

Multidrug-Resistant Tuberculosis From New York City to South Africa and Beyond

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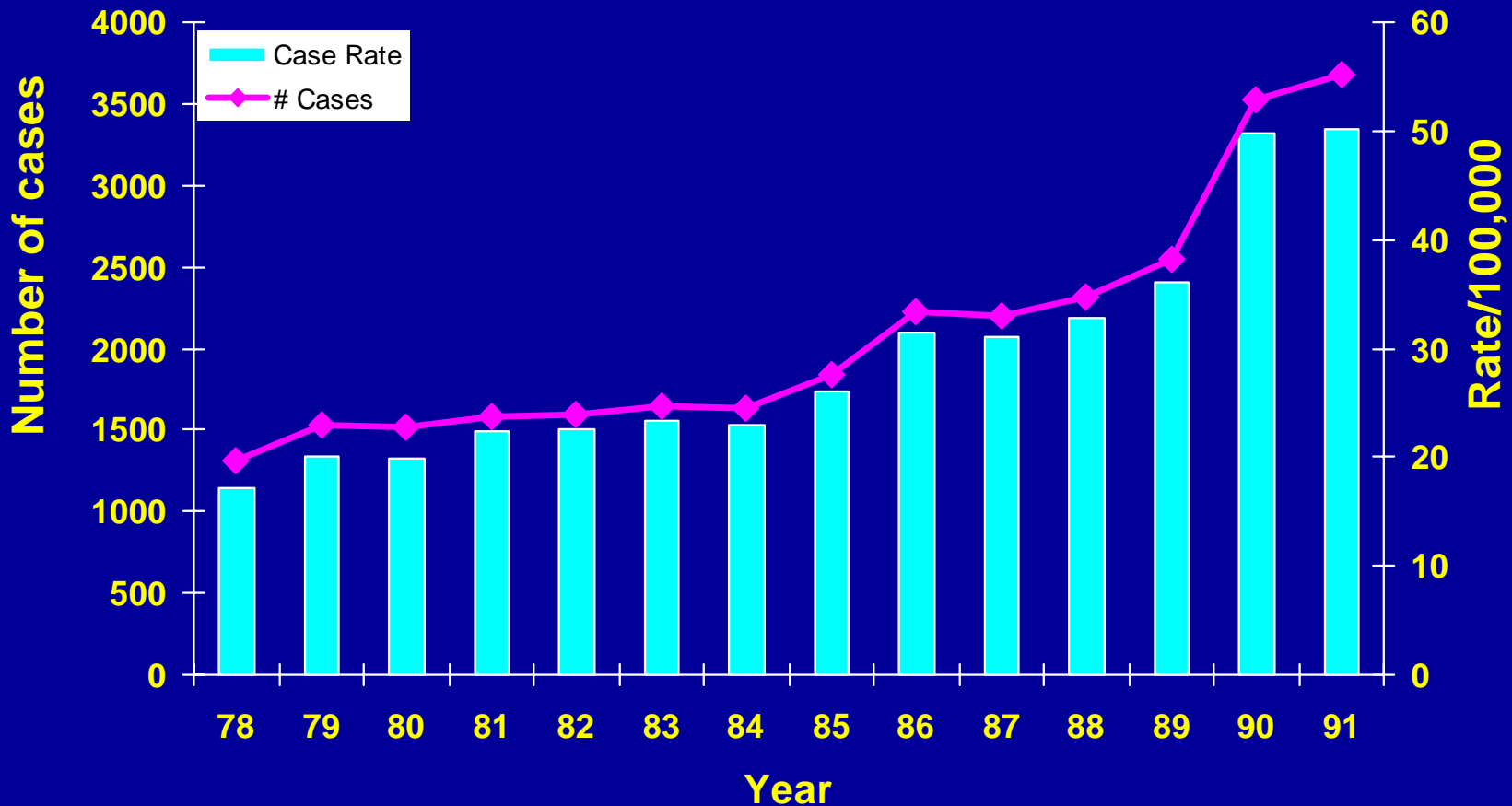
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Today I will review...

- Recent NYC TB epidemic and measures implemented for its control
- MDRTB global epidemiology
- XDRTB outbreak in South Africa
- Global response to XDRTB
- Similarities between outbreaks in NYC and South Africa
- A look ahead...

Tuberculosis Cases and Rates New York City, 1978 - 1991



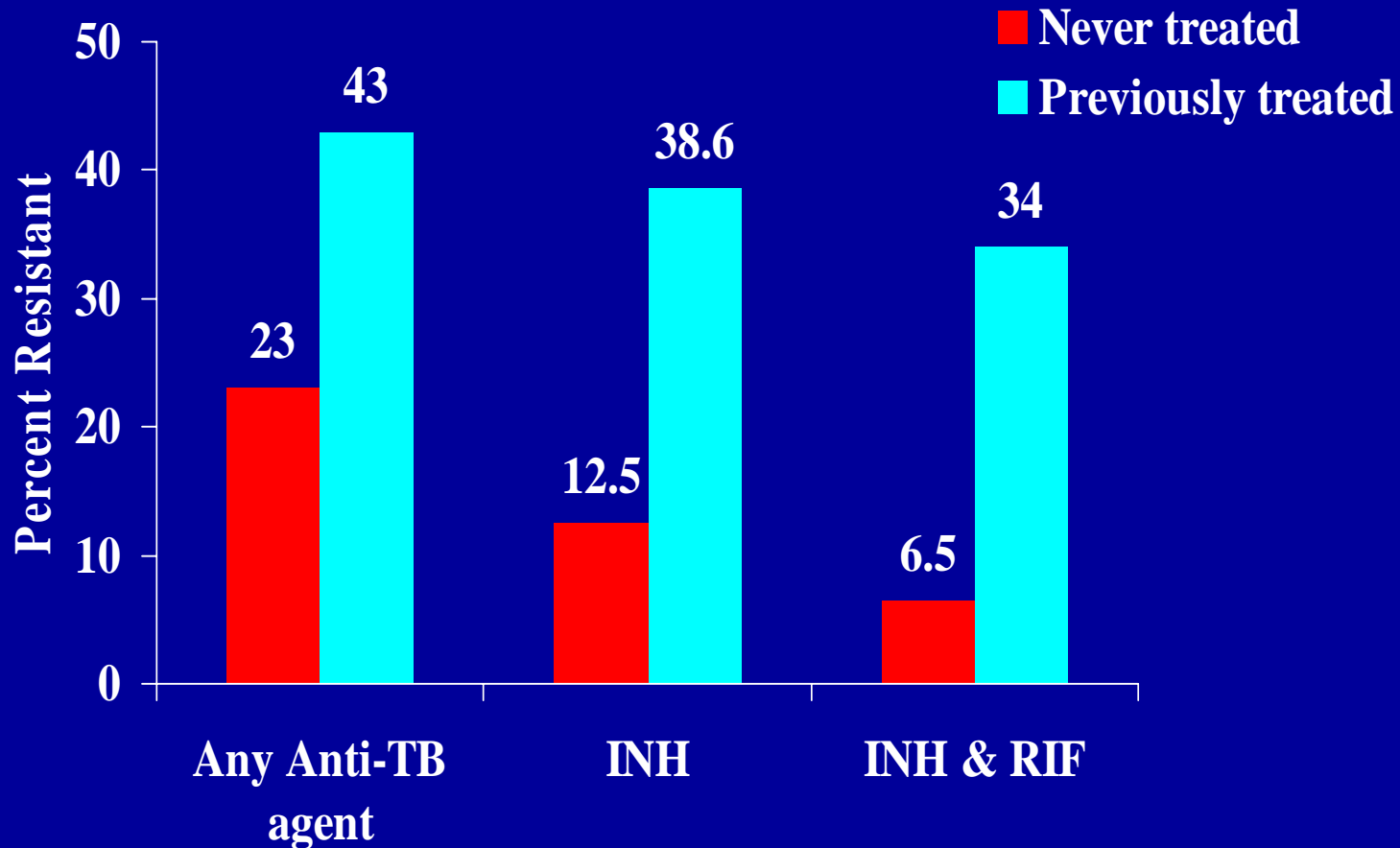
Causes of resurgent TB in New York City

- Poverty, homelessness, crowding, substance abuse
- HIV/AIDS epidemic
- Decline of public health infrastructure
 - Marked reduction in TB control program staff and clinic facilities
 - lack of accessible health care
- TB abroad on the rise; immigration from high prevalence countries

