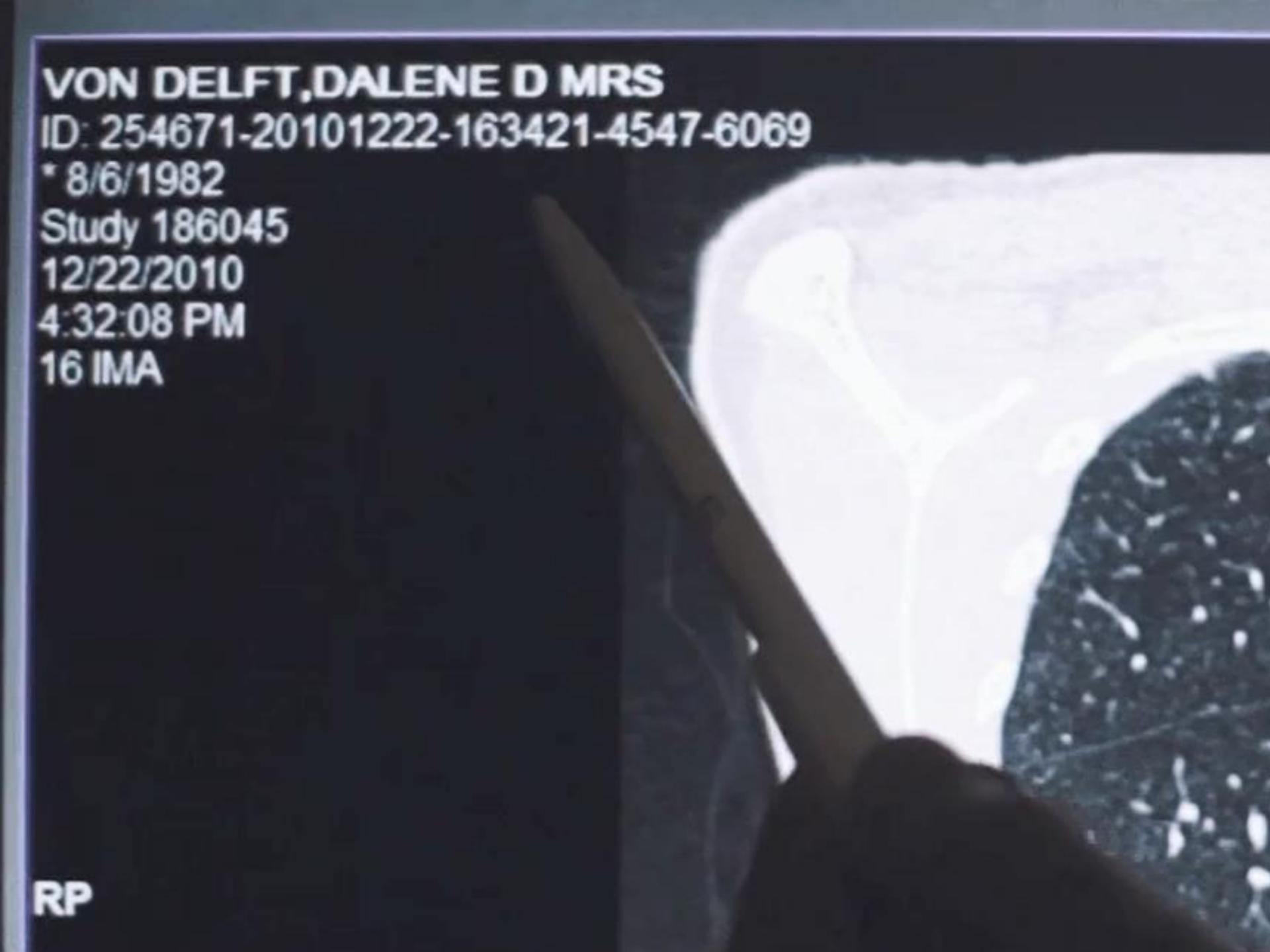
CDC PUBLIC HEALTH GRAND ROUNDS

Multidrug-resistant Tuberculosis: Tools for Tackling a New Face of an Old Foe

March 18, 2014

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

- **In 2010, I was diagnosed with Multidrug-resistant Tuberculosis (MDR TB)**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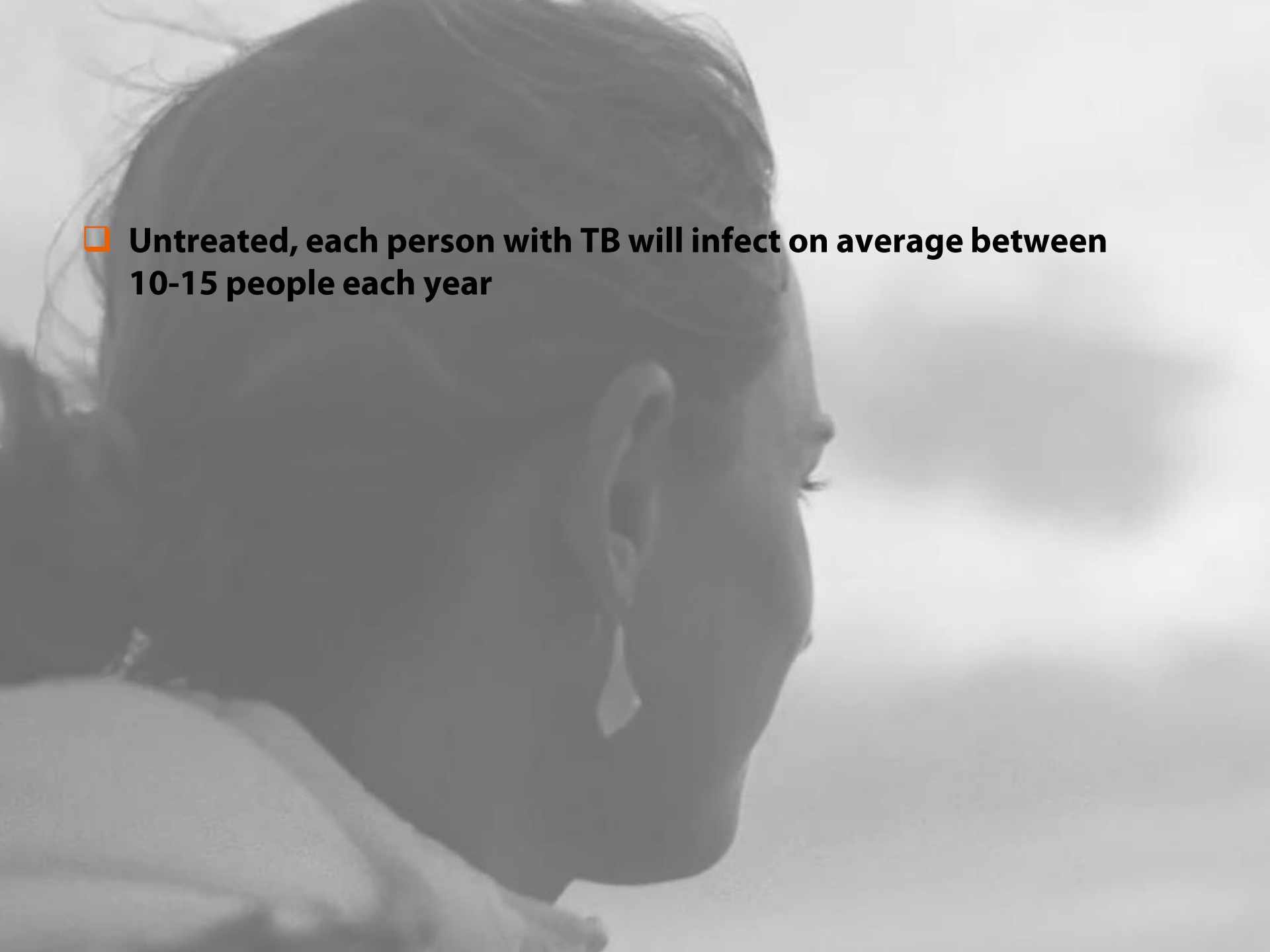
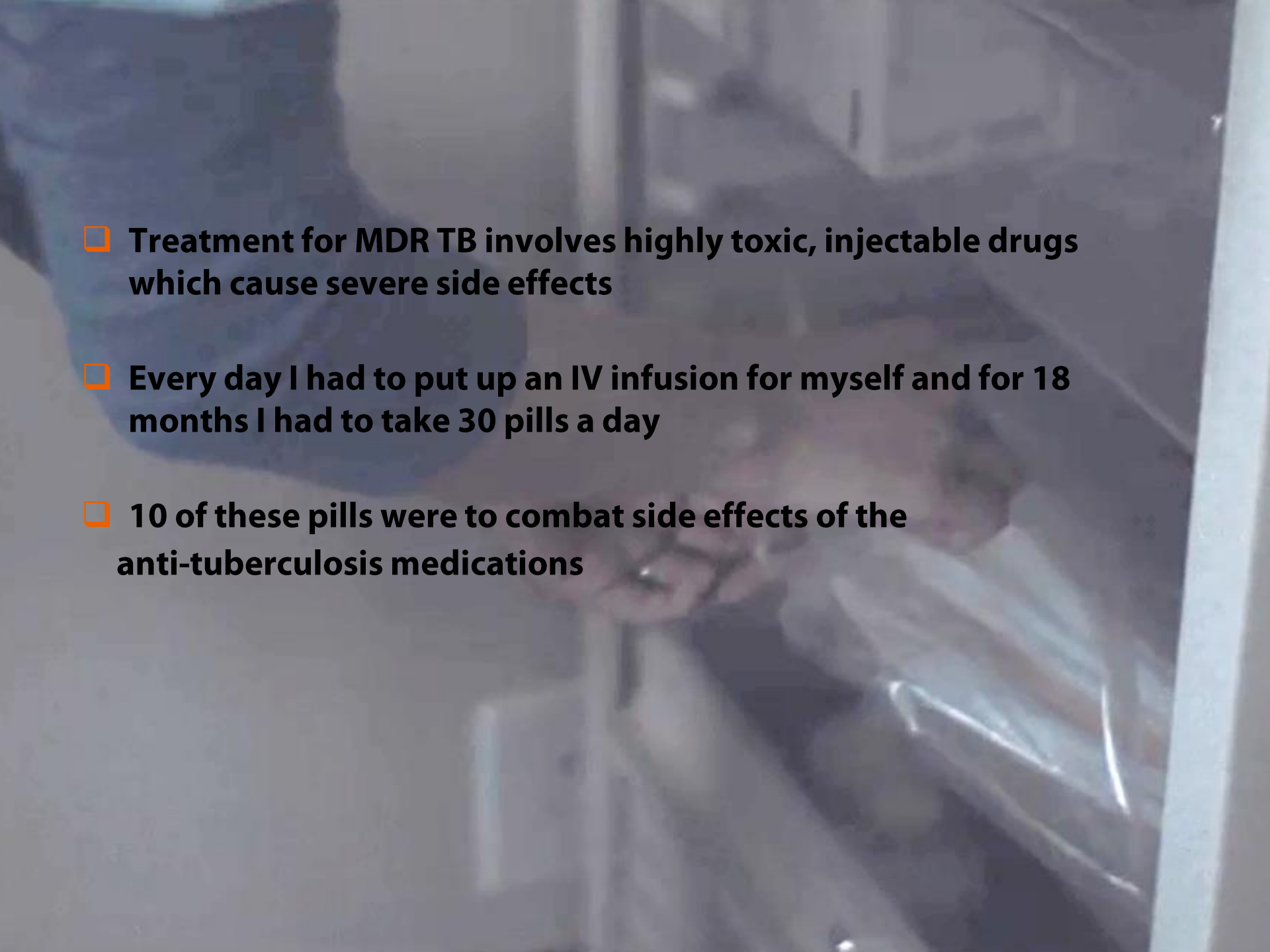


