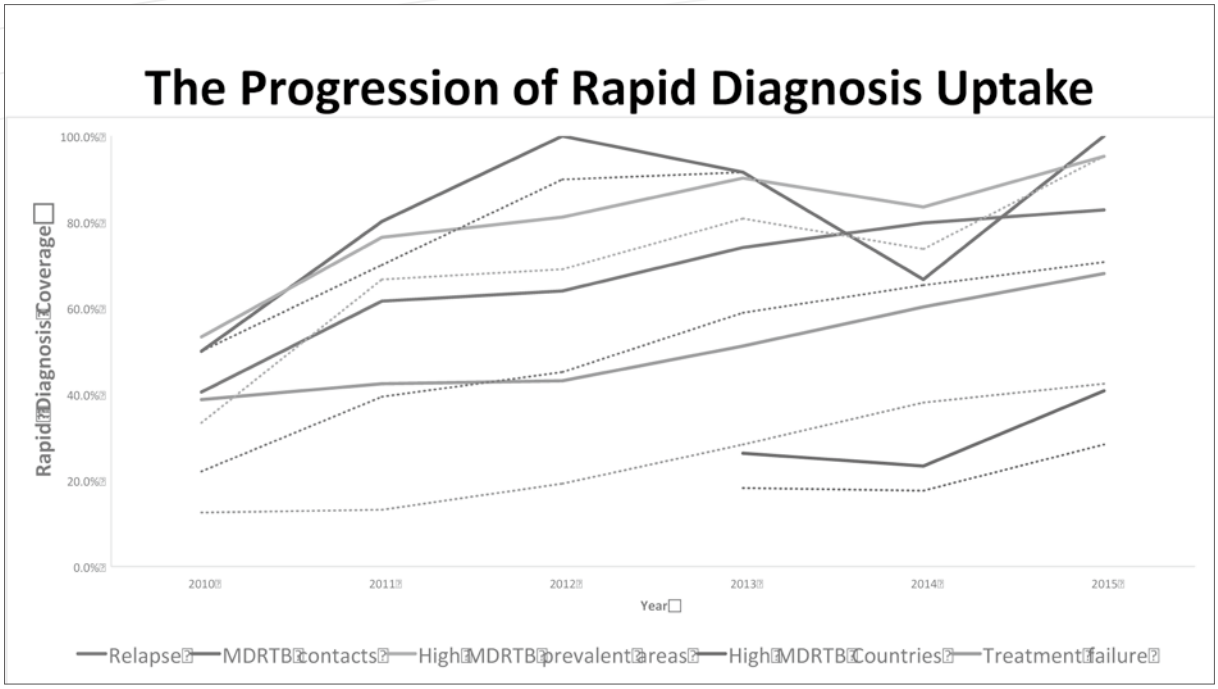

TB Incidence (2005-2015)
New Case
Incidence
72.5
45.7
16,472
10,711
Case number
Cases per 10^5 population
20000
18000
16000
14000
12000
10000
70
60
50
40
30
20
10
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

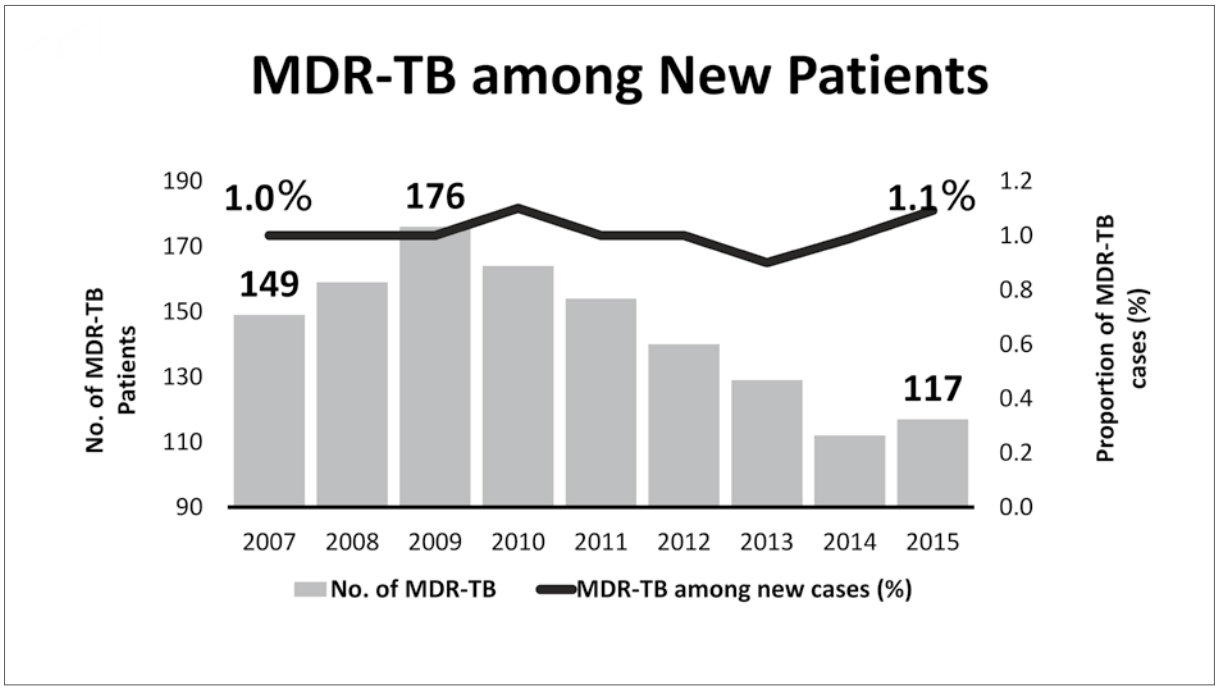

2015 TB Notification
Reported: 14,614
Confirmed: 10,711
Smear / Culture (+): 78%
Smear (+): 39%
MDRTB: 117
Chronic case: 6
(case managing, included the reported case before 2015)
Incidence rate of 2015 was 45.7/10^5 persons

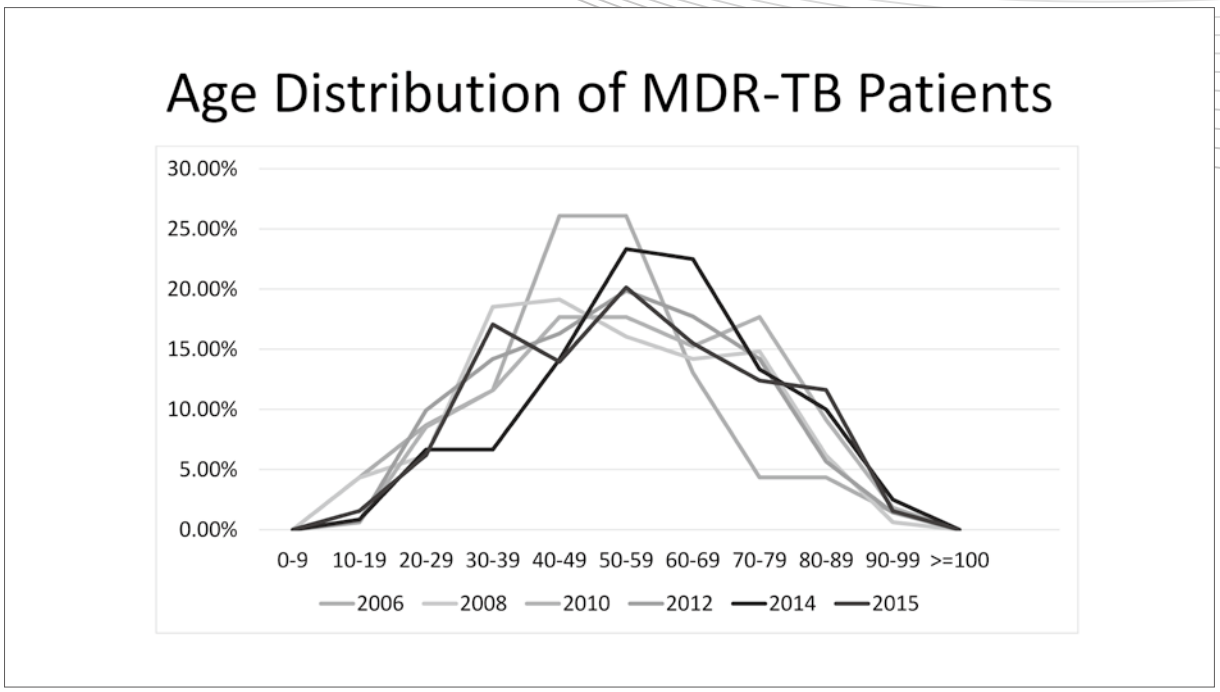

Passive Case Finding
Notifications for MDRTB Patients
Every TB isolate for first-line DST
Enforced by Communicable Disease Prevention Act
Confirmed by National Mycobacteria Lab

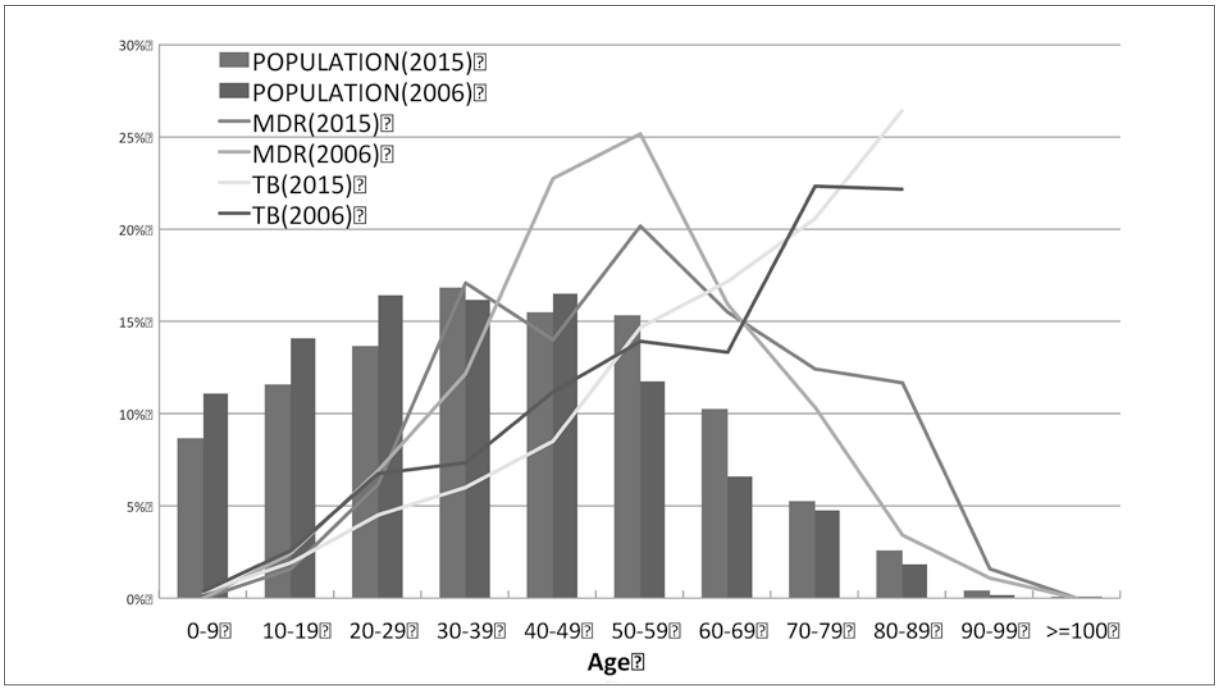

MDR-TB Confirmation
Clinical MDR MTBC isolates
Non-MTBC
Identification
Real-time PCR
No TB
MTBC
Molecular drug susceptibility testing
GenoType MTBDRplus
Sequencing
MDR MTBC
Non-MDRTB
TB treatment
First-line drug susceptibility testing
(H/R/S/E/Z)
MDR MTBC
Second-line drug susceptibility testing
(FQNs/KM/AMK/CAP/ETH/PAS/RBT/CFM/LZD)
Individualized MDR-TB treatment


Policy for Detection and Prevention
High coverage of DOTS since 2006
Restriction of fluoroquinolone usage among TB patients
Rapid diagnosis for MDR-TB among high risk populations

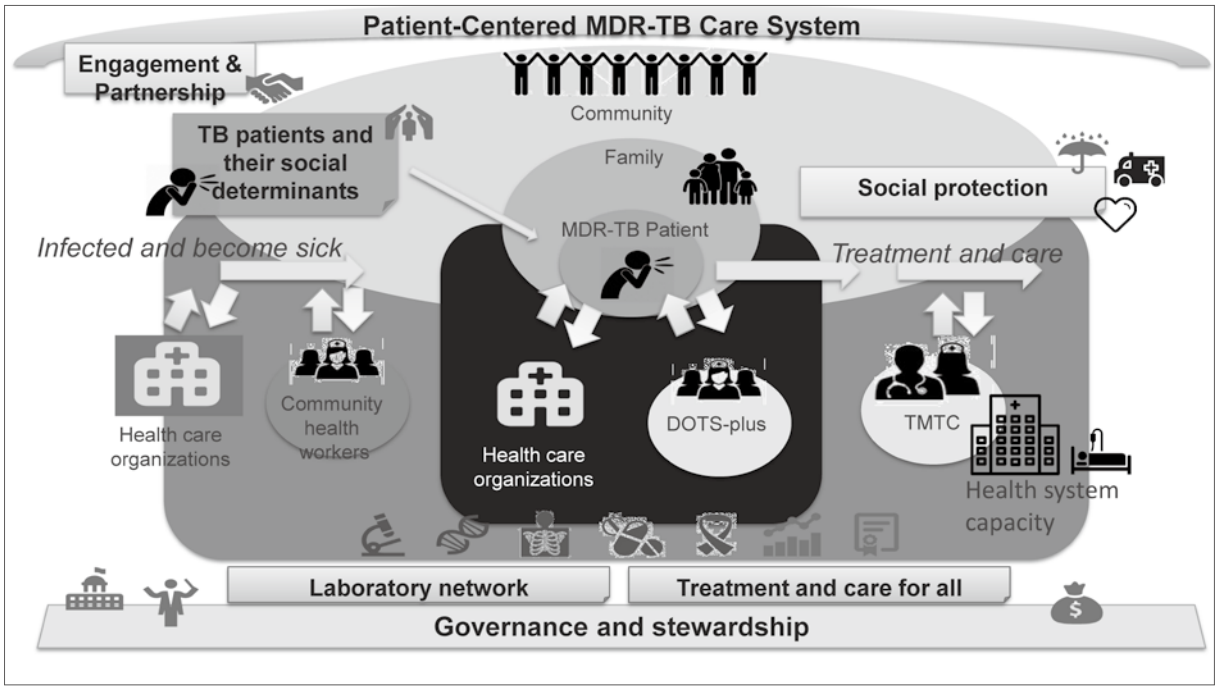

The Progression of Rapid Diagnosis Uptake
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
2010
2011
2012
2013
2014
2015
Year
Relapse
MDRTB contacts
High MDRTB prevalent areas
High MDRTB Countries
Treatment failure


MDR-TB among New Patients
190
170
150
130
110
90
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.0%
176
1.1%
149
117
2007
2008
2009
2010
2011
2012
2013
2014
2015
No. of MDR-TB Patients
Proportion of MDR-TB cases (%)
No. of MDR-TB
MDR-TB among new cases (%)

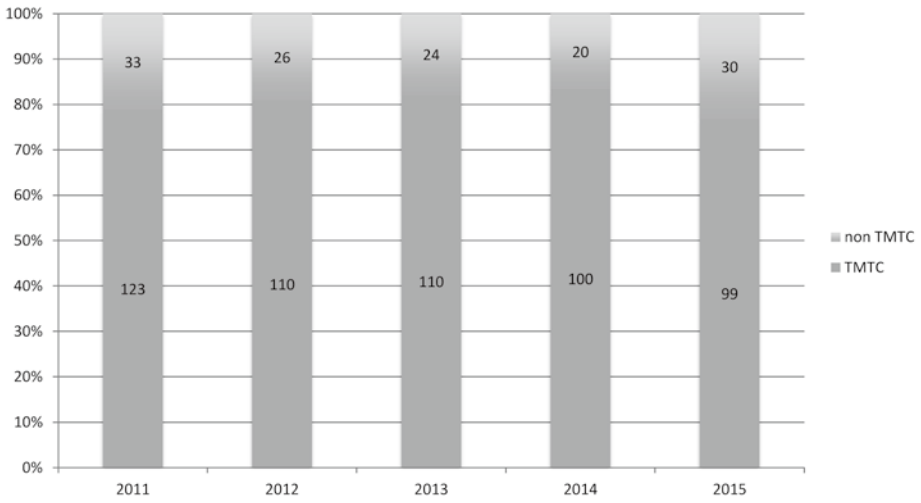

Age Distribution of MDR-TB Patients
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
90-99
>=100
2006
2008
2010
2012
2014
2015


POPULATION(2015)
POPULATION(2006)
MDR(2015)
MDR(2006)
TB(2015)
TB(2006)
30%
25%
20%
15%
10%
5%
0%
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
90-99
>=100
Age

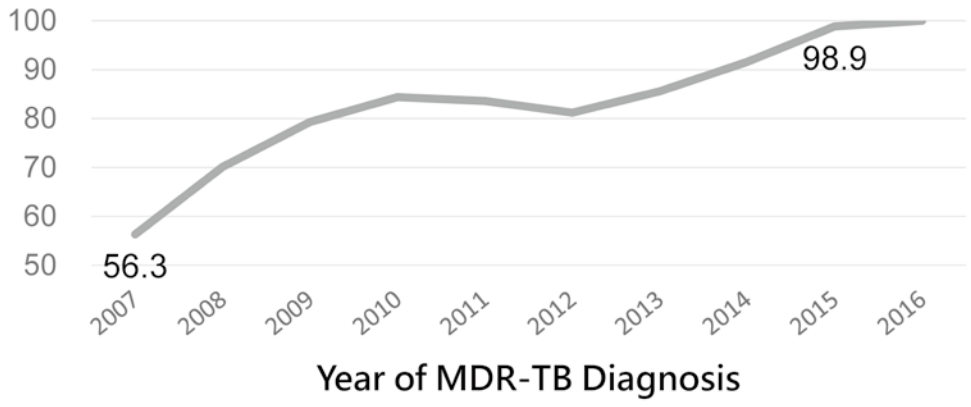

Care System
• Patient-centered
• Effective delivery


Patient-Centered MDR-TB Care System
Engagement & Partnership
Community
TB patients and their social determinants
Family
Social protection
MDR-TB Patient
Infected and become sick
Treatment and care
Health care organizations
Community health workers
Health care organizations
DOTS-plus
TMTC
Health system capacity
Laboratory network
Treatment and care for all
Governance and stewardship

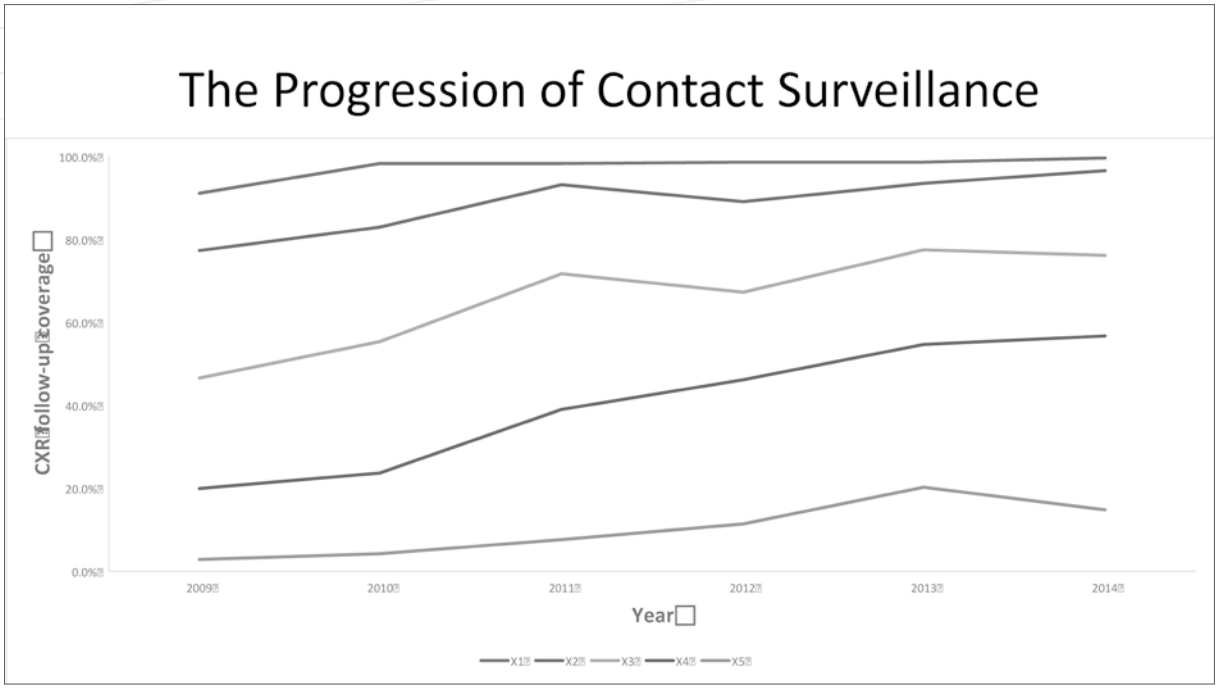
Coverage of TMTC for MDR-TB Patients

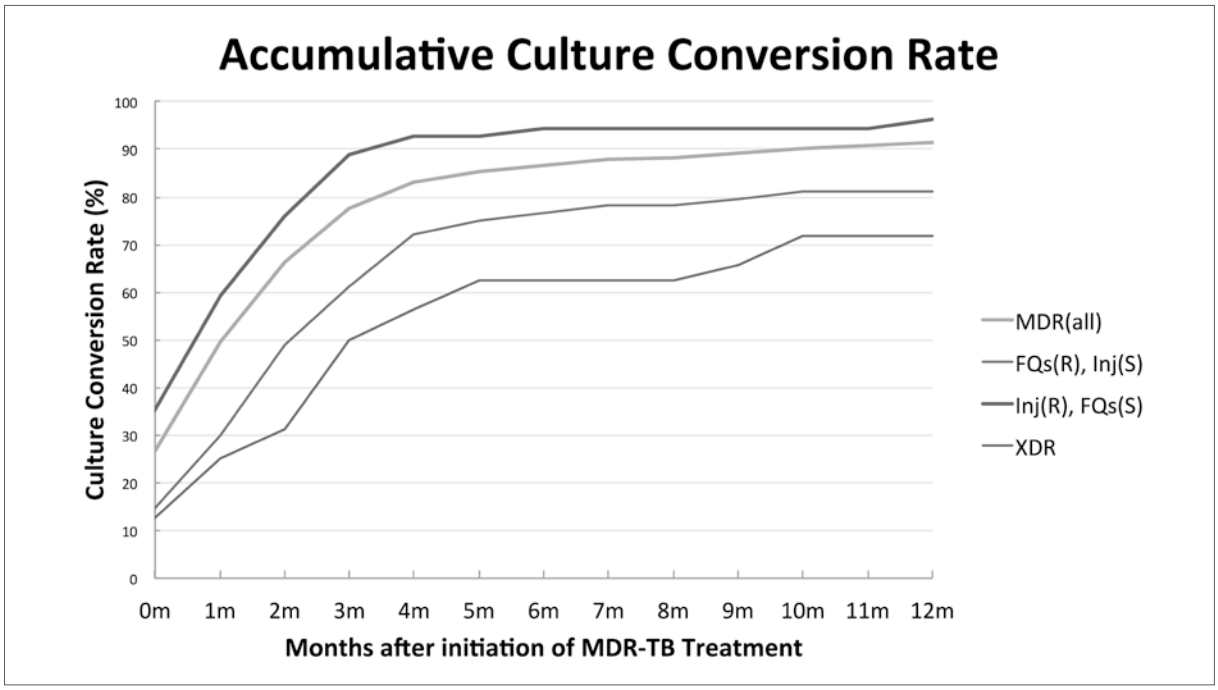


The Progress of Timeliness of Referral



Definitions of timely referral：the interval between sputum collection for MDR-TB diagnosis & enrolled in the TMTC < 4 months


The Progression of Contact Surveillance
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
2009
2010
2011
2012
2013
2014
Year
X1
X2
X3
X4
X5


Accumulative Culture Conversion Rate
Culture Conversion Rate (%)
100
90
80
70
60
50
40
30
20
10
0
0m
1m
2m
3m
4m
5m
6m
7m
8m
9m
10m
11m
12m
Months after initiation of MDR-TB Treatment
MDR(all)
FQs(R), Inj(S)
Inj(R), FQs(S)
XDR

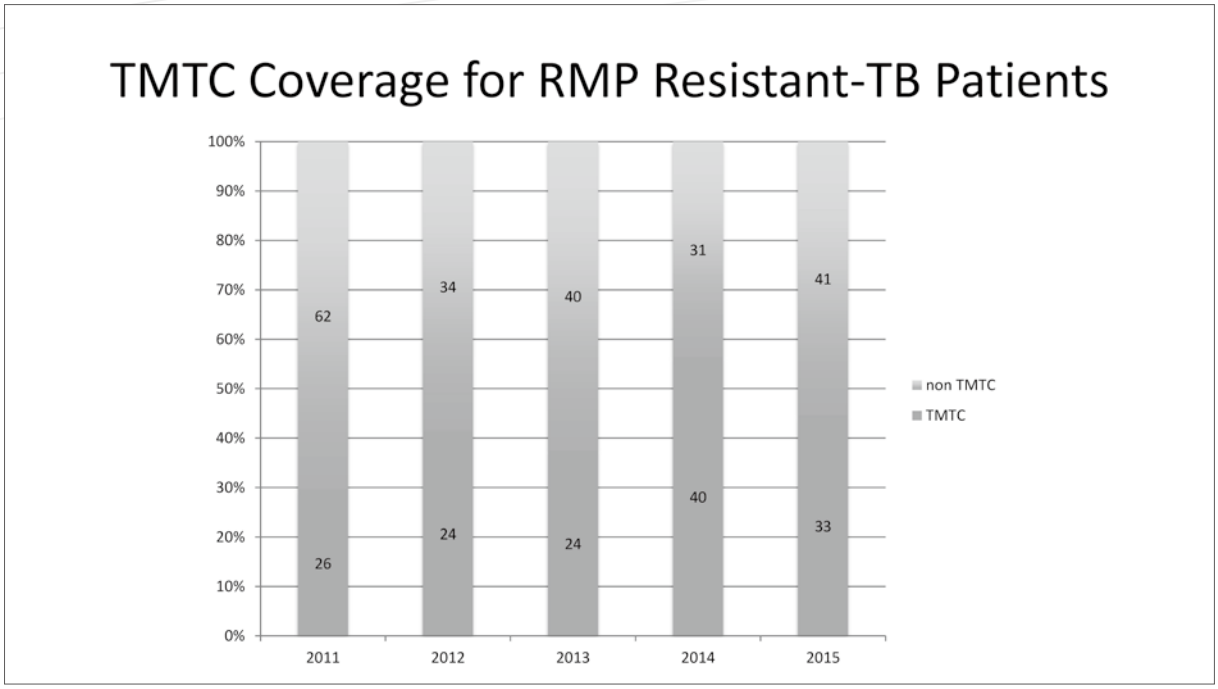
Relapse Rates

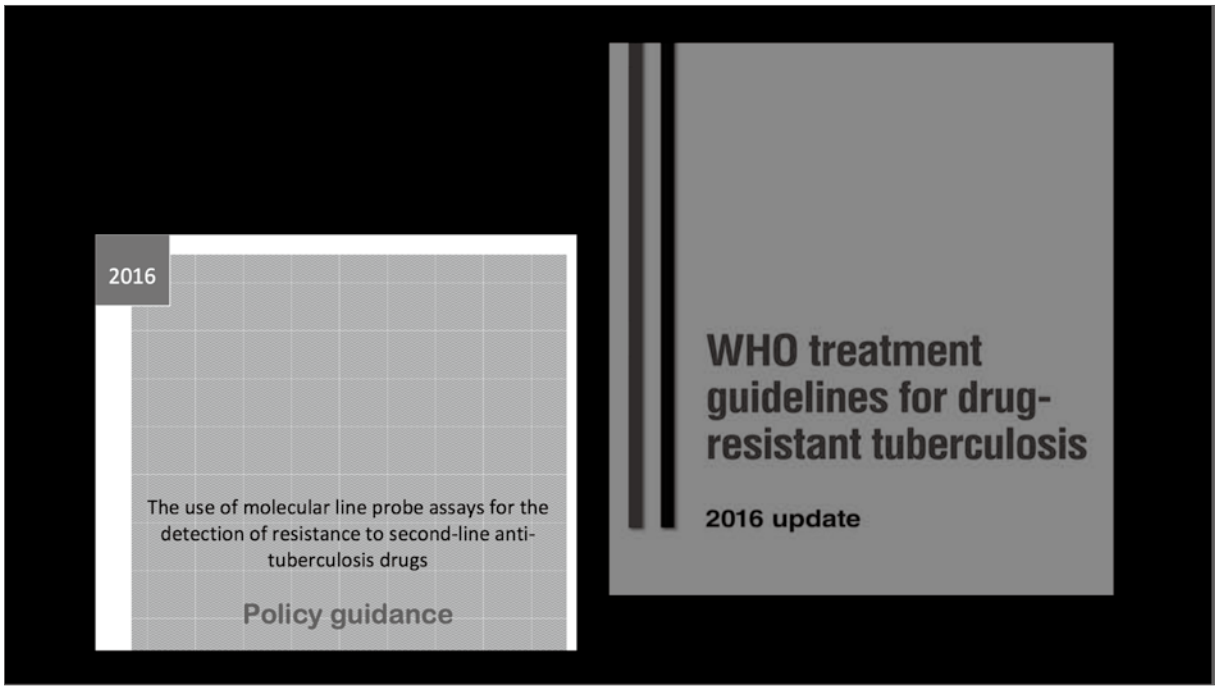
- Recurrence rates were analysed by time from treatment completion in 295 MDR-TB patients in a national cohort.
- Ten (3%) patients experienced MDR-TB recurrence during a median follow-up of 4.8 years (median time to recurrence: 2 years).
- The overall recurrence rate was 0.6 cases per 1000 person-months.
- MDR-TB patients with cavitary lesions and resistance patterns of XDR-TB or pre-XDR-TB are at the highest risk of recurrence.

MY Chen et al. un published data

Challenges

- Domestic issues
- International collaboration


TMTC Coverage for RMP Resistant-TB Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
62
26
34
24
40
24
31
40
41
33
2011
2012
2013
2014
2015
non TMTC
TMTC

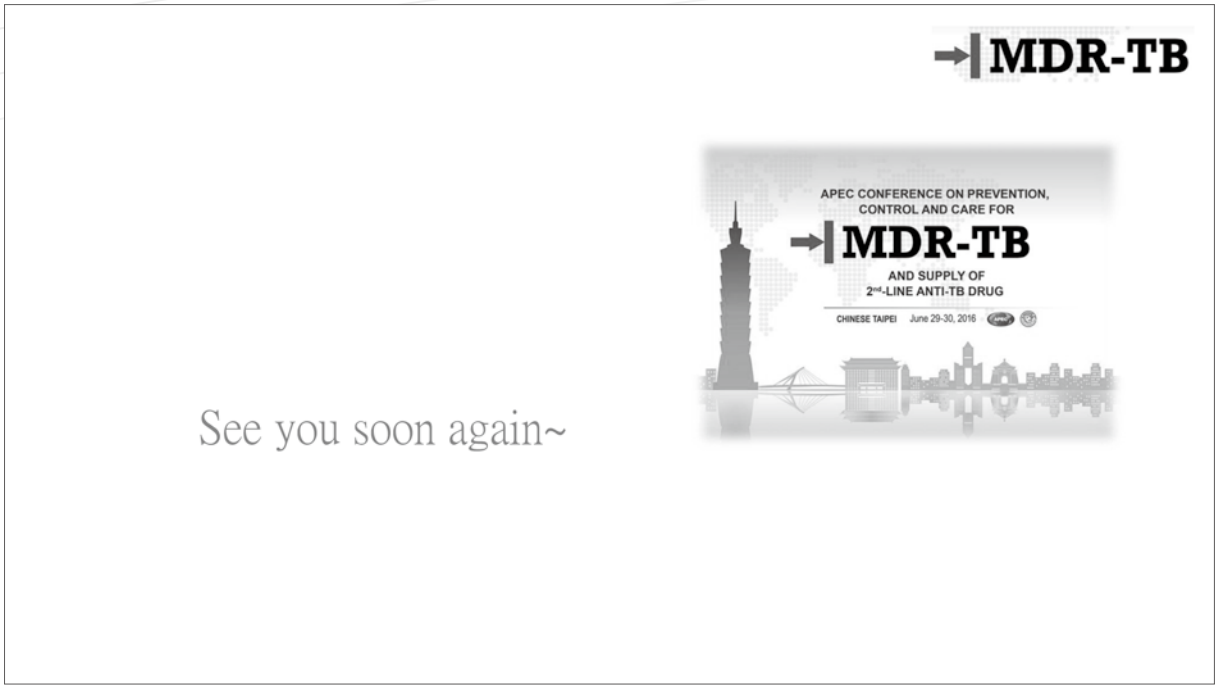

2016
The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs
Policy guidance
WHO treatment guidelines for drug-resistant tuberculosis
2016 update

Challenges

- MDR-TB Patients from foreign countries
- No preventive therapy for LTBI among MDR-TB contacts
- Funding gaps exist for the full coverage of new diagnostic tools, medications and services

International Collaboration

- Join PETTS study
- Contribution of Individual patient data for pediatric and adult MDR-TB
- New Southbound Policy


MDR-TB
APEC CONFERENCE ON PREVENTION,
CONTROL AND CARE FOR
MDR-TB
AND SUPPLY OF
2nd-LINE ANTI-TB DRUG
CHINESE TAIPEI June 29-30, 2016
See you soon again~

Session II

Deepening Understanding of DR-TB Prevention, Control and Care Measures

Moderator

Yi-Wen Huang
President, Taiwan Society of Tuberculosis and Lung Disease, Chinese Taipei

Rosalind G. Vianzon
Division Chief, Disease Prevention and Control Bureau, Department of Health, the Philippines

Moderator

Yi-Wen Huang

Position: Director
Department/Organisation: Taiwan Society of Tuberculosis and Lung Disease
Economy: Chinese Taipei

Educational Background

- Doctor of Philosophy, Institute of Medicine, Chang Shan Medical University, Taichung
- Bachelor of Medicine, Kaohsiung Medical University, Kaohsiung

Professional Experience

- Deputy Commander of Central Region, Communicable Disease Control Medical Network
- Chief of Acute Critical Care Department, Chang-Hua Hospital, Minister of Health and Welfare

Recent Publications

- Chin-Wen Su, Yi-Wen Huang, Mu-Kuan Chen, Shih-Chi Su, Shun-Fa Yang, and Chiao-Wen Lin. Polymorphisms and Plasma Levels of Tissure inhibitor of Metalloproteinase-3:Impact on Genetic Susceptibility and Clinical Outcome of Oral Cancer. Medicine, 2015,94(46):e2092.
- Wen-Cheng Chao1,2, Yi-Wen Huang3, Ming-Chih Yu4, Wen-Ta Yang5, Chou-Jui Lin6, Jen-Jyh Lee7, Ruay-Ming Huang8, Chi-Chang Shieh1, Shun-Tien Chien9* and Jung-Yien Chien9,10*:Outcome correlation of smear-positivity but culture-negativity during standard anti-tuberculosis treatment in Taiwan. BMC Infectious Diseases (2015) 15:67.
- Hsin-Chieh Tsai, Yi-Wen Huang. Investigation of the Causes of High Tuberculosis Death in Changhua County Between 2005-2006. Journal of Medicine and Health, 3(2), 37-46.
- Pei-Chun Chan, Su-Hua Huang, Ming-Chih Yu, Shih-Wei Lee, Yi-Wen Huang, Shun-Tien Chien, Jen-Jyh Lee, and the TMTC. Effectiveness of a government-organized and hospital-initiated treatment for multidrug-resistant tuberculosis patients – A retrospective cohort study. PLOS ONE. 2013; 8(2) e57719: 1-11.
- Y-W Huang, G-H. Shen, J-J. Lee, W-T. Yang. Latent tuberculosis infection among the close contacts of MDR-TB patients in central Taiwan. Int J Tuberc Lung Dis. 2010; 14(11):1430-5.

Moderator

Rosalind Vianzon

Position: Division Chief
Department/Organisation: Disease Prevention and Control Bureau, Department of Health
Economy: the Philippines

Educational Background

- Doctor of Medicine (MD) and Masters in Public Health (MPH)

Professional Experience

- Rural Health Physician/ Municipal Health Officer
- DOH Representative
- Medical Specialist II – as TB Technical Staff
- Medical Specialist III – as TB Technical Staff
- Medical Specialist IV – as NTP Manager
- Division Chief – as Chief of Infectious Disease Prevention and Control Programs

Recent Publications

- Manual of Procedures, Philippine NTP, 5th edition.
- Philippine Plan of Action to Control TB, 2010-2016.
- Updated PhilPACT, 2013-2016.
- Jointr Program Review of the Philippine NTP, 2012-2013.

APEC CONFERENCE ON PREVENTION, CONTROL AND CARE FOR

MDR-TB AND SUPPLY OF 2nd-LINE ANTI-TB DRUG

Speaker

Yanlin Zhao
Vice Director, Chinese Center for TB Control and Prevention, Chinese Center for Disease Control and Prevention, China

Ruwen Jou
Director, Tuberculosis Research Center, Centers for Disease Control, Chinese Taipei

Peter Cegielski
Team Leader, Global TB Branch, Division of Global HIV and TB, Centers for Disease Control and Prevention, the United States

Chawetsan Namwat
Director, Bureau of Tuberculosis, Department of Disease Control, Thailand

Hoang Thi Thanh Thuy
Focal Person, Programmatic Management of Drug-Resistant Tuberculosis, National TB Programme, Vietnam

Hyungseok Kang
Director, Department of Chest Medicine, Masan National Hospital, Republic of Korea

Chou-Jui Lin
Attending Physician, Taoyuan General Hospital, Ministry of Health and Welfare, Chinese Taipei

Speaker

Yanlin Zhao

Position: Vice Director
Department/Organisation: Chinese Center for TB Control and Prevention, Chinese Center for Disease Control and Prevention
Economy: China

Educational Background

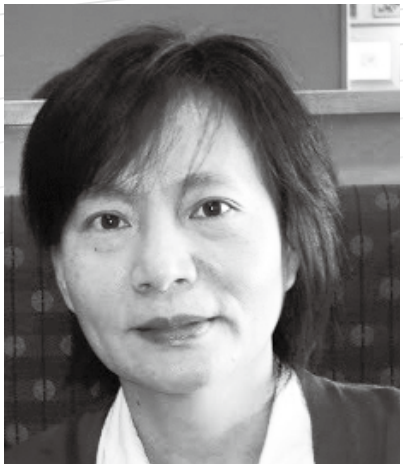
- PhD. & MD 2000-2003, Beijing Thoracic & Tuberculosis Research Institute Peking University Health Science Center, China
- Master Degree
  Beijing Thoracic & Tuberculosis Research Institute 1997-2000
  Peking union medical college ,China 1997-1998
- Medical Training(Bachelor degree)
  Beijing medical university 1994-1997
  Beijing capital medical college 1988-1991

Professional Experience

- Oct. 2010-now, Vice Director of National Tuberculosis Control and Prevention Center Chinese Center for Disease Control and Prevention of P. R. China.
- Aug. 2004-now, Director of National Tuberculosis Reference Laboratory of China CDC
- July. 2003-Aug. 2004, Department of mycobacteriology, Beijing Tuberculosis & Thoracic Tumor Research Institute.
- 1991-1994, Physician, People's Hospital, WuShen banner, Inner Mongolia, China

Recent Publications

- Pang Y, Dong H, Tan Y, Deng Y, Cai X, Jing H, Xia H, Li Q, Ou X, Su B, Li X, Zhang Z, Li J, Zhang J, Huan S, Zhao Y. Rapid diagnosis of MDR and XDR tuberculosis with the MeltPro TB assay in China. Sci Rep. 2016 May 6;6:25330.
- Pang Y, Zhao A, Cohen C, Kang W, Lu J, Wang G, Zhao Y, Zheng S. Current status of new tuberculosis vaccine in children. Hum Vaccin Immunother. 2016 Mar 22:1-11.
- Pang Y, Du J, Qin ZZ, Greenwald Z, Liu Y, Mi F, Zhao Y, Li L. An overview on tuberculosis-specific hospitals in China in 2009: results of a national survey. Eur Respir J. 2016 May;47(5):1584-7. doi: 10.1183/13993003.01854-2015. Epub 2016 Feb 25. PubMed PMID: 26917612.
- Raju RM, Raju SM, Zhao Y, Rubin EJ. Leveraging Advances in Tuberculosis Diagnosis and Treatment to Address Nontuberculous Mycobacterial Disease. Emerg Infect Dis. 2016 Mar;22(3):365-9.
- Yuen CM, Amanullah F, Dharmadhikari A, Nardell EA, Seddon JA, Vasilyeva I, Zhao Y, Keshavjee S, Becerra MC. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. Lancet. 2015 Dec 5;386(10010):2334-43.