Causes of resurgent TB in New York City - 2

- Poor infection control practices in hospitals
- Poor treatment practices
 - No drug susceptibility results for most patients
 - Inappropriate regimens
 - By 1989, fewer than half of patients who began treatment were cured

Patients with resistant isolates New York City, April 1991 (N=466)



How to get MDRTB

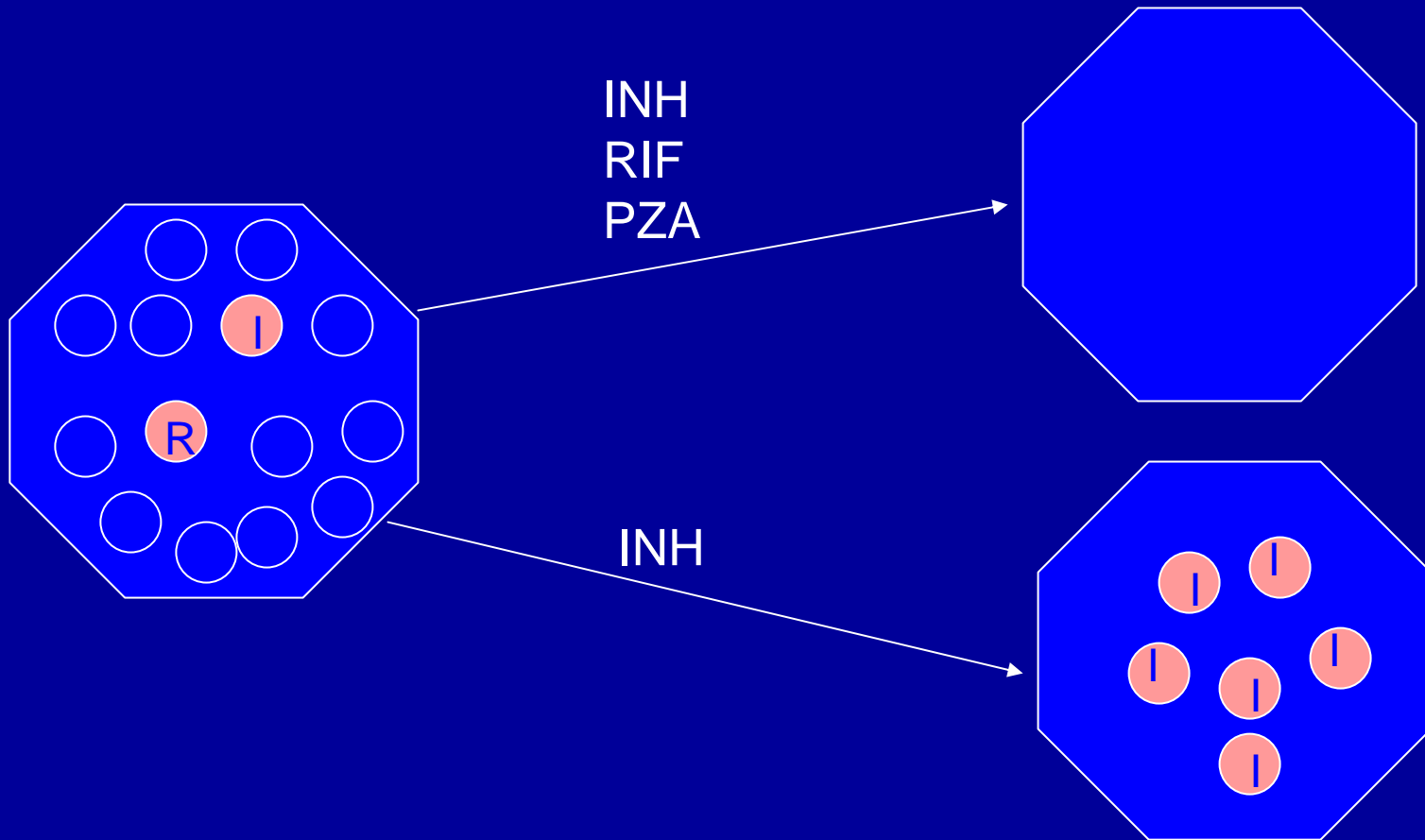
- Acquired resistance
 - nonadherence to therapy
 - inappropriate therapy due to poor regimen selection, erratic drug supply
- Primary resistance
 - nosocomial transmission
 - community transmission

Rates of natural resistance in *M. tuberculosis*

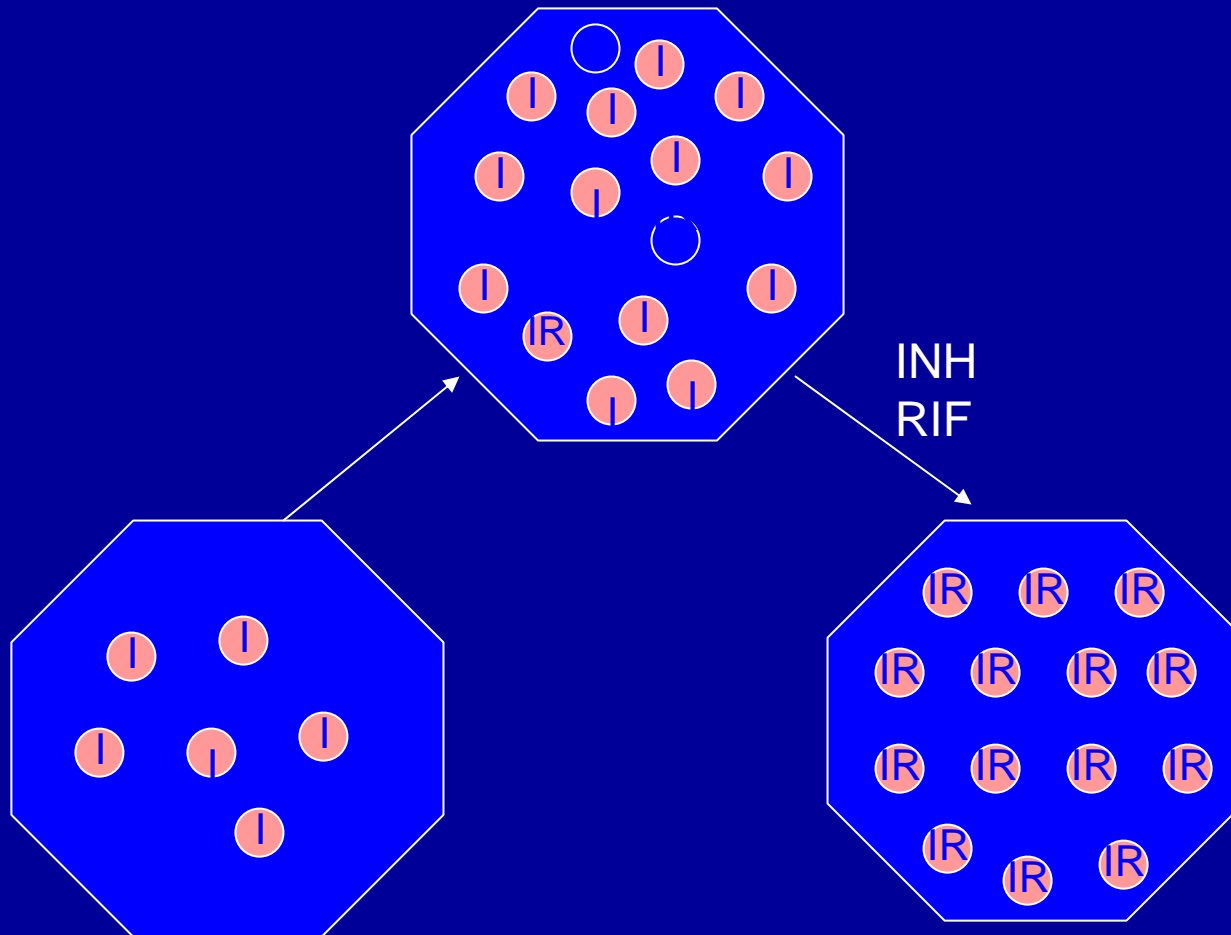
- Isoniazid 1 in 10^6
- Rifampin 1 in 10^8
- Ethambutol 1 in 10^6
- Streptomycin 1 in 10^5
- INH & RIF 1 in 10^{14}