- **Untreated, each person with TB will infect on average between 10-15 people each year**

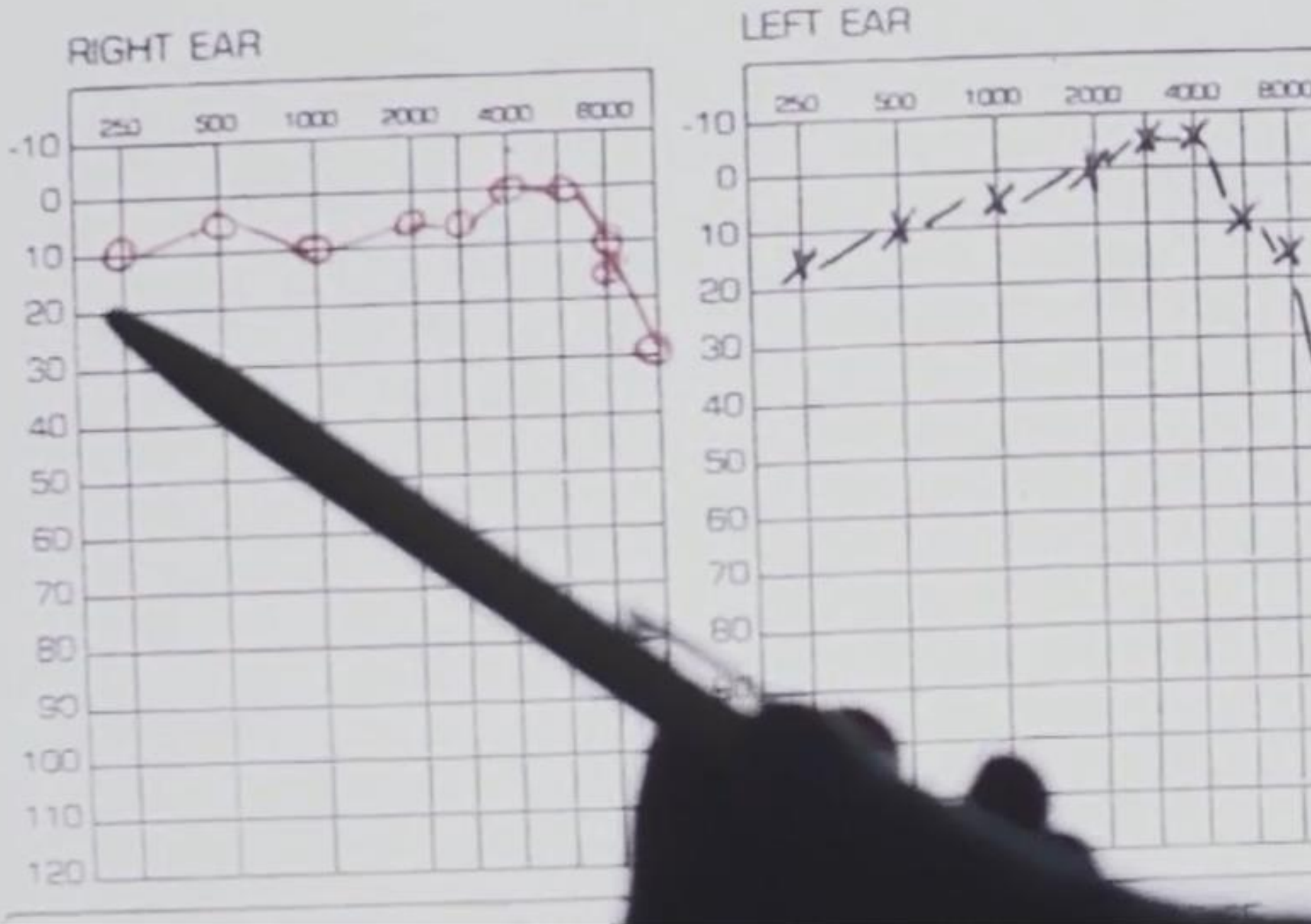
- Only 42% of MDR TB patients in South Africa are cured
- Side effects of treatment may include hearing loss, neurologic, and psychiatric symptoms



- Treatment for MDR TB involves highly toxic, injectable drugs which cause severe side effects
- Every day I had to put up an IV infusion for myself and for 18 months I had to take 30 pills a day
- 10 of these pills were to combat side effects of the anti-tuberculosis medications

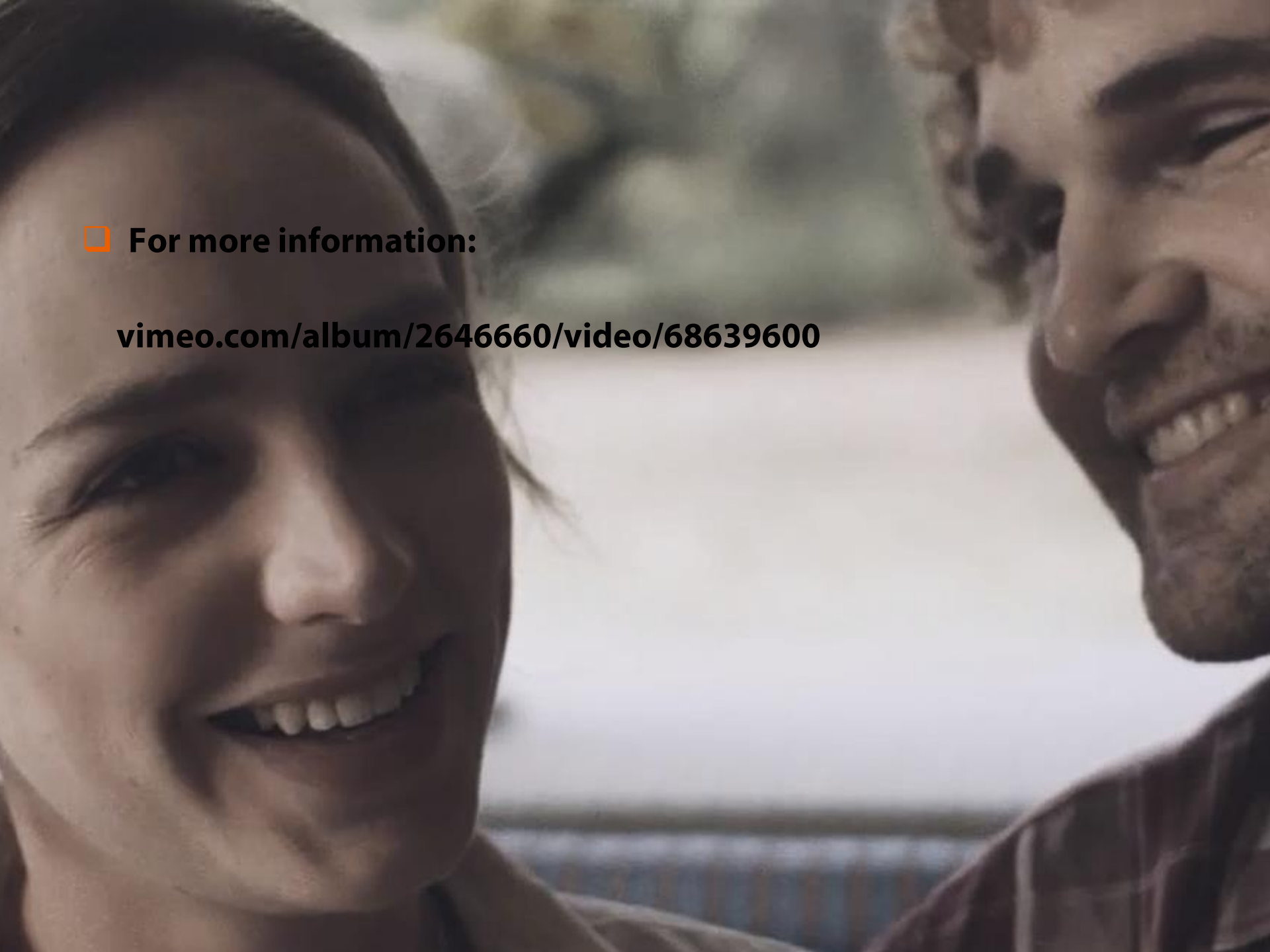
DIOMETER

PURE TONE AUDIOGRAM



- **Bedaquiline is the first new drug to treat TB to be approved by the U.S. Food and Drug Administration in over 40 years**

- **I was cured of MDR TB one year after being granted "compassionate" use of bedaquiline**



- **For more information:**

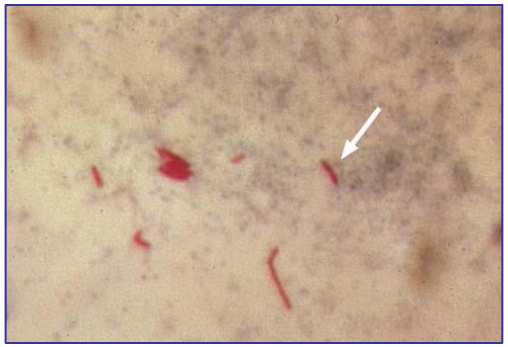
  vimeo.com/album/2646660/video/68639600

