

MDR TB

Dr A.L. Pozniak

**Chelsea and Westminster Hospital
London, UK**

Drug Resistance -biology

Mutation rates

Drug

Rifampicin	3.1×10^{-8}
Isoniazid	3.5×10^{-6}
Ethambutol	5×10^{-5}
Streptomycin	3.8×10^{-6}

NB cavities contain 10^7 to 10^9 bacilli

Some Definitions

Antituberculosis drug resistance

- **Mono-resistance.** resistance in vitro to one first-line antituberculosis drug.
- **Poly-resistance.** resistance in vitro to more than one first-line antituberculosis drug,
 - other than both isoniazid and rifampicin.
- **MDR-TB.** Resistance in vitro to at least isoniazid and rifampicin.
- **Plus**

Antituberculosis drug resistance

Definition -agreed October 2006

- **XDR-TB** = MDR-TB plus resistance to:
 - a fluoroquinolone and
 - ≥ 1 of 3 injectable second-line drugs
capreomycin, kanamycin, amikacin

Epidemiology

Global TB Estimates (2006)

Estimated Cases

Estimated Deaths

All Forms TB

8.8 million

1.6 Million

MDRTB

424,000

116,000

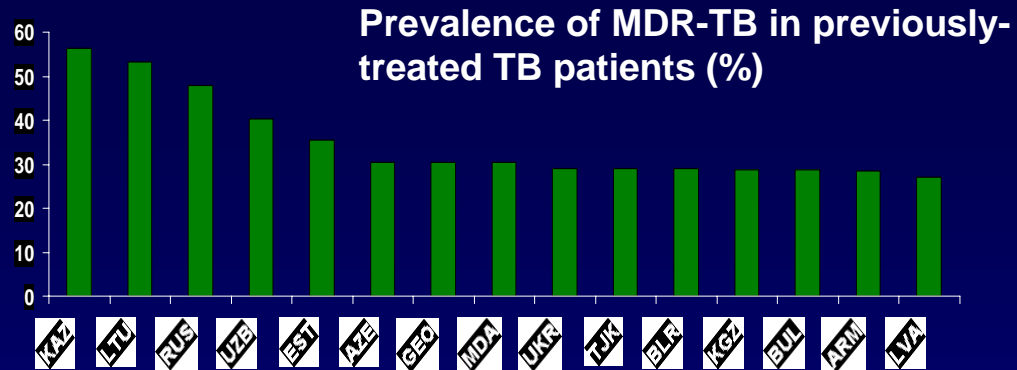
XDR-TB

27,000

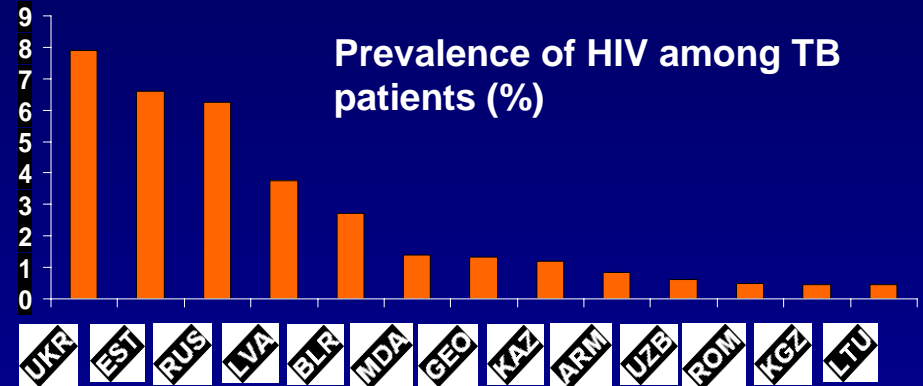
16,000

Challenges for TB control in the WHO/Europe

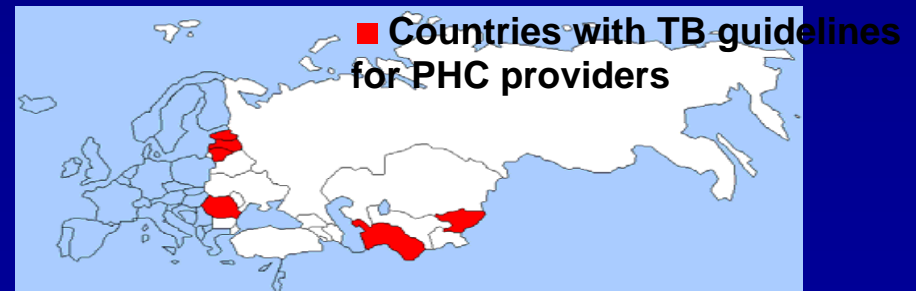
Multidrug resistant TB (MDR-TB) about 70,000 per year, among them up to 20% are XDR-TB - virtually untreatable



HIV-related TB (TB/HIV) from increasing pool of PLWH



Health systems weak and under reform



TB in the European Union (EU)

50/100 000 - overall TB incidence in WHO/Europe

13/100 000:

first fifteen members of the EU

27/100 000:

ten new members of the EU (enlargement in 2004)

