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Extensively Drug Resistant Tuberculosis: An Update

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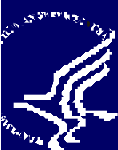

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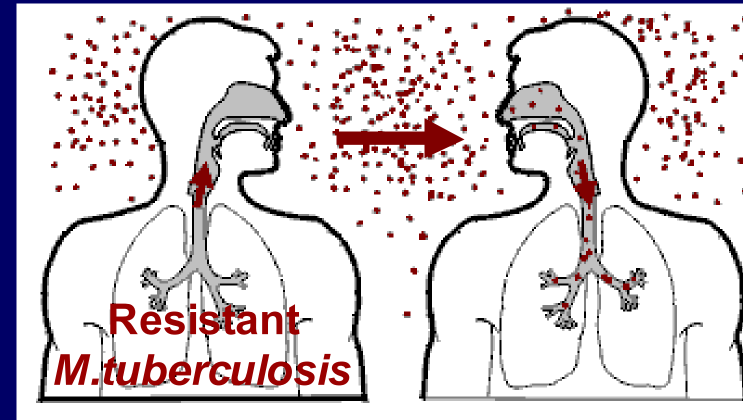
Definitions – I

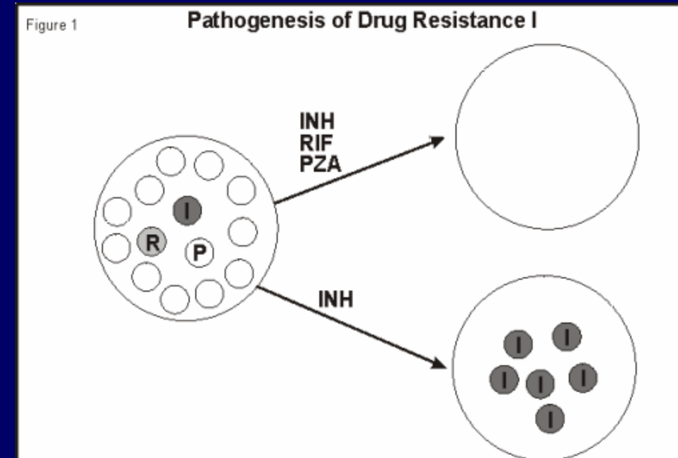
Initial (Primary) resistance

- TB patient's initial *Mycobacterium tuberculosis* population resistant to drug



Acquired (Secondary) resistance

- Drug-resistant *M. tuberculosis* in initial population selected by inappropriate drug use (inadequate *Rx* regimen or non-adherence)



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Definitions – II

Multidrug resistant (MDR) TB

- TB patient's *M. tuberculosis* isolate resistant to ≥ isoniazid and rifampin

Extensively drug resistant (XDR) TB

- MDR with additional resistance to at least a fluororquinolone and one second-line injectable (amikacin, kanamycin, capreomycin)

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XDR TB Background

- Anecdotal descriptions of virtually untreatable TB patients with multi-drug resistant *M. tuberculosis* isolates and additional/extensive drug resistance
- Initial reports of XDR-TB, Oct 2005
  - Shah et al.
  - Holtz et al.

  36th World Congress on Lung Health
  IJTLD 2005;9(Suppl. 1):S77, S258
- Study proposal Oct 2005; initial publication Mar 2006

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*, the bacterium that causes tuberculosis (TB). Worldwide, TB remains one of the leading causes of death from

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

During the 1990s, multidrug-resistant (MDR) tuberculosis (TB), defined as resistance to at least isoniazid and rifampin,

*Defined as cases in persons with TB whose isolates were resistant to isoniazid and rifampin and at least three of the six main classes of SLDs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicyclic acid).

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Global WHO/IUATLD/CDC Survey*

- Convenience sample (17,690 isolates) submitted to participating international SRL network, 2000-2004
  - 3520 (20%) of isolates MDR TB
  - 347 (2%) of isolates XDR TB
- XDRTB in all regions, more common FSU and Asia (Republic of Korea)
- Denominator information unavailable

* *MMWR* 2006;55:301-305

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KZN Hospital Background*

- 119 patients in TB/ARV integration study
  - 14 deaths
  - 10 (71%) of 14 with MDRTB
  - 6/10 MDRTB resistant to all tested first and second line drugs for TB
    - INH, RIF, EMB, STR, KANA, CIPRO
- Suggestive of probable extensive drug resistant TB in this hospital

* Moll A, Gandhi NR, Pawinski R, Lalloo U, Sturm AW, Zeller K, Andrews J, Friedland G. HIV associated Extensively Drug-Resistant TB (XDR-TB) in Rural KwaZulu-Natal (South Africa MRC Expert Consultation Sept 8, 2006)

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KZN Drug Resistant TB Survey Results*

