

# MDR and XDR Tuberculosis

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# Multidrug-Resistant TB

I have been treated several times over the past five years and I'm still coughing and can't gain weight!



# Background

- Tuberculosis (TB) is a major public health problem in Bangladesh since long. Estimates suggest that daily about **880 new TB cases and 176 TB deaths** occur in the country.
- Nearly one-third of the global population, i.e. **two billion** people, is infected with Mycobacterium tuberculosis and thus at risk of developing the disease. More than **nine million** people develop active TB every year and about **two million** die.

- More than 90% of global TB cases and deaths occur in the developing world, where 75% of cases are in the most economically productive age group (15-54 years). It is estimated that 480,000 people developed MDR TB in 2014. About 190,000 people died as a result of it.

# Global status of TB

- Multidrug-resistant TB (MDR-TB) has emerged in nearly every country of the world.
- Extensively drug-resistant TB (XDR-TB) has been identified in **117** countries and in all geographical regions.
- The total number of new TB cases is still **rising** slowly as the case load continues to grow in the African, Eastern Mediterranean and **South-East Asia** regions.

# The burden of illness

- Usually 1 in 10 infected people are in chance of developing disease
- Greater risk in poor, malnourished or co-morbidities.
- Without treatment, there is more than a 50% chance death in TB.
- The overall goal of TB control is to reduce morbidity, mortality and transmission of TB.

# Drug-Resistant Tuberculosis

MDR-TB is a manmade problem... It is costly, deadly, debilitating and is a major threat to our current control strategies.