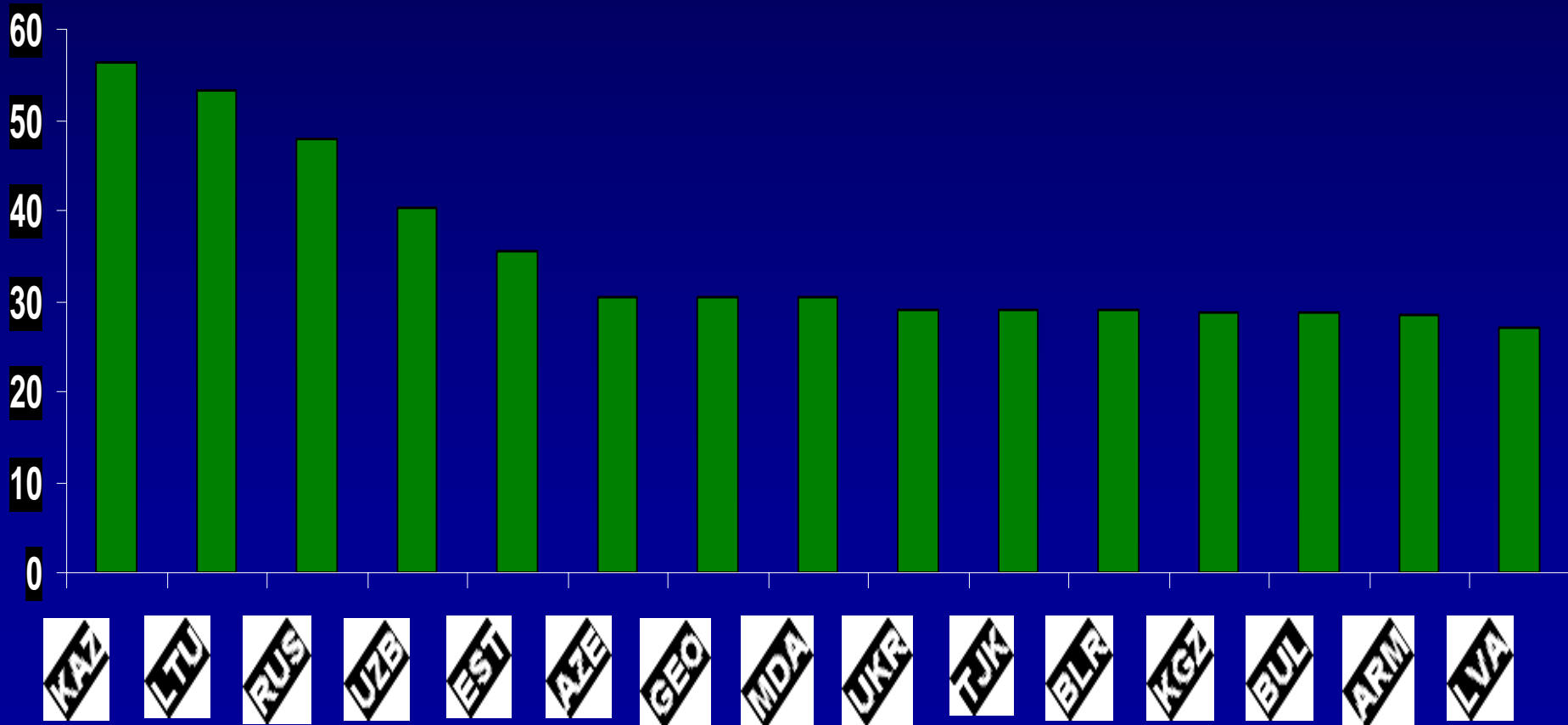
53/100 000:

four countries accessing the EU

98/100 000:

countries bordering EU

Prevalence of MDR-TB in previously-treated TB patients (%)



Challenges for TB control

- **Insufficient political and financial commitment (lack of human and financial resources)**
- **TB in prisons (incidence 50 times and mortality 28 times higher than in civil sector)**
- **Immigration from high burden countries**

Factors in spread of MDR TB

Causes of inadequate antituberculosis treatment

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS

Inappropriate guidelines
Noncompliance with
guidelines
Absence of guidelines
Poor training
No monitoring of
treatment
Poorly organized or funded
TB control programmes

DRUGS: INADEQUATE SUPPLY/QUALITY

Poor quality
Unavailability of certain
drugs (stock-outs or
delivery disruptions)
Poor storage conditions
Wrong dose or
combination

PATIENTS: INADEQUATE DRUG INTAKE

Poor adherence (or poor
DOT)
Lack of information
Lack of money (no treatment
available free of charge)
Lack of transportation
Adverse effects
Social barriers
Malabsorption
Substance dependency
disorders

Risk Factors for MDR-TB

- **Any past history of tuberculosis, particularly if there has been erratic or incomplete treatment**
- **Contact with a person with know drug-resistance**
- **Birth, travel or residence in an a high prevalence area of resistance**
- **Persistently positive sputum smears after two months' anti-tuberculosis treatment or**
- **Positive sputum culture after three months' treatment**

“Amplifier effect”

- Short-course chemotherapy for patients infected with drug-resistant strains may create even more resistance to the drugs in use.

Drug resistance

Country of origin

Population

Primary Resistance Rate

- New arrivals from Haiti 32%
- Haitians living in USA 12%
- non- Haitians 4.5%

Does initial H resistance lead to MDR-TB?

Treatment with short course TB Rx

	N	(%)
• Resistant to H	320	
• Treatment failure	60	(19)
• MDR	32	(10)

Close contacts of MDR-TB

Index	N	contact time months	PPD+ve	Active TB
-------	---	------------------------	--------	-----------

- MDR 133 43 44% 4%
- D-S 231 3-4 37% 4%

Is HIV an independent risk factor for MDR-TB ?

- Outbreaks associated with HIV
- Outside of outbreaks are HIV patients more likely to have MDR-TB?
- Poor drug absorption?