Speaker

Ruwen Jou

Position: Director
Department/Organisation: Tuberculosis Research Center, Centers for Disease Control
Economy: Chinese Taipei

Educational Background

- PhD, The Ohio State University, USA

Professional Experience

- 2016-Director, Tuberculosis Research Center, Centers for Disease Control, Ministry of Health and Welfare
- 2015-Scientific Committee Member, International Tuberculosis Research Center, South Korea
- 2013-Council Member, Taiwan Society of Microbiology
- 2011-Adjunct Professor, Institute of Microbiology and Immunology, National Yang-Ming University
- 2010-Research Fellow & Laboratory Head, Reference Laboratory of Mycobacteriology, Centers for Disease Control

Recent Publications

- Wei-Lun Huang, Zen-Jie Hsu, Tsung Chain Chang, Ruwen Jou*, Rapid and accurate detection of rifampin and isoniazid-resistant Mycobacterium tuberculosis using an oligonucleotide array, Clinical Microbiology and Infection, 20(9):O542-9, 2014.
- Ming-Chih Yu, Huang-Yao Chen, Shen-Hsuan Chien, Ruwen Jou*, An integrated management program for MDR-TB results in favourable outcomes in northern Taiwan, European Respiratory Journal, 45(1):272-5, 2015.
- Ekaterina V. Kurbatova, J. Peter Cegielski, Christian Lienhardt, Rattanawadee Akksilp, Jaime Bayona, Mercedes C. Becerra, Janice Caoili, Carmen Contreras, Tracy Dalton, Manfred Danilovits, Olga V. Demikhova, Julia Ershova, Victoria M. Gammino, Irina Gelmanova, Charles M. Heilig, Ruwen Jou, Boris Kazennyy, Salmaan Keshavjee, Hee Jin Kim, Kai Kliiman, Charlotte Kvasnovsky, Vaira Leimane, Carole D. Mitnick, Imelda Quelapio, Vija Riekstina, Sarah E. Smith, Thelma Tupasi, Martie van der Walt, Irina A. Vasilieva, Laura E. Via, Piret Viiklepp, Grigory Volchenkov, Allison Taylor Walker, Melanie Wolfgang, Martin Yagui, Matteo Zignol, Evaluation of sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis, The Lancet Respiratory Medicine, 3(3):201-9, 2015.
- Cegielski JP, Kurbatova E, van der Walt M, Brand J, Ershova J, Tupasi T, Caoili JC, Dalton T, Contreras C, Yagui M, Bayona J, Kvasnovsky C, Leimane V, Kuksa L, Chen MP, Via LE, Hwang SH, Wolfgang M, Volchenkov GV, Somova T, Smith SE, Akksilp S, Wattanaamornkiet W, Kim HJ, Kim CK, Kazennyy BY, Khorosheva T, Kliiman K, Viiklepp P, Jou R, Huang AS, Vasilyeva IA, Demikhova OV; Global PETTS Investigators. Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial Versus Acquired Second-Line Drug Resistance. Clinical Infectious Disease. 2016 Feb 15;62(4):418-30. doi: 10.1093/cid/civ910. Epub 2015 Oct 27.
- Yuen CM, Kurbatova EV, Tupasi T, Caoili JC, Van Der Walt M, Kvasnovsky C, Yagui M, Bayona J, Contreras C, Leimane V, Ershova J, Via LE, Kim H, Akksilp S, Kazennyy BY, Volchenkov GV, Jou R, Kliiman K, Demikhova OV, Vasilyeva IA, Dalton T, Cegielski JP, Association between Regimen Composition and Treatment Response in Patients with Multidrug-Resistant Tuberculosis: A Prospective Cohort Study. PLoS Medicine. 2015 Dec 29; 12(12):e1001932. doi: 10.1371/ journal.pmed.1001932. eCollection 2015 Dec.

Speech Abstract

Introducing Novel Diagnostic Tools to Fortify Laboratory Capacity: Experience from Chinese Taipei Economy

Ruwen Jou

Director

Tuberculosis Research Center, Centers for Disease Control, Chinese Taipei

Timely diagnosis of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) remain a clinical and public health priority. To improve utilization of molecular diagnostics for case management, in support of the goal to end the global TB epidemic by 2035, we adopt WHO endorsed molecular diagnostics and implement algorithms for intensifying TB case finding. In Taiwan, the GeneXpert MTB/RIF (Xpert) is recommended for clinical and programmatic decision making to diagnose patients with suspected TB with chest X-ray findings and/or with TB contact history. Besides, a streamlined molecular diagnostic process using Xpert and line-probe assays is implemented in the control program. The Xpert test is an add-on diagnostic for testing Individuals known or suspected at high risk of MDR-TB. Sputum sample identified by the Xpert as Mycobacterium tuberculosis complex with rifampicin (RIF) resistance is subsequently and simultaneously tested using 2 line-probe tests for identifying MDR/XDR-TB. The GenoType MTBDRplus test can detect resistance to RIF and isoniazid, and the GenoType MTBDRslv2 can identify of resistance to fluoroquinolones and second-line injectable drugs including kanamycin, amikacin and capreomycin. The average turnaround time is 3 days. Besides, an on-line reporting system can faciliate prompt patient-centered care.

Introducing Novel Diagnostic Tools to Fortify Laboratory Capacity: Experience from Chinese Taipei Economy

Ruwen Jou

Tuberculosis Research Center, Centers for Disease Control

1

Stop TB Partnership Announcement
13 May 2016

View this email in your browser

THE STOP TB PARTNERSHIP

Leading the fight against TB

Photo: Shehzad Noorani/South Africa

Rapid diagnostic tests, shorter treatment: TB programmes now must scale up to treat and cure all people affected by MDR-TB

13 May 2016 – Geneva, Switzerland – The TB community welcomes the new WHO recommendations that aim to speed up detection and improve treatment outcomes for multidrug resistant tuberculosis (MDR-TB) through use of a novel rapid diagnostic test and a shorter, cheaper regimen.

New WHO recommendations to speed up MDR-TB detection and improve treatment outcomes

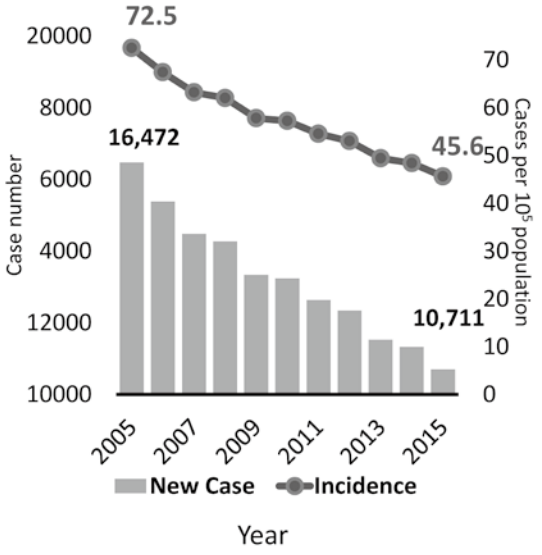
2

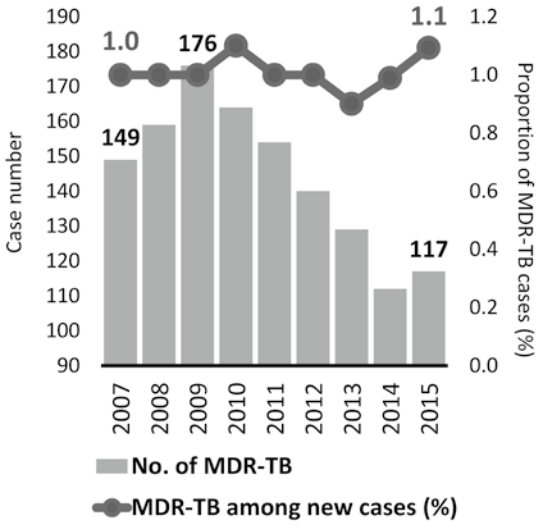
Outline

- **Practice and progress**
  - Laboratory network
  - Application of novel diagnostics
- **Challenge**
- **The way forward**

3

Incidence of TB & MDR-TB cases

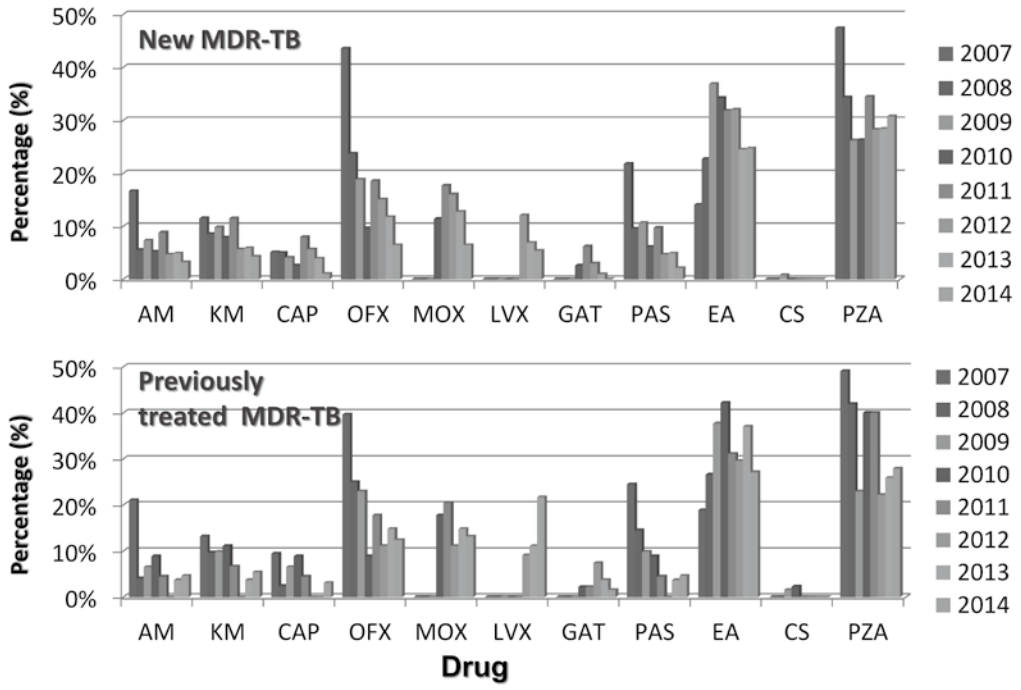




RIF resistance: New cases: 2%; retreatment cases: 10%
INH resistance: New cases: 9%; retreatment cases: 18%

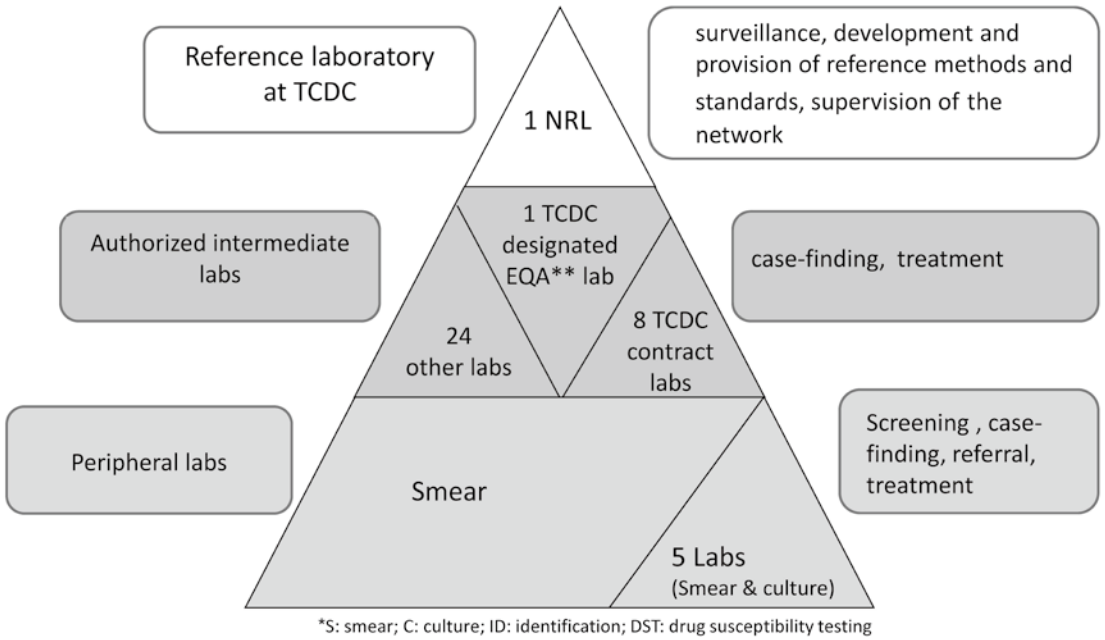
4

Surveillance of second-line drug resistance



5

Three tiers of TB laboratory services



*S: smear; C: culture; ID: identification; DST: drug susceptibility testing
** EQA: external quality assurance

6

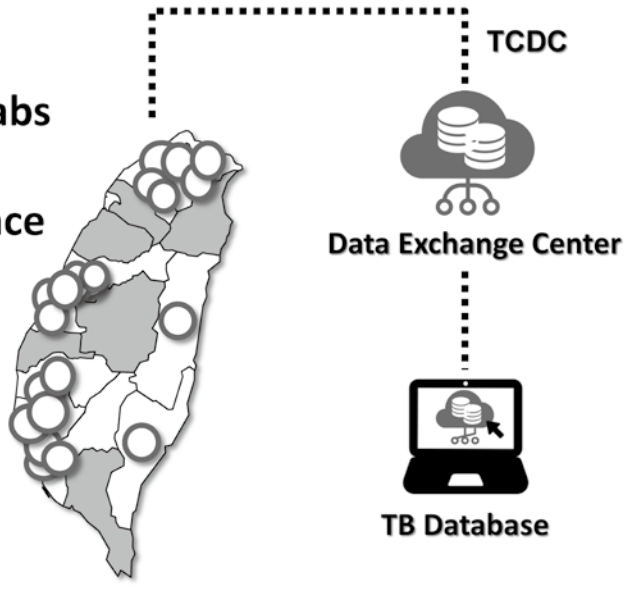
Timeline and algorithm of TB diagnosis

AFS smear microscopy	Molecular diagnosis	Culture	Identification	Universal DST
AFS 1 days all cases	ID 3-7 days all AFS(+) cases	Solid 28-42 days all cases	ICT 7 days all case with positive culture	Solid 28 days all case with MTBC
	ID & DST 3-7 days MDR-TB high-risk populations	Liquid 10-14 days all case		
	ID (BCG) 14 days Specimens from extra-pulmonary TB cases aged ≦5			

7

Timely on-line reporting of lab data

- Cover 32 authorized labs
- Receive daily reports
- Conduct DR Surveillance
- Monitor Lab quality
  - Quality index
  - Turn-around-time



8

WHO's recommendations for appropriate testing at different levels of a TB laboratory network

Laboratory level	Function	Tests
Peripheral (subdistrict and community)	Screening , case-finding, referral, treatment	AFB smear exams using either Ziehl–Neelsen stain with light microscopy, or fluorochrome stain with fluorescence microscopy (preferably with LED illumination); **Xpert MTB/RIF assay**
Intermediate (regional and district)	Case-finding, treatment follow up	All tests performed at the peripheral level and possibly culture on solid media and **LPA directly from AFB smear-positive sputum**
Central (reference)	Case-finding, treatment follow up, surveillance, development and provision of reference methods and standards, supervision of laboratories in the network	All tests performed at the peripheral and intermediate levels plus liquid culture, DST for first-line and second line anti-TB agents (including fluoroquinolones and injectable agents) on solid or in liquid media; **LPA on positive cultures and AFB-positive sputum; and rapid speciation tests**

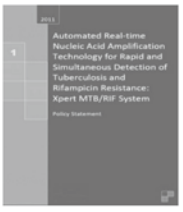
AFB, acid-fast bacilli; LED, light-emitting diode; LPA, line-probe assay; DST, drug-susceptibility testing.

9

implementation%20of%20TB%20diagnostics%209789241508612_eng.pdf

The Xpert MTB/RIF test

- In September 2010, WHO approved the Xpert MTB/RIF test
- In December 2010, WHO endorsed the Xpert MTB/RIF test
- In 2011, WHO published 3 documents



http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf

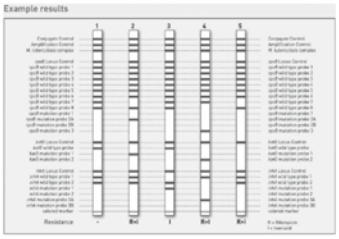
http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf

http://whqlibdoc.who.int/hq/2011/WHO_HTM_TB_2011.12_eng.pdf

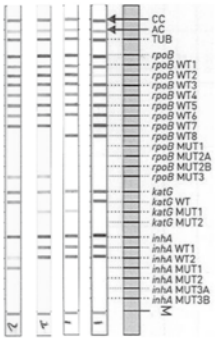
- WHO strongly recommended to test Individuals known or suspected of having TB and at high risk of MDR-TB

10

The GenoType MTBDR*plus* test



- In 2008, WHO endorsed this FL-LPA to detect resistance to isoniazid and rifampin.
- Sample:
  - direct testing of sputum smear-positive specimens
  - *M. tuberculosis* complex isolates

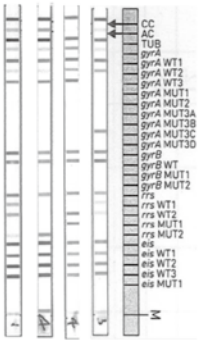


- WHO recommended to screen Individuals at high risk of MDR-TB.

http://www.who.int/tb/features_archive/policy_statement.pdf 10

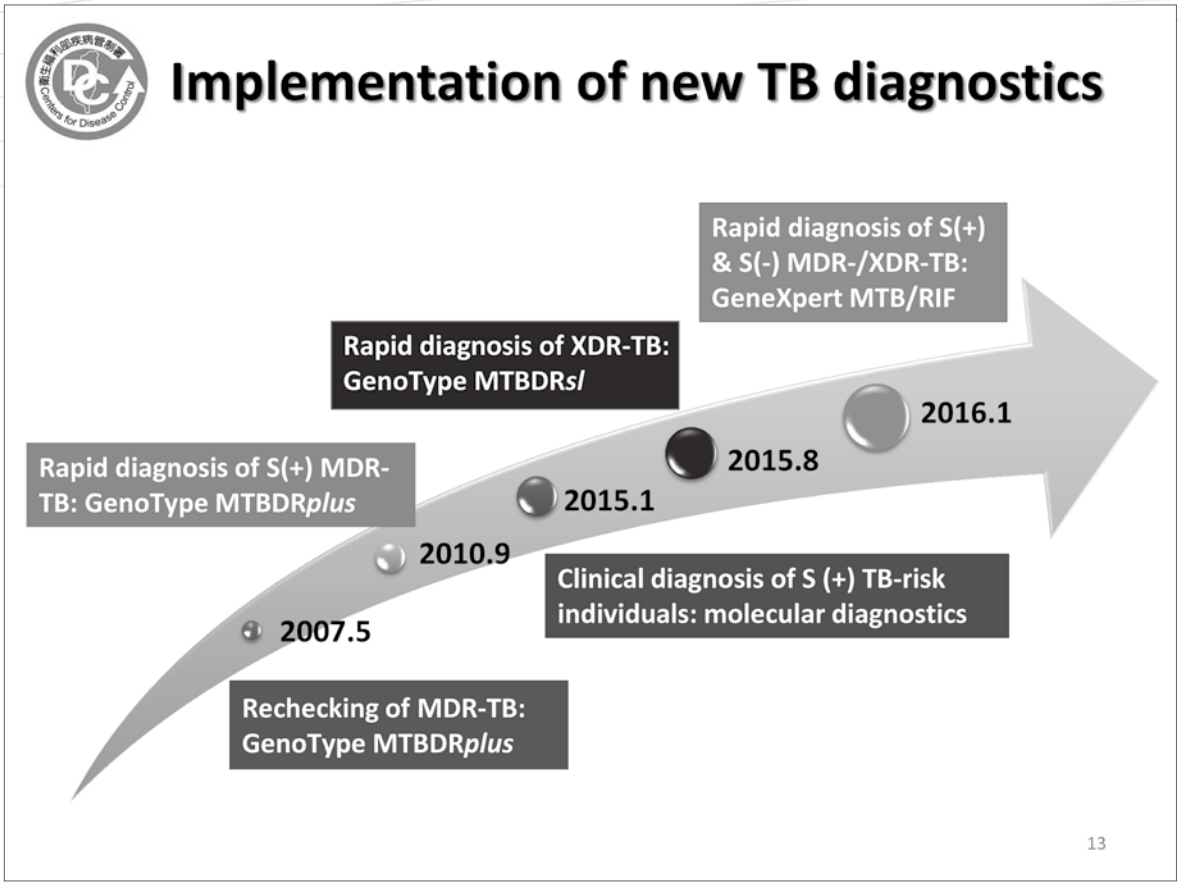
The GenoType MTBDR*sl* test

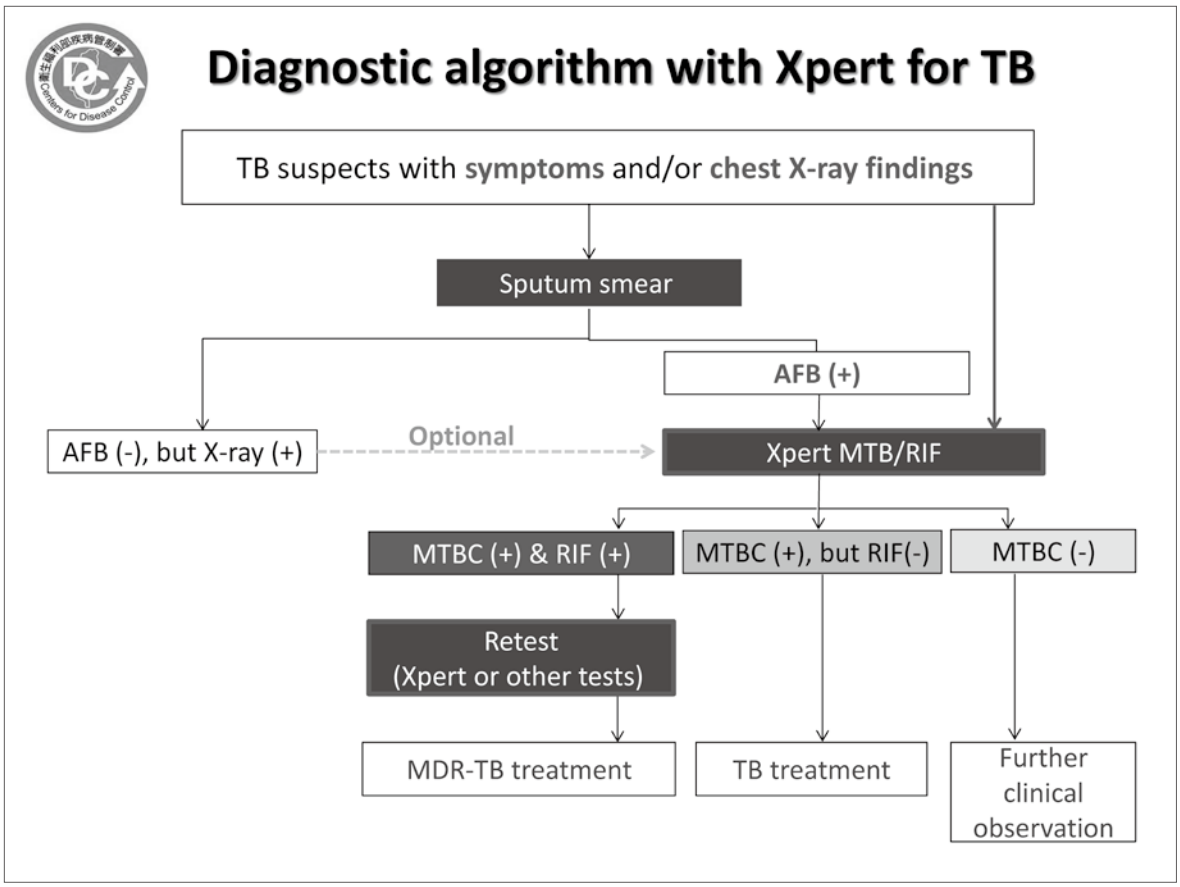
- In May 2016, WHO recommended this SL-LPA test to detect resistance to Fluoroquinolones (FLQs) and second-line injectable drugs (SLIDs).
- Sample
  - direct testing of sputum smear-positive and smear-negative specimens
  - *M. tuberculosis* complex isolates



- For patients with confirmed rifampicin-resistant TB or MDR-TB as the initial test to detect resistance to FLQs and the SLIDs, instead of phenotypic culture-based drug-susceptibility testing.

http://who.int/tb/Factsheet_SLLPAfinal.pdf?ua=1 10


Implementation of new TB diagnostics
Rapid diagnosis of S(+) & S(-) MDR-/XDR-TB: GeneXpert MTB/RIF
Rapid diagnosis of XDR-TB: GenoType MTBDRsl
2016.1
2015.8
Rapid diagnosis of S(+) MDR-TB: GenoType MTBDRplus
2015.1
2010.9
Clinical diagnosis of S (+) TB-risk individuals: molecular diagnostics
2007.5
Rechecking of MDR-TB: GenoType MTBDRplus
13


Diagnostic algorithm with Xpert for TB
TB suspects with symptoms and/or chest X-ray findings
Sputum smear
AFB (+)
AFB (-), but X-ray (+)
Optional
Xpert MTB/RIF
MTBC (+) & RIF (+)
MTBC (+), but RIF(-)
MTBC (-)
Retest (Xpert or other tests)
MDR-TB treatment
TB treatment
Further clinical observation

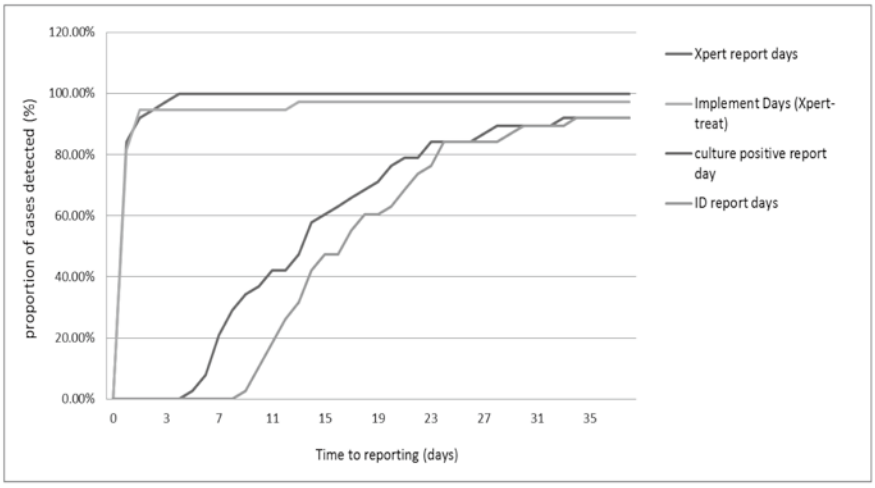
Performance of the Xpert MTB/RIF test

AFB Smear (no.)	Xpert	Culture (no.)		Culture & identification (no.)		Sensitivity (%)	Specificity (%)	PPV* (%)	NPV* (%)
		positive	negative	MTBC	Non-MTBC				
Positive (38)	positive	29	1	29	0	93.5	100.0	100.0	71.4
	negative or error	7	1	2	5				
Negative (143)	positive	5	2	4	1	57.1	95.6	80.0	88.0
	negative or error	25	111	3	22				
Scanty (6)	positive	1	0	1	0				
	negative	3	2	1	2				

* PPV: positive predictive value; NPV: negative predictive value

13

Time to diagnosis and treatment



- Turnaround time for MTBC culture-positive cases: 14 days (5-41 days)
- Turnaround time for 38 Xpert-positive cases: 0.31 day (0-4 days)
- Treatment initiation: 1st day 81.6 % and within 2 days 94.7 %

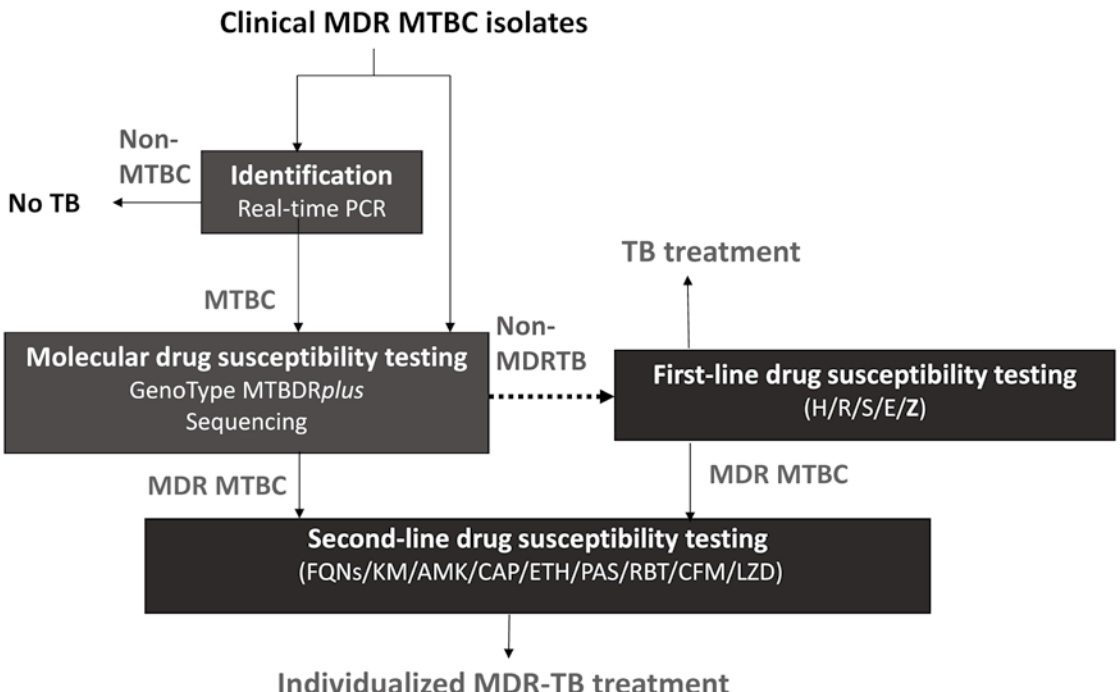
14

Molecular diagnostics adopted by TB authorized labs

IVD diagnostics	Company	Number of authorized lab
COBAS® TaqMan® MTB Test	Roche, USA	17
Xpert® MTB/RIF Test	**Cepheid, USA**	**12**
DR. MTBC Screen™ IVD Kit	DR. Chip Biotech., Chinese Taipei	9
Fastsure® TB Rapid Test	MP Biomedicals, USA	2
RAPID™ BAP-MTB Test	AsiaGen, Chinese Taipei	2
Blue Point MycoID Test	Bio Concept Inc., Chinese Taipei	2
BD ProbeTec™ ET TB Test kits	Becton, Dickinson and Company, USA	1

7

Diagnostic algorithm with FL-GenoType for MDR-TB



17

Rechecking of MDR MTBC using FL-GenoType

Case No. \ Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total	171	416	261	213	192	151	143	122	126
True MDR-TB	147	356	234	194	177	141	135	120	123
Non-MDR* (%)	**24 (14.0)**	**46 (14.4)**	**27 (10.3)**	**19 (8.9)**	**15 (7.8)**	**10 (6.6)**	**6 (4.2)**	**2 (1.6)**	**3 (2.4)**
NTM	6	14	10	6	4	2	2	0	0
Mono-INH R	4	14	4	4	3	2	2	0	0
Mono-RIF R	4	7	0	1	2	2	2	2	1
Pan-susceptible	10	25	13	8	6	4	0	0	2

*Quality and accuracy of DST; borderline resistance (agar proportion method); mixed culture of MTBC/NTM

19

Targeted diagnosis of MDR-TB

- **Targeted populations**
  - Retreatment cases
  - MDR-TB contacts or MDR-TB high-risk individuals
  - Cases from high MDR-TB incidence areas
  - Who ever lived or had a prolonged stay (more than 1 month within 1 year) in TB or MDR-TB high-burden countries

- **Case definition**

  (**2010-2015**)

  2 smear-positive specimens with positive GenoType test results

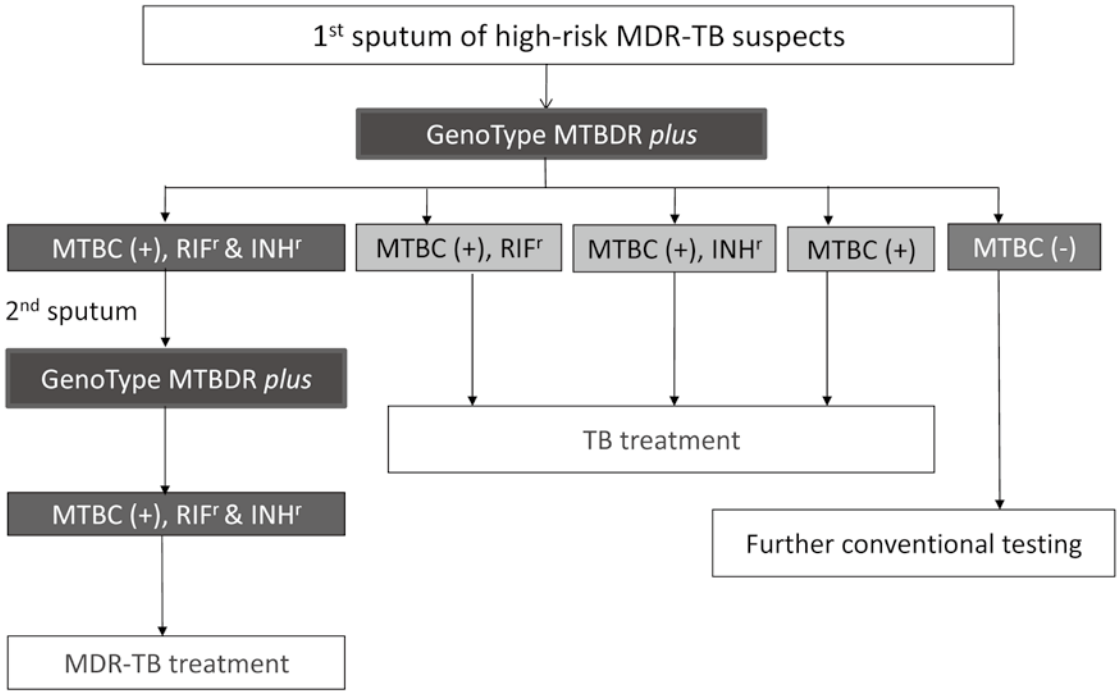
  (**2016**)

  1 specimens with both positive Xpert and GenoType test results

20

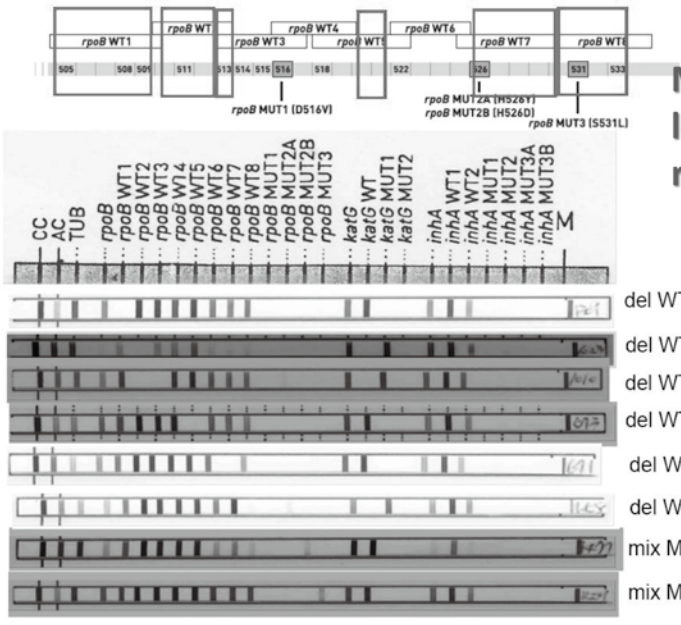
Diagnosis algorithm with FL-GenoType for MDR-TB

2010-2015



21

Discordant results between FL-GenoType and conventional DST



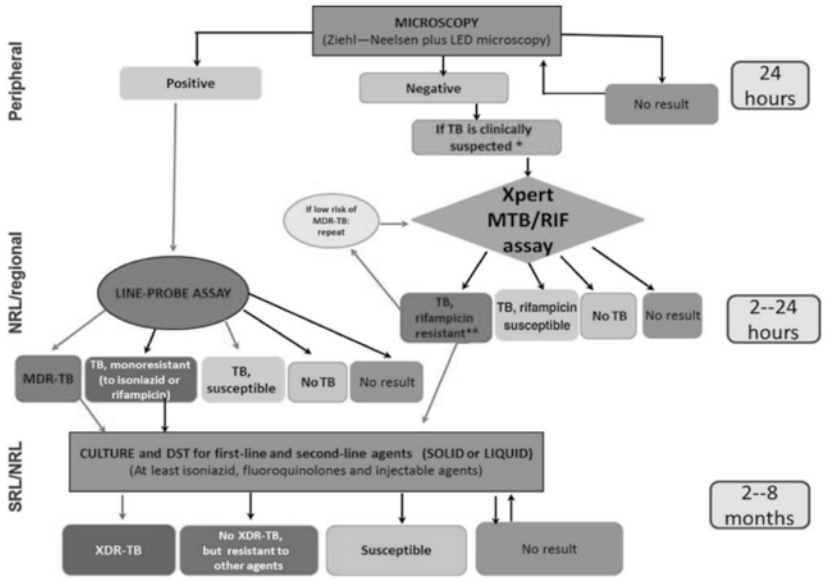
Mutations occur in the low-concentration resistance region

	GenoType	DST
del WT1 (*rpoB* 505-509)	MTBC/RIF^r	S
del WT2 (*rpoB* 511)	MTBC/RIF^r	S
del WT2,3 (*rpoB* 513)	MTBC/RIF^r	S
del WT5 (*rpoB* 520-521)	MTBC/RIF^r	S
del WT7 (*rpoB* 526-529)	MTBC/RIF^r	S
del WT8 (*rpoB* 531-533)	MTBC/RIF^r	S
mix MUT2B (*rpoB* 526)	MTBC/RIF^r	S
mix MUT3 (*rpoB* 531)	MTBC/RIF^r	S

22

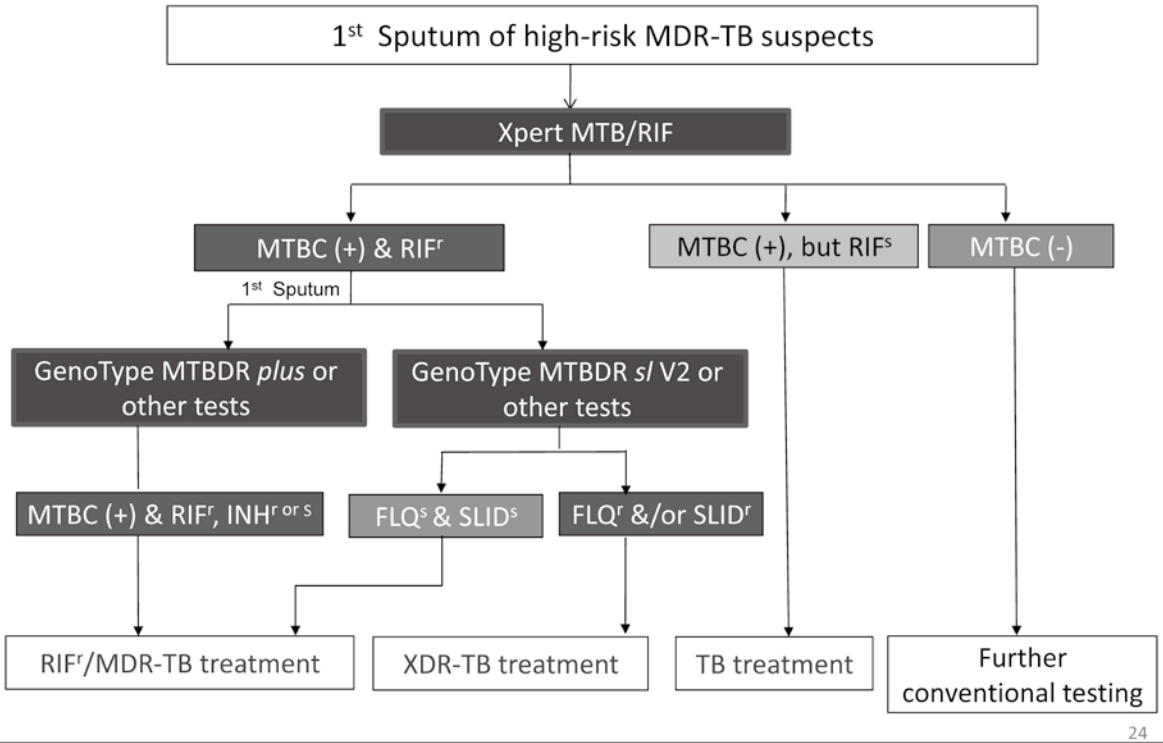
Diagnosis algorithm with Xpert/GenoType for MDR-TB

Algorithm 4. Using LPA and the Xpert MTB/RIF assay as follow-up diagnostic tests to microscopy for TB with drug-susceptibility testing for second-line anti-TB agents when necessary



23

Diagnosis algorithm with Xpert/GenoType for MDR-TB



24

Identification of MDR-TB using Xpert and SL-GenoType

2016.1.1-2016.5.20

Risk category	Case No.		Case No. (%) MTBC	RMP(R)*#	INH(R)#	MDR
Default	28	+	7 (1.7)			
		-	21			
Failure	247	+	154 (38.1)	**4**	2	**2**
		-	93			
Relapse	354	+	116 (28.7)	**12**	7	**6**
		-	238			
MDR-TB contacts	13	+	3 (0.7)			
		-	10			
Cases from high MDR-TB incidence areas	147	+	53 (13.1)			
		-	94			
Cases from high burden countries	296	+	71 (17.6)	**3**	2	**2**
		-	225			
Total case no. (%)	1,085		404 (37.2)	19 (4.7)		10 (2.5)

*: Xpert ; # : GenoType MTBDR*plus*

25

Identification of XDR-TB using SL-GenoType

2015.8.1 – 2016.5.20

Sample (Method)	Days of reporting [median]	No. (%)	FLQ	KAN	AMK	CAP	PZA
MTBC isolate (sequencing)	1-10 [3]	36 (55)	S	S	S	S	S
		20 (30)	S	S	S	S	R
		4 (6)	R	S	S	S	S
		4 (6)	R	S	S	S	R
		1 (2)	S	R	S	S	R
		1 (2)	R	R	R	R	R
Sputum[a] (SL-GenoType)	1-6 [2]	33 (72)	S	S	S	S	ND**
		5 (11)	S	R	R	R	ND
		4 (9)	R	S	S	S	ND
		4 (9)	I*	I	I	I	ND

*I, indeterminate (very low DNA content); **ND, Not done
a, follow-up test of the Xpert test

26

Challenges

- Reducing cost of new diagnostics
- Recognizing high-risk TB & DR-TB cases
- Finding smear-negative TB cases
- Screening of INH-resistant cases
- Resolving discordant results
- Improving services particularly in regions without authorized TB labs

27

The way forward

- **Policy**: Promote the use of molecular diagnostics for all patients suspected of TB
- **TAT**: Shorten time between laboratory testing and other program services
- **M&E**: Continue EQA program & impact analysis
- **R&D**: Support new diagnostics innovation

28

Acknowledgements

- TCDC contract and authorized laboratories
- Taiwan Society of Medical Technologists

- TCDC Reference laboratory of Mycobacteriology
  - Mei-Hua Wu, Pei-Hua Chuang, Wan-Hsuan Lin, Shin-Yuan Fan
  - Wei-Lun Huang, Tin-Yi Chiang, Chao-Chieh Tseng
  - Pei-Chun Chuang, Chin-Yu Chen
  - Chuan-Hsu Wang, Keng-Yu Lin

29

APEC Asia-Pacific Economic Cooperation

Thanks for your attention.