1539 samples tested

544 (35%) Cx+ *M. tuberculosis*

995 (65%) Cx Negative

221(41%) MDRTB

323 (59%) Susceptible

53 (10%) XDRTB (24% of MDRTB)

* Gandhi NR, Moll A, Sturm AW, Pawinski R, Govendar T, Lalloo U, Zeller K, Andrews J, Friedland G. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006;368:1575-80

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XDR TB in KZN: Patient Characteristics*

Characteristic	No. (%)
No prior TB treatment (n=47)	26 (55)
Prior hospitalization [last 2 yrs] (n=42)	28 (67)
Previous TB treatment (n=47)	
Cured or completed	14 (30)
Failure or default	7 (15)
HIV infection (n=44)	44 (100)
Dead: includes 15 (34%) on ARVs	52 (98)
Identical genotype (n=46)	39 (85)

* Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, Zeller K, Andrews J, Friedland G. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006;368:1575-1580

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Profile of Selected HIV-related MDR TB Outbreak Investigations in U.S., 1988–92

Hospital	Total Cases	% HIV Infected	% Deaths	Median Wks Dx to Death
A	65	93	72	7
B	51	100	89	16
C	70	95	77	4
D	29	91	83	4
E	7	14	43	4
F	16	82	82	4
I	13	100	85	4
J	28	96	93	4
Prison	42	98	79	4

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Reported TB Cases*
United States, 1982–2006

No. of Cases

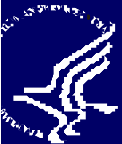
National Action Plan to Combat MDR TB, New Congressional Appropriations

28,000
26,000
24,000
22,000
20,000
18,000
16,000
14,000
12,000

1982 1986 1990 1994 1998 2002 2006

Year

*Updated as of April 6, 2007.



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Primary MDR TB
United States, 1993–2006*

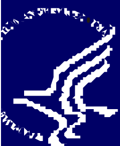
No. of Cases | Percentage

500 | 3
400 |
300 | 2
200 |
100 | 1
0 | 0

93 94 95 96 97 98 99 00 01 02 03 04 05 06

No. of Cases — Percentage

*Updated as of April 6, 2007.



Note: Based on initial isolates from persons with no prior history of TB.
MDR TB defined as resistance to at least isoniazid and rifampin.

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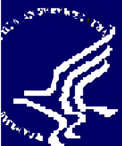
XDR TB Cases by State of Residence, United States, 1993–2006*

(Provisional Data, Not for Citation)

1
2
8
NYC 16
New Jersey 3
1
1
2
11
2
1



* Based on Initial DST results

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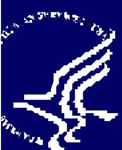
XDR TB Cases by Origin, United States,1993–1999 vs. 2000–2006*
(Provisional Data, Not for Citation)

Origin**	1993-1999	2000-2006
U.S.-born	17 (65%)	5 (25%)
Foreign-born	9 (35%)	15 (75%)

* Based on Initial DST results

** Two cases of unknown origin



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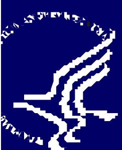
XDR TB Cases by HIV Status, United States, 1993–1999 vs. 2000–2006* (Provisional Data, Not for Citation)

HIV Status	1993 – 1999	2000 – 2006
HIV positive	14 (50%)	2 (10%)
HIV negative	4 (14%)	9 (45%)
Unknown	10 (36%)	9 (45%)

* Based on initial DST results



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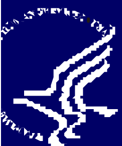
XDR TB Cases by Fatality, United States,1993–2006*
(Provisional Data, Not for Citation)

Dead at diagnosis (2) or during *Rx* (15)	17 (35%) of 48
Avg. time to death (from start of *Rx*)	117 days
Median time to death (from start of *Rx*)	45 days
Range, time to death (from start of *Rx*)	0 – 984 days
No. dead (cases with known outcome)	17/33 (52%)



* Based on initial DST results

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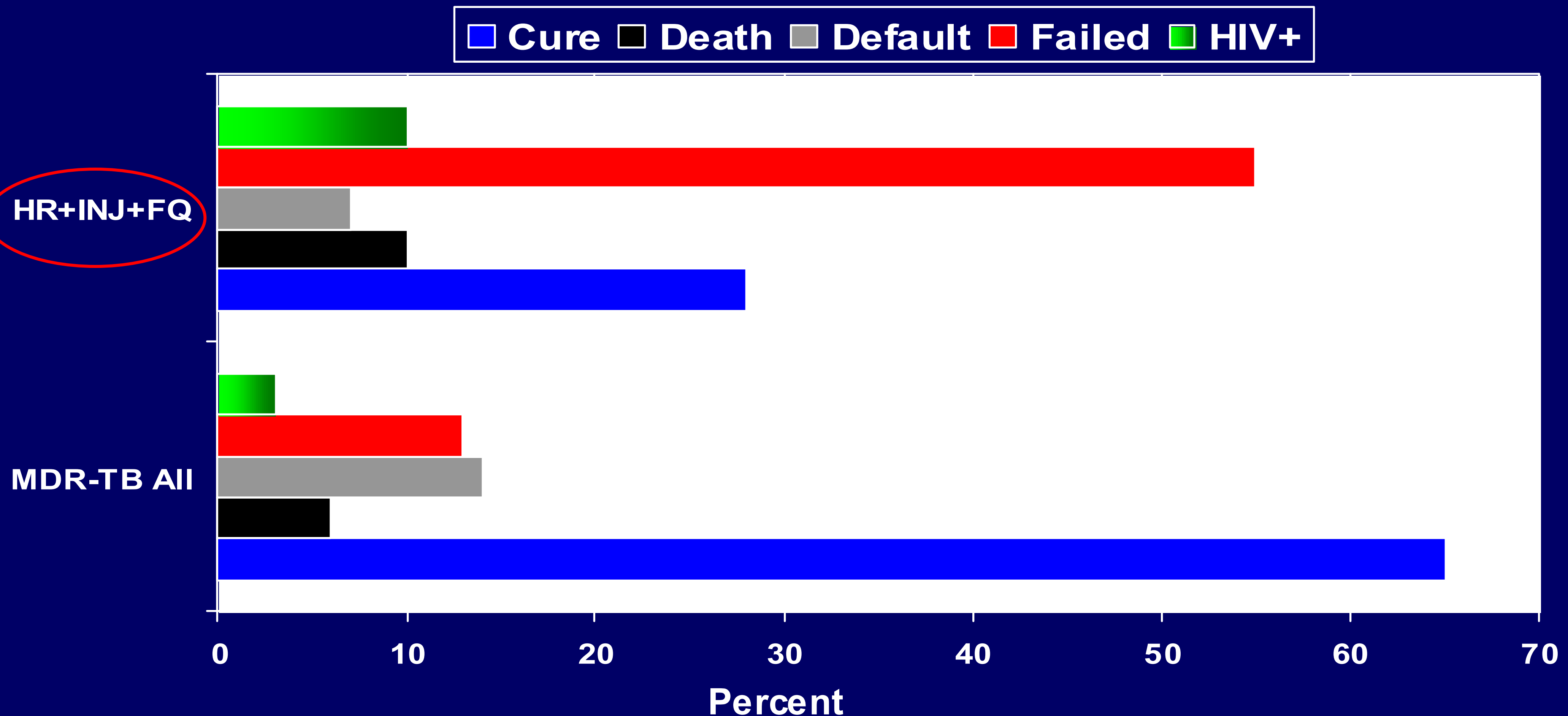
TB Treatment Outcomes, by Selected Drug Resistance Patterns, Latvia, 2000-2003*



* Leimane V, et al. First Global XDR TB Task Force Meeting. Oct 9, 2006
(from N = 820 evaluated)

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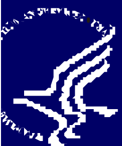
MDR, XDR TB: Why be Concerned?

- Treatment requires 18–24 mo (vs 6–8 mo)
- Relapse rates ~30-40% (vs < 5%)
- Higher case fatality
- Prolonged infectiousness
- Adverse events common
- Higher costs (> 100-fold increase)
  - Avg hospitalization cost for XDR $477,000



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XDR TB as a Global Emerging Threat: Why Now?

- Convergence of factors creating “the perfect storm”
  - Suboptimal TB control practices
  - High HIV prevalence
  - High TB burden
  - Introduction of second-line TB drugs into low and middle income countries

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Global 7-point Action Plan to Combat XDR TB

Emphasizes Essentials of Proper TB Control

1. **Conduct rapid surveys of XDR-TB (determine burden)**
2. **Enhance laboratory capacity (emphasis on rapid DST)**
3. **Improve technical capacity of clinical and public health practitioners to effectively respond to XDR-TB outbreaks and manage patients**
4. **Implement infection control precautions (PLHA focus)**
5. **Increase research support for anti-TB drug development**
6. **Increase research support for rapid diagnostic test development**
7. **Promote universal access to ARVs under joint TB/HIV activities**

MRC Consultation, Johannesburg, South Africa. Sept 7, 2006

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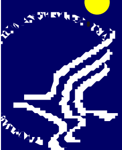

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WHO/HTM/TB/2007.387

The Global MDR-TB & XDR-TB Response Plan 2007-2008

Strategic Plan 2006–2015

- Assess epidemiologic impact of interventions by regions and cost
- 10-yr cost $56.1 billion (need $30.8 billion)

Supplemental Plan $2.15 billion

Emphasis on

- Basic TB control
- 7 Action Steps

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