MDR-TB SA

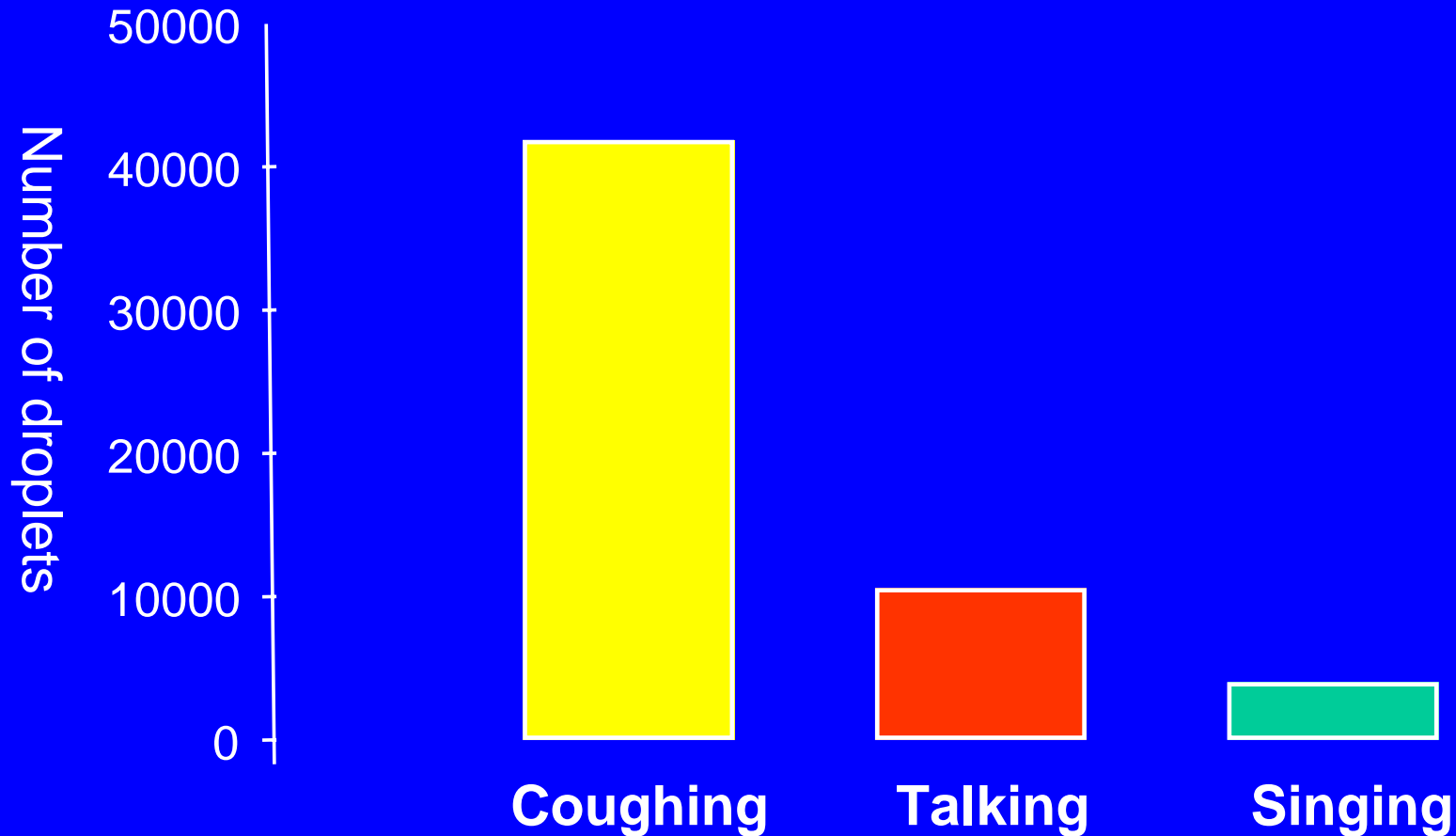
	HIV+	HIV-
N(%)	42	253
MDR	1(2)	29(12)
R>1 only	14(33)	93(37)

Anastasis IUTLD 1997

MDR-TB

Outbreaks

Number of Droplets produced by Different Aerosol Producing Manoeuvres



Loudon RG, et al. Am Rev Respir Dis 1968;98:297-300

MDR - TB outbreaks

- **Factors responsible**

- Inadequate control programmes
- Inadequate compliance
- Infection control procedure breakdown
- **Immunosuppressed convergence**
- Index of suspicion low
- Inadequate lab. communication
- Infectiousness prolonged

MDR - TB outbreaks

?where

- hospitals
- clinics HIV // substance abuse
- prisons
- shelters

HIV associated multi- drug-resistant tuberculosis outbreaks January 1990 to August 1992 in USA

Facility	Total cases	Resistance pattern	HIV infection %	Mortality	Median interval TB diagnosis to death
Hosp A	65	H, R, (E,Eth)	93	72	7
Hosp B	35	H,S,(R,E)	100	89	16
Hosp C	70	H,R,S (E,Eth,Ka,B)	94	82	4
Hosp D	29	H,R (E,Eth)	91	83	4
Hosp E	7	H,R,S(E Eth Ka RB)	20	60	4
Hosp F	16	H,R,S (Eth Ka RB)	82	82	4
Hosp G	13	HR (E)	100	85	4
Prison System	42	HR (S,E, Eth,Ka,RB)	91	74	4

Common RFLP Types New York 1991 - 4

Type	No of patient	No of hospitals	
W	199	30	MDR
P	30	15	MDR
N2	30	16	MDR
W1	24	16	MDR
AB	20	10	MDR

