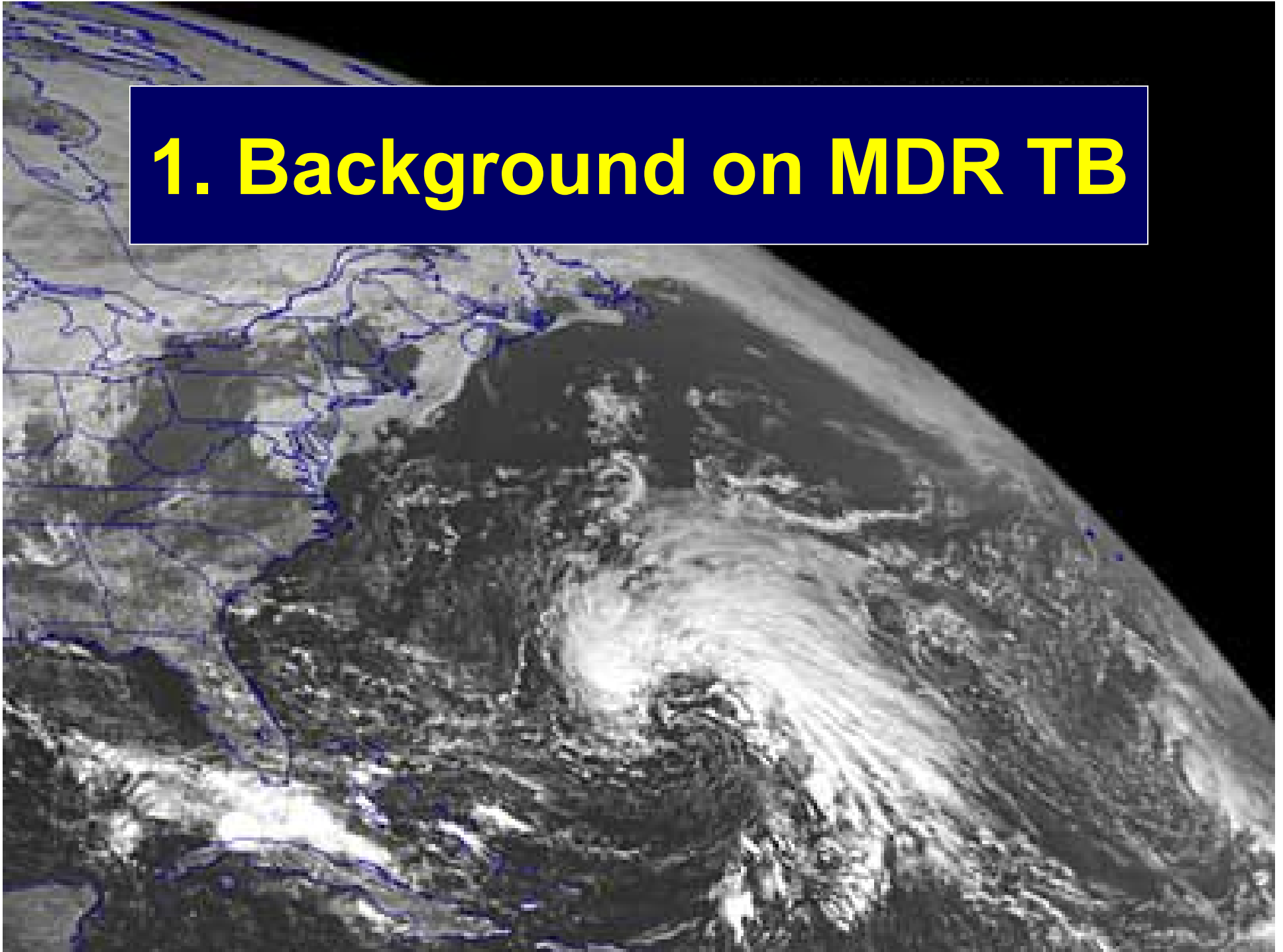




HIV – MDR/XDR TB The Perfect Storm?

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Department of Health and Human Services

1. Background on MDR TB



Multidrug Resistant (MDR) TB

- TB with resistance to isoniazid and rifampin
- Results from poor TB programs
 - Low completion rates / poor clinical practices
 - Erratic supply and poor quality of drugs
- Results in:
 - Longer treatment (6mos→24mos)
 - Toxic, complicated regimens (4-6 mos inj.)
 - Cost/case increases by 10 to 100-fold
- Leads to:
 - Lower cure rates (<80%)
 - Higher death rates (with HIV)
- Poor infection control + MDR TB + HIV = disaster

MDR TB Outbreaks in Industrialized Countries, 1988-1995

High Mortality with HIV Infection

Facility	% HIV-infected	% Mortality	Median interval (weeks)
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. Argen.	98	79	4

First-line Drugs and Treatment of Drug-susceptible TB

1. Isoniazid
 2. Rifampicin
 3. Pyrazinamide
 4. Ethambutol
 5. Aminoglycosides
 6. Capreomycin
 7. Quinolones
 8. Thioamides
 9. Cycloserine
 10. PAS
- Standardized TB treatment
 - 4 drugs, 6-9 months
 - Safe, effective, inexpensive
 - 95% cure, \$20 (drug costs)
 - Based on evidence from ~ 30 years of drug discovery and clinical trials



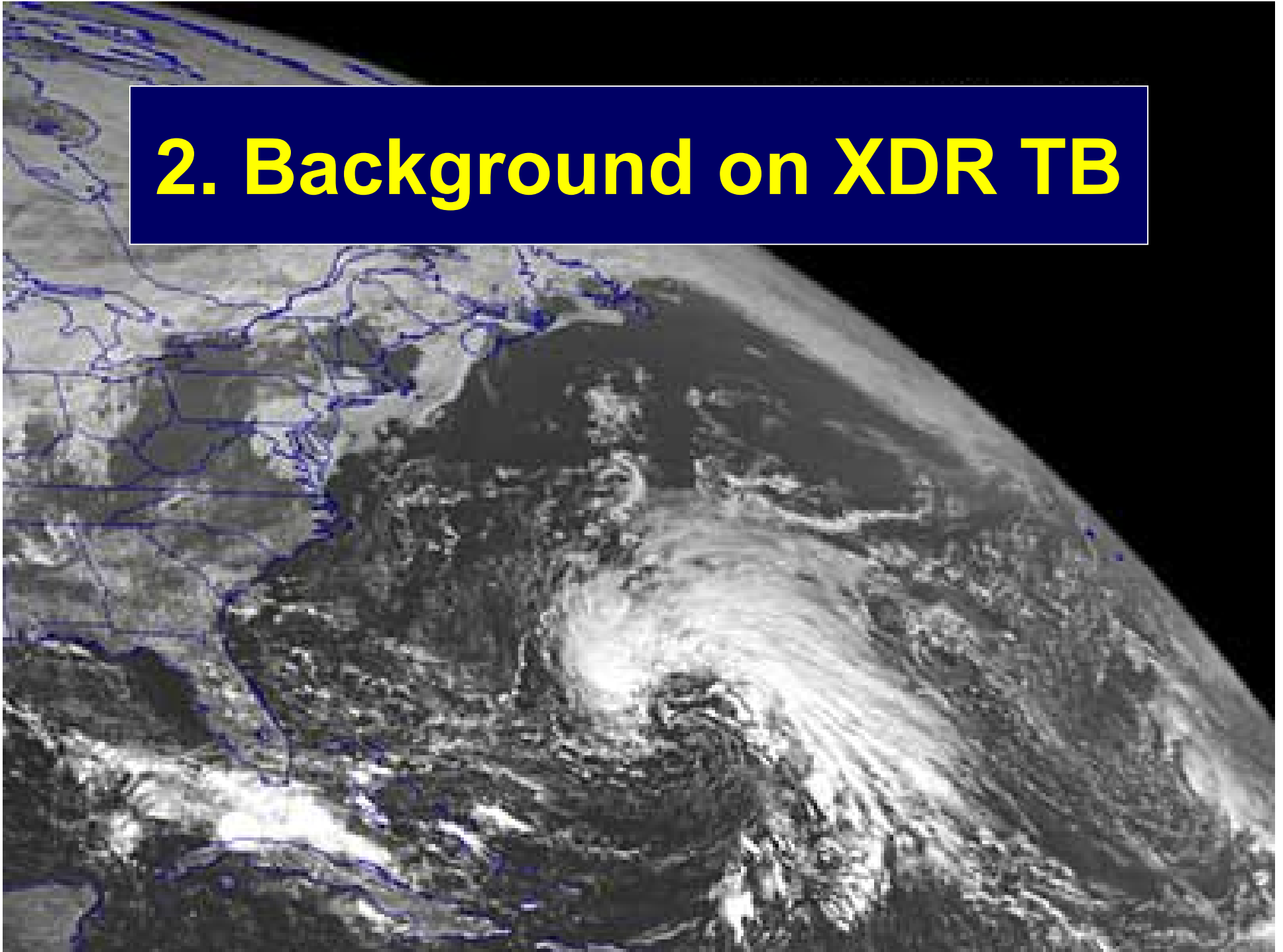
Second-line Drugs and Treatment of Multidrug-Resistant TB