Number of organisms in a TB cavity = 10^9 - 10^{11}

Pathogenesis of Drug Resistance I



Pathogenesis of Drug Resistance II



Never add a single drug to a failing regimen!

Nosocomial, HIV-related outbreaks of MDRTB as of October, 1992

<i>Facility</i>	<i>Location</i>	<i>Time Period</i>	<i>Total</i>
Hospital A	Miami	1988-91	65
Hospital B	NYC	1989-91	51
Hospital C	NYC	1989-92	70
Hospital D	NYC	1990-91	29
Hospital E	NYS	1990-91	7
Hospital F	NYC	1990-91	16
Hospital I	NJ	1990-92	13
Hospital J	NYC	1991-92	28
Prisons*	NYS	1990-92	42
Total Cases			297

* 24 prison cases are also counted with Hospital C

Prevalence of HIV and mortality of patients with MDRTB as of Oct 1992

<i>Facility</i>	<i>HIV+</i>	<i>Mortality</i>	<i>Median Interval</i>
Hospital A	93%	72%	7 weeks
Hospital B*	100%	89%	16 weeks
Hospital C	95%	77%	4 weeks
Hospital D	91%	83%	4 weeks
Hospital E	14%	43%	4 weeks
Hospital F	82%	82%	4 weeks
Hospital I	100%	85%	4 weeks
Hospital J	96%	93%	4 weeks
Prison System**	98%	79%	4 weeks

* HIV infection was part of case definition

** Includes 24 cases also counted with Hospital C

Characteristics of Strain W Multi-Institutional Outbreak

- Strain W isolates: resistant to I/R/E/S/Rbt/Kanamycin +/- PZA
- 357 patients met susceptibility definition from 1/1/90-8/1/93; 267 confirmed by RFLP
 - 237 isolates had strain W pattern
 - 30 isolates had strain W1 pattern
- Patients lived in all five boroughs and were managed at 41 facilities
- 230/249 tested (92%) were HIV+
 - 96% of HIV+ had pulm TB
 - Median survival for HIV+ patients was 66 days

Characteristics of strain W outbreak

Epidemiological links

- 186 (70%) of 267 were epidemiologically linked
 - 178 (96%) occurred in 11 different hospitals (range 1-76 cases/hospital)
 - 3 (2%) were linked in the correctional system
 - 5 (3%) were linked in the community
- Outbreaks lasted up to 38 months and most took place in 4 hospitals
- Median time from exposure to disease was 17 weeks

Nosocomial TB - *Common Characteristics*

- Diagnosis was not considered or late diagnosis
- CXR often “atypical” for TB
- Ineffective or inadequate isolation
- Most cases in HIV seropositive patients
- Multidrug-resistant strains
 - standard treatment not effective
 - Appropriate treatment also often ineffective for prolonged periods
 - Laboratory results delayed

Tuberculosis Cases and Rates

New York City, 1982 – 2006*

954 Cases in 2006, rate 11.9/100,000



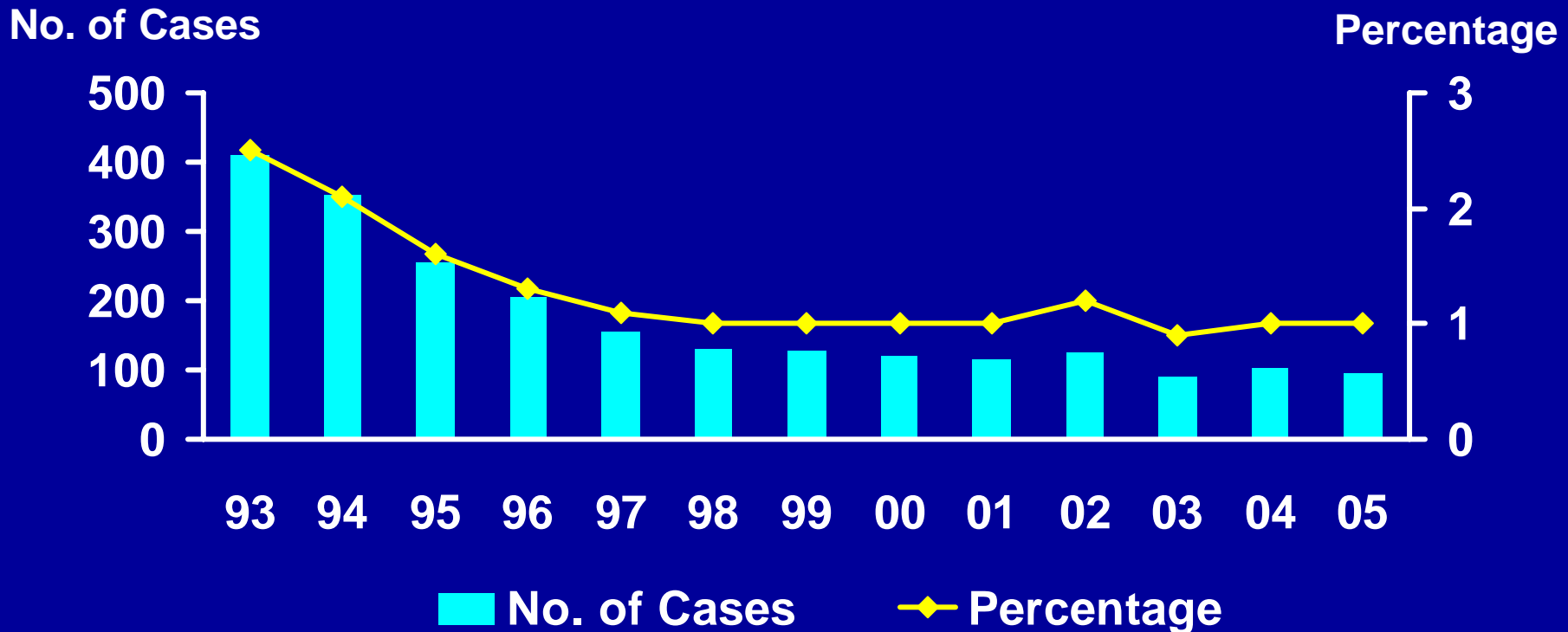
* Rates since 2000 are based on 2000 Census data.