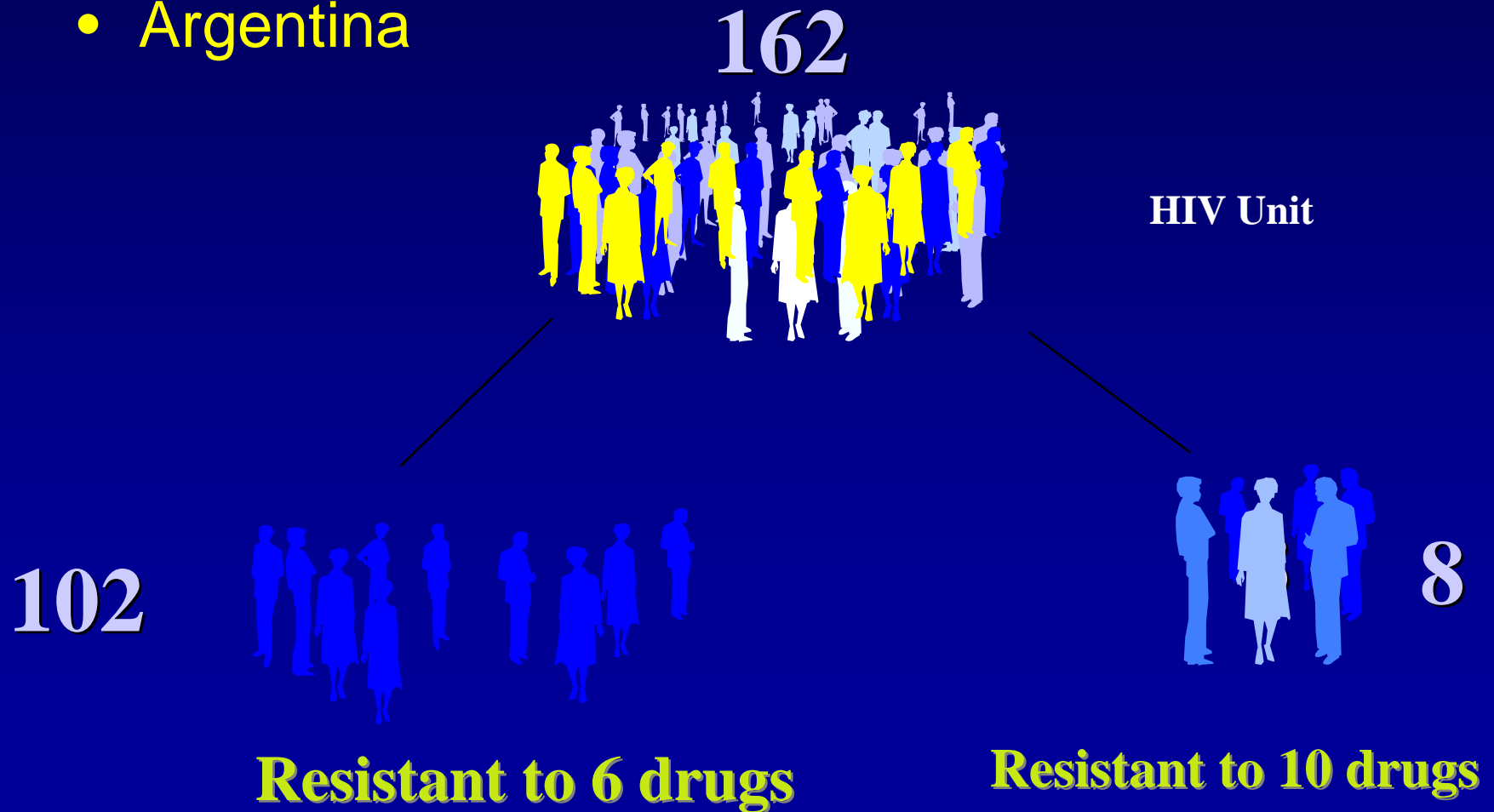
Reports on the control of outbreaks of noscomial tuberculosis at acute health are facilities

Control measure (s) used

Location, hospital	Admin measures	Engineering measures	PPE masks
Miami, Hospital A	Extensive	Extensive	Submicron
Miami, Jackson Mem.	Extensive	Extensive	Submicron
New York, Hospital D	Extensive	Extensive	Submicron
New York, Cabrini	Extensive	Exhaust fans	Extensive
New York, Roosevelt	Extensive	Later	Not stated
Atlanta, Grady Mem.	Extensive	Exhaust fans	Submicron

MDR – TB outbreak

- Argentina



MDR -TB

- Mortality
 - 87 died prior to Rx starting
 - 49 died on standard Rx
 - 10 died on tailored Rx
 - 16 alive on tailored Rx
- Epidemiology
 - 77/92 indistinguishable RFLP TYPE
 - all 77 contact with index case
- Control
 - cohort nursing
 - contact tracing

cost of 1case =£60000 in UK

Outbreak 1-UK

- Index + 7 other all HIV+ 2 alive now
- 187 HIV+ contacts
- 60 staff
- 57 community contacts

Outbreak 2-UK

- Index HIV- + 6 other HIV+
- 1298 general medical patients exposed
- 169 recalled
- 898 staff
- 64 HIV patients
- 476 HIV outpatients
- R H,R, ANS, Clo, Cyclo+/- Z, Cla, Cip
- S Eth, Cap, Strep, Ethio, Amik
- Prophylaxis PAS + ETH offered to 400
- 12 on prophylaxis 10 stopped most by 2 wks

XDR TB

Emergence of XDR-TB

March 2006



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 infectious disease. An estimated 2 billion persons (i.e., one third of the world's population) are infected with *M. tuberculosis*. Each year, approximately 9 million persons become ill from TB, and approximately 2 million die as a result. World TB Day provides an opportunity for TB programs, nongovernmental organizations, and other partners to describe TB-related problems and solutions and to support TB control worldwide.

During 1985–1992, after more than 30 years of decline, the number of TB cases reported in the United States increased by 20%. This resurgence generated a renewed emphasis on TB control and prevention during the 1990s, which reversed the trend. Although the 2005 TB rate was the lowest recorded in the United States since national reporting began in 1953, the average annual decline has slowed during the past 3 years, multidrug-resistant TB remains a threat, and disparate rates of TB persist among certain racial, ethnic, and foreign-born populations.

Many states are offering educational programs organized by local TB coalitions in recognition of World TB Day. For example, the Georgia Department of Human Resources, Division of Public Health, Tuberculosis Program is hosting an observance recognizing the activities of a coalition working to reduce disparities in TB among blacks in the Atlanta area. Additional information about World TB Day and CDC TB-elimination activities is available at <http://www.cdc.gov/nceh/tb/worldtbdays/2006/activities.htm>.