1. Isoniazid
2. Rifampicin
3. Pyrazinamide
4. Ethambutol
- 5. Aminoglycosides**
- 6. Capreomycin**
- 7. Quinolones**
- 8. Ethionamide**
- 9. Cycloserine**
- 10. PAS**

- Treatment based on laboratory drug-resistance testing and epidemiology information
- 4-6 drugs, 2 years
- Less effective, ↑ toxicity and \$
- <80% cure
- \$3,500 - \$5,000 (drug costs)
- No clinical trials evidence to guide treatment or prevention



2. Background on XDR TB





MMWRTM

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 infectious disease. An estimated 2 billion persons (i.e.,

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

Extensively Drug Resistant TB (XDR TB)

- Inadequate MDR TB treatment → 2nd-line drug resistance
- MDR TB with resistance to multiple 2nd-line drugs may be virtually untreatable
 - ≥4 classes needed for MDR TB treatment
 - Flouroquinolones and injectable agents are key
- CDC / WHO undertook survey to map extent of 2nd-line drug resistance
- Surveyed 14/24 SNR labs during 2005-06
- Collected data on >17,000 TB isolates tested by SNRLs during 2000–2004



Extensively Drug Resistant (XDR) TB

“A Tale of Two Definitions”

- **XDR** ^(3/06-10/06) - MDR TB + resistance to $\geq 3/6$ of major classes of 2nd-line drugs
 - Need \geq four 2nd-line drugs for Rx
- **XDR** ^(Since 10/06) - MDR TB + resistance to at least Fq & any injectable 2nd-line (amikacin, kanamycin, capreomycin)
 - Need at Fq + injectable for better outcomes
 - Treatment outcomes (Latvia) - ~60% vs. <30%



Extensive Drug Resistance Among MDR TB Isolates Submitted to 14 SNR Labs, by Region 2000–2004

Geographic Region	Total MDR TB (n)	XDR TB n (%)
Industrialized nations	821	53 (6)
Latin America	543	32 (6)
Eastern Europe	406	55 (14)
Africa and Middle East	156	1 (<1)
Asia	1,572	204 (13)
Total	3,418	345 (10)

Conclusions from SNR Lab Survey

- **Worldwide occurrence of XDR TB**
- **XDR TB in countries and regions already having high rates of MDR TB**
- **Poorly controlled use of 2nd-line drugs for MDR TB treatment is occurring**

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PUBLISHED IN SOUTH AFRICA



The Zuma saga
Page 5

9/11 FIVE YEARS ON
Special Report
Pages 13 to 15



End of a dynasty
Page 12

Killer TB tightens fatal grip

Despite indications that SA is in the forefront of infection, health minister tries to put a clamp on news and snubs global conference

BY CHRIS MAKHAYE
AND CHARLENE SMITH

Itzhak Meir Shtrikman died in the Church of Scotland Hospital, Tugela Ferry, in the early hours of Thursday. He was the latest victim of extreme drug-resistant tuberculosis (XDR-TB) - a deadly strain of the disease that kills almost everyone who contracts it and is almost impossible to cure.

It was announced at an emergency international conference in Johannesburg this week that XDR-TB is being recorded across South Africa, Lesotho, Mozambique and Swaziland. Yet, while it appears to be a huge problem in South Africa, nobody from the health department attended the seminar, having been reportedly ordered by Manto Tshabalala-Msimang, the health minister, to stay away.

Tuberculosis is airborne and stays in the air for four hours after an infected person has left a room. Research completed this month in Mpumalanga by the Medical Research Council shows that multi-drug resistant tuberculosis (MDR-TB, the parent of XDR-TB) is significantly more infectious than was first believed.

South Africa has the world's second worst rate of MDR-TB, with 8-100 cases a year. It emerges when TB treatment is not administered effectively.

But while some need to be aware of it from World Health Organisation offices in Europe, the Centre for Disease Control in the United States and all the Southern African Development Com-



Zenobe Madonsela sits next to her daughter in the female ward at the Church of Scotland hospital in Tugela Ferry, KwaZulu-Natal

PHOTO: KENNETH

missioned patients and warned them not to speak to the media or allow journalists into their premises.

11 patients in the ward, with three more waiting to be admitted. The hospital is the site of a number of

At Church of Scotland Hospital the first case of XDR-TB was recorded in February 2005. The woman has a

medical manager and acting hospital manager, said some hospital staff had died but could have contracted the

Prospect of an epidemic sets medics trembling

BY CHARLENE SMITH AND LIZ CLARKE

At just one small hospital in Tugela Ferry a sixth of the world's known XDR-TB cases have been found.

Dr Tony Mall of Church of Scotland Hospital at Tugela Ferry said: "We have seen HIV move in and create havoc in our community. We tremble in our boots with XDR-TB. Up to 86 percent of new cases are TB co-infected with HIV."

A large proportion of deaths were attributed to Aids, but a recent study from January 2005 to March 2006 shows that 71 percent of those receiving antiretrovirals who died had MDR-TB.

"Worldwide, there are 347 cases of XDR-TB. We picked up 53 cases in our small hospital alone; 51 percent had no prior TB, 28 percent had prior treatment and 14 percent were newly infected with drug resistant strains. We lost two health workers to XDR-TB."

He said "28 of the 53 died within 16 days of sputum collection; many died before sputum results came out. We have two to five new patients with XDR-TB each month."

A South African scientist who has supervised the clinical research said this week that "the options for patients with this extreme strain" were not running out - they had already run out.

There were no alternative drugs available, warned Professor Umesh Laloo of the University of KwaZulu-Natal's Nelson Mandela School of Medicine in Durban, the leader of MDR-TB research at Tugela Ferry.

"Several drugs are under investigation but still far from clinical use. That is why this is such a tragedy. It shows more than ever the urgent need to fast-track TB drug development, but even

epidemic," said Laloo.

All those in contact with the extreme form of TB were at risk of developing it, including health personnel: "That is the calamity."

Patients diagnosed with MDR-TB should be hospitalised to ensure adherence and efficacy, he said. "The support and tracking of such patients is central to any programme to manage and prevent the spread of MDR-TB."

While all the resources needed were in place, having freely available drugs was a serious problem if they were not issued as part of a well-defined programme: "We are the most resourced country on the continent in respect of TB, yet we have one of the worst cure rates for TB."

Fifty-two of the 53 patients diagnosed with MDR-TB have already died at Tugela Ferry and continuing research points to the strain having spread to other regions of the country.

The extent of this virtually untreatable strain is not known, however, as mass screening is expensive and difficult to monitor. Many patients are dying without having been diagnosed. All 53 patients studied so far had XDR-TB.

And the place where you are most likely to catch a lethal strain of TB? In a South African hospital, because of inadequate infection controls there.

Dr Karin Weyer, who heads the Medical Research Council's TB programme, said: "South Africa is the epicentre of HIV and TB. HIV has the capacity to fast-track MDR into an uncontrollable epidemic. If the epidemic gets out of control the impact... could be severe."

