

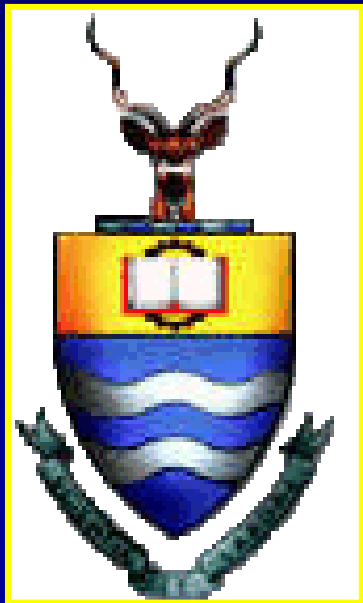
"A view from the South"

Clinical Research on Infectious Diseases: Tuberculosis

Martin P. Grobusch
Infectious Diseases Unit
University of the Witwatersrand and
National Health Laboratory Service

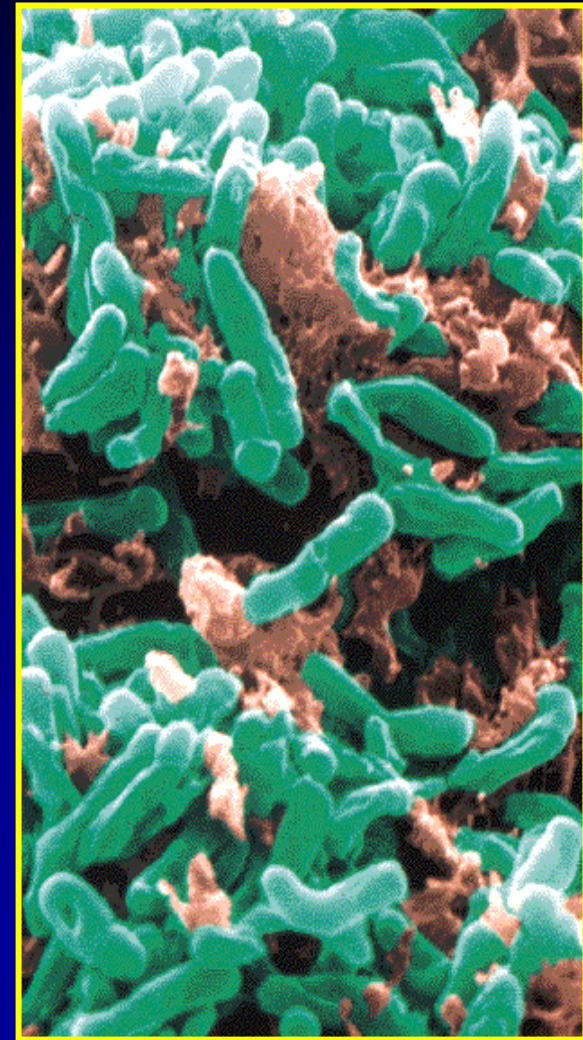
Hôpital Albert Schweitzer
Lambaréné, Gabon

CRCDC Geneva May 2008