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, emerged as a threat to TB control, both in the United States (1) and worldwide (2). MDR TB treatment requires the use of second-line drugs (SLDs) that are less effective, more toxic, and costlier than first-line isoniazid- and rifampin-based regimens (3). In 2000, the Stop TB Partnership's Green Light Committee was created to increase access to SLDs worldwide while ensuring their proper use to prevent increased drug resistance. While assisting MDR TB treatment programs worldwide, the committee encountered reports of multiple cases of TB with resistance to virtually all SLDs. To assess the frequency and distribution of extensively drug-resistant (XDR) TB cases,* CDC and the World Health Organization (WHO) surveyed an international network of TB laboratories. This report summarizes the results of that survey, which determined that, during 2000–2004, of 17,690 TB isolates, 20% were MDR and 2% were XDR. In addition, population-based data

* Defined as cases in persons with TB whose isolates were resistant to isoniazid and rifampin and at least three of the following classes of SLDs (antifolate, glycopeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid).

INSIDE

- 305 Trends in Tuberculosis — United States, 2005
- 306 Increased Use of Colorectal Cancer Tests — United States, 2002 and 2004
- 311 Update: Influenza Activity — United States, March 5–11, 2006
- 313 Notice to Readers
- 315 Contents

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

XDR = Multidrug-resistant TB (MDR-TB) plus resistance to (i) any *fluoroquinolone*, and (ii) at least 1 of 3 injectable second-line drugs *capreomycin*, *kanamycin*, *amikacin* (new definition agreed October 2006)

MDR-TB = resistance to at least *isoniazid* and *rifampicin*, the two most powerful first-line anti-TB drugs

Of 17,690 isolates from 49 countries during 2000–2004, 20% were MDR-TB and 2% were XDR-TB