Professor Rob Warren of Stellenbosch University has been genotyping XDR-TB. He said it had been found in KwaZulu-Natal, Limpopo, Western

XDR TB Outbreak, Rural KZN Province South Africa, 2005-06

- **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 (SLD) for TB**
 - **INH, RIF, EMB, STR, KANA, CIPRO**
- **Suggestive of probable extensive drug resistant TB in this hospital**
- **Prompted survey Jan 2005-Mar 2006**

* 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)

KZN Drug Resistant TB Survey*

1539 isolates tested

542 (35%) Cx+
M. tuberculosis

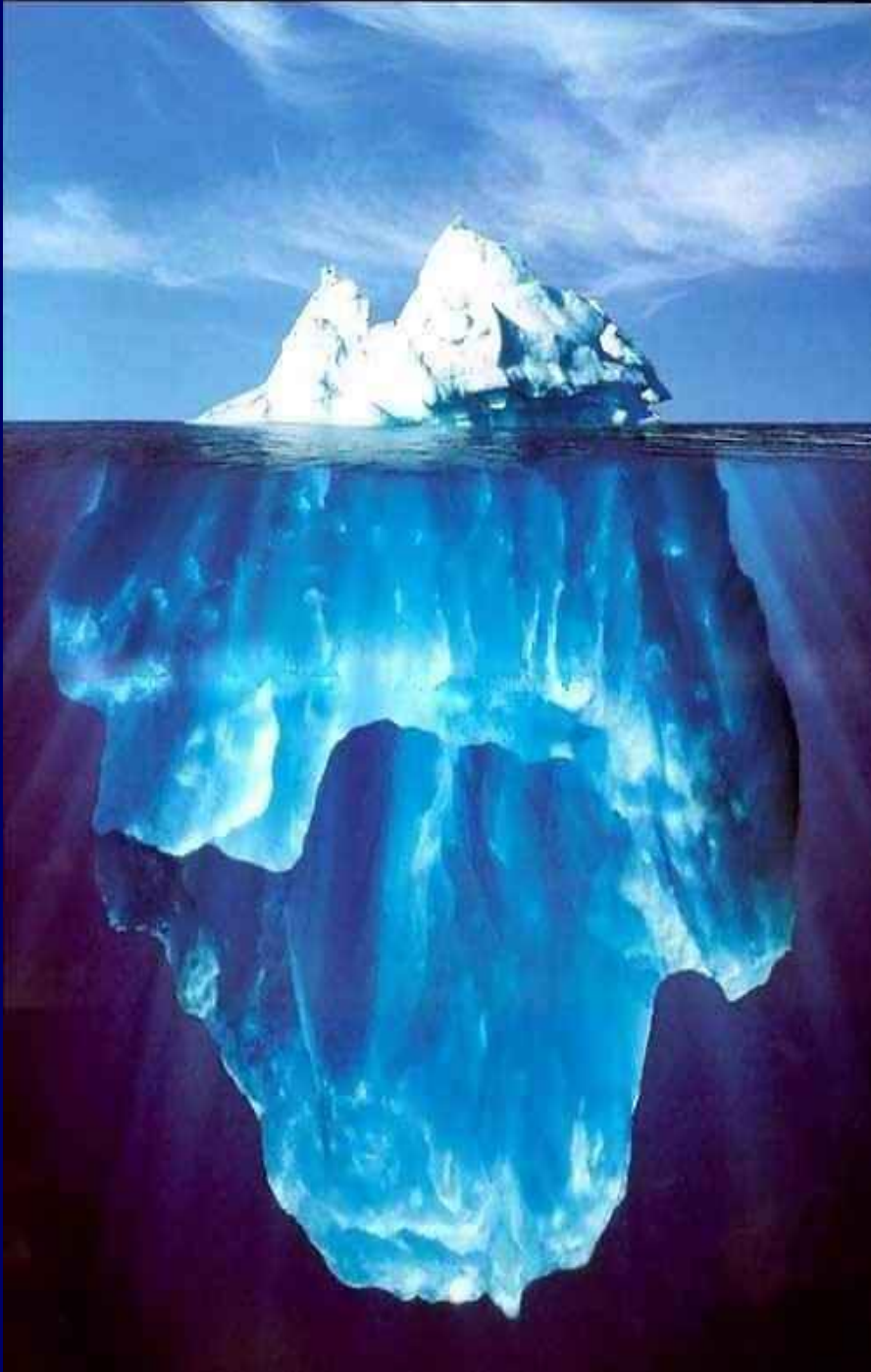
995 (65%) Cx Negative

221 (41%) MDRTB

323 (59%) Susceptible

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

* Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, Zeller K, Andrews J, Friedland G. Extensively Drug-Resistant TB 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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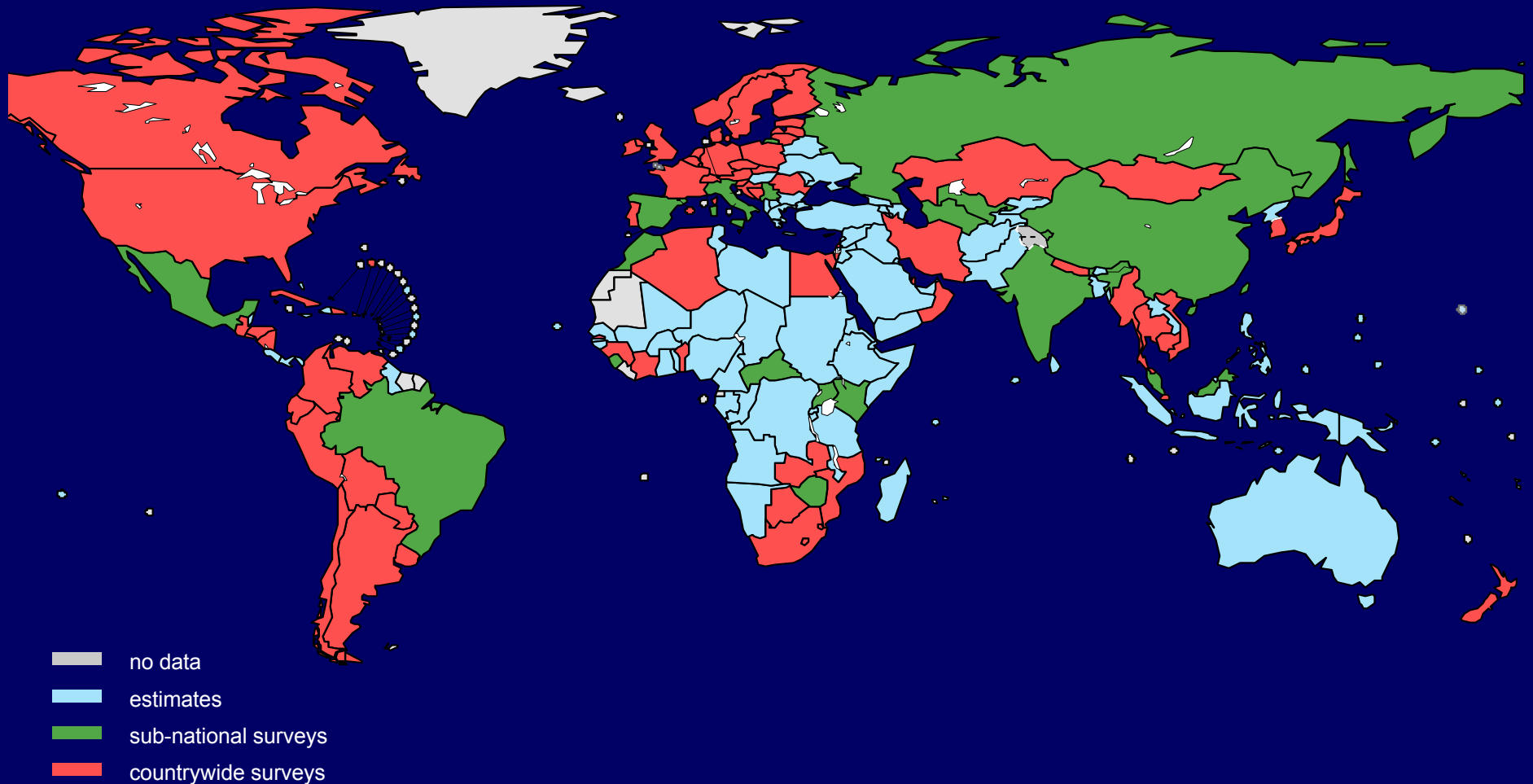
Global Burden of MDR TB

[N= ~425,000]