The Public Health Importance of Drug-resistant Tuberculosis

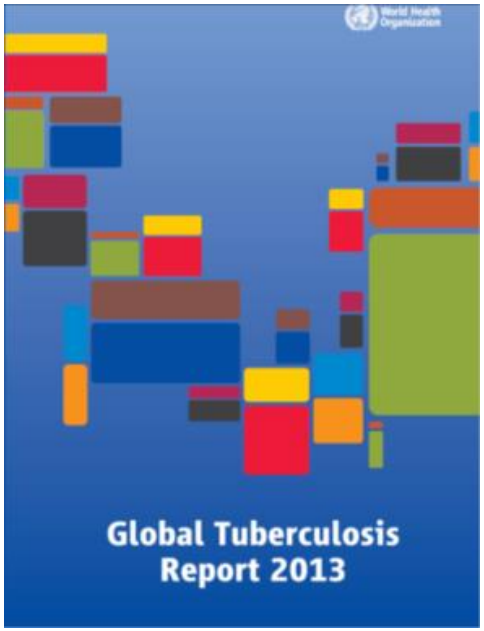
Sarita Shah, MD, MPH
Associate Chief for Science
International Research and Programs Branch
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

Tuberculosis

- **Ancient disease dating to ~3400 BC**
  - *Mycobacterium tuberculosis* discovered by Robert Koch in 1882
- **Can cause latent TB infection (LTBI) and TB disease**
- **Primary involvement in lungs**
- **Airborne transmission by respiratory droplets**
  - Highest risk in congregate settings, poor ventilation, or prolonged exposure
  - HIV infection an important contemporary risk factor
- **Diagnosis by sputum smear microscopy**
- **First anti-TB drugs developed in 1940s**



Tuberculosis: Global Health Importance

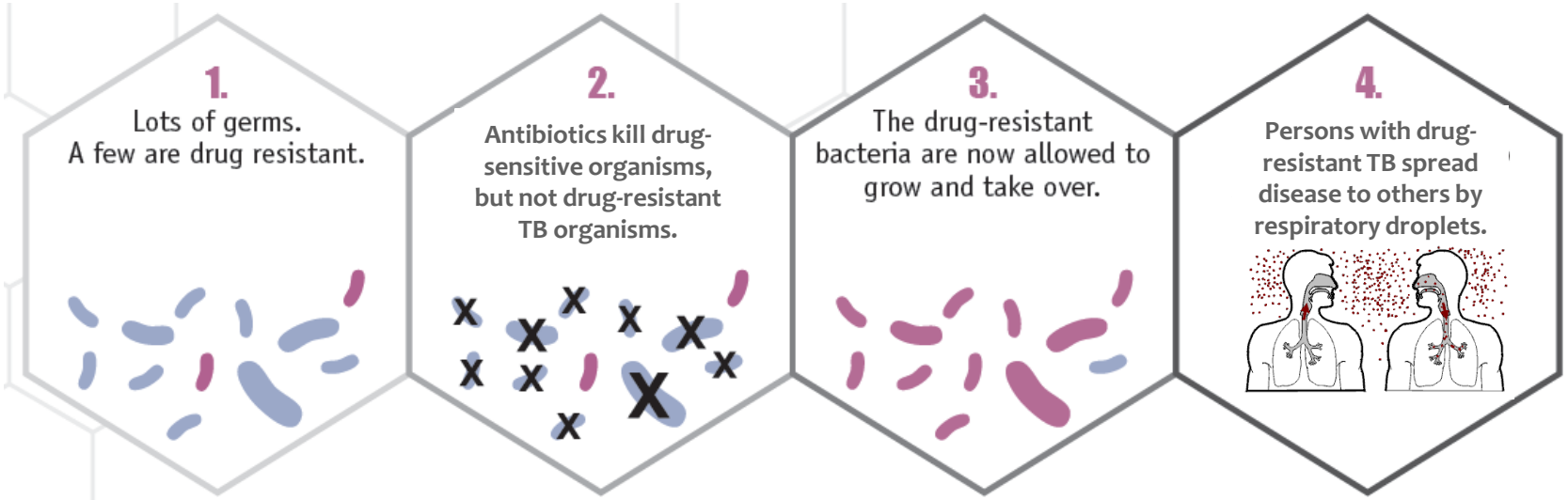


- **8.6 million new TB cases each year worldwide**
- **More than 95% cure rate**
  - Combination (4-drug) standard therapy
  - Uninterrupted 6-month treatment under directly observed therapy
- **Case notification and cure rates under program conditions below targets**
  - 66% (5.7 million) case notification rate
  - 87% treatment success rate

World Health Organization. *Global Tuberculosis Report 2013.* Available at: www.who.int/tb/publications/global_report/en/

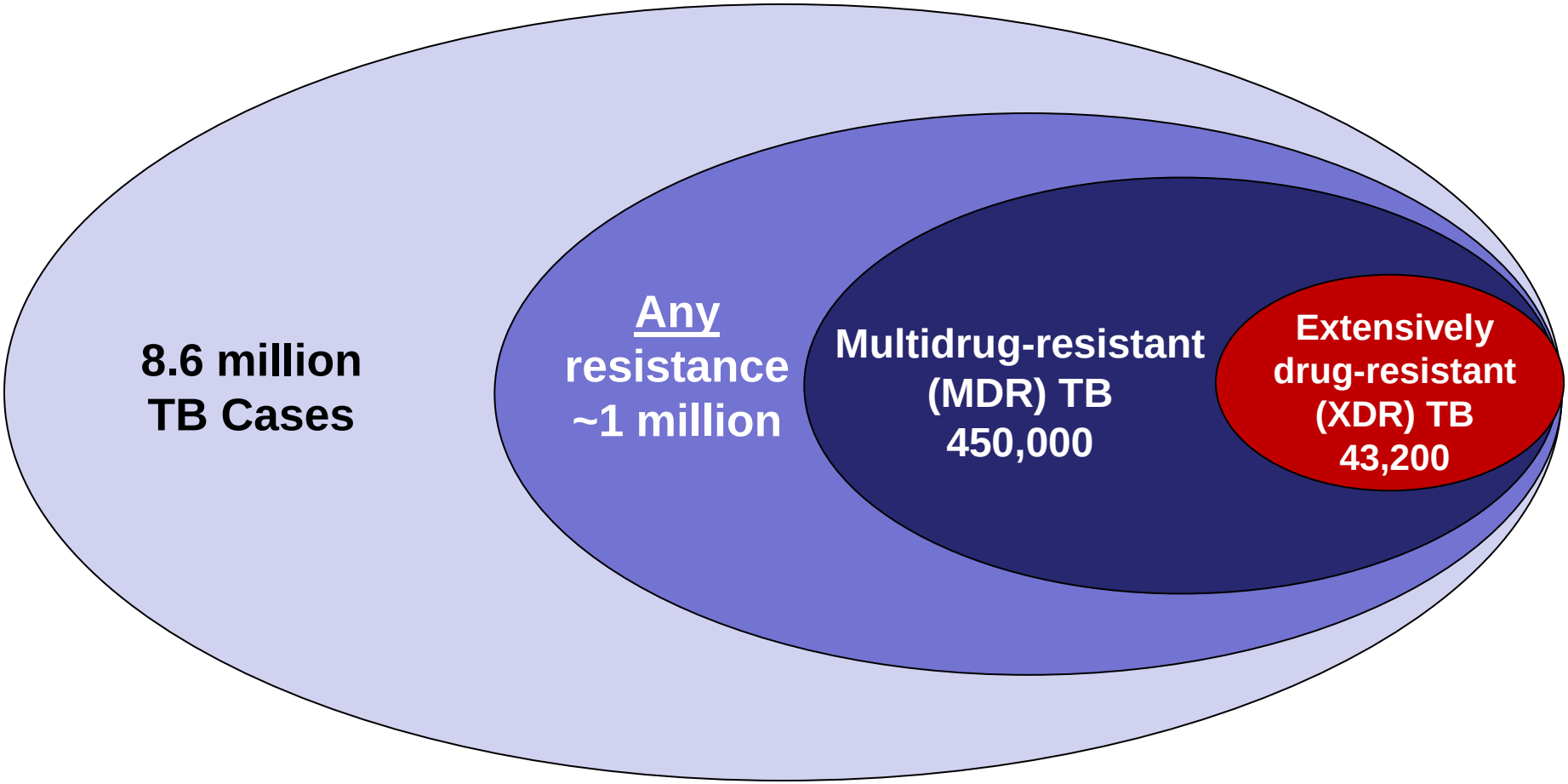
Drug-resistant Tuberculosis

- Development of resistance can occur spontaneously in large replicating bacterial populations (once in 10^6–10^8 bacteria)
- Drug resistance largely caused by nonstandard treatment regimen or incomplete adherence to treatment
- Spread of drug-resistant strains through person to person transmission



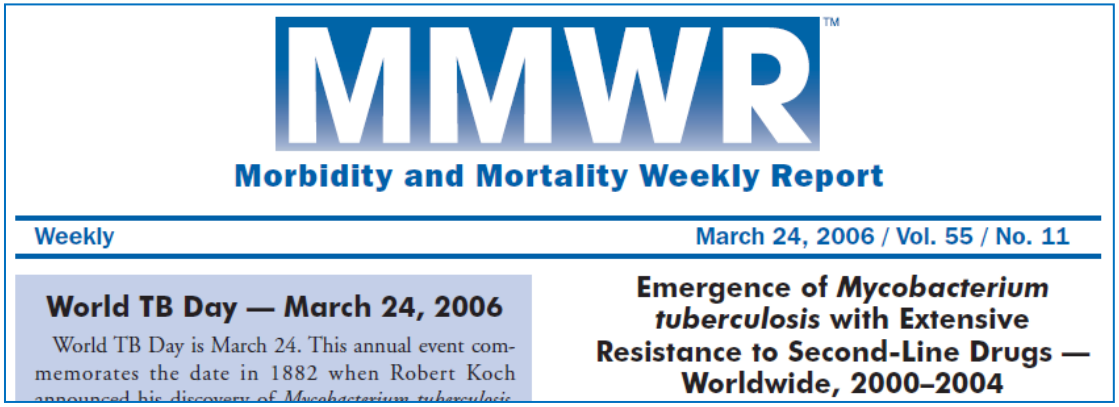
Adapted from: CDC. *Antibiotic Resistance Threats in the United States, 2013.* www.cdc.gov/drugresistance/threat-report-2013.

Global Burden of Drug-resistant TB



World Health Organization. *Global Tuberculosis Report* 2013. WHO/HTM/TB/2013.11.

