CDC PUBLIC HEALTH GRAND ROUNDS

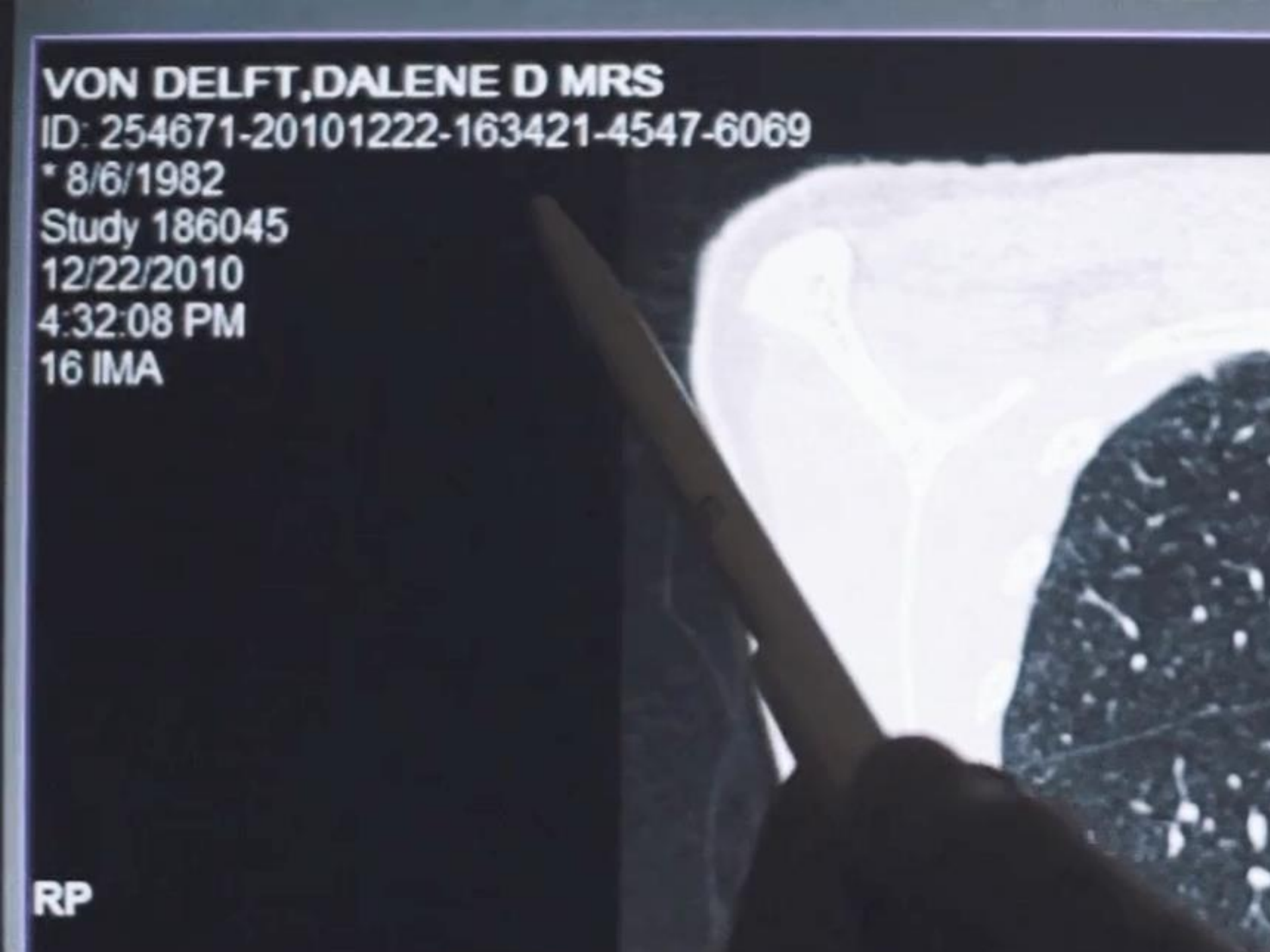
Multidrug-resistant Tuberculosis: Tools for Tackling a New Face of an Old Foe