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

Zignol et al, JID 2006

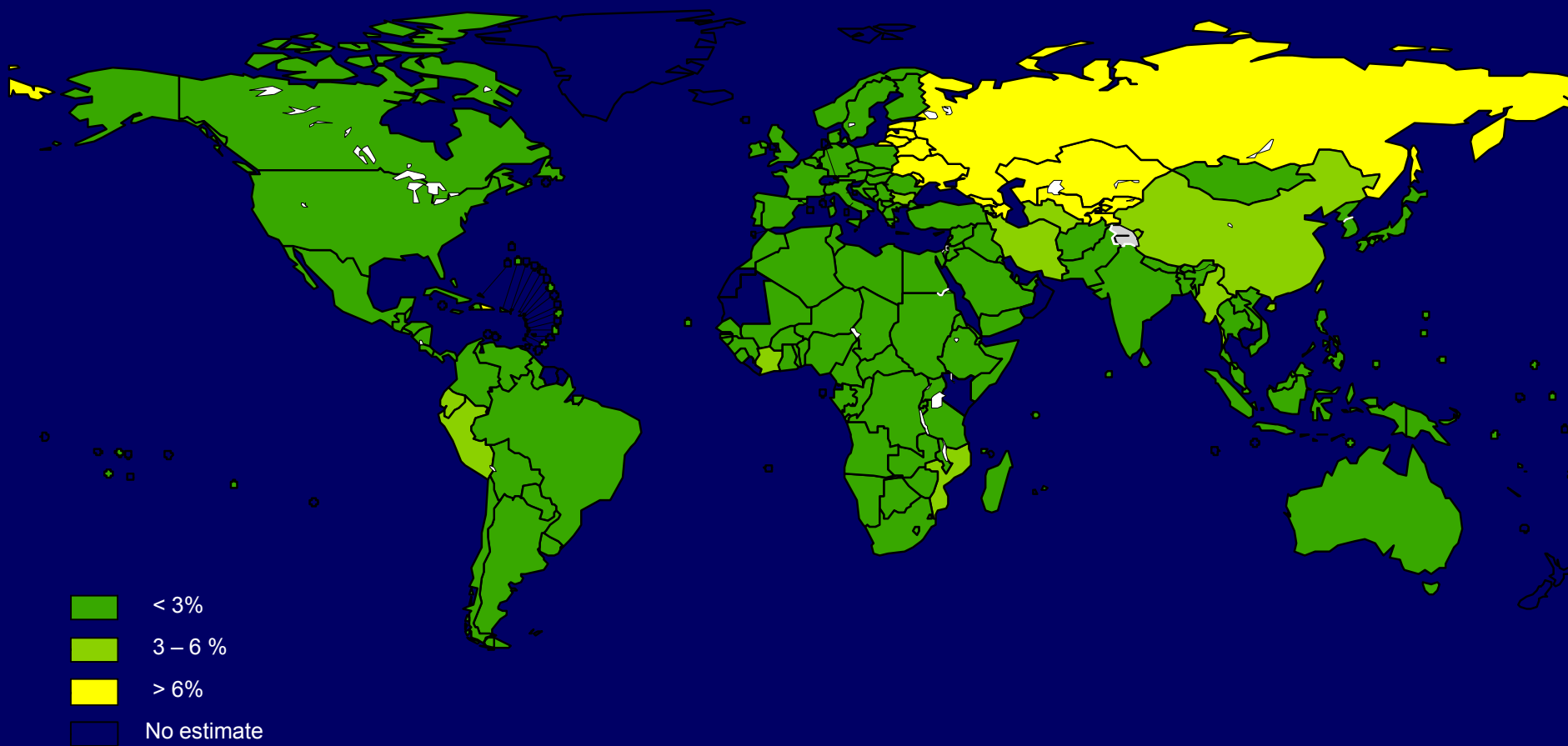
Coverage of Anti-Tuberculosis Drug Resistance Surveillance



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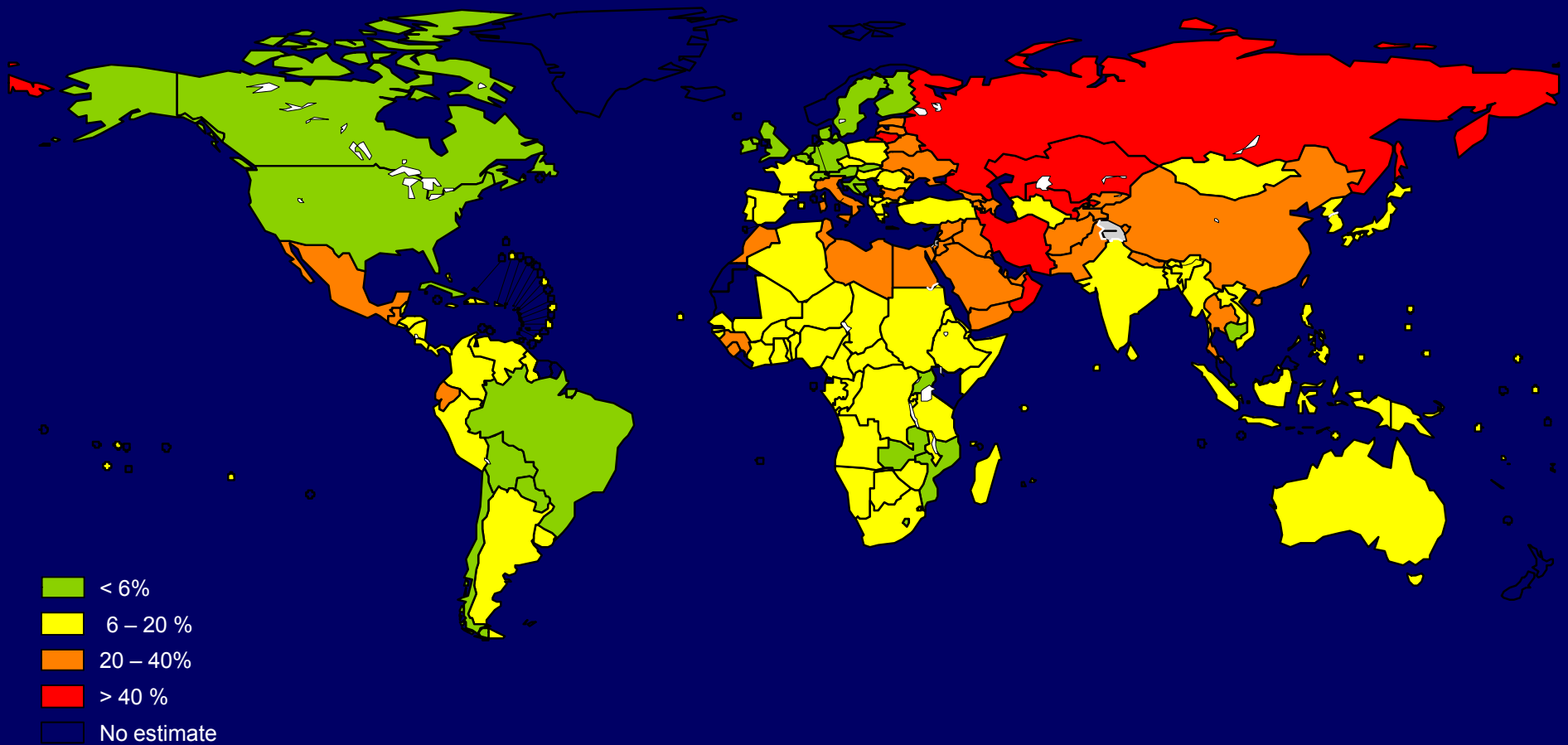
Rates of MDR among new TB cases



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Rates of MDR among previously treated TB cases