Global Emergence of XDR TB



MMWR™

Morbidity and Mortality Weekly Report

Weekly March 24, 2006 / Vol. 55 / No. 11

World TB Day — March 24, 2006

World TB Day is March 24. This annual event commemorates the date in 1882 when Robert Koch announced his discovery of *Mycobacterium tuberculosis*

Emergence of *Mycobacterium tuberculosis* with Extensive Resistance to Second-Line Drugs — Worldwide, 2000–2004

THE SUNDAY INDEPENDENT

SEPTEMBER 10 2006 | R9,50 (INC VAT) | ANNUAL SUBSCRIBERS: R7,67 | BUSINESSREPORT | PUBLISHED IN SOUTH AFRICA

The Zuma saga Page 5

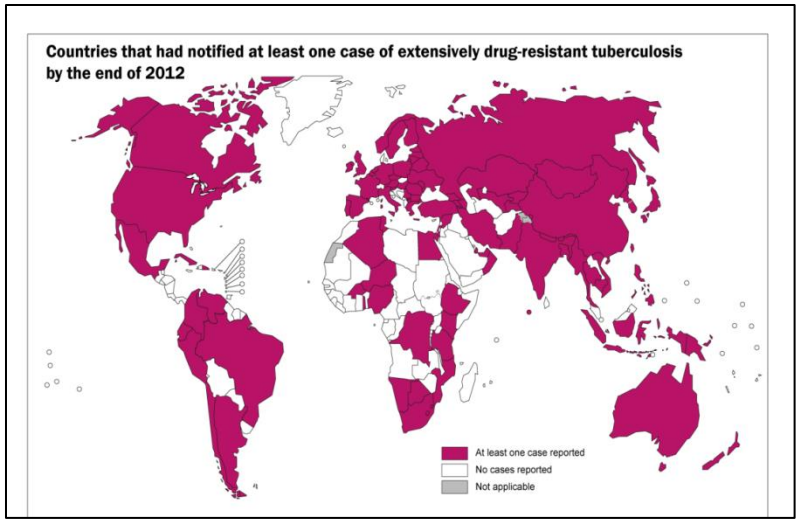
9/11 FIVE YEARS ON Special Report Pages 13 to 15

End of a dynasty Page 12

Killer TB tightens fatal grip

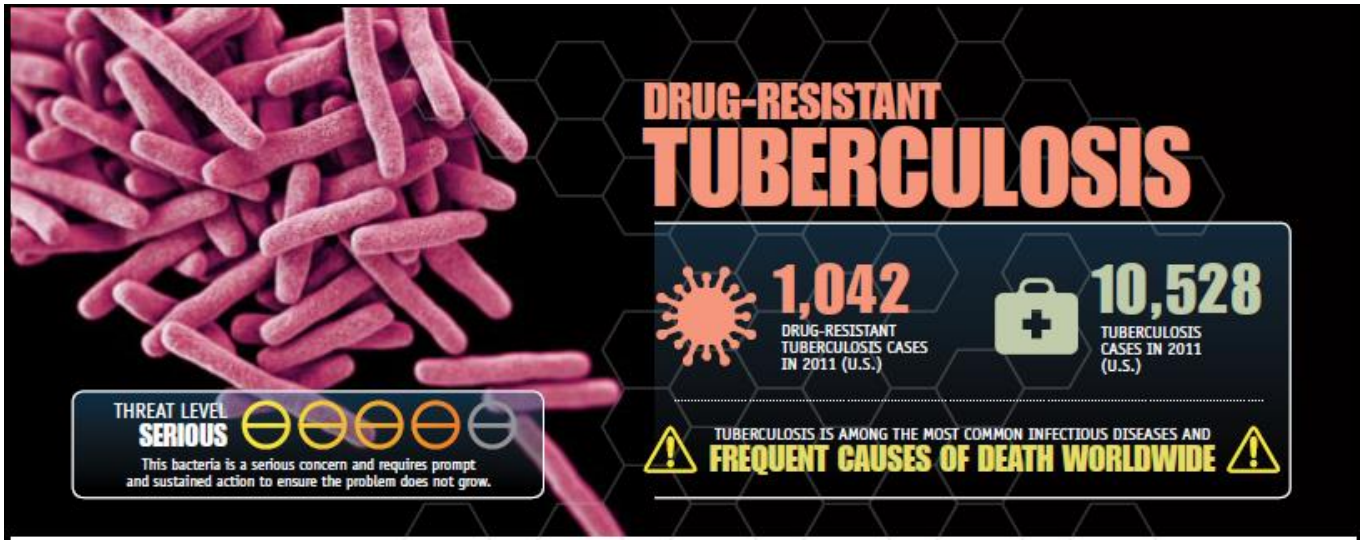
Despite indications that SA is in the forefront of infection, health minister tries to put a clamp on news and snubs global conference

Prospect of an epidemic sets medics trembling



CDC. *Morbidity and Mortality Weekly Report*. 2006;55:301–305.
Gandhi NR, Moll A, Sturm AW, et al. The Lancet 2006; 368:1575-80.
World Health Organization. *Global Tuberculosis Report* 2012. WHO/HTM/TB/2012.6.

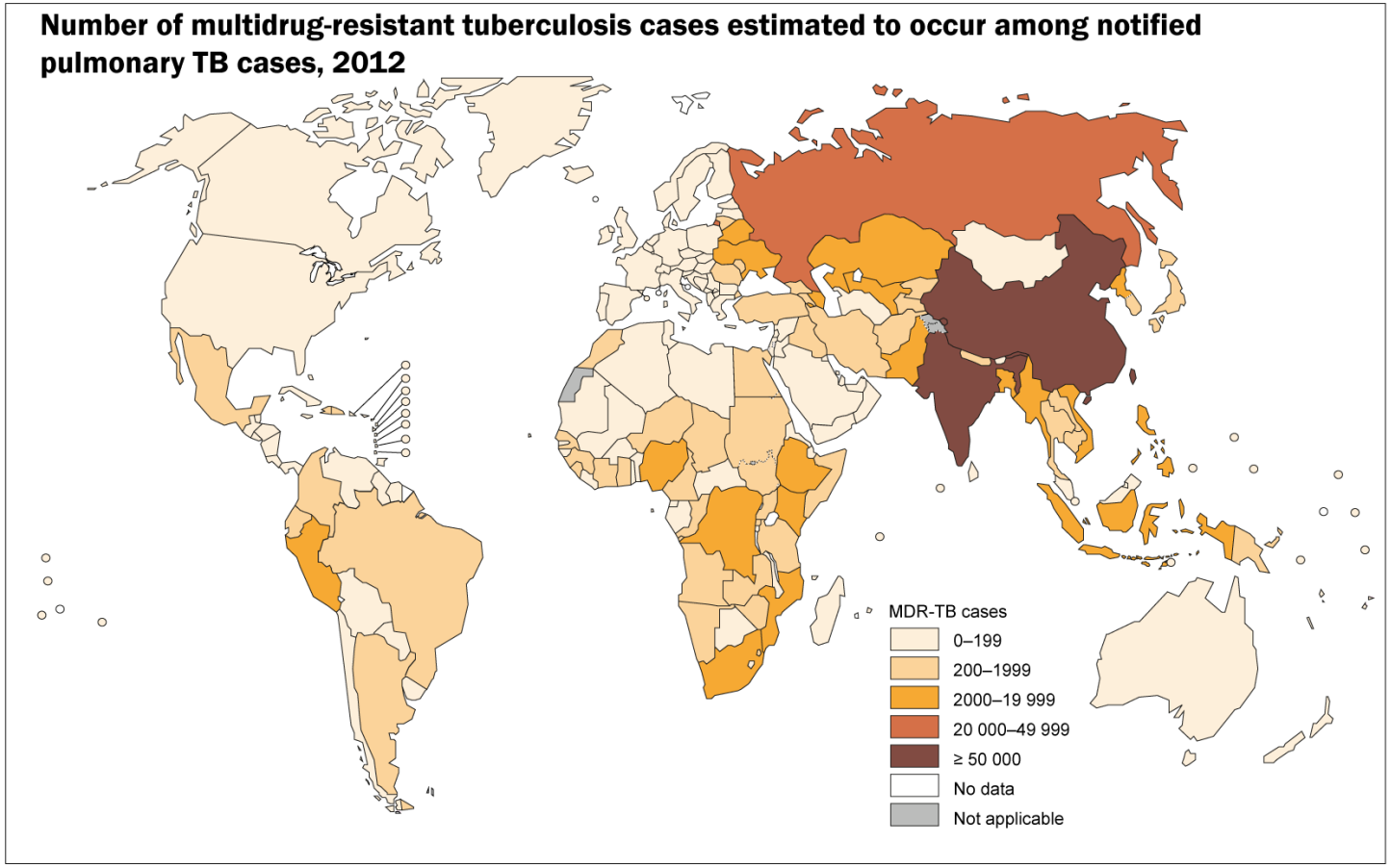
Growing Threat of Antimicrobial Resistance



- **Drug-resistant TB a serious threat in United States and globally**
- **Among 10,528 U.S. TB cases in 2011, 9.9% had drug resistance**
  - 124 cases of MDR TB = 1.2% of TB cases
  - 6 cases of XDR TB = 4.8% of MDR TB cases

CDC. *Antibiotic Resistance Threats in the United States*, 2013.

Highest Burden of Global MDR TB in India, Russia and China



World Health Organization. *Global Tuberculosis Report* 2013. WHO/HTM/TB/2013.11.

Diagnostic Challenges for Drug-resistant TB

Drug-resistant TB cannot be diagnosed by smear microscopy

- **Diagnosis requires culture and drug-susceptibility testing or molecular testing**
- **Key barriers**
  - Inadequate laboratory infrastructure, investment, and capacity
  - Limited patient access to adequate testing facilities
    - <5% of TB patients have access to diagnosis of drug resistance
  - Policies that limit who can be tested, and when
    - Due to resource limitations

World Health Organization. *Global Tuberculosis Report* 2012. WHO/HTM/TB/2012.6.

Underdiagnosis of Drug-resistant TB

- **20% of total estimated MDR TB cases detected in 2012**
  - Case detection even lower in India (6%) and China (3%)
  - Limited data on children; case detection lower than for adults

- **Only 5% of new cases and 9% of previously treated cases are tested for drug resistance**
  - Testing capability for XDR TB even more limited

- **In 2009, World Health Assembly called for universal access to TB culture and drug-susceptibility testing**
  - Achieving this goal will require massive laboratory and health system strengthening
  - CDC is involved in global initiatives to address this critical need

World Health Organization. *Global Tuberculosis Report* 2012. WHO/HTM/TB/2012.6.