Accessible Version: https://youtu.be/YrLP9UE-6Kk

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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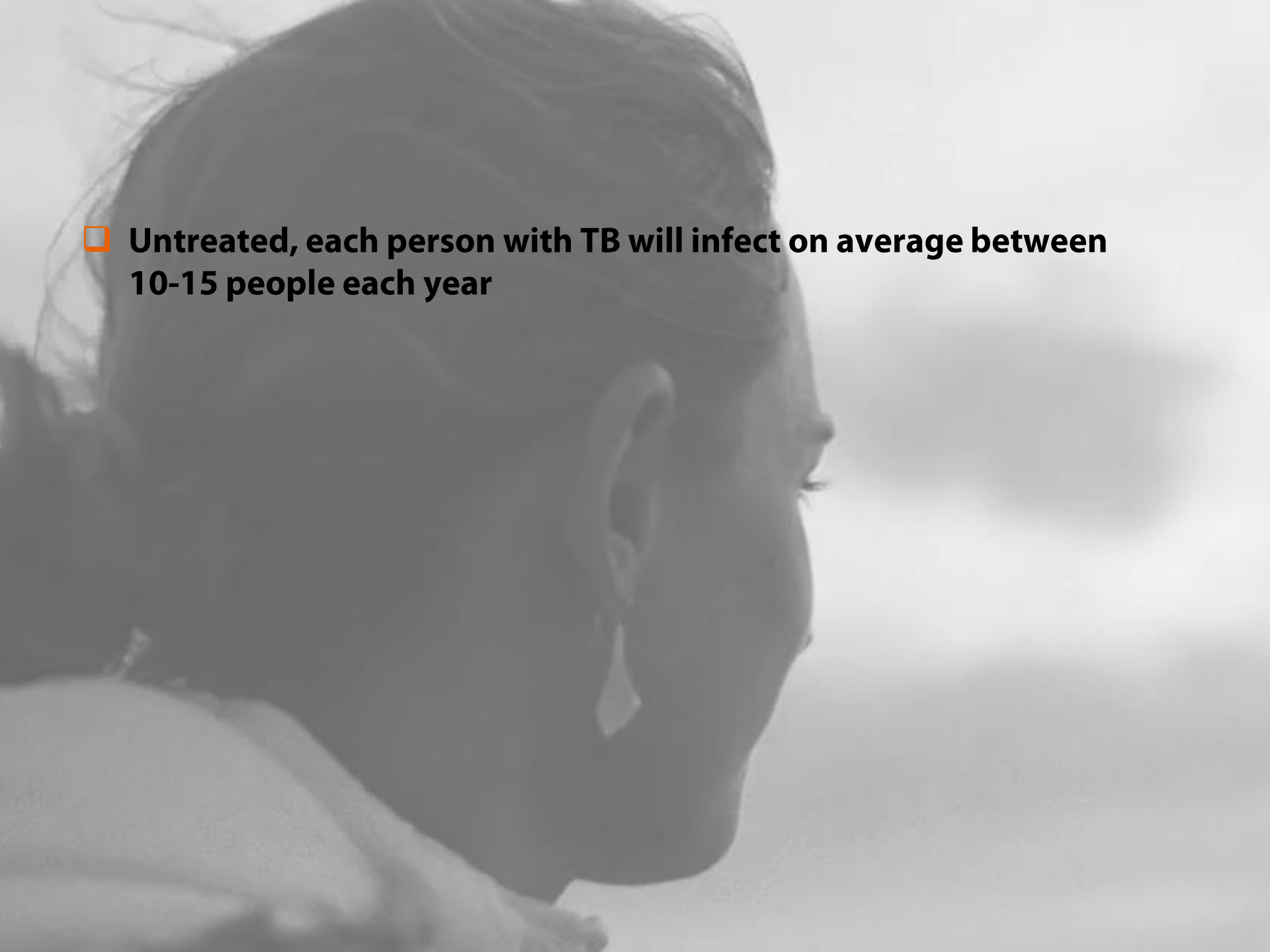
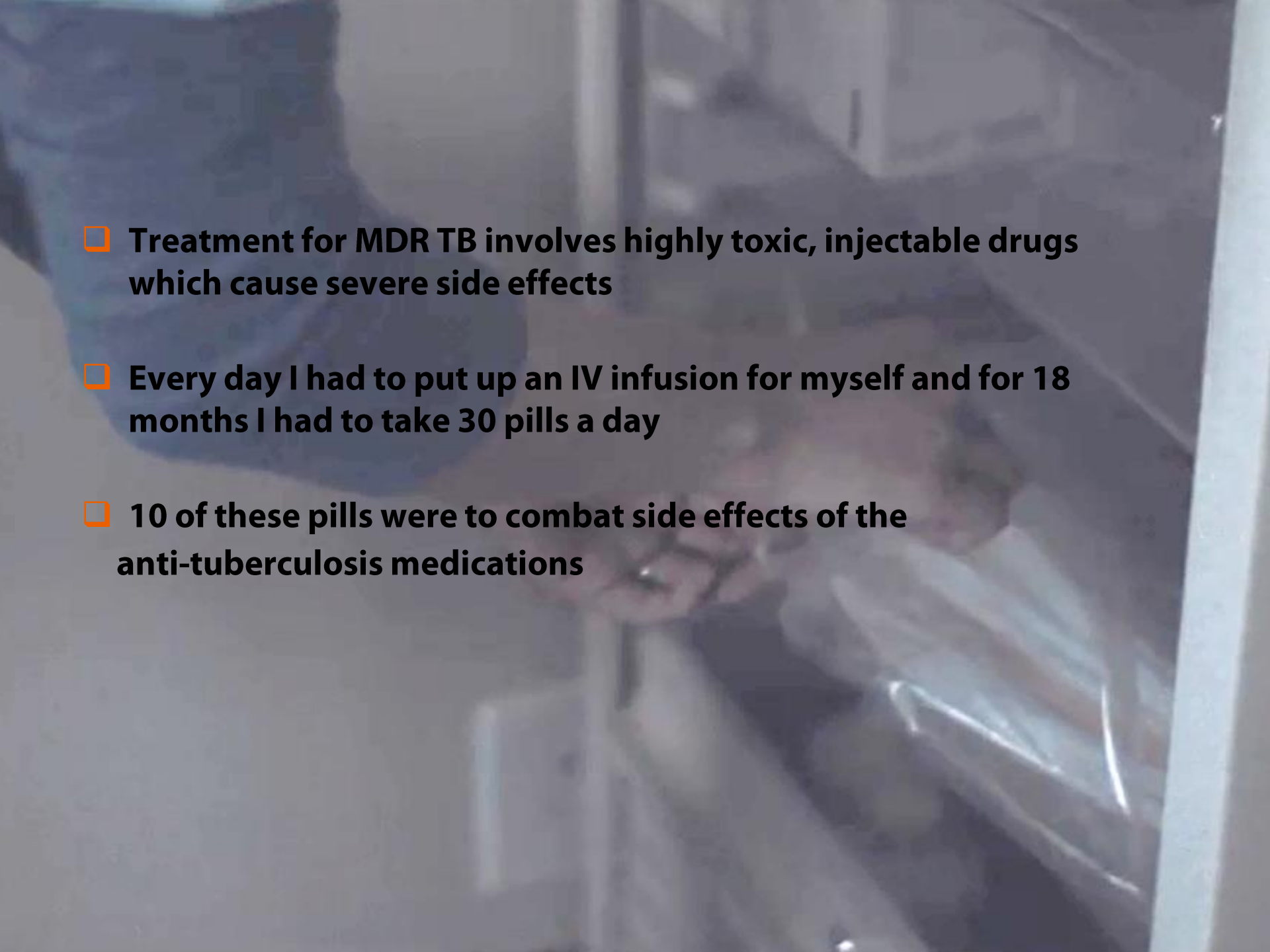


- **Untreated, each person with TB will infect on average between 10-15 people each year**

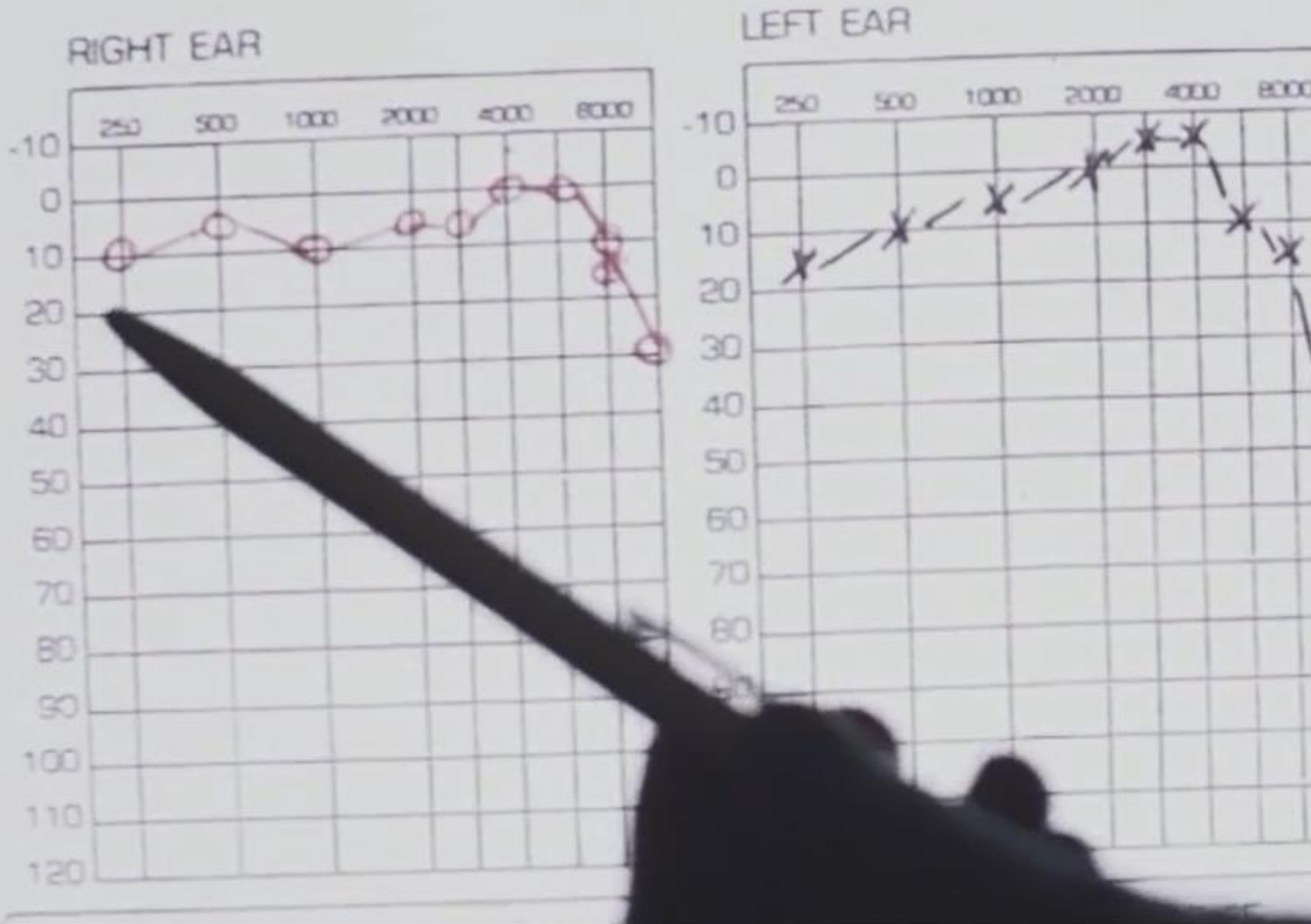
- Only 42% of MDR TB patients in South Africa are cured
- Side effects of treatment may include hearing loss, neurologic, and psychiatric symptoms