From MDRTB to XDRTB

How did we get there?

Was it inevitable?

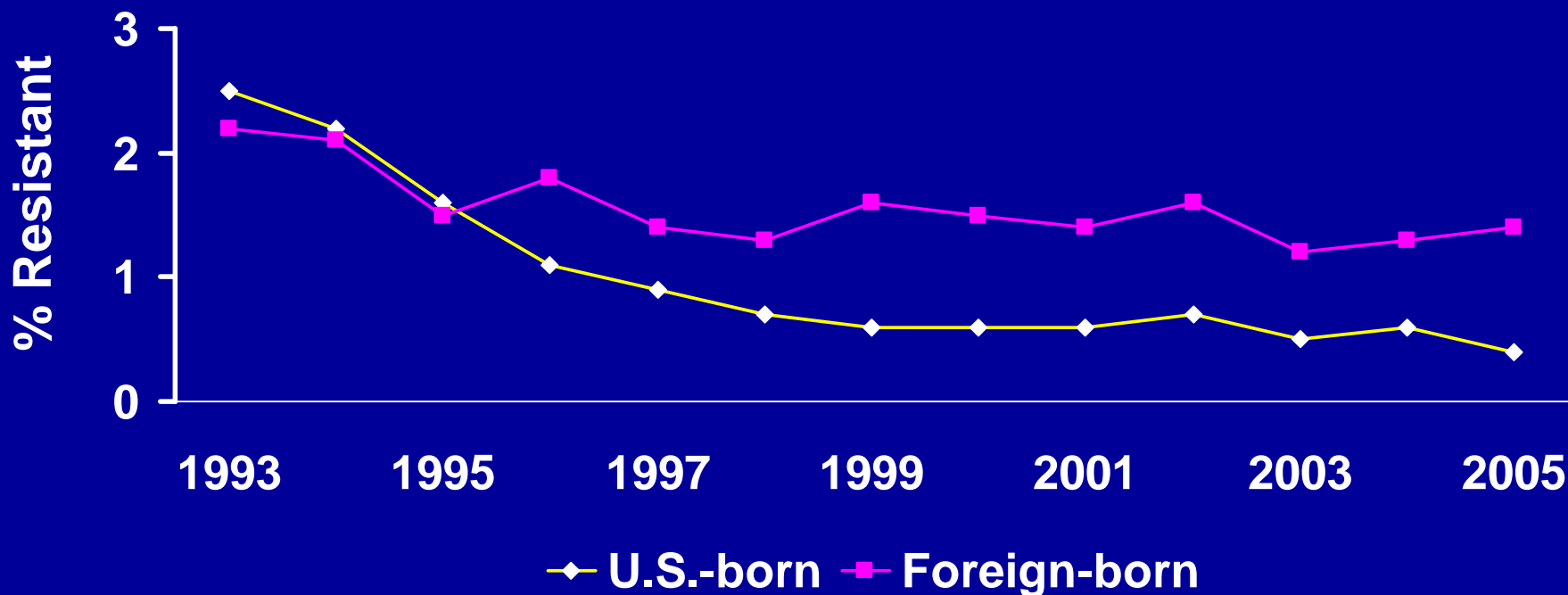
Primary MDR TB United States, 1993–2005*



*Updated as of March 29, 2006.

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

Primary MDR TB in U.S.-born vs. Foreign-born Persons, United States, 1993–2005*



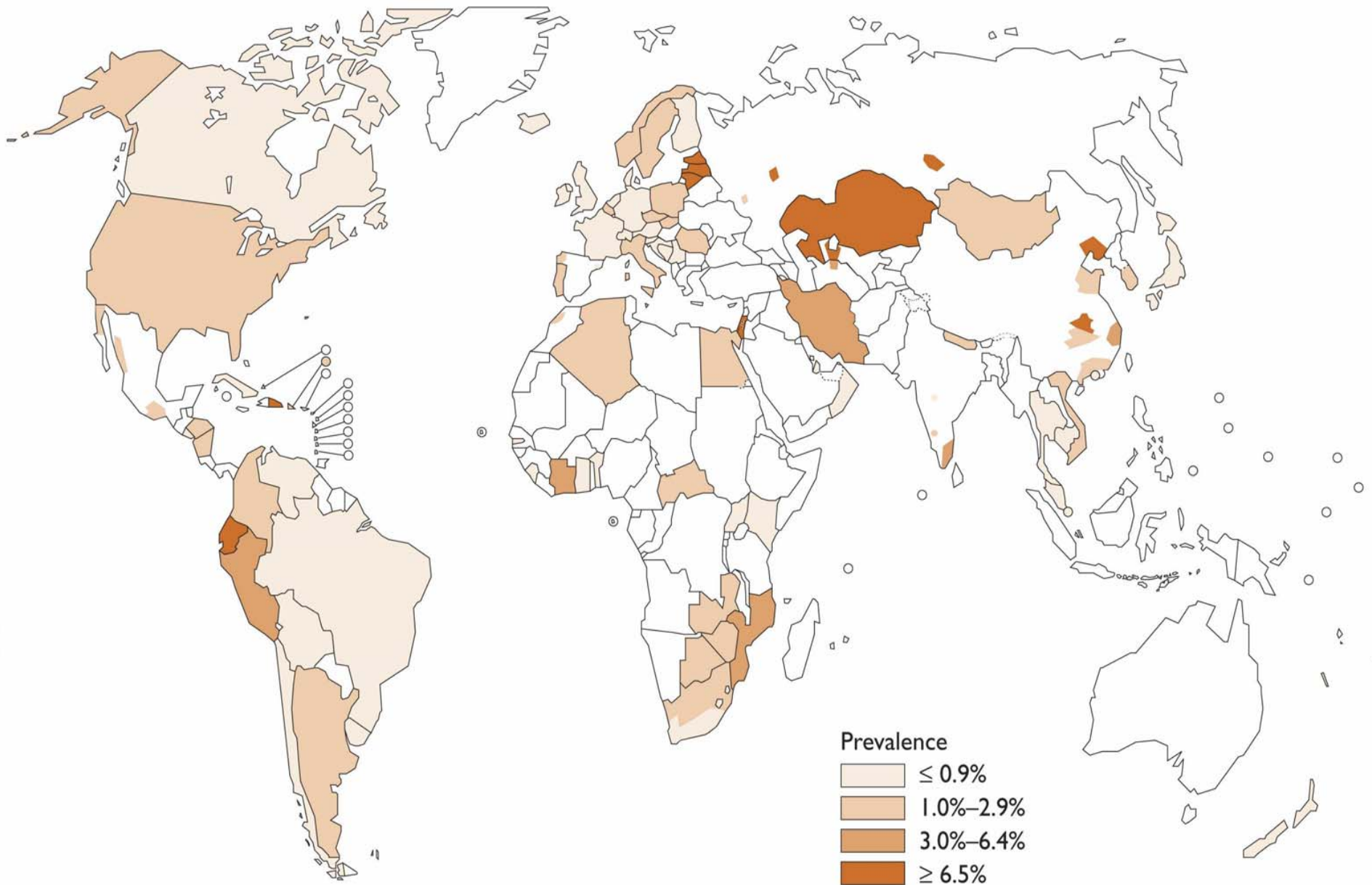
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MDRTB Outbreaks in Industrialized Countries, 1988-1995