XDR-TB found in:
USA: 4% of MDR-TB
Latvia: 19% of MDR-TB
S Korea: 15% of MDR-TB

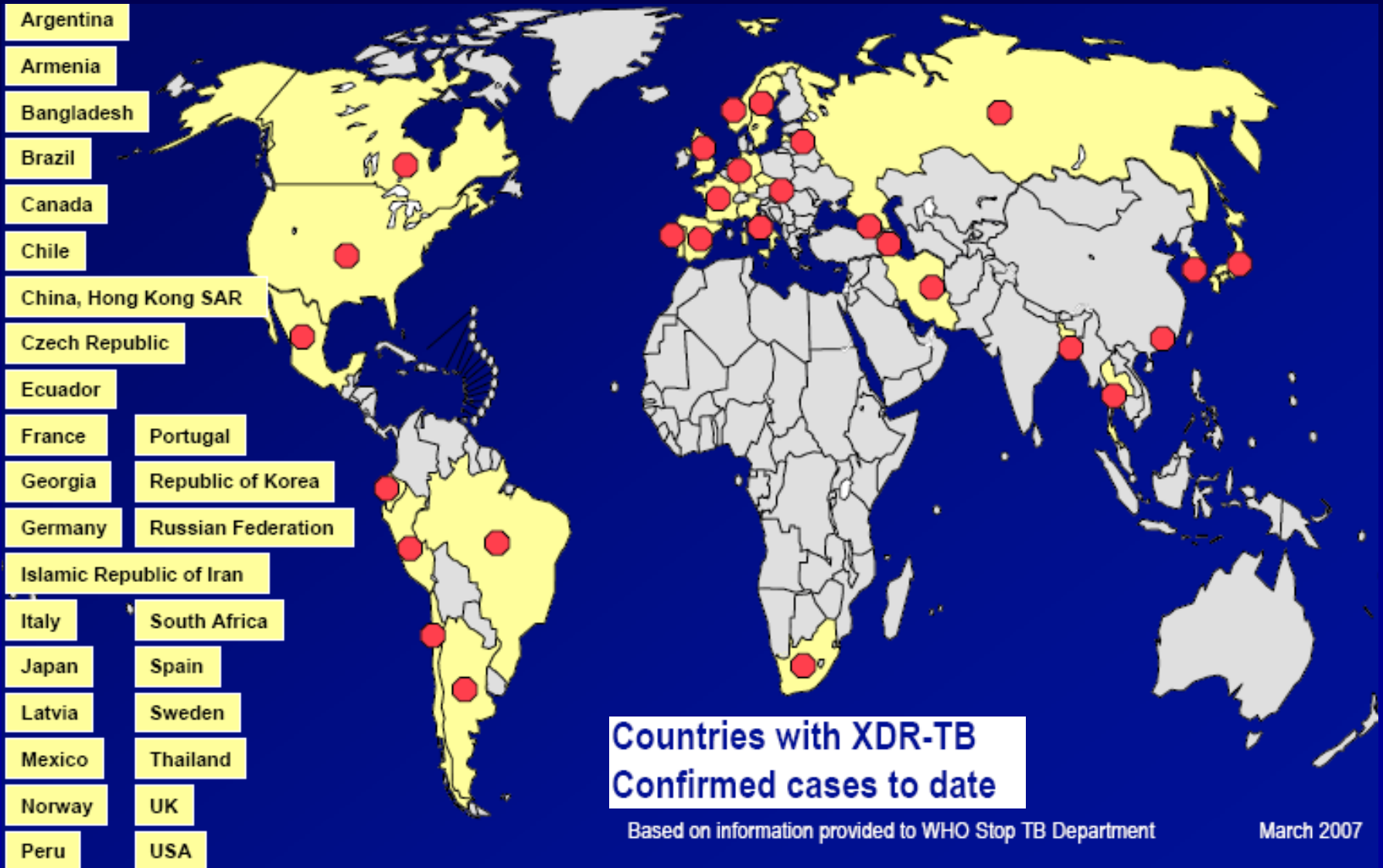
Extensive drug resistance TB / XDR-TB

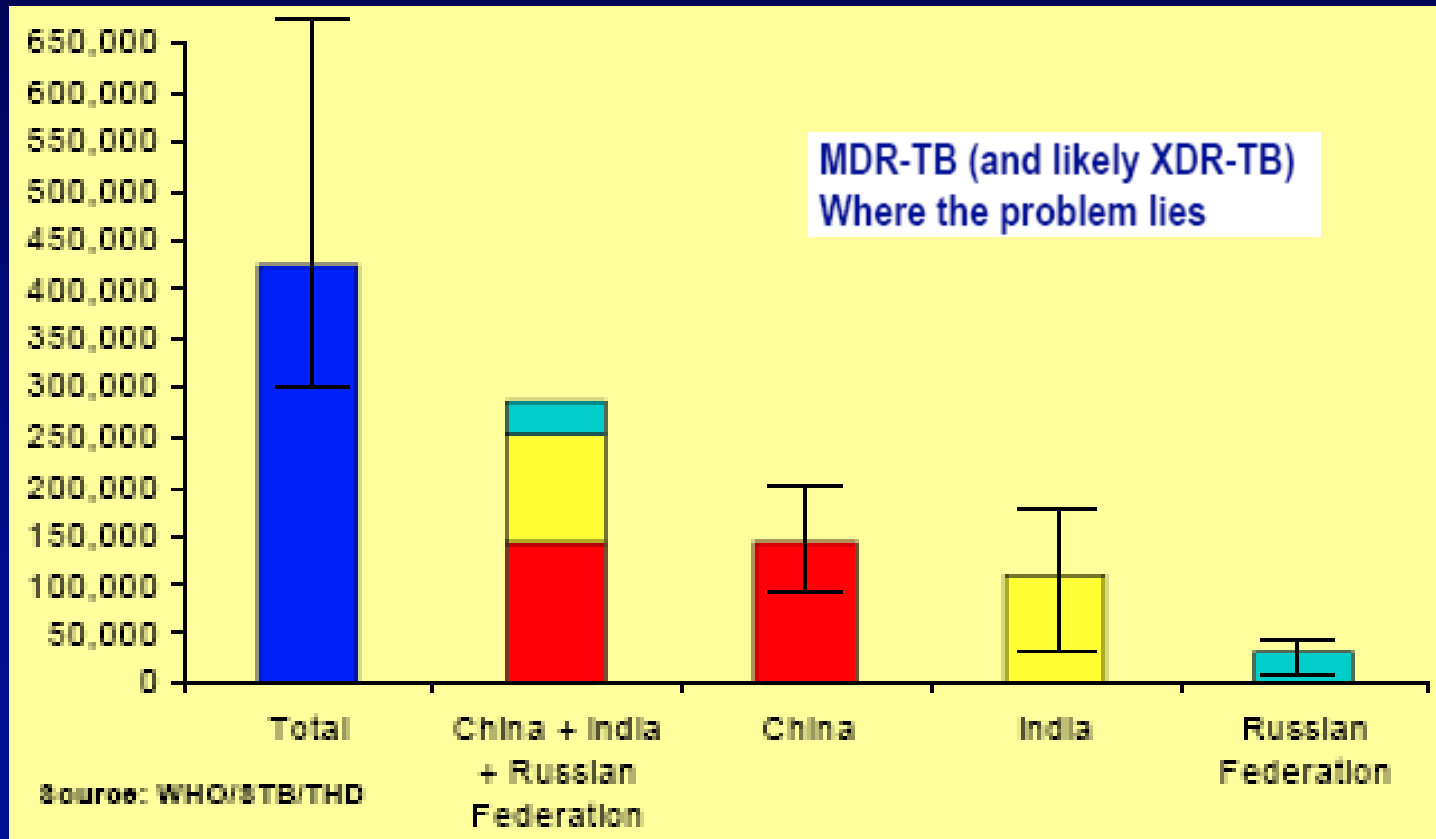
- XDR-TB documented in all regions of the world surveyed
- National representative data showed that in USA 4% of MDR-TB were XDR-TB, while the figure in Latvia was 19%.

CDC's Morbidity and Mortality Weekly Report, March 2006

- Joint WHO/CDC survey of 14 supranational TB reference laboratories using samples from 48 countries

Countries with confirmed XDR-TB





The bulk of the problem of XDR-TB resides in those countries with high numbers of MDR-TB and two thirds of MDR is in just 3 countries - China, India and the Russian Federation.

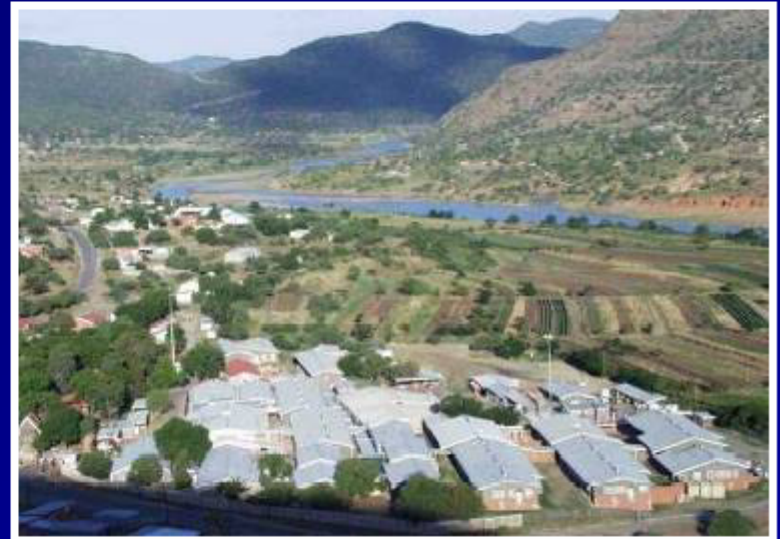
XDR-TB in Southern Africa

August 2006



Church of Scotland Hospital, Tugela Ferry, KwaZulu-Natal Province, South Africa

- 53 of 544 patients defined as XDR-TB cases
- 52 of the 53 patients died on average within 25 days, including those on antiretroviral therapy
- Further investigations being carried out
- XDR-TB likely in bordering African countries