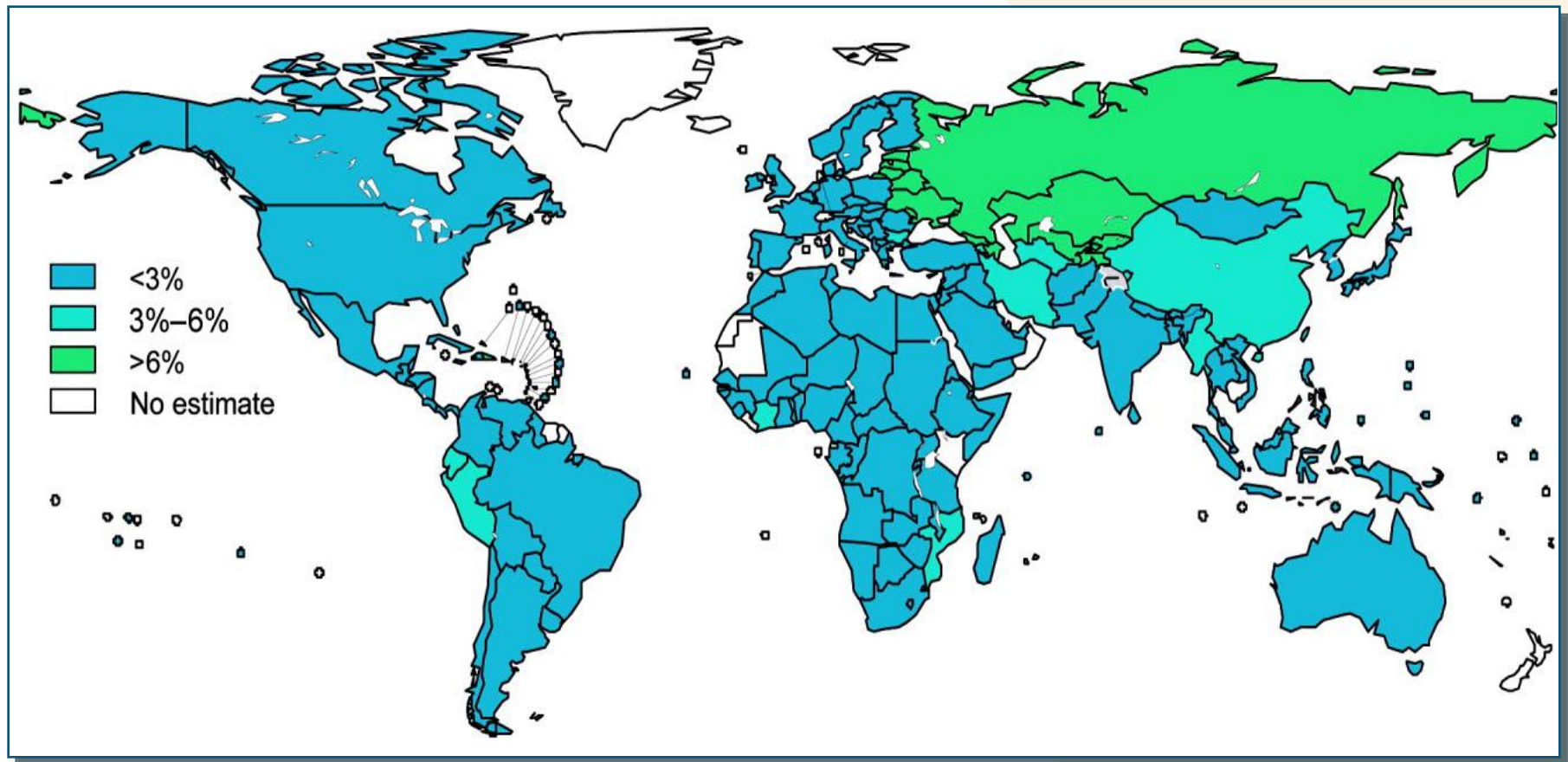


# Drug-Resistant TB: Definitions

- **Multidrug-resistant (MDR):**  
In-vitro resistance to at least isoniazid and rifampicin
- **Extensively drug-resistant (XDR):**  
MDR plus resistance to fluoroquinolones and at least 1 of the 3 second-line injectable drugs (amikacin, kanamycin, capreomycin)