30

Speaker

Peter Cegielski

Position: Team Leader
Department/Organisation: Global TB Branch, Division of Global HIV and TB, Centers for Disease Control and Prevention
Economy: the United States

Educational Background

- MPH, University of North Carolina 1995
- Infectious Diseases Fellowship, Duke University Medical Center 1990
- Internal Medicine Residency, Duke University Medical Center 1987
- MD, University of California 1984
- BS in Biochemistry, Harvard University 1978

Professional Experience

- 2015-now Team Leader for TB Prevention Care and Treatment, Division of Global HIV and TB, US CDC
- 1998-2015 Medical Officer, then Team Leader for Drug-Resistant TB, Division of TB Elimination, US CDC
- 1996-1998 Assistant Professor, Department of Epidemiology, Johns Hopkins University School of Public Health
- 1994-1996 Assistant Professor, Department of Medicine, University of Texas Health Science Center Tyler
- 1991-1994 Assistant Professor, Division of Infectious Diseases, Duke University Medical Center

Recent Publications

- Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial versus Acquired Second-Line Drug Resistance. Clin Infect Dis. 2016;62:418-430.
- Yuen CM, Kurbatova EV, Tupasi TE, et al., including Cegielski JP (as senior author). Association between Regimen Composition and Treatment Response in Patients with Multidrug-Resistant Tuberculosis: A Prospective Cohort Study PLoSMed 2015; 12(12).
- Kurbatova EV, Cegielski JP, Lienhardt C, et al. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. Lancet Respir Med 2015; 3(3):201-209.
- Cegielski JP, Griffith DE, McGaha PK, Wolfgang M, Robinson CB, Clark PA, Hassell WL, Robison VA, Walker KP Jr., Wallace C. Eliminating tuberculosis, one neighborhood at a time. Am J Public Health. 2014;104 Suppl 2:S214-233
- Cegielski JP, Dalton T, Yagui M, et al. Extensive Drug Resistance Acquired During Treatment of Multidrug-Resistant Tuberculosis. Clin Infect Dis 2014; 59(8): 1049-1063.

Speech Abstract

Reinforcing Surveillance System of Drug-Resistant Tuberculosis

Peter Cegielski

Team Leader

Global TB Branch, Division of Global HIV and TB, U.S. Centers for Disease Control and Prevention

"Global surveillance for drug-resistant tuberculosis is the largest and oldest drug resistance surveillance program in the world. It is based on 3 core principles: proper sampling, accurate laboratory testing, and treatment history. The backbone of this system is the Supranational Reference Laboratory Network which has grown to 33 labs by 2015. The best strategy is routine, systematic drug susceptibility testing for all TB cases; by 2015, 80 countries have this system. Next best is periodic cross-sectional nationally representative surveys. By 2015, 153 countries have contributed drug resistance surveillance data representing >95% of the world's TB cases and population. MDR TB is not increasing in the short-term, but obviously has increased dramatically since rifampicin was introduced in the 1960s. In the future we will see increasing coverage, increasing testing for second-line drugs, and increasing use of molecular tests. Most importantly, drug resistance surveillance enables the public health response to be guided by evidence."

Reinforcing the Surveillance System for Drug-Resistant Tuberculosis

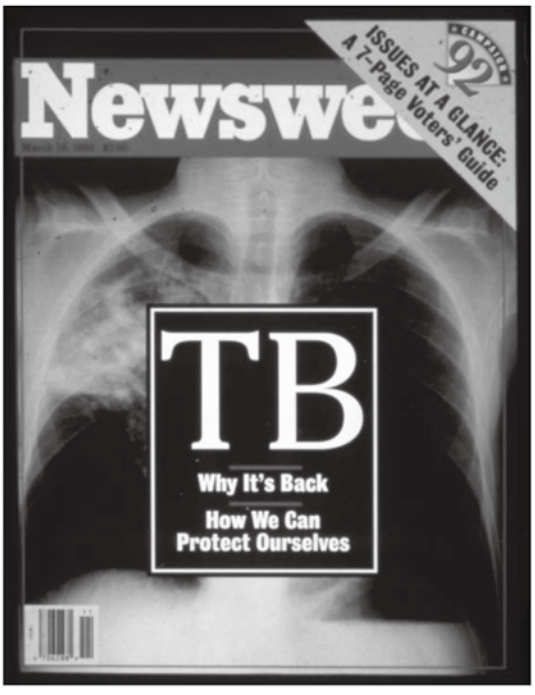
APEC Conference on
Prevention, Control and Care of MDR TB

29 June 2016
Taipei

Peter Cegielski, MD, MPH
Team Leader for Prevention, Care and Treatment
Global Tuberculosis Branch
Division of Global HIV and TB

CDC

1992: Global Awareness of Multidrug-resistant (MDR) TB



CDC

WHO / Union Global Project on Anti-TB Drug Resistance Surveillance

Oldest, largest drug resistance surveillance program worldwide

- Policy guidance describing methods and procedures for uniformity updated every 3-6 years
- Cumulative total: 153 countries
  - >95% global population and TB cases
- Number of cases
  - Cumulative total through 2010 report: 470,254
  - 2015 Global TB Report: 328,759 new + 404,731 previously treated cases with DST results in 2014

CDC

Global TB Drug Resistance Surveys: 3 Key Principles

1. Sampling
2. Laboratory testing
3. Treatment history

CDC

1. Sampling

A. Statistically valid sample accurately representing population under study
   1) Sampling strategy
   2) Clear inclusion criteria (usually sputum microscopy AFB-positive)
B. Sufficient sample size for precise estimates
   1) Usually based on new patients
   2) Determined beforehand by program
C. Efficient, cost-effective cluster sampling

CDC

2. Laboratory Testing

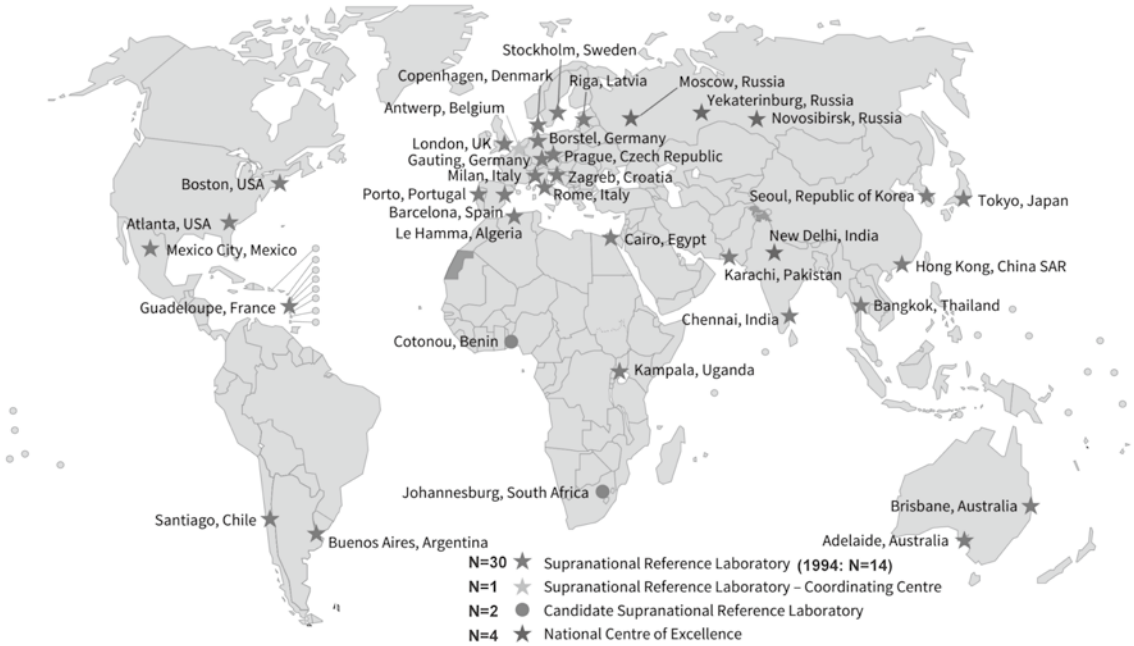
A. Quality-assured drug susceptibility testing using "gold standard" methods to ensure valid results
   1) First-line drugs: at least rifampicin, isoniazid

B. Supranational TB Reference Laboratory Network
   1) Testing centers first wave of DRS, 1994-7
   2) Transitioned to partners for training, mentoring, support for NRLs
   3) Repeat testing for ongoing EQA

CDC

SRL Network, 2016

The WHO TB Supranational Reference Laboratory Network



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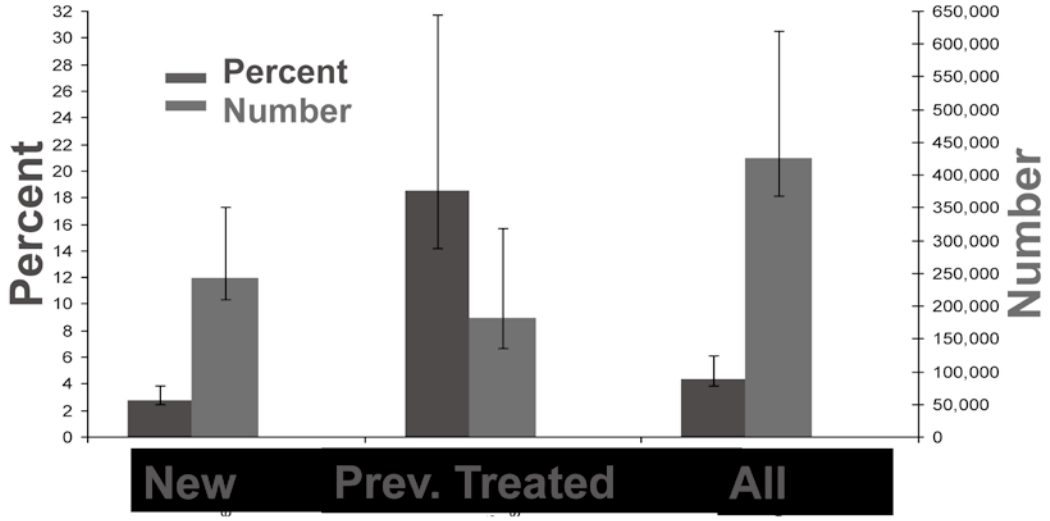
3. Treatment History: New vs. previously treated cases



WHO/IUATLD. Global DRS 4th Report, 2008.

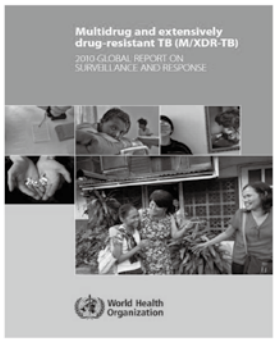
CDC

TB Drug Resistance Surveillance: 3 Distinct Strategies

1. Continuous surveillance: routine, systematic DST for all culture-positive cases
2. Cross-sectional surveys repeated every ~5 years
3. Sentinel sites

CDC

Quality of continuous drug resistance surveillance first reported 2010



- Case detection, culture positivity, DST coverage, DST accuracy
- Class A
  - >50% case detection or sputum smear positive rate
  - Positive culture >50% of notified cases
  - DST result >75% culture-positive cases
  - >95% DST accuracy INH and RIF
- Class B
  - Positive culture >35% of notified cases
  - DST result >50% culture-positive cases

Coverage of surveillance and surveys 2015:
153 countries with >95% of global population and TB cases

- **80 Countries with continuous surveillance based on routine drug susceptibility testing of TB patients**
  - **RIF result for ≥ 60% of new pulmonary TB cases**
  - **RIF result for ≥ 75% of previously treated TB cases**
  - **WHO Standards and Benchmarks: RIF result for ≥ 75% of new pulmonary TB cases**
- **73 Countries with cross-sectional epidemiological surveys of nationally representative sample of TB patients**
  - **10-15 surveys each year are ongoing**

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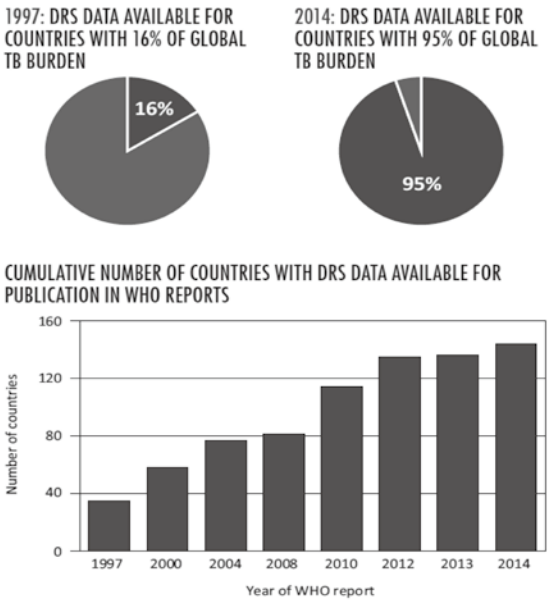
Increase in Coverage of Global DRS 1997 - 2014



WHO 2014
Global TB Report

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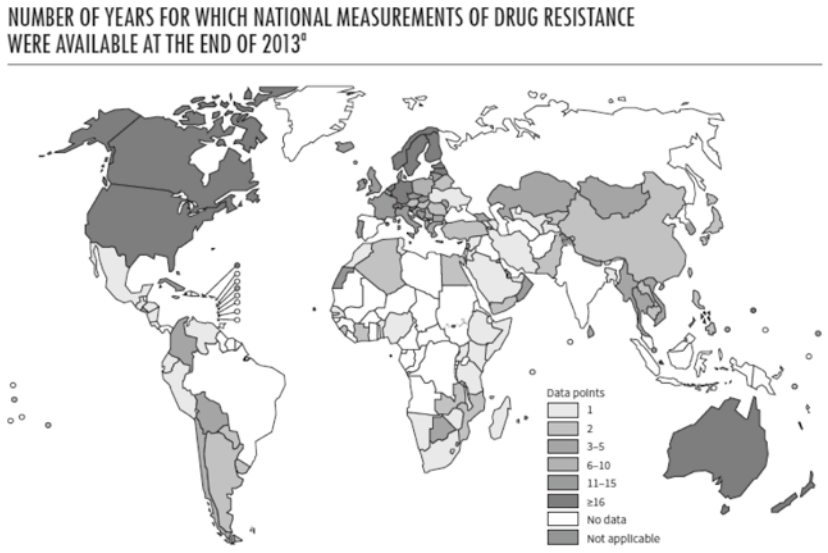
Trends in MDR TB
Continuous Surveillance or Repeated Surveys



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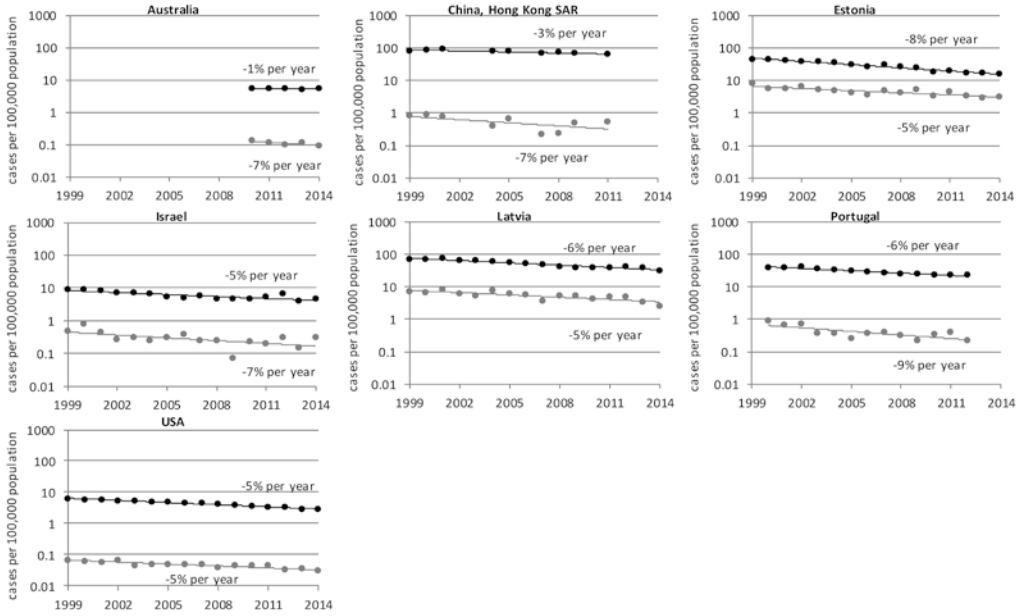
Estimated Annual Change in MDR TB*

Data from 74 countries / territories with ≥2 measurements show no clear trend at the global or regional level.

Region	Best Estimate	Low Estimate	High Estimate
Global	**- 0.3%**	**- 14.7%**	**14.1%**
Africa	5.6%	- 7.5%	18.7%
Americas	0.2%	- 17.1%	17.5%
E. Med.	- 0.7%	- 23.5%	22.0%
Europe	3.5%	- 4.8%	11.9%
SE Asia	- 1.3%	- 31.4%	28.8%
W. Pacific	- 4.5%	- 12.7%	3.8%

Decreasing trend in TB and MDR-TB 1999-2014



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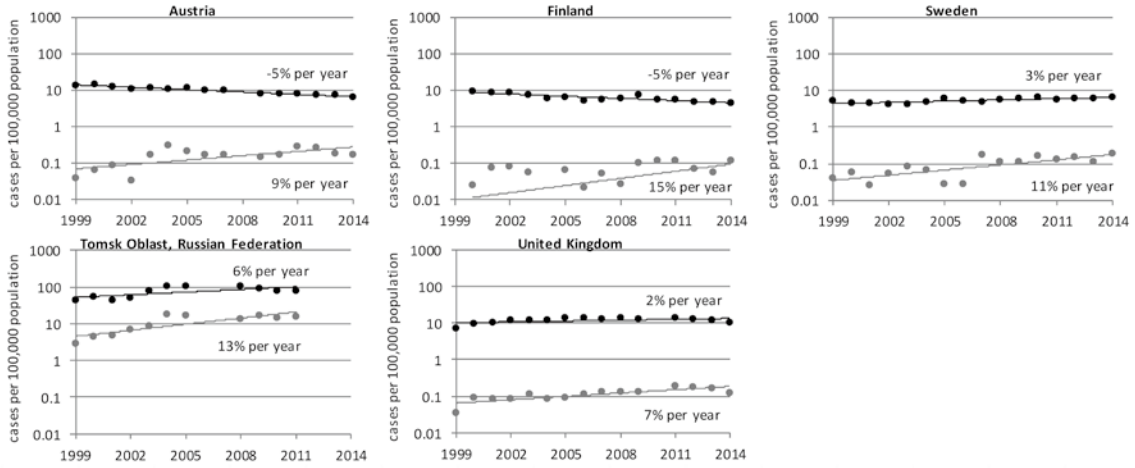
Increasing trend in MDR-TB 1999-2014



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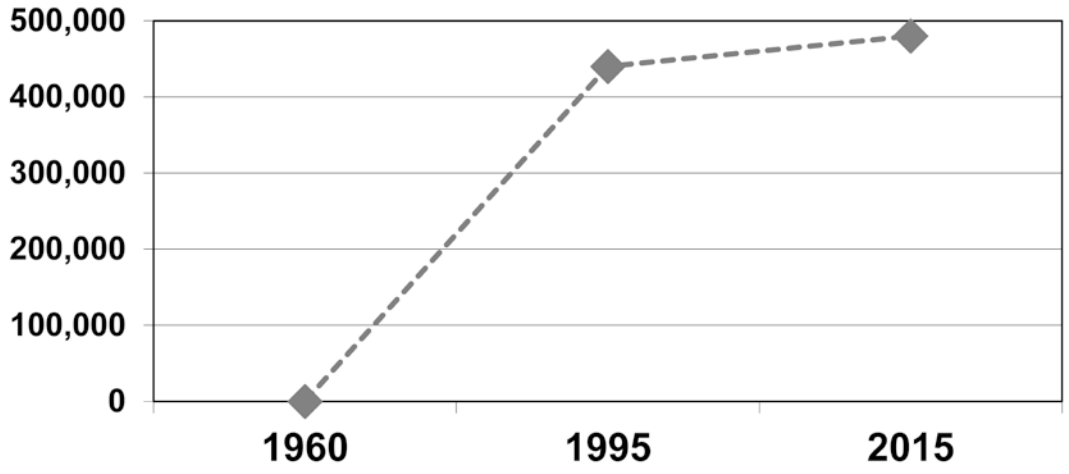
Global Trend in MDR TB, 1960-2015



CDC

Global coverage on second-line resistance among MDR-TB patients: 78 countries

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Innovations and Future Directions

- Expand testing to include more drugs
- Increase number of countries with continuous surveillance
- Incorporate molecular tests

CDC

Expand Testing to Include More Drugs

- Many countries with continuous DRS include PZA in routine testing, a few include fluoroquinolones (FQ)
- In 2013, 5 more countries incorporated testing for PZA and FQ into surveys
  - Preliminary results:
    - RIF resistance associated with PZA resistance
    - FQ resistance > RIF resistance in Asia
    - FQ resistance < RIF resistance elsewhere
- More countries adding PZA and FQ
- Need to add injectable drugs, linezolid, clofazimine, bedaquiline, delamanid

CDC

Many more countries should build capacity for continuous surveillance

- 50 countries by 2010
- 80 countries by 2015
- Includes countries with coverage only of sub-national regions (Russia, China)
- Repeat cross-sectional surveys in interim

CDC

Incorporate Molecular Tests

- Gene Xpert MTB/RIF
- Reduces logistical challenges for sample transport
- Reduces demand on labs (expertise, time, cost)
- *Universal coverage for rifampicin could be achieved*
- Depending on algorithm, does not identify resistance patterns not associated with RIF resistance, but
  - RIF resistance necessitates a change in treatment regimen
  - RIF resistance usually associated with other drug resistance

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Surveys based on molecular assays

- 18 countries
  - 6 have already used Xpert MTB/RIF
  - 7 are using Xpert MTB/RIF in 2016
  - 5 have already used line probe assays

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Use of DNA sequencing in DRS

- Most accurate molecular test available
- High throughput: up to ~ 200 strains per batch / 3-4 days
- Still requires culture, but possibly direct from sputum in near future
- Test accuracy:
  - RIF: possibly equivalent to phenotypic test
  - PZA: possibly equivalent to phenotypic test
  - INH: low sensitivity compared to phenotypic test
  - FQ: low sensitivity compared to phenotypic test
  - SLI: low sensitivity compared to phenotypic test
  - New drugs (BDQ, DLM): yet to be studied

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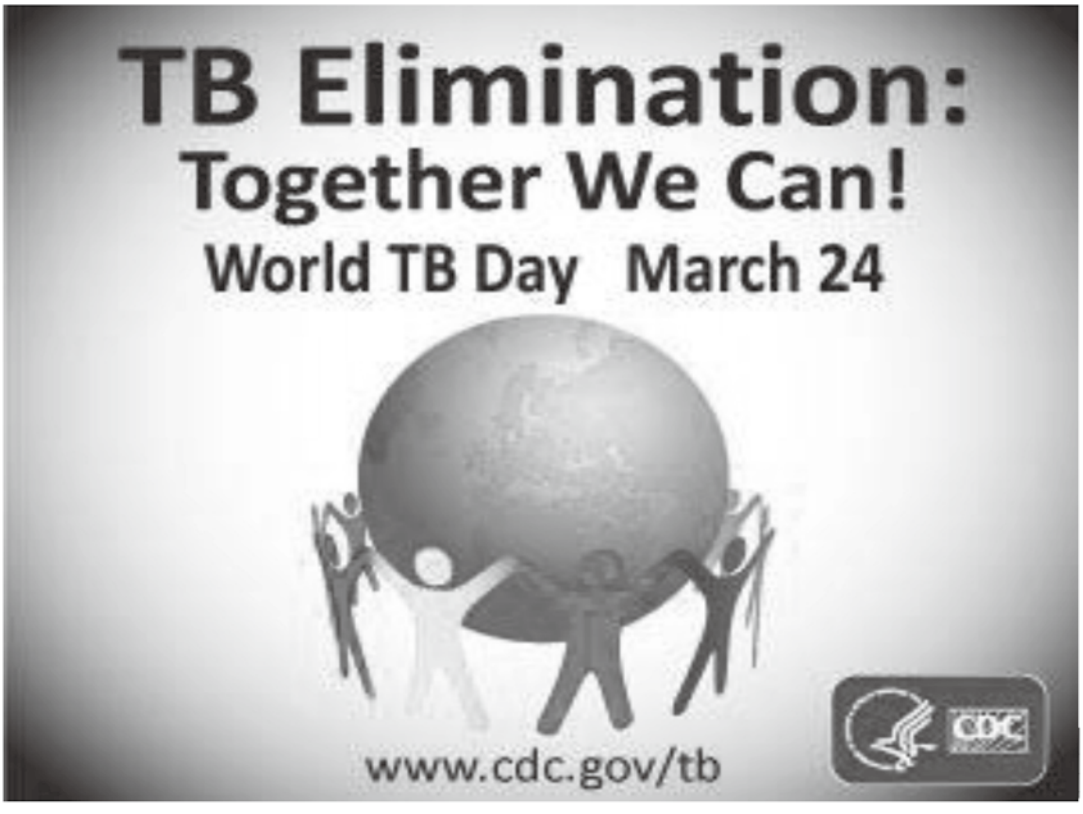
Public Health Response to MDR TB Guided by Data

- Globally, prevalence of MDR TB is low (<3%) among new TB cases in most countries
  - Nearly all of Western Hemisphere
  - Most countries in W Europe
  - Many countries in Africa and SE Asia
- Some countries have serious MDR TB epidemics
  - Eastern Europe and Central Asia (former USSR)
- >1/2 of global MDR TB in 3 countries: India, Russia, China
- MDR TB not increasing in the short term
- MDR TB not systematically associated with HIV infection
- Prevalence does not differ in children and adults

CDC

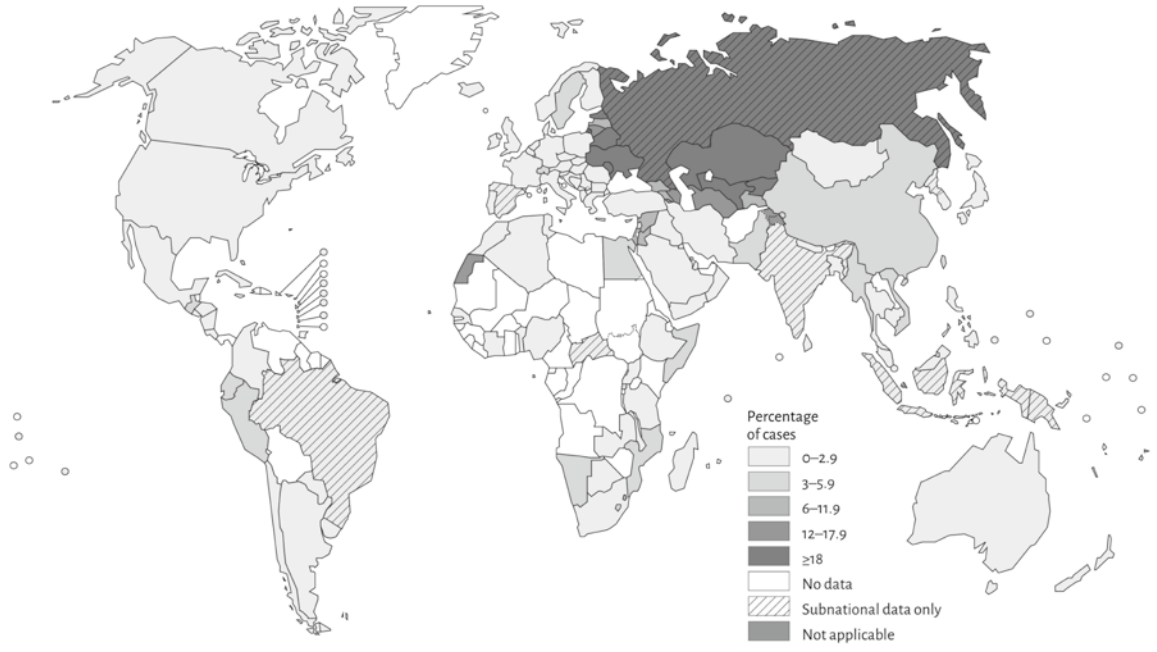

TB KILLS
OVER 4,100
PEOPLE
EVERY DAY
12
Source: TB Alliance
Photo by Yawar Nazir/Getty Images


TB Elimination:
Together We Can!
World TB Day March 24
www.cdc.gov/tb
CDC

Extra Slides

CDC

Percentage of new TB cases with MDR-TB



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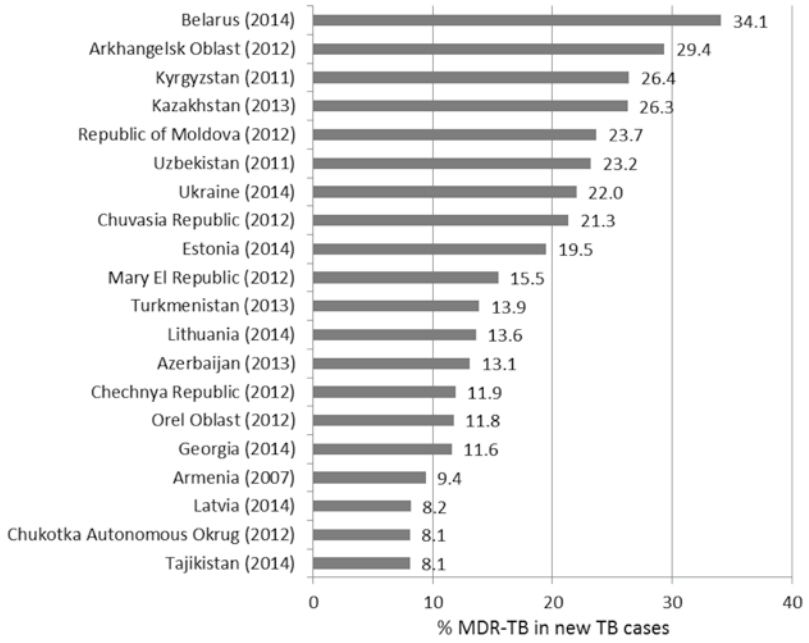
Eastern Europe & Central Asia: the highest % of MDR- TB in new TB cases in the world



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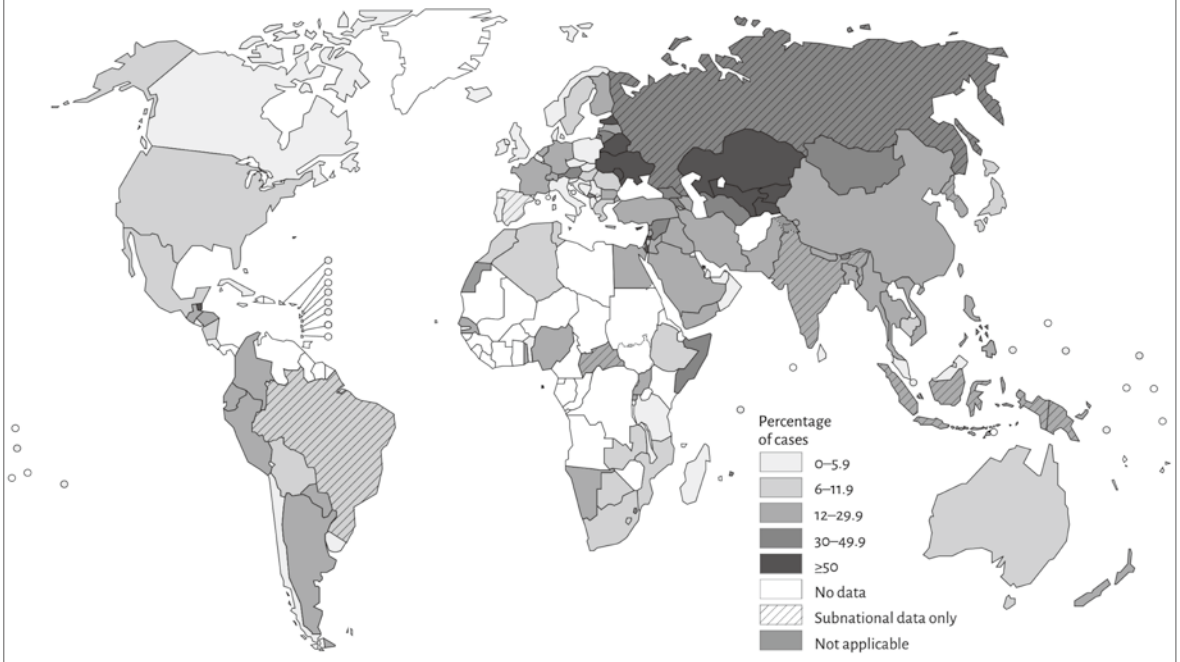
Previously treated cases with MDR-TB (%)



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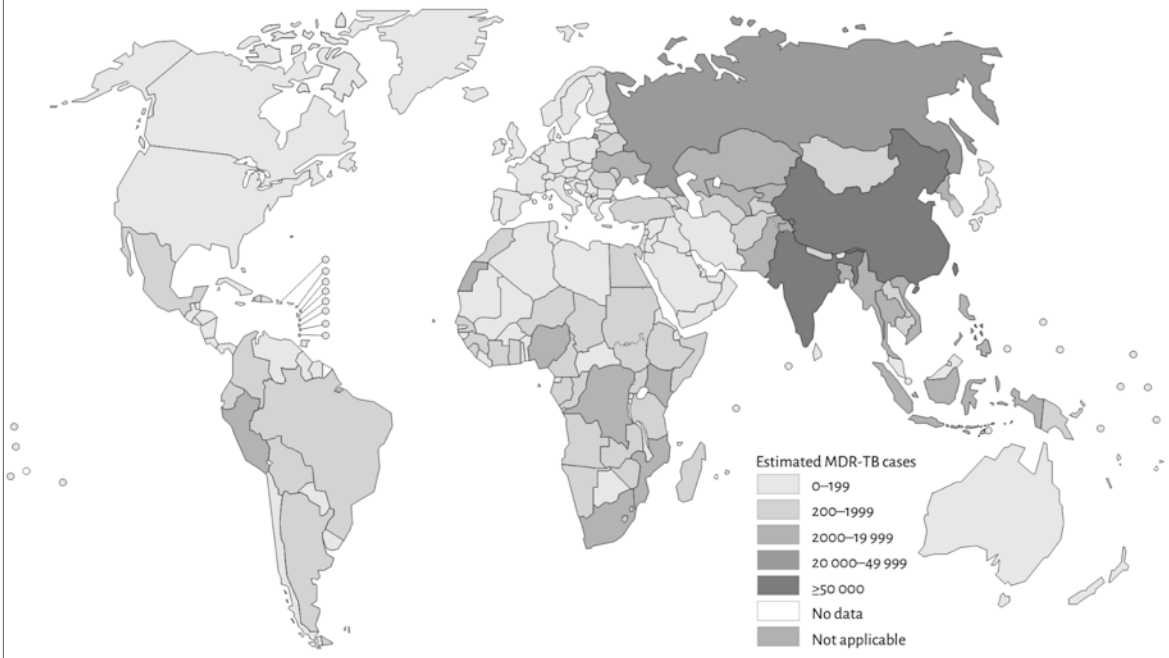
MDR-TB cases estimated to occur among notified pulmonary TB cases, 2014



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New and previously treated TB cases with MDR-TB by region and globally (%)

(latest available data)

	ESTIMATED % OF NEW TB CASES WITH MDR-TB[a]	95% CONFIDENCE INTERVAL	ESTIMATED % OF RE-TREATMENT TB CASES WITH MDR-TB[a]	95% CONFIDENCE INTERVAL
AFR	2.1	0.5–3.7	11	6.7–16
AMR	2.4	1.3–3.5	11	6.5–16
EMR	3.2	2.3–4.1	18	12–25
EUR	15	10–20	48	43–53
SEAR	2.2	1.9–2.6	16	14–18
WPR	4.4	2.5–6.3	22	18–25
Global	**3.3**	**2.2–4.4**	**20**	**14–27**

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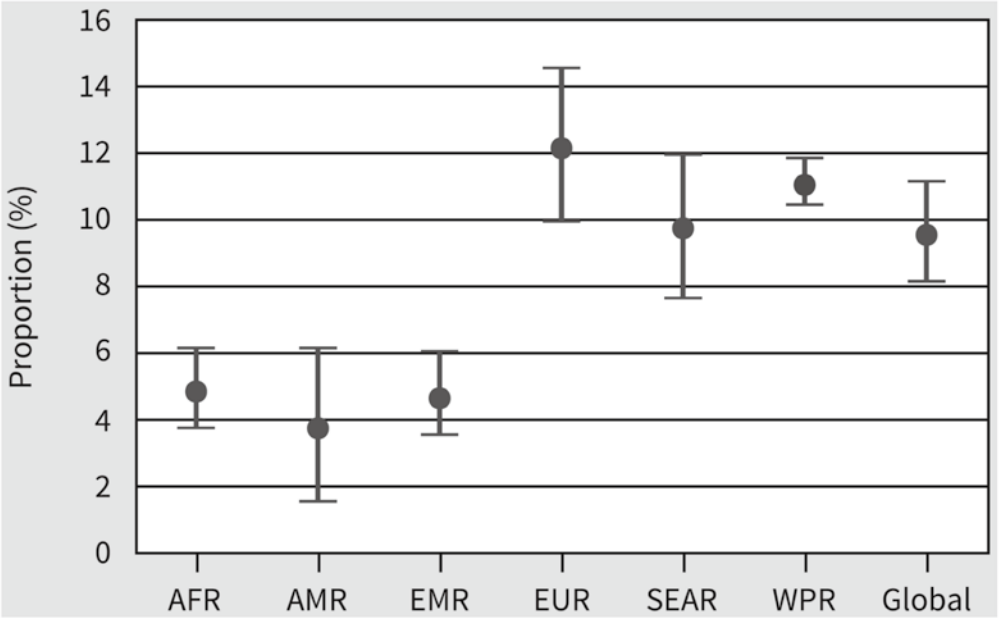
Percent TB cases with resistance to isoniazid but without resistance to rifampicin, 1994-2014



World Health Organization

GLOBAL TB PROGRAMME

END TB

Speaker

Chawetsan Namwat

Position: Director
Department/Organisation: Bureau of Tuberculosis, Department of Disease Control
Economy: Thailand

Educational Background

- Medical Doctor, Khon Kaen University, Thailand
- Master in Public Health, Mahidol University, Thailand
- Diploma, Preventive Medicine (Field Epidemiology)

Professional Experience

Epidemiology Surveillance in:
1. Communicable disease
2. Injury Surveillance
3. AIDS, TB, & STI

Research: HIV vaccine research's protocol physician

Recent Publications

- Extended evaluation of the virologic, immunologic, and clinical course of volunteers who acquired HIV-1 infection in a phase III vaccine trial of ALVAC-HIV and AIDSVAX B/E. J Infect Dis , Vol. 207 , pp. 1195-1205 , 2013 (co-author).
- Molecular evolution of the HIV-1 Thai epidemic between the time of RV144 immunogen selection to the execution of the vaccine efficacy trial. J Virol , Vol. 87 , pp. 7265-7281 , 2013 (co-author).
- The Thai phase III trial (RV144) vaccine regimen induces T cell responses that preferentially target epitopes within the V2 region of HIV-1 envelope. J Immunol , Vol. 188 , pp. 5166-5176 , 2012 (co-author).
- Is a HIV vaccine a viable option and at what price? An economic evaluation of adding HIV vaccination into existing prevention programs in Thailand. BMC Public Health , Vol. 11 , pp. 534 , 2011 (co-author).
- Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med , Vol. 361 , pp. 2209-2220 , 2009 (co-author).