Given the underlying HIV epidemic in Africa,
drug-resistant TB could have a major impact on mortality
and requires urgent action on care and prevention

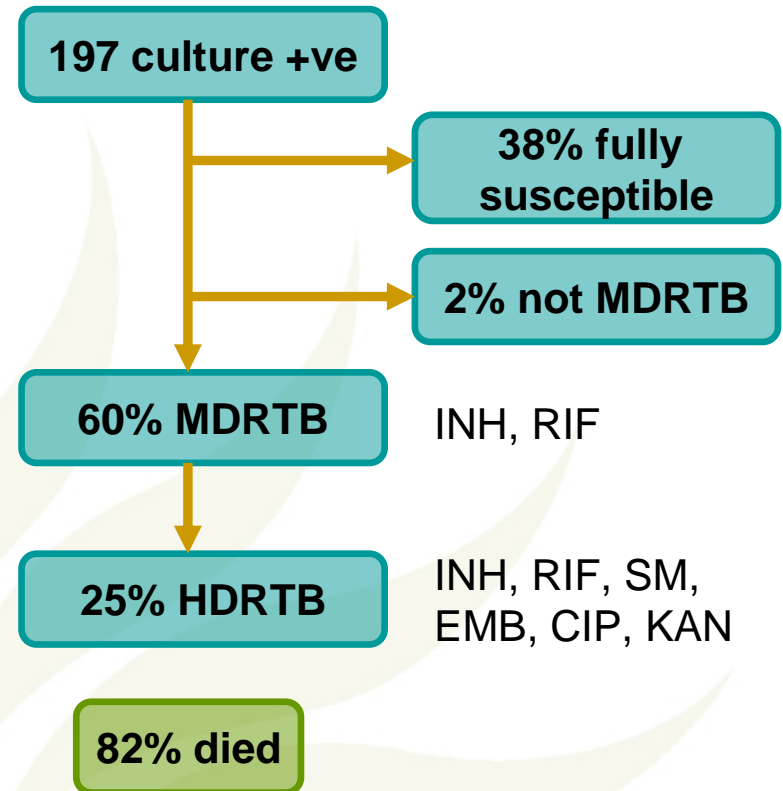
MDRTB more common than sensitive TB in rural Kwa-Zulu

- **Background:**

- TB leading cause of death in S. Africa
- 83% TB cases HIV +ve
- Case fatality 40% despite DOT
- Typing identified 6-drug MDRTB strain in Kwa-Zulu

- **Design:**

- Retrospective X-sectional analysis rural hospital
- All suspected / confirmed TB cases Feb – Dec 05
- Sample spoligotyped



Conclusion: highly resistant MDRTB common in rural Kwa-Zulu

Treatment

MDR DOTS strategy

- Sustained political commitment
- A rational case-finding strategy including accurate, timely diagnosis through quality-assured culture and DST
- Appropriate treatment strategies that use second-line drugs under proper case management conditions
- Uninterrupted supply of quality-assured antituberculosis drugs
- Standardized recording and reporting system

Antituberculosis Drugs

First-Line Drugs

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine

Second-Line Drugs

- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin*
- Moxifloxacin*
- Gatifloxacin*

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB

Other drugs

- **clofazimine**
- **clarithromycin**
- **azithromycin**
- **sparfloxacin**
- **thiacetazone**
- **amoxicillin - clavulanate**
- **rifabutin**

Treatment Principles

- Single new drug should never be added to a failing regimen; it may lead to acquired resistance to the added drug
- Add at least three new drugs (e.g., fluoroquinolone, ethionamide, and an injectable drug: SM, amikacin, kanamycin, or capreomycin) to the existing regimen being cognizant of the possibility of drug resistance

Potential Regimes for Patients with Tuberculosis with Various Patterns of Drug Resistance

Resistance	Suggested Regimen	Duration of Therapy
H S Z	R Z E	6 - 9 m
H E +/- S	R Z OFL or CIP AMK	6 - 12m
H R +/- S	Z E OFL or CIP AMK	18 - 24 m
H R E +/- S	E OFL or CIP AMK plus 2	24m after con
H R Z +/- S	E OFL or CIP AMK plus 2	24m after con
H R Z E +/-S	OFL or CIP AMK plus 3	24m after con

New TB drug pipeline : GOOD NEWS?

AIDSMAP.COM

(NEWS) DEC 05

DRUG DISCOVERY		PRE-CLINICAL	CLINICAL TRIALS
Carboxylates GATB, Wellesley College	Nitrofuranylamides NIAID, University of Tennessee	Diamine SQ-109* Sequella Inc	Moxifloxacin Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, GATB
Cell Wall Inhibitors Colorado State University, NIAID	Nitroimidazole Analogs NIAID, Novartis Institute for Tropical Diseases, GATB	Dipiperidines (SQ-609) Sequella Inc.	Gatifloxacin OFLOTUB Consortium, Lupin, NIAID TBRU, Tuberculosis Research Centre, WHO TDR
Dihydrolipoamide Acyltransferase Inhibitors Cornell University, NIAID	Novel Antibiotic Class GlaxoSmithKline, GATB	Non-Fluorinated Quinolone TaiGen	TMC207 Diarylquinoline Johnson & Johnson
InhA Inhibitors GlaxoSmithKline, GATB	Picolinamide Imidazoles NIAID, TAACF	Synthase Inhibitor FAS20013* FASgen Inc.	Nitroimidazole PA-824 Chiron Corporation, GATB