Treatment Challenges in Drug-resistant TB

Compared to drug-susceptible TB, treatment of MDR TB is

- Less effective
- More toxic
  - 90% experience side effects, some severe (e.g., hearing loss, neuropathy, or psychosis)
- Lengthier
  - Up to 2 years vs. 6 months
- More costly
  - 10–100 times more costly ($2500 and up)

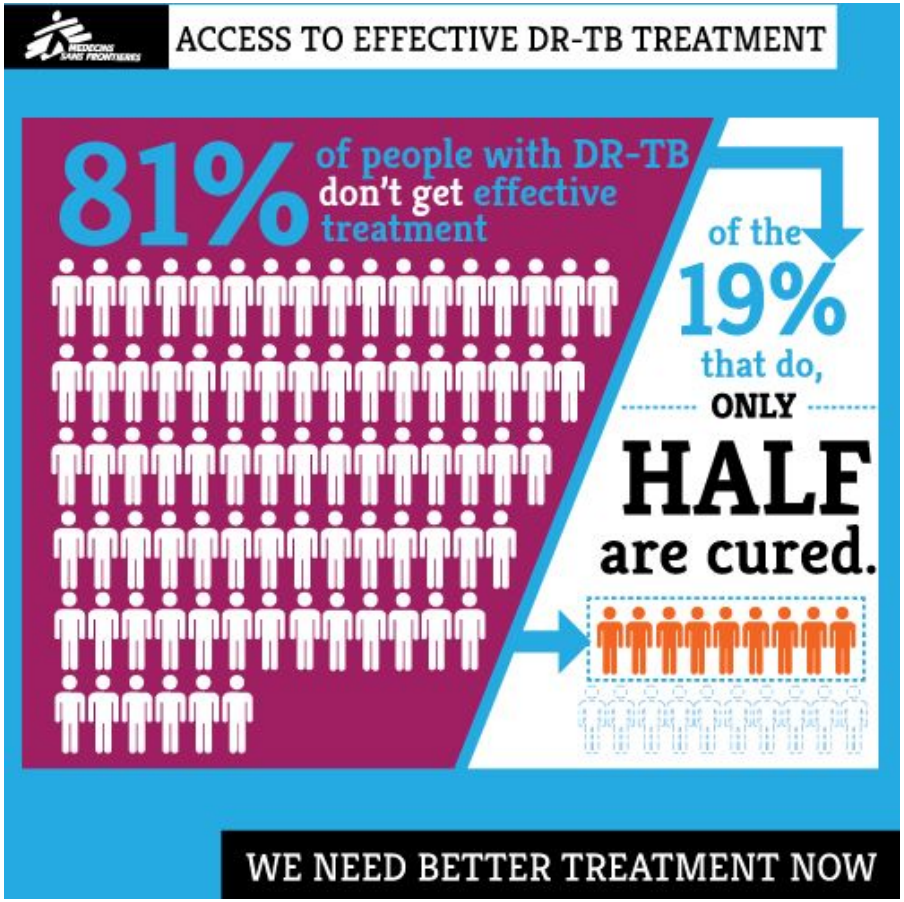
Source: Médecins San Frontières

WHO. *Multidrug and Extensively Drug-Resistant (M/XDR –TB): 2010 Global Report on Surveillance and Response.* WHO/HTM/TB/2010.3

Pooran A, et al. PLoS One 2013. 8(1):e54587.

Mauch V, Bonsu F, Gyabpon M, et al. *Int J Tuberc Lung Dis.* 2013;17:381-7.

Treatment Challenges in Drug-resistant TB



- **Among the minority of those who are treated:**
  - Low cure rates (48%-54%)
  - Low treatment completion rates due to:
    - Loss to follow-up (14%-23%)
    - Death (15%)
    - Treatment failure (8%-9%)

Ahuja SD, *PLoS Med* 2012;9:e1001300.

Summary

- Drug-resistant TB (MDR and XDR TB) causes extensive morbidity and mortality globally
- CDC considers drug-resistant TB to be a serious health threat
- Major challenges with diagnosis and treatment
- High-burden countries including India, China, and Russia face substantial economic, logistic, and policy barriers to improving diagnosis and treatment
- New diagnostics and new drugs offer promise

Rapid Diagnosis of MDR TB: A Laboratory Systems-based Approach

Thomas M. Shinnick, PhD

Associate Director for Global Laboratory Activities

Division of Tuberculosis Elimination

National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Lack of Laboratory Services is a Barrier to the Control of TB and Drug-resistant TB

- Only ~53% of new cases and 63% of new smear-positive cases are detected
- In high HIV prevalence settings, AFB smear-based testing is less sensitive
- Only 19% of estimated MDR TB cases laboratory confirmed
- Many XDR TB cases are not detected due to the lack of second-line DST

- **Molecular diagnostics may help solve the challenge**

AFB: acid-fast bacilli
DST: drug susceptibility testing
World Health Organization. *Global Tuberculosis Report* 2013. WHO/HTM/TB/2013.11.

WHO-Endorsed Molecular Tests for TB

- **Molecular Line Probe Assay (LPA)**
  - Regional or national-level laboratory
  - Smear-positive sputum or MTB cultures

- **Cepheid Xpert® MTB/RIF test**
  - Sub-district or district hospital level laboratory
  - Smear-positive or negative pulmonary and extra-pulmonary specimens from adults and children

MTB: Mycobacterium tuberculosis

Xpert® MTB/RIF Improves TB Testing

A Single Xpert® MTB/RIF Test

- Is about as sensitive and specific as one culture on solid media
- Can increase TB case detection by 40% over direct smear microscopy alone
- Takes only 2 hours to complete, compared to weeks for culture
- Uses simple sputum processing steps
- Detects presence of MTB and rifampicin resistance simultaneously
- Does not require sophisticated BSL-3 facilities or specialized expertise

Sample → **Cartridge** → **Module** → **4 Module Instrument**

MTB: Mycobacterium tuberculosis
BSL-3: Biosafety level 3

Performance of Xpert® MTB/RIF for Rifampicin Resistance and MDR TB

- **Rifampicin resistance (RIF-R) is a marker for MDR TB**
  - >85% of RIF-R strains are MDR strains in most countries
  - WHO recommended treatment of RIF-R TB is similar to MDR TB

- **Strong recommendation by WHO to use Xpert® MTB/RIF as the initial diagnostic test in individuals suspected of having MDR TB**
  - Excellent sensitivity (95%) and specificity (98%) for detecting rifampicin resistance
  - Implementing Xpert® MTB/RIF will cost less than conventional culture and DST to meet diagnostic targets for MDR TB

DST: drug susceptibility testing

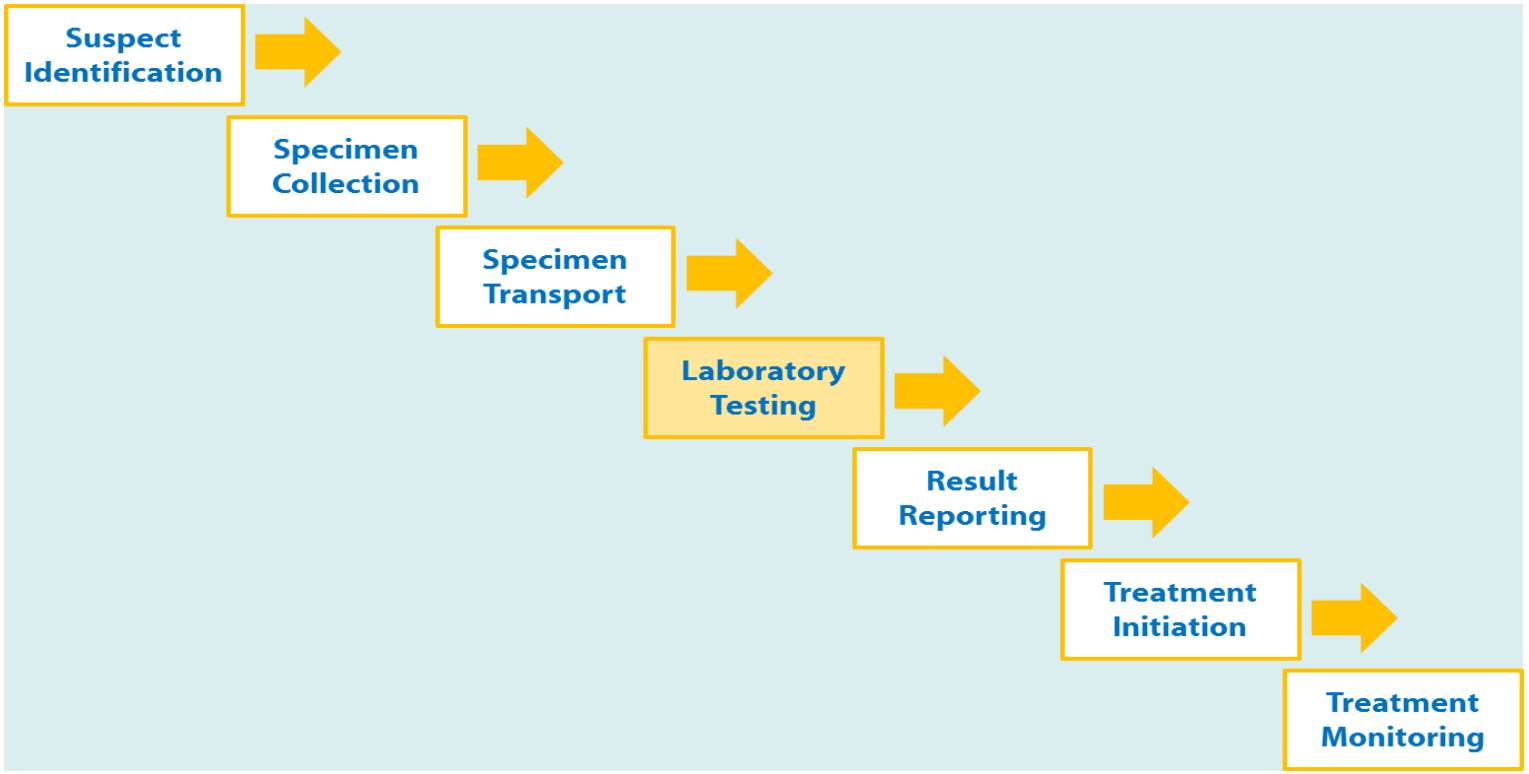
World Health Organization. 2013. *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update.* WHO/HTM/TB/2013.14.