Reinforcing Surveillance System of Drug-Resistance TB in Thailand

Dr. Chawetsan Namwat
Director, Bureau of Tuberculosis, DDC
Thailand

29-30 June 2016
APEC Conference on Prevention, Control and Care for Multi-Drug Resistance Tuberculosis (MDR-TB), and Supply of Second-Line Anti-Tuberculosis Drug.
Taiwan

TB Situation in Thailand, 2014

Thailand ■ Population 2014 **68 million**

Estimates of TB burden[a] 2014

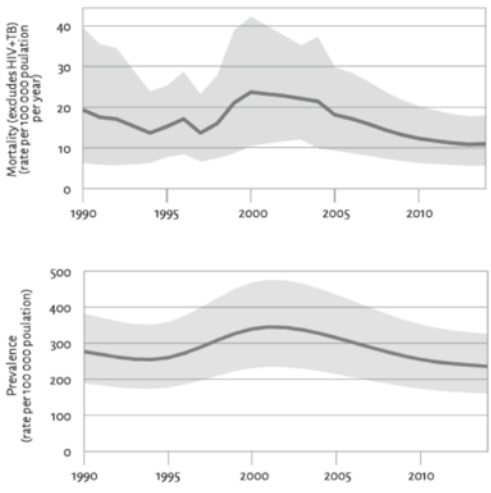
	NUMBER (thousands)	RATE (per 100 000 population)
Mortality (excludes HIV+TB)	7.4 (3.9–12)	11 (5.7–18)
Mortality (HIV+TB only)	4.5 (2.3–7.4)	6.6 (3.4–11)
Prevalence (includes HIV+TB)	160 (110–220)	236 (161–326)
Incidence (includes HIV+TB)	120 (61–190)	171 (90–276)
Incidence (HIV+TB only)	15 (7.8–24)	22 (12–36)
Case detection, all forms (%)	59 (36–110)	

Estimates of MDR-TB burden[a] 2014

	NEW	RETREATMENT
% of TB cases with MDR-TB	2 (1.4–2.8)	19 (14–25)
MDR-TB cases among notified pulmonary TB cases	1 100 (780–1 600)	1 100 (800–1 500)

TB case notifications 2014

	NEW[b]	RELAPSE
Pulmonary, bacteriologically confirmed	34 394	1 969
Pulmonary, clinically diagnosed	21 115	0
Extrapulmonary	10 244	0



Source : Global TB Report, WHO 2015

สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้กัน ป้องกันได้

TB in Thailand

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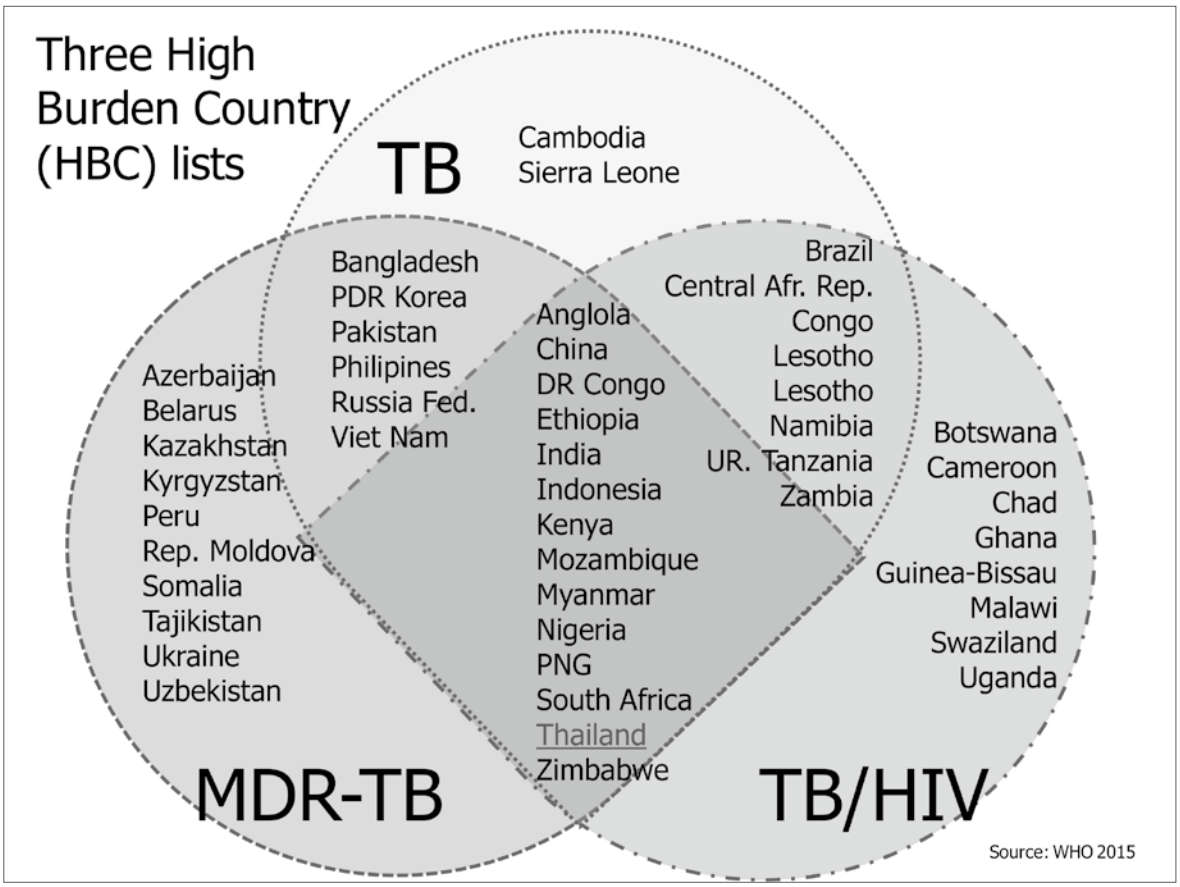


สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้กัน ป้องกันได้

Surveillance system of DR-TB

- Since 2009, there are 100 MDR-TB centers located in capital districts and large urban areas countrywide.
- During 2009-2012, MDR-TB reports from these centers were not successful due to no laboratory data for M/XDR-TB detection among risk groups.
- 9-17 October 2012, GLC monitoring visit was organized and the expert recommended the revision of R&R and full participation of community hospitals on MDR-TB care.

7

สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้กัน ป้องกันได้

PMDT Monitoring Visit,Oct.2012

24/06/2016

สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้กัน ป้องกันได้

Revised R & R of PMDT,Oct.2012

สุขภาพดี เริ่มต้นที่นี่

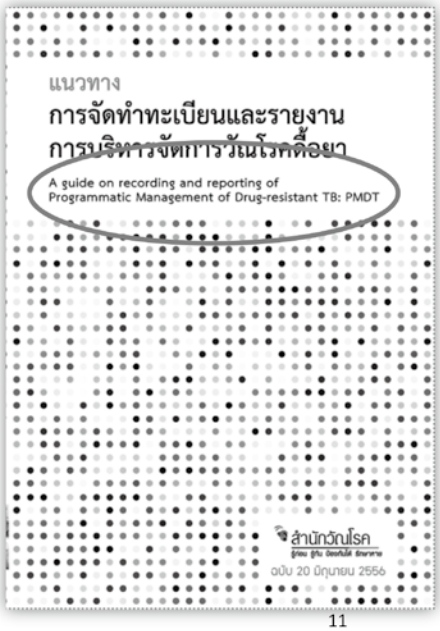
DDC กรมควบคุมโรค
รู้ก่อน รู้กัน ป้องกันได้

- **Adding PMDT items into the auditing system of the "Quality TB Clinic"**

สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้กัน ป้องกันได้

Implementing revised TB register & PMDT R&R forms to include results of culture & DST for risk groups of MDR-TB



สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้กัน ป้องกันได้

TB Register (TB 03)

TB 03 (TB Register) ว/ด/ป ขึ้นทะเบียน (Date of registration)..... TB Number..... ปีงบประมาณ (Fiscal Year).....

ผู้ป่วย (Patient information)	ที่อยู่ (Address) และเบอร์โทรศัพท์ (Tel)	ว/ด/ป ที่เริ่มรักษา และยาที่รักษา (Date of starting TB treatment and detail of regimen)	การจำแนกผู้ป่วย (Anatomical Site of TB)	ประเภทผู้ป่วย (Type of TB patients)	ผลเอกซเรย์ปอด (CXR)	ผลการตรวจเสมหะด้วยกล้องจุลทรรศน์ (Sputum smear microscopy)				ผลการรักษา (Treatment outcome)
						เดือนที่เริ่มวินิจฉัย (0)	ระยะเข้มข้น (Intensive phase)		ระยะต่อเนื่อง (Continuation phase)	
							ผู้ป่วยใหม่ เดือนที่ 2(3)	ผู้ป่วยรักษาซ้ำ เดือนที่ 3(4)	เดือนที่ 5	เดือนสิ้นสุดการรักษา (End of treatment)	
HN.....		...../...../.....	☐ P	☐ N	☐ ปกติ (Normal)					☐ รักษาหาย (Cured)
เลขที่บัตรประชาชน (National ID number)		สูตรยา.....	☐ EP	☐ R	☐ ผิดปกติชนิดมีแผลโพรง (Cavity)					☐ รักษาครบ (Completed)
ชื่อ.....		ยา / ขนาดยา (mg)/จำนวนเม็ด/วัน	สำแหน่ง.....	☐ TAF	☐ ผิดปกติชนิดไม่มีแผลโพรง (No cavity)					☐ ล้มเหลว (Failed)
สกุล.....		H		☐ TAD	☐ ไม่ได้ตรวจหรือตรวจไม่ได้ (Not done or Not applicable)					☐ ตาย (Died)
เพศ (Sex) ☐ ชาย (M) ☐ หญิง (F)		R		☐ TI						☐ ขาดยา > 2 เดือน ติดต่อกัน (Defaulted)
อายุ (Age).....ปี (Year)		Z		☐ Others		Lab. No.	Lab. No.	Lab. No.	Lab. No.	Lab. No.
น้ำหนัก (B.W.).....กก.		E								☐ โอนออก (Transferred out).....
☐ ไทย (Thai) ☐ ไม่ใช่ไทย (Non-Thai)		S				ว/ด/ป	ว/ด/ป	ว/ด/ป	ว/ด/ป	จำหน่าย (D/M/Y of treatment outcome)
☐ เรือนจำ (Prison)		อื่นๆ				...../...../.....	...../...../.....	...../...../.....	...../...../.....	...../...../.....

ผู้กำกับการกินยา (DOT observer)	การให้การปรึกษา/ผลการตรวจเลือด (HIV counseling/HIV testing)		การเจาะเลือดตรวจ CD4	การได้รับยาต้านไวรัส (ARV)	การป้องกันโรคติดเชื้อฉวยโอกาสอื่นๆ (OI)
☐ เจ้าหน้าที่สาธารณสุข (HCW)	การให้การปรึกษา (HIV counseling)	☐ ไม่ได้รับ (No) ☐ ได้รับ (Yes)	ครั้งที่ 1 วันที่ ...../...../.....	☐ ไม่ได้รับ (No)	☐ ไม่ได้รับ (No)
☐ อสม., ผู้นำชุมชน (VHV or leaders)	การตรวจเลือด (HIV testing)	☐ ไม่ยินยอม (No) ☐ ยินยอม (Yes)	ผล.....	☐ ได้รับก่อนการรักษาวัณโรค (Yes, before TB treatment) สูตรยา.....	☐ ได้รับยา Co-trimoxazole
☐ ญาติ (Family)	ผลเลือด (Result)	☐ ลบ (Neg) ☐ บวก (Pos)	ครั้งที่ 2 วันที่ ...../...../.....	☐ ได้รับหลังการเริ่มรักษาวัณโรค (Yes, after TB treatment) สูตรยา.....	☐ ยาอื่นๆ (Other) (ระบุ).....
☐ ไม่มีผู้กำกับการกินยา (No DOT)	• ผู้ป่วยที่มีผลเลือดบวกเดิม (Existing HIV positive person)		ผล.....	วันที่...../...../.....	
	• ชื่อสถานพยาบาล (Name of the hospital)			☐ NAPHA No.	
	• วันที่ (Date of HIV positive) ...../...../.....				

กรณีสงสัยวัณโรคดื้อยาหลายขนาน (Risk categories for drug resistant TB)

เพื่อเพาะเชื้อและทดสอบความไวต่อยา (Date of sputum collected for culture and DST) วันที่...../...../.....

ระบุประเภทผู้ป่วย (Type of TB)

☐ 1. ผู้ป่วยใหม่ (New)
- ○ 1.1 มีความเสี่ยง เช่น TB/HIV, มีประวัติสัมผัสผู้ป่วย MDR, ผู้ต้องขัง (Risk factors such as contact of MDR, TB/HIV, prisoners, other)
- ○ 1.2 ไม่มีความเสี่ยง (No risk factors)

☐ 2. ผู้ป่วยที่มีประวัติเคยรักษาวัณโรคมาก่อน (Relapse, TAF, TAD)

☐ 3. ผู้ป่วยระหว่างการรักษา (Still on treatment)

ได้ผลการเพาะเชื้อ (Date of results reported) วันที่...../...../.....

ผล ☐ Growth (Culture number.....) ☐ No Growth ☐ Contaminated

ผลการทดสอบความไวต่อยารักษาวัณโรค (DST results)

R = Resistant, S = Susceptible, C = Contaminated

วันที่ (Date) เก็บ (Collected)	วันที่ (Date) ได้รับผล (Reported)	วิธี[1]	S	H[2] µg/ml	H[3] µg/ml	R	E	Z	Ofx	Km	Cs	Eto	PAS	Cm	Lfx		

H^2 ช่องแรก คือ ปริมาณยา 0.2 µg/ml (Solid) หรือ 0.1 µg/ml (Liquid) ซึ่งเป็น cut off point ของการดื้อยา หมายถึง ปริมาณ H ขนาดต่ำสุดที่สามารถยับยั้งเชื้อวัณโรคได้หรือไม่ หากเชื้อไม่เติบโต แสดงว่า "ไม่ดื้อยา" แต่หากเชื้อเติบโต แสดงว่า "ดื้อยา"

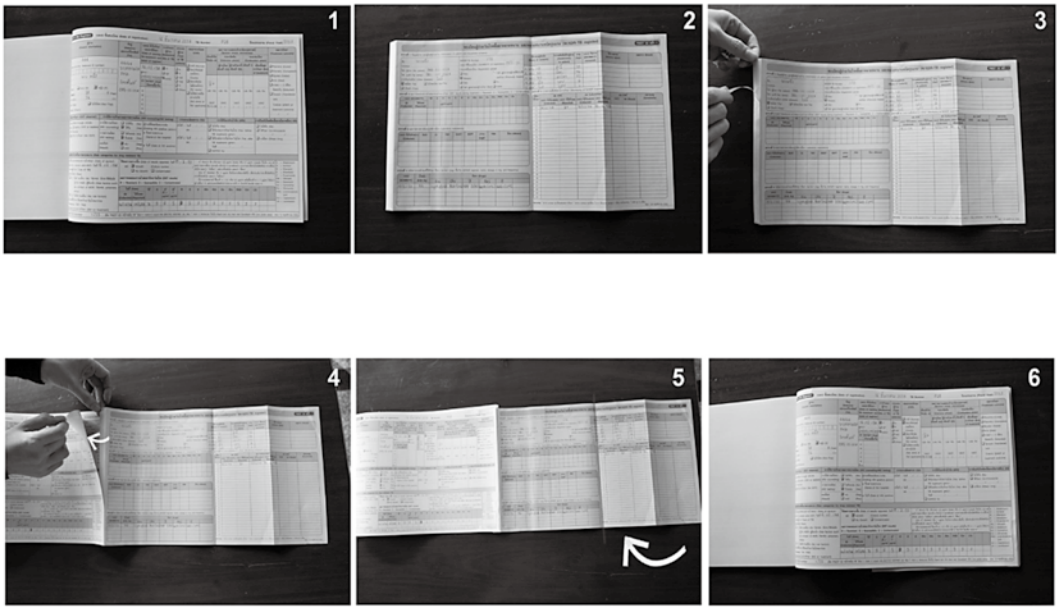
ส่วน H^3 ช่องที่สอง คือ 1 µg/ml ซึ่งเป็นการเพิ่มยาเพิ่มขึ้น เพื่อประเมินว่าหากเชื้อได้หรือไม่หากเชื้อไม่เติบโต แสดงว่า "ไม่ดื้อยา"

ซึ่งการแปลผลกรณี ดื้อยาที่ H = 0.1 หรือ 0.2 µg/ml แต่ไม่ดื้อยาที่ H = 1 µg/ml ให้มีนัยว่า ผู้ป่วยเชื้อดื้อยา H แต่ด้วยแพทย์ตัดสินใจว่ายังสามารถใช้ H รักษาได้ โดยเพิ่ม dose ยา

S = Streptomycin
H = Isoniacid
R = Rifampicin
E = Ethambutol
Z = Pyrazinamide
Ofx = Ofloxacin
Km = Kanamycin
Cs = Cycloserine
Eto = Ethinamide
PAS = *p*-aminosalicylic acid
Cm = Capreomycin
Lfx = Levofloxacin

☐ MDR-TB Number ..... (ดึง PMDT 03 หน้าหลัง) วิธี ได้แก่ 1. Solid 2. Liquid เช่น BACTEC MGIT960 และ BACTEC 460 3. Alert 3. Molecular ซึ่งเป็น Rapid test เช่น Hain test GeneXpert หรือ Line probe assay [1] ปรับปรุง: 12 พฤศจิกายน 2555

TB Register & PMDT (TB 03 & PMDT 03)



Detection of M/XDR TB, 2013

2013	Registered in TB07	Culture	DST	RR-TB	MDR-TB	XDR-TB
New(M+ & M-)	16643	4012	2467	0	115	0
Relapse	931	569	372	0	38	2
TAF of New	149	95	53	0	13	0
TAF of PrevHxRx	46	37	22	0	5	0
TALF	332	198	122	0	8	0
Other	3590	324	157	0	15	0
Total	21691	5235	3193	0	194	2

Detection of M/XDR TB, 2014

2014	Registered in TB07	Culture	DST	RR-TB	MDR-TB	XDR-TB
New(M+ & M-)	27770	6661	4655	68	149	9
Relapse	1880	826	554	21	64	1
TAF of New	268	199	114	8	20	1
TAF of PrevHxRx	65	42	30	3	6	0
TALF	416	271	197	8	19	0
Other	6171	686	307	14	39	2
Total	36570	8685	5857	122	297	13

15

Detection of M/XDR TB, 2015

2015	Registered in TB07	Culture	DST	RR-TB	MDR-TB	XDR-TB
New(M+ & M-)	33873	8986	6387	56	190	4
Relapse	1913	1127	799	20	69	1
TAF of New	255	207	147	9	23	0
TAF of PrevHxRx	95	71	46	2	15	0
TALF	437	317	248	9	17	0
Other	6018	863	504	10	55	0
Total	42591	11571	8131	106	369	5

16

Conclusion

- PMDT surveillance has been established as paper- and electronic-based system since 2012
- The detection of M/XDR is improving
- However there is still big gap for development in case detection

17

Challenges and lessons learned

- **Low coverage of DST among risk groups**
- **Limitation of paper-based reporting system**
- **Limited capacity of health care staff at community level to provide care for M/XDR-TB patients**
- **DOT for M/XDR-TB patients**
- **Inadequate living support for M/XDR-TB patients**
- **Guideline for practice staff such as psycho-social support for M/XDR-TB patients, side effect assessment/management**

18

สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้ทัน ป้องกันได้

Next steps for 2017

- Strengthen the case detection
- Improve coverage and quality of PMDT reports to monitor the progress
- Develop web-based R/R system including PMDT module
- Strengthen PMDT in all public hospitals through auditing "Quality TB Clinic"
- Build capacity of staff at community level through training, practice guide
- Secure the external fund for living support

19

สุขภาพดี เริ่มต้นที่นี่

DDC กรมควบคุมโรค
รู้ก่อน รู้ทัน ป้องกันได้

Thank you

Speaker

Hoang Thi Thanh Thuy

Position: Focal Person
Department/Organisation: Programmatic Management of Drug Resistant Tuberculosis in Viet Nam, National TB control Programme of Viet Nam/ National Lung Hospital
Economy: Viet Nam

Educational Background

- Ph.D (Life and Science), Open University, UK, 2016
- Master of Science (Public Health), Hanoi Medical University (2001-2003)
- Medical Doctor (General Practitioner), Hanoi Medical University (1989-1995)

Professional Experience

- 2010-now
  Head of MDR-TB group of NTP
  Trainers for training courses on management of drug resistant in Vietnam, since 2010
  Member of NTP secretariat
  Technical Advisor on MDR-TB issues of the Global Fund Project for TB in Vietnam
  Member of the National Treatment Committee on clinical management of drug resistant tuberculosis since 2015
  Member of the Green Light Committee of the Western Pacific Region (term from 2016-2017)
- 2008-2010
  Additional responsibility as head of PSM (Procurement and Supply Management) group/NTP
- 2004-2008
  Additional responsibility as a member of planning group /NTP
  Member of MDR-TB group of NTP
  Member of NTP secretariat
- 1995-2003
  Serving as a doctor in the NTP/ National Lung Hospital
  Supervisor in TB control for some provinces
  Coordinator in some researches

Recent Publications

- Thuy Hoang Thi Thanh, Sy Dinh Ngoc, Nhung Nguyen Viet, Hung Nguyen Van, Peter Horby, Frank GJ Cobelens and Heiman FL Wertheim. A household survey on screening practices of household contacts of smear positive tuberculosis patients in Vietnam. BMC Public Health 2014, 14:713.
- ThuyThi Thanh Hoang, Nhung Viet Nguyen, Sy Ngoc Dinh, Hoa Binh Nguyen, Frank Cobelens, Guy Thwaites, Huong Thien Nguyen, Anh Thu Nguyen, Pamela Wright and Heiman F. L. Wertheim. Challenges in detection and treatment of multidrug resistant tuberculosis patients in Vietnam. BMC Public Health 2015, 15:980.

Speech Abstract

Promising Specialized and Friendly Patient-Centred Care

Authors:
Nguyen Viet Nhung[1,2], Hoang Thi Thanh Thuy[1]

Affiliations:
[1] National Tuberculosis Control Programme of Vietnam- National Lung Hospital (VNTP-NLH)
[2] Vietnam Association for Tuberculosis and Lung Disease, Hanoi, Vietnam

ABSTRACT :

Background:

Globally, only 50% of multi –drug resistant tuberculosis (MDR-TB) patients were successfully treated. That leaves about 50% patients died, failure, lost to follow up or not assessed. This unfavorable outcome may relate to lack of adherence to treatment due to adverse drug reaction (ADR), inconvenience treatment service, stigma, other psychology-socio-economy (PSE) difficulties. In order to improve adherence to treatment, reduce stigmatization and better treatment outcomes, the WHO have recommended patient center approach. The approach establishes collaboration between patient and provider with their rights and responsibilities to achieve treatment success with dignity.

Vietnam ranks at 11st among 30 countries with high burden of MDR-TB with estimation of 5.100 MDR-TB cases among notified TB cases per year. Vietnam has started programmatic management of drug resistant TB (PMDT) since 2009). Policy for patient centered approach has been stepwise developed and introduced in the light of the WHO recommendation.

Policy and activities:

Patient centered approach to increase the number of MDR-TB patients enrolled on treatment and improve treatment outcome. Variety of activities have been stepwise proposed and introduced as promising specialized and friendly care including (i) increase accessibility to treatment service by expansion of PMDT network and development of suitable models of care (ii) establishment of patient support system to increase adherence to treatment and reduce stigma with directly observed treatment (DOT) supporters, enable for food and travelling, health insurance system, PSE supporters, (iii) introduce pharmacovigilence (PV) system to detect and treat adverse drug reaction to improve treatment outcome and reduce lost to follow-up, (iv) establish the collaboration between PMDT and non-PMDT servicefor referring patients between two sectors and ensure treatment quality in non PMDT service, (v) Introduce short course regimen for MDR-TB to facilitate adherence, new drug (Bedaquiline) to improve treatment outcome of for patients resistant with second line TB drugs, patients intolerable or have ADR with current MDR-TB drugs, (vi) pilot a strategy (FAST)that contribute to shorten time from notification to treatment and ensure effective treatment.

Result and recommendation:

The number of MDR-TB patients enrolled for treatment increased over the years (up to 1500-2000 MDR-TB cases per year). The treatment success rate for MDR-TB in Vietnam has been stable at around 70%, which is higher than global level. This result may reflect a promising Patient-Centred Care adopted by PMDT of Vietnam. However, so far a significant number of patients diagnosed but not enrolled for treatment (5-10%), died (7-8%), failure (7%), lost to follow up (7-10%, even much higher among patient treated outside PMDT). For these reasons, Vietnam need to continue improve treatment enrollment and treatment outcome using patient centered care approach.

Vietnam-Promising Specialized and Friendly Patient-Centred Care

Taipei, June 2016

Content

- Introduction about Vietnam's Programmatic Management of Drug resistant Tuberculosis (PMDT) and drug resistant tuberculosis (TB) situation
- Patient centred approach:
  - The approach recommended by the WHO
  - Policy and activities implemented in Vietnam
- Result and recommendation

Vietnam

- Surface 330.000 km^2
- Border: China, Laos, Cambodia
- Provinces: 63
- Districts: 683
- Communes: 11,042
- Pop.: 92 milion

Situation of Drug-resistant TB in Viet Nam

	DRS 3 (06-07)	DRS 4 (11-12)
MDR rate among new TB patients	2.7 % (2.0-3.6%)	**4.0 % (2.5 - 5.4%)**
MDR rate among retreated patients	19% (14-25%)	**23.3% (16.7-29.9)**
The number of MDR-TB patients among the number of new TB patients every year	2000 (1500-2700)	3000
The number of MDR-TB patients among the number of retreated patients every year	1700 (1200-2200)	2100
Total number of MDR-TB patients among total number of TB patients every year	3700	5100
XDR-TB/MDR-TB		**5.6%**
FQ res/MDR-TB		**16.7%**

The result of 4th DRS (2011)

- Result is similar to Western Pacific countries (WHO report 2012):
  - New: 4.8% (95% CI: 3.4 – 6.1)
  - Retreatment: 22% (95% CI: 18 – 26)
- Drug resistance has increased so NTP should continue to prioritise:
  - Scale-up and strengthen Programmatic Management of Drug resistant TB (PMDT)
  - Improve the detection and enrollment for treatment
  - Strengthen treatment management, especially when implement 6 month regimen with Rifampicine during entire treatment course to ensure that cured rate is high and the increase of Multi-Drug resistant TB (MDR-TB) is controlled

Patient centred approach recommended by the WHO

- **Rational:**
  - Globally, only 50% of MDR-TB patients were successfully treated→50% patients died, failure, lost to follow up or not assessed
  - Poor outcome relates to lack of adherence to treatment due to adverse drug reaction (ADR), inconvenience treatment service, stigma, other psychology-socio-economy (PSE) difficulties→ need to address to improve adherence to treatment and treatment outcome
- **Recommendation**
  - Patient center approach: establishes collaboration between patient and provider with their rights and responsibilities to achieve treatment success with dignity.

Patient centred approach - implemented in Vietnam

- **Policy to implement patient centered approach to :**
  - Increase the number of MDR-TB patients enrolled on treatment
  - Improve treatment outcome.
- **Activities under the policy**

Patient centred approach implemented in Vietnam-activities

- Increase accessibility to treatment service:
  - Expansion of PMDT network: More treatment sites and satellite sites → patients not have to travel so far, willing to be enrolled and adhere to treatment
  - More suitable models of care to facilitate patient's adherence: hospital based care (at TB hospital or general hospital in province without TB hospital available), ambulatory clinic based care (DOT clinic at province, district or communal levels)

Year	2009	2010	2011	2012-2013	2014-2015	2016
PMDT provinces	1	6	20	35	45	51

Patient centred approach implemented in Vietnam-activities

- Patient support system to increase adherence to treatment and reduce stigma:
  - Directly observed treatment (DOT) supporters:
    - Oil-slick training model is used for cost saving
    - Provide information to patients and family about TB treatment prior to and during treatment
    - Observation of drugs taken

Patient centred approach implemented in Vietnam-activities

- Patient support system to increase adherence to treatment and reduce stigma:
  - Directly observed treatment (DOT) supporters:
    - Education of infection control (IC)
    - Recognition of ADR
    - Members involved : health staff, family member, cured MDR-TB patients

Patient centred approach implemented in Vietnam-activities

- Patient support system to increase adherence to treatment and reduce stigma:
  - PSE supporters
    - Trained on communication skills and psychology of TB patients
    - Give consultation for any psychological difficulties challenged the patients to reduce stigma
    - Currently recruited PSE staff, to be involved by community volunteers in the future

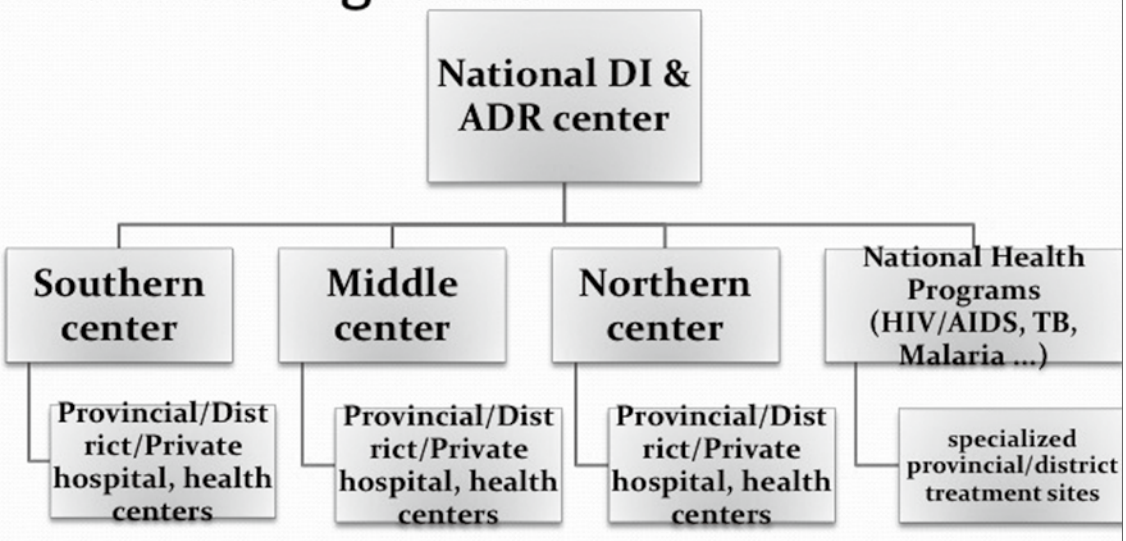
Patient centred approach implemented in Vietnam-activities

- Patient support system to increase adherence to treatment and reduce stigma:
  - Enable for food and travelling: Global Funds, local charity organization
  - Health insurance system

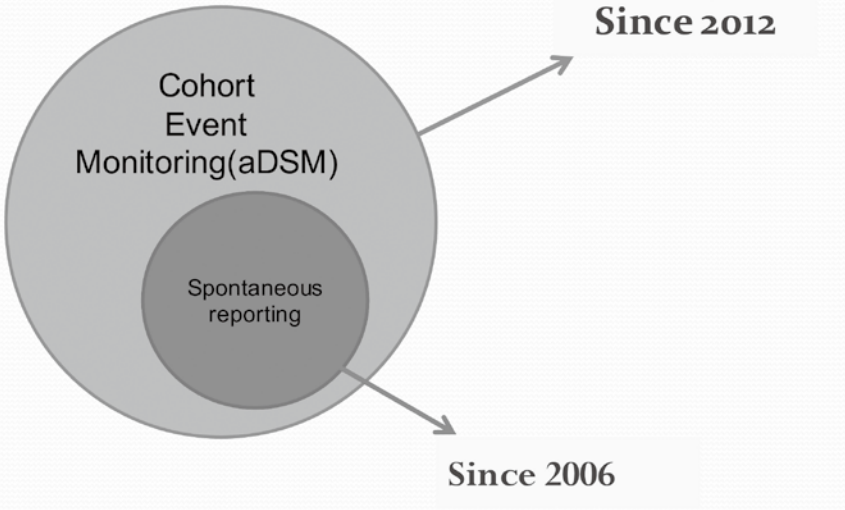
Patient centred approach implemented in Vietnam-activities

- Introduction of pharmacovigilence (PV) system to detect and treat adverse drug reaction to improve treatment outcome and reduce lost to follow-up
- Ancillary drugs for adverse reaction treatment

Pharmacovigilance



PV methods in NTP



Patient centred approach implemented in Vietnam-activities

- Establish the collaboration between PMDT and non-PMDT service:
  - For referring MDR-TB presumptives from non PMDT-PMDT service to increase MDR-TB diagnosis
  - To provide quality of treatment service to MDR-TB patients (general hospital) by training, facility upgrade
  - Mechanism to refer patients between two sectors based on patient's need to ensure the continuation of treatment

Patient centred approach implemented in Vietnam-activities

- Pilot a strategy (FAST)that contribute to shorten time from notification to treatment and ensure effective treatment:
  - **FAST is a strategy** consists of components: Finding TB and MDR TB cases Actively, Separating safely, ***Treating effectively***
  - **Measuring times as important process indicators**
    - Time from cough detection to sputum collection
    - Time from sputum collection to lab
    - Time from lab to result
    - Time from result to notification
    - ***Time from notification to treatment***
  - Adaptation to different settings (criteria, protocol , Algorithm for diagnosis and treatment initiation, Monitoring,Recording/ reporting,Supervision and evaluation)

Results

- The number of MDR-TB patients enrolled for treatment increased over the years

Enrollment	2009	2010	2011	2012	2013	2014	2015	Total
The number of enrolled patients	101	97	578	713	948	1532	2131	6100
% of enrollment	3%	3%	16%	19%	25%	30%	42%	

Results

- The treatment success rate for MDR-TB in Vietnam has been stable at around 70%, which is higher than global level

Year	cured	Com.	Died	Failled	Loss to f.up	Not acessed	Success
2009	62%	11%	8%	7%	9%	3%	73%
2010	72%	6%	8%	7%	6%	0%	78%
2011	61%	11%	7%	7%	13%	1%	72%
2012	55%	15%	10%	6%	12%	3%	70%
2013	53%	16%	9%	7%	14%	1%	69%

Conclusion and recommendation

• The increased number of patients enrolled for treatment and the favorable success rate achieved may reflect a promising Patient-Centred Care adopted by PMDT of Vietnam.

• However:

- •So far a significant number of patients diagnosed but not enrolled for treatment (5-10%)
- •Unfavorable treatment outcome: died (7-8%), failure (7%), lost to follow up (7-10%, increase when expansion, higher among patient treated outside PMDT)

→ Vietnam need to continue improve treatment enrollment and treatment outcome using patient centered care approach.


CHƯƠNG TRÌNH CHỐNG LAO QUỐC GIA
BỘ Y TẾ
THANK YOU

Speaker

Hyungseok Kang

Position: Director
Department/Organisation: Department of Chest Medicine, Masan National Hospital
Economy: Republic of Korea

Educational Background

- Mar. 2008- Feb. 2009 Residentship, Department of Chest Medicine, Masan National Hospital, Changwon-si, Korea
- Mar. 2006- Aug. 2006 Fellowship, Department of Thoracic and Cardiovascular Surgery, Daegu Catholic University Medical Center, Daegu, Korea
- Mar. 1999- Feb. 2003 Residentship, Department of Thoracic and Cardiovascular Surgery, Daegu Catholic University Medical Center, Daegu, Korea
- Mar. 1992-Feb. 1998 School of Medicine, Catholic University of Daegu, Daegu, Korea

Professional Experience

- Sep. 2014-now, Director, Dep. of Chest Medicine, Masan National Hospital
- Apr. 2008-Aug. 2014, Medical and Research Staff, Dep. Of Chest Medicine, Masan National Hospital
- Sep. 2006-Mar. 2008, Research Doctor (Medical Official), Clinical Research Center, Masan National Hospital Clinical Research Department, International Tuberculosis Research Center

Recent Publications

- Impact of diabetes and smoking on mortality in tuberculosis. PLoS One. 2013;8(2):e58044.
- Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort. Int J Tuberc Lung Dis. 2012 Jul;16(7):961-6.
- Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries,.Lancet. 2012 Oct 20;380(9851):1406-17.
- Evaluation of Reverse Hybridization Assay for Detecting Fluoroquinolone and Kanamycin Resistance in Multidrug-Resistance Mycobacterium tuberculosis Clinical Isolates, Tuberc Respir Dis 2012;72:44-49.
- Patterns of pncA mutations in drug-resistant Mycobacterium tuberculosis isolated from patients in South Korea. Int J Tuberc Lung Dis. 2012 Jan;16(1):98-103.

Speech Abstract

Promising Specialized and Friendly Patient-Centred Care

Hyungseok Kang
Director
Department of Chest Medicine, Masan National Hospital, Republic of Korea

The best way to lead an MDR TB patient to a successful outcome is through patient-centered care based on his/her need and mutual respect between the patient and the provider. In the aspect of PMDT, patient-centered approach has been endorsed and emphasized through a variety of recommendations and guidelines in the manner of standard care.

I would like to introduce the program and system provided to MDR TB patents in a TB hospital setting in Korea; deciding the appropriate regimen, delivering the medications, monitoring, educating and counseling from A to Z as well as continuing care after discharge in the perspective of patient centered care.

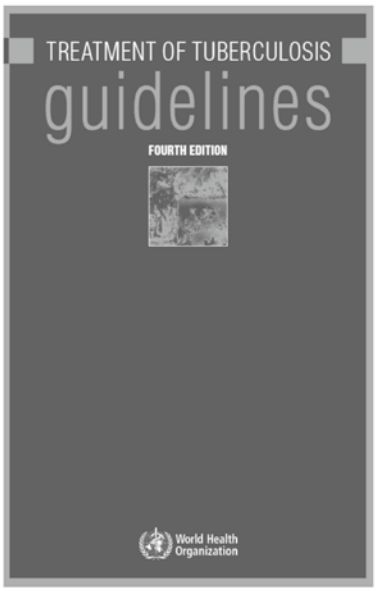
The history of fighting against Tb in Korea has been successful but still there are several barriers that slow down our country in reaching the state of 'Elimination of TB'. Since 2006, 'Plan 2030' was announced, a variety of case management services in the aspect of patient centered approach started to help MDR TB patients and to speed up the decrease in the number of notified TB cases. We have noted a remarkable improvement of MDR TB management indices.

Key Words: MDR TB, patient-centerd care, PMDT

Promising Specialized and Friendly Patient-Centered Care

Masan National TB Hospital, Korea

Director of Dep. of Chest Medicine
Dr. Hyungseok Kang



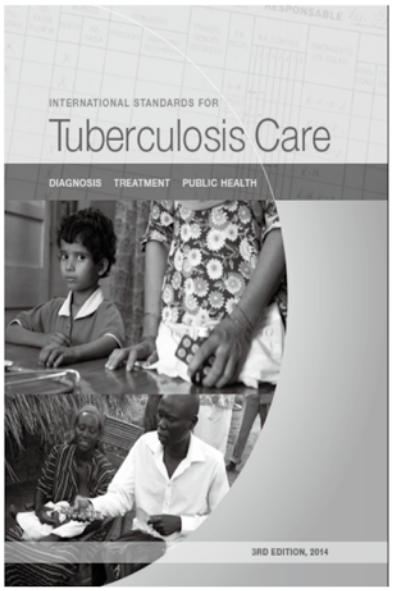
6

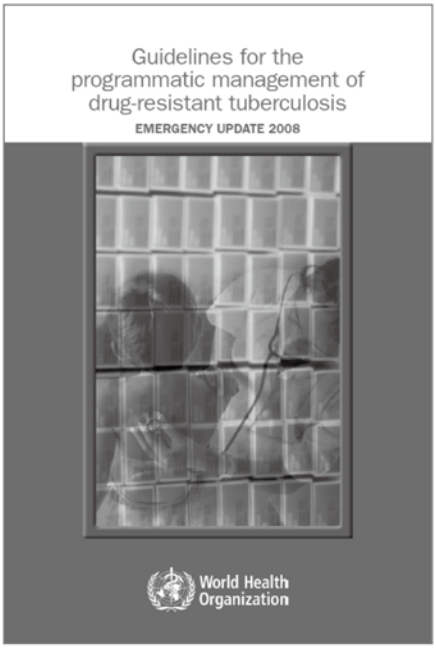
Supervision and patient support

6.4 Using a patient-centred approach to care and treatment delivery

'It is essential that these approaches be based on ethical principles regarding the needs, rights, capabilities and responsibilities of patients, their families and their communities.'

Standard 9. A patient-centered approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider.





CHAPTER 19

Managing DR-TB through patient-centred care

Successful management of DR-TB requires putting the patient at the centre of a comprehensive programme of care that includes allows patients to exercise their rights. This, in turn, enables patients to fulfill their responsibilities and assist in the treatment success.

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PERSPECTIVES

Language in tuberculosis services: can we change to patient-centred terminology and stop the paradigm of blaming the patients?