New TB drug pipeline

AIDSMAP.COM (NEWS) DEC 05

DRUG DISCOVERY

PRECLINICAL

CLINICAL TRIALS

Isocitrate Lyase Inhibitors (ICL) GlaxoSmithKline, GATB	Pleuromutilins GlaxoSmithKline, GATB	Translocase I Inhibitors* Sequella Inc., Sankyo	Nitroimidazo-oxazole, OPC-67683 Otsuka Pharmaceuticals
Macrolides GATB, University of Illinois at Chicago	Quinolones KRICT/ Yonsei University, NIAID, TAACF, GATB		Sudoterb, Pyrrole LL-3858 Lupin Limited
Methyltransferase Inhibitors Anacor Pharmaceuticals	Screening and Target Identification AstraZeneca		
Natural Products Exploration BIOTEC, California State University, ITR, NIAID, TAACF, University of Auckland	Thiolactomycin Analogs NIAID, NIH		

Last chance saloon

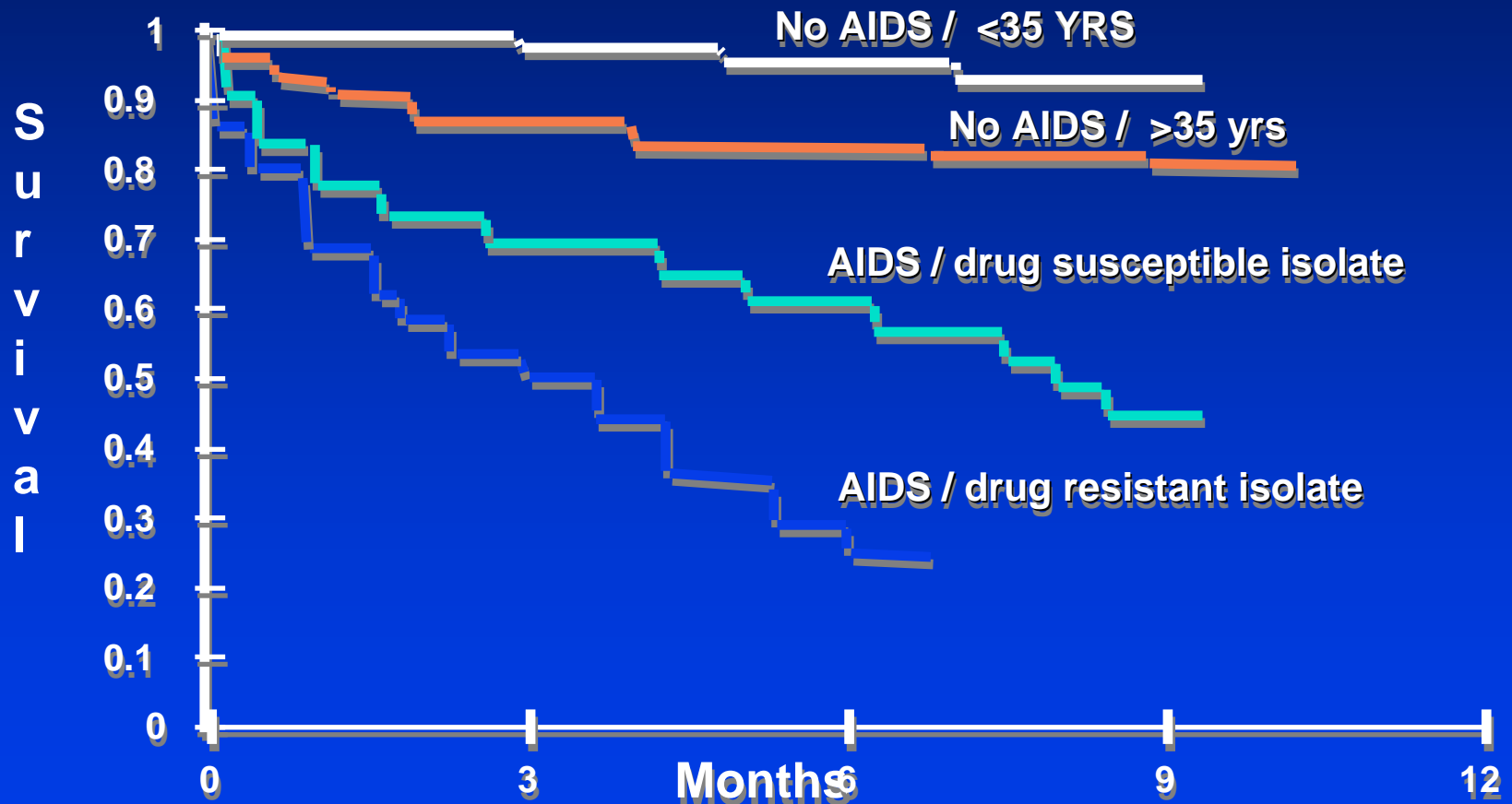
- Pulmonary resection - Local disease
 - Good C-P reserve
 - Mycobacterial burden low
- Immune stimulants - *M.vaccae*
 - Interferon alpha Aerosol

Prevention of MDR TB in contacts

- If infection and disease progression likely then:
 - ethambutol and pyrazinamide
 - ofloxacin / ciprofloxacin & pyrazinamide
 - ?BCG

Outcomes

Survival in patients with proven MTB and no prior therapy



MDR - TB

HIV negative

- 7-8 months in hospital
- 30% adverse drug reaction
- 35% treatment failure
- 14% relapse
- 46% death

Predictors of Survival

- Starting two drugs to which the organism is susceptible within two weeks of diagnosis

The March of Resistance



*or limited resistance manageable with 4 drug regimen - DOTS

Resistance to H&R –
Treatable with 2nd line drugs

Resistance to 2nd line drugs –
treatment options seriously restricted

Resistance to all available drugs – **no treatment options**

§ Worse outcomes in people with HIV infection

MDR TB

Dr A.L. Pozniak

**Chelsea and Westminster Hospital
London, UK**