Lessons from Early Implementers of Xpert® MTB/RIF Testing

- **Clinical and public health impact varies with the epidemiologic setting, target population, laboratory testing algorithm, and treatment algorithms**
  - Can increase detection of bacteriologically confirmed and rifampicin-resistant cases, as well as decrease time to diagnosis in resource-limited settings
  - Has less impact in settings where clinicians initiate TB treatment in the absence of bacteriological confirmation
- **Private sector must be engaged**
- **Diagnostic and treatment capacity need to be matched**

Realizing the Potential of Xpert® MTB/RIF to Treat More People with MDR TB More Quickly

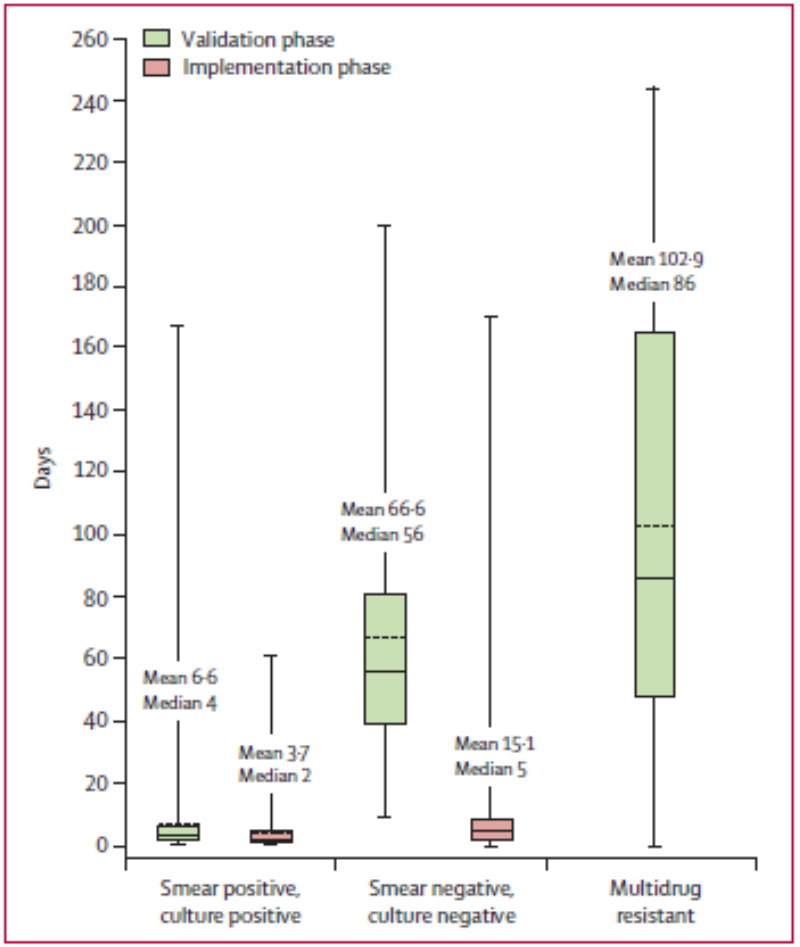
- A systems approach is needed to strengthen all steps in the process
- Testing must be linked to drug access and program capacity



Impact of Xpert® MTB/RIF Testing on Time To Treatment

Xpert® MTB/RIF may reduce the median time to treatment

- For culture-diagnosed cases, from 56 days to 5 days
- For MDR TB, from 86 days to 5 days



Boehme C et al. *The Lancet*. 2011 Apr 30;377(9776):1495-505.

Scale-up of PMDT in Parallel with Xpert® MTB/RIF Scale-up

- **Laboratory capacity**
  - Conventional culture and DST
  - Other molecular methods (e.g., line-probe assays)
  - Specimen referral and reporting of results
- **Treatment capacity**
  - Hospital based and ambulatory care
  - Patient support and palliative care
  - Infection control
- **Second-line drug management**
  - Forecasting and ordering

PMDT: programmatic management of drug-resistant tuberculosis
DST: drug susceptibility testing

Summary

- Lack of laboratory services is a crucial barrier to an effective response to TB ~~and~~ MDR TB
- Molecular diagnostics may revolutionize TB lab services
- Xpert® MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR TB
- Xpert® MTB/RIF should increase detection of TB and MDR TB cases and shorten the time to begin treatment
- Need to scale-up PMDT program in parallel with increased use of Xpert® MTB/RIF, so that the anticipated increased number of cases can be treated more effectively

PMDT: programmatic management of drug-resistant tuberculosis

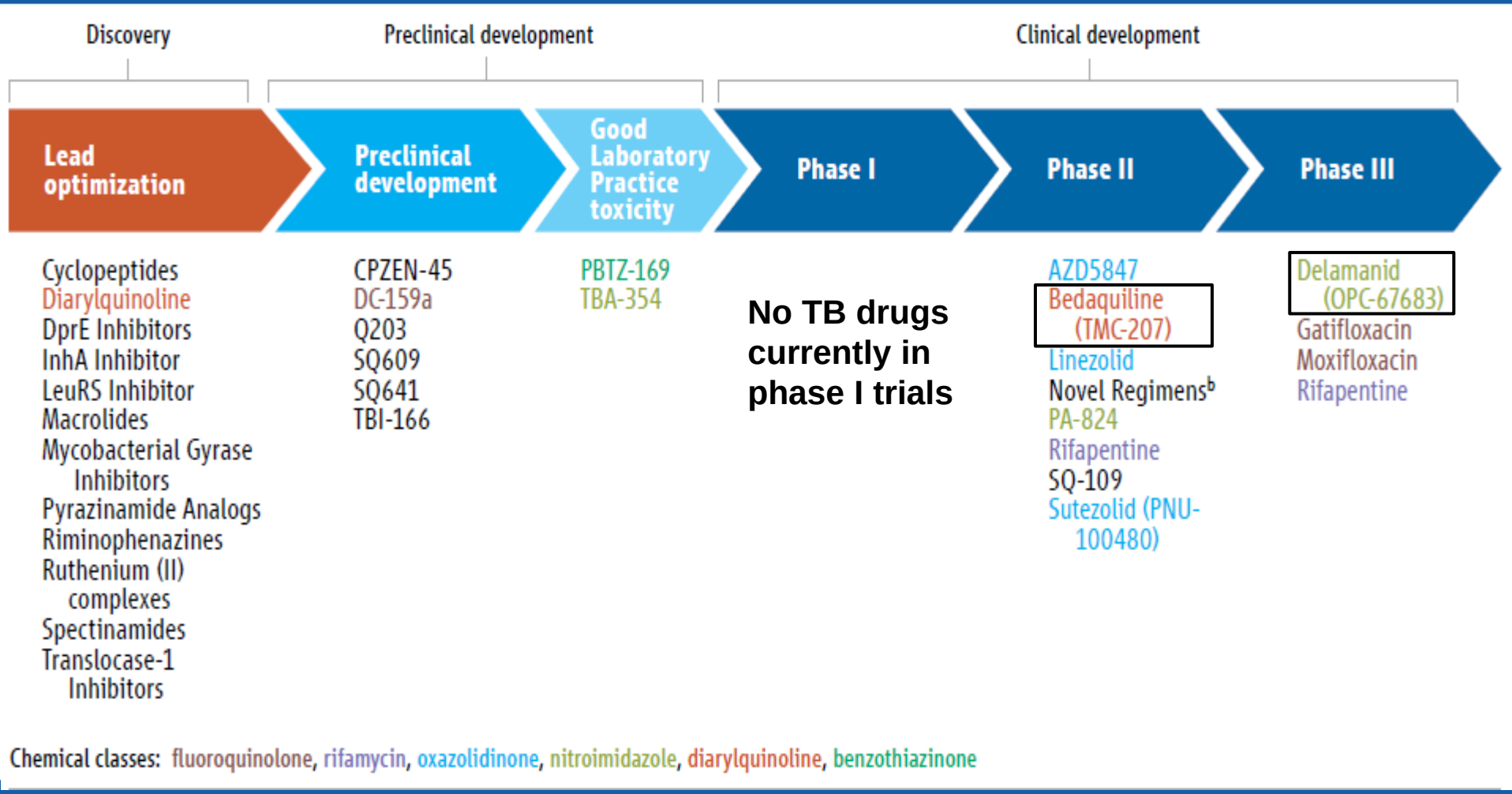
Rational Use of New Drugs for Treatment of MDR TB: Context and Challenges

Christian Lienhardt, MD, MSc, PhD
Senior Research Advisor
Global TB Programme
World Health Organization
Geneva, Switzerland

World Health Organization

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

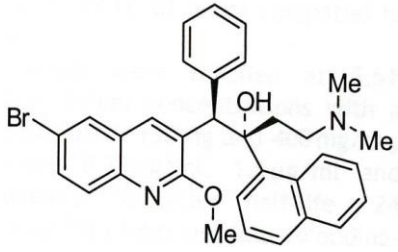
Global TB Drug Pipeline



Working Group on New TB Drugs *www.newtbdrugs.org*

New Drugs: Bedaquiline (BDQ)

- **Novel target: ATP synthase inhibitor**
- **Chemical class: diarlyquinoline**
  - First new TB drug class in over a generation
- **Phase IIb data: placebo-controlled trial of BDQ in combination with background MDR TB therapy (BT)**
  - Primary endpoint: time to sputum culture conversion and proportion with sputum culture conversion at 6 months
  - Showed greater efficacy of BT with BDQ, than BT with placebo
- **Approved by FDA (accelerated procedure) in December 2012 "as part of combination therapy to treat adults with multi-drug resistant TB when other alternatives are not available"**



Bedaquiline

ATP: adenosine triphosphate

Diacon AH, Pym A, Grobusch M, Patientia R, Rustomjee R, et al. *N Engl J Med* 2009;360:2397-405.

Interim Guidance by WHO for Use of Bedaquiline

- **June 2013 - BDQ recommended for use in MDR TB treatment under five strict conditions:**
  - Treatment under close monitoring
  - Proper patient selection
  - Patient informed consent required
  - Treatment design based on WHO recommendations
  - Active pharmacovigilance (drug safety monitoring)

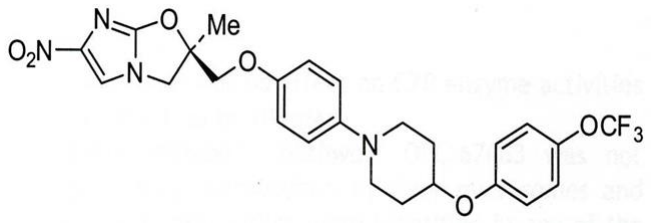
World Health Organization. *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis.* 2013.