R. Zachariah,* A. D. Harries,†‡ S. Srinath,§ S. Ram,¶ K. Viney,# E. Singogo,** P. Lal,§ A. Mendoza-Ticona,††
A. Sreenivas,§ N. W. Aung,‡‡ B. N. Sharath,§§ H. Kanyerere,¶¶ N. van Soelen,## N. Kirui,*** E. Ali,*
S. G. Hinderaker,††† K. Bissell,† D. A. Enarson,† M. E. Edginton†

~~'defaulter'~~	→	'person lost to follow-up'
~~'TB suspect'~~	→	'person with presumptive TB'
~~'control'~~	→	'prevention and care'

Masan National Tuberculosis Hospital

Key Component of Patient Centered Care

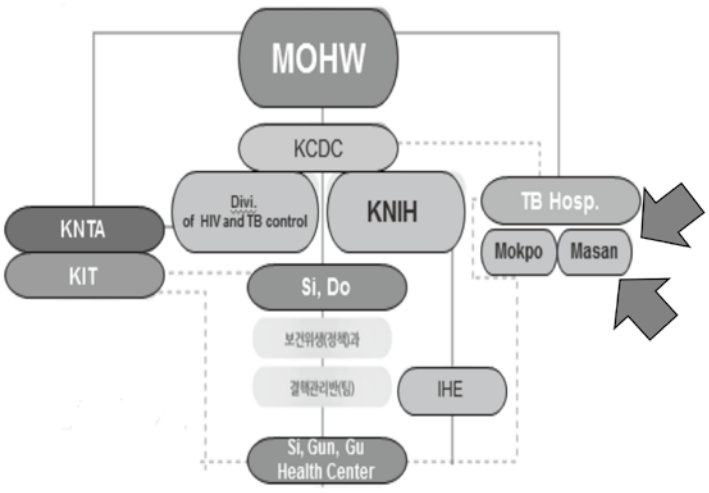
1. Respect for patient's values, preferences and expressed needs
2. Coordination and integration of care
3. Information, communication and education
4. financial, Physical, emotional Support
5. Involvement of family and friends
6. Transition and continuity

Masan National Tuberculosis Hospital

Contents

1. Patient centered Care
– TB Hospital based

2. Patient centered Care
– PMDT in Korea



Masan National Tuberculosis Hospital

Role of MNTH

Masan National Tuberculosis Hospital

Patient Profile in MNTH, 2013

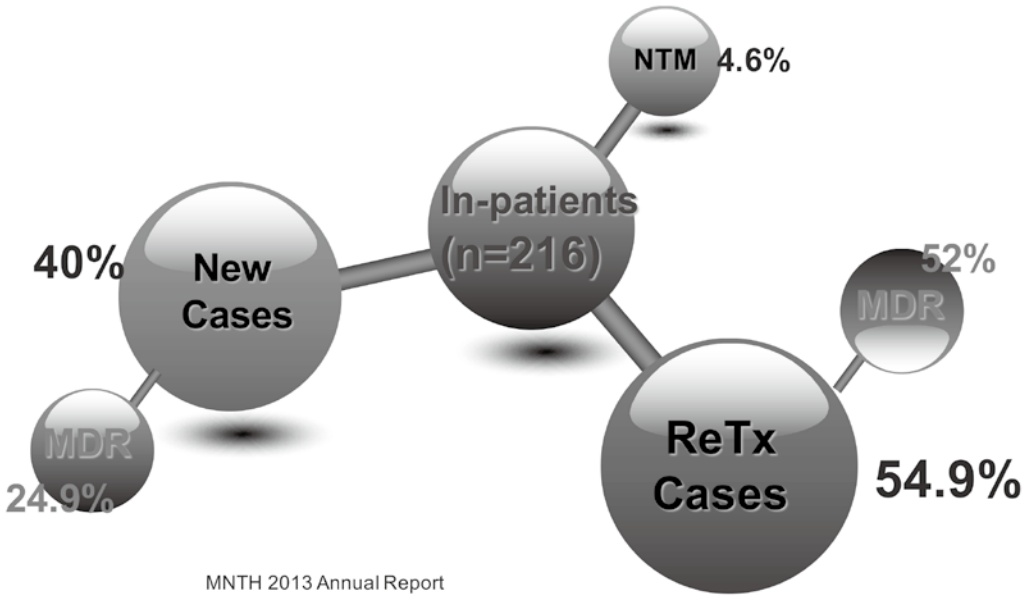
- The largest TB referral hospital in Korea
  : More than 80% of patients are transferred cases.

▪ # of admitted patients/year	569 patients
▪ Annual outpatient visits	4,244 visits
▪ Average No. of inpatients/day	216 patients
▪ Mean duration of admission/patient	118 days

MNTH 2013 Annual Report

Masan National Tuberculosis Hospital

Classification of Inpatients, 2013



MNTH 2013 Annual Report

Masan National Tuberculosis Hospital

" 5 A'S : Assess
Advise
Agree
Assist
Arrange

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2014, WHO

Masan National Tuberculosis Hospital

	Responsibility
Attending physician	Integration Of 5 A'S Assess patient's goals at the start Assess patient's clinical status, classify/identify relevant treatments Assess for the presence of adverse effects Correct any inaccurate knowledge Discuss the options (different treatment delivery options, regimens,, palliative care) • Provide treatments/medication • Provide other medical treatments
Attending nurse	Assess patient's adherence to their medications Assess factors associated with the patient's lifestyle that might prevent adherence to therapy Evaluate the importance the patient gives to the indicated treatment Provide a written or pictorial summary of the plan Provide a DOT provider and/or drug-resistant TB treatment supporter Provide skills and tools to assist with self-management and adherence Link to available support: Friends and family

Masan National Tuberculosis Hospital

	Responsibility
PPM nurse	Advise on the social protection schemes the patient is eligible Link to available support: Community services Arrange follow-up care and a follow-up visit to monitor treatment progress and to reinforce key messages Arrange a way for the patient to contact you if problems arise
Social worker	Assess the financial situation (job, education, dependents) Provide with sickness certificate to facilitate access to social protection schemes Link to available support: Community services
Religious facility	Assess patient's knowledge, beliefs, concerns and daily behaviours related to drug-resistant TB and its treatment Link to available support: Community services

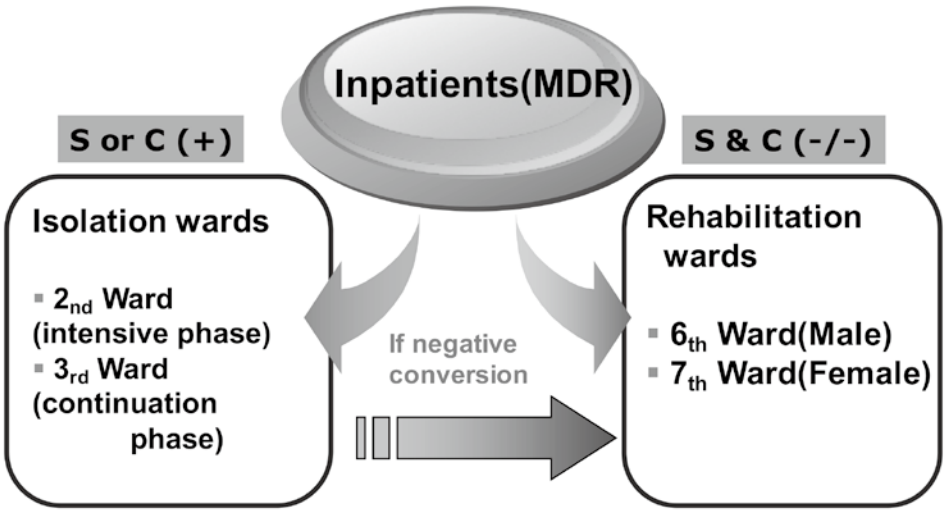
Masan National Tuberculosis Hospital

System & Program for Management

1. Arrangement
2. Management
3. Education & Support
4. DOT

Masan National Tuberculosis Hospital

1. Admission : Arrangement of Patients



Masan National Tuberculosis Hospital

2. Management

- **Appropriate regimen & monitoring**
  - **MNTH TB Management Guideline & Care Plan-**
- **Appropriate facilities**
- **TB chart and catabase**
- **Referral system**
- **LAB and Imaging study facility**
- **Special clinics**

Masan National Tuberculosis Hospital

2. Education and Counseling

" Through the Patients' eye" Education Program:

	schedule	Topic	provider	tool	Material
DR-TB	Day 1-2	- General Instruction(DOT) - Alcohol abstinence, Stop smoking	nurse	Face to face	Self Management Pocket book
	Week 1	- Video Education(self Management)	nurse	Online lecture	Educational Video
	Month 1	- TB medication facts	nurse	Face to face	Hand book
	Month 2	- Self Management - Prevention of acquired resistance	nurse	Online lecture	Educational Video
	Month 3	-TB Management -Knowing where I am	nurse	Face to face	Hand book
	Month 4	- Continuous Care after Discharge	nurse	Face to face	leaflet
Obligatory Hospitalization	Week 1	- Understanding of Obligatory Hospitalization - Contact Investigation	PPM nurse	Face to face	Hand book
	At the time of Lifting	- Supporting system after discharge	PPM nurse	Face to face	Hand book

Masan National Tuberculosis Hospital

Education Program: Diabetes and Hypertension

	Topic	Provider	tool	material
Diabetes	Tuberculosis and diabetes	nurse	lecture	PPT slides
Hypertension	Management of hypertension	nurse	lecture	PPT slides

Improving awareness through education(2015)
: Annual survey and feedback on the program

Question(awareness)	Degree of awareness	before	after
Infectiousness of TB	Well known	73%	98%
Disease progression	Well known	67%	99%
Significance of TB treatment	Well known	64%	95%
Specific TB medications	Well known	33%	77%
Dosage and usage of medication	Well known	24%	67%
Side effects of medications	Well known	39%	83%
Treatment duration	Well known	52%	97%
Hazard from drug discontinuation	Well known	54%	95%

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Counseling with social worker:

- Restoration of medical insurance
- Financial support for patient's basic life
  link exterior funds to patients
- Link patient to sanatorium, mental nursing facility etc.

Counseling with PPM nurse:

- Communication with outside medical facilities
- Follow –up program after discharge
- Support from NTP
  'Obligatory Admission and Isolation"

Masan National Tuberculosis Hospital

4. In-Patient DOT

- DOT Since Dec. 2004 for all in-patients

Masan National Tuberculosis Hospital

Contents

1. Patient centered Care
– TB Hospital based

2. Patient centered Care
– PMDT in Korea

Masan National Tuberculosis Hospital

Hx of TB in Korea(1)

❖ 1970' – 2000'

1980 Adoption of short course chemotherapy

Table 1. Trend of tuberculosis situation according to the national prevalence surveys

	1965	1975	1980	1985	1990	1995	2006	2010
Annual Risk of Infection	5.3	2.3	1.8	1.2	1.1	0.5	*0.21*	*0.16*
Infection rate(0~29,%)	44.5	46.9	41.7	38.7	27.3	15.5	*8.4*	*6.5*
Prevalence								
Radiologically active (%)	5.1	3.3	2.5	2.2	1.8	1.0	*0.486*	*0.380*
No. of patients(1,000)	1,240	1,014	852	798	728	429	*224*	*178*
Bacillary positives (%)	0.94	0.76	0.54	0.44	0.24	0.22	*0.095*	*0.079*
No. of patients(1,000)	226	235	186	164	95	91	*44*	*37*
Smear positives (%)	0.69	0.48	0.31	0.24	0.14	0.09	*0.039*	*0.033*
No. of patients(1,000)	170	146	104	89	56	39	*18*	*15*
Drug resistance (%)								
Initial resistance	26.2	27.3	23.8	19.0	15.4	5.8		
Acquired resistance	55.2	73.3	74.5	58.6	54.3	25.0		
Combined resistance	38.0	38.3	47.5	35.3	27.4	9.9		

Italics are estimated figure
Estimation of annual risk of infection; calculated by the regression equation using infection rate of 5~9 years old; LnY=6.37253−0.07485 * X (R−square: 0.96)
Estimation of prevalence; calculated by the age−specific reduction rate using the 1980~1995 year survey.

Hx of TB in Korea(2)

❖ 2000' ~

2006 9. "Stop TB Plan 2030"
2008 3. "2030 plan for TB Elimination Revision"
2011 "New 2020 plan"
2013 TB Control Master Plan Stage I(2013-2017)

KCDC, MOHW, Korea new plan 2020

NTP
TB Control Master Plan Stage I(2013-2017)

Policy Objectives

Halve the TB Incidence till 2020

'11 100/10^5 ⇨ '20 50/10^5

Basic Directions

01 Active and rapid case detection with customized intensive care

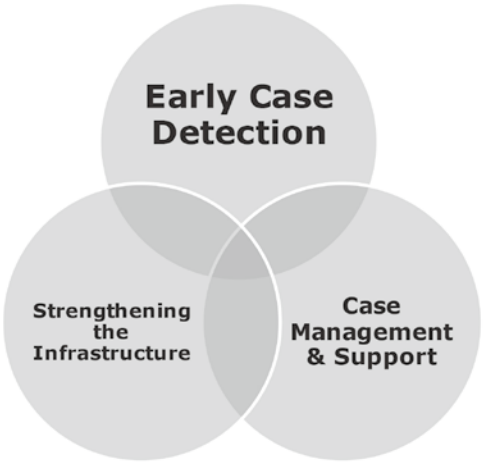
02 Build-up overall management system from monitoring to project evaluation

03 National investment and focusing attention toward TB

Masan National Tuberculosis Hospital

NTP
TB Control Master Plan Stage I(2013-2017)

Strategies and Projects



Masan National Tuberculosis Hospital

NTP – Case Management services, 2015

1. Support Budget for TB nurse

   Facility(>100 Notified cases a year
   or >200 National Insurance reimbursement claims)

2. Case Management Fee
   9000 won/case

3. Support Expenses of TB Patients
   support 50% of cost(other than insurance coverage)
   → free from July, 2016

Masan National Tuberculosis Hospital

NTP – Case Management Services, 2015

4. Contact Case Management :
   Free screening for TB of Family members
   Free LTBI Treatment

5. Epidemiologic Survey in Outbreak
   school, company office, military camp, shelter etc.
   " Central Outbreak Survey Task Force Team in KCDC"

Masan National Tuberculosis Hospital

NTP –
Case Management Services, 2015

6. " Obligatory Hospitalization":

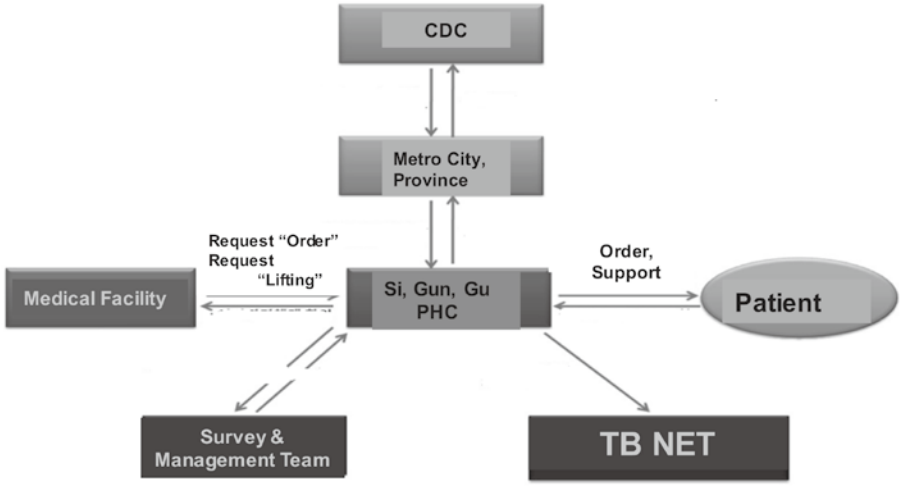
***Eligibility**: infectious MDR TB cases*
infectious non-compliant TB cases

full Support : in-patient cost
medication cost not covered by insurance
financial support for minimum cost-of-living
partial Support : caregiver cost
in patient cost not covered by national insurance

***Lifting**: more than 2 weeks medication*
& 3 more consecutive smear negativity
& attending physician's approval

NTP –
Case Management Services, 2015

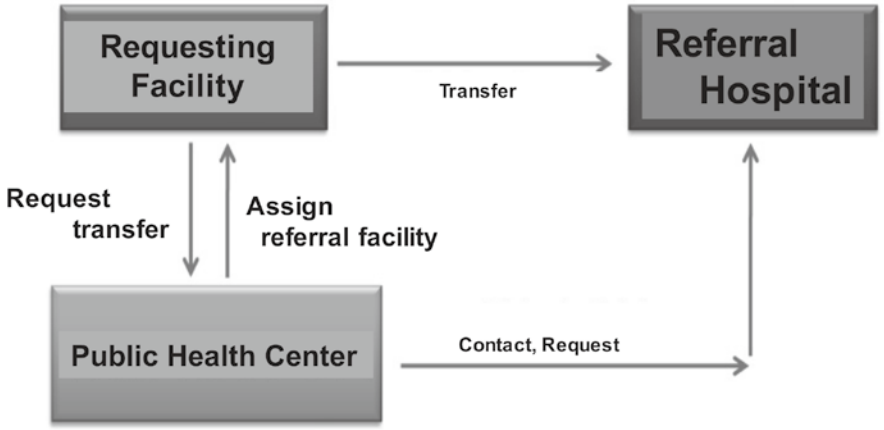
6. " Obligatory Hospitalization"



Masan National Tuberculosis Hospital

NTP – Case Management Services, 2015

6. " Obligatory Hospitalization" –Referral System



Masan National Tuberculosis Hospital

NTP – Case Management Services, 2015

6. " Obligatory Hospitalization": Masan National TB Hospital

year	2011	2012	2013
# of cases	79	109	134

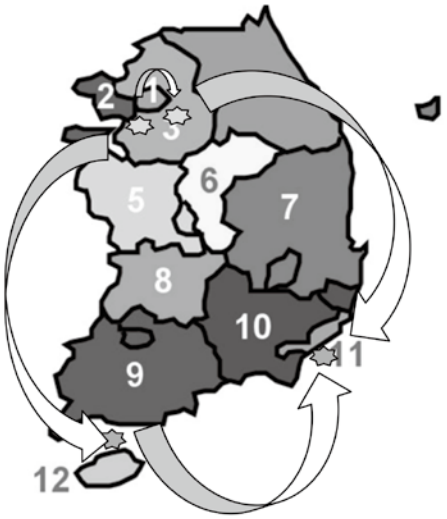
Nationwide cases

	# of Cases(%)			Refuse to follow the order
	Total	MDR	Non compliant	
total	1,372(100)	980(71.4)	393(28.6)	15
2011	329(100)	184(55.9)	145(44.1)	2
2012	472(100)	335(71.0)	137(29.0)	5
2013	571(100)	459(80.4)	112(19.6)	8

Masan National Tuberculosis Hospital

NTP –
Case Management Services, 2015

6. " Obligatory Hospitalization":
TB Safety Belt(National TB Hospital Chain)



National Medical Center
Seoul Metropolitan Seobuk Hospital
Masan National Hospital
Mokpo National Hospital

국립중앙의료원 National Medical Center
국립마산병원 Masan National Hospital
국립목포병원 MOKPO NATIONAL HOSPITAL
서울특별시서북병원

Masan National Tuberculosis Hospital

MDR TB Notification

Notified MDR TB cases 2011-2015

year	*2011*	*2012*	***2013***	***2014***	***2015***
# of cases	*975*	*1212*	***951***	***856***	***787***

KCDC http://tbfree.cdc.go.kr
Annual TB Report 2015

Masan National Tuberculosis Hospital

XDR TB Notification

Notified XDR TB cases 2011-2015

year	2011	2012	2013	2014	2015
# of cases	140	158	113	83	58

KCDC http://tbfree.cdc.go.kr
Annual TB Report 2015

Masan National Tuberculosis Hospital

Speaker

Chou-Jui Lin

Position: Attending Physician
Department/Organisation: Taoyuan General Hospital, Ministry of Health and Welfare
Economy: Chinese Taipei

Educational Background

- Department of Medicine, National Cheng Kung University

Professional Experience

- 2004-now Attending Physician, Department of Internal Medicine, Taoyuan General Hospital, Ministry of Health and Welfare
- 2002-2004 Research Fellow, Department of Internal Medicine, National Taiwan University Hospital
- 1999-2002 Resident, Department of Internal Medicine, National Taiwan University Hospital

Recent Publications

- Chao WC, Huang YW, Yu MC, Yang WT, Lin CJ, Lee JJ, Huang RM, Shieh CC, Chien ST, Chien JY. Outcome correlation of smear-positivity but culture-negativity during standard anti-tuberculosis treatment in Taiwan. BMC Infectious Diseases 2015; 15:67.
- Chou-Han Lin, Chou-Jui Lin, Yao-Wen Kuo, Jann-Yuan Wang, Chia-Lin Hsu, Jong-Min Chen, Wern-Cherng Cheng, Li-Na Lee. Tuberculosis mortality: Patient characteristics and causes. BMC Infectious Diseases 2014; 14:5.
- Chan PC, Yang CH, Chang LY, Wang KF, Kuo YC, Lin CJ, Lee SW, Hsueh PR, Fang CT, Huang LM. Lower prevalence of tuberculosis infection in BCG vaccinees: a cross-sectional study in adult prison inmates. Thorax. 2013 Mar;68(3):263-8.

Speech Abstract

Promising Specialized and Friendly Patient-Centered Care

Chou-Jui Lin
Attending Physician
Chest Medicine, Taoyuan General Hospital, Ministry of Health and Welfare, Chinese Taipei

Through the coverage of National Health Insurance and National Surveillance Network of Communicable Diseases, tuberculosis (TB) in Chinese Taipei Economy has been controlled and monitored at the central level with minimal out-of-pocket expense from the patients. The implementation of directly observed treatment (DOT) has further brought down the prevalence and the relapse of tuberculosis. However, the increase in the numbers of multidrug-resistant tuberculosis (MDRTB) patients still represents a growing threat to our public health.

From a local study published in 2006 in European Respiratory Journal, the treatment outcome of MDRTB from 1992 to 1996 in Chinese Taipei Economy was suboptimal, with only 50% of cure rate and a default rate as high as nearly 30%. The lengthy treatment duration and toxic side effects from the medications poses a particular challenge to the issue of adherence. And since default is a decision made by the patients solely, it is only reasonable to adopt a patient-centered approach to address the difficulties they encountered in order to retain them in treatment.

To combat MDRTB, political commitment is of paramount importance. Our CDC has made a loud-and-clear statement by taking several critical measures in this uphill battle against MDRTB. First, by providing sufficient funding, both the designated hospitals and the patients can get rid of the financial constrains from the National Insurance bureau and from being socio-economically deprived. Second, by adopting a hospital-led treatment plus DOT care model, the community-based care can be considered as a continuity of hospital-based care; and it further enables early detection and management of any side effects and sings of poor adherence. Last but the least, by constructing Taiwan MDRTB Consortium (TMTC), treatment consensus and standardized management, coordinated to a central level, can be built upon regular meetings and discussions among these hospitals and CDC.

There has been a substantial improvement in MDRTB treatment outcome since the initiation of TMTC. It proves that to confine the MDRTB patients under the care of designated hospitals, which deliver treatment/DOT in an individualized and flexible way, not only reduces the default rate tremendously, but also secures the treatment success in return.

PROMISING SPECIALIZED AND FRIENDLY PATIENT-CENTERED CARE

Rebecca C.J. Lin, M.D.

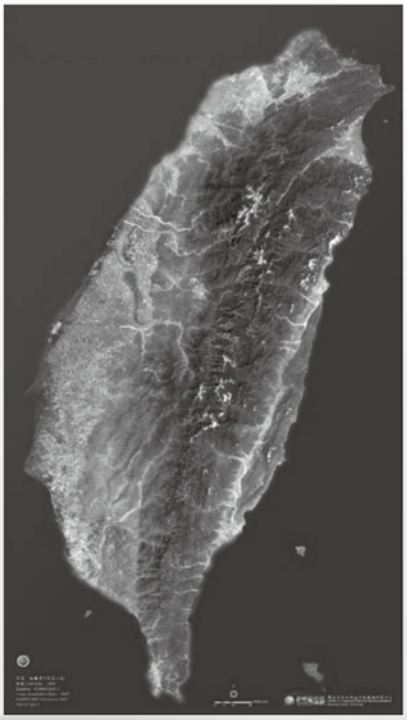
Taoyuan General Hospital, Ministry of Health and Welfare

1

BACKGROUND INFORMATION

- Area: 36,193 Km2
- Population: 23 million
- TB prevalence: 72.5 (2005) to 45.6 (2015)
- National health insurance
- National surveillance network of communicable diseases

Easy access to medical care
Universal coverage of health insurance
Real-time electronic monitoring system



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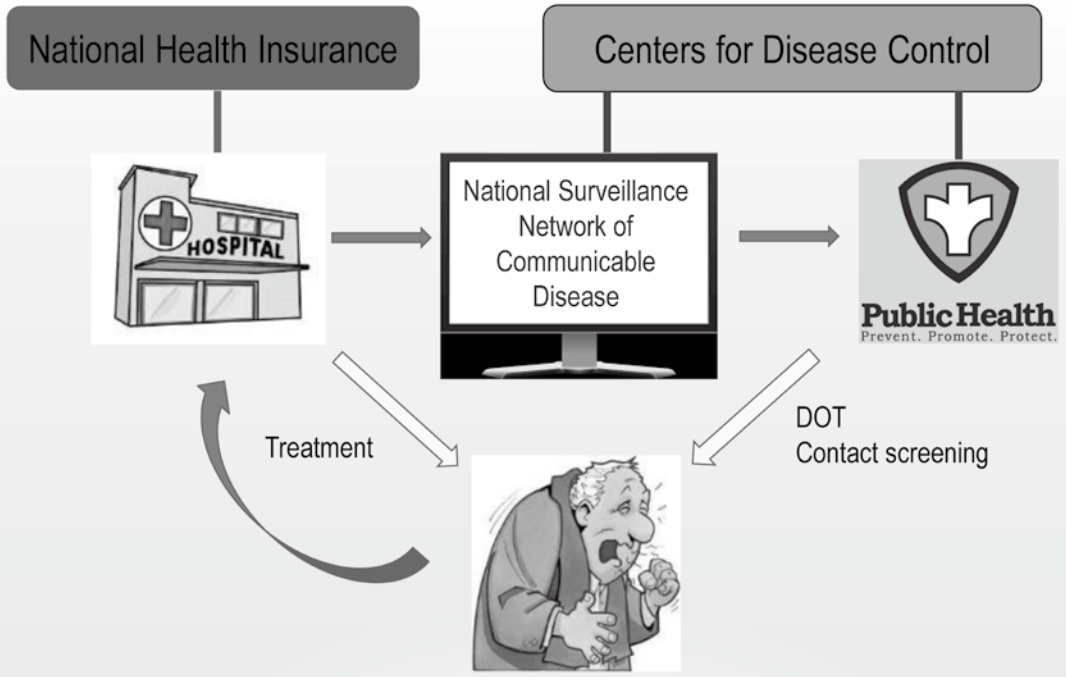
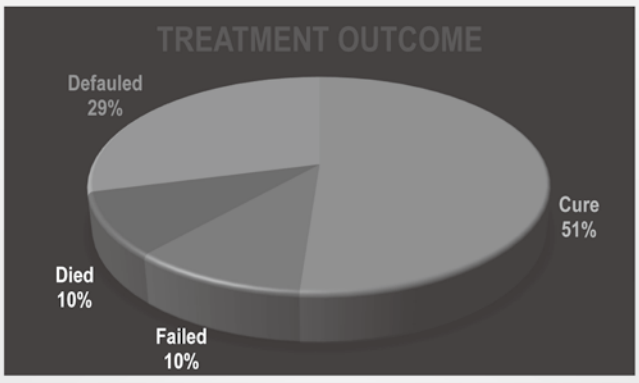


3

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+

- 299 pts from 1992-1996
- 215 males, 84 females, mean age: 47.3 y/o



Eur Respir J 2006; 28: 980-985

4

LOW CURE RATE

- Treatment factors:
  - Diagnostic delay
  - Ineffective regimen
  - Co-morbidity
- System factors:
  - Lack of programmatic approach
  - Coordination with public health
  - Doctor/hospital shopping

5

HIGH DEFAULT RATE

- Medication related:
  - Adverse effect
  - Long duration
  - Pain associated with injection
  - High pill burden
- Service provider related:
  - Conflicting timing of jobs
  - Behavior of service provider
  - Poor counseling

PLOS ONE | DOI:10.1371/ August 24, 2015

6

HIGH DEFAULT RATE

- Socio-economic factors:
  - Stigma and discrimination
  - Lack of family and social support
  - Unemployment and financial constrains
- Patient related:
  - Lack of awareness
  - Myths and misbeliefs regarding disease
  - Substance abuse
  - Confidentiality issues

PLOS ONE | DOI:10.1371/ August 24, 2015

7

HOW WE TACKLE THE PROBLEMS?

POLITICAL COMMITMENT

8

SPECIALIZED MDRTB PROGRAM

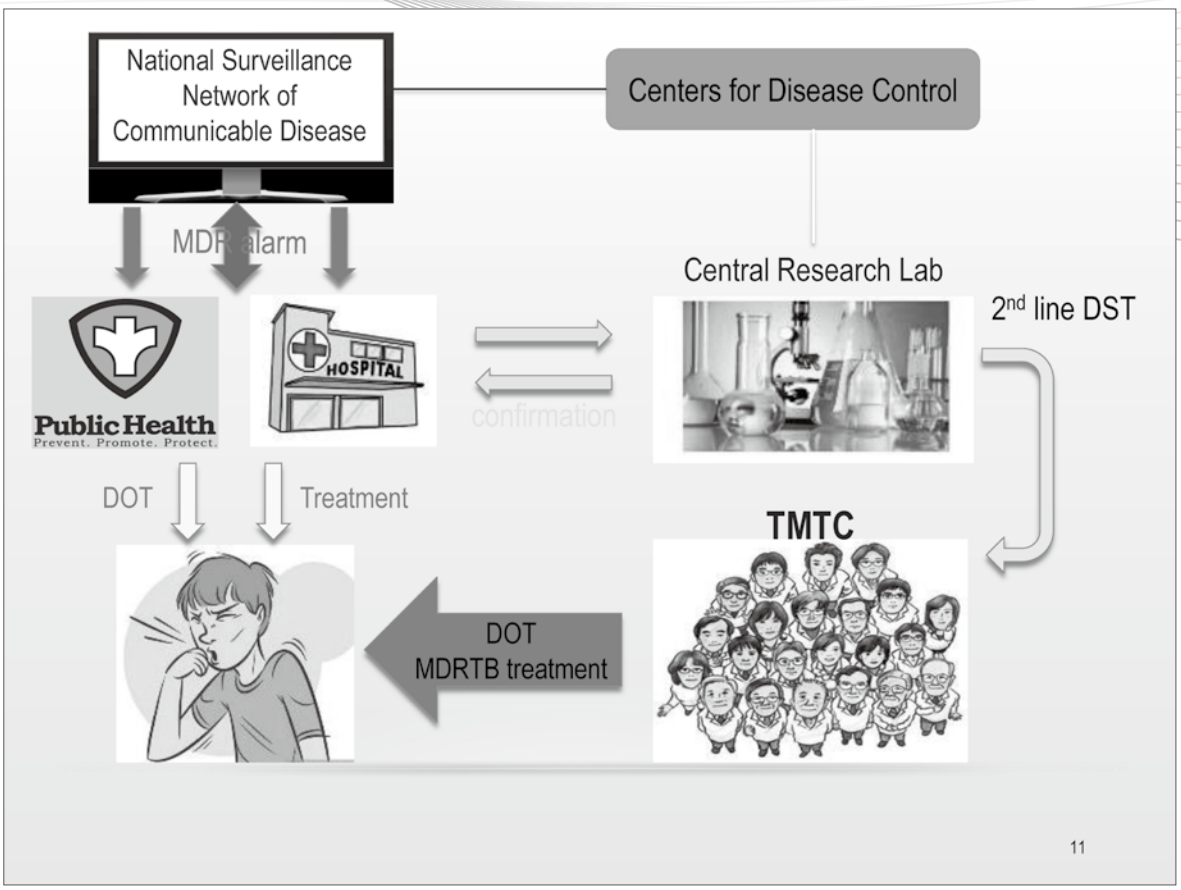
- National surveillance network:
  - Previous TB treatment record
  - System alarm upon MDRTB detection
- Central research lab:
  - Rapid diagnosis: GenoType® MTBDR, GenoType® MTBDRsl
  - Standardized lab result: phenotypic 2nd line DST
  - Cluster investigation
- Taiwan MDRTB Consortium
  - MDRTB treatment team

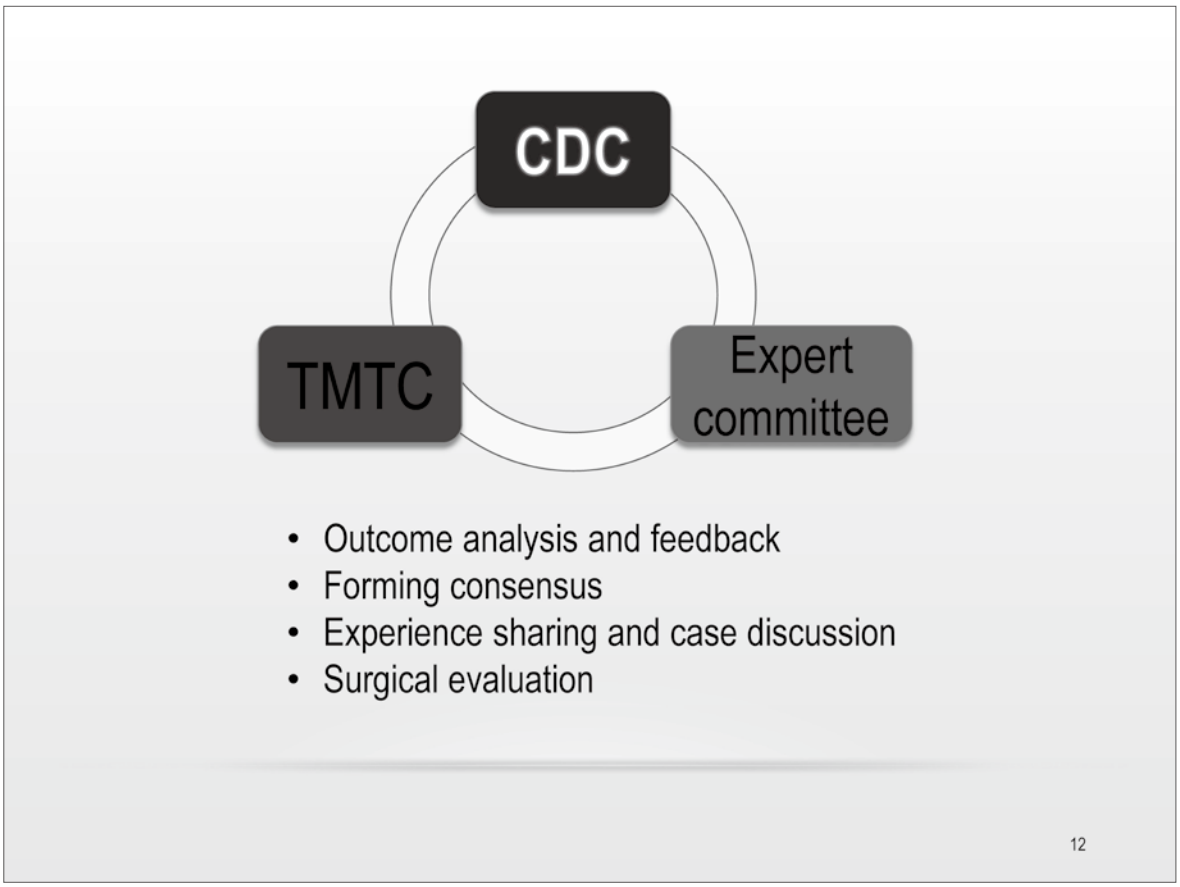
9

TAIWAN MDRTB CONSORTIUM (TMTC)

- Designated treatment network
- 5 medical teams to cover 5 different regions
- Hospital-led care and DOT
- No out-of-pocket expenses from patients
- Full reimbursement of medical expenses from government funding
- Quarterly meeting

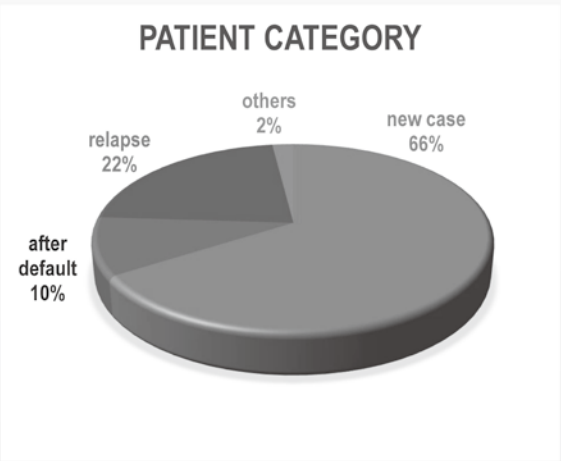
10

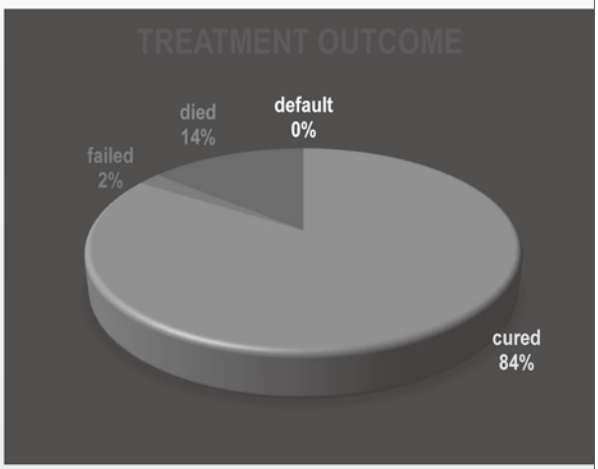

National Surveillance Network of Communicable Disease
Centers for Disease Control
MDR alarm
Central Research Lab
2nd line DST
HOSPITAL
Public Health
Prevent. Promote. Protect.
confirmation
DOT
Treatment
TMTC
DOT
MDRTB treatment
11


CDC
TMTC
Expert committee
• Outcome analysis and feedback
• Forming consensus
• Experience sharing and case discussion
• Surgical evaluation
12

TYGH EXPERIENCE

Totally 100 patients from May, 2007 till now

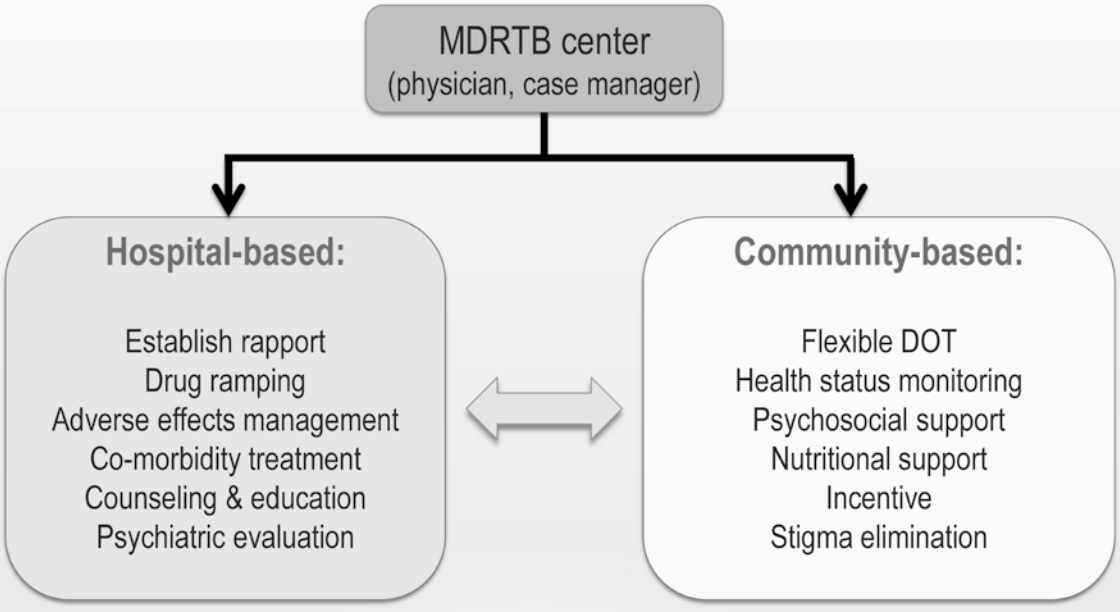




Co-morbid condition: DM (29%) Alcohol abuse (26%) Psychiatric disorder (14%)