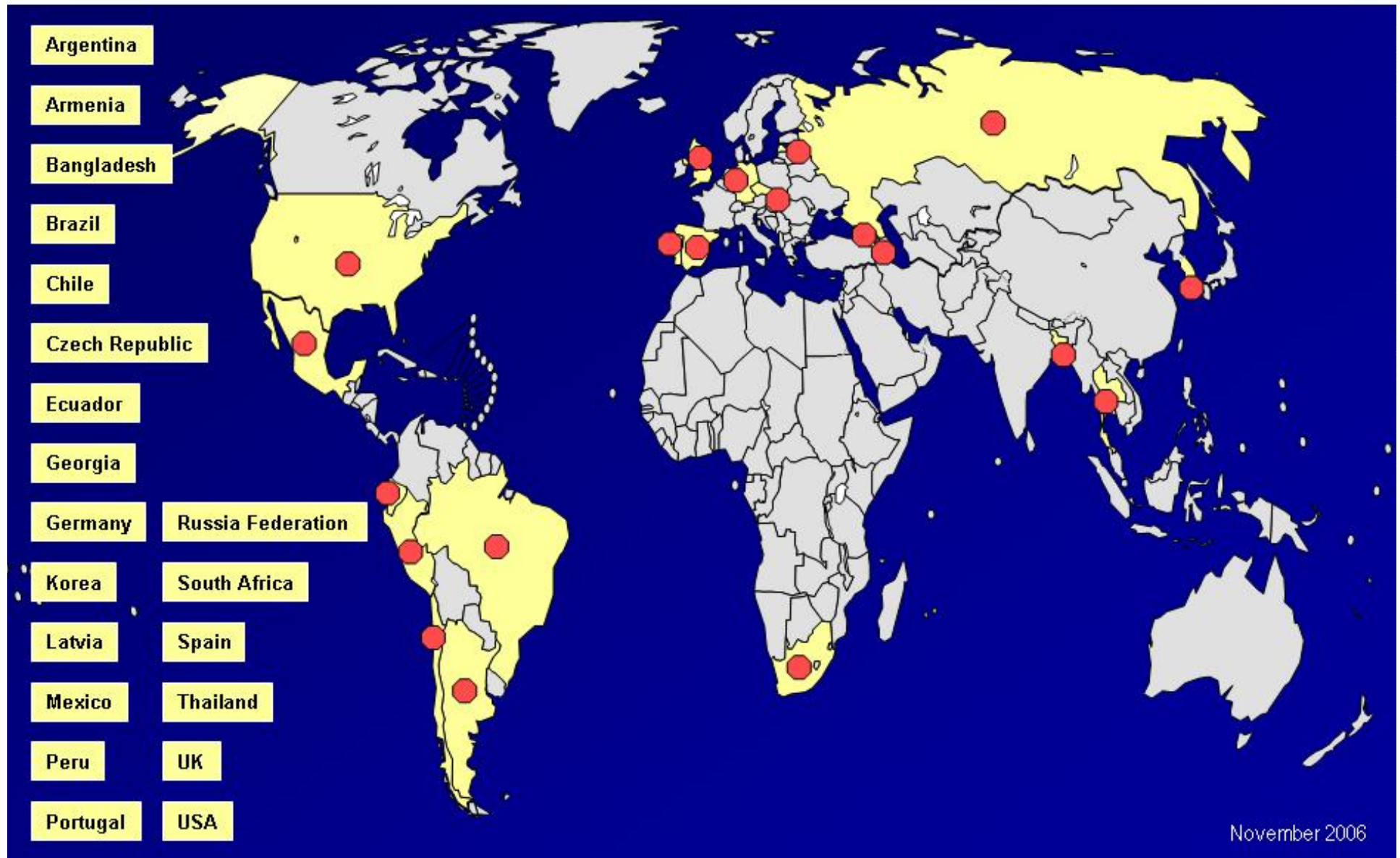


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Countries with XDR-TB

Confirmed cases to date



XDR TB in South Africa*



- Reported in at least 39 provincial hospitals and elsewhere in RSA
- ≥ 30 new cases reported monthly in KZN

* Singh JA, Padayatchi N. XDR TB in South Africa: no time for denial or complacency. PLoS Medicine 2007;4(1):e50.doi:10.1371/journal.pmed.0040050

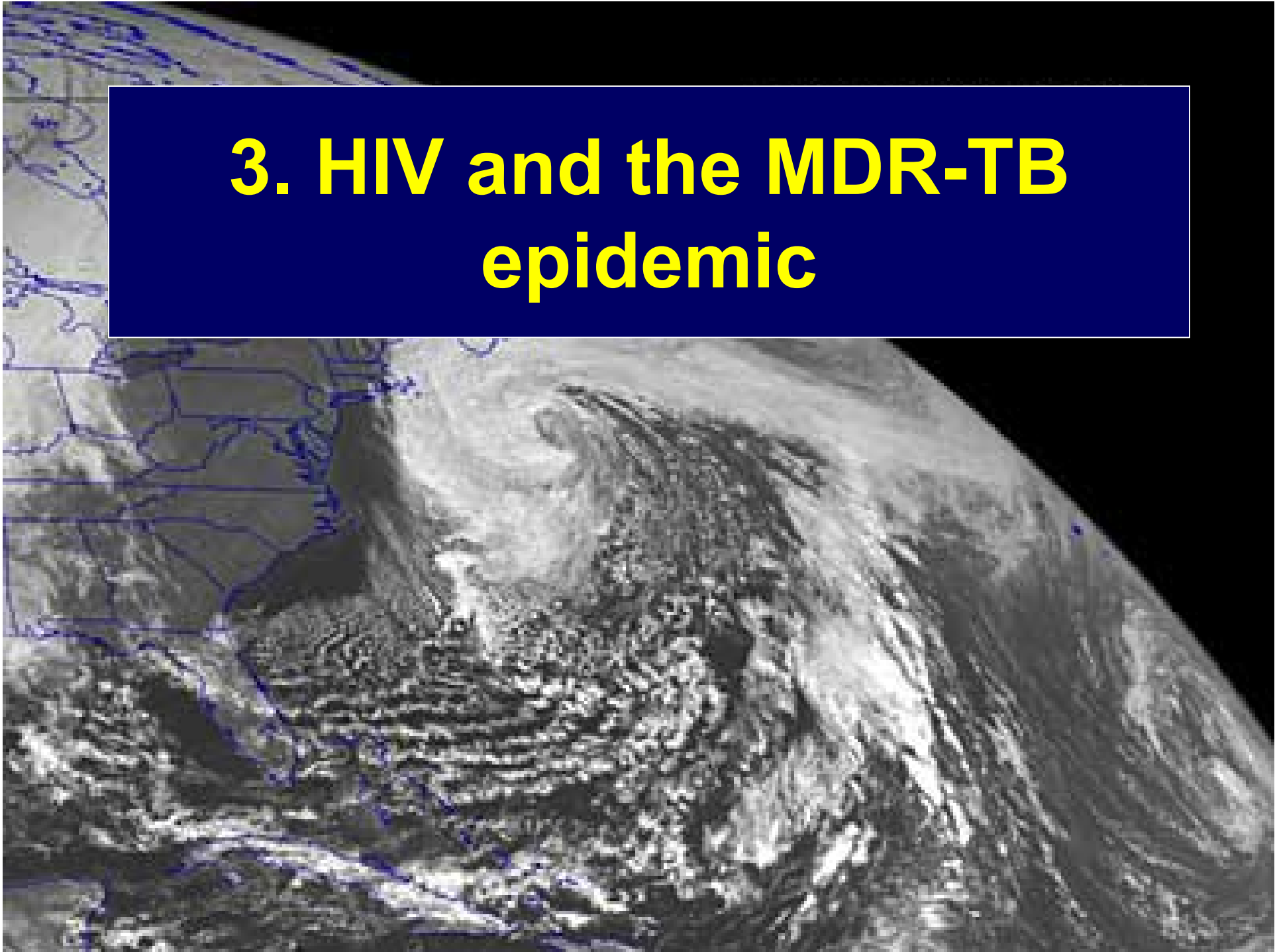


XDR TB As an Emerging Threat, Why Now?