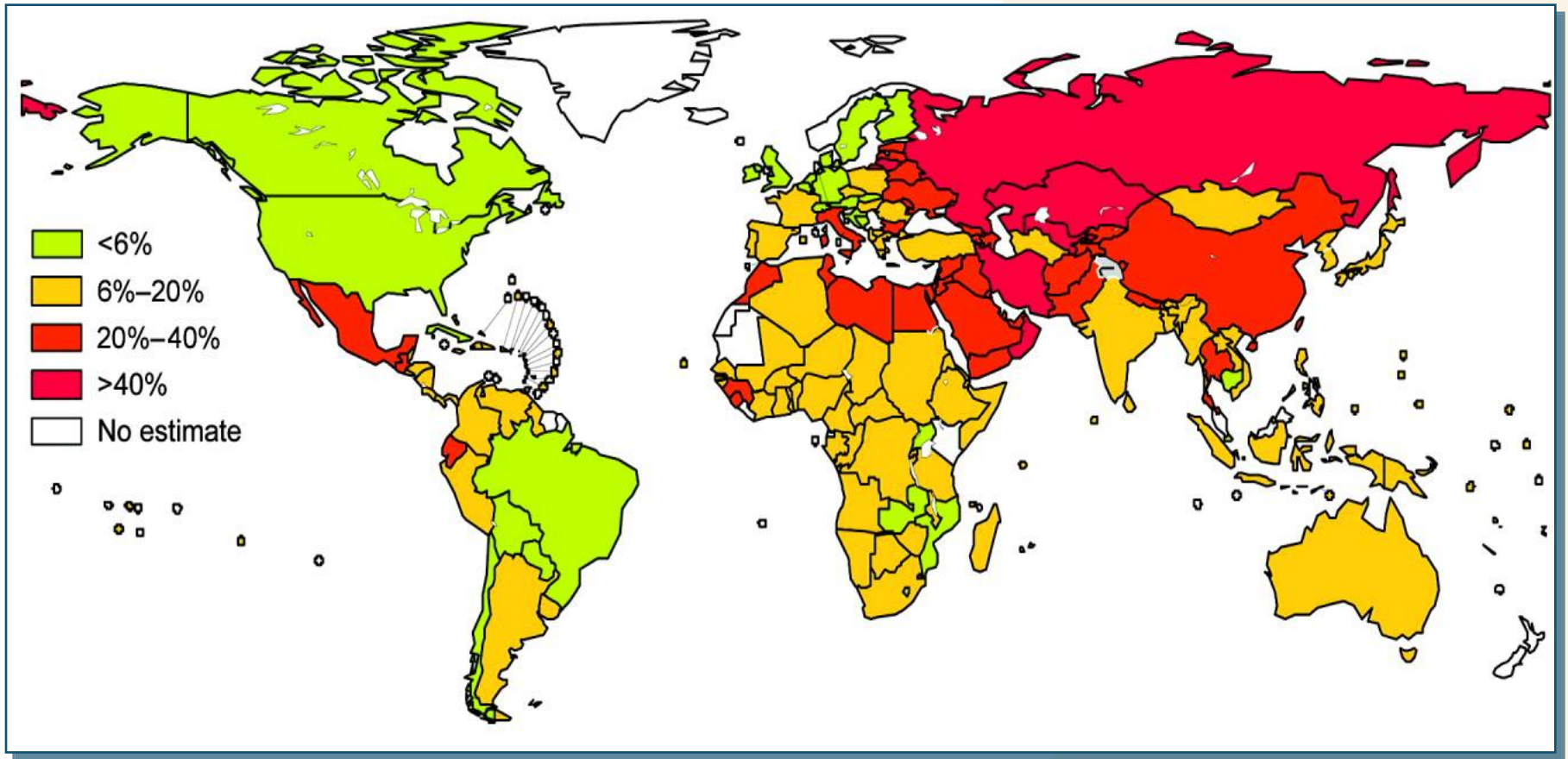


# Distribution of MDR: No Prior Treatment



Distribution of MDR rates among new cases (previously untreated)

# Distribution of MDR: Prior Treatment



Distribution of MDR rates among previously treated cases

# Countries that had reported at least one XDR-TB case by September 2009



Argentina	Burkina Faso	Georgia	Kenya	Nepal	Qatar	Swaziland
Armenia	Canada	Germany	Latvia	Netherlands	Republic of Korea	Sweden
Australia	China	India	Lesotho	Norway	Republic of Moldova	Thailand
Azerbaijan	Colombia	Iran (Islamic Rep. of)	Lithuania	Oman	Romania	Ukraine
Bangladesh	Czech Republic	Ireland	Mexico	Peru	Russian Federation	United Arab Emirates
Belgium	Ecuador	Israel	Mozambique	Philippines	Slovenia	United Kingdom
Botswana	Estonia	Italy	Myanmar	Poland	South Africa	United States of America
Brazil	France	Japan	Namibia	Portugal	Spain	Uzbekistan
						Viet Nam



# Individual Impact of MDR

- Average direct medical costs per case in the US: \$27,752 [Burgos, et al. *CID* 2005; 40: 968-75]
- In BD it is about **15-20 lakh**.
- Long treatment duration (**18-24 months**), often difficult and toxic
- Long periods of isolation may be necessary
- Depression is common
- Disease may be incurable (chronic)
- Higher rate of death

# Factors that Lead to Drug Resistance

## **Causes of inadequate treatment:**

- Patient-related factors
- Healthcare provider-related factors
- Healthcare system-related factors

# Strategies to Prevent MDR

Common Causes	Interventions
<b>Nonadherence, default</b>	Patient-centered DOT, education, support, incentives
<b>Management errors, lack of expertise</b>	Consultation with experts, vigilant patient monitoring for treatment failure, provider training
<b>Inadequate regimen in presence of drug resistance</b>	Improved access to drugs and susceptibility testing

# Diagnosis of MDR-TB



# Diagnosis of MDR-TB

**Appropriate diagnosis and timely treatment intervention for MDR-TB is facilitated by:**

- Recognition of risk factors for MDR-TB
- Early recognition of treatment failure
- Drug-susceptibility testing (DST)