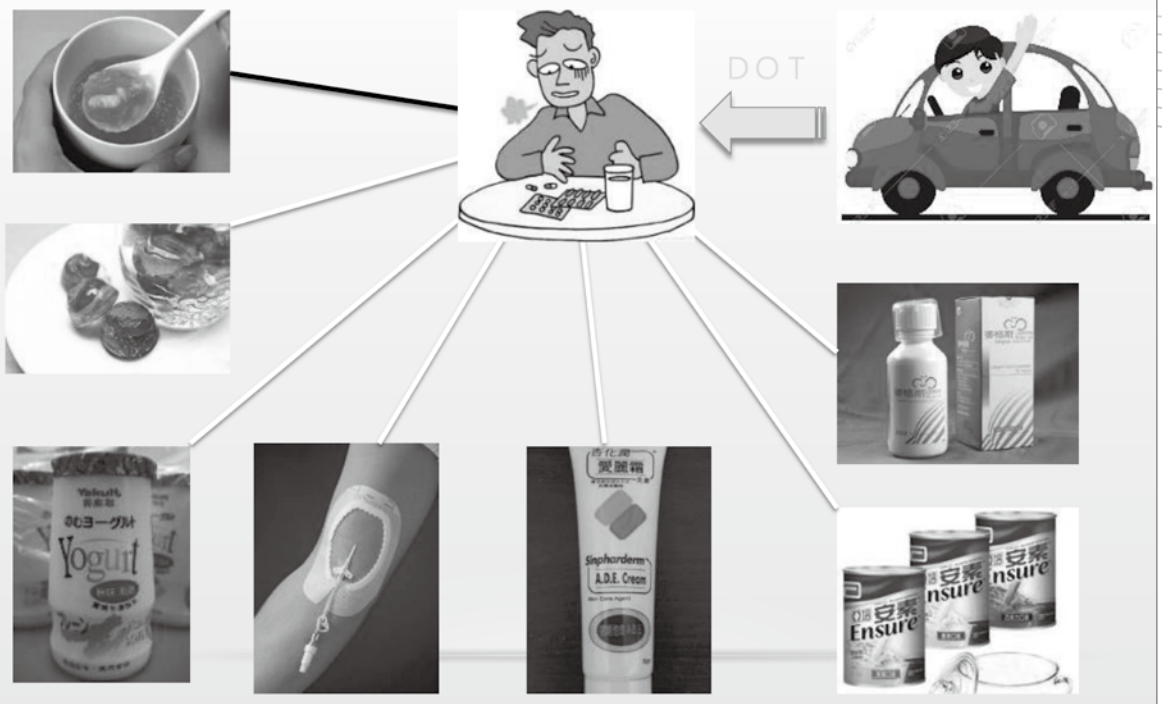
13

PATIENT-CENTERED CARE MODEL



14

SIDE EFFECTS MANAGEMENT

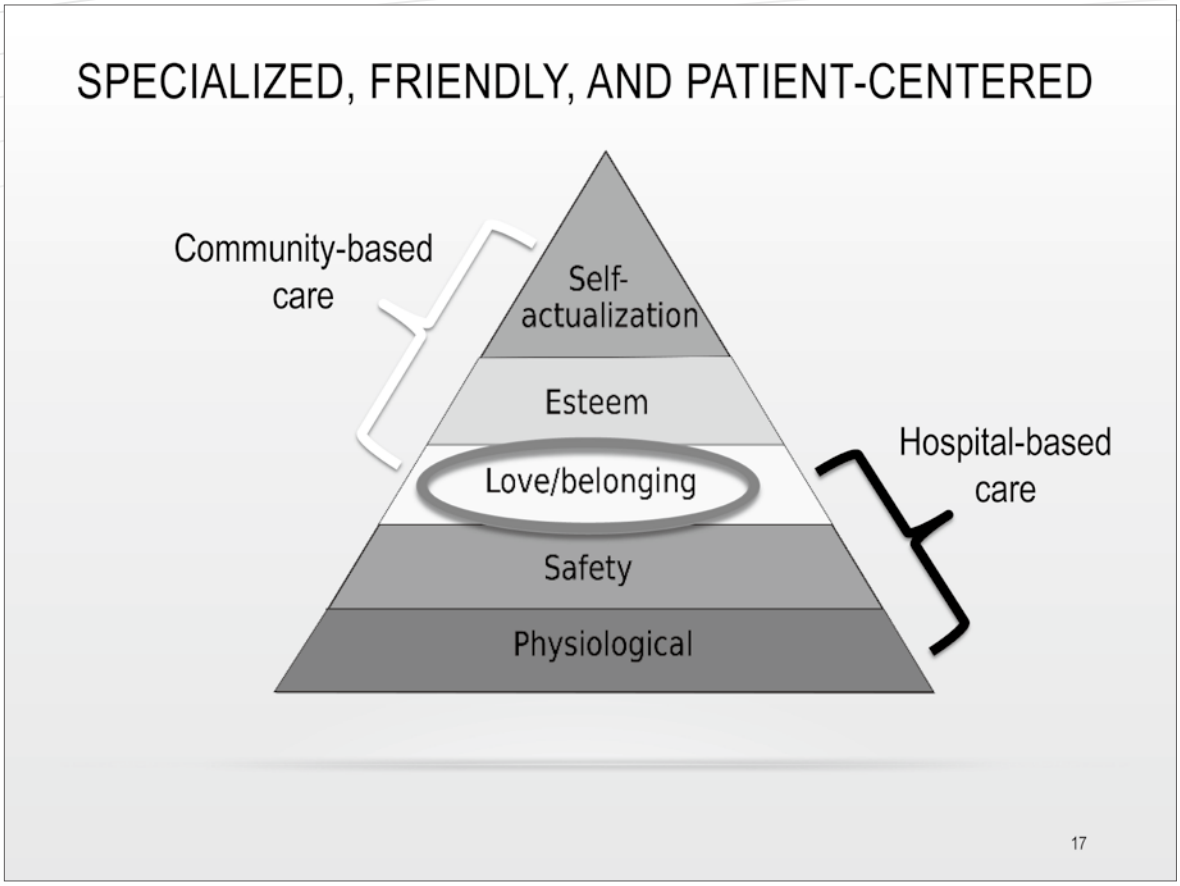


15

CO-MORBIDITY MANAGEMENT

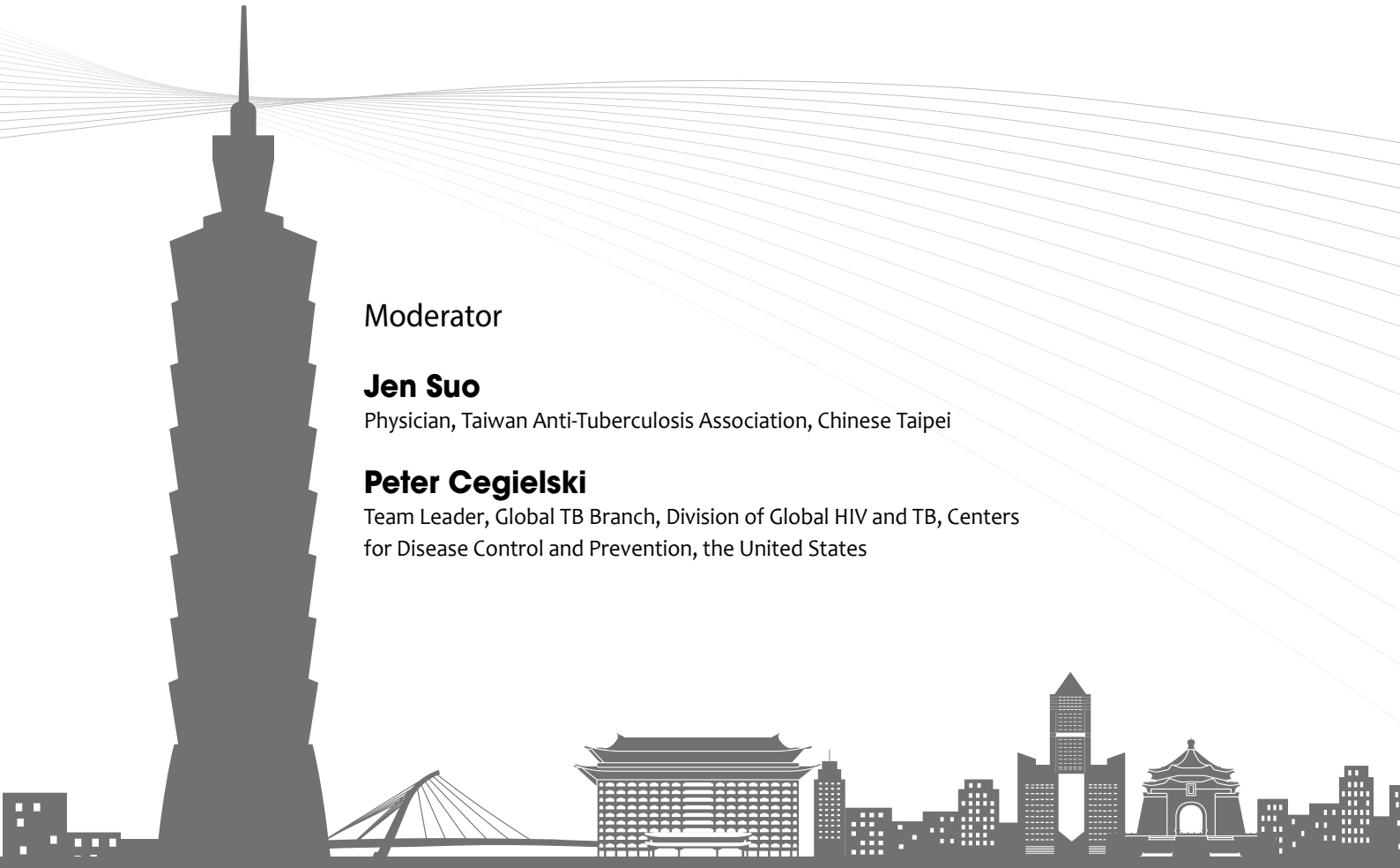
Co-morbidity	Hospital-based care	Community-based care
Diabetes mellitus	• Optimize sugar control • Diet consultation and education • DM-related complication evaluation	• Monitor finger blood sugar • Diet control • Lifestyle modification • Insulin injection
Alcoholism	• Withdrawal management • Psychiatric evaluation • Complication evaluation • Liver function monitoring	• Lifestyle monitoring • Psychosocial support
Psychiatric disease	• Psychiatric evaluation: ✓ Diagnosis ✓ Treatment ✓ Behavioral consultation	• Rehabilitation • Psychosocial support

16


SPECIALIZED, FRIENDLY, AND PATIENT-CENTERED
Community-based care
Self-actualization
Esteem
Love/belonging
Safety
Physiological
Hospital-based care
17

Session III

Taking Action to Secure Supply of Second Line Drugs



Moderator

Jen Suo
Physician, Taiwan Anti-Tuberculosis Association, Chinese Taipei

Peter Cegielski
Team Leader, Global TB Branch, Division of Global HIV and TB, Centers for Disease Control and Prevention, the United States

Moderator

Jen Suo

Position: Physician
Department/Organisation: The First Chest Clinic, Taiwan Anti-Tuberculosis Association
Economy: Chinese Taipei

Educational Background

- National Taiwan University, College of Medicine. Bachelor of Medicine

Professional Experience

- National TB Association. Doctor, 2005-
- TaoYuan General Hospital, DOH. Doctor, 2002-2005
- Center for Chest Disease, DOH. Director, 2002-
- Chronic Disease Control Bureau, DOH. Director, 2001-2002
- Chronic Disease Control Bureau, DOH. Deputy Director, 1999-2001
- Taipei County Chronic Disease Control Station. Doctor, 1997-1999
- Chronic Disease Control Bureau, DOH. Section Chief, 1989-1997
- FETP , DOH. Trainee, 1989-1991
- National Jewish Center for Immunology and Respiratory Disease, USA. Research Associate, 1987-1988
- Taiwan Provincial Tuberculosis Control Bureau. Section Chief, 1983-1989
- Taiwan Provincial Tuberculosis Control Bureau. Doctor, 1982-1983

Recent Publications

- Lo HY, Suo J, Chang HJ, Yang SL, Chou P. Risk Factors Associated With Death in a 12-Month Cohort Analysis of Tuberculosis Patients: 12-Month Follow-up After Registration. Asia Pac J Public Health 2011 Dec 23. Epub.
- Chiang CY, Bai KJ, Lee CN, Enarson DA, Suo J, Luh KT. Inconsistent dosing of anti-tuberculosis drugs in Taipei, Taiwan. Int J Tuberc Lung Dis. 2010; 14:878-83.
- Chan PC, Huang LM, Suo J. It is time to deal with latent tuberculosis infection in Taiwan. J Formos Med Assoc. 2009 Dec;108(12):901-3.
- Chiang CY, Enarson DA, Bai KJ, Suo J, Wu YC, Lin TP, Luh KT. Factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion. Int J Tuberc Lung Dis. 2008; 12:441-6.
- Kuo LK, Lin RL, Lin FJ, Wu CL, Suo J. Causes of death of notified tuberuclosis patients from 2000-2004 in a medical center in Taipei. Thorac Med 2007; 22:305-312.

Moderator

Peter Cegielski

Position: Team Leader
Department/Organisation: Global TB Branch, Division of Global HIV and TB, Centers for Disease Control and Prevention
Economy: the United States

Educational Background

- MPH, University of North Carolina 1995
- Infectious Diseases Fellowship, Duke University Medical Center 1990
- Internal Medicine Residency, Duke University Medical Center 1987
- MD, University of California 1984
- BS in Biochemistry, Harvard University 1978

Professional Experience

- 2015-now Team Leader for TB Prevention Care and Treatment, Division of Global HIV and TB, US CDC
- 1998-2015 Medical Officer, then Team Leader for Drug-Resistant TB, Division of TB Elimination, US CDC
- 1996-1998 Assistant Professor, Department of Epidemiology, Johns Hopkins University School of Public Health
- 1994-1996 Assistant Professor, Department of Medicine, University of Texas Health Science Center Tyler
- 1991-1994 Assistant Professor, Division of Infectious Diseases, Duke University Medical Center

Recent Publications

- Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial versus Acquired Second-Line Drug Resistance. Clin Infect Dis. 2016;62:418-430.
- Yuen CM, Kurbatova EV, Tupasi TE, et al., including Cegielski JP (as senior author). Association between Regimen Composition and Treatment Response in Patients with Multidrug-Resistant Tuberculosis: A Prospective Cohort Study PLoSMed 2015; 12(12).
- Kurbatova EV, Cegielski JP, Lienhardt C, et al. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. Lancet Respir Med 2015; 3(3):201-209.
- Cegielski JP, Griffith DE, McGaha PK, Wolfgang M, Robinson CB, Clark PA, Hassell WL, Robison VA, Walker KP Jr., Wallace C. Eliminating tuberculosis, one neighborhood at a time. Am J Public Health. 2014;104 Suppl 2:S214-233
- Cegielski JP, Dalton T, Yagui M, et al. Extensive Drug Resistance Acquired During Treatment of Multidrug-Resistant Tuberculosis. Clin Infect Dis 2014; 59(8): 1049-1063.

APEC CONFERENCE ON PREVENTION, CONTROL AND CARE FOR

MDR-TB AND SUPPLY OF 2nd-LINE ANTI-TB DRUG

Speaker

Kaspars Lunte
Team Leader, Global Drug Facility, Stop TB Partnership

Vadim Testov
Leading Researcher, Central TB Research Institute, Russian Federal Agency of Scientific Organizations, Russia

Chen-Yuan Chiang
Consultant, Department of Tuberculosis and HIV, International Union Against Tuberculosis and Lung Disease

Speaker

Kaspars Lunte

Position: Team Leader
Department/Organisation: Sourcing and Special Projects, Global Drug Facility, Stop TB Partnership

Educational Background and Professional Experience

Dr. Kaspars Lunte is the Team Leader for Sourcing and Special Projects at the Global Drug Facility of the Stop TB Partnership and joined GDF in 2009.
In addition, Dr. Lunte has over ten years of experience in the private sector, mostly with the pharmaceutical industry supervising product supply management and serving as general manager at regional and country levels.
Dr. Lunte holds MD and MBA degrees and Diploma in international economic relations.

Recent Publications

- The Global Drug Facility as an intervention in the market for tuberculosis drugs Nimalan Arinaminpathy, Thierry Cordier-Lassalle, Kaspars Lunte & Christopher Dye doi: 10.2471/BLT.14.147256.
- Reducing the price of treatment for multidrug-resistant tuberculosis through the Global Drug Facility Kaspars Lunte, Thierry Cordier-Lassalle & Joel Keravec doi: 10.2471/BLT.14.145920
- Hwang TJ, Dotsenko S, Jafarov A, Weyer K, Falzon D, Lunte K, Nunn P, Jaramillo E, Keshavjee S, Wares DF. Clofazimine in the treatment of multidrug- and extensively drug-resistant tuberculosis. BMJ Open 2014.

Publications in The International Union Against Tuberculosis and Lung Disease world congresses:

- 2011-The Global Drug Facility: increasing access to MDR-TB drugs through innovation and action K Lunte, M Sarquella, P Marroquin Lerga, I Avchyan, R Boler, J Geer
- 2012-New partnership model for improving access to multidrug-resistant tuberculosis treatment K Lunte, S Pal, M Springsklee
- 2013-Towards healthy MDR-TB medicines supplier base: Global Drug Facility and its activities in China K Lunte (4th Asia-Pacific Region Union Conference)
- 2013-Drug-resistant TB treatment costs through Global Drug Facility vs. private market prices: comparison analysis K Lunte, J Keravec, T Cordier-Lassalle, N Arinaminpathy

Speech Abstract

Access to Quality and Affordable Drugs through the Global Drug Facility

Dr Kaspars Lunte

Team Leader

Global Drug Facility of the Stop TB Partnership

Summary:

Established in 2001, the Stop TB Partnerships Global Drug Facility (GDF) is an operating mechanism to support the Stop TB Strategy Goal 3: - to facilitate world-wide, equitable access to TB medicines and diagnostics, including new tools, across public and private sectors

GDF is one-stop, bundled procurement mechanism for quality assured TB commodities and targeted country-level technical assistance, to manage and coordinate market activities across all stakeholders for the full portfolio of TB medicines, regimens, and diagnostics.

As the largest supplier of quality assured anti-TB medicines and diagnostics worldwide in the public sector, GDF plays a key role in the procurement of anti-TB medicines for:

- drug sensitive TB, or first-line drugs (FLDs),
- paediatric anti-TB medicines,
- medicines for drug resistant-TB (second line drugs – SLDs),
- new diagnostics being today a key source for GeneXpert,
- is the sole procurement mechanism for SLDs for the Global Fund.

Through its activities GDF is ensuring:

Saved lives by expanding access to high quality TB treatments

Active market shaping for better priced TB products

Addressing stock-outs in countries by providing capacity building and technical assistance

Recently, GDF started to offer:

- new child-friendly pediatric and adequately-dosed formulations,
- Two new life-saving TB medicines for MDR-TB, making both available via the GDF to countries eligible for Global Fund TB Financing: Bedaquiline (via USAID donation program) and Delamanid.

Major achievements:

Since GDF inception in 2001, 133 countries benefited from GDF mechanism, with delivered:

> 25.5 M Adult FLD treatments

> 1,5 M pediatric treatments

> 197,778 SLD patient treatments

GDF has reduced the price of several key SLDs, resulting in a more than 40% reduction in the overall cost of treatment as compared to 2012/13, thanks to strong partnership with our manufacturers.

GDF also consolidated orders by using Strategic Rotating Stockpile (SRS), and increased number of eligible suppliers for TB products, contributing to a healthier market with improved security supply of TB commodities.

In 2015, GDF provided 46 monitoring/technical assistance missions to support countries. This support took the form of tailored technical assistance, innovative tools to countries/organizations in need and enhance partners' engagement for technical and financial support. GDF also provided support to countries to strengthen their national capacity for procurement and supply chain management.

In addition to monitoring missions, GDF has supported the roll-out of new monitoring tools for regular planning and enhanced programming at country level, such as QuanTB, in close collaboration with partner MSH.

Conclusion:

Global Drug Facility's operations since 2001 have favorably influenced the dynamics of the market for internationally quality-assured tuberculosis drugs and diagnostics. A mechanism such as GDF can support public sector markets for quality medicines and secure lower prices for drugs and diagnostics, and improve drug management at country level.

Improving Access for Quality-Assured TB Medicines and Diagnostics

Access to Quality and Affordable Drugs through the Global Drug Facility

Taipei, 30 June 2016

Dr Kaspars Lunte
Team Leader Sourcing and Special Projects, GDF

ISO 9001 CERTIFIED

Stop TB Partnership
GLOBAL DRUG FACILITY

What is the Global Drug Facility (GDF)?

An initiative of the Stop TB Partnership (2001), mainly funded by USAID, hosted in UNOPS and managed by the Stop TB Partnership secretariat

An operating mechanism to support the Stop TB Strategy Goal 3:

- **to facilitate world-wide, equitable access to TB medicines and diagnostics, including new tools, across public and private sectors.**

GDF began supplying FLDs in 2001, and in 2007 added the supply of SLDs & pediatric medicines & 2010 new diagnostics (key source for GeneXpert); BDQ – 2014, DLM - 2016

ISO 9001 CERTIFIED

Stop TB Partnership
GLOBAL DRUG FACILITY

GDF Strategic Objectives

1. Manage and coordinate market activities across all stakeholders for the full portfolio of TB medicines, regimens, and diagnostics

2. Develop state-of-the-art business intelligence and data-driven approaches through early adoption of cutting-edge technology

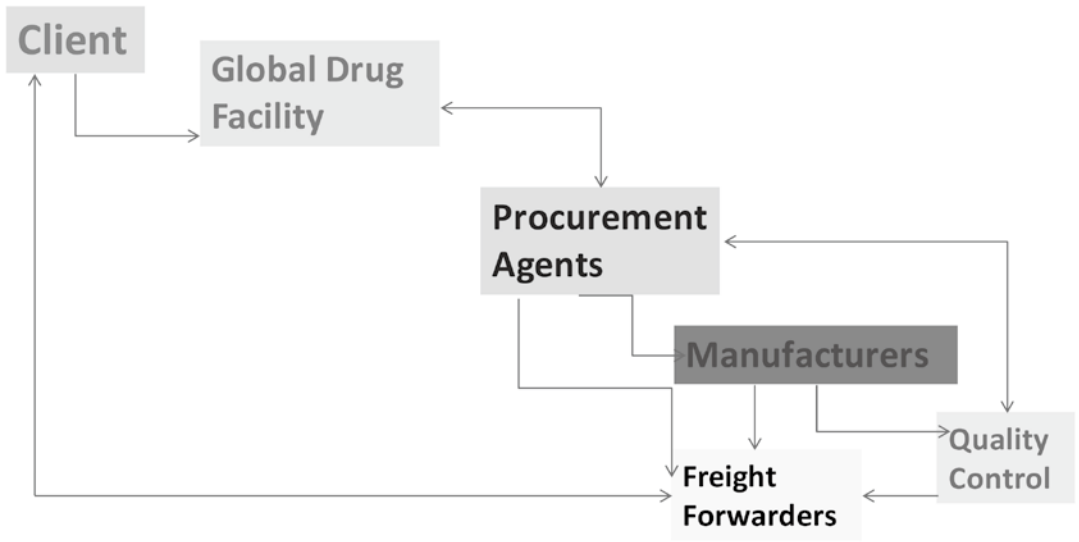
3. Undertake strategic procurement and execute innovative logistics solutions for TB medicines and diagnostics

4. Accelerate the uptake of new TB medicines, regimens, and diagnostics using GDF "launchpad" in close collaboration with TB Reach and WHO's working groups on new TB medicines

ISO 9001 CERTIFIED ISO QUALITY MANAGEMENT SYSTEM

Stop TB Partnership GLOBAL DRUG FACILITY

GDF model



ISO 9001 CERTIFIED ISO QUALITY MANAGEMENT SYSTEM

Stop TB Partnership GLOBAL DRUG FACILITY

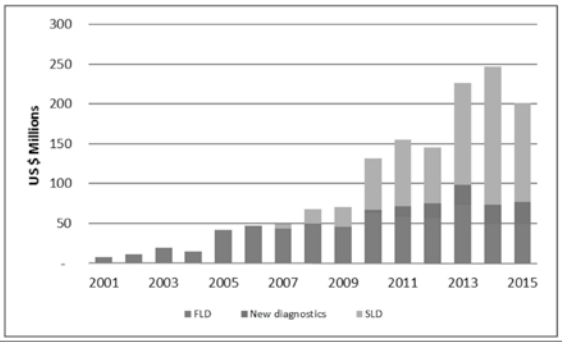
Key GDF Milestones

133 countries benefited from GDF procurement / bundled mechanism with

- > 25.5 M Adult FLD treatments
- > 1,5 M pediatric treatments
- > 197,778 SLD patient treatments

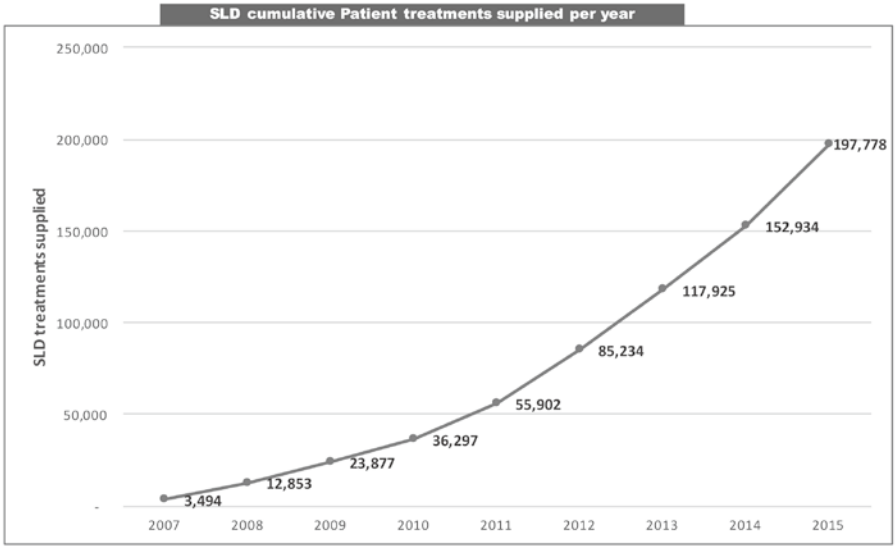
=> 27M treatments delivered as of 2015 since GDF inception in 2001

GDF has processed orders for TB products with a total value of approximately US $1.44 billion since 2001



Stop TB Partnership GLOBAL DRUG FACILITY

MDR Treatments supplied



Stop TB Partnership GLOBAL DRUG FACILITY

Capacity building and technical assistance

In only 2015, 46 **monitoring/technical assistance missions** were conducted to support countries with:

- tailored technical assistance,
- provision of innovative tools to countries/organizations in need and
- enhancing partners' engagement for technical and financial support.
- strengthen national capacity for procurement and supply chain management.

Expanding capacity building outreach:

- strong collaboration with key partners, e.g. the Global Fund, UNION, MSH and KNCV.
- GDF is actively engaged with various partners, such as DR-TB Scale-up Treatment Action Team (STAT), NTPs, MSF, PIH and the Global Fund to improve demand and supply coordination

Stop TB Partnership GLOBAL DRUG FACILITY

GDF Product Portfolio

Goal of GDF QA Policy

- To guarantee the Safety, Efficacy and Quality of the Finished Pharmaceutical Products (FPP) procured through GDF

- The products to be:
  - ✓Recommended for use by WHO
  - ✓Authorized for use by NDRA of recipient countries
  - ✓Product Quality Monitoring Programme in place

Model quality assurance system for Procurement Agencies:
http://apps.who.int/medicinedocs/documents/s21492en/s21492en.pdf

Stop TB Partnership GLOBAL DRUG FACILITY

Stringent standards

Anti-TB medicines	Diagnostics
WHO-PQ [1], **or** **Approved by a Stringent Regulatory Authority (SRA)** = ICH members, observers and associates [2]	**Authorized for use in destination country**
If products meeting these criteria are not available on the market:	**WHO recommended**
ERP authorized products	**Mostly SRA** approval

1. WHO Prequalification of Medicines Programme **(PQP):** www.who.int/prequal
2. **SRAs:** Listed in each organization's QA policy

Stop TB Partnership GLOBAL DRUG FACILITY

Rapid risk assessment by Expert Review Panel (ERP)[1]

Dossier assessment	Inspection
Product dossier must have been accepted for review by WHO-PQP or a SRA (if the medicine/strength is invited for WHO prequalification) ▶ **ERP** reviews abridged dossier	Manufacturing site (production line) must be GMP-certified by WHO-PQP or by an ICH or PIC/s member ▶ **ERP** verifies GMP status

Positive ERP opinion is valid for one year

Outcomes[2] are used by:

GDF; Global Fund; UNITAID, UNFPA; MSF; ICRC; UNICEF (for ACTs)

1. Expert Review Panel, hosted by WHO. More information on ERP: http://apps.who.int/prequal/info_press/pq_news_27April2012_ERP.htm
2. ERP-approved products are listed online at www.theglobalfund.org/en/procurement/quality/pharmaceutical/#Lists

Stop TB Partnership GLOBAL DRUG FACILITY

Bidding

- **Frequency of Bidding:**
  1. FLDs: every 1-2 years
  2. For SLDs: each year (in 2016 India and ROW combined)
  3. April to April

On behalf of the Stop TB Partnership Global Drug Facility (GDF), the GDF contracted procurement agent invites eligible suppliers (compliant with GDF's Quality Assurance policy and procedures) to submit a bid for the items described in the Invitation to Bid (ITB).

- **Bidding's Objective: adherence with principles of public procurement**
  1. Best value for money
  2. Fairness, integrity and transparency
  3. Effective international competition
  4. Interest of the organisation

Stop TB Partnership GLOBAL DRUG FACILITY

Bidding

- **Evaluation of the bids and awards based on:**
  1. Price (lowest)
  2. Supplier performance on delivery lead time (highest)
  3. Shelf life (longest)
  4. Production lead time (shortest)
  5. Minimum Oder Quantity (lowest)
  6. Product registration (most)

- **Market share allocation***

  100%/0% for primary-sole supplier/auxiliary supplier
  55%/45%/0% for primary/secondary/auxiliary supplier(s)
  50%/30%/20%/0% for primary/secondary/tertiary/auxiliary supplier(s)

*allocation is indicative only, and the actual allocation might deviate due to importation requirements, client preferences, registration status and other factors as deemed necessary by GDF or its clients.

Stop TB Partnership GLOBAL DRUG FACILITY

GDF Product Catalogue

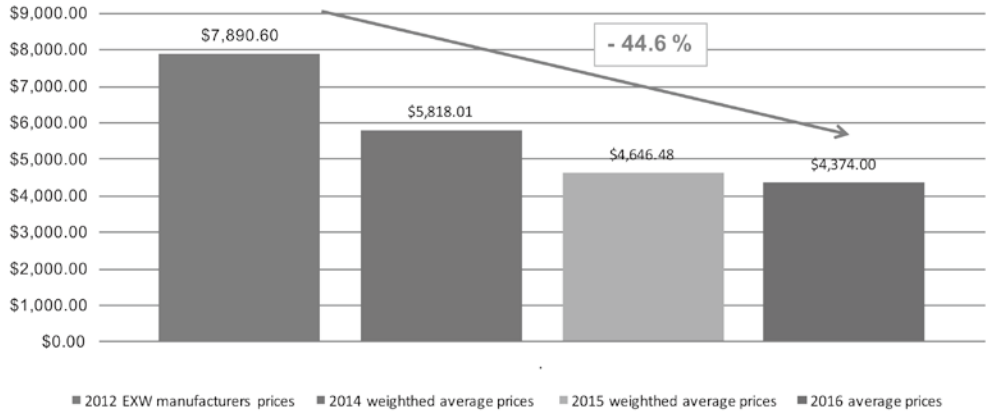
ISO 9001 CERTIFIED ISO QUALITY MANAGEMENT SYSTEM

Stop TB Partnership GLOBAL DRUG FACILITY

Key achievements

MDR Treatment Costs

2013/2016 Change in Regimen costs: High end regimen
12 Cm Pto Cs Mxf PAS/ 12 Pto Cs Mfx PAS

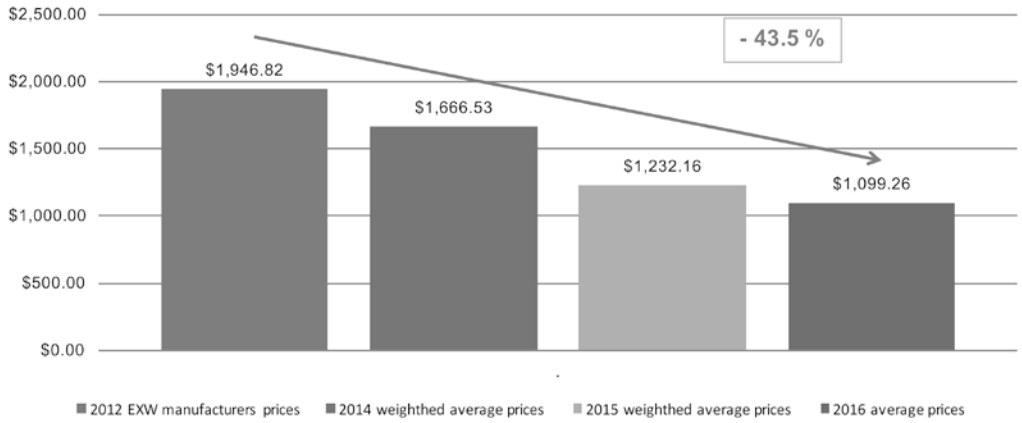


Stop TB Partnership GLOBAL DRUG FACILITY

Key achievements

MDR Treatment Costs

2013/2016 Regimen costs: Mid regimen
8 Z Km Lfx Eto Cs / 12 Z Lfx Eto Cs

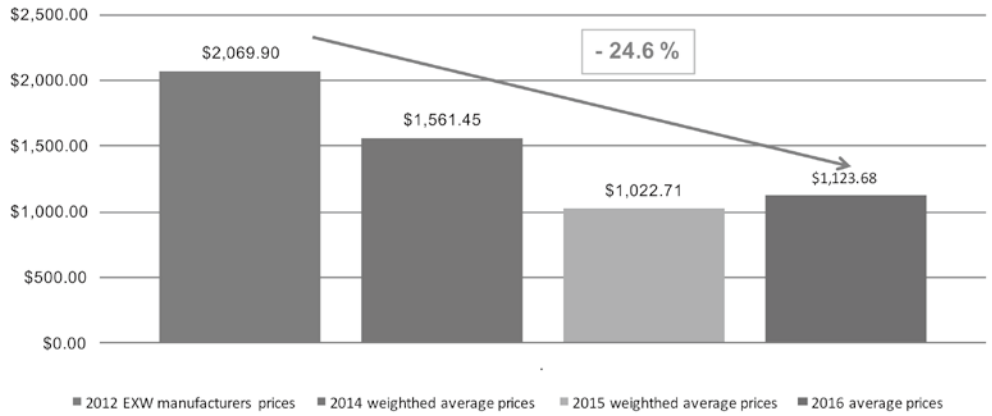


Stop TB Partnership GLOBAL DRUG FACILITY

Key achievements

MDR Treatment Costs

2013/2016 Change in Regimen costs: Low end regimen
8 Am Eto Cs Lfx/ 16 Eto Cs Lfx



Influenced by Cs price change vs 2015 (0.25 vs 0.20 USD per capsule)

Stop TB Partnership GLOBAL DRUG FACILITY

The USAID Bedaquiline Donation Program

- March 6, 2015 USAID & Johnson & Johnson, signed an agreement to provide bedaquiline free-of-charge to eligible countries, according to WHO interim recommendations on the use of the drug.
- Under the agreement, Janssen will donate 30,000 treatment courses over a 4 year period.
- All countries eligible for Global Fund financing (>100) are eligible for the donation
- The donation is provided through USAID's agreement with the Stop TB Partnership's Global Drug Facility (GDF).
- Countries must declare that they are able to meet all five of the conditions as per the WHO Interim Policy Guidance on bedaquiline
  - If these 5 conditions are not met, countries can request Technical Assistance to USAID
  - Adverse events reported directly to Janssen or via GDF: BDQAE@StopTB.org

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Delamanid Purchase via the GDF

- Effective 1 March, 2016 delamanid available for purchase via GDF
- Price USD 1,700 for a full treatment course (6 months)
- Over 100 countries eligible for TB Financing by the Global Fund to Fight AIDS, TB and Malaria can access delamanid via the GDF at this price
- Countries must declare that they are able to meet all five of the conditions as per the WHO Interim Policy Guidance on delamanid
  - Adverse events reported to Otsuka via the GDF: DLMAE@StopTB.org
- Delamanid will be added to GDF Strategic Rotating Stockpile

Stop TB Partnership GLOBAL DRUG FACILITY

Summary Bedaquiline & Delamanid

- 2 New life-saving TB medicines for MDR-TB
- Both available via the GDF to countries eligible for Global Fund TB Financing
  - Bedaquiline via donation program
  - Delamanid at $1700/treatment course (6 months)
- Both Available in GDF Strategic Rotating Stockpile
- Both require submission of a form signed by NTP stating WHO Guidelines being followed – including pharmacovigilance
  - Bedaquiline adverse events filed directly to Janssen or via GDF;
  - Delamanid adverse events filed to Otsuka via the GDF

Stop TB Partnership GLOBAL DRUG FACILITY

5 WHO Requirements for Use of Bedaquiline & Delamanid

1. **Effective treatment and monitoring:** Treatment must be closely monitored for effectiveness and safety
2. **Proper patient inclusion:** Special caution is required when bedaquiline is used in people aged 65 and over, and in adults living with HIV. Use in pregnant women and children is not advised.
3. **Informed consent:** Patients must be fully aware of the potential benefits and harms of the new drug, and give documented informed consent before embarking on treatment.
4. **Adherence to WHO recommendations:** four effective second-line drugs. Bedaquiline alone should not be introduced into a regimen in which the companion drugs are failing to show effectiveness.
5. **Active pharmacovigilance and management of adverse events:** ensure early detection and proper management of adverse drug reactions and potential interactions with other drugs.

ISO 9001 CERTIFIED ISO QUALITY MANAGEMENT SYSTEM

Stop TB Partnership GLOBAL DRUG FACILITY

Availability of new paediatric formulations

New paediatric formulations (RHZ & RH) are available from GDF

- ✓ Rifampicin 75mg + isoniazid 50 mg + pyrazinamide 150 mg
- ✓ Rifampicin 75 mg + isoniazid 50 mg

- Manufacturer: Macleods, ERP ½
- The products dissolve in water, have fruit flavour and are simple to administer.
- Technical assistance for development of a strategic plan for transition to the new paediatric formulations is available.
- Technical Briefing Note to switch to new paediatrics formulations:

http://stoptb.org/news/stories/2016/ns16_009.asp

ISO 9001 CERTIFIED ISO QUALITY MANAGEMENT SYSTEM

Stop TB Partnership GLOBAL DRUG FACILITY

Improving Access for Quality-Assured TB Medicines and Diagnostics

Supply Chain Management: Tackling Challenges to Secure Second Line Drugs at Regional Level

Taipei, 30 June 2016

Dr Kaspars Lunte
Team Leader Sourcing and Special Projects, GDF

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Process Mapping for Procurement via GDF

- ✓ Provision of the Procurement Request Form by client: *http://stoptb.org/gdf/drugsupply/procurement_forms.asp*
- ✓ Provision of Price Quote by GDF for Programme review and approval
- ✓ Confirmation and payment of the order
- ✓ Manufacturing, PSI, Quality control.
- ✓ Packing, preparation of shipment documents
- ✓ Shipping documents approval by the consignee
- ✓ Shipment freighted

http://www.stoptb.org/gdf/oms/default.asp

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GDF ORDER MANAGEMENT SYSTEM - 1

www.stoptb.org/gdf/oms

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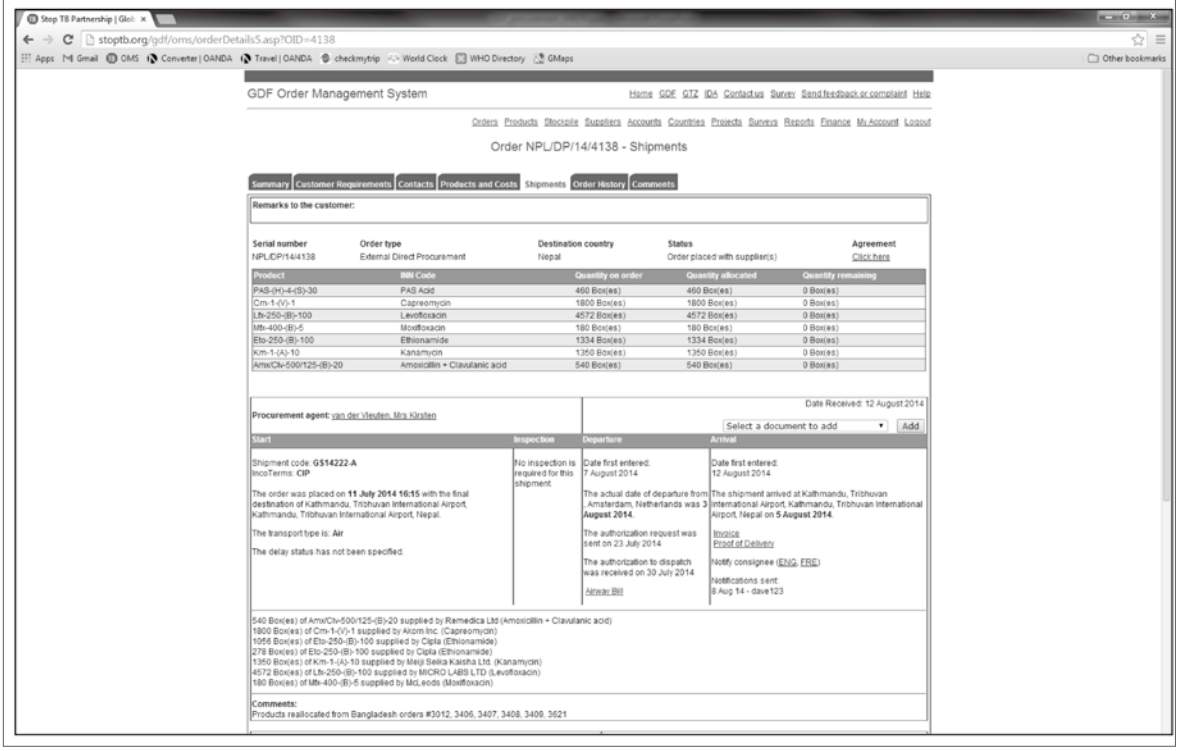
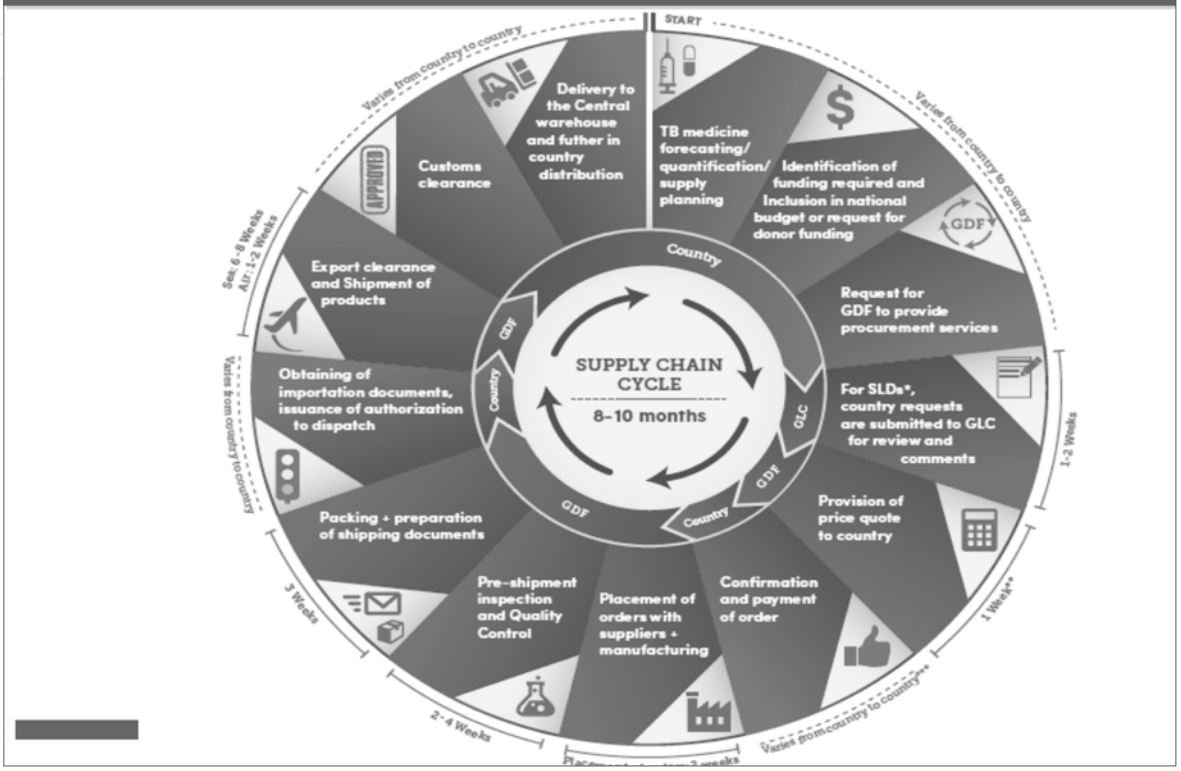
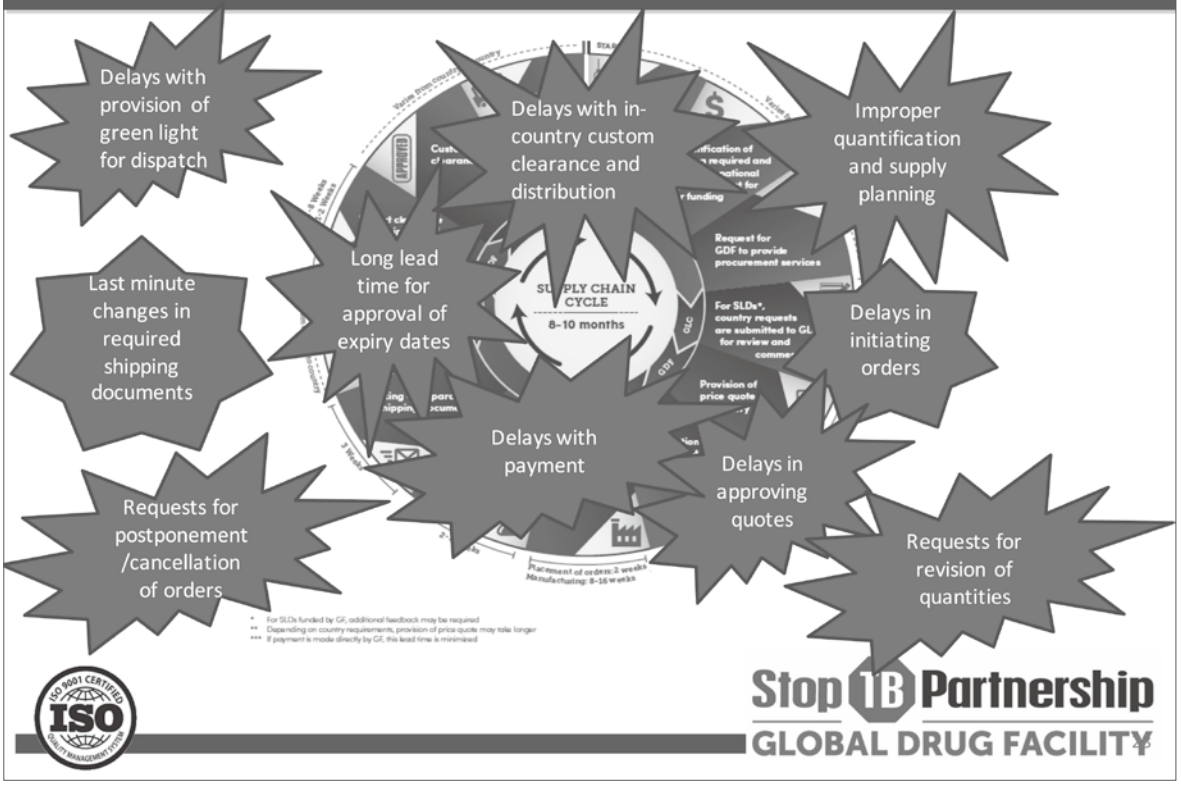
GDF ORDER MANAGEMENT SYSTEM - 2



TB medicine supply chain cycle through GDF



Challenges in the supply chain cycle (1)



Challenges in the supply chain cycle (2)

- ✓ NTP role in supply planning might be marginal - or critical
- ✓ Challenges in coordination among NTPs, PRs, donors, technical agencies, …
- ✓ Hectic procurement schedules/lack of clear planning based on sound inventory management
- ✓ Forecasting and quantification: usually based on planned cohorts, not on actual consumption needs.
- ✓ Order cancellations/postponements due to over-ordering
- ✓ Expiries and waste of medicines resulting in stock-outs
- ✓ Key challenge: lack of valid data required for decision making by all players – NTP and PRs supply planning and ordering, and realistic available funding

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QuanTB

- An electronic forecasting, quantification and early warning system tool
- Designed to improve procurement processes, ordering and planning for TB treatments
- Free downloadable desktop application for PC and Mac (http://siapsprogram.org/tools-and-guidance/quantb)
- Customizable: pre-loaded with all medicines from GDF catalogue and sample of WHO-recommended TB treatment regimens for exercises
- Allows forecasting of needs for any type of TB treatment regimen or combination of medicines for any period of time

Stop TB Partnership GLOBAL DRUG FACILITY

Thank You!