Factors converging for “the perfect storm”:

- **Suboptimal TB control practices**
 - High default rates
 - Drug supply issues
- **Introduction of 2nd-line TB drugs into low and middle income countries**
- **Lack of attention to infection control**
- **High HIV prevalence**
- **High TB burden**

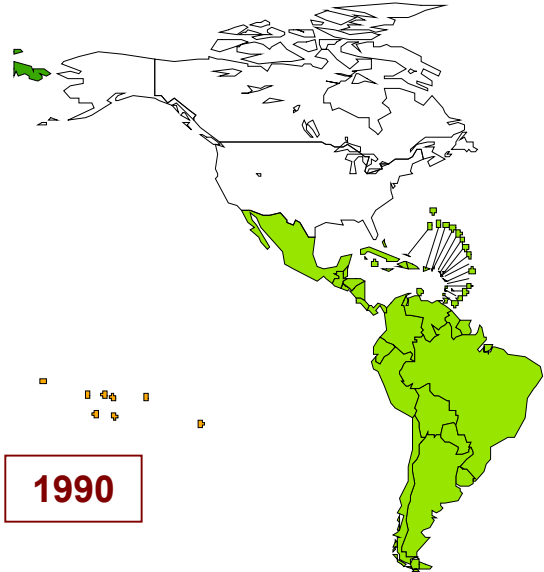
3. HIV and the MDR-TB epidemic



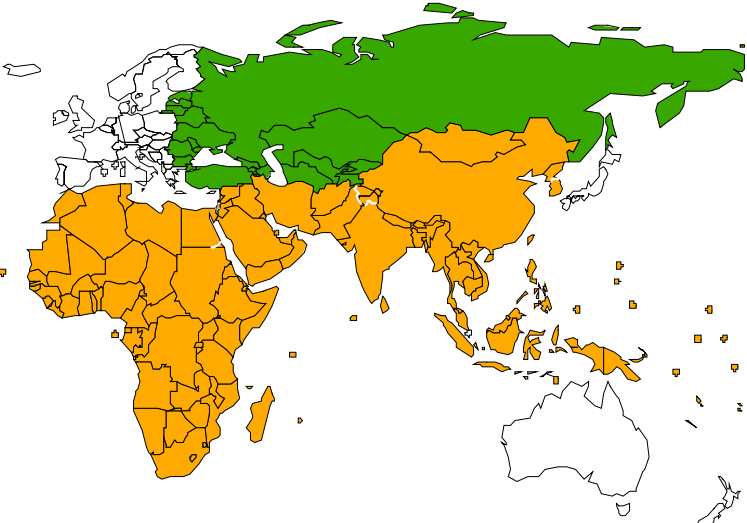
Possible Ways HIV Impacts MDR TB / XDR TB

- **Increasing HIV-associated TB burden → overwhelmed public health systems**
- **Poor IC and nosocomial transmission**
- **Malabsorption of anti-TB drugs**
- **Acquired rifamycin resistance**
 - **Advanced immunosuppression**
 - **Drug/drug interactions**
- **Use of isoniazid preventive therapy (?)**
- **2nd-line drug use for concomitant illnesses**