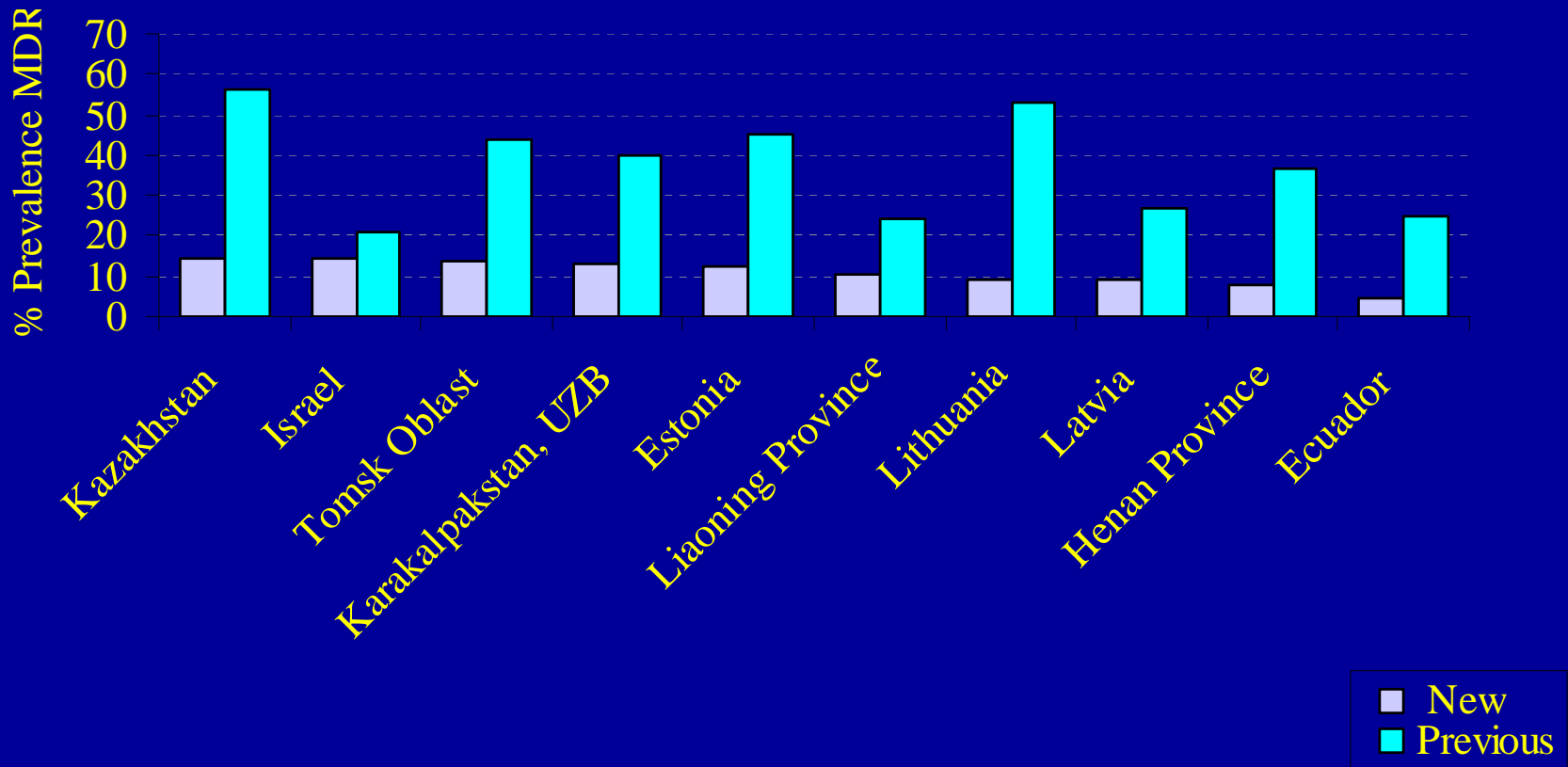
Facility	% HIV-infected	% Mortality	Median Interval (wks)
Hosp Florida	93	72	7
Hosp NYC	100	89	16
Hosp NYC	95	77	4
Hosp NYC	91	83	4
Hosp Italy	98	95	6-8
Hosp Spain	100	98	7
Hosp Argent.	98	79	4

Prevalence of MDR-TB among new TB cases, 1994–2002



The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dashed lines represent approximate border lines for which there may not yet be full agreement.

Prevalence of MDR by treatment status, WHO survey, ranked by new cases



WHO DR Survey, 2002

Estimated Global Burden of MDRTB in 2005 is about 425,000 cases

Vast majority not receiving appropriate treatment

Region	Total TB	Total MDRTB	% MDR
AFRO	2,800,000	60,000	2.2
Americas	390,000	11,500	2.9
EMRO	555,000	18,500	3.3
EURO	510,000	67,500	14.0
SEARO	3,300,000	115,000	3.5
WPRO	2,170,000	152,000	7.0