Contact Information:

Kaspars Lunte
KasparsL@stoptb.org

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Speaker

Vadim Testov

Position: Leading Researcher
Department/Organisation: TB Surveillance, Central TB Research Institute, Russian Federal Agency of Scientific Organizations
Economy: Russia

Educational Background

- 2015 Central TB Research Institute; Moscow, Russian Federation - postgraduate training for licenses of phtisiologist and pulmonologist
- 2006 New Jersey Medical School, New York, USA - TB Cohort Review Process; World Health Organization, Geneva, Switzerland- Workshop on Programmatic Management of Drug-Resistant Tuberculosis for WHO Staff4
- 2006 WHO Collaborating Centre for Research and Training in Management of MDR-TB - Second MDR-TB Consultant Course;
- 2005 WHO Collaborating Centre for Research and Training in Management of MDR-TB – Management of MDR-TB;
- 1996, 2001 Moscow Medical Academy – postgraduate trainings for licenses of phtisiologist, pulmonologist and surgeon;
- 1990-1991 Central TB Research Institute; Moscow, Russian Federation – postgraduate student, phtisiology, surgery of lungs;
- 1988-1990 Central TB Research Institute; Moscow, Russian Federation – traineeship for specialist in surgery of lungs;
- 1978-1984 2nd Moscow Medical Institute Moscow, Russian Federation – Medical Doctor Diploma

Professional Experience

- Research Institute; Moscow, Russian Federation;
- 1995-2001 Senior Researcher - Central TB Research Institute; Moscow, Russian Federation;
- 2001-2013 WHO Professional Officer for WHO TB Control Programme in the Russian Federation – WHO Country Office for the Russian Federation;
- 2013–now Leading Researcher - Central TB Research Institute; Moscow, Russian Federation

Recent Publications

- Sterlikov S., Testov V., Vasilieva I.,"Treatment results of patients with multiple and extensive drug resistance registered in 2012 in the Russian Federation and in the World", Tuberculosis and Lung Diseases, 2016, N1, pp. 22-27 (in Russian).
- Testov V, Puzanov V., Yakimova M, Punga V. "Drug resistance among new TB cases in some Russian regions" European Respiratory Journal, Volume 46, Supplement 59, September 2015, PA 2717.
- Testov V., Vasilyeva I., Sterlikov S., Erokhin V., Kasayeva T. "Monitoring of MDR-TB treatment outcomes in the Russian Federation" The International Journal of Tuberculosis and Lung Disease, Volume 18, N 11, November 2014, Supplement 1, PD 946-31, p. 343.
- Testov V., Sterlikov S., Vasilyeva I., Erokhin V., Kasayeva T. "Impact of social support programme on MDR-TB patients treatment outcomes" European Respiratory Journal, Volume 44, Supplement 58, September 2014, p. 2682.
- Testov V. , Sterlikov S., Vasilyeva I., Erokhin V., Kasaeva T. "Results of chemotherapy in patients with multidrug-resistant tuberculosis in the regions of the Russian Federation", Tuberculosis and Lung Diseases, 2014, N4, pp. 9 -13 (in Russian).

Speech Abstract

Supply Chain Management of Second Line Drugs: Russian Example

V. Testov[1], I. Vasilyeva[1], A. Samoilova[1], V. Gulshina[2]

[1] Central TB Research Institute, Moscow; [2] Ministry of Health of the Russian Federation

Background

The Russian Federation is a high MDR-TB burden country. Since 2001 TB incidence has been decreasing (1.7 times during 15 years). The proportion of MDR-TB cases among the new TB cases comprised 25.2-26.8% during the last years. The total number of the newly registered MDR-TB cases in 2014 was 36.230 and in 2015 – 32.216. The Russian Federation is a federative state with 85 Subjects of federation. In accordance with the federal legislation, all TB patients, citizens of Russia, should receive treatment free of charge. There are federal regulations and recommendations on TB Control including TB treatment. But each Subject of the State is fully responsible for the organization of TB treatment in local (regional) health facilities with their own budget. All second line TB drugs (SLD), bedaquilin and WHO recommended drugs from the fifth group have national registration. Due to the high expenditure of SLD, the Ministry of Health of the Russian Federation supports the SLD supply through special yearly transfers from the federal budget.

Supply Chain Management of SLD

There are special managerial procedures to provide proper SLD supply. The Russian MoH and the federal TB expert responsible team developed a set of tools for drug management including recommendation on SLD calculation and planning of supply. According to the timeline, during the first step of SLD Supply Chain (January-February), TB teams in Subjects asses their needs in SLD taking the number of patients who started treatment in previous year, the total number of registered MDR-TB patients, the rest of SLD on stocks and the requirements to have buffer stock of SLD for 6 months. The federal TB expert team is responsible for: technical support for Subjects, supervision of needs assessment and confirmation that both financial sources (Federal and Subject's budgets) cover SLD needs of the Subject. The second step (March) is to approve Subject's request by the Head TB expert of MoH and to transfer the federal money to Subject. During the third step (April –August), the authorities of the Subjects provide purchase of SLD through local markets according to the state regulations and procedures. The fourth step (September- November) is to supply SLD to the Subject Central Drug Stock (or to two-three sub-regional drug stocks for large Subjects). The fifth step (during the next year) is to distribute SLD to local health facilities and treat MDR-TB patients.

Results

In 85 Subjects of the Russian Federation: 21.904 MDR-TB patients started treatment and totally 35.480 MDR-TB patients received treatment in 2014; 28.423 MDR-TB patients started treatment and totally 44.850 MDR-TB patients received treatment in 2015.

Supply Chain Management of Second Line Drugs: Russian Example

Dr Vadim V. Testov
Central TB Research Institute, Moscow,
the Russian Federation

Context

Drug management – general principles;

TB in the Russian Federation;

Russian model of SLD management;

Russian example – achievements, challenges and perspectives

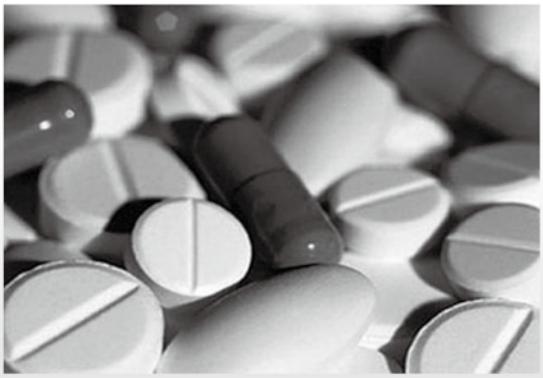
What is proper drug management?

- Full set of drugs where you need and when you need;
- For all patients
- For full course of treatment;
- With proper quality;
- With proper shelf life;
- Minimal rest of drugs but buffer stock
- **Reasonable costs**

Quality of drugs

- Problem of improper quality of drugs:
- **1%** of all drugs on markets in developed countries;
- **More than 10–30%** of all drugs on markets in developing countries (depends on geographical area)

(*IMPACT, 2008*)



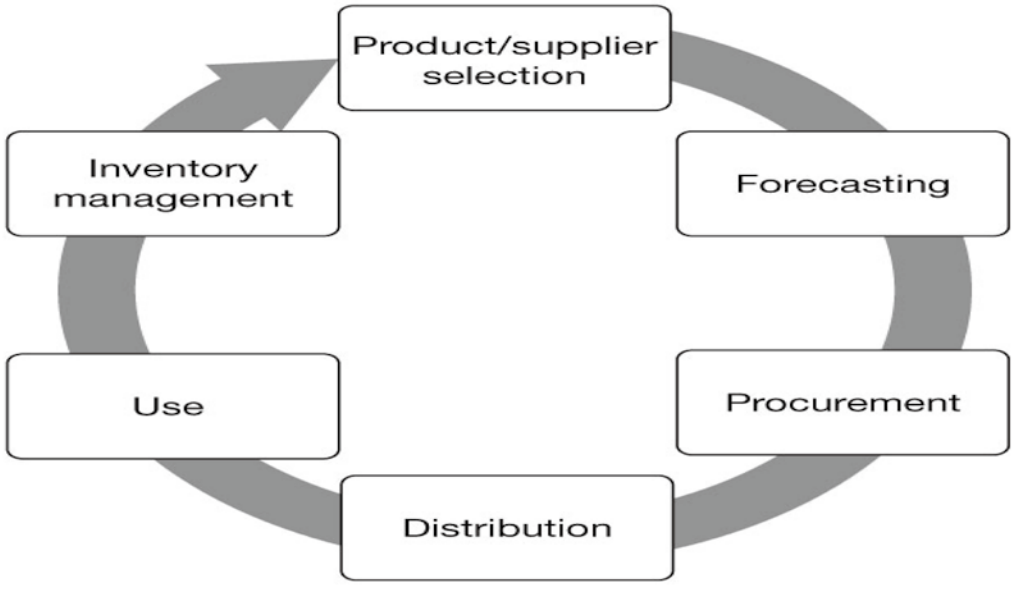
What we need to know for proper planning of SLD supplies

National pharmaceutical regulations and pharmacovigilance;
Estimated number of MDR-TB patients;
Clinical protocols for treatment of MDR-TB patients;

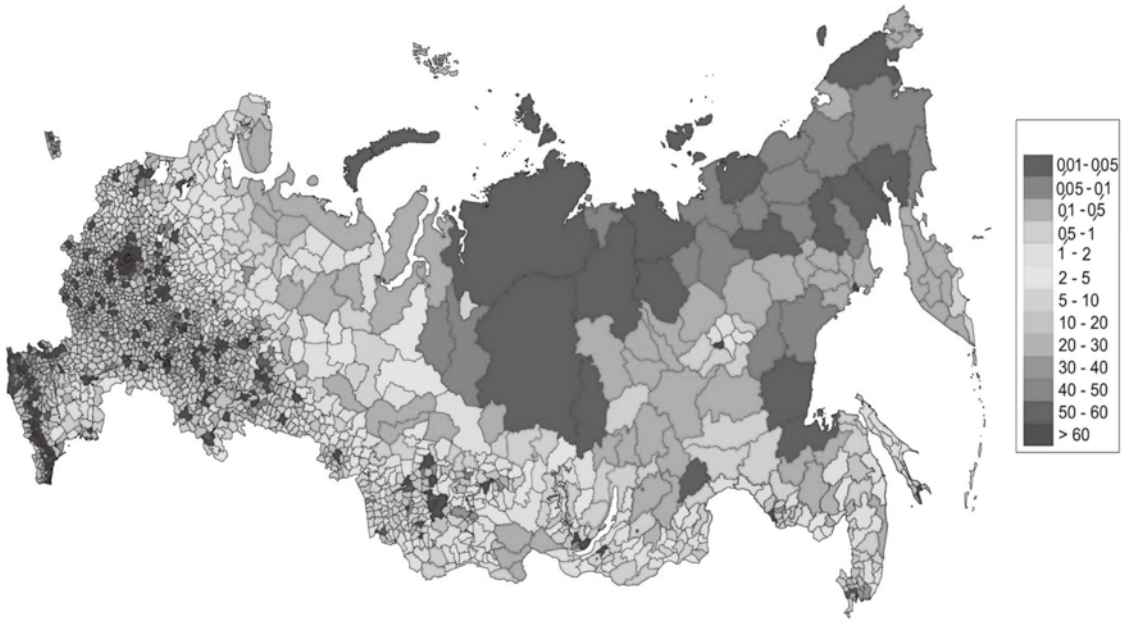
Drug calculation
Prices of SLD
Logistics of SLD

BUDGET

Drug management cycle

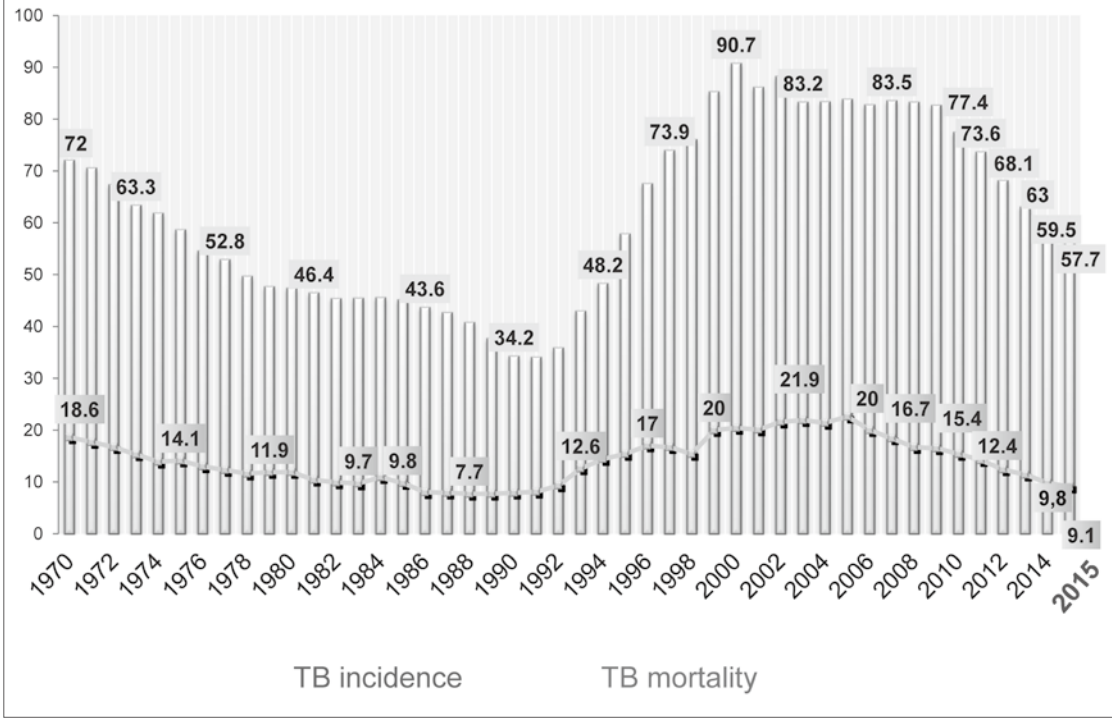


The Russian Federation



Total population in **2015** – 146544710

TB incidence and TB mortality rates



Registration of TB cases in the Russian Federation		
2013	New cases and relapses including MDR-TB	106.053 36.230
2014	New cases and relapses Including MDR-TB	99.103 32.216

Principles of TB Control in the Russian Federation

- Federal legislation and regulations for TB Control;
- Federal surveillance and monitoring of TB;
- TB care for citizens of the Russian Federation is free of charge;
- Subjects (Regions) of the State is fully responsible for the organization of TB treatment in local (regional) health facilities with their own budgets.

Implementation of M/XDR-TB Programmatic Management in the Russian Federation

- 1999 - 2007 Implementation of DOTS-Plus regional projects;
- in 3 Russian Subjects with support of WHO and international humanitarian organizations - total number of treated MDR-TB patients about 1.000;
- October 2007 – May 2010 treatment of MDR-TB patients implementation of GLC approved projects in 23 Russian Subjects within GF TB Control project, Round 4 - total number of treated MDR-TB patients - 7.500;
- Since June 2010 all Russian Subjects (Regions) provide treatment of MDR-TB patients with national resources

DR survey in three Subjects (new TB patients)

Anti-TB Drugs	H (%)	R (%)	S (%)	E (%)	Z (%)	HR (%)	Ofx (%)	Km (%)
Penza	44.1	37.0	47.4	24.6	14.2	36.0	6.2	12.8
Ulyanovsk	47.1	38.7	41.7	27.0	11.0	36.5	7.6	14.7
Astrakhan	44.8	34.6	43.8	26.3	9.7	29.4	8.3	11.8
95% IC	42.4-48.6	33.6-39.6	40.7-46.9	23.5-29.0	9.5-13.4	30.5-36.4	6.0-9.4	11.1-15.3

Registration of Drugs for MDR-TB treatment in the Russian Federation	
Drugs for MDR-TB treatment	National registration
kanamycin	yes
amikacin	yes
capreomycin	yes
levofloxacin	yes
moxifloxacin	yes
gatifloxacin	yes
ofloxacin	yes
ethionamide	yes
prothionamide	yes
cycloserine	yes
terizidone	yes
p-aminosalicylic acid	yes

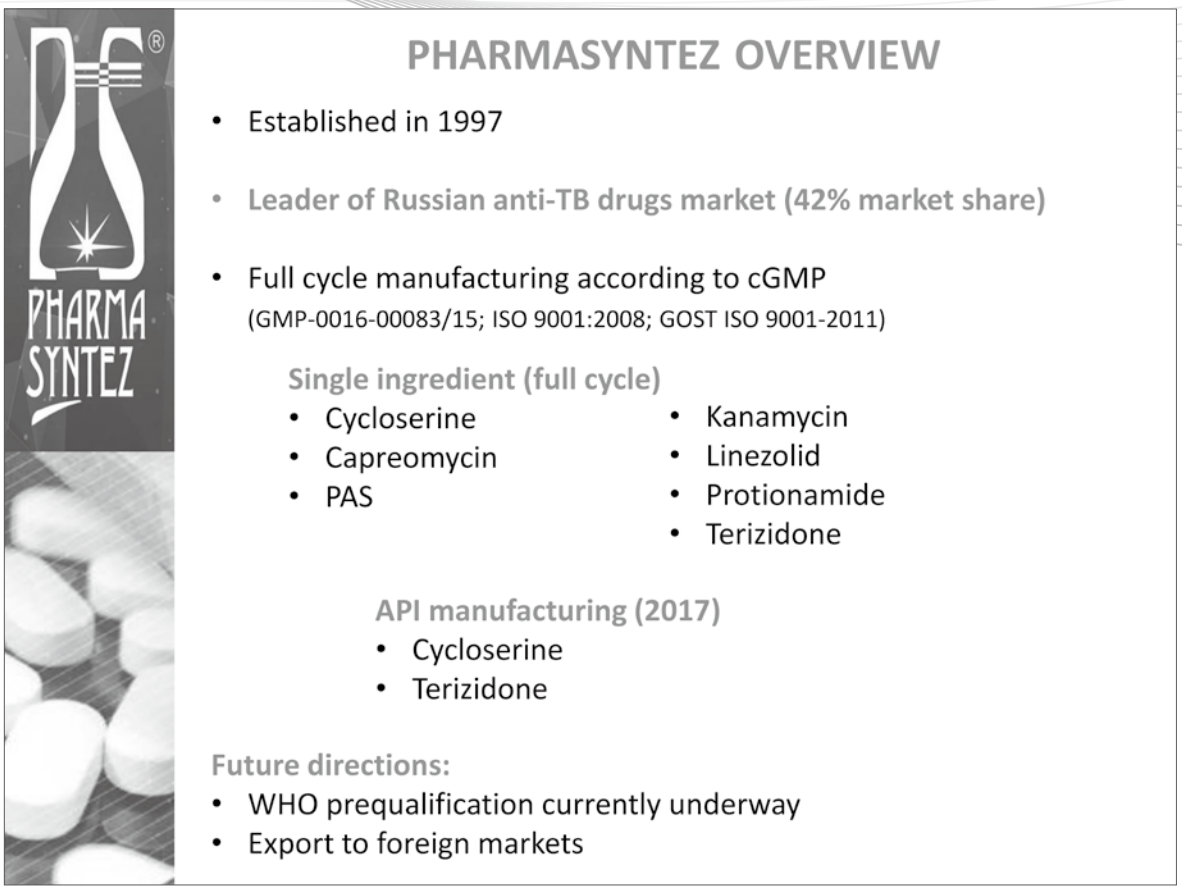
Registration of Drugs for MDR-TB treatment in the Russian Federation	
Drugs for MDR-TB treatment	National registration
bedaquilin	yes
linezolid	yes
amoxicillin/clavulanate	yes
thioacetazone	yes
clarithromycin	yes
imipenem	yes

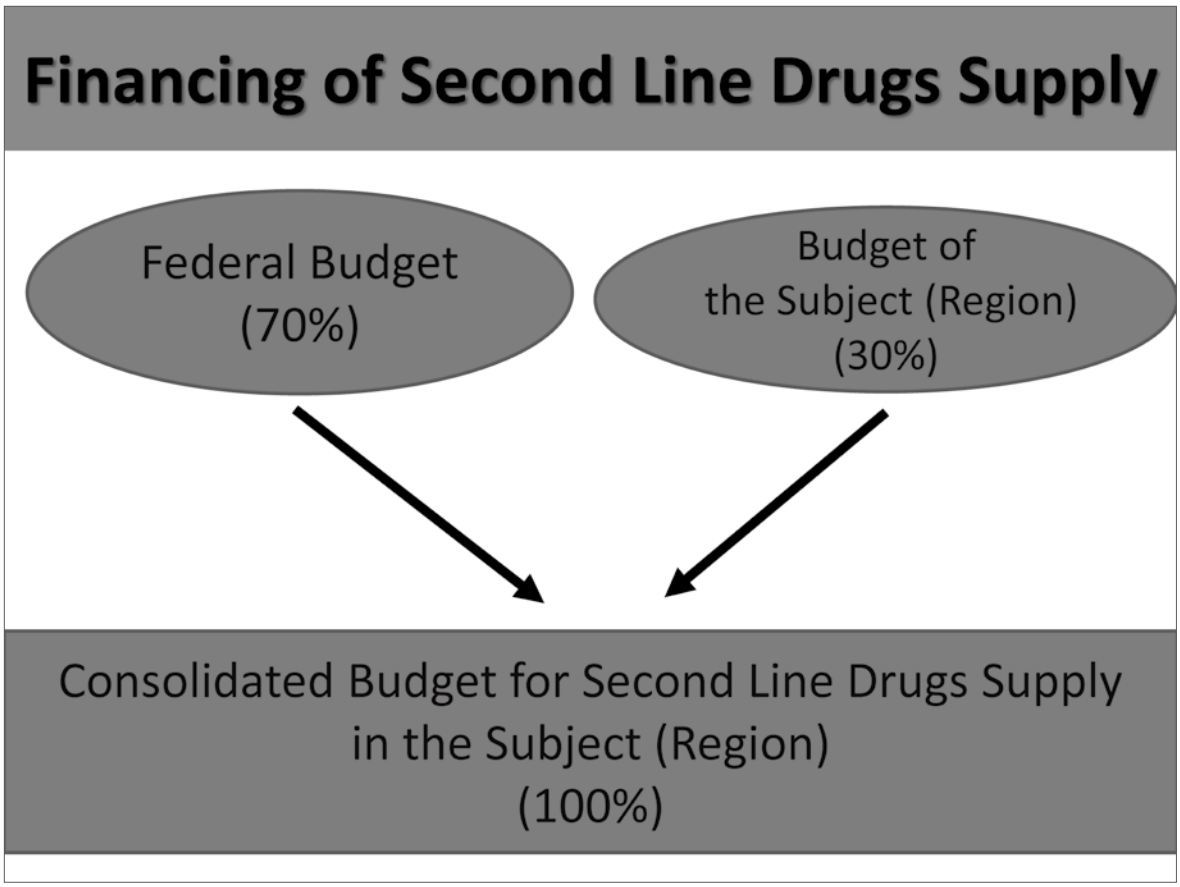
Russian market of Second Line Drugs

- More than 30 traders regularly participate in tenders;
- 17 Russian manufactures of Second Line Drugs;
- More than 10 offers for each international Nonproprietary Name of anti-TB drugs;
- Competition of prices

Quality of Second Line Drugs

- National legislation and regulations on drugs quality control;
- Correspondence to the national regulation and national registration;
- GMP is not obligatory for participation in the bidding


PHARMA SYNTEZ
PHARMASYNTEZ OVERVIEW
• Established in 1997
• Leader of Russian anti-TB drugs market (42% market share)
• Full cycle manufacturing according to cGMP
(GMP-0016-00083/15; ISO 9001:2008; GOST ISO 9001-2011)
Single ingredient (full cycle)
• Cycloserine
• Capreomycin
• PAS
• Kanamycin
• Linezolid
• Protionamide
• Terizidone
API manufacturing (2017)
• Cycloserine
• Terizidone
Future directions:
• WHO prequalification currently underway
• Export to foreign markets


Financing of Second Line Drugs Supply
Federal Budget (70%)
Budget of the Subject (Region) (30%)
Consolidated Budget for Second Line Drugs Supply in the Subject (Region) (100%)

Russian Second Line Drugs Management Cycle

Set of recommendations and tools

- Timelines for Second Line Procurement;
- Recommendation on Second Line Drugs Calculation;
- Federal legislation on public biddings;
- Standard Agreement between Russian Ministry of Health and Local Health Administration in the Subject for the federal transfer

Second Line management Cycle. Russian example

The First Step

(January- February)

- Assessment of Second Line needs and preparation request for drug supply by local TB team;
- The federal TB expert team is responsible for: technical support for Subjects, supervision of needs assessment and confirmation that both financial sources (Federal and Subject's budgets) cover SLD needs of the Subject;

Second Line management Cycle. Russian example

The Second Step

(March)

- Approval of the request for drug supply by federal TB Head specialist;
- Transfer of the federal money for Second Line Purchase to the Subject

Second Line management Cycle. Russian example

The Third Step

(April –August)

- The authorities of the Subjects provide purchase of SLD through local markets according to the state regulations and procedures

Second Line management Cycle. Russian example

The Forth Step

(September- November)

- Supply SLD to the Subject Central Drug Stock (or to two-three sub-regional drug stocks for large Subjects)

Second Line management Cycle. Russian example

The Fifth Step

(during the next year)

- Distribution of Second Line Drugs to local health facilities and treatment of MDR-TB patients

Principles of drug management in Subject (Region)

- One responsible person;
- Central drug stock;
- Centralized SLD monitoring system (all health facilities report to one responsible person);
- Current monitoring of SLD rests in health facilities and shelf life;
- Buffer stock in Subject (Region)

Costs of anti-TB drugs for MDR-TB treatment

- Costs of anti-TB drugs for one 24-months MDR-TB treatment course with bedaquilin and linezolid comprised in 2015 – USD 9.200;
- Costs of anti-TB drugs for the first 12 month of the treatment –USD 6.324;
- Costs of anti-TB drugs for the second 12 month of the treatment –USD 2.876

Results

- In 2014: 21.904 MDR-TB patients started treatment and totally 35.480 MDR-TB patients received treatment;
- In 2015: 28.423 MDR-TB patients started treatment and totally 44.850 MDR-TB patients received treatment

Challenges

High level of XDR-TB

estimated proportion of XDR-TB among all detected MDR-TB cases in Russia is 17.0%

Increasing of costs for treatment

How to improve national system of Second Line Drugs Management?

- Implementation of national (all Russian) electronic TB register with incorporated tools for Drug Management: programme for Drug calculation and monitoring of drug consumption;
- Centralization of Second Line Drugs bidding on federal level with long-time contracts for decreasing of prices

Thank you for your attention!

Speaker

Chen-Yuan Chiang

Position: Consultant
Department/Organisation: Department of Tuberculosis and HIV, International Union Agaihts, International Union Against Tuberculosis and Lung Disease, Paris, France

Educational Background

- Doctor Philosophiae (DrPhilos), University of Bergen, Norway
- Master of Public Health (MPH), School of Public Health, University of California, Berkeley, USA
- MD, Kaohsiung Medical University, Chinese Taipei

Professional Experience

Current position:

- Consultant, Department of Tuberculosis and HIV, The Union, Paris, France
- Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Chinese Taipei
- Associate Professor, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Chinese Taipei

Recent Publications

- Chiang C-Y, Van Deun A, Rieder HL. Gatifloxacin for short and effective treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2016 (in press).
- Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y, Keshavjee S, Koh W-J, Shiraishi Y, Viiklepp P, Yim J-J, Pasvol G, Robert J, Shim YT, Shin SS, Menzies D, on behalf of "The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB". Surgery as an adjunctive treatment for multi-drug resistant tuberculosis: an individual patient data meta-analysis. Clin Infect Dis. (2016) doi: 10.1093/cid/ciw002.
- Lo H-Y, Yang S-L, Lin H-H, Bai K-J, Lee J-J, Lee T-I, Chiang C-Y. Does enhanced diabetic management reduce the risk and improve the outcome of tuberculosis? Int J Tuberc Lung Dis 2016; 20(3):376–382.
- Lai T-C, Chiang C-Y, Wu C-F, Yang S-L, Liu D-P, Chan C-C, Lin H-H. Ambient air pollution and risk of tuberculosis: a cohort study. Occup Environ Med 2016;73(1):56-61.
- Chiang C-Y, Yu M-C, Yang S-L, Yen M-Y, Bai K-J. Surveillance of tuberculosis in Taipei: the influence of nontuberculous mycobacteria. PLoS One 10(11): e0142324. doi:10.1371/journal.pone.0142324.

Speech Abstract

Novel Regimen Options for DR-TB Treatment

Chen-Yuan Chiang

Consultant

International Union Against Tuberculosis and Lung Disease, Paris, France

The inexpensive, short, and highly effective 9-month regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB) piloted in Bangladesh comprised high-dose gatifloxacin (800 mg for body weight >50 kg and 600mg for 33-50kg), clofazimine, ethambutol, and pyrazinamide throughout, supplemented by kanamycin, prothionamide and isoniazid during an intensive phase of at least 4 months. If sputum smear microscopy results were positive at month 4, the intensive phase was extended until sputum smear conversion occurred or bacteriological treatment failure was declared. The continuation phase had a fixed duration of 5 months. In the most recently reported cohort of 515 consecutive patients receiving this regimen, 435 (84%) had a successful treatment outcome, 29 (6%) died on treatment, 40 (8%) were lost to follow-up, 7 (1%) failed, and 4 (1%) relapsed. This regimen was introduced in Niger with the modification to prolong the continuation phase to 8 months as a precaution against relapse.3 Of the 65 patients, 58 (89%) were cured, 6 (9%) died, and 1 (2%) was lost to follow-up. Among the 58 cured, 49 (84%) remained culture-negative at 24 months' follow-up, and no relapse was documented. The "Bangladesh regimen" was also used in Cameroon with three modifications, 1) an extension of the continuation phase from 5 to 8 months, 2) a standard dose of gatifloxacin (400mg), and 3) prothionamide given throughout the treatment course. Of the 150 patients, 134 (89%) had a successful treatment outcome, 1 (1%) failed, 10 (7%) died and 5 (3%) were lost to follow-up.

According to the WHO Global TB Report 2015, globally the proportion of MDR-TB patients who successfully completed treatment was 50%, while 24% of cases were reported as lost to follow-up or had no outcome information. WHO has updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation on the use of shorter MDR-TB regimens. This new recommendation is expected to benefit the majority of MDR-TB patients worldwide. However, outcome of MDR-TB patients with fluoroquinolone resistance treated with shorter MDR-TB regimens was not satisfactory. New drugs are needed for the management of fluoroquinolone-resistant MDR-TB.

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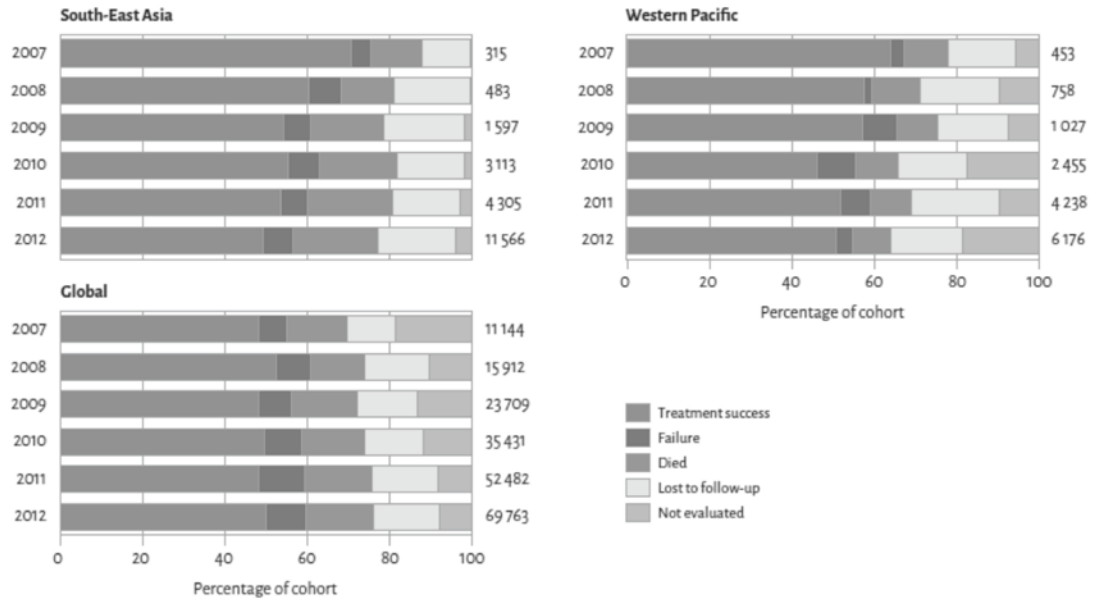
Novel Regimen Options for DR-TB Treatment

Chen-Yuan Chiang

International Union Against Tuberculosis and Lung Disease (The Union), Paris, France

1

Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2007–2012 cohorts



WHO. Global Tuberculosis Report 2015

Unsatisfactory outcome of MDR-TB

- Long duration of treatment
- High frequency of adverse drug reactions
- Mixture of MDR-TB, fluoroquinolone-resistant MDR-TB, and XDR-TB

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Short standardized treatment of multidrug-resistant tuberculosis

Intensive phase: GEZC KHP 4 months, extended till sputum conversion	Continuation phase: GEZC 5 months
Kanamycin (K)	
Prothionamide (P)	
Isoniazid (H)*	
Gatifloxacin (G)*	Gatifloxacin (G)*
Clofazimine, C	Clofazimine, C
Ethambutol, E	Ethambutol, E
Pyrazinamide, P	Pyrazinamide, P

*high dose

Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684–692

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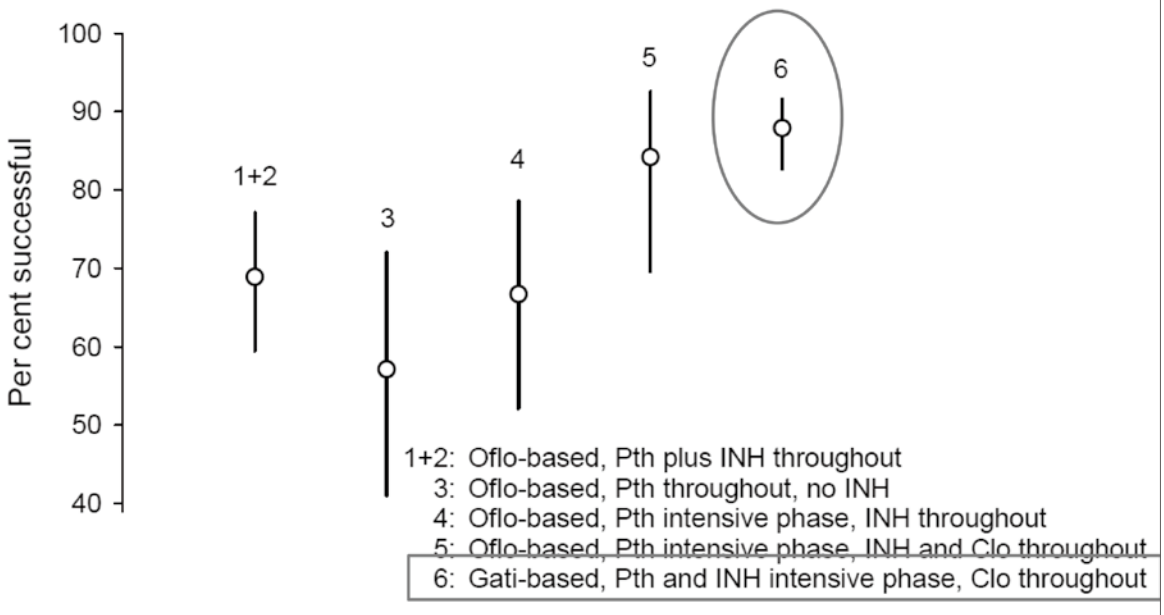
Daily Drug Dosages Used For Standardized Multidrug-resistant Antituberculosis Treatment, Bangladesh Damien Foundation Projects

	Weight group		
Drug	<33 kg	33–50 kg	>50 kg
Kanamycin*	500 mg	750 mg	1,000 mg
Ofloxacin	400 mg	600 mg	800 mg
Gatifloxacin†	400 mg	600 mg	800 mg
Prothionamide‡	250 mg	500 mg	750 mg
Clofazimine	50 mg	100 mg	100 mg
Isoniazid	200 mg	300 mg	300 mg
Isoniazid high dose‡	300 mg	400 mg	600 mg
Ethambutol	800 mg	800 mg	1,200 mg
Pyrazinamide	1,000 mg	1,500 mg	2,000 mg

*KM reduced by 25% for patients aged ≧45, later precisely as 15 mg/kg, 3 times weekly 4th month onward
† Gatifloxacin was used at a lower dosage for the first 50 patients enrolled
‡The high dose of isoniazid was used with the gatifloxacin-based regimen, whereas the normal dose was given in all ofloxacin-based regimens

Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684–692 International Union Against Tuberculosis and Lung Disease

Proportion of patients with a successful treatment outcome for multidrug-resistant tuberculosis, by regimen, Bangladesh



Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684–692 International Union Against Tuberculosis and Lung Disease

MDR-TB, Niger

- 12-month standardised regimen:
  4 Km Gfx Pto H Cfz E Z / 8 Gfx Cfz E Z (Gfx, high dose)
- 65 MDR-TB patients
  - Cure: 58 patients (89.2%, 95%CI 81.7–96.7),
  - died 6
  - Defaulted 1.
- No relapse at the 24-month follow-up after cure (49 patients)

Piubello A, et al. Int J Tuberc Lung Dis 2014;18:1188–1194

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High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon

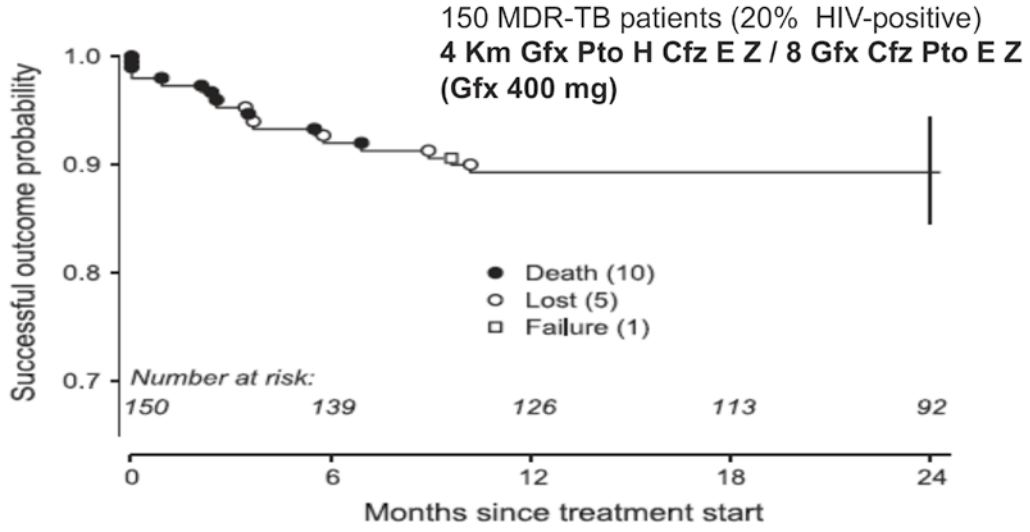

Figure 2 Kaplan-Meier estimate of successful treatment outcome, Cameroon, treatment of patients with MDR. MDR = multidrug resistance.