New Drugs: Delamanid (DLM)

- **Chemical class: nitroimidazole**

- **Phase IIb data: placebo-controlled trial of Delamanid in combination with optimized background therapy (OBT)**
  - 2 test arms: (i) Delamanid (100mg bid) + OBT
    (ii) Delamanid (200mg bid) + OBT
  - Primary endpoint: 2-month sputum culture conversion
  - Showed greater efficacy of OBT with DLM, than OBT with placebo

- **Phase III trial launched in September 2011**



Delamanid

Gler MT, Skripconoka V, Sanchez-Garavito E, *et al. N Engl J Med* 2012;366:2151-60

Delamanid: Regulatory Status

- **Approved in December 2013 by the European Medicines Agency (EMA) *"as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability."***
- **Not yet approved by FDA**
- **Planned review by WHO in April 2014**

www.ema.europa.eu
www.clinicaltrials.gov/ct2/show/NCT01424670?term=delamanid&rank=3

Public Health Challenges of Introduction of New TB Drugs in Countries

- Determine optimal regimens for use of newly developed or re-purposed drugs for treatment of drug-susceptible and DR TB under programmatic conditions
- Evaluate patient eligibility requirements
- Assess programmatic feasibility
- Evaluate cost-effectiveness

Public Health Challenges of Introduction of New TB Drugs in Countries

- **Ensure proper surveillance and pharmacovigilance**
  - Especially in case of accelerated approval
  - Safety monitoring, especially for Bedaquiline
- **Ensure responsible use**
  - Appropriate indication, doses, drug combinations, and treatment duration
  - Prevent unwarranted off-label use and emergence of resistance
- **Encourage equitable access**

Other New Treatment Regimens Involving Previously Approved Drugs

- **Short course regimen for treatment of MDR TB**
  - Treatment series in Bangladesh with various combinations and durations of treatment
  - Best outcome with 9 months duration regimen
    - Minimum 4 months of 7 drug combination (KmCfzGfxEHZPto) prolonged if necessary until culture negative
    - Followed by 5 months of 4 drug combination (GfxEZCfz)

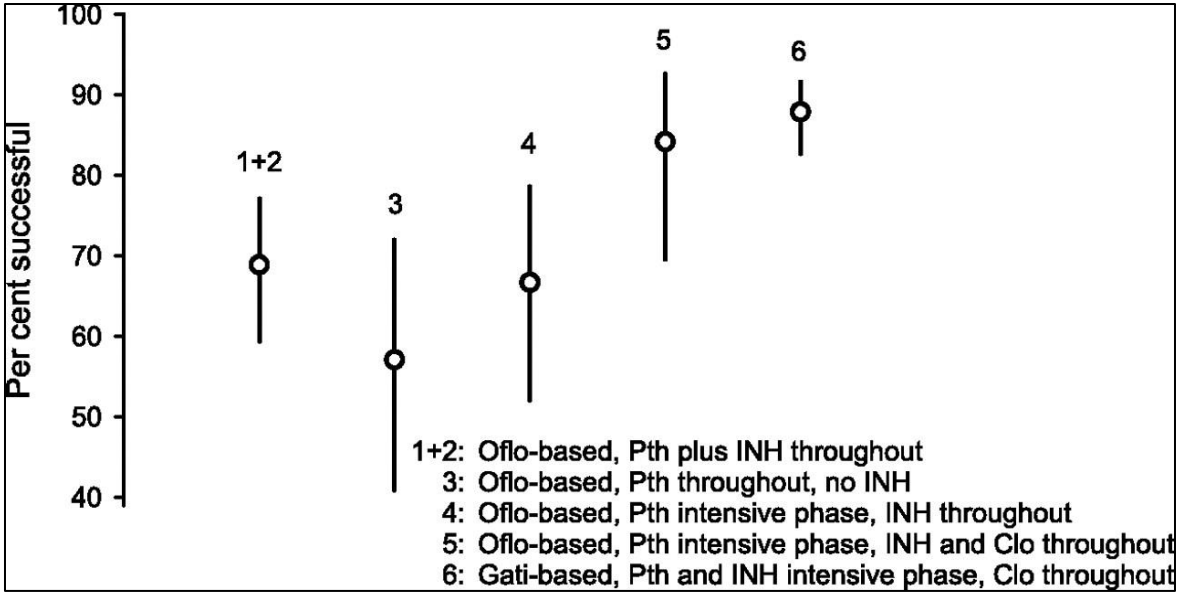
Km=kanamycin
Cfz=clofazimine
Gfx=gatifloxacin
E=ethambutol
H=high-dose isoniazid
Z=pyrazinamide
Pto=prothionamide

van Deun A et al (2010), AJRCCM 182(5):684–92.

Bangladesh Study: Patient Outcome Data

Outcome (regimen 6):

- **Cure 82.5%**
- Completion 5.3%
- Death 5.3%
- Default 5.8%
- Failure 0.5%
- Relapse 0.5%



Proportion of patients with a successful outcome in the treatment of multidrug-resistant tuberculosis

(Clo = clofazimine; Gati = gatifloxacin; INH = isoniazid; Oflo = ofloxacin; Pth = prothionamide)

van Deun A et al (2010), AJRCCM 182(5):684–92.

Treatment Options for XDR TB Remain Limited

- **Lack of evidence for the best drug regimens for treating patients with XDR TB**
- **Recent review of treatment outcomes did not find any associations between specific drugs or treatment regimens and successful outcomes**
  - However, success highest if at least 6 drugs used in intensive phase and 4 in continuation phase
- **Successful treatment is possible, but requires**
  - Early and accurate diagnosis of resistance to second-line drugs
  - Availability of multiple classes of second-line drugs
  - Access to clinicians who have special expertise in treating such cases

Falzon D, Gandhi N, Migliori GB et al. Eur Respir J. 2013 Jul;42(1):156-68. Epub 2012 Oct 25.
Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Clin Infect Dis. 2010 Jul 1;51(1):6-14.

Pediatric Formulations of Current Drugs and Trials of New Drugs are Urgently Needed

- **Few estimates on burden of disease in children**
  - Estimated to be 6%-10% of adult burden
  - Does not include children exposed to DR TB
- **Current diagnostics limited; Xpert® shown to be useful**
- **Limited pharmacokinetic data, few child-friendly formulations**
- **TB treatment programs often separate from child health programs**
- **Lack of capacity and expertise among providers**
- **Limited funding**
- **Small proportion of children actually treated, although those treated have excellent outcomes**
  - Among 315 patients, 81% success rate

Becerra et al., 2012, Ettehad et al., 2012, Hesseling et al, 2013; Furin et al., 2013, Graham et al., 2012

Preventive Therapy for Contacts of MDR and XDR TB Cases

- **Robust evidence to support the efficacy of INH preventive therapy (PT) to reduce the risk of disease progression in child and adult contacts of drug-susceptible TB**
  - 11 randomized controlled trials (RCT) involving over 73,000 persons
- **No RCT comparing preventive regimens for contacts of MDR TB**
- **Pediatric cohort of MDR TB contacts in Cape Town, South Africa**
  - Treated with INH + ethambutol + ofloxacin
  - Among 168 children treated, regimen well-tolerated and only 3.2% developed active TB

INH: isoniazid

Smieja MJ, Marchetti CA, Cook DJ et al. Cochrane Database Syst. Rev. 2000; (1): CD001363.

Preventive Therapy for Contacts of MDR and XDR TB Cases

- **Outbreak investigation in Chuuk, Micronesia**
  - 5 MDR TB cases and 119 infected adult and child contacts
  - All contacts offered preventive therapy (PT) for 12 months (FQ alone or with another agent)
  - None of the 104 contacts who received PT developed TB, but 3 of 15 untreated contacts progressed to disease

- **RCT study "TB-CHAMP" in late stages of development to assess preventive therapy with INH or levofloxacin in children exposed to drug-resistant TB in South Africa**

Seddon et al., 2013
Bamrah S, Brostrom R, Fred D, et al. Int J Tuberc Lung Dis (in press)
INH: isoniazid
FQ: fluoroquninolone

Conclusions

- **Two newly approved medications for the treatment of MDR TB are Bedaquiline (FDA approved) and Delamanid (EMA approved)**
- **Multiple scientific and program challenges remain as these drugs are used more widely**
  - Need for data collection under "real world" conditions
- **New combinations of existing and repurposed medicines show potential for treatment shortening of MDR TB**
- **Areas requiring additional investigation include XDR TB treatment, pediatric regimens to treat MDR TB, and preventive therapy for contacts of both MDR and XDR TB cases**

Drug Resistance in TB: What Public Health Can Do Now and in the Future

Tom Kenyon, MD, MPH
Director
Center for Global Health
Centers for Disease Control and Prevention

How Did We Get Here?
A Brief History of Drug-susceptible TB

- 19th century: Microscopy, culture, tuberculin skin testing, radiology
- 20th century: Stepwise improvements in these diagnostics
- 1940s-1960s: Effective, safe TB drugs discovered, multidrug therapy established by extensive clinical trials
- 1970s-1980s: Systematic 5-part TB control strategy based on diagnosis by microscopy and standard short-course treatment elaborated
- 1990s to date: Systematic 5-part TB control strategy implemented and expanded worldwide

Global Progress in TB Care and Control, 2000-2012

Global incidence decreased 15%

Global mortality decreased 40%

World Health Organization. *Global Tuberculosis Report 2013*

Progress Toward 2015 Millennium Development Goals Related to TB as of 2012

Indicator	Target	Global Status
Incidence	Falling incidence rate	**Target met**
Prevalence	50% decrease compared with 1990	Not on track to meet target
Mortality	50% decrease compared with 1990	**On track to meet target**
Case Detection	70% of estimated number of cases	66%
Treatment Success	85% among new sputum smear-positive cases	**87%**

www.un.org/millenniumgoals/

How Did We Get Here?
A Brief History of Drug-resistant TB

- **1947: Emergence of drug-resistant TB documented**
- **1955: First nationwide survey documented widespread drug resistance in the United Kingdom**
- **1980s-1990s: Worldwide outbreaks of MDR TB**
- **1990s-present: WHO and IUATLD Global Project on anti-TB Drug Resistance Surveillance**
- **1990s-2000s: Pilot testing services for DR TB in middle- and low-income countries**

IUATLD: International Union Against Tuberculosis and Lung Disease
Streptomycin Committee, Central Office Veterans Administration. Am Rev Tuberc, 1947
British Tuberculosis Association. Tubercle (London), 1963.
WHO/IUATLD Global Project on Anti-Tuberculosis Drug-Resistance Surveillance, 1997, 2000, 2002, 2007, and 2010.
WHO. *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of Multidrug-Resistant Tuberculosis.* 2000.