XDR-TB Definition

Resistance to at least isoniazid and rifampin

MDR

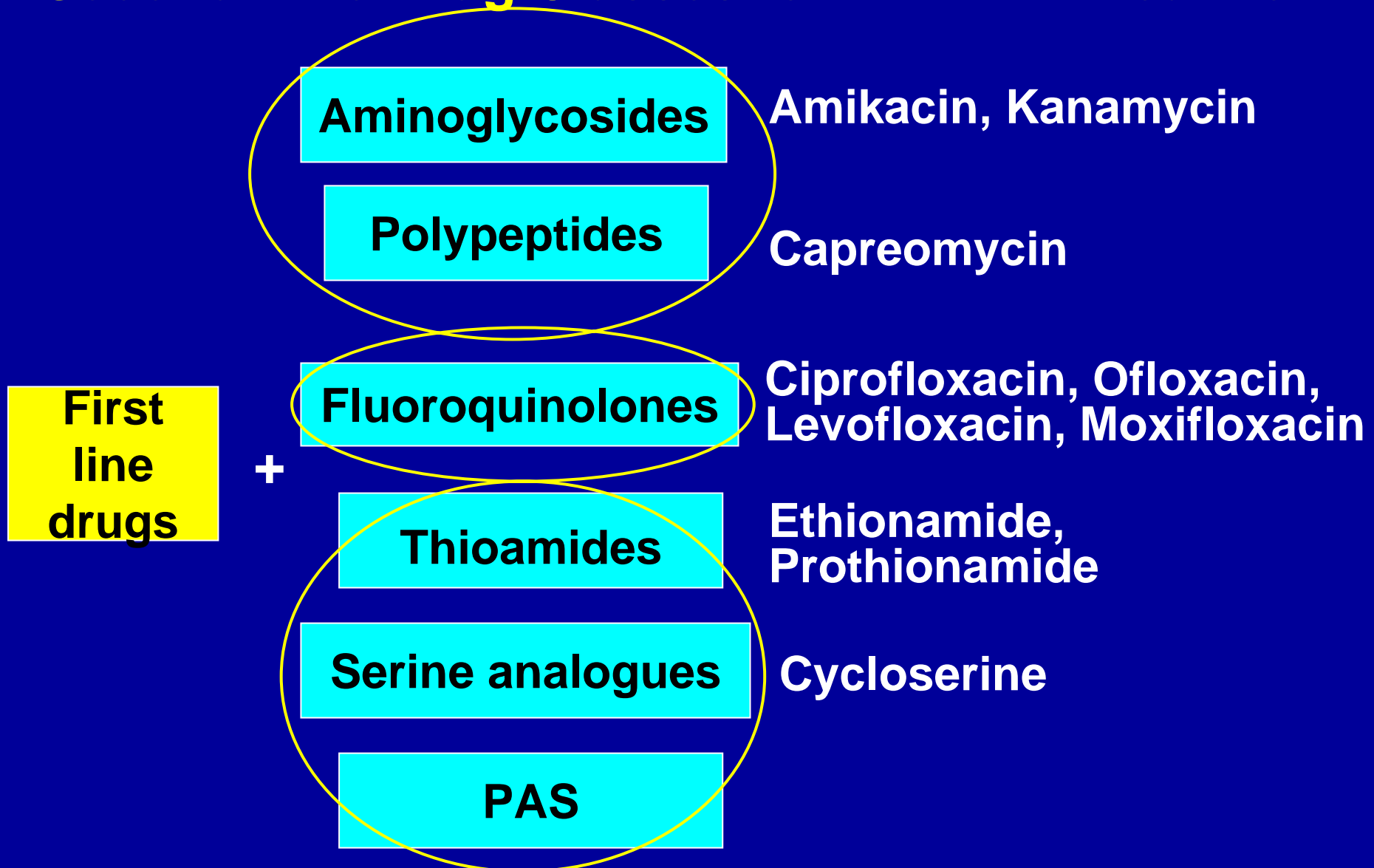
plus resistance to

Fluoroquinolones

AND

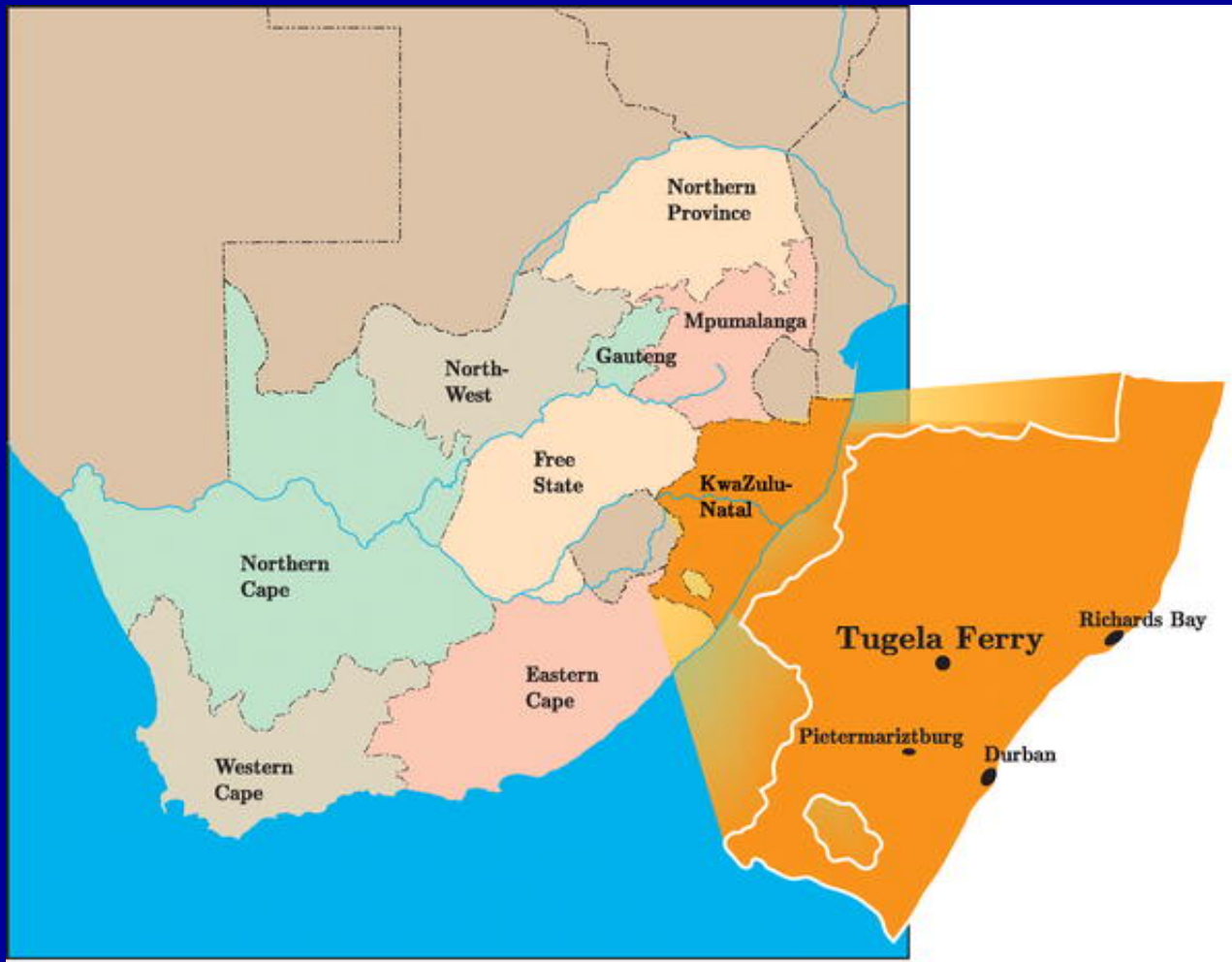
one of the second line injectable drugs
(amikacin, kanamycin or capreomycin)

Second-Line Drug Classes for MDR TB Treatment



WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. 2006.

KwaZulu Natal, South Africa



From 1/2005 to 3/2006
544 patients
Culture-Positive for *M.tb*

323 (59%)
Not Resistant
to both Isoniazid & Rifampicin

221 (41%)
Resistant to Isoniazid & Rifampicin
(MDR TB)

53 XDR TB
(24% of MDR, 10% Culture-Positive)
Resistant to all tested drugs

New Infection with XDR TB

- Majority never previously treated or had previous cure or treatment completion
 - Suggests newly infected with drug-resistant TB strains
 - Not development of drug resistance on therapy
- 64% of patients hospitalized for any cause before onset of XDR TB
- 2 healthcare workers died with confirmed XDR TB
 - 4 other workers died with suspected XDR TB
 - Nosocomial transmission in hospitals probable
- Transmission in community also possible since 36% XDR TB patients with no prior hospitalizations
- 26 of 30 (87%) XDR TB isolates found to be genetically similar, c/w recent infection with DR strain

Mortality in KwaZulu Natal Outbreak

- 44/44 (100%) tested were HIV-infected
- 52/53 (98%) XDR TB patients have died
- Median survival from sputum collection 16 days (range 2-210 days)
 - No significant difference by demographics, data collection group, previous TB or hospitalizations, HIV status, or use of ARVs