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Kuaban C, et at. Int J Tuberc Lung Dis 2015; 19:517–524

Bangladesh MDR-TB, 2005-2011
4 Km Gfx Pto H Cfz E Z / 5 Gfx Cfz E Z

- relapse-free treatment success 84% (N = 515)

– cured	423 (82%)
– completed	12 (2%)
– defaulted	40 (8%)
– died	29 (6%)
– failed	7 (1%)
– relapsed	4 (0.8%)

Aung KJM *et al.* Int J Tuberc Lung Dis 2014;18:1180–1187

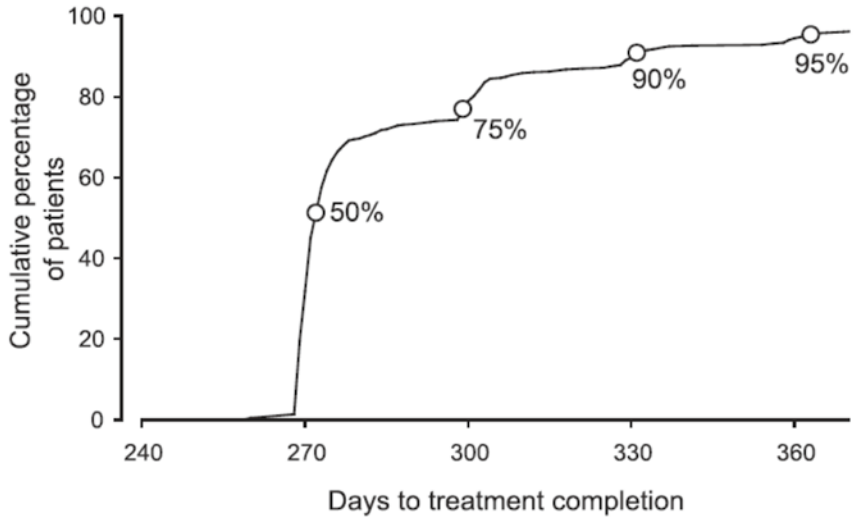

Figure 1 Number of days to treatment completion among the 439 patients who did not end treatment prematurely (due to death, default or treatment failure).

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Table 1 Treatment outcome among patients with multidrug-resistant tuberculosis. Treatment success comprises cured and treatment completed; all other standard outcomes together constitute non-success

	n (%)	95%CI
Total ($n = 515$)		
Success ($n = 435$, 84.5%)		
Completion	17 (3.3)	2.1–5.2
Cure, 0 months follow-up	4 (0.8)	0.3–2.0
Cure, 6 months follow-up	7 (1.4)	0.7–2.8
Cure, 12 months follow-up	11 (2.1)	1.2–3.8
Cure, 18 months follow-up	36 (7.0)	5.1– 9.5
Cure, 24 months follow-up	358 (69.5)	65.4–73.3
Cured, reinfection disease	2 (0.4)	0.1–1.4
Non-success ($n = 80$, 15.5%)		
Failure	7 (1.4)	0.7–2.8
Death, first 60 days	14 (2.7)	1.6–4.5
Death, after 60 days	15 (2.9)	1.8–4.7
Default, first 60 days	19 (3.7)	2.4–5.7
Default, after 60 days	21 (4.1)	2.7–6.2
Relapse	4 (0.8)	0.3–2.0

CI = confidence interval.

Successful '9-month Bangladesh regimen' for MDR-TB patients

Of the 515 patients

- Eleven patients failed (n=7) or relapsed (n=4)
- Amplification of drug resistance occurred only once, in a patient strain that was initially only susceptible to kanamycin and clofazimine

Acquired Resistance to Fluoroquinolones Among 832 Adults With Pulmonary Multidrug-Resistant Tuberculosis Starting Treatment With Second-line Drugs, 2005–2010, in 9 Countries

Of those without baseline resistance to specific second-line drugs,

- 68 (8.9%) acquired extensively drug-resistant (XDR) tuberculosis,
- 79 (11.2%) acquired fluoroquinolone (FQ) resistance, and
- 56 (7.8%) acquired resistance to second-line injectable drugs

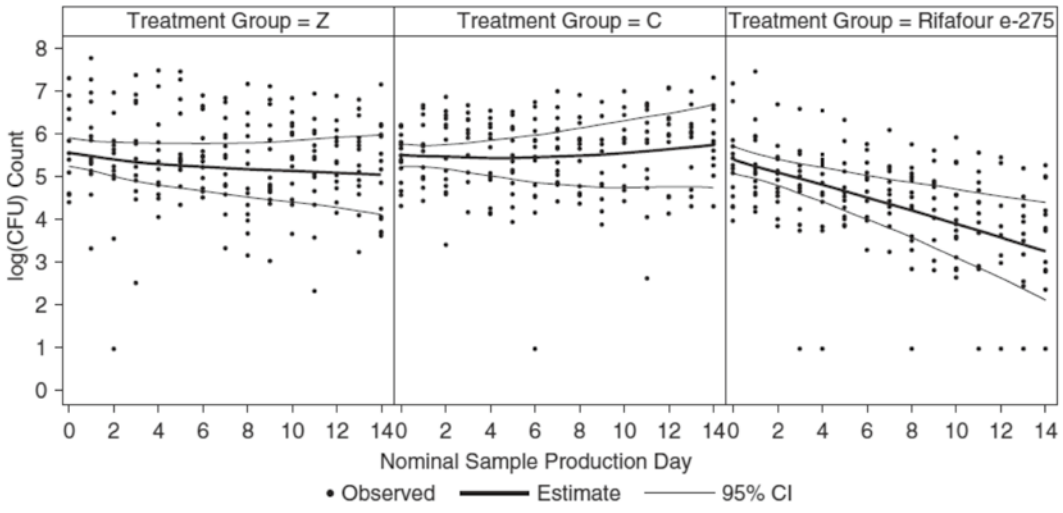
Cegielski JP, et al. Clin Infect Dis 2014;59:1049–63

Acquired Resistance to Fluoroquinolones Among 832 Adults With Pulmonary Multidrug-Resistant Tuberculosis Starting Treatment With Second-line Drugs, 2005–2010, in 9 Countries

Baseline DST	Acquired FQ resistance	RR (95% CI)
Ethambutol		
Resistance	17.4%	1.86 (1.14–3.05)
susceptible	7.9%	1
kanamycin		
Resistance	36.8%	6.14 (4.08–9.24)
susceptible	6.0%	1
Ethionamide		
Resistance	11.5%	0.95 (.55–1.63)
susceptible	12.1%	1

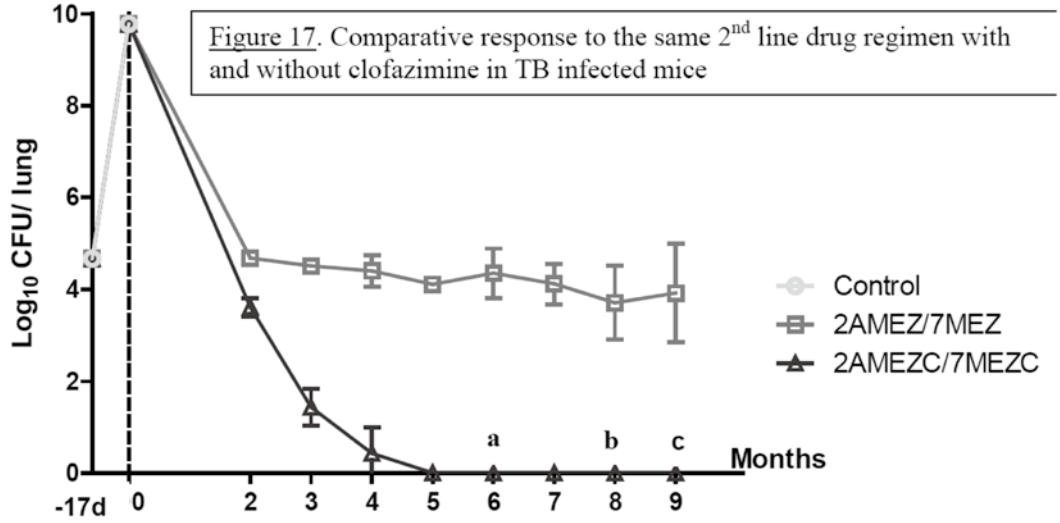
Cegielski JP, et al. Clin Infect Dis 2014;59:1049–63

Mean log_{10}CFU over time. Observed values (dots) and posterior estimates calculated from the joint Bayesian nonlinear mixed-effects regression model with 95% CIs of mean logCFU over time



Diacon AH, et al. Am J Respir Crit Care Med 2015

Clofazimine



Study designed and supervised by: Jacques Grosset, MD
And conducted by: Sandeep Tyagi, BS, Si-yang Li, BS, Deepak Almeida, PhD, Paul Converse, PhD

The Bangladesh MDR-TB regimen

- The core drug is likely high-dose gatifloxacin, acting both as bactericidal and sterilizing agent.
- Kanamycin as a powerful companion drug protecting the fluoroquinolone.
- It is likely that clofazimine plays an important yet not fully understood role.
- Not satisfactory for fluoroquinolone-resistant MDR-TB

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STREAM

The Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB

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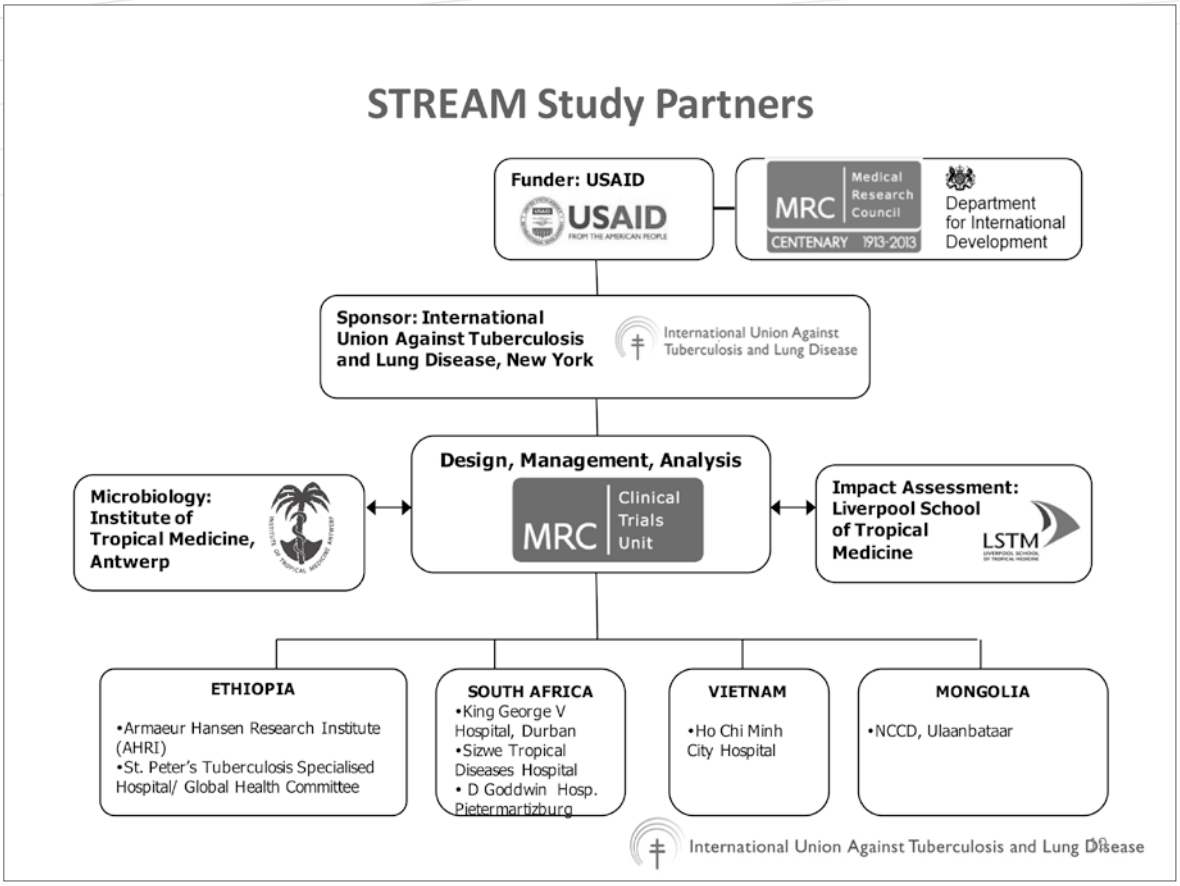

STREAM study design

- STREAM is a randomised controlled trial of non-inferiority design
- Study population: MDR-TB patients
  - Patients with resistance to either fluoroquinolone or second line injectables are excluded
- The control regimen is the locally used WHO recommended regimen in the participating countries
- The study regimen is closely similar to the regimen used by Van Deun in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin

STREAM Stage 2

- Early in 2013 in recognition of the progress made to date in STREAM and noting the provisional licensing of the first new drug for TB for almost 50 years we were asked to consider:
  - is it possible to include additional regimens to the STREAM trial in its present form?
  - if so, what would be the appropriate regimens to evaluate?

Additional regimens proposed for Stage 2

- After extensive discussions between the study team, the local investigators and other experts it was agreed that the primary interest to patients and programmes would be:
  - a fully oral 9-month regimen
  - a 6-month simplified regimen
- Both of these regimens would include bedaquiline

Regimen C

- In Regimen C, the fully oral regimen, **kanamycin is replaced by bedaquiline** and **moxifloxacin by levofloxacin**

Product	Weeks	**Weight group**		
		Less than 33 kg	**33 kg to 50 kg**	**More than 50 kg**
Bedaquiline	**1 – 40**	**400 mg once daily for first 14 days/200 mg thrice weekly thereafter**		
Levofloxacin	**1 – 40**	**750 mg**	**750mg**	**1000 mg**
Clofazimine	1 – 40	50 mg	100 mg	100 mg
Ethambutol	1 – 40	800 mg	800 mg	1200 mg
Pyrazinamide	1 – 40	1000 mg	1500 mg	2000 mg
Isoniazid	1 – 16	300 mg	400 mg	600 mg
Prothionamide	1 – 16	250 mg	500 mg	750 mg


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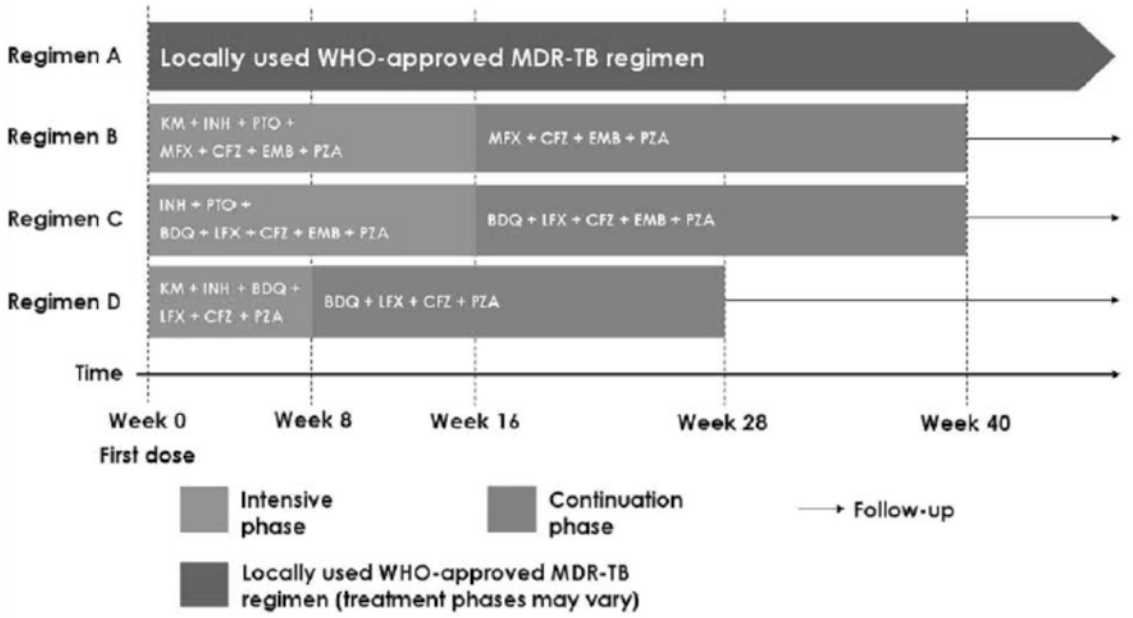
Regimen D

- In Regimen D prothionamide is replaced by bedaquiline, moxifloxacin is replaced by levofloxacin, ethambutol is removed, the dose of isoniazid is increased and the total duration is reduced from 40 to 28 weeks

Product	**Weeks**	**Weight group**				
		Less than 33 kg	**33 kg to less than 40 kg**	**40 kg to less than 50 kg**	**50 kg to less than 60 kg**	**More than 60 kg**
Bedaquiline	**1 – 28**	**400 mg once daily for first 14 days/200 mg thrice weekly thereafter**				
Levofloxacin	**1 – 28**	**750 mg**	**750 mg**		**1000 mg**	
Clofazimine	**1 – 28**	50 mg	100 mg		100 mg	
Pyrazinamide	**1 - 28**	1000 mg	1500 mg		2000 mg	
Isoniazid	**1 – 8**	**400 mg**	**500 mg**	**600 mg**	**800 mg**	**900 mg**
Kanamycin	**1 – 8**	15 mg per kilogram body weight (maximum 1g)				

24

Treatment phases of investigational regimens



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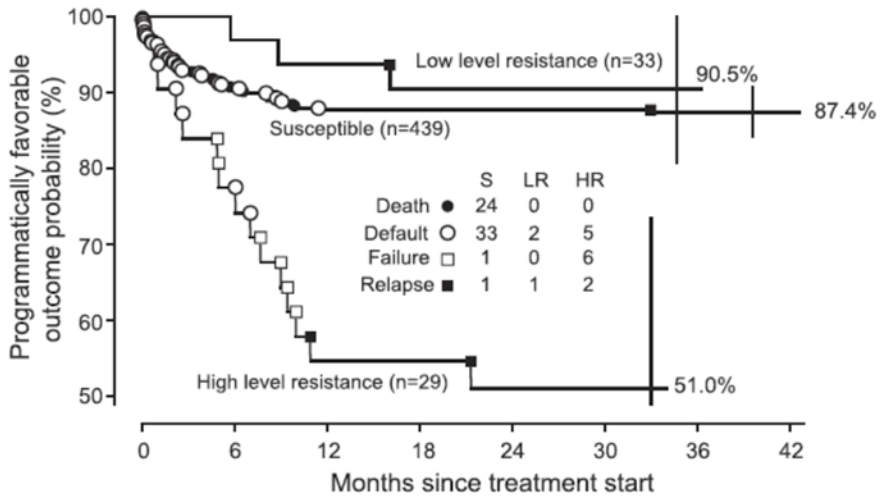

Figure 3 Programmatically favorable treatment outcome probability derived from a Cox's proportional hazard model among 501 patients, stratified by initial fluoroquinolone susceptibility test result, adjusted for age and sex. S = susceptible to ofloxacin and/or GFX at the standard critical concentration; LR = low-level resistance (GFX MIC 0.5–1.0 mg/l); HR = high-level resistance (GFX MIC ⩾2 mg/l); GFX = gatifloxacin; MIC = minimum inhibitory concentration.

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Cascade of regimens

Rifampicin	Quinolone	Treatment approach
Susceptible		First line anti-TB treatment
Resistant	Susceptible	Second line anti-TB treatment (9-month regimen)
Resistant	Resistant	New drugs needed

Closing Remarks Speaker

Steve Hsu-Sung Kuo

Position: Director-General
Department/Organisation: Centers for Disease Control
Economy: Chinese Taipei

Educational Background

- SEF. 2002 John F. Kennedy School of Government, Harvard University, U.S.A.
- Ph.D. 1987-91 Department of Epidemiology and Public Health, School of Medicine, Yale University, U.S.A.
- M.P.H.1982-84 College of Public Health, National Taiwan University, Chinese Taipei
- M.D. 1975-82 National Yang-Ming Medical College, Chinese Taipei

Professional Experience

- 2014-present Director-General, Centers for Disease Control, Ministry of Health and Welfare, Chinese Taipei
- 2010-2014 Senior Advisor, Taipei Economic and Cultural Representative Office (TECRO), Washington, D.C., U.S.A.
- 2004-2010 Director-General, Centers for Disease Control, Department of Health (currently known as Ministry of Health and Welfare), Chinese Taipei
- 2003 Chief Coordination Officer and Spokesman of the Taiwan SARS Task Force
- 1998-2002 Director-General, Bureau of Health Planning and Evaluation, Department of Health (currently known as Ministry of Health and Welfare), Chinese Taipei
- 1991-1998
  Secretary General, National Yang-Ming University, Chinese Taipei
  Associate Dean, Faculty of Medicine, National Yang-Ming University, Chinese Taipei
  Associate Professor, Epidemiology and Medicine, National Yang-Ming University, Chinese Taipei

Recent Publications

- Lu CY, Ni YH, Chiang BL, Chen PJ, Chang MH, Chang LY, Su IJ, Kuo HS. Humoral and cellular immune responses to a hepatitis B vaccine booster 15-18 years after neonatal immunization. J Infect Dis. 2008, 197(10):1419-26.
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Participant List

Australia

Alex Stephens

Program Manager
Papua New Guinea Infrastructure and Social Development, Australian Department of Foreign Affairs and Trade
alex.j.stephens@dfat.gov.au
61 2 6261 1910

Chile

Tania Herrera

Director
TB Program, Ministry of Health
tania.herrera@minsal.cl
56 991589055

Carlos Pena

Adviser
TB Program, Ministry of Health
Carpemanti@hotmail.com
56 991589055

China

Xiaoqiu Liu

Director
Department of Policy and Program, National Center for Tuberculosis Control and Prevention, China CDC
Leon@chinatb.org
861058900515

Yunzhou Ruan

Vice Director
Department of Drug-resistant TB control, National Center for TB Control and Prevention, CDC, China
ruanyunzhou@chinatb.org
86-10-58900559

Wei Su

Staff
Department of Drug-resistant TB control, National Center for TB Control and Prevention, CDC, China
suwei@chinatb.org
861058900559

Yanlin Zhao

Director, National Tuberculosis Reference Laboratory
Vice-Director, National Center for TB Control and Prevention, CDC, China
zhaoyanlin@chinatb.org
86-10-58900779

Indonesia

Endang Budi Hastuti

Deputy of National TB Program
Directorate of Prevention and Control of Communicable Disease, MOH Indonesia
endangb22@yahoo.com
62 81287634185

Endang Lukitosari

Focal Person for TB-MDR
Directorate of Prevention and Control of Communicable Disease, MOH Indonesia
endanglukitosari@yahoo.com
62 815 991 2747

Elon Sirait

Deputy Director
Pharmacy Management and Clinical, Directorate of Pharmaceutical Services, MOH Indonesia
elsirait2001@yahoo.com
628195176755

Japan

Takashi Yoshiyama

Deputy Head
Respiratory Diseases Center, Fukujuji Hospital, Japan
Yoshiyama@jata.or.jp
81-424-92-4765

Korea

Hyungseok Kang

Director
Department of Chest Medicine, Masan National Hospital, Republic of Korea
johnofkathy@naver.com
82-10-9555-5366

Malaysia

Akashah Abdullah

Public Health Specialist
Ministry of Health Malaysia
akashahabdullah@gmail.com
6012 287 8767

Asmah Razali

Senior Assistant Principal Director
TB Sector, Ministry of Health Malaysia
dr.asmahrazali@moh.gov.my
6016 553 2462

The Philippines

Lucky Cindy Ricafrente

Administrative Officer I
Administrative Service, Department of Health, the Philippines
cindzricafrente@yahoo.com
6517800#3502

Jeff Carl Estioco

Senior Health Program Officer
National Capital Regional Office, the Philippines
jaycee_estioco@yahoo.com
63-5354593

Rosalind G. Vianzon

Division Chief
Disease Prevention and Control Bureau, Department of Health, the Philippines
rgvianzon10@yahoo.com
63 29179075091

Russia

Valeriya Gulshina

Head of unit
Ministry of Health of the Russian Federation
gulshinava@rosminzdrav.ru
7 4997859187

Vadim Testov

Leading Researcher
Central TB Research Institute, Russian Federal Agency of Scientific Organizations
testov.vadim@mail.ru
7 4997859187

Singapore

Suay Hong Gan

Principal Resident Physician
Tuberculosis Control Unit, Tan Tock Seng Hospital
suay_hong_gan@ttch.com.sg
65 65113731

Switzerland

Kaspars Lunte

Team Leader
Global Drug Facility, Stop TB Partnership
KasparsL@stoptb.org
41792061078

Thailand

Chawetsan Namwat

Director
Bureau of Tuberculosis, Dept. of Disease Control, Thailand
chawetsan@gmail.com
66818445468

Saijai Smithtikarn

Chief of NTRL
Bureau of Tuberculosis, Department of Disease Control, Ministry of Public Health
saijaitb@hotmail.com
66 932265355

United States

Peter Cegielski

Team Leader
Global TB Branch, Division of Global HIV and TB, US Centers for Disease Control and Prevention, the United States
gzc2@cdc.gov
1-404-639-5329

Susan Maloney

Chief
Global TB Branch, Division of Global HIV and TB, US Centers for Disease Control and Prevention, the United States
szm7@cdc.gov
404 579 4141

Vietnam

Hoang Thi Thanh Thuy

Director
National TB Programme, Vietnam
hoangthanht@gmail.com
844 986329468

Pham Thi Thu Cuc

Official
Medical Service Administration, Ministry of Health of Vietnam
ptcuc.kcb@gmail.com
844 62732135

Trinh Thi Ngoc Linh

Official
Int'l Cooperation Dept., Ministry of Health of Vietnam
Trinhlinh1984@gmail.com
844 62732195

Chinese Taipei

Hao-Yuan Cheng

Medical Officer
Centers for Disease Control, Chinese Taipei
dr.hao.tw@gmail.com
886-956-720623

Chen-Yuan Chiang

Consultant
Department of Tuberculosis and HIV, International Union Against Tuberculosis and Lung Disease, Paris, France
cychiang@theunion.org
886-933723426

Hsiao-Hsuan Chiang

Professional Nurse
Northern Regional Center, Centers for Disease Control, Chinese Taipei
cute65@cdc.gov.tw
886-3-3982789#131

Shu-Li Chiang

Assistant Technical Specialist
Taipei Regional Center, Centers for Disease Control, Chinese Taipei
hope@cdc.gov.tw
886-2-85905025

Hui-Yi Chien

Program Coordinator
International Cooperation Office, Centers for Disease Control, Chinese Taipei
ivy0311@cdc.gov.tw
886-2-23989825*3602

Shun-Tien Chien

Chief of Chest Medicine
Chest Hospital , Ministry of Health and Welfare
chiendog@ms22.hinet.net
886-932-634-850

Mei-Yu Chiou

Professional Nurse
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
fairy@cdc.gov.tw
886-0223959825#3013

Inn-Wen Chong

Superintendent
Kaohsiung Medical University Chung-Ho Memorial Hospital
Chong@kmu.edu.tw
886-7-3121101#5102

Jih-Haw Chou

Deputy Director-General
Centers for Disease Control, Chinese Taipei
jchou@cdc.gov.tw
886-2-23959825#3900

Ting-Chen Chou

Research Assistant
Taoyuan Gerneral Hospital, Ministry of Health and Welfare
tinjane73@hotmail.com
886-987-362-700

Po-Wei Chu

TB Officer
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
poweichu@cdc.gov.tw
886-0223959825 #3733

Jen-Hsiang Chuang

Deputy Director-General
Centers for Disease Control, Chinese Taipei
jhchuang@cdc.gov.tw
886-2-23959825#3906

Yin-Ching Chuang

Superintendent
Chi Mei Liouying Hospital
m961193@mail.chimei.org.tw
886-6-622-6999 #72007

You-Juo Chung

Assistant Researcher
Taipei Regional Center, Centers for Disease Control, Chinese Taipei
Sophie079@cdc.gov.tw
886-2-85905018

Zen-Kong Dai

Vice Dean
College of Medicine, Kaohsiung Medical University
zenkong@kmu.edu.tw
886-975-355877

Chun-Ru Du

Associate Researcher
Taipei Regional Center, Centers for Disease Control, Chinese Taipei
dcr2004@cdc.gov.tw
886-926-596576

Tien-Yi Feng

Officer
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
gnnhuo@cdc.gov.tw
886-2-23959825#4081

Hsin-Yin Ho

Assistant Technical Specialist
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
cdchyh@cdc.gov.tw
886-223959825#4033

Yu-Ting Hou

Professional Nurse
Northern Regional Center, Centers for Disease Control, Chinese Taipei
tin@cdc.gov.tw
886-3-3982789#133

Jui-Wei Hsieh

Deputy Center Director
Southern Regional Center, Centers for Disease Control, Chinese Taipei
hsiehjw@cdc.gov.tw
886-6-2696211#101

Wan-Ting Hsieh

Health Policy Officer
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
hwt1221@cdc.gov.tw
886-2-23959825#3079

Ying-Yu Hsieh

Registered Professional Nurse
Public Health Bureau, Yilan County
hsiehyingyu@gmail.com
886-972-212-396

Yu-Chen Hsu

Assistant Researcher
International Cooperation Office, Centers for Disease Control, Chinese Taipei
yuchen@cdc.gov.tw
886-2-23989825 #3601

Po-Ren Hsueh

Professor
National Taiwan University Hospital
hsporen@ntu.edu.tw
886-2-2312-3456 #65355

Chien-Chung Huang

Assistant Researcher
Kaohsiung-Pingtung Regional Center, Centers for Disease Control, Chinese Taipei
cch@cdc.gov.tw
886-7-8011651#22

Ruay-Ming Huang

Convener of Eastern Hospitals
Hualien General Hospital, Ministry of Health and Welfare
hrm440301@gmail.com
886-37648760

Shih-Tse Huang

Medical Officer
Centers for Disease Control, Chinese Taipei
sthuang@cdc.gov.tw
886-2-23959825 #3171

Song-En Huang

Medical Officer
Centers for Disease Control, Chinese Taipei
huang.songen@cdc.gov.tw
886-2-23959825

Su-Hua Huang

Section chief
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
good@cdc.gov.tw
886-223959825#3000

Wei-Chang Huang

Attending Physician
Taichung Veterans General Hospital
huangweichangtw@gmail.com
886-916-147996

Yen-Fang Huang

Division Director
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
emily@cdc.gov.tw
886-2-23959825#3048

Yu-Ching Huang

Senior Researcher
International Cooperation Office, Ministry of Health and Welfare, Chinese Taipei
icyc@mohw.gov.tw
886-2-85907657

Yu-Ping Huang

Assistant Technical Specialist
Taipei Regional Center, Centers for Disease Control, Chinese Taipei
Af4248@cdc.gov.tw
886-2-85905034

Shiow-Jiuan Jaw

Associate Researcher
International Cooperation Office, Centers for Disease Control, Chinese Taipei
shou34@cdc.gov.tw
886-2-23989825*3603

Miao-Jung Jian

Professional Nurse
Pingtung Hospital, Ministry of Health and Welfare
miao@pntn.mohw.gov.tw
886-958-617-858

Ru-Wen Jou

Director
Tuberculosis Research Center, Centers for Disease Control, Chinese Taipei
rwj@cdc.gov.tw
886-2-265313700

Sheng-Nung Kao

Research Assistant
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
Ghd123483@hotmail.com
886-0933541879

Hsaing-Lan Kuo

Chief
Disease Control Division, Keelung City Health Bureau
ksl@klchb.gov.tw
886-2-2423-0180 #1404

Steve Hsu-Sung Kuo

Director-General
Centers for Disease Control, Chinese Taipei
886-2-2395-9825

An-Chi Lai

Section Chief
International Cooperation Office, Centers for Disease Control, Chinese Taipei
angellai@cdc.gov.tw
886-2-23989825 #3600

Chih-Hsin Lee

Attending Physician
Wan Fang Hospital Chest Medicine
Chlee.tw@gmail.com
886-970-746523

Chun-Ming Lee

Superintendent
St. Joseph's Hospital
leecm4014@yahoo.com.tw
886-975-835125

CoCo Lee

Section Chief
International Cooperation Office, Ministry of Health and Welfare, Chinese Taipei
iccoco@mohw.gov.tw
886-2-85907660

Feng-Jung Lee

Professional Nurse
Eastern Regional Center, Centers for Disease Control, Chinese Taipei
nur1601@cdc.gov.tw
886-89-219971

Jen-Jyh Lee

Section Chief
TB Lab Section, Buddhist Tzu Chi General Hospital
e0139@tzuchi.com.tw
886-919-963-848

Mei-Chu Lee

Technical Specialist
Eastern Regional Center, Centers for Disease Control, Chinese Taipei
0104@cdc.gov.tw
886-3-8242262

Pin-Hui Lee

Medical Officer
Centers for Disease Control, Chinese Taipei
leepinhui@cdc.gov.tw
886-2-23959825 #3062

Shih-Wei Lee

Chief
Pulmonary Departemanet of internal medicine, Taoyuan General Hospital, Ministry of Health and Welfare
chestman9@gmail.com
886-927-360-610

Susan Shin-Jung Lee

Chief
Division of Infectious Diseases, Kaohsiung Veterans General Hospital
ssjlee@gmail.com
886-975-581-736

Yun-Tsan Liao

Officer
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
yuntsan@cdc.gov.tw
886-2-23959825#3131

Chen-His Lin

Public Health Inspector
Public Health Bureau of Hsinchu County Government
10007991@hchg.gov.tw
886-3-551-8160 #216

Chih-Bin Lin

Chief
Pulmonary Medicine, Hualien Tzu Chi Hospital
ferlin@tzuchi.com.tw
886-970-332-212

Ching-Hsiung Lin

Chief
Chest Medicine, Changhua Christian Hospital
47822@cch.org.tw
886-10440307

Chou-Jui Lin

Attending Physician
Chest Medicine, Taoyuan General Hospital, Ministry of Health and Welfare, Chinese Taipei
dejavu1114@gmail.com
886-3-3699721*3788

Hsien-Ho Lin

Associate Professor
College of Public Health, National Taiwan University
hsienho@gmail.com
886-2-33668023

Hsuan-Chu Lin

Assistant Researcher
Northern Regional Center, Centers for Disease Control, Chinese Taipei
phyllis@cdc.gov.tw
886-3-3982789#132

Ling-Ling Lin

Assistant Technical Specialist
Taipei Regional Center, Centers for Disease Control, Chinese Taipei
lingling@cdc.gov.tw
886-2-85905019

Shiou-Pin Lin

Contract employee
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
splin@cdc.gov.tw
886-2-23959825#3040

Ching-Han Liu

Stationed Agent
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
angel_liu@cdc.gov.tw
886-2-2395-9825#4060

Hsiao-Ying Liu

Nurse
Taitung County Health Department
Greencat0626@gmail.com
886-926-700-649

Bao-Yun Lu

Professional Nurse
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
baoyun@cdc.gov.tw
886-2-23959825#3067

Chun-Yi Lu

Secretary-General
Taiwan Paediatric Infectious Diseases Society
cylu@ntu.edu.tw
886-72651492

Min-Ju Lu

Officer
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
minjulu@cdc.gov.tw
886-2-23959825#3130

Su-Lan Lu

Subsection Chief
Department of Public Health, Taoyuan
tyhsllu839@tychb.gov.tw
886-3-3340935 #2115

Pei-Ning Lung

Executive Secretary
Taiwan Anti-Tuberculosis Association
ntbtpe@ms43.hinet.net
886-2-2553-8828#303

Angel Peng

Professional Nurse
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
angela@cdc.gov.tw
886-2-23959825#3739

Chin-Chung Shu

Attending Physician
National Taiwan University Hospital
Ccshu@ntu.edu.tw
886-972-653-087

Hung-Chieh Sun

Physician
Mennonite Christian Hospital
hcsunjames@gmail.com
886-937-148-125

Jen Suo

Physician
Taiwan Anti-Tuberculosis Association, Chinese Taipei
fsolo030@gmail.com
886-928605780

Shao-Hui Tsai

Associate Researcher
Central Regional Center, Centers for Disease Control, Chinese Taipei
shtsai@cdc.gov.tw
886-912-968-668

Hsiang-I Tsao

Contractual Technician
International Cooperation Office, Centers for Disease Control, Chinese Taipei
agnestsao@cdc.gov.tw
886-2-23989825*3605

Thomas Chang-Yao Tsao

Vice president
Chung Shan Medical University
tcyt@csmu.edu.tw
886-935-885889

Hsiao-Ping Tung

Section Chief
Taipei Regional Center, Centers for Disease Control, Chinese Taipei
ping@cdc.gov.tw
886-2-85905003

Jann-Yuan Wang

Pulmonologist
National Taiwan University Hospital
jywang@ntu.edu.tw
886-972-652-037

Kung-Ching Wang

Medical Officer
Centers for Disease Control, Chinese Taipei
Kcwang@cdc.gov.tw
886-910-070-499

Ting-Fang Wang

Assistant Researcher
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
tingfang@cdc.gov.tw
886-2-23959825#3027

Hsin-Yi Wei

Medical Officer
Centers for Disease Control, Chinese Taipei
januarylly@cdc.gov.tw
886-2-85905016

Zhi-Chieh Wei

Assistant Technical Specialist
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
gary60106@cdc.gov.tw
886-223959825#3115

Hsing-Chu Wu

Tuberculosis Case Manager
Taoyuan General Hospital, Ministry of Health and Welfare
0522joy@gmail.com
886-912-757-043

Ying-Hsun Wu

Director
Internal Medicine, Chest Hospital , Ministry of Health and Welfare
ysw@ccd.mohw.gov.tw
886-910-895-701

Chih-Yun Yang

MD
Kaohsiung Veteran General Hospital
chihyunyang@gmail.com
886-52413978

Shiang-Lin Yang

Senior Health Policy Specialist
Division of Chronic Infectious Diseases, Centers for Disease Control, Chinese Taipei
cafe@cdc.gov.tw
886-2-23959825 #3003

Wen-Ta Yang

Supervisor
Department of Internal Medicine, Taichung Hospital, Ministry of Health and Welfare
Taic3057@gmail.com
886-4-22294411 #5516

Yi-Wen Huang

President
Taiwan Society of Tuberculosis and Lung disease,
Chinese Taipei
tb990328@gmail.com
886-952374023

Ming-Chih Yu

Specialist
Pulmonary and Critical Care Medicine, Taipei Municipal
Wan Fang Hospital
mingchih@w.tmu.edu.tw
886-970-746-520

Yen-Chi Yu

Officer
Taipei Regional Center Centers for Disease Control,
Chinese Taipei
loriyu@cdc.gov.tw
886-2-85905029

Yao-Mei Zhuang

Director
Hualien County Chronic Disease Center
gougbin04@ms.hlshb.gov.tw
886-975-513-187

Memo

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Disease Control