TB Incidence Rate



1990

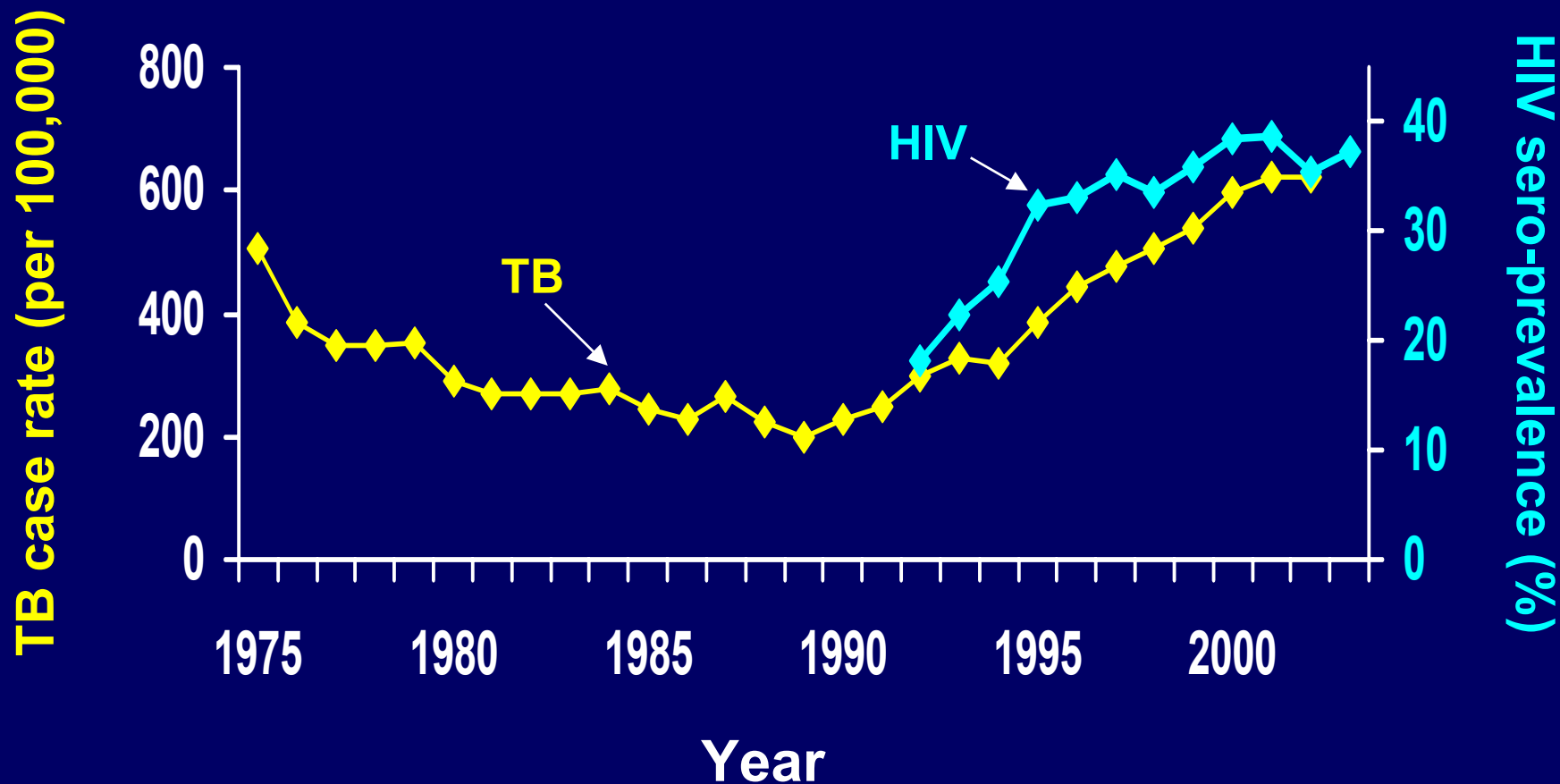


2005

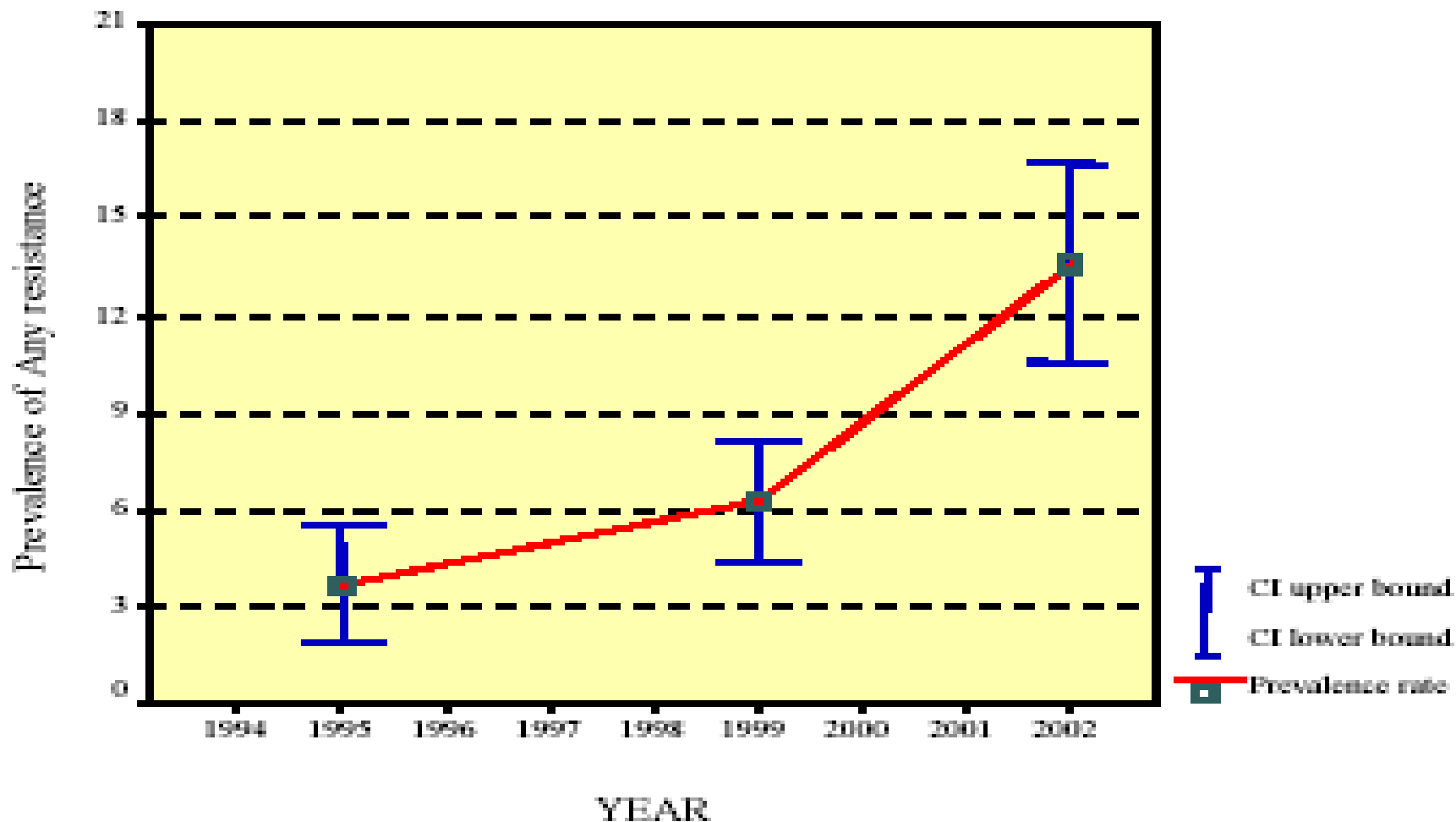
- < 50
- 50-100
- 100-200
- 200-300
- 300 and more



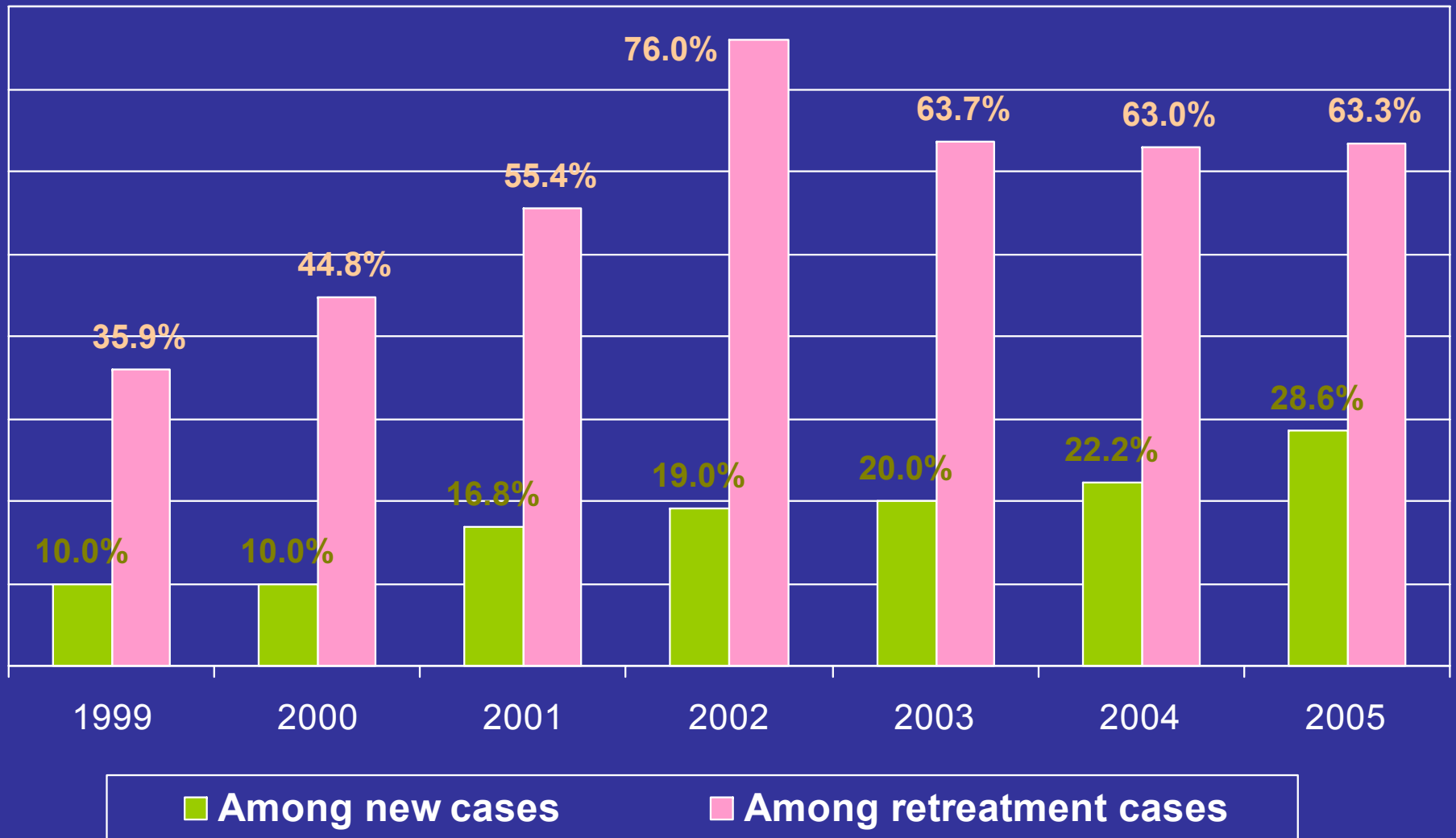
TB Notification Rate Botswana, 1975–2002 & HIV Prevalence Antenatal Women, 1992-2003



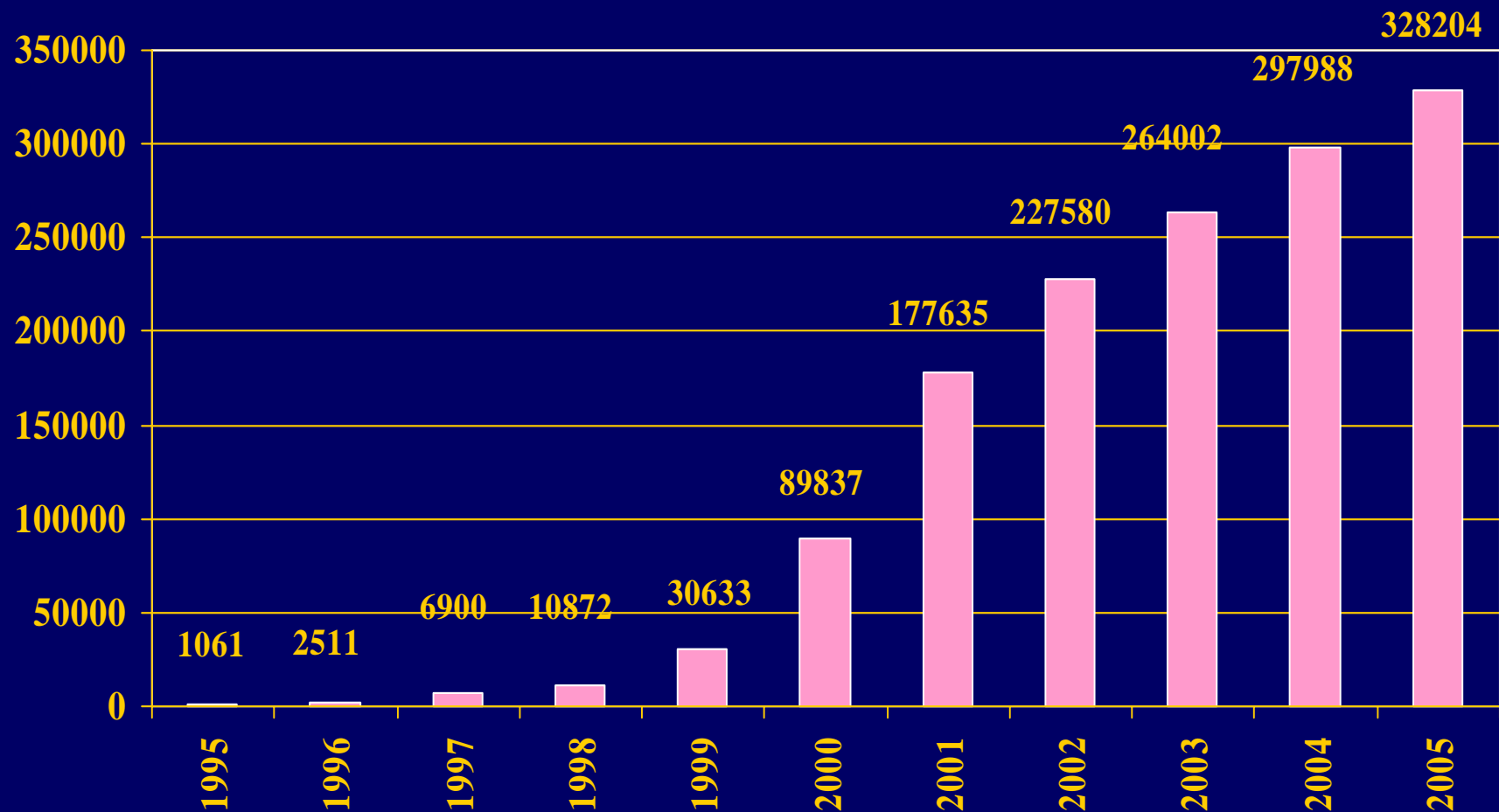
Any Drug Resistance Among New TB Cases, Botswana, 1995 - 2002