Gandhi et. al. IAS Conference 2006 and Lancet 2006

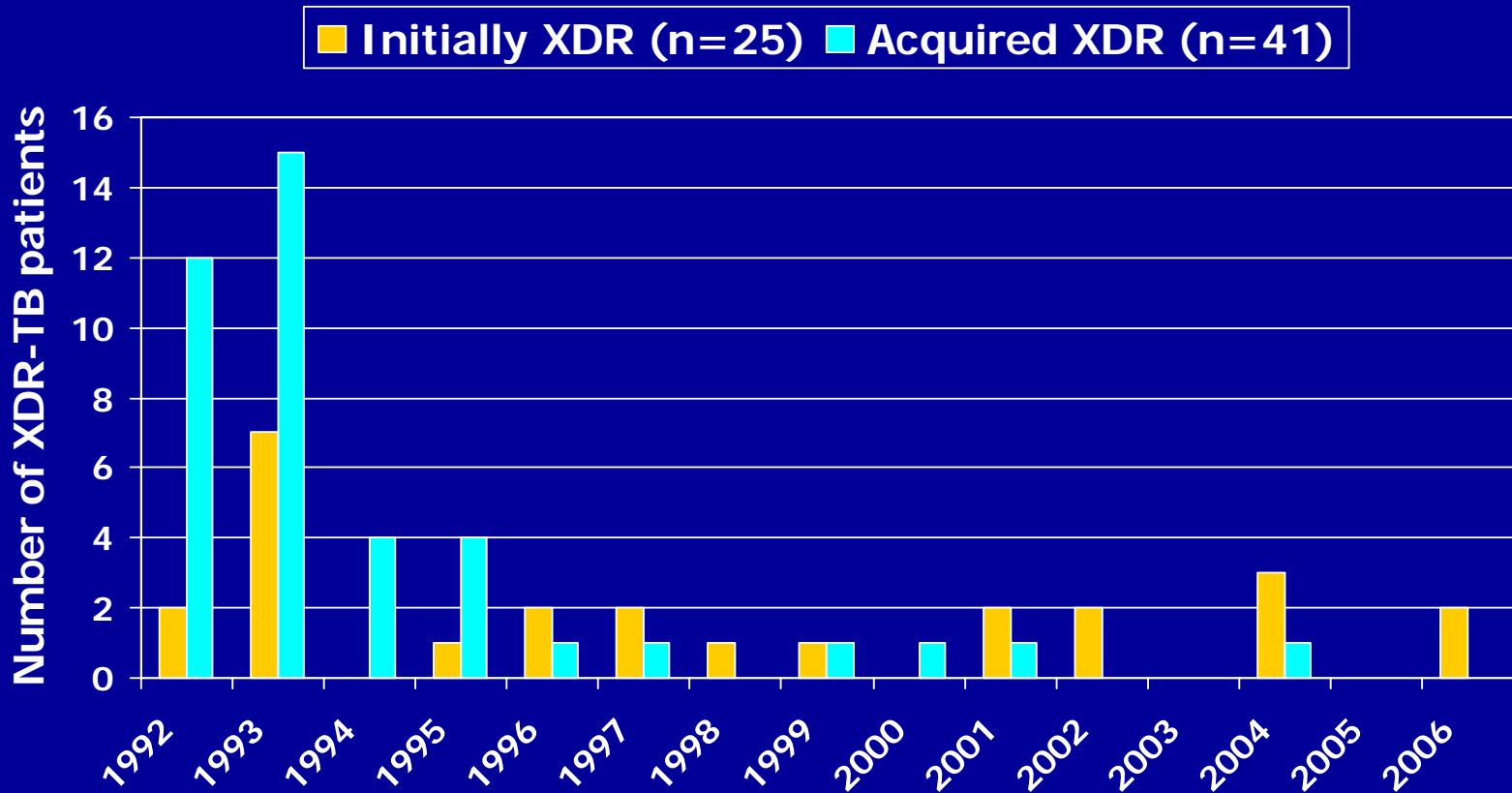
XDR-TB in NYC

- Data based on NYC TB registry data
- 66 XDR-TB patients since 1992
 - 25 (38%) based on initial DST
 - 41 (62%) that acquired XDR-TB while on treatment in NYC

Initial vs. Acquired XDR-TB

- Initial XDR-TB
 - Patients that were diagnosed with XDR-TB at initial TB diagnosis based on their first drug susceptibility test (DST) results (usually within 30 days of TB diagnosis)
- Acquired XDR-TB
 - Patients whose initial DST did not indicate XDR, however, later DST results indicate that XDR-TB developed while on treatment

Epidemiologic curve (N=66)



RFLP patterns of NYC XDR-TB isolates

Strain	Initial XDR (n=25)	Acquired XDR (n=41)	Total (n=66)
W	9 (36%)	19 (46%)	28 (42%)
W1	1 (4%)	4 (10%)	5 (8%)
P	0 (0%)	2 (5%)	2 (3%)
H	1 (4%)	2 (5%)	3 (4%)
Unique	11 (44%)	14 (34%)	25 (38%)
Unknown strain	3 (12%)	0 (0%)	3 (4%)

NYC XDRTB Cases

Demographic Characteristics

	Number (N=66)	
Age (median, range)	38	17-64
Male	41	62%
US-born (includes Puerto Rico)	47	71%
Non-US born	18	27%
Years in US (median, range)	0	0-24

NYC XDRTB Cases Countries of Origin*

- Argentina
- **China**
- **Colombia**
- **Dominican Republic**
- **El Salvador**
- **Indonesia**
- **India**
- **Malawi**
- Peru
- South Korea
- Trinidad & Tobago
- Ukraine
- Vietnam

*Countries that are bolded have patients with primary XDR-TB (not acquired in NYC)

NYC XDRTB Cases Outcomes by Initial vs. Acquired XDR-TB*

	Initial (n=25)	Acquired (n=41)	Total (N=66)
Completed treatment	10 (40%)	13 (32%)	22 (33%)
Died prior to treatment completion	12 (48%)	25 (61%)	37 (56%)
Moved outside NYC	1 (4%)	2 (5%)	3 (4%)
Still on treatment	2 (8%)	1 (2%)	4 (6%)

*As of 1/17/07

NYC, 1992 and South Africa, present

Control measures implemented in NYC

1. DR survey done in 1991 and periodically thereafter
2. Performance and reporting of susceptibility made mandatory- test free at PHL
3. Labs required to upgrade testing methods and improve turnaround - More rapid and accurate diagnosis, resulting in appropriate treatment
4. Developed treatment guidelines to ensure appropriate treatment
5. Extensively educated providers

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

NYC, 1992 and South Africa, present - 2

Control measures implemented in NYC

6. **Directly Observed Therapy (DOT) for outpatients** ensured treatment and reduced number of infectious patients entering hospitals, shelters, jails etc.
7. **Intensive Case Management**
1989 < 50% completed Rx
1994 90% completed Rx
8. **Improved Infection Control:**
Limited spread of disease by infectious persons who entered those facilities
9. **MDRTB and HIV/TB patient care coordination with providers**
10. **Procured second line drugs**
11. **Detention until cure:** Last resort for ~1% of patients

Global 7-point Action Plan to Combat XDR TB –Con't

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

**From: MRC Consultation, Sept 7, 2006
Johannesburg, South Africa.**

In addition: Detention and Quarantine are being debated

But Are The Available
Measures Enough?