- 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

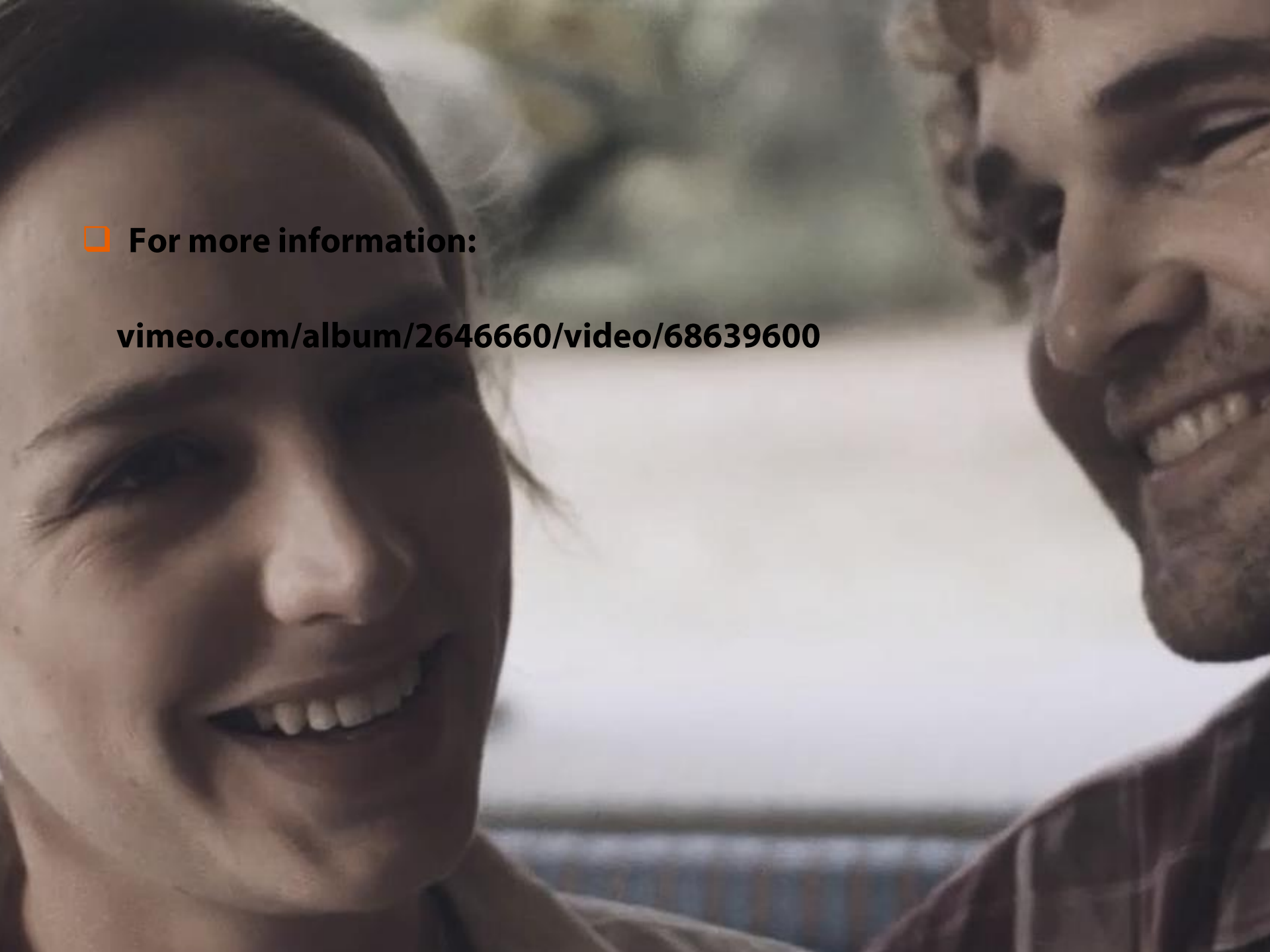
DIOMETER

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

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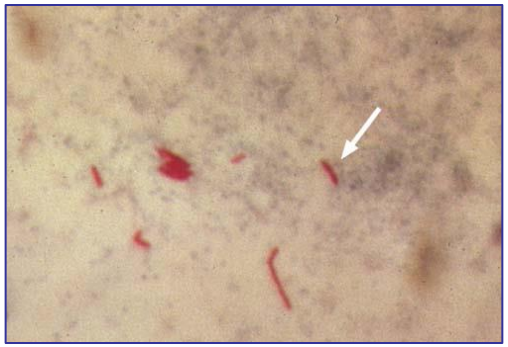
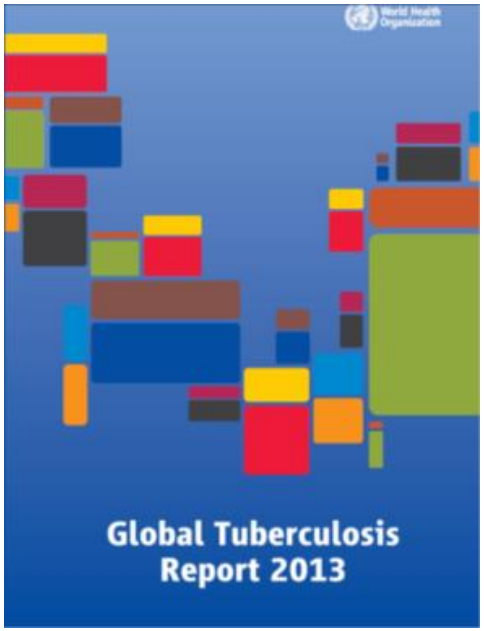
International Research and Programs Branch
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

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

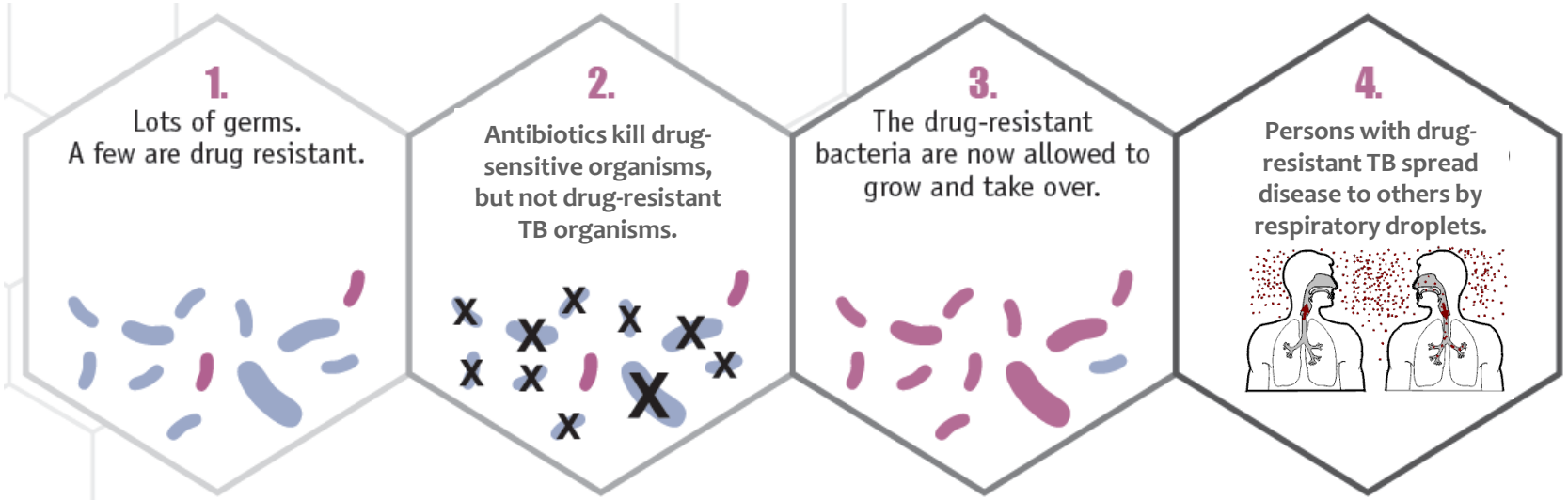


- **8.6 million new TB cases each year worldwide**
- **More than 95% cure rate**
  - Combination (4-drug) standard therapy
  - Uninterrupted 6-month treatment under directly observed therapy
- **Case notification and cure rates under program conditions below targets**
  - 66% (5.7 million) case notification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

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

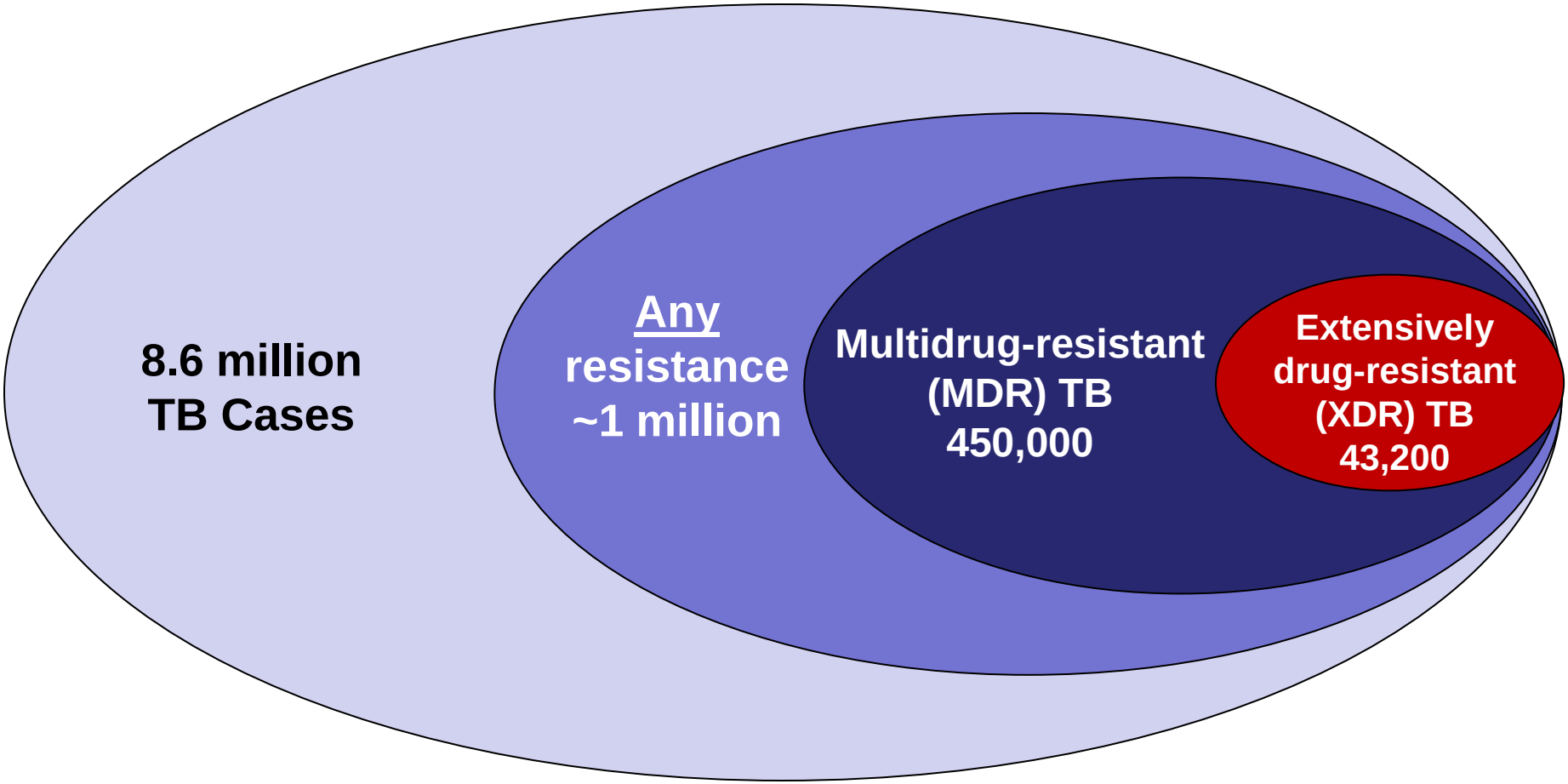
Drug-resistant Tuberculosis

- 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



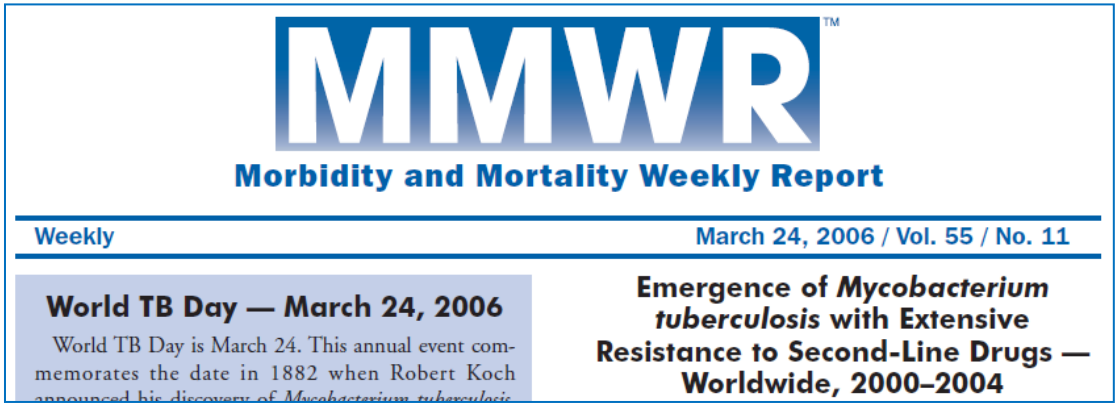
Adapted from: CDC. *Antibiotic Resistance Threats in the United States, 2013.* www.cdc.gov/drugresistance/threat-report-2013.

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

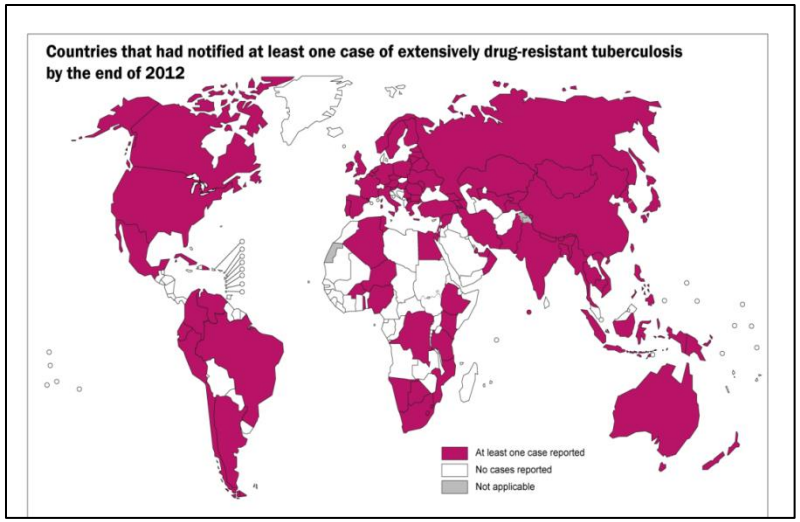
9/11 FIVE YEARS ON Special Report Pages 13 to 15

End of a dynasty Page 12

Killer TB tightens fatal grip

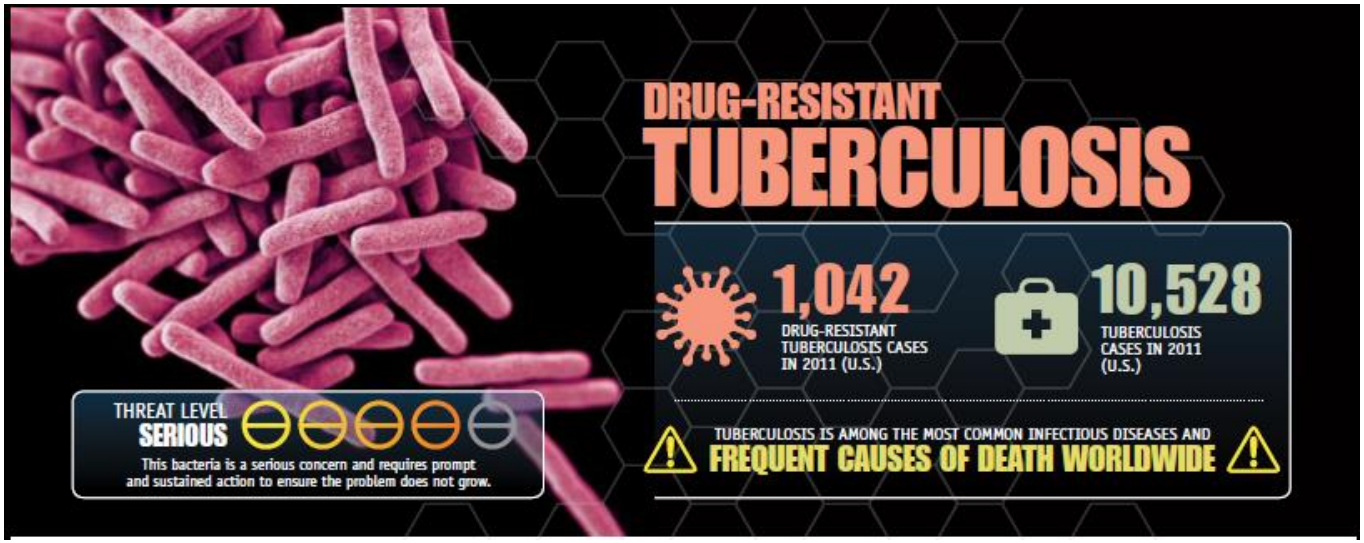
Despite indications that SA is in the forefront of infection, health minister tries to put a clamp on news and snubs global conference

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.

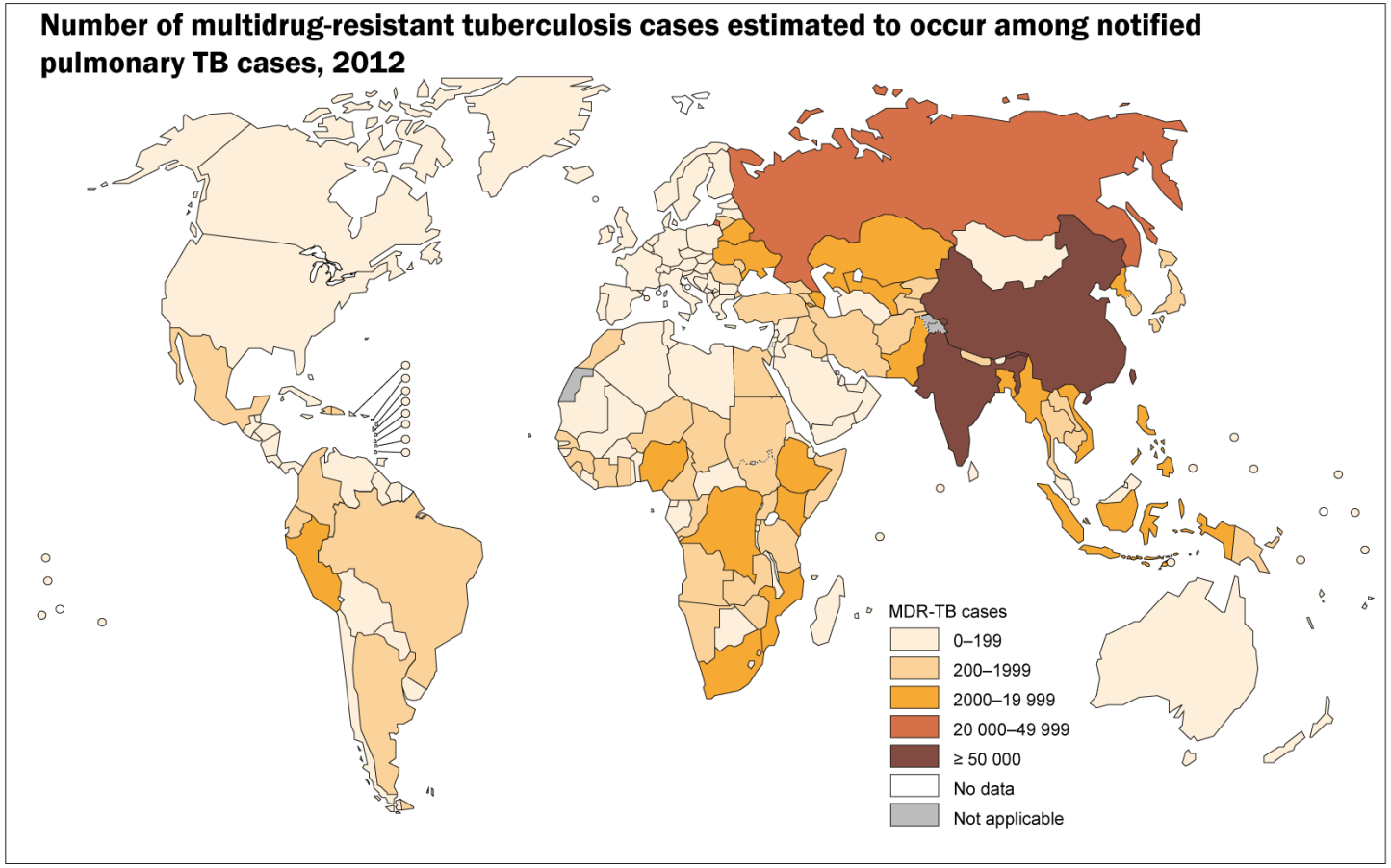
Growing Threat of Antimicrobial Resistance



- **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)

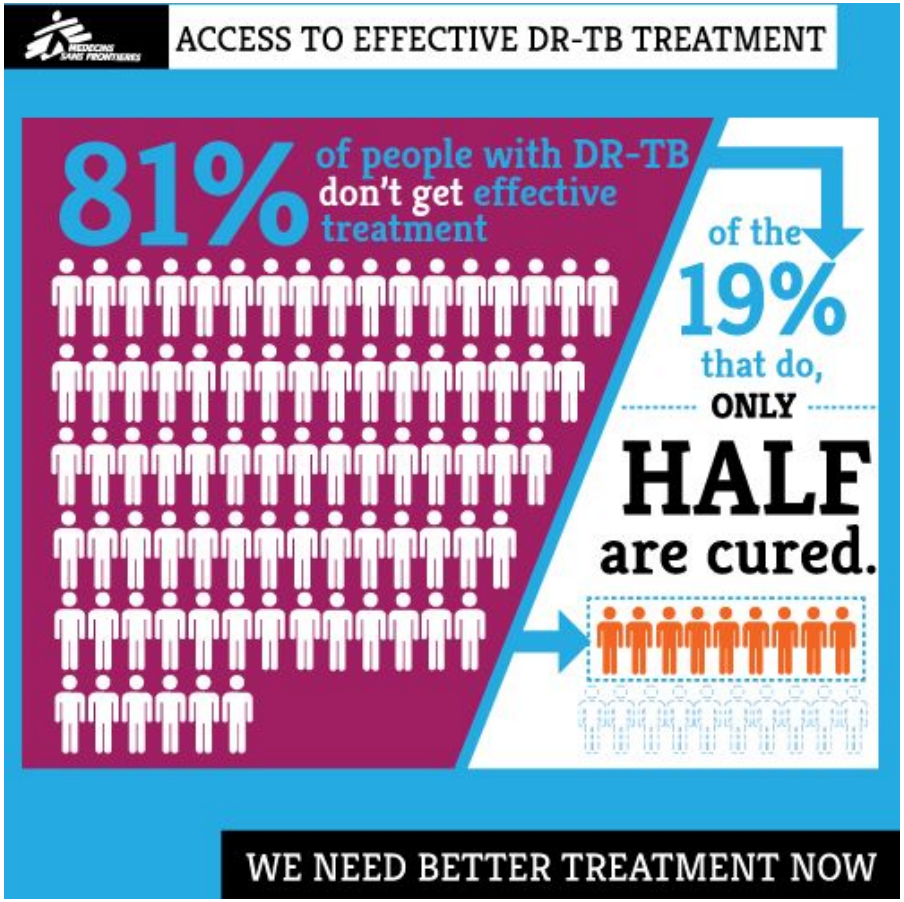
Source: Médecins San Frontières

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

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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

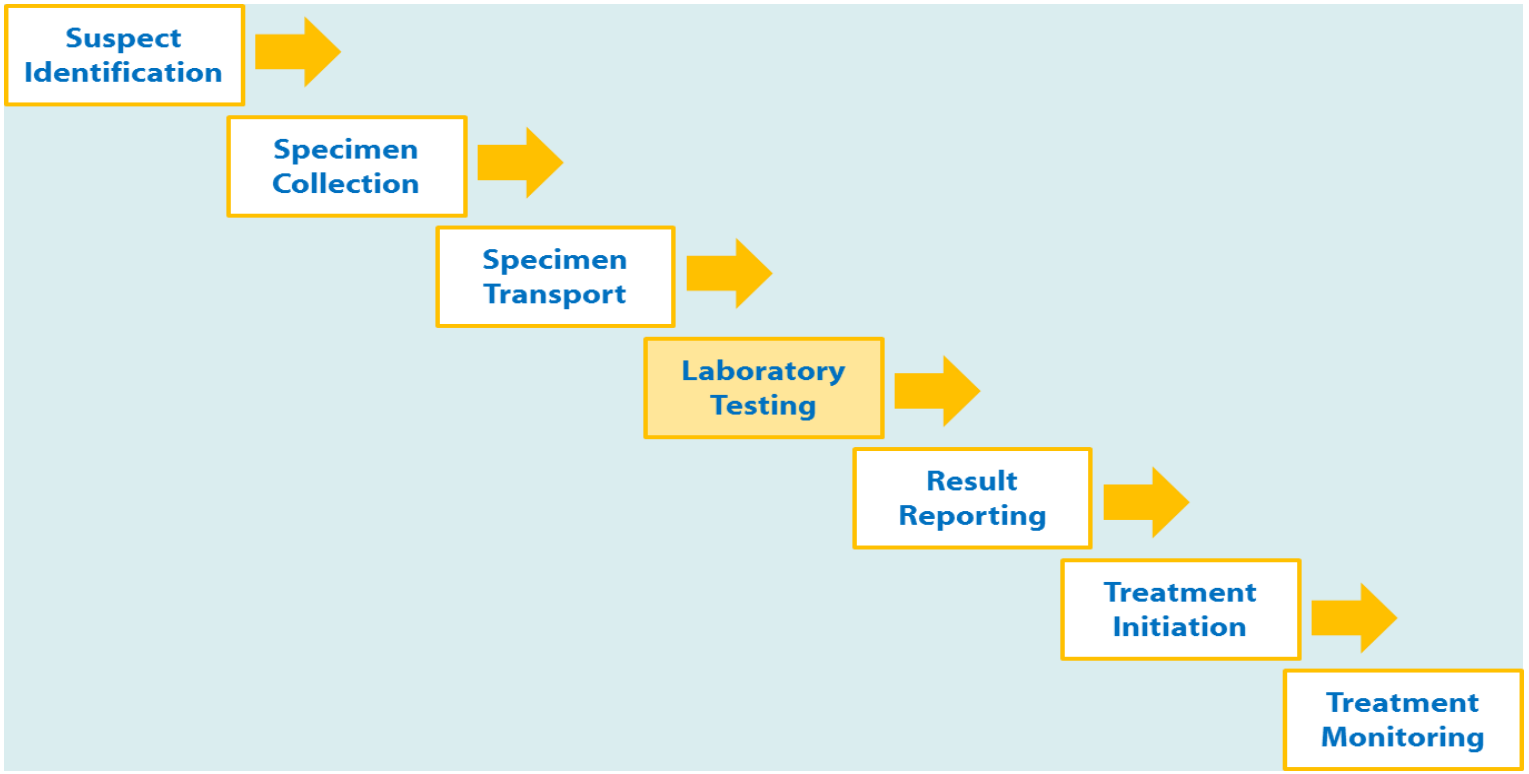
World Health Organization. 2013. *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update.* WHO/HTM/TB/2013.14.

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

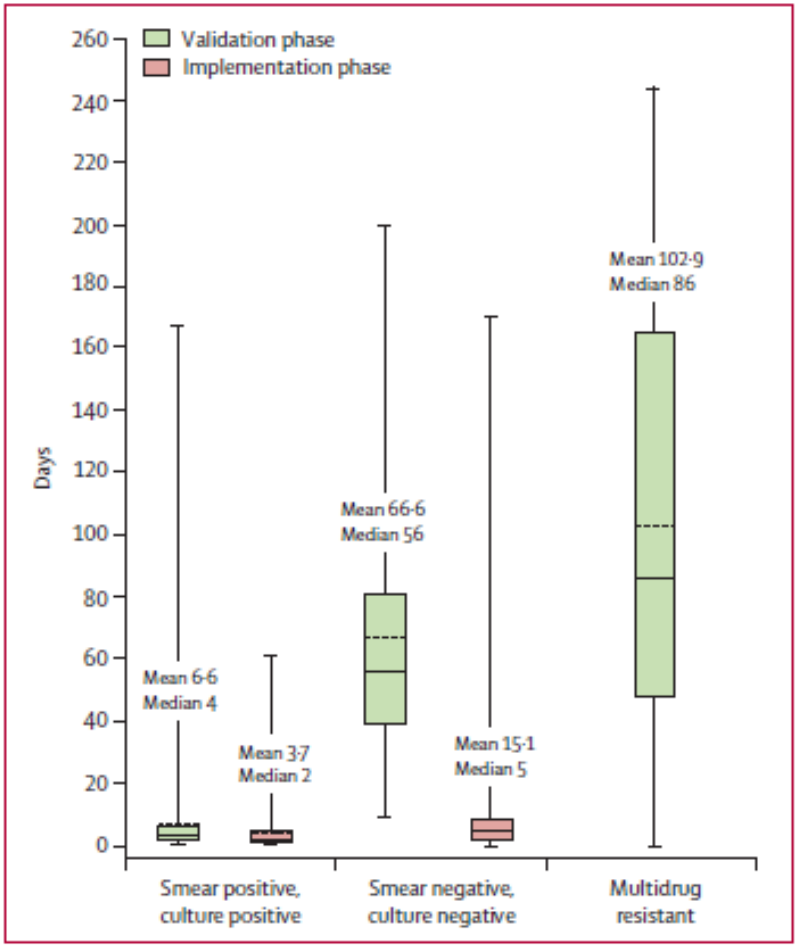
- A systems approach is needed to strengthen all steps in the process
- Testing must be linked to drug access and program capacity



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

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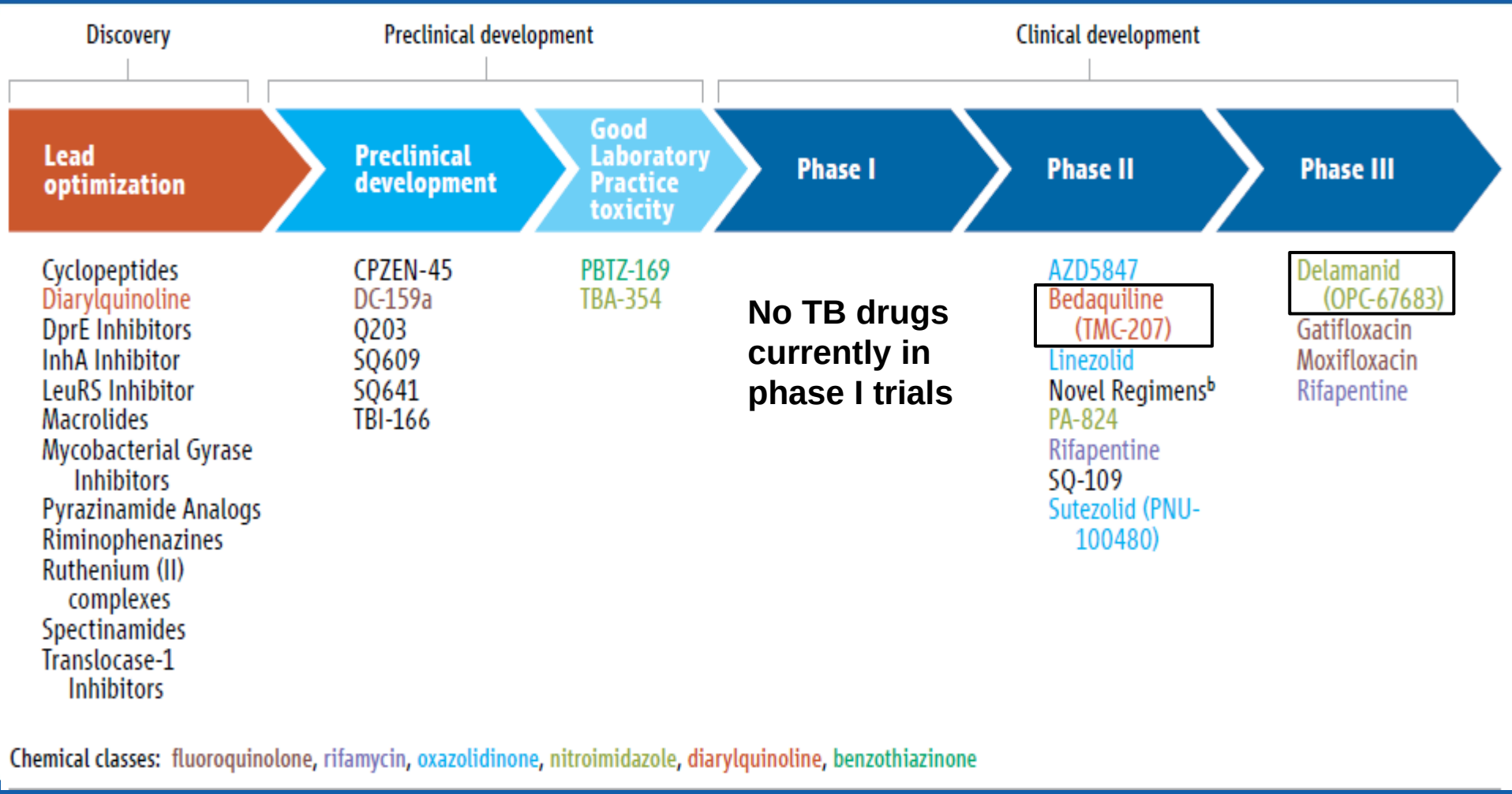
Geneva, Switzerland

World Health Organization

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

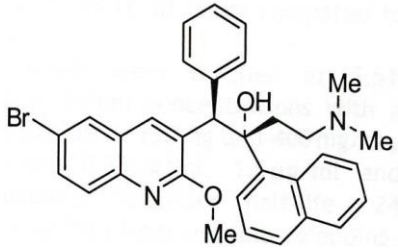
Global TB Drug Pipeline



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)

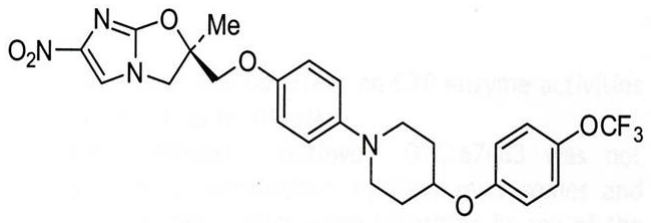
World Health Organization. *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis.* 2013.

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)

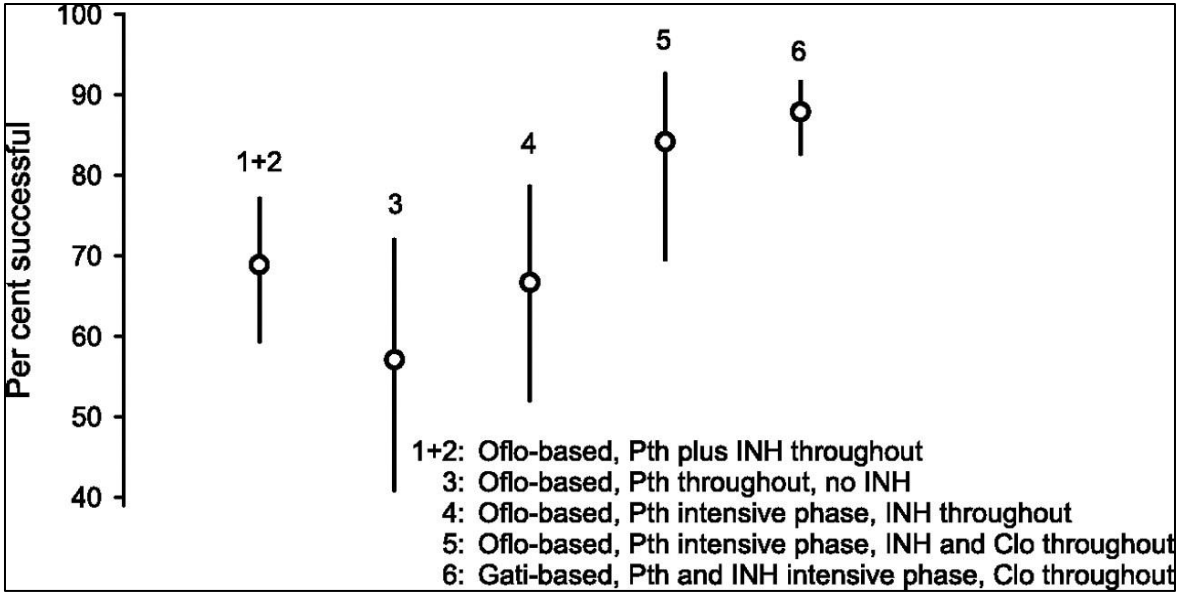
Km=kanamycin
Cfz=clofazimine
Gfx=gatifloxacin
E=ethambutol
H=high-dose isoniazid
Z=pyrazinamide
Pto=prothionamide

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

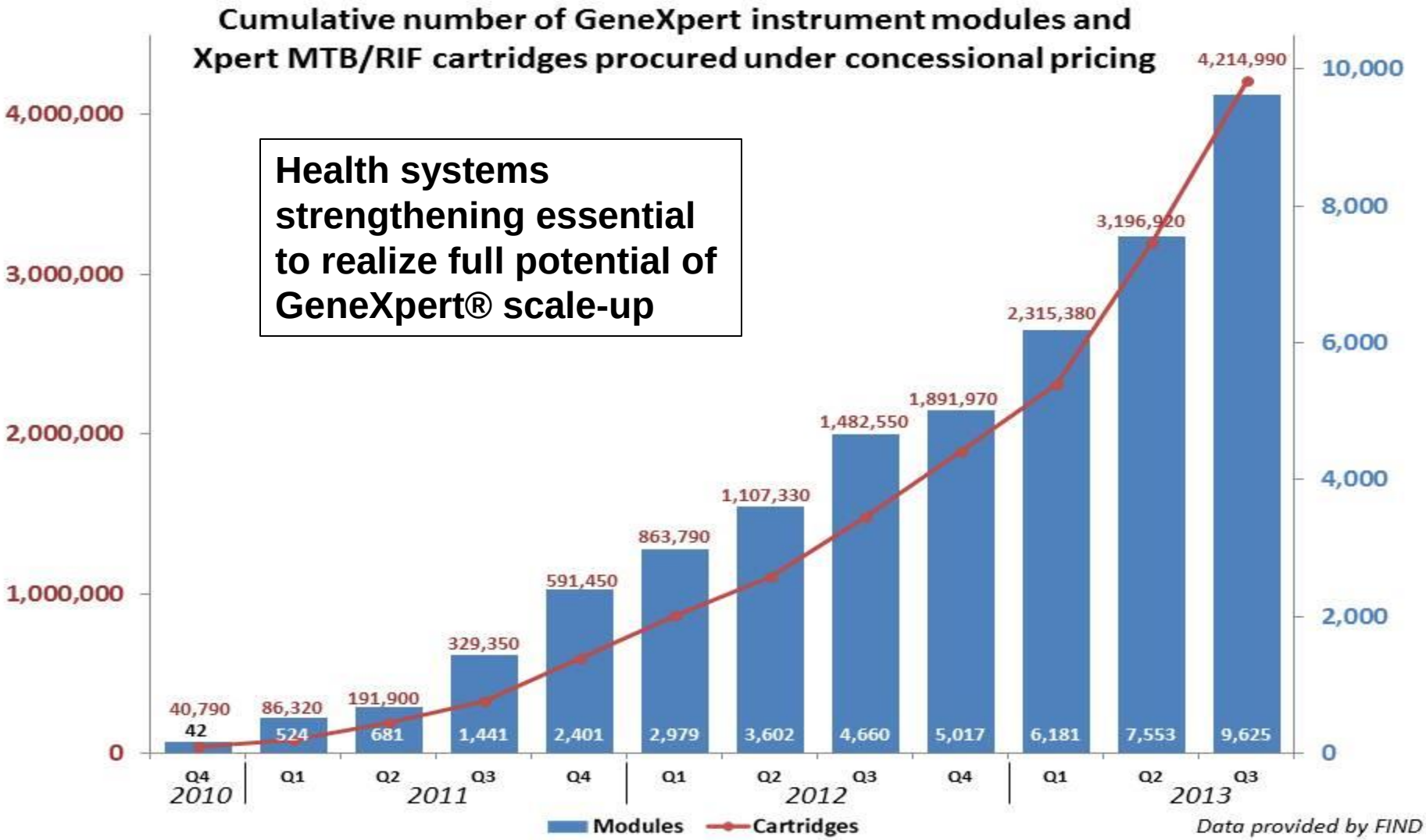
- **Shortfalls in progress toward 2015 Goals for case detection and treatment success**
  - Case detection target 100%, current status 20%
  - Treatment success target 75%, current status 48%

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

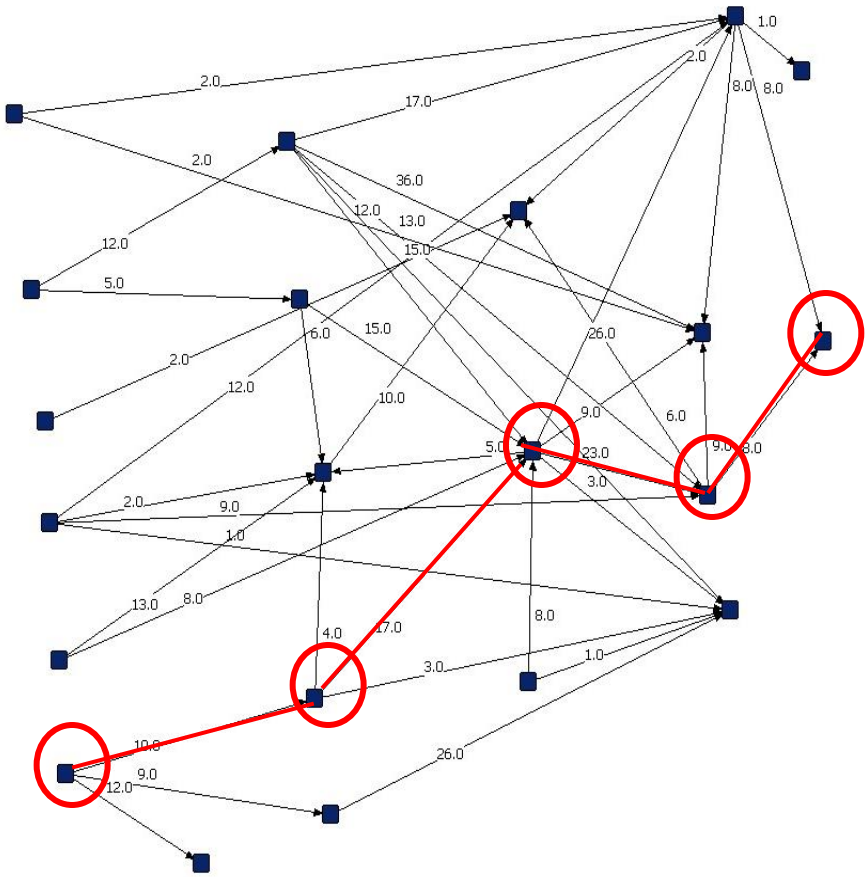
Importance of Infection Control: Estimating Global Role of Transmission

- **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