# Clinical Suspicion for MDR-TB

## **Recognition of risk factors:**

- History of prior therapy (most powerful predictor)
- History of non-adherence, default
- Residence in an MDR-endemic area
- Exposure to known or suspected MDR-TB case (“incurable” TB or TB requiring multiple treatment courses)
- HIV infection (in some settings)

# Clinical Suspicion for MDR-TB (2)

## **Early recognition of treatment failure:**

- Cough should improve within the first two weeks of effective treatment
- **Signs of failure might include:**
  - lack of sputum conversion,
  - persistent or recurrent cough,
  - continued fever and/or night sweats, and
  - failure to gain weight

# Laboratory Diagnosis of MDR

**Drug-susceptibility testing should be prioritized when:**

- Risk factors for MDR are present
- There is evidence of treatment failure

**Results can both:**

- Confirm diagnosis of drug resistance
- Guide treatment choices

# Drug-Susceptibility Test Limitations

- Identification of MDR may take 4–8 weeks, and second-line drug sensitivity testing 6–12 weeks for results
  - 2–4 weeks for initial culture to become positive
  - Additional 2–4+ weeks to get 1st-line susceptibilities
  - Additional 2–4+ weeks (sent to reference laboratory) to get 2nd-line susceptibilities
- ➔ In view of this inherent delay, don't wait to treat with an augmented regimen if MDR suspicion is high and resistance pattern can be predicted

# Treating drug-resistant and MDR-TB



# Standard 12: Management of Drug-Resistant TB

- Patients with MDR/XDR TB organisms should be treated with specialized regimens containing 2<sup>nd</sup> line anti-TB drugs.
- The regimen chosen may be standardized or based on suspected or confirmed DST.
- **At least 4 drugs** to which the organisms are known or presumed to be susceptible, **including an injectable agent**, should be used and treatment should be given for at least **18-24** months beyond culture conversion

# Standard 12: Management of Drug-Resistant TB (2)

- **Patient-centered measures**, including observation of treatment, are required to ensure adherence
- **Consultation** with a provider experienced in treatment of patients with MDR/XDR tuberculosis should be obtained

# Conditions to be consider before treatment

- Malnutrition
- Diabetes mellitus
- Renal insufficiency
- Liver disease
- Thyroid disease
- Mental illness
- Pregnancy
- Seizure
- HIV infection



# Treatment Strategies

## Recommended MDR-TB treatment approaches:

### ■ Standard regimen

- Settings where **DST is not readily available**
- Based on drug-resistance surveillance data or history of drug usage in country

### ■ Individualized treatment regimen

- Based on patient's past history of drug use and on DST results
- Ideal, but resources must be considered

# Anti-tuberculosis Drug Groups

- Group 1 First-line drugs:** isoniazid, rifampicin, ethambutol, pyrazinamide
- Group 2 Injectable agents:** streptomycin, kanamycin, amikacin, capreomycin
- Group 3 Fluoroquinolones:** ofloxacin, levofloxacin, moxifloxacin
- Group 4 Oral bacteriostatic agents:** ethionamide, protionamide, cycloserine, para-aminosalicylic acid (PAS)
- Group 5 Agents with unclear role in drug-resistant treatment:** Amoxicillin/clavulanate, linezolid, clofazimine, imipenem/cilastatin, high-dose INH

# Treatment Principles

- Use direct observation of treatment (DOT)
- Use daily, not intermittent, administration
- Treatment duration of a minimum of 18-24 months
- When possible, continue injectable for at least six months post-culture conversion
- Continue at least three oral drugs for full treatment duration

# Standardized Treatment Regimens

## Intensive Phase (minimum 8 months)

- kanamycin
- Ethionamide
- PZA
- Levofloxacin
- (Ethambutol)
- cycloserine

## Continuation Phase (minimum 12 months)

- Ethionamide
- Levofloxacin
- PZA
- cycloserine
- (Ethambutol)