MDR-TB in Arkhangelsk Oblast 1999- 2005



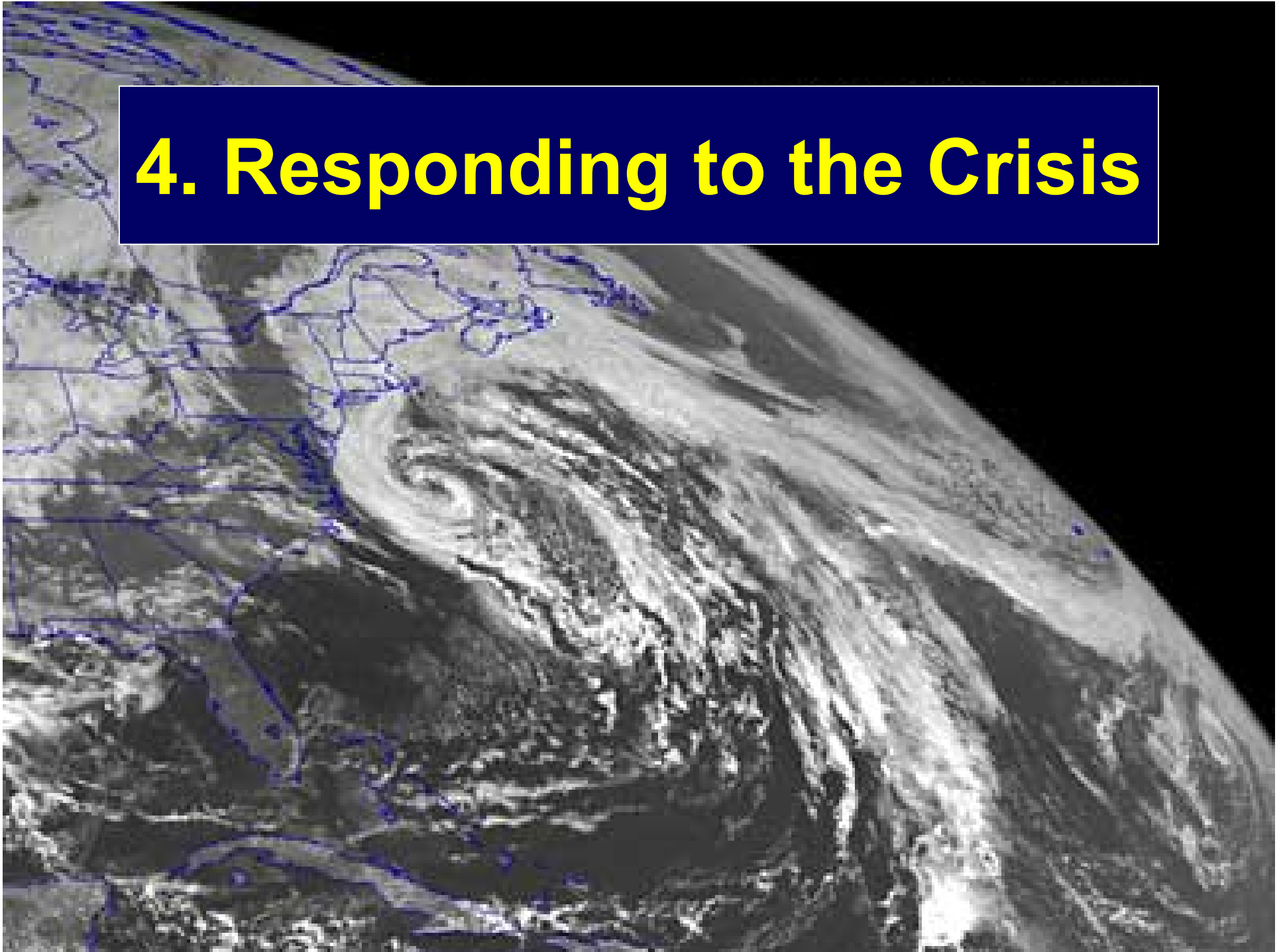
Cumulative Number of PLHA Registered in Russia by Year (1995-2005)



Countries with Higher Risk for MDR TB and HIV Convergence

- **AFRO: S Africa, Nigeria, Ethiopia, DRC, Cote d'Ivoire, Mozambique, Tanzania, Zimbabwe, Kenya**
- **PAHO: Haiti, Dominican Republic, Honduras, Peru, (Mexico)**
- **EURO: Ukraine, Russia, Estonia, Latvia**
- **EMRO: Sudan, Djibouti**
- **SEARO: Myanmar, (India)**
- **WPRO: Papua New Guinea, Vietnam, (China)**

4. Responding to the Crisis



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 practitioners to respond to XDR TB outbreaks and manage patients**
- 4. Implement infection control precautions (PLHA focus)**
- 5. Increase research support for new anti-TB drugs**
- 6. Increase research support for rapid diagnostics**
- 7. Promote universal access to ARVs under joint TB/HIV activities**

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

Outcomes from First Global XDR TB Task Force, October 8-9, 2006

- **Defined key issues, made recommendations and identified urgent action steps:**
 - **Management of XDR TB suspects (high & low HIV)**
 - **Programmatic management of XDR TB treatment and Rx design**
 - **Laboratory XDR TB definition**
 - **Infection control to protect HCW and patients, with emphasis on high HIV prevalence settings**
 - **Immediate XDR TB surveillance activities and investigations**
 - **Advocacy, communication, social mobilization strategies**
- **Develop comprehensive plans for appropriate global response, and within countries**

Conclusions and Way Forward

- **MDR TB and XDR TB represent a serious public health problem, and require urgent response by global community**
 - *Revision of GPSTB, 2006-2015*
 - *Country level plans and TA response by partners*
- **Need to know precise burden and extent**
 - *Rapid surveys, capacity building, and support*
- **Wake up call to underperforming TB control programs**
 - *Improve basics, eg. adherence, supervision, labs*
 - *Implement infection control precautions*
 - *Improve management of MDR TB*
 - *Identify subject matter expertise and partner support*
- **Urgent need for new diagnostic and treatment tools**

Fighting TB and HIV

“We can’t fight AIDS unless we do much more to fight TB”.

Nelson Mandela,
International AIDS
Conference, Thailand
14 July, 2004.



*Nelson Mandela at 2004 International AIDS Conference
Image source: BBC News Online
(<http://news.bbc.co.uk/1/hi/world/asia-pacific/3895525.stm>)*