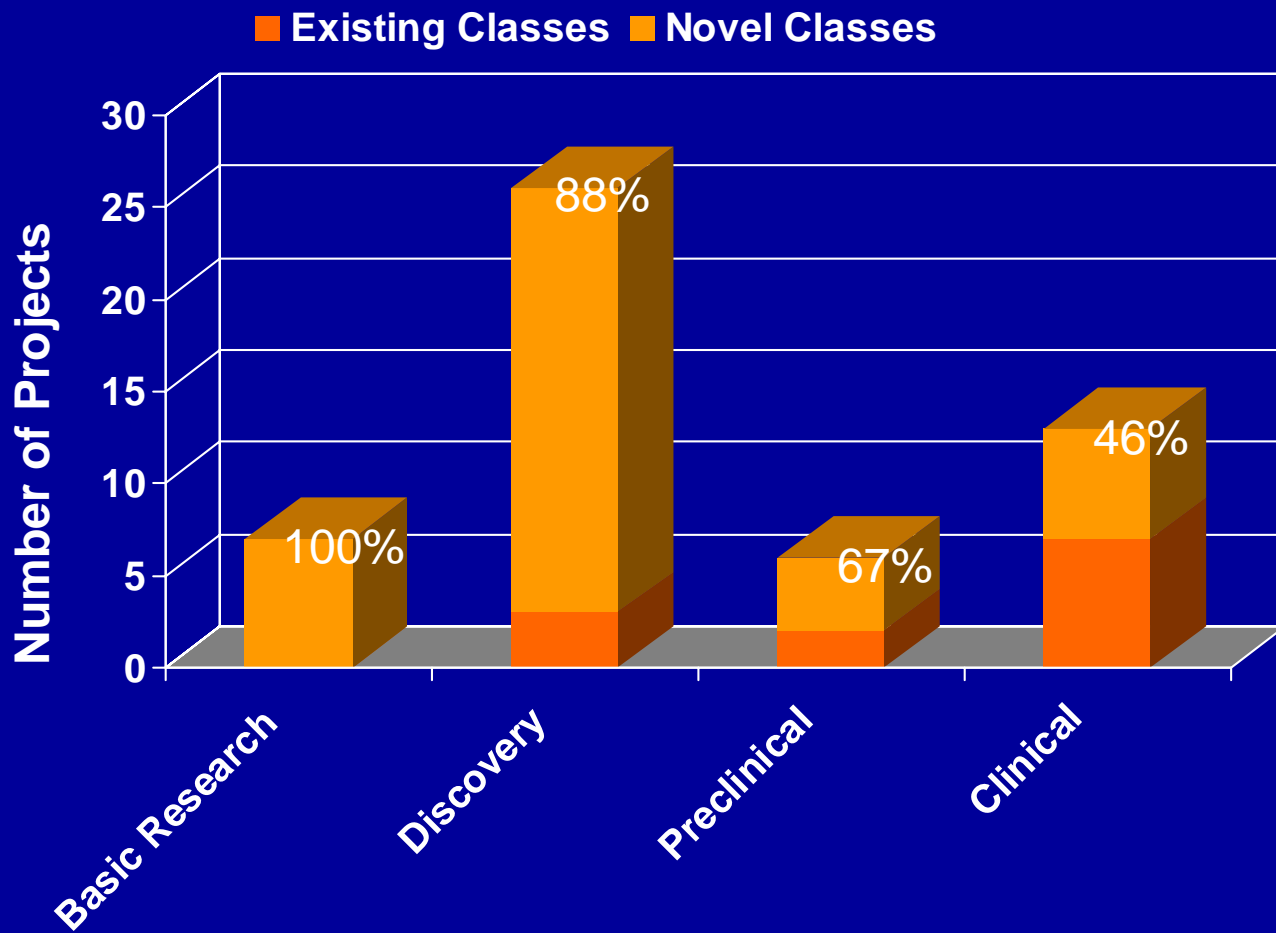
We need clinical trials for MDRTB

- With current available drugs, best possible completion rate is about 70% for MDRTB (among HIV uninfected)
- Treatment is long, arduous, toxic and expensive
- Default from treatment is high
- Most second line drugs not very effective
- Resistance to second line drugs inevitable and now well documented

Are we ready for MDRTB Trials?

- New drugs are being evaluated in clinical trials among patients with drug-susceptible TB
- MDR-TB is uncommon and is a heterogeneous disease - different patterns of drug resistance and prior drug exposure
- Clinical trials for MDR-TB will be more expensive and take longer than studies of drug-susceptible TB
- However, we cannot wait until we define roles of new drugs in trials of drug-susceptible TB
- These clinical trials should be guided by extensive testing of dose, dosing frequency, and drug combinations in animal models that mimic human PK

Current Global TB Drug Pipeline



* Number on top of bar indicates % of projects focusing on novel classes

Types of Studies – Active TB

- Phase 1 – initial use in humans; dose-ranging
- Phase 2 – Early Bactericidal Activity, early assessment of efficacy and tolerability of multidrug therapy
- Phase 3 – treatment failure/relapse
- Phase 4 – evaluation of tolerability, efficacy in very large cohorts to detect rare side effects, unusual treatment outcomes, key subgroups

PK studies

PD analysis

What kind of trials are needed to optimize MDRTB treatment?

- Phase 2
 - Early Bactericidal Activity (EBA)
 - Initial evaluation in multidrug therapy – pick dose, dosing interval from studies of drug-susceptible disease, if possible
- Phase 3 – try to define how to use drugs with promising activity in Phase 2
 - Treatment duration
 - Dosing frequency

MDRTB Initial Trial: Proposed Designs

- Randomize to:
 - Optimized therapy (based on treatment experience and drug susceptibility testing) + placebo
 - Optimized therapy + new drug
 - Immediate empiric regimen, followed by individualization with DST results
 - Randomization prior to DST
- Possible endpoints
 - 2-month culture conversion
 - Change in quantitative sputum culture
- Questions remain about which rapid tests & endpoints (bacteriological endpoints)

Limitations of MDR-TB clinical trials

- Limited numbers of patients (in most settings)
- Substantial heterogeneity in clinically-relevant factors
 - Extent of drug resistance
 - Extent of prior drug exposure (whether associated with resistance or not)
 - Severity of pulmonary disease
 - HIV serostatus
- Very limited funding

New York Times, March 20, 2007

THE DOCTOR'S WORLD
Lawrence K. Altman, M.D.

Rise of a Deadly TB Reveals A Global System in Crisis

LOS ANGELES — The spread of a particularly virulent form of tuberculosis in South Africa illustrates a breakdown in the global program that is supposed to keep the disease, one of the world's deadliest, under control.

The program was intended to detect tuberculosis cases, make sure patients were taking their antibiotics, test patients for resistance to those drugs and monitor the spread of the disease.

But international tuberculosis experts say the system is in deep trouble for an array of reasons: misuse of antibiotics; other bad medical practices, like failing to segregate high-risk patients in hospitals and clinics; and cuts in government spending for such basics as adequate supplies of drugs and laboratories to do the testing.



Karin Weyer/South African Medical Research Council

AWAITING TREATMENT During a tuberculosis outbreak in South Africa, patients often infected one another in clinics not designed to allow a quick quarantine.

...reported at the international AIDS meeting

Lessons Learned, Unlearned and Now Re-learned?

- HIV and TB and congregate settings are deadly combinations
- Infection control essential to TB Control
- Implementation of TB control basics will decrease development and spread of drug resistant TB
- Rapid diagnostic and susceptibility tests urgently needed to make early diagnosis, initiate effective isolation, and start effective treatment early
- Adequate supply of drugs has to be maintained
- New drugs with more effective and shorter regimens needed