**Use ethambutol in both phases of treatment if strains are still susceptible.**

# Bangladesh short course regimen

- Total treatment duration -9 to 12 months
- **Initial phase(4-6 months):**  
Kanamycin, moxifloxacin, prothionamide, clofazamine, pyrazinamide, high dose of isoniazide , ethambutol
- **Continuation phase(5 months)**  
Moxifloxacin, clofazimine,pyrazinamide ethambutol

# Cross-Resistance: WHO

- **All rifamycins:** high level cross-resistance
- **Fluoroquinolones:** variable, but probably should be assumed to be cross-resistant
- **Amikacin and kanamycin:** generally highly cross-resistant, but both should be tested
- **Capreomycin and aminoglycosides:** occasional cross-resistance, susceptibilities should be tested

# Drug Contraindications: WHO

- Known severe drug allergy
- Unmanageable drug intolerance
- Risk of severe toxicity, with symptoms such as renal failure, hepatitis, hearing loss, depression, and psychosis
- Drugs of unknown quality.

# Directly Observed Treatment

## Effect on Resistance and Relapse

	<b>Self-RX</b> N = 407 (pre 1987)	<b>DOT</b> N = 581 (1987 +)
<b>Primary R</b>	13.0%	6.7%
<b>Secondary R</b>	10.3%	1.4%
<b>Relapse</b>	20.9%	5.5%
<b>MDR relapse</b>	6.1%	0.9%

\* P < 0.001

Weis SE, et al. *NEJM* 1994; 330(17): 1179-84



# Monitoring

- Collect sputum specimens for smear and culture **monthly during treatment until culture negative** then periodically until treatment completed
- Obtain **end-of-treatment sputum** specimen for smear and culture
- Clinical evaluation **monthly** until culture conversion then every 2-3 monthly
- Perform chest radiograph periodically during treatment and at end of treatment
- **Post-treatment:** monitor quarterly during first year, then every 6 months during second year

# Treatment of XDR TB (Standard Regimen)

- **Intensive phase(12 months):**
  - ❖ Capreomycin, pyrazinamide, moxifloxacin, para-aminosalicylic acid, cycloserine, amoxicillin/clavulanate, linezolid, cofazimine
- **Continuation phase(12 months):**
  - ❖ Pyrazinamide, moxifloxacin, para-aminosalicylic acid, cycloserine, amoxicillin/clavulanate, linezolid, cofazimine

# Common Adverse Effects

Adverse Effect	Potentially Offending Drug
<b>G.I. complaints</b>	Ethionamide Cycloserine PAS Fluoroquinolones Clofazimine
<b>Hepatotoxicity</b> (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice)	Ethionamide PZA PAS Fluoroquinolones

# Common Adverse Effects (2)

Adverse Effect	Potentially Offending Drug
<b>Peripheral neuropathy</b>	Ethionamide Cycloserine Linezolid
<b>Rash</b>	All
<b>Headache</b>	Fluoroquinolones Cycloserine Ethionamide Ethambutol
<b>Seizures</b>	Cycloserine

# Common Adverse Effects (3)

<b>Adverse Effect</b>	<b>Potentially Offending Drug</b>
<b>Hypothyroidism</b>	Ethionamide, PAS
<b>Hearing loss, Vestibular toxicity</b>	Aminoglycosides, Capreomycin
<b>Behavioral changes</b>	Cycloserine, Ethionamide, Fluoroquinolones
<b>Visual changes</b>	Ethambutol, Rifabutin, Linezolid
<b>Renal failure Hypokalemia, Hypomagnesemia</b>	Aminoglycosides, Capreomycin

# Summary

- Treatment of MDR-TB is complex and costly. It is much easier to prevent than to treat
- Expert consultation should be obtained when MDR-TB is suspected
- Patients can be treated with a standardized or an empiric regimen
- Ideally the regimen should be guided by drug-susceptibilities

# Summary.....

- Considerable attention must be paid to treatment supervision and support
- A patient-centered approach to DOT is an important element of successful care
- Adverse effects of second-line drugs are common and may be severe. Monitoring for these effects is essential!

Thank You!