Global Scale-up of Services for Drug-resistant TB

- **2009: World Health Assembly resolution declaring that all TB cases should be appropriately diagnosed and treated**

- **Unprecedented pace of scale-up; among 450,000 incident cases of MDR TB worldwide:**
  - 2009: ~5% of MDR TB cases detected and treated worldwide
  - 2013: ~20% of MDR TB cases detected and treated worldwide

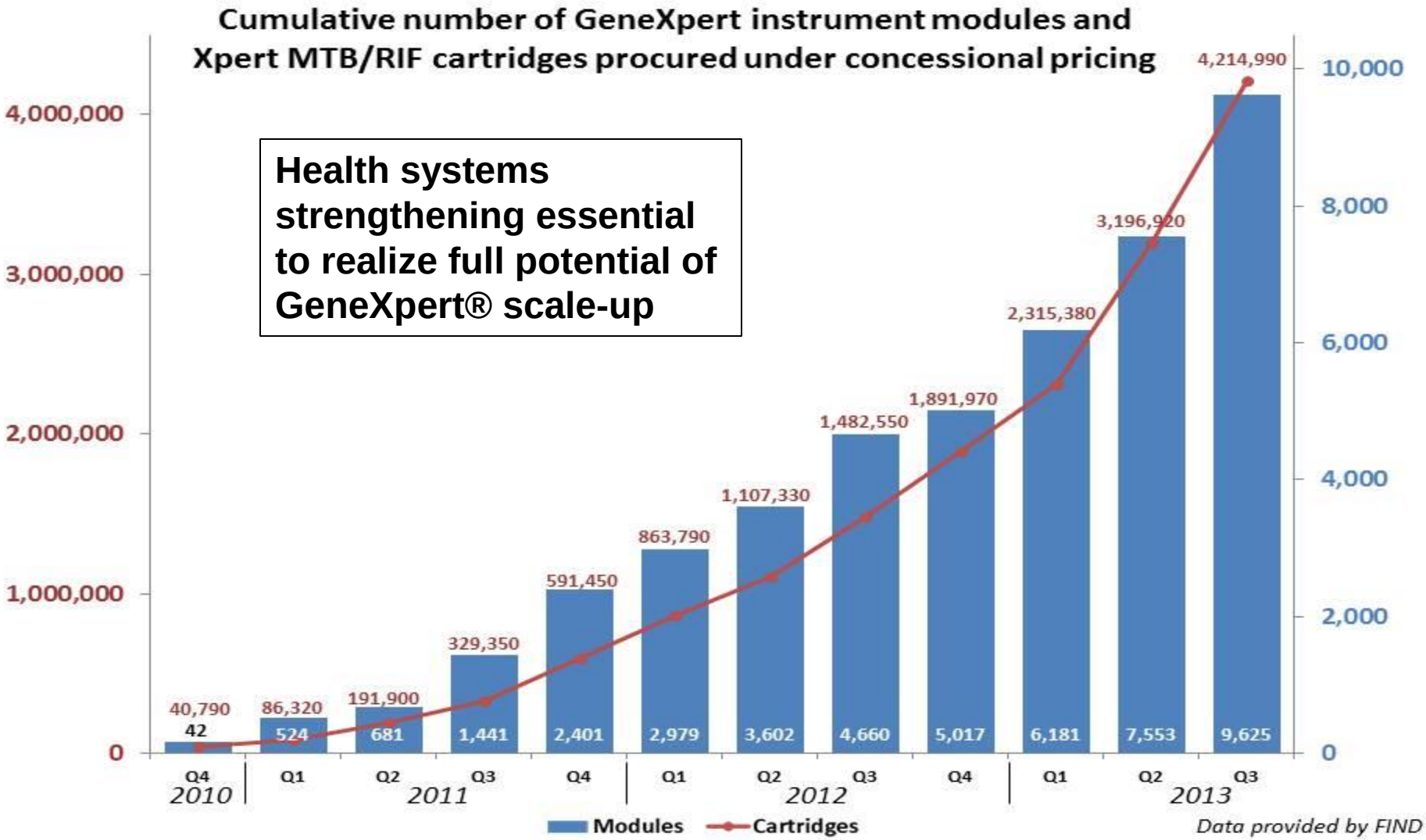
- **Shortfalls in progress toward 2015 Goals for case detection and treatment success**
  - Case detection target 100%, current status 20%
  - Treatment success target 75%, current status 48%

WHO. *Global Tuberculosis Report 2013*
Global Plan to Stop TB. Available at: www.stoptb.org/global/plan/

Rapid Scale-up of Services for Drug-resistant TB

- **Unprecedented leadership and political commitment**
  - World Health Assembly, World Health Organization
  - Public and private sectors worldwide
- **Unprecedented economic support**
  - The Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund); UNITAID; PEPFAR; BMGF; USAID
- **New technology**
  - Gene Xpert® and other rapid molecular methods
  - Rapid expansion and implementation worldwide
- **Better treatment**
  - Global Drug Facility: quality-assured anti-TB drugs at reduced prices
  - New drugs (Bedaquiline, Delamanid) and drugs with new indications (e.g., linezolid)

PEPFAR: President's Emergency Fund for AIDS Relief
BMGF: Bill and Melinda Gates Foundation
USAID: US Agency for International Development



As of 30 September 2013, a total of 1,843 GeneXpert instruments (comprising 9,625 modules) and 4,214,990 Xpert MTB/RIF cartridges had been procured in the public sector in 95 of the 145 countries eligible for concessional pricing.

FIND: Foundation for Innovative Diagnostics

Prevention and Control of Drug-resistant TB

- **Primary Prevention**
  - Strengthen basic TB control services to detect and cure all drug-susceptible TB cases
    - Don't create new cases of DR TB
  - Detect and treat existing drug-resistant TB cases
    - Prevent transmission to others
  - Infection control
    - Prevent transmission
- **Secondary Prevention**
  - Detect and treat contacts of DR TB cases
    - Prevent progression from LTBI to active disease

LTBI: latent tuberculosis infection

Obstacles to Detect and Treat Existing Cases of MDR TB

- **Case Detection and Diagnosis**
  - Need to strengthen laboratories to provide classic culture and susceptibility testing
  - Rapid molecular methods not yet widely available
- **Effective treatment**
  - Limited quality assured second-line drug supply
  - Paucity of evidence from clinical trials
  - Need for data on use of new drugs

Rates of Baseline and Acquired XDR TB

Total number baseline MDR TB isolates	Baseline isolate XDR n (%)	Baseline isolate simple MDR TB	Acquired XDR TB n (%)
832	66 (7.9%)	766	68 (8.9%)

Green Light Committee*	Acquired XDR TB, %	Risk Ratio (95% CI) unadjusted	p-value
GLC-approved	3.7	0.27 (0.16, 0.47)	<0.001
Non-GLC	15.6	Referent	

***The GLC serves as a technical advisory body to the Stop TB Partnership and the World Health Organization**

Cegielski JP, et al., 2014
GLC: Green Light Committee

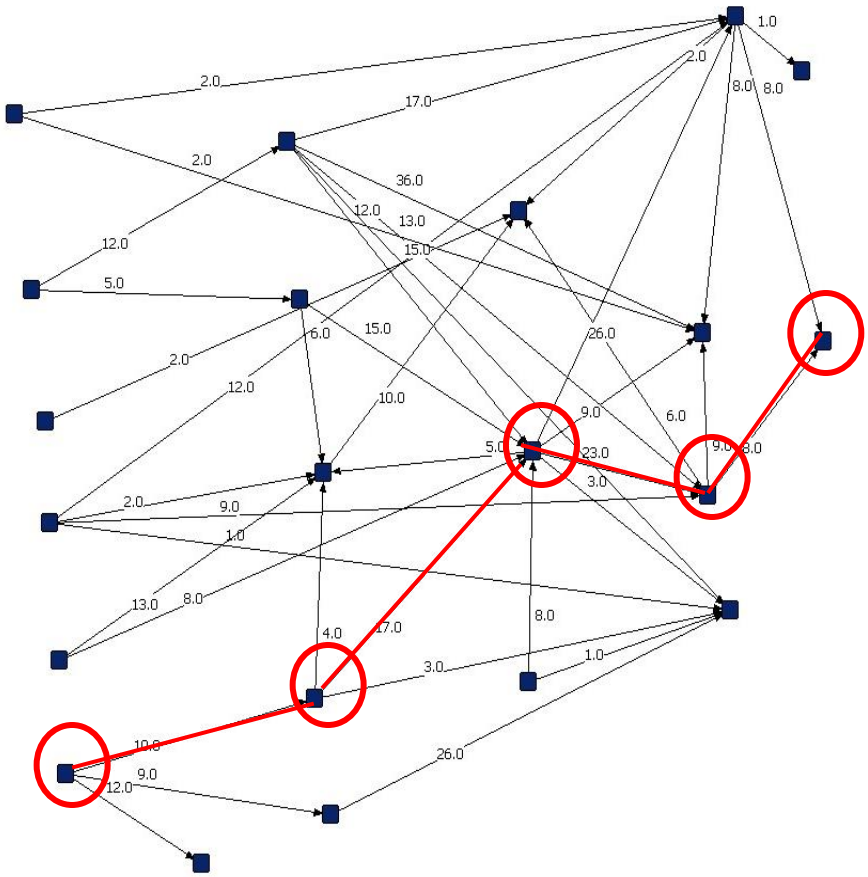
Importance of Infection Control: Estimating Global Role of Transmission

- **WHO: 74% of MDR TB cases globally arise from transmission rather than acquired resistance**
- **China: 78% of MDR TB due to transmission**
- **Meta-analysis of 31 cohorts: 90% of XDR TB cases with no history of MDR TB treatment**
  - Initially infected with XDR TB strains

Zhao et al. NEJM 2012
Falzon et al. Eur Resp J 2013
WHO 2010 Drug-Resistance Report

Transmission of XDR TB, 2005-2009, Tugela Ferry, South Africa

- Largest XDR TB cluster reported worldwide
- Total of 516 cases culture confirmed
- Genotyping revealed that >85% of cases had single predominant genetic fingerprint
- Epidemiologic investigation and social network analysis demonstrated up to 5 generations of transmission in hospital



Red line = single chain of transmission

Gandhi et al. J Inf Dis 2013

CDC / USAID Partnership

- **Technical assistance for MDR TB scale-up in countries with underperforming Global Fund grants**
  - Phase 1 (starting 2013): six countries (Philippines, Bangladesh, Vietnam, Mozambique, Uganda, Nigeria)
  - Phase 2 (starting 2014): eight more countries (India, Kenya, Haiti, Lesotho, Swaziland, Botswana, Tanzania, Zambia)

- **"New model" of technical assistance – long term strengthening of local human resources instead of "fly-in, fly-out" short term assistance**

USAID: US Agency for International Development

Additional CDC Contributions

- **Antimicrobial Resistance Initiative**
  - CDC report: Antimicrobial Resistance Threats
    - White House and Congressional Support
  - WHO and IUATLD reports: Global Anti-TB Drug Resistance Surveys

- **Global Health Security Agenda**
  - MDR TB and XDR TB
  - Prevent – Detect – Respond model applies to TB, both as endemic disease and in outbreak settings
  - Example of Uganda, 2013
    - Enhanced communications
    - Enhanced laboratory capacity and specimen referral systems
    - Improved outbreak response capacity

IUALTD: International Union Against Tuberculosis and Lung Disease
CDC. Antimicrobial Resistance Threats in the United States, 2013.
Tappero J et al. *MMWR*, 2014.

Looking Past the Millennium Development Goals: Three Pillars of the Post-2015 Strategy

- **Integrated, patient-centered TB care and prevention**
- **Bold policies and supportive systems**
  - Example: global recommendation for using Xpert® MTB/RIF as a primary diagnostic test for RIF-resistance simultaneous with the diagnosis of TB itself, leading to numerous initiatives for rapid worldwide scale-up
- **Intensified research and innovation**

Multidrug-resistant Tuberculosis: Tools for Tackling a New Face of an Old Foe

March 18, 2014

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention