HEARTLAND
NATIONAL TB CENTER
A PARTNERSHIP OF UT HEALTH NORTHEAST AND TCID

Strategies for Successful Treatment of Drug Resistant Tuberculosis in the U.S.

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Barbara Seaworth, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Objective -
Improved Management of Drug Resistant TB

Recognize which patients are at risk of drug resistant TB

Discuss recommendations for management of drug resistant TB

- Should I start treatment before I know the 2nd line susceptibility results?
- How many drugs? Which ones? How long?
- How do I monitor for treatment response?
- How should INH resistant TB be treated?

Identify the management of close contacts of MDR/XDR TB

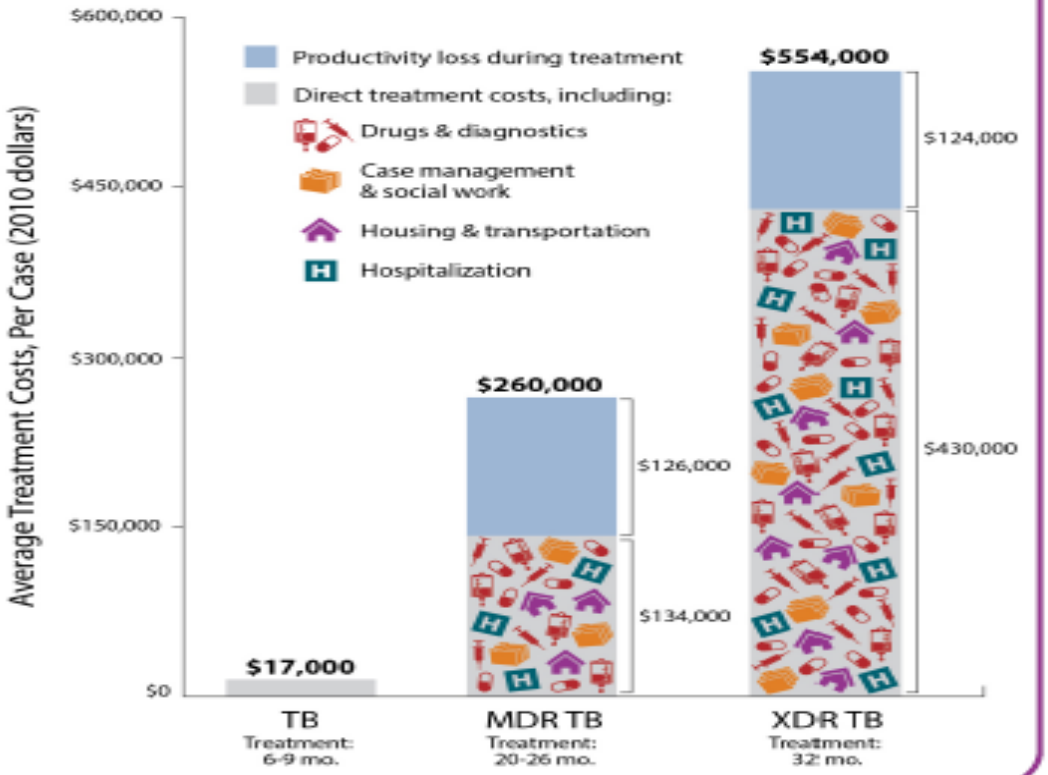
THE COSTLY BURDEN OF DRUG-RESISTANT TB IN THE U.S.

Multidrug-resistant (MDR) tuberculosis is a major health threat globally. Nearly half a million MDR TB[1] cases are estimated to occur worldwide annually, including cases that are extensively drug-resistant (XDR).[2]

While MDR and XDR TB are relatively rare in the U.S., their treatment comes at a terrible price – it is very expensive, takes a long time, disrupts lives, and has potentially life-threatening side effects.

The Outsized Financial Toll of MDR and XDR TB

Cost increases with greater resistance:

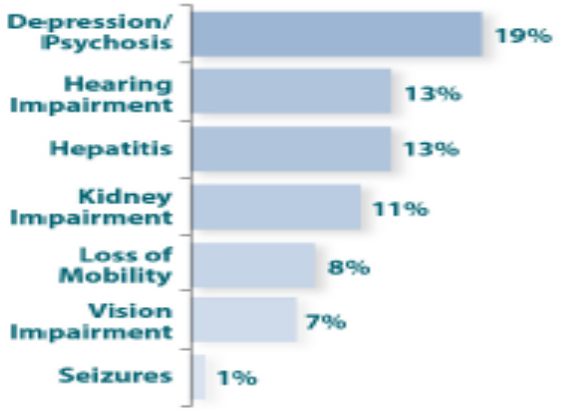


A Major Human Cost

Of those treated for drug-resistant TB:

- **9%** Die During Treatment
- **27%** Stop Working
- **73%** Hospitalized
- **37%** Require Home Isolation

Severe Treatment Side Effects



CDC March 2014

WHO 2018 Report: TB Epidemic

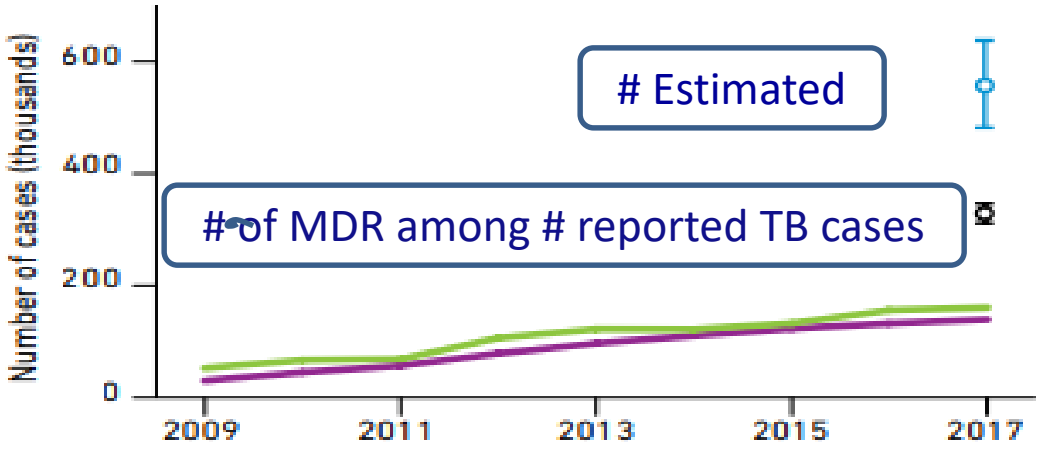
"Even Bigger Than We Thought"

- 10.0 million new cases of TB
  - 500,000 more TB cases than previously estimated (2014 reported 9.0 million)
- 1.3 million deaths (1.5 or 4000 each day 2014)
- 558,000 Estimated new Rifampin Resistant TB cases (82% MDR and 8.5% of these are XDR)

Not Good Enough!

FIG. 4.12

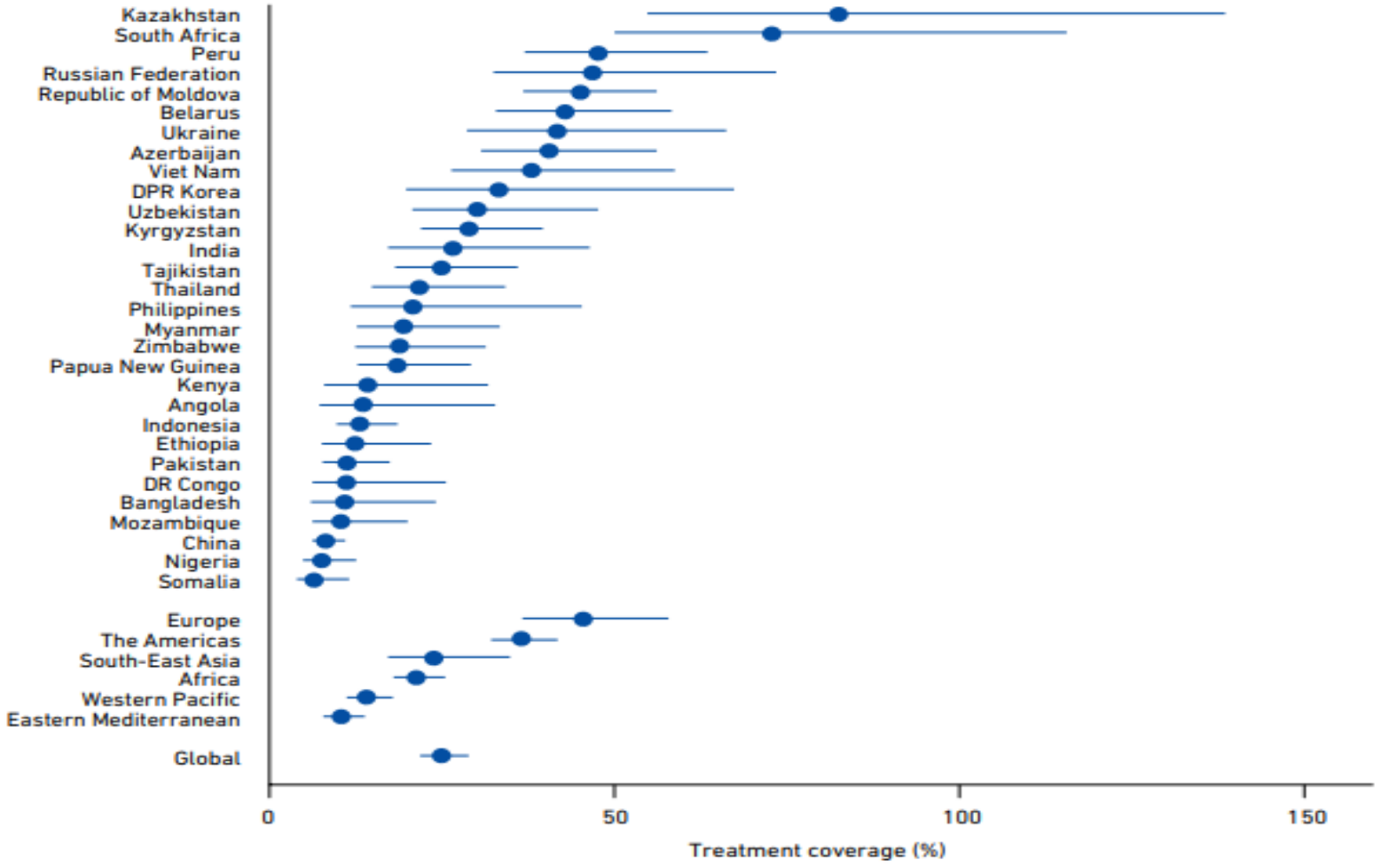
Global number of MDR/RR-TB cases detected (green) and number enrolled on MDR-TB treatment (purple), 2009–2017, compared with estimate for 2017 of the number of incident cases of MDR/RR-TB (uncertainty interval shown in blue) and the number of MDR/RR-TB cases among notified pulmonary cases (uncertainty interval shown in black)



Treatment Coverage for MDR/RR TB 2017

FIG. 4.20

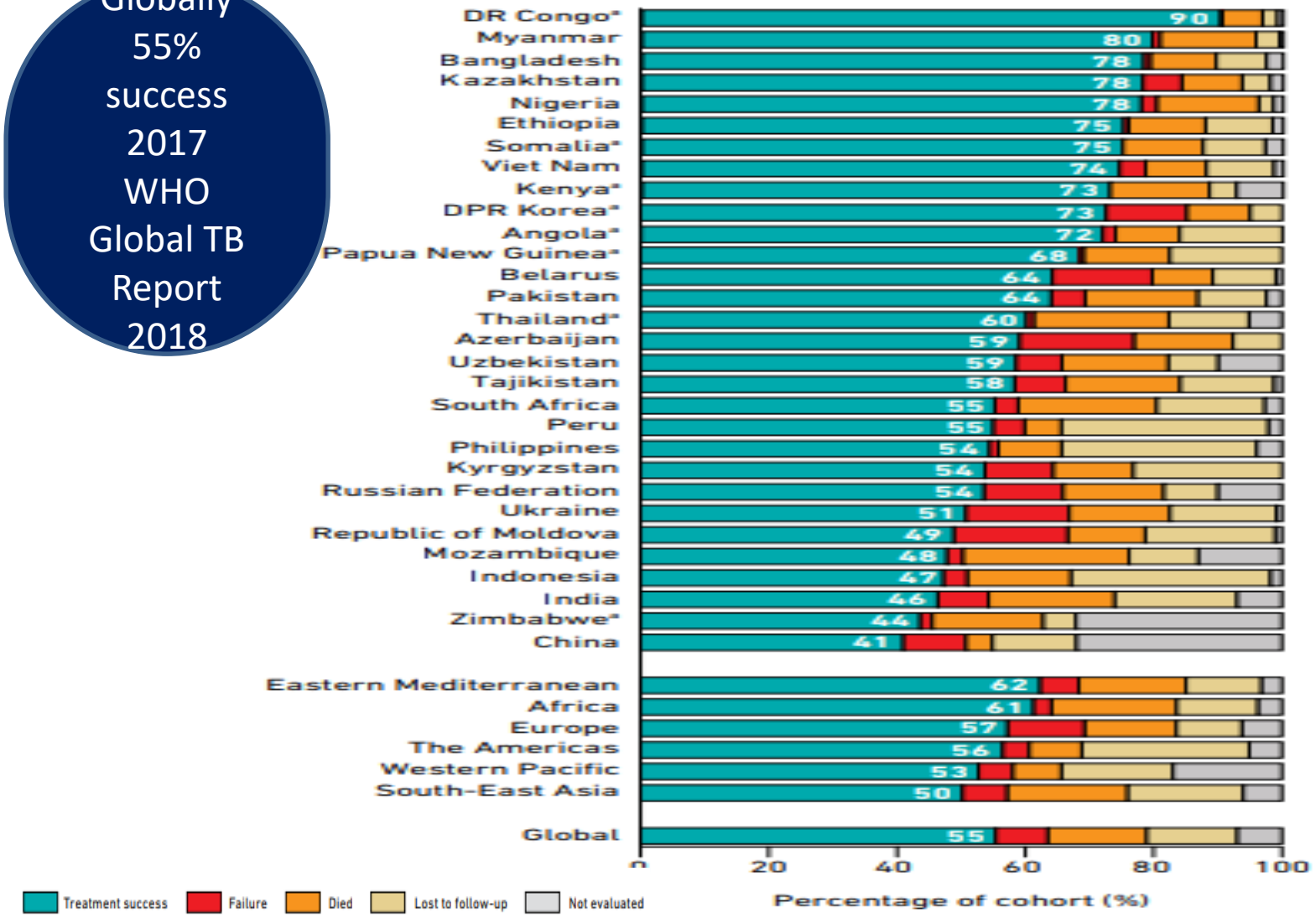
Estimated treatment coverage for MDR/RR-TB (patients started on treatment for MDR-TB as a percentage of the estimated incidence of MDR/RR-TB) in 2017, 30 high MDR-TB burden countries, WHO regions and globally



Globally 55% success 2017 WHO Global TB Report 2018

FIG. 4.26

Treatment outcomes for MDR/RR-TB cases started on treatment in 2015, 30 high MDR-TB burden countries, WHO regions and globally

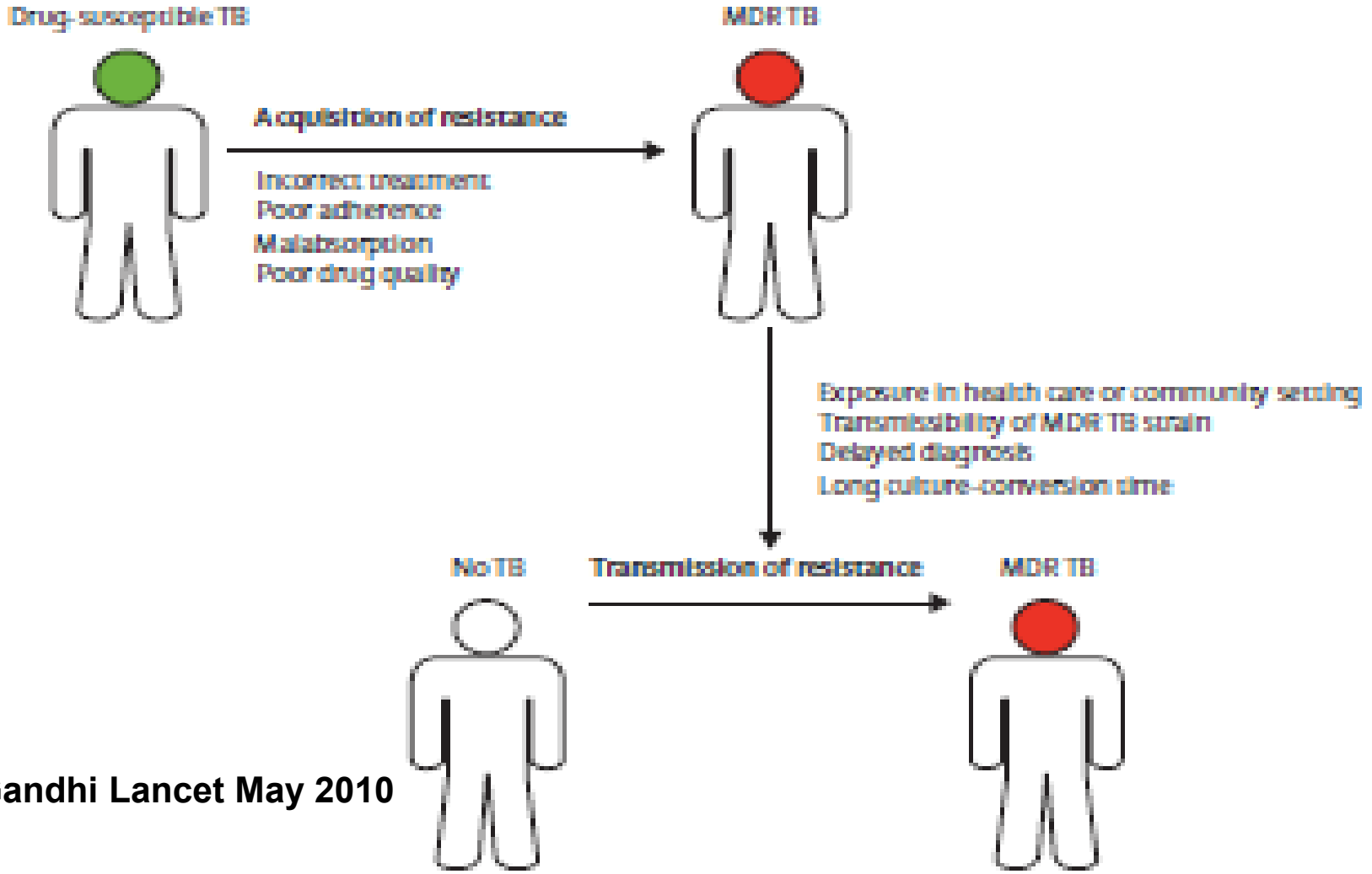


CLASSIFICATION OF DRUG RESISTANCE

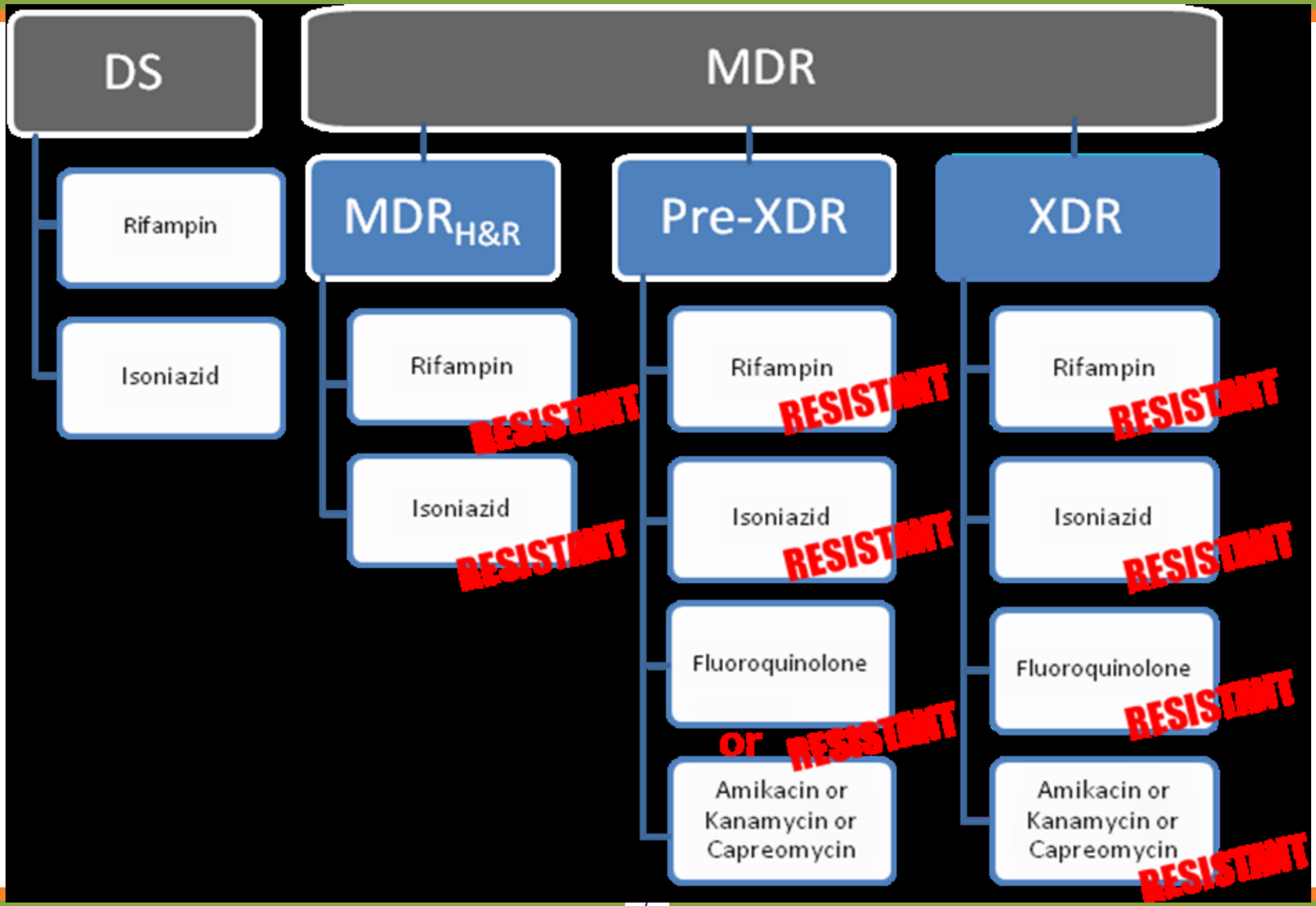
- PRIMARY DRUG RESISTENCE
  - No previous treatment
  - First isolate a person has is drug resistant

- ACQUIRED DRUG RESISTENCE
  - Resistance develops during inadequate treatment

Pathway to Drug Resistance



Gandhi Lancet May 2010


DS
MDR
Rifampin
Isoniazid
MDR H&R
Rifampin
RESISTANT
Isoniazid
RESISTANT
Pre-XDR
Rifampin
RESISTANT
Isoniazid
RESISTANT
Fluoroquinolone
or
RESISTANT
Amikacin or
Kanamycin or
Capreomycin
XDR
Rifampin
RESISTANT
Isoniazid
RESISTANT
Fluoroquinolone
RESISTANT
Amikacin or
Kanamycin or
Capreomycin
RESISTANT

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Why Do We Have Drug Resistant TB?

Increase In Streptomycin-Resistant Mutants During Monotherapy

Weeks of treatment	SM-resistant mutants	SM-resistant mutants (%)
0 (before)	1 / 88,750	0.0011
2	1 / 13,174	0.0075
3	1 / 817	0.12
4	1 / 588	0.17
5	1 / 367	0.27

Pyle M. Proc Mayo Clinic 1947;22:465

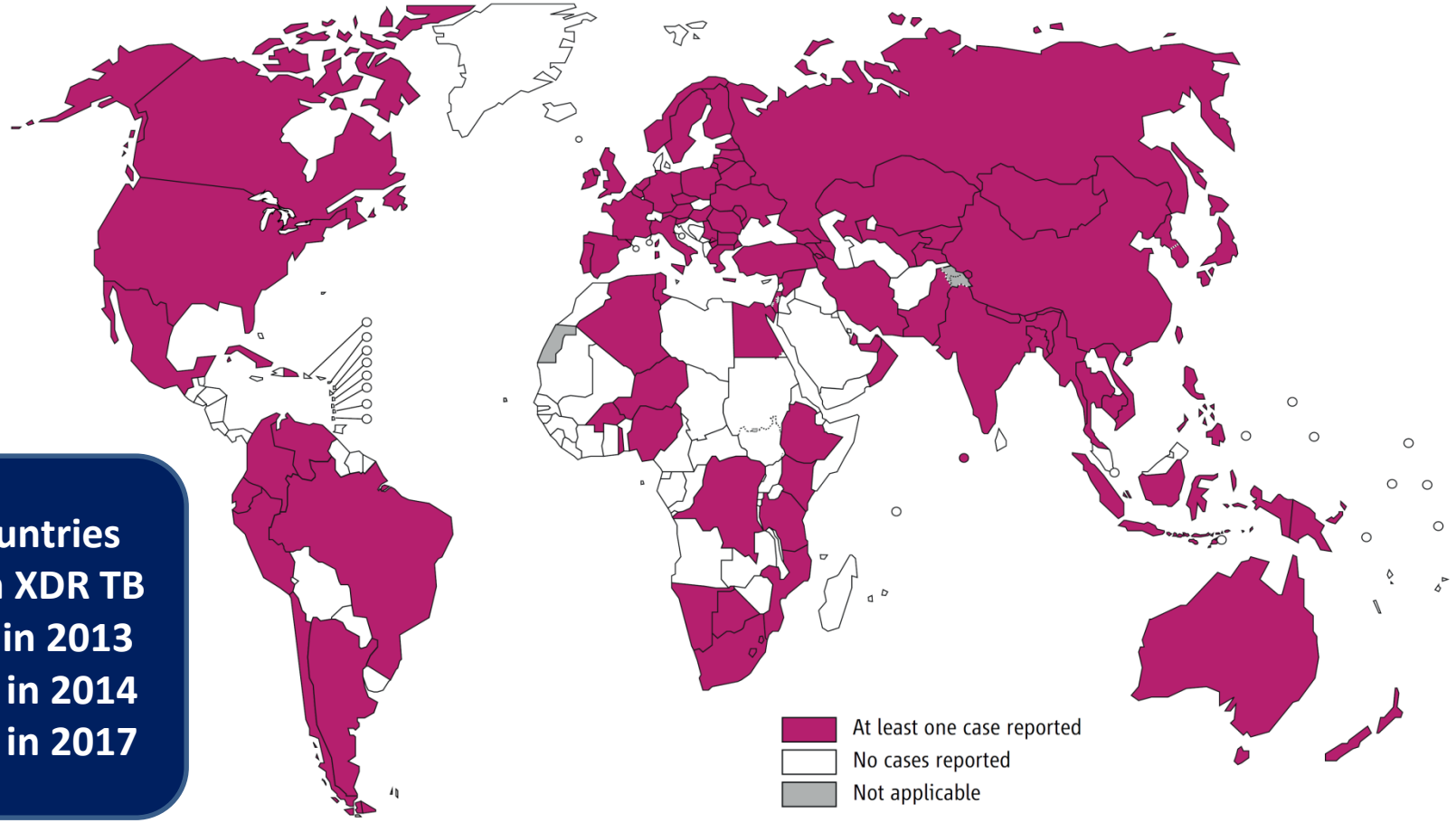
Isoniazid Resistance After 2 Months of Isoniazid Monotherapy

- Retrospective analysis from isoniazid treatment trial 1952 among patients with drug-susceptible isolates before starting

#Patients	Cavities	%Cult +	% resistant
45	0	40%	22%
57	1+	44%	40%
89	2+	70%	61%
43	3+	88%	87%

Fox W, Sutherland I. Thorax 1955;10:85-98

Countries that had reported at least one XDR-TB case by Oct 2013



Countries with XDR TB
-92 in 2013
105 in 2014
127 in 2017

Extensive Drug Resistance Acquired During Treatment of Multidrug-Resistant Tuberculosis

J. Peter Cegielski,[1] Tracy Dalton,[1] Martin Yagui,[2] Wanpen Wattanaamornkiet,[3] Grigory V. Volchenkov,[4] Laura E. Via,[5] Martie Van Der Walt,[6] Thelma Tupasi,[7] Sarah E. Smith,[1] Ronel Odendaal,[6] Vaira Leimane,[8] Charlotte Kvasnovsky,[1] Tatiana Kuznetsova,[4] Ekaterina Kurbatova,[1] Tiina Kummik,[9] Liga Kuksa,[8] Kai Kliiman,[9] Elena V. Kiryanova,[10] HeeJin Kim,[11] Chang-ki Kim,[11] Boris Y. Kazennyy,[10] Ruwen Jou,[12] Wei-Lun Huang,[12] Julia Ershova,[1] Vladislav V. Erokhin,[13] Lois Diem,[1] Carmen Contreras,[14] Sang Nae Cho,[15,16] Larisa N. Chernousova,[13] Michael P. Chen,[1] Janice Campos Caoili,[7] Jaime Bayona,[14] and Somsak Akksilp[3]; for the Global Preserving Effective TB Treatment Study (PETTS) Investigators[a]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia; [2]National Institute of Health, Lima, Peru; [3]Department of Disease Control, Ministry of Public Health, Bangkok, Thailand; [4]Vladimir Oblast Tuberculosis Dispensary, Russian Federation; [5]National Institute for Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; [6]Medical Research Council, Pretoria, Republic of South Africa; [7]Tropical Disease Foundation, Manila, Republic of the Philippines; [8]Riga East University Hospital Centre of Tuberculosis and Lung Diseases, Latvia; [9]Tartu University Hospital, Estonia; [10]Orel Oblast Tuberculosis Dispensary, Russian Federation; [11]Korean Institute of Tuberculosis, Seoul, Republic of Korea; [12]Taiwan Centers for Disease Control, Taipei; [13]Central Tuberculosis Research Institute, Russian Academy of Medical Sciences, Moscow; [14]Socios en Salud Sucursal, Lima, Peru; and [15]International Tuberculosis Research Center, Changwon, and [16]Yonsei University College of Medicine, Seoul, Republic of Korea

(See the Editorial Commentary by Daley and Horsburgh on pages 1064–5.)

Cegielski CID 2014

Background. Increasing access to drugs for the treatment of multidrug-resistant (MDR) tuberculosis is crucial but could lead to increasing resistance to these same drugs. In 2000, the international Green Light Committee (GLC) initiative began to increase access while attempting to prevent acquired resistance.

Methods. To assess the GLC's impact, we followed adults with pulmonary MDR tuberculosis from the start to the end of treatment with monthly sputum cultures, drug susceptibility testing, and genotyping. We compared the frequency and predictors of acquired resistance to second-line drugs (SLDs) in 9 countries that volunteered to participate, 5 countries that met GLC criteria, and 4 countries that did not apply to the GLC.

Risk of Acquired Drug Resistance During Treatment

- Does inadequate treatment of MDR → XDR?
- PETTS Study n(%)

	Cure/Comp	Failure	Death
Green Light	585 (65)	47 (5.2)	82 (9.1)
Programatic	373 (52.7)	55 (7.8)	145 (20.5)

- Emergence of XDR GLC 21% __ non GLC 51%
- Emergence of FQN R GLC 10.1%____ non GLC 20.8%

- PETTS : Preserving Effective TB Treatment Study,
  - Dalton et al. Lancet epub August 30, 2012

CHEST

Original Research

TUBERCULOSIS

Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli

Super Extensively Drug-Resistant Tuberculosis or Totally Drug-Resistant Strains in Iran

Ali Akbar Velayati, MD; Mohammad Reza Masjedi, MD; Parissa Farnia, PhD; Payam Tabarsi, MD; Jalladein Ghanavi, MD; Abol Hassan ZiaZarifi, PhD; and Sven Eric Hoffner, MD

Background: **The study documented the emergence of new forms of resistant bacilli (totally drug-resistant [TDR] or super extensively drug-resistant [XDR] tuberculosis [TB] strains) among patients with multidrug-resistant TB (MDR-TB).**

Methods: **Susceptibility testing against first- and second-line drugs was performed on isolated *Mycobacterium tuberculosis* strains. Subsequently, the strains identified as XDR or TDR *M tuberculosis* were subjected to spoligotyping and variable numb[illegible] (VNTR).**

Results: **Of 146 MDR-TB strains, 8 XDR isolates (5.4%) a[illegible] 15 TDR isolates (10.3%) were identified. The remaining strains were either susceptible (67%) o[illegible] patterns (20%). Overall, the median of treatments and drugs previously received by MDR-TB patients was two courses of therapy of 15 months' duration with five drugs (isoniazid [INH], rifampicin [RF], streptomycin, ethambutol, and pyrazinamide). The median of *in vitro* drug resistance for all studied cases was INH and RF. The XDR or TDR strains were collected from both immigrants (Afghan, 30.4%; Azerbaijani, 8.6%; Iraqi, 4.3%) and Iranian (56.5%) MDR-TB cases. In such cases, the smear and cultures remained positive after 18 months of medium treatment with second-line drugs (ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, and ciprofloxacin). Spoligotyping revealed Haarlem (39.1%), Beijing (21.7%), EAI (21.7%), and CAS (17.3%) superfamilies of *M tuberculosis*. These superfamilies had different VNTR profiles, which eliminated the recent transmission among MDR-TB cases.**

Conclusions: **The isolation of TDR strains from MDR-TB patients from different regional countries is alarming and underlines the possible dissemination of such strains in Asian countries. Now the next question is how one should control and treat such cases.**

(CHEST 2009; 136:420–425)

World Report

January 2012 CID

India reports cases of totally drug-resistant tuberculosis

Mismanagement of tuberculosis in Mumbai has led to the emergence of India's first known cases of a totally drug-resistant form of the disease, say doctors. Samuel Loewenberg reports.

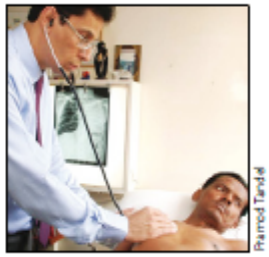
Researchers in Mumbai have identified 12 patients with a virulent strain of tuberculosis that seems to be resistant to all known treatments. The cases of so-called totally drug-resistant tuberculosis (TDR-TB) have been detected in the city in the past 3 months. Worldwide, the only other episodes of TDR-TB reported were in Iran in 2009 and Italy in 2007.

"Basically, it is a failure of public health, and that has to be accepted in this country", said Zarir F Udwadia, who has been treating the patients at the P D Hinduja National Hospital and Medical Research Centre, and who,

than 12 million people, is beset by poverty, overcrowding, and harsh living conditions.

Udwadia says that although the DOTS (Directly Observed Therapy, Short Course) programme has generally been successful for people with normal tuberculosis who do access it, for those with drug-resistant tuberculosis, it causes more than 8 months of delay as people are forced to go through standard treatments before they are diagnosed. All the time, they are generating further resistance.

Research in Mumbai. There is "poor infection control at most of these settings", said Mistry, and people with resistant tuberculosis could well be infecting patients with a regular tuberculosis infection. A 5-year study done by the Foundation with the Wellcome Trust found that most patients were resistant to two or three of the first-line drugs, and some to all four. The city could have as many as 3500 cases of multidrug-resistant tuberculosis (MDR-TB) each year, but lacks the laboratory infrastructure in the public system to identify and confirm



Parrod Tandel

Zarir Udwadia examines one of the patients with TDR-TB

For the ***CID* letter** see *Nature* 2012; DOI:10.1093/cid/cir889

For more on the **stigma of tuberculosis** see **Newsdesk** *Lancet Infectious Diseases* 2011; **11:** 663

Challenges and Controversies in Defining Totally Drug-Resistant Tuberculosis

Peter Cegielski ✉ (/eid/article/18/11/12-0256_article.htm#comment) , **Paul Nunn, Ekaterina V. Kurbatova, Karin Weyer, Tracy L. Dalton, Douglas F. Wares, Michael F. Iademarco, Kenneth G. Castro, and Mario Raviglione**

Author affiliations: Author affiliations: Centers for Disease Control and Prevention, Atlanta, Georgia, USA (P. Cegielski, E.V. Kurbatova, T.L. Dalton, M.F. Iademarco, K.G. Castro); World Health Organization, Geneva, Switzerland (P. Nunn, K. Weyer, D.F. Wares, M. Raviglione)

Suggested citation for this article (#suggestedcitation)

- Proposed definitions are ambiguous. No evidence that proposed totally resistant TB differs from XDR TB.
- Susceptibility tests for several drugs are poorly reproducible. Few laboratories can test all drugs.
- No consensus list of all anti-TB drugs. Many drugs are used off-label. New drugs would render the proposed category obsolete.

- Labeling TB strains as totally drug resistant might lead providers to
- think infected patients are untreatable.

Susceptibility Studies

First Line

- Resistant
  - INH
  - Rifampin
  - Rifabutin
  - PZA
  - Ethambutol
  - Streptomycin

Second Line

- Resistant
  - Amikacin
  - Kanamycin
  - Capreomycin
  - Ethionamide
  - Ofloxacin
  - PAS

XDR TB in 2014

Susceptibility Studies

- Susceptible
  - Linezolid < 0.4
  - Cycloserine
  - Clofazimine < 0.06 mcg/ml
  - Moxifloxacin = 1.0 mcg/ml
    - Usually has MIC < 0.5
    - MIC of 1.0 is the Clinical Cutpoint and likely that high dose moxifloxacin will be effective

4 drugs
Moxi ?

…and now **BDQ, Delamanid, Pretomanid Meropenems**

New Drugs Likely To Change The Designation of MDR/XDR TB

Linezolid

Bedaquiline

Delamanid

Pretomanid

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How Can We Do Better?

Management Strategies Must be Individualized by Patient and Drug Susceptibility

Early Recognition of Which Patients are at Risk of MDR/XDR TB

- Those who were:
  - Born/reside in a country with high incidence of drug resistant TB
  - Exposed to a patient with relapse or failure

- Those with a history of
  - Prior treatment for TB
  - Treatment failure
  - Clinical deterioration during 4 drug therapy

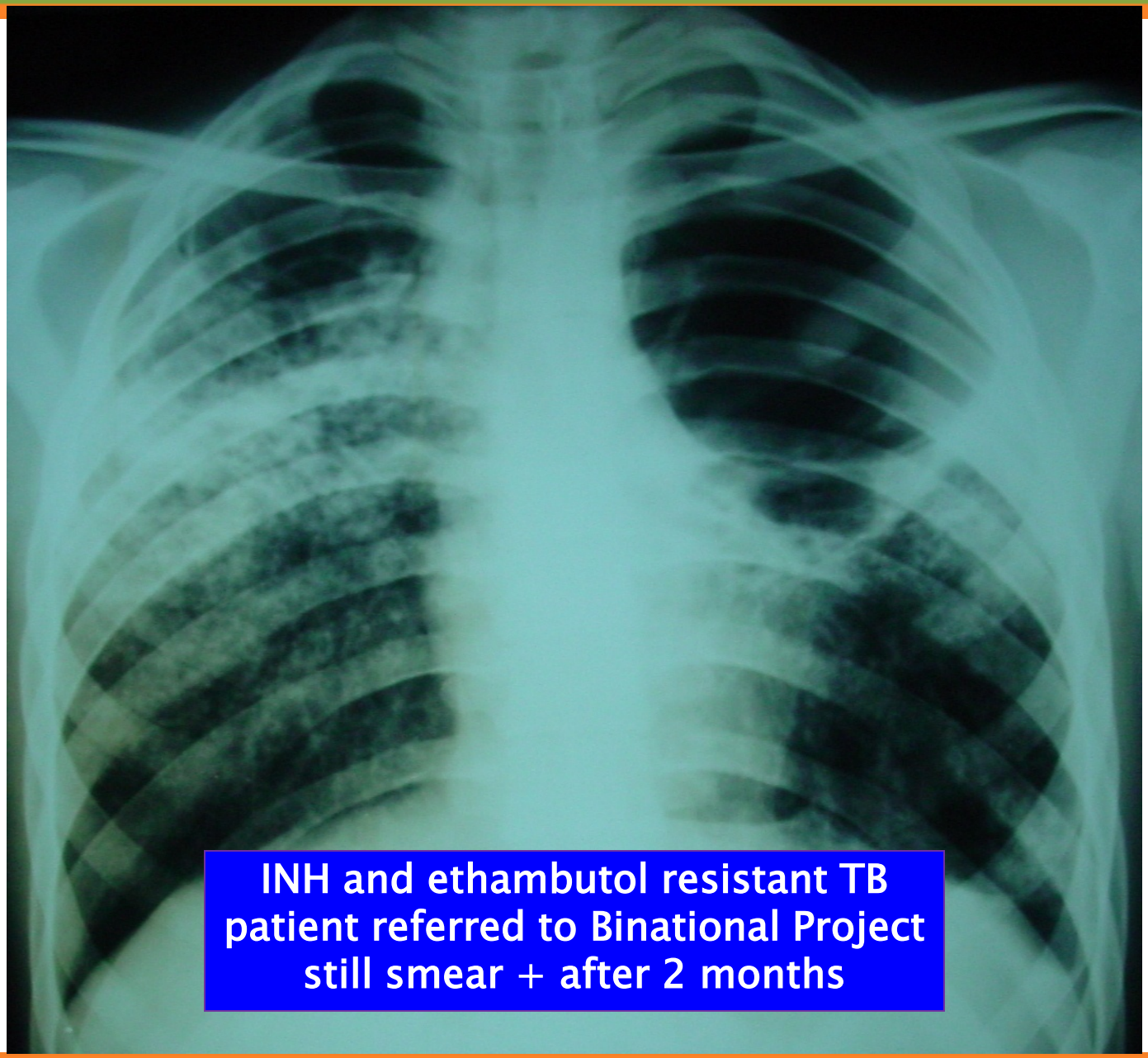
Bad Bugs – Primary XDR TB

- 56 yr. old male, born in U.S. - no history of TB
- TST positive, abnormal CXR,
- Cough, fever, sweats, weight loss
- Culture + M TB **Resistant to:**
  - INH,
  - Rifampin, Rifabutin
  - PZA
  - Ethambutol
  - Streptomycin, Capreomycin, Amikacin
  - Levofloxacin
  - Ethionamide

Acquired XDR TB

Contact to father who died with XDR TB in 1994

- Father's culture resistant to:
  - INH,
  - Rifampin, Rifabutin
  - PZA
  - Ethambutol
  - Streptomycin, Capreomycin, Amikacin
  - Ofloxacin
  - Ethionamide
- Father was drug susceptible at first diagnosis!


INH and ethambutol resistant TB
patient referred to Binational Project
still smear + after 2 months

INH and Ethambutol Resistant TB

- Initial culture resistant to: INH, ethambutol
- At 10 weeks of therapy patient remains ill and AFB +
  - Providers ask to add moxifloxacin
- **Best approach?**
  - Always plan treatment so that further resistance does not occur
  - Stop therapy if possible
  - **Know what the current resistance pattern is now**
    - that means new specimen and molecular testing

Never Treat Active TB With A Single Drug!

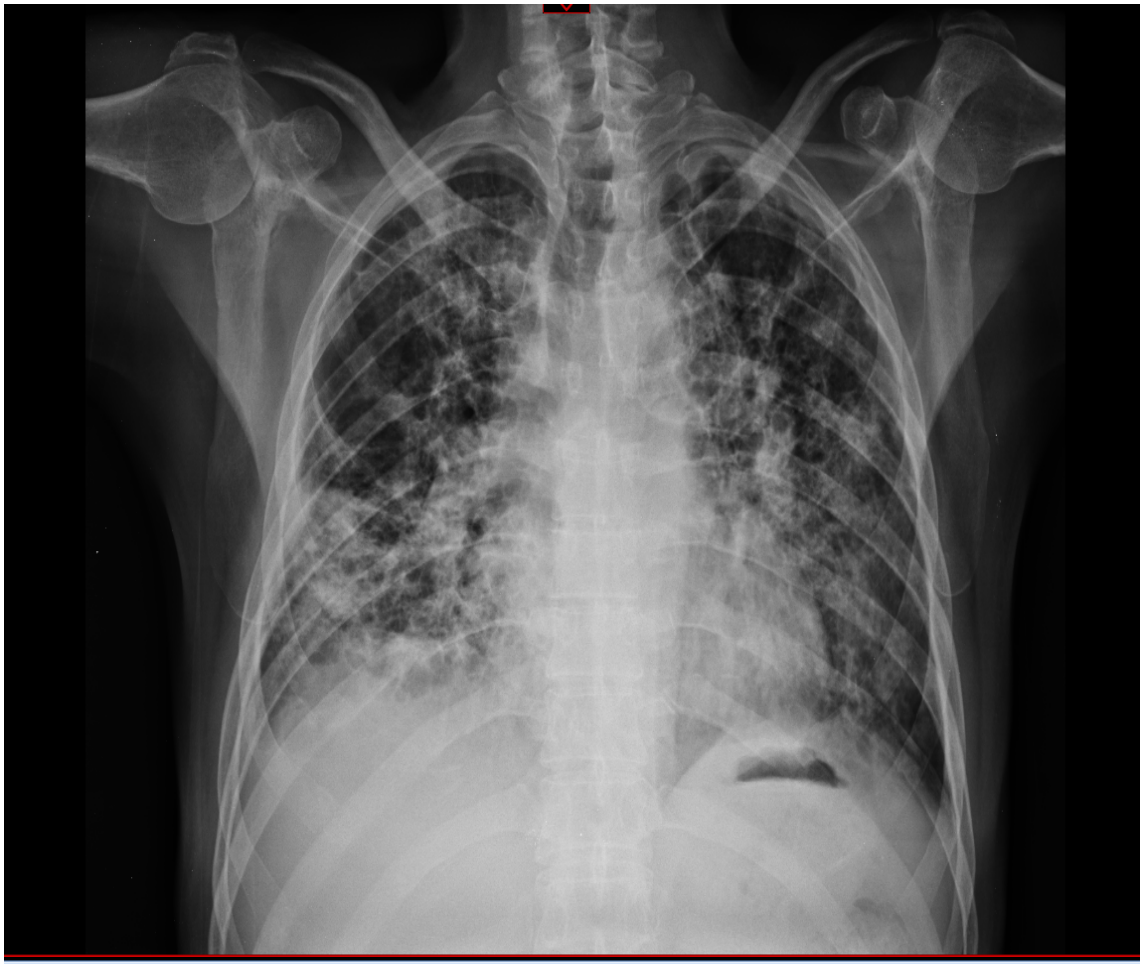
Never Add a Single Drug to a Failing Treatment Regimen!

Always Use At Least 2 Drugs To Which The TB Is Susceptible.

PZA only works on slowly growing M TB; it should not be counted as a 2nd drug to protect Rifampin

Baseline Resistance to INH, ethambutol, and all injectables

Patient started on standard 4 drug treatment



INH and Ethambutol Resistant TB

- Initial culture resistant to:

Streptomycin, kanamycin, amikacin, and capreomycin plus INH and ethambutol

- At 10 weeks of therapy patient is still quite sick cough, poor appetite, no energy and positive smears

- After two months of RIPE treatment, - 2nd culture – pre XDR TB
  - new Rifampin resistance
  - Resistance to INH, ethambutol
  - Streptomycin, kanamycin, amikacin, and capreomycin

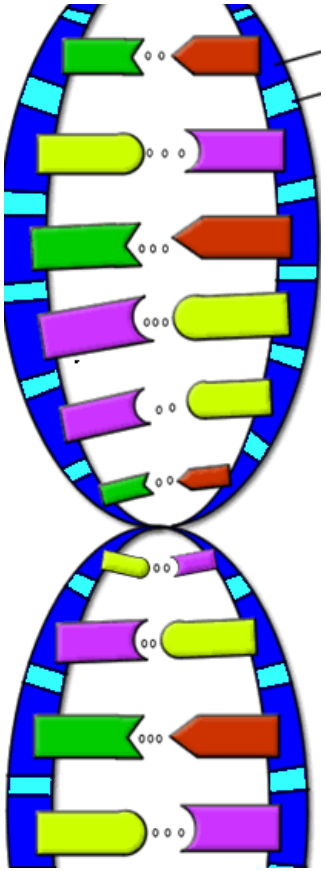
How Does Detection of Genetic Mutations Causing Resistance Fit Into Management of a New TB Case?

2011 WHO Guidelines

Rapid drug susceptibility testing of INH and Rifampin or Rifampin alone is recommended

- On all **before** treatment - most cost-effective strategy to avert deaths and prevent additional resistance
- For both INH and Rifampin if MDR –TB prevalence is > 1% and INH resistance is > 2% (U.S. qualifies!)
- Should provide a diagnosis within two days of testing
- Only molecular tests meet this criterion

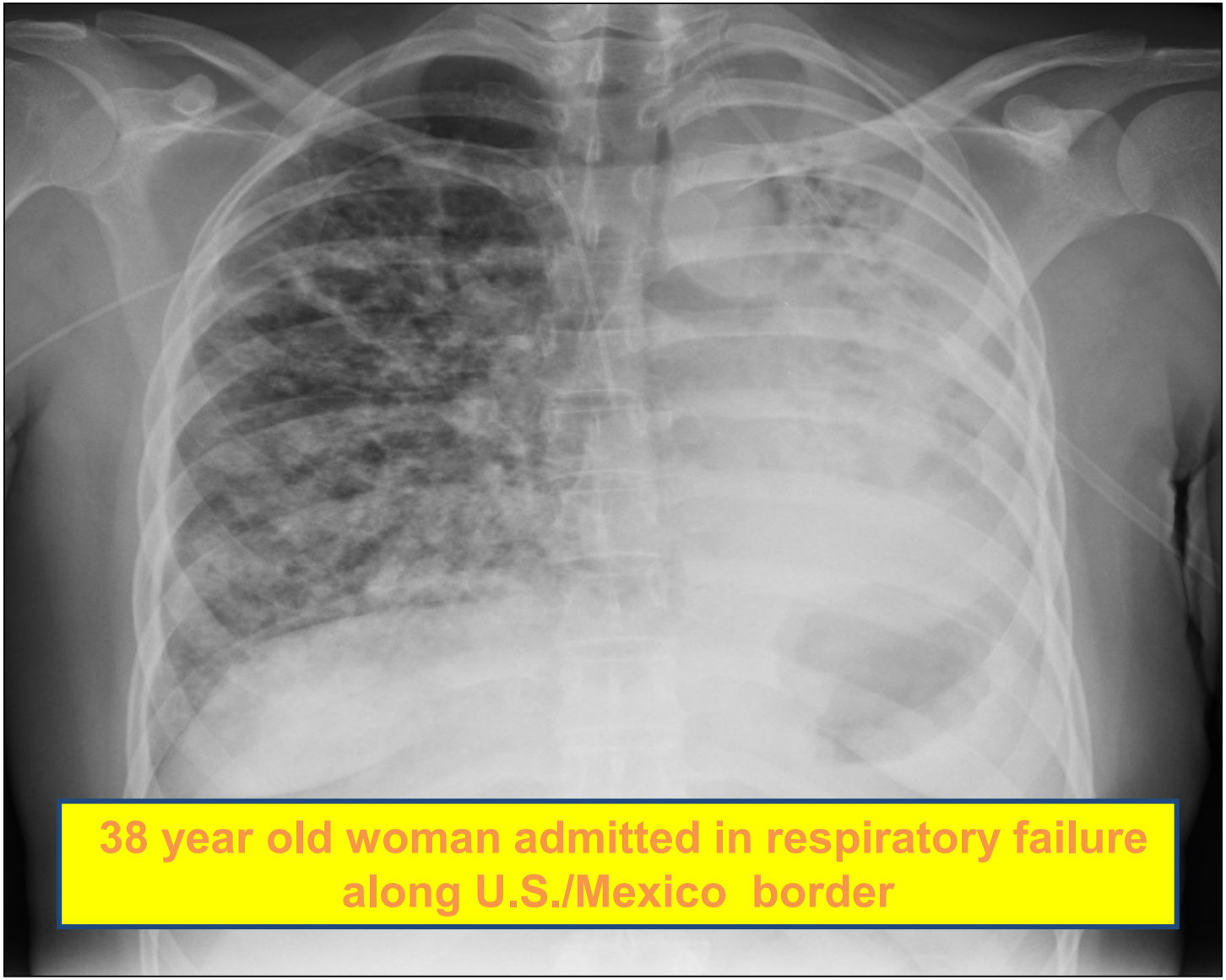
CDC - Molecular Detection of Drug Resistance (MDDR) Testing (Sanger sequencing)



Drug	Gene	Sensitivity (%)	Specificity (%)
Rifampin	*rpoB*	96.1	97
INH	*inhA* + *katG*	88.6	98.7
FQ	*gyrA*	82.2	97
Kanamycin	*rrs* + *eis*	86.8	96.9
Amikacin	*rrs*	87.9	99
Capreomycin	*rrs* + *tlyA*	44.6	85.9

When Should an Empiric Treatment Regimen for MDR TB Be Started?

- If patient is stable and no high risk contacts in the home, it is best to wait until molecular tests suggest a viable regimen.
- If patient is unstable, start treatment.
- Most experts would often start with an aggressive regimen using molecular testing to guide choices


38 year old woman admitted in respiratory failure
along U.S./Mexico border

10/09/2012 12:45 FAX 4046395491 CDC-TB-LAB 002/002

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (NCHHSTP)
Division of Tuberculosis Elimination (DTBE) Laboratory Branch
Reference Laboratory

Report Status: Interim

rpoB mutation – GAC>GTC; Asp516Val

Mutation predicts Rifampin resistance but Rifabutin susceptibility

Austin, TX 78714-9347 ph:512-776-7580

PO Box 149347, Austin, TX 78714-9347
Ken Jost/Lab

CDC Specimen ID: 2013200993
Specimen: Processed sputum
Medium: N/A

Date Collected: 09/30/2012
Date Received: 10/05/2012
Date Reported: 10/09/2012

Patient: [redacted] *Submitter Specimen Identifiers:* UN2012015

Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel); Conventional Drug Susceptibility Test in progress.

Locus (region) examined*	Result	Interpretation (based on in-house evaluation of 550 clinical isolates)
rpoB (RRDR)	Mutation: GAC>GTC; Asp516Val	Rifampin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are RMP-R.)
inhA (promoter)	No mutation	Cannot rule out INH resistance. (86% of INH-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at one or both of these loci.)
katG (ser315 codon)	No mutation	
embB (Met306,Gly406)	No mutation	Cannot rule out ethambutol resistance. (79% of EMB-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)
pncA (promoter, coding region)	Silent mutation: CTG>TTG; Leu172Leu	Cannot rule out PZA resistance. (86% of PZA-R isolates in our in-house evaluation of 550 clinical isolates have a mutation other than the one detected at this locus.) The Leu172Leu mutation is a synonymous (silent) single-nucleotide polymorphism (SNP) and does not result in an amino acid change and is not considered clinically significant.
gyrA (QRDR)	No mutation	Cannot rule out fluoroquinolone resistance. (80% of FQ-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)
rrs (1400 region)	No mutation	Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, amikacin). (In our in-house evaluation of 550 clinical isolates: • 91% of AMK-R isolates have a mutation in the rrs locus; • 87% of KAN-R isolates have a mutation in either the rrs locus or the eis locus; • 55% of CAP-R isolates have a mutation in either the rrs locus or the tlyA locus.)
eis (promoter)	Unable to interpret data; No result	
tlyA (entire ORF)	Unable to interpret data; No result	

*A negative results (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.

MDDR assays were developed and the performance characteristics determined by the DTBE Reference Laboratory. They have not been cleared or approved by the Food and Drug Administration.

Reviewed by: Beverly Metchock

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Address: 1600 Clifton Road, MS FO8, Atlanta, GA 30333

“Low level” Resistance to Rifampin

- Some rpoB mutations can cause low-level resistance to rifampin* These are called “disputed mutations” by some.

- Strains with these mutations often test as susceptible in MGIT broth (test concentration is 1ug/ml) but may be resistant on agar

*Williamson, DA, et al. 2012. IJTLD 16(2):216

"Low Level" Resistance to Rifampin

Do MICs from 0.25-0.5 lead to treatment failure?

- Williamson article* cites 3 treatment failure cases
  - Retrospective study of INH resistant patients (49 cases)
    - 3/3 with rpoB mutation failed
    - 2/49 without rpoB mutation failed

- Van Deun looked at difficult isolates in CDC performance tests
  - Those with rpoB mutations failed in 6 of 14 instances and relapsed after initial cure in 5/14. Clinical information not available in 2, one cure.

- Increased rifampin exposure (20mg/kg/day) will likely overcome some low level resistance

*Williamson, DA, et al. 2012. IJTLD 16(2):216

**Van Deun et al. 2009. J.Clin. Microb. 47(11): 3501

***

Molecular Detection of Drug Resistance Shows XDR TB

Results for Molecular Detection of Drug Resistance; Conventional Drug Susceptibility Test in progress.

rpoB (RRDR)	Mutation: TCG>TTG; Ser531Leu	Rifampin resistant. (100% of isolates in our in-house evaluation of 254 clinical isolates with this mutation are RMP-R.)
inhA (promoter)	No mutation	Isoniazid resistant. (100% of isolates in our in-house evaluation of 254 clinical isolates with this mutation are INH-R.)
katG (ser315 codon)	Mutation: AGC>ACC; Ser315Thr	
embB (Met306,Gly406)	Mutation: ATG>GTG; Met306Val	Probably ethambutol resistant. (93% of isolates in our in-house evaluation of 254 clinical isolates with this mutation are EMB-R.)
pncA (promoter, coding region)	Mutation: CAC>CCC; His57Pro Silent Mutation: TCC>TCT; Ser65Ser	Cannot rule out PZA resistance. The significance of the His57Pro mutation regarding predicting resistance to PZA is unknown. The Ser65Ser mutation is a synonymous (silent) single-nucleotide polymorphism (SNP) and does not result in an amino acid change and is not considered clinically significant.
gyrA (QRDR)	Mutation: GCG>GTG; Ala90Val	Probably ofloxacin resistant. (96% of isolates in our in-house evaluation of 254 clinical isolates with this mutation are ofloxacin-R.)
rrs (1400 region)	Mutation: A1401G	Amikacin resistant and Kanamycin resistant. (100% of isolates in our in-house evaluation of 254 clinical isolates with this mutation are AMK-R and KAN-R.) Possibly Capreomycin resistant. (In our studies, 45% of isolates with this mutation are capreomycin resistant; other investigators have found this percentage to be higher.)
eis (promoter)	No mutation	
tlyA (entire ORF)	No mutation	

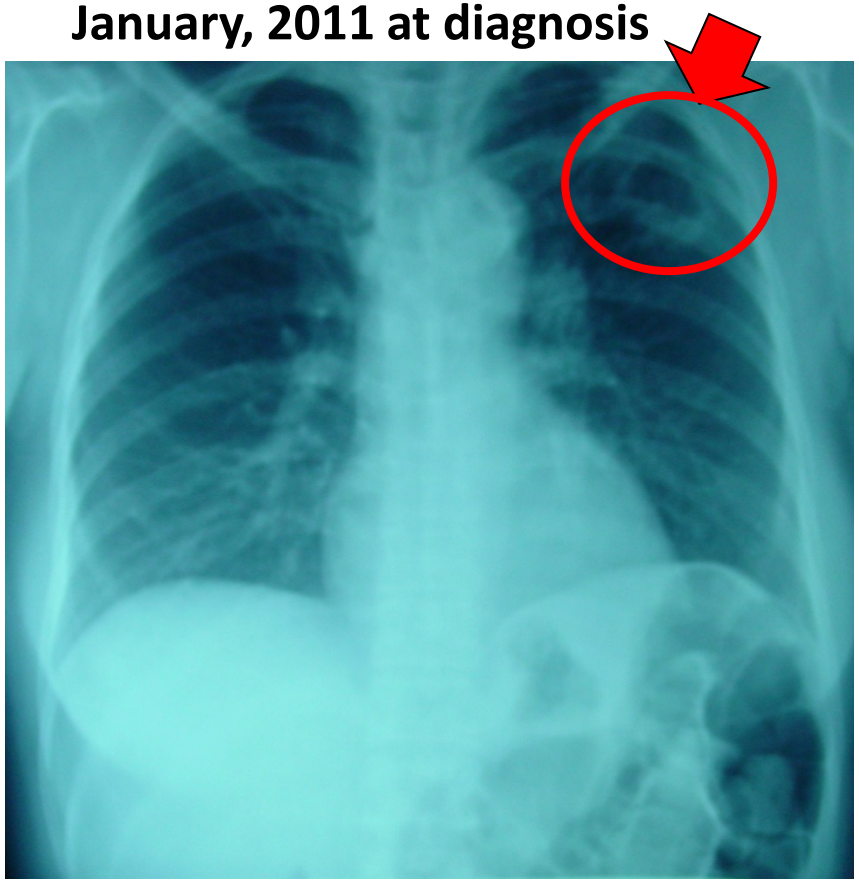
- 24 yr immigrant-prior TB therapy
- PZA resistance detected
  - suspected INH, rifampin, EMB
- 3 days later MDDR notes XDR
  - Ofloxacin resistant **Ala90Val**
  - Moxifloxacin ?
  - Resistant to all injectable drugs
- Case about to start graduate school at time of diagnosis
  - Hospitalized in isolation

When Can DNA Sequencing Help Better Characterize Susceptibility of an Isolate?

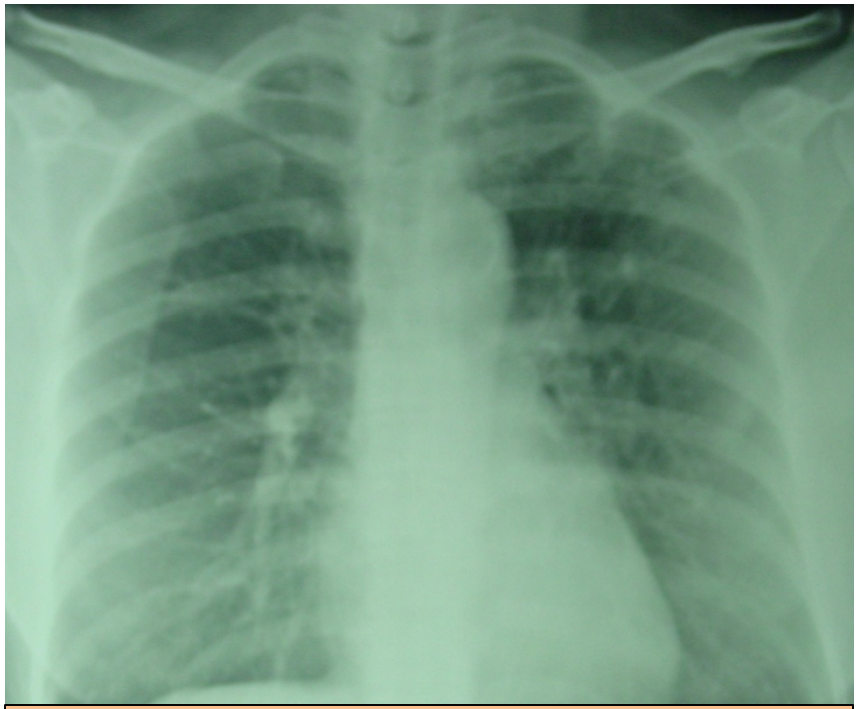
- Resistance to rifampin (*rpoB*)
  - Low level rifampin resistance may be missed (treatment failure)
  - Rifabutin susceptible strains may be missed
- May help predict susceptibility or resistance to moxifloxacin in cases of ofloxacin resistance
- PZA results on MGIT may give **false resistance**
  - repeat susceptibility test and request molecular test (*pncA*)
- Confirm EMB susceptibility for INH-Resistant cultures
  - MGIT may give **falsely susceptible ethambutol** results

MDR TB Reported After 2 Months of Treatment with INH, Rifampin, Ethambutol, and PZA

January, 2011 at diagnosis



March 29, 2011 after 2 mo RX



Smear negative – but culture quickly becomes positive

F/U of MDR TB 4 Years After Standardized First Line Therapy

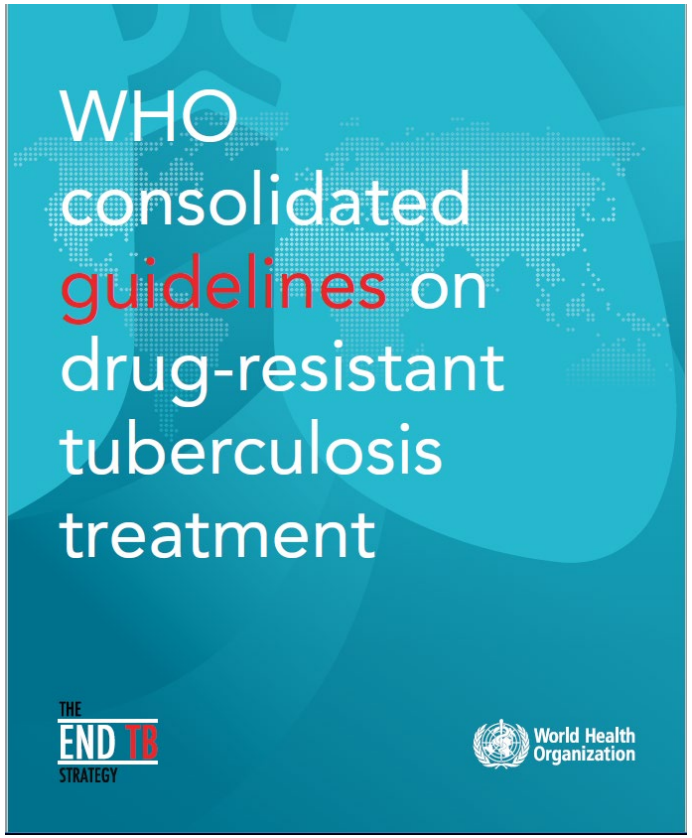
- New and retreatment MDR TB cases managed by standard treatment – all treated 3 x/week
  - RIPE x 2, Rif/INH x 4 : for new cases 83% cure
  - RIPES x 2, Rif/INH/EMB x 6 : for retreatment 66% cure

- 4 years later:
  - Recurrence: 61%
  - Death due to TB: 36%

- Treatment with FLD is highly ineffective in curing MDR – TB even if the reported cure rate is high initially
  - Patients were evaluated for cure with sputum smears only

He GX et al, PloS ONE, May 2010

WHO Guidelines 2019



ATS/CDC/ERS/IDSA
….pending release late 2019

- Waiting….
- Formed in close cooperation with WHO
  - Expected to align with most recommendations

Evidence-base supporting the guidelines:

The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB treatment

Articles

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Holtz, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Mase, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies

N. Ahmad, et al., Lancet, 2018

Articles

Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

Federica Fregonese, Shama D Ahuja, Onno W Akkerman, Denise Arakaki-Sanchez, Irene Ayakaka, Parvaneh Baghaei, Didi Bang, Mayara Bastos, Andrea Benedetti, Maryline Bonnet, Adithya Cattamanchi, Peter Cegielski, Jung-Yien Chien, Helen Cox, Martin Dedicoat, Connie Erkens, Patricio Escalante, Dennis Falzon, Anthony J Garcia-Prats, Medea Gegia, Stephen H Gillespie, Judith R Glynn, Stefan Goldberg, David Griffith, Karen R Jacobson, James C Johnston, Edward C Jones-López, Awal Khan, Won-Jung Koh, Afranio Kritski, Zhi Yi Lan, Jae Ho Lee, Pei Zhi Li, Ethel L Maciel, Rafael Mello Galliez, Corinne S C Merle, Melinda Munang, Gopalan Narendran, Viet Nhung Nguyen, Andrew Nunn, Akihiro Ohkado, Jong Sun Park, Patrick P J Phillips, Chinnaiyan Ponnuraja, Randall Reves, Kamila Romanowski, Kwonjune Seung, H Simon Schaaf, Alena Skrahina, Dick van Soolingen, Payam Tabarsi, Anete Trajman, Lisa Trieu, Velayutham V Banurekha, Piret Viiklepp, Jann-Yuan Wang, Takashi Yoshiyama, Dick Menzies

F. Fregonese, et al., Lancet Resp, 2018

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Holtz, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Mase, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies

Summary

Background Treatment outcomes for multidrug-resistant tuberculosis remain poor. We aimed to estimate the

Lancet 2018; 392: 821–34

Compared with failure or relapse, **treatment success** was positively associated with the use of: **linezolid, levofloxacin, carbapenems, moxifloxacin, bedaquiline, and clofazimine.**

There was a significant association between **reduced mortality** and use of: **linezolid, levofloxacin, moxifloxacin or bedaquiline.**

Compared with regimens without any injectable drug, amikacin provided modest benefits, but kanamycin and capreomycin were associated with worse outcomes.

Association of PZA use with Success and Death

Use vs No Use	N pairs	aOR (95% CI)	aRD (95% CI)
PZA vs No PZA - Strains susceptible to PZA			
Success	1818	**0.7 (0.5, 0.9)**	**-0.03 (-0.04, -0.01)**
Death	1986	**0.7 (0.6, 0.8)**	**-0.03 (-0.05, -0.01)**
PZA vs No PZA - Strain			
Success			
Death			

For success (success vs failure/relapse)
Better outcome : aOR > 1, aRD > 0 (increase success)
The higher, the better

For death (death vs success/failure/relapse)
Better outcome : aOR < 1, aRD < 0 (decrease death)
The lower, the better

Bold green: significantly better
Bold red: significantly worse

Association of FQ use with Success and Death

	N pairs	aOR (95% CI)	aRD (95% CI)
Ofloxacin (susceptible) vs No FQ			
Success	1865	1.0 (0.8, 1.2)	-0.01 (-0.04, 0.01)
Death	2285	**0.6 (0.5, 0.7)**	**-0.08 (-0.11, -0.06)**
Levofloxacin (susceptible) vs No FQ			
Success	1450	**4.2 (3.3, 5.4)**	**0.15 (0.13, 0.18)**
Death	1632	**0.6 (0.5, 0.7)**	**-0.06 (-0.09, -0.04)**
Moxifloxacin (susceptible) vs No FQ			
Success	1031	**3.8 (2.8, 5.2)**	**0.11 (0.08, 0.14)**
Death	1145	**0.5 (0.4, 0.6)**	**-0.07 (-0.10, -0.04)**
Lfx/Mfx vs Ofx (resistant to Ofx but not tested or Sens to Lfx/Mfx)			
Success	715	**1.7 (1.3, 2.2)**	**0.08 (0.04, 0.13)**
Death	927	0.9 (0.8, 1.2)	0.02 (-0.01, 0.06)

Injectable Drug Summary

- **If sensitive:** Overall effect of injectables – modest benefit
  - Amikacin appears to be the best
  - Streptomycin may still be useful (if sensitive)
  - Capreomycin and kanamycin appears to have no benefit

- **If resistant:** Use of all injectable drugs associated with worse outcomes or no benefit
- Capreomycin has no benefit in XDR treatment, even for susceptible isolates

Association of Injectable use with Success and Death

	N pairs	aOR (95% CI)	aRD (95% CI)
Streptomycin (susceptible) vs No injectable			
Success	1017	**1.5 (1.1, 2.1)**	0.02 (-0.00, 0.04)
Death	1121	0.8 (0.6, 1.1)	-0.02 (-0.04, 0.01)
Amikacin (susceptible) vs No injectable			
Success	1393	**2.0 (1.5, 2.6)**	**0.06 (0.04, 0.08)**
Death	1644	1.0 (0.8, 1.2)	-0.00 (-0.03, 0.02)
Kanamycin (susceptible) vs No injectable			
Success	2523	**0.5 (0.4, 0.6)**	**-0.07 (-0.08, -0.05)**
Death	2958	1.1 (0.9, 1.2)	0.01 (-0.01, 0.02)
Capreomycin (susceptible) vs No injectable			
Success	938	0.8 (0.6, 1.1)	-0.03 (-0.06, -0.00)
Death	1114	**1.4 (1.1, 1.7)**	**0.04 (0.01, 0.07)**

Association of Bedaquiline use with Success and Death

Bdq vs No Bdq	N pairs	aOR (95% CI)	aRD (95% CI)
All patients			
Success	490	**2.0 (1.4, 2.9)**	**0.10 (0.05, 0.14)**
Death	548	**0.4 (0.3. 0.5)**	**-0.14 (-0.19, -0.10)**
High income countries			
Success	85	3.0 (0.9, 10.1)	0.05 (-0.05, 0.15)
Death	93	0.6 (0.2, 1.9)	-0.03 (-0.11, 0.05)

Usual Bdq dosage: 400 mg/day for 2 weeks, then 200 mg/day three times weekly for 22 weeks; 1 study used prolonged Bdq treatment (>24 weeks)

Use of Bdq associated with more resistance, XDR, but also other newer drugs

Association of Linezolid use with Success and Death

Lzd vs No Lzd	N pairs	aOR (95% CI)	aRD (95% CI)
All patients			
Success	799	**3.4 (2.6, 4.5)**	**0.15 (0.11, 0.18)**
Death	883	**0.3 (0.2, 0.3)**	**-0.20 (-0.23, -0.16)**
600 mg/day patients (80% of all patients)			
Success	529	**3.1 (2.2, 4.3)**	**0.15 (0.11, 0.20)**
Death	578	**0.2 (0.2, 0.3)**	**-0.19 (-0.23, -0.14)**
High income countries			
Success	516	**3.9 (2.6, 5.8)**	**0.12 (0.08, 0.16)**
Death	556	1.3 (0.8, 2.2)	0.01 (-0.01, 0.04)

Usual Lzd dosage: 600 mg/day (80%); 1200 mg/day (10%); 300 mg/day (10%)

Use of LZD associated with more resistance, XDR, but also other newer drugs

Association of Clofazimine use with Success and Death

Cfz vs No Cfz	N pairs	aOR (95% CI)	aRD (95% CI)
All patients			
Success	564	**1.5 (1.1, 2.1)**	**0.06 (0.01, 0.10)**
Death	679	0.8 (0.6, 1.0)	-0.04 (-0.08, 0.00)
High income countries			
Success	212	1.3 (0.7, 2.5)	0.03 (-0.03, 0.09)
Death	233	1.4 (0.7, 2.7)	0.04 (-0.01, 0.09)

Usual Cfz dosage: 100 mg/day

Use of Cfz associated with more resistance, XDR, but also other newer drugs

XDR – New/Repurposed Drugs

	N pairs	aOR (95% CI)	aRD (95% CI)
Lfx/Mfx vs No FQ			
Success	359	1.2 (0.8, 1.6)	0.01 (-0.05, 0.06)
Death	482	**0.6 (0.4, 0.8)**	**-0.07 (-0.12, -0.02)**
Lzd vs No Lzd			
Success	280	**6.6 (4.1, 10.6)**	**0.31 (0.24, 0.38)**
Death	314	**0.2 (0.1, 0.3)**	**-0.29 (-0.36, -0.23)**
Cfz vs No Cfz			
Success	173	1.5 (0.9, 2.6)	0.04 (-0.04, 0.13)
Death	216	**0.4 (0.2, 0.6)**	**-0.18 (-0.27, -0.10)**
Bdq vs No Bdq			
Success	139	**2.5 (1.3, 4.8)**	**0.12 (0.03, 0.21)**
Death	155	**0.5 (0.2, 0.9)**	**-0.09 (-0.17, -0.02)**

Association of Number of Possibly Effective Drugs with Outcome

	N pairs	aOR (95% CI)	aRD (95% CI)
Initial phase - Success vs Fail/Relapse			
0-2 drugs	Reference	1.0 (Reference)	
3	1891	**1.8 (1.5, 2.1)**	**0.08 (0.06, 0.10)**
4	2243	**2.0 (1.8, 2.4)**	**0.09 (0.07, 0.10)**
5	1262	**2.6 (2.1, 3.2)**	**0.12 (0.10, 0.14)**
6+	642	**2.7 (2.0, 3.6)**	**0.14 (0.10, 0.17)**
Initial phase - Death vs Success/Fail/Relapse			
0-2 drugs	Reference	1.0 (Reference)	
3	2223	**0.6 (0.6, 0.7)**	**-0.06 (-0.08, -0.05)**
4	2666	**0.7 (0.6, 0.8)**	**-0.04 (-0.06, -0.03)**
5	1403	**0.4 (0.3, 0.5)**	**-0.14 (-0.16, -0.12)**
6+	708	**0.4 (0.3, 0.5)**	**-0.19 (-0.22, -0.15)**

Possibly effective drug = drug with previously published evidence of effectiveness, and the isolates were confirmed susceptible on DST.

Lzd/Cfz/Bdq were counted as effective if DST results were not available.

Association of Number of Possibly Effective Drugs with Outcome

	N pairs	aOR (95% CI)	aRD (95% CI)
Continuation Phase - Success vs Fail/Relapse			
0-1 drugs	Reference	1.0 (Reference)	
2	1807	1.6 (1.4, 1.9)	0.06 (0.04, 0.08)
3	2177	1.7 (1.5, 2.0)	0.05 (0.03, 0.07)
4	1097	**2.8 (2.2, 3.5)***	**0.13 (0.11, 0.15)***
5+	476	**1.7 (1.3, 2.3)**	**0.13 (0.09, 0.16)***
Continuation phase - Death vs Success/Fail/Relapse			
0-1 drugs	Reference	1.0 (Reference)	
2	2087	0.7 (0.6, 0.8)	-0.04 (-0.06, -0.02)
3	2543	0.8 (0.7, 0.9)	-0.02 (-0.04, -0.00)
4	1211	**0.5 (0.4, 0.6)***	**-0.10 (-0.12, -0.08)***
5+	529	**0.5 (0.4, 0.7)***	**-0.12 (-0.15, -0.08)***

Possibly effective drug = drug with previously published evidence of effectiveness, and the isolates were confirmed susceptible on DST.

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0-1 drugs	Reference	1.0 (Reference)	
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Lzd/Cfz/Bdq were counted as effective if DST results were not available.

Ethambutol & Group 4 drugs

Use of Ethambutol:

- When susceptible – No benefits
- When resistant – Worse outcomes

Use of Ethionamide/Prothionamide or PAS:

- When susceptible – No benefits
- When resistant – Worse outcomes

Use of Cycloserine/Terizidone:

- When susceptible – Beneficial
- When resistant – No benefit

Conclusions

Benefit of each individual drug		
Pyrazinamide	No clear benefit	“Bad”
Capreomycin	No benefit	“Worse”
Later generation FQ	Significant benefit	“Better”
Linezolid	Significant benefit	“Better”
Bedaquiline	Significant benefit	“Better”
Clofazimine	Weak benefit	“Good”

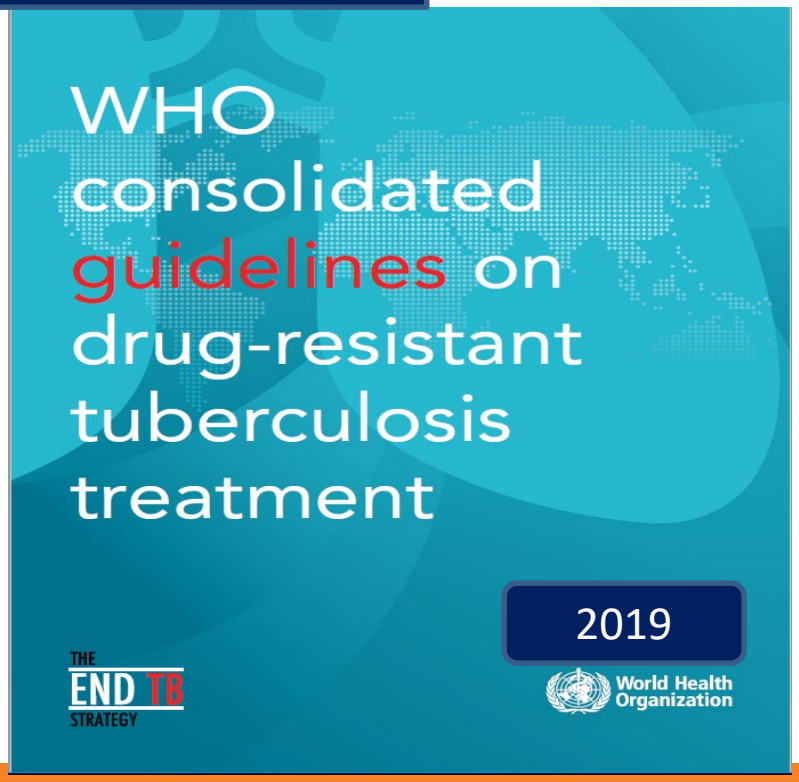
Dr. Tommy Lan McGill NAR 2018

IPD-MA includes:
13,1000 records patients treated with longer MDR Rx – 40 countries
2,600 records from patients treated with 9 – 12 months shorter MDR RX – 15 countries
Recently completed Phase III trials of delamanid
Pk and safety data from BDQ and Delamanid patient < 18 yrs. of age.

Important departure from prior: Injectable agents are no longer among the priority medicines when designing longer MDR-TB regimen

Fully oral regiments preferred option for most patients

Three medicines – FQNs, BDQ and LZD are strongly recommended to use in a longer regimen



Prioritize

Add Next

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Composition of Longer MDR Regimens

- MDR/RR TB
  - All 3 Group A agents and at least one Group B agent should be included to ensure that treatment with at least 3 agents are included for the rest of the treatment after BDQ is stopped.
  - If only one or two Group A agents are used, both Group B agents are to be included
  - If regimen cannot be composed with agents from Groups A and B alone, Group C agents are added

Medications

Group A

- Fluoroquinolones, bedaquiline and linezolid were considered **highly effective and strongly recommended** for inclusion in all regimens unless contra-indicated

Group B

- Clofazimine and cycloserine were conditionally recommended as agents of second choice

Group C Drugs included all other medicines that can be used when a regimen cannot be composed with Group A and B agents. The medications are ranked by the relative balance of benefit to harm usually expected of each.

Prioritize

Add Next

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Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Composition of Longer MDR Regimens

- Ethionamide may be included only if BDQ, linezolid, clofazimine or delamanid are not used or if better options are not possible

- PAS may be included only if BDQ, linezolid, clofazimine or delamanid are not used or if better options are not possible

DOES IT WORK?

New Options Now Available

- Data from drug trials and cohorts show efficacy of newer drugs
- BDQ and Delamanid have significant early bactericidal activity and are sterilizing
  - WHO recommends use of BDQ for treatment of MDR TB 2013
  - WHO recommends use of Delamanid for treatment of MDR TB 2014
  - WHO recommends linezolid and clofazimine as “Core TB Drugs” 2016
  - South African TB Program recommends injectable free MDR regimen for all and provides bedaquiline for all 2018
    - Improved treatment success and decreased mortality
  - WHO recommends injectable free treatment of MDR 2018

health
Department:
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REPUBLIC OF SOUTH AFRICA

2030 NDP

MEDIA STATEMENT

To: Editors & Health Journalists
Issued by: Department of Health
Date: Monday, 18 June 2018

New Bedaquiline data shows reduction in TB mortality cases

Retrospective cohort analysis
All receiving BDQ: 41% Increase in success
Three fold decrease in mortality

Pretoria: The Department of Health has released new data on reduction in TB mortality cases from drug resistant Tuberculosis (DR - TB) in South Africa through use of the latest medicine, called Bedaquiline.

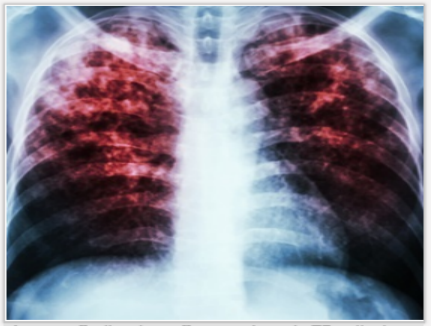
15,000 receiving or have received BDQ

UPDATED 20 JUNE 2018

SA first country to break all barriers to revolutionary TB drug

Cure rates for XDR-TB (extensively drug-resistant TB) patients taking the new drug bedaquiline are as high as 80%.

South Africa made history on Monday when the health department announced that all drug-resistant tuberculosis (DR-TB) patients will be eligible to receive the new medicine, bedaquiline.


A more effective drug offers new hope to TB patients.

"The Department of Health's [DoH] commitment is momentous globally and marks a new era of DR-TB management where we are really prioritising the patient," Doctors Without Borders' Dr Anja Reuter told Health-e News.

Little chance of being cured

Up until recently treating patients with DR-TB has been "difficult, with old medicines used, which had many negative side effects and over long periods – often up to 24 months", noted the DoH in a press statement.

Even if patients take their full course of toxic medicines they have little chance of being cured and risk long-term disability, including permanent deafness.

In 2012, before bedaquiline, fewer than one in five (19%) South African patients with extensively drug-resistant TB (XDR-TB) were cured, according to the DoH's Dr Norbert Ndjeka.

He said new government data showed that, by 2015, after all XDR-TB patients became eligible for the drug, the portion of patients who completed treatment successfully shot up to 51%.

According to this data, cure rates for XDR-TB patients taking bedaquiline are as high as 80% in

Treatment Principles

- Ahead of enrollment on MDR-TB treatment, all patients should receive appropriate counselling to enable informed and participatory decision-making.
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- Patient information material needs to reflect the new changes so that patients are appropriately informed about their treatment options.
- Social support to enable adherence to treatment is very important to ensure a patient-centered approach to the delivery of care.
- The patient's MDR strain should be tested for susceptibility to medicines included or planned to be included to maximize effectiveness
  - **Drugs that are resistant should not be used.**
- Active TB drug safety monitoring and management (aDSM) is essential for all patients enrolled on MDR-TB treatment.

Table 2.3. Serious adverse events (SAEs) in patients on longer MDR-TB regimens*

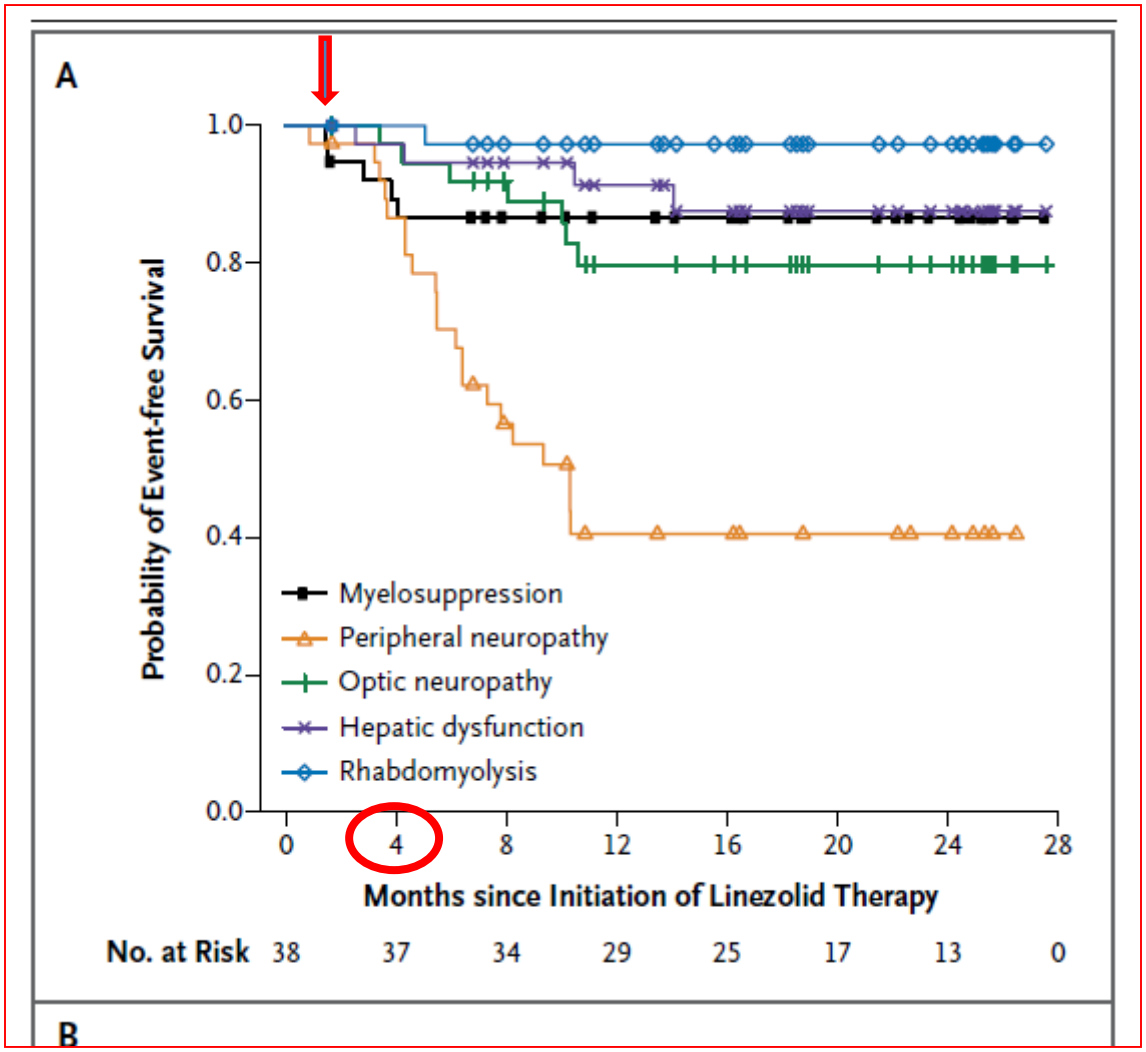
Medicine	Absolute risk of SAE	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine/terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide/prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
p-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

* From an "arm-based network" meta-analysis of a patient subset from the 2016 IPD for which AEs resulting in permanent discontinuation of a TB medicine (27 studies) or classified as Grade 3–5 (3 studies) were reported. There were insufficient records on delamanid, imipenem–cilastatin and meropenem to estimate risks. Agents that are not in Groups A, B or C are italicized.

Monthly Toxicity Monitoring

- Lab: CBC, CMP, (TSH, calcium, Mg for BDQ)
- EKG if on BDQ and > one other QTc lengthening drug
  - (usually on BDQ, clofazimine and a FQN)
- Neuropathy Screen: Linezolid,
- Vision Screen (acuity and Ishihara plates)
  - Linezolid and ethambutol
- Personality changes: cycloserine
- High quality audiogram (to 8000 Hz) if amikacin

Timing of Linezolid Toxicity



Lee NEJM Oct 2012

Three Signals are Clear from Current Scientific Evidence Assessment:

Choice of a MDR-TB regimen

- Treatment options for MDR-TB are increasingly becoming more individualised as a result of innovations in diagnostics and growing scientific understanding of the molecular basis for drug resistance and the pharmacokinetics and pharmacodynamics of TB medicines. Three signals are clear from the current scientific evidence assessment:
  - The feasibility of effective and **fully oral treatment regimens** for most patients;
  - The need to ensure that **drug resistance is excluded** (at least to the fluoroquinolones and injectables) before starting patients on treatment, especially for the shorter MDR-TB regimen;
  - The need for **close monitoring** of patient safety and treatment response and **a low threshold for switching non-responding patients or those experiencing drug intolerance** to alternative medicines and/or new regimens based on the regrouping of agents in Table 1.

- http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf

WHY? Patient Centered Care

- Injectable agents are very uncomfortable and inconvenient
- WHO Ethical Guidance - Patient now decides how much can be “tolerated” rather than provider
  - Treatment should be: “acceptable, accessible, affordable and appropriate”.
- Patients should be provided with information on the risks and benefits of all medications available

Evidence-base supporting the guidelines:

The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB treatment

Articles

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Holtz, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Mase, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies

N. Ahmad, et al., Lancet, 2018

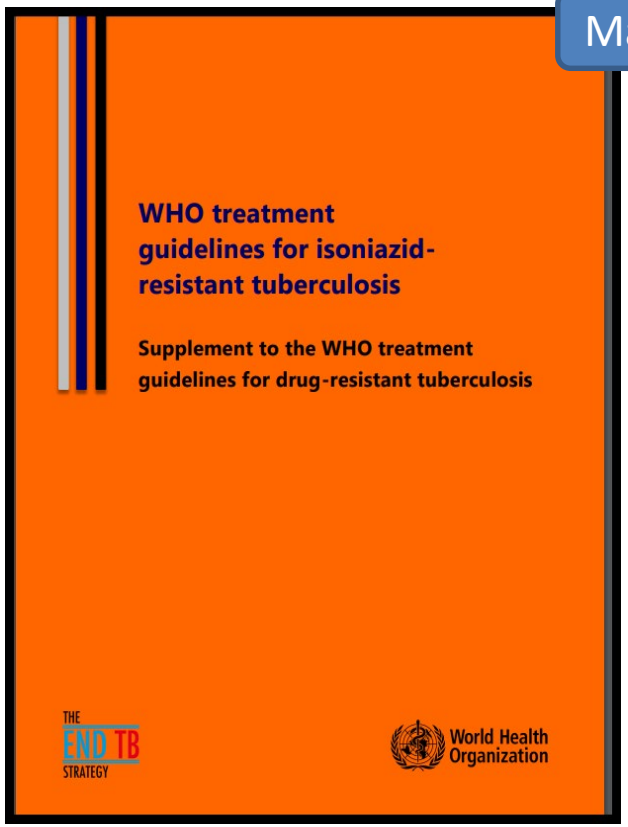
Articles

Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

Federica Fregonese, Shama D Ahuja, Onno W Akkerman, Denise Arakaki-Sanchez, Irene Ayakaka, Parvaneh Baghaei, Didi Bang, Mayara Bastos, Andrea Benedetti, Maryline Bonnet, Adithya Cattamanchi, Peter Cegielski, Jung-Yien Chien, Helen Cox, Martin Dedicoat, Connie Erkens, Patricio Escalante, Dennis Falzon, Anthony J Garcia-Prats, Medea Gegia, Stephen H Gillespie, Judith R Glynn, Stefan Goldberg, David Griffith, Karen R Jacobson, James C Johnston, Edward C Jones-López, Awal Khan, Won-Jung Koh, Afranio Kritski, Zhi Yi Lan, Jae Ho Lee, Pei Zhi Li, Ethel L Maciel, Rafael Mello Galliez, Corinne S C Merle, Melinda Munang, Gopalan Narendran, Viet Nhung Nguyen, Andrew Nunn, Akihiro Ohkado, Jong Sun Park, Patrick P J Phillips, Chinnaiyan Ponnuraja, Randall Reves, Kamila Romanowski, Kwonjune Seung, H Simon Schaaf, Alena Skrahina, Dick van Soolingen, Payam Tabarsi, Anete Trajman, Lisa Trieu, Velayutham V Banurekha, Piret Viiklepp, Jann-Yuan Wang, Takashi Yoshiyama, Dick Menzies

F. Fregonese, et al., Lancet Resp, 2018

March 16, 2018



In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months [Conditional recommendation, very low certainty in the estimates of effects ⊕◯◯◯]

Notes.– The 4-drug "HREZ" fixed-dose combination (FDC) with *isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z)* – may be used (as there is no approved REZ FDC available), to limit the need for using single drugs. Drug susceptibility to fluoroquinolones should preferably be confirmed ahead of start of treatment (*See text below for other important remarks*).

♦♦♦

In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen [Conditional recommendation, very low certainty in the estimates of effects ⊕◯◯◯]

http://www.who.int/tb/publications/2018/WHO_guidelines_isoniazid_resistant_TB/en/

Adding a FQ to ≥6(H)REZ. Success versus failure/relapse

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
≥6(H)REZ **&FQ** *	245/251	**2.8 (1.1; 7.3)**	+5% (0 to +9%)
≥6 (H)REZ	1253/1350	1.0 (reference)	Reference
FQ are only moxifloxacin/levofloxacin/gatifloxacin			
≥6(H)REZ &**FQ**	161/165	2.9 (0.9; 9.3)	+6% (-2% to +14%)
≥6 (H)REZ	1253/1350	1.0 (reference)	Reference

Median duration of FQ: 6 months
Acquired RIF resistance: **Significantly lower if received a FQ -No patient who received a FQ developed MDR**
Findings virtually identical in patients who did not receive any INH

Treatment of INH Resistant TB – WHO

March 2018

- No evidence that INH adds benefit but may use 4-drug RIPE FDC
- Ensure that isolate is rifampin susceptible before adding FQN
- Empirical treatment INH-R TB not generally advised
- Treat to achieve 6 months of FQN (usually added to regimen after a period of RIPE).

Treatment of INH Resistant TB – WHO March 2018

- Addition of FQN to all patients with INH-R TB except those
  - In whom resistance to rifampin cannot be excluded
  - Known or suspected to have resistance to FQN
  - Known to be intolerance to a FQN
  - Known or suspected to have risk for prolonged QTC interval
  - Pregnant or breastfeeding (not an absolute contra-indication)

- In cases when FQN not used give 6 months (I)RPE

The medicine and syringes to treat one MDR-TB patient for one year. Patients need to undergo treatment from 18–24 months

IDSA fact sheet 2013

- **Staggering Medication Burden**

Conference Dates and Location:
February 13–16, 2017 | Seattle, Washington

Abstract Number:
80LB

THE NIX-TB TRIAL OF PRETOMANID, BEDAQUILINE AND LINEZOLID TO TREAT XDR-TB

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Abstract Body:
Patients with Extensively Drug Resistant (XDR) tuberculosis (TB) have had limited options for treatment and high mortality. Nix-TB is an ongoing open label study in South Africa of bedaquiline (400 mg qd for 2 weeks followed by 200 mg tiw), pretomanid (200 mg qd) and linezolid (1200 mg qd) given orally for 6 months.

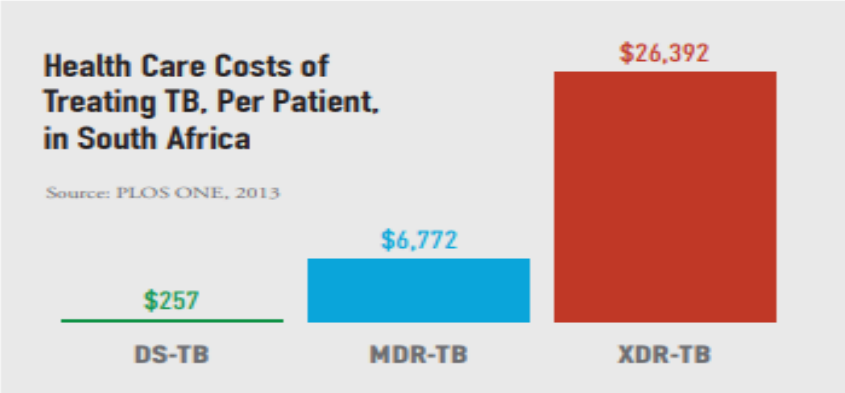
Participants are required to have documented XDR-TB, or MDR TB treatment intolerance or failure (TI or Fr). The primary endpoint is bacteriologic failure, relapse or clinical failure at 6 months after treatment. Participants who are culture positive at 4 mos treatment may extend treatment for 3 mos. Clinical, laboratory and sputum liquid culture evaluations are performed at baseline and wks 1, 2, 4, 6, 8 and then every 4-6 wks through treatment. Eye examinations with slit lamp are made 3 times. Participants who complete treatment are followed for 24 mos after treatment end with repeat clinical assessments and sputum cultures.

Since April 2015, 61 participants have been enrolled as of 15 December 2016 at 2 sites. 49% of the participants are HIV positive, 79% have XDR-TB and 21% have MDR TI or Fr to prior therapy. 34 have completed the 6 months of therapy with the drug regimen and 20 have been followed to the primary endpoint at 6 months after treatment. All surviving patients were culture negative by 4 mos, with 74% negative at 8 wks. 4 participants died within the first 8 wks of therapy; 3 had multi-organ TB on autopsy and 1 had a GI bleed due to erosive esophagitis. 27% had serious adverse events (AE). No surviving participants have withdrawn from the study due to any clinical AE or lab abnormalities. The expected linezolid toxicities of peripheral neuropathy (PN) and myelosuppression (MSPN) were common but manageable. 71%, of participants had at least one linezolid dose interruption (22% of all participants due to MSPN and 28% due to PN), during the 6 mos of treatment. One had peak ALT and AST > 3 X ULN and total bili > 2X ULN, but these improved and treatment restarted without a recurrence. There were 7 cases of grade 3 or 4 transaminitis and all resolved and allowed the study regimen to be continued. There were no cases of optic neuritis. As of 15 December, 2016, there has been 1 microbiological relapse.

Nix-TB:
Testing a New Potential Treatment for XDR-TB

Tuberculosis has evolved faster than our medicines

Extensively drug-resistant tuberculosis, or XDR-TB, is a strain of tuberculosis, airborne and infectious, that is resistant to four commonly used anti-TB drugs. Essentially, there is no cure and XDR-TB is often considerd a death sentence. XDR-TB has been confirmed in more than 100 countries around the world. There are an estimated 40,000 people infected with XDR-TB today—nine percent of all multidrug resistant-TB (MDR-TB) cases—and the problem is growing worse. Without new treatments, XDR-TB is emerging as an extremely deadly and costly global health threat that the world is inadequately equipped to tackle.



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34 completed 6 mo of RX and 20 followed to primary endpoint at 6 mo after RX
49% HIV +; 79% XDR, 21% MDR
All surviving patients culture negative by 4 months, 74% negative at 8 weeks
4 died within first 8 weeks
27% SAEs
None withdrawn due to AE or lab abnormalities
As of 15 December 2016 one microbiological relapse
CROI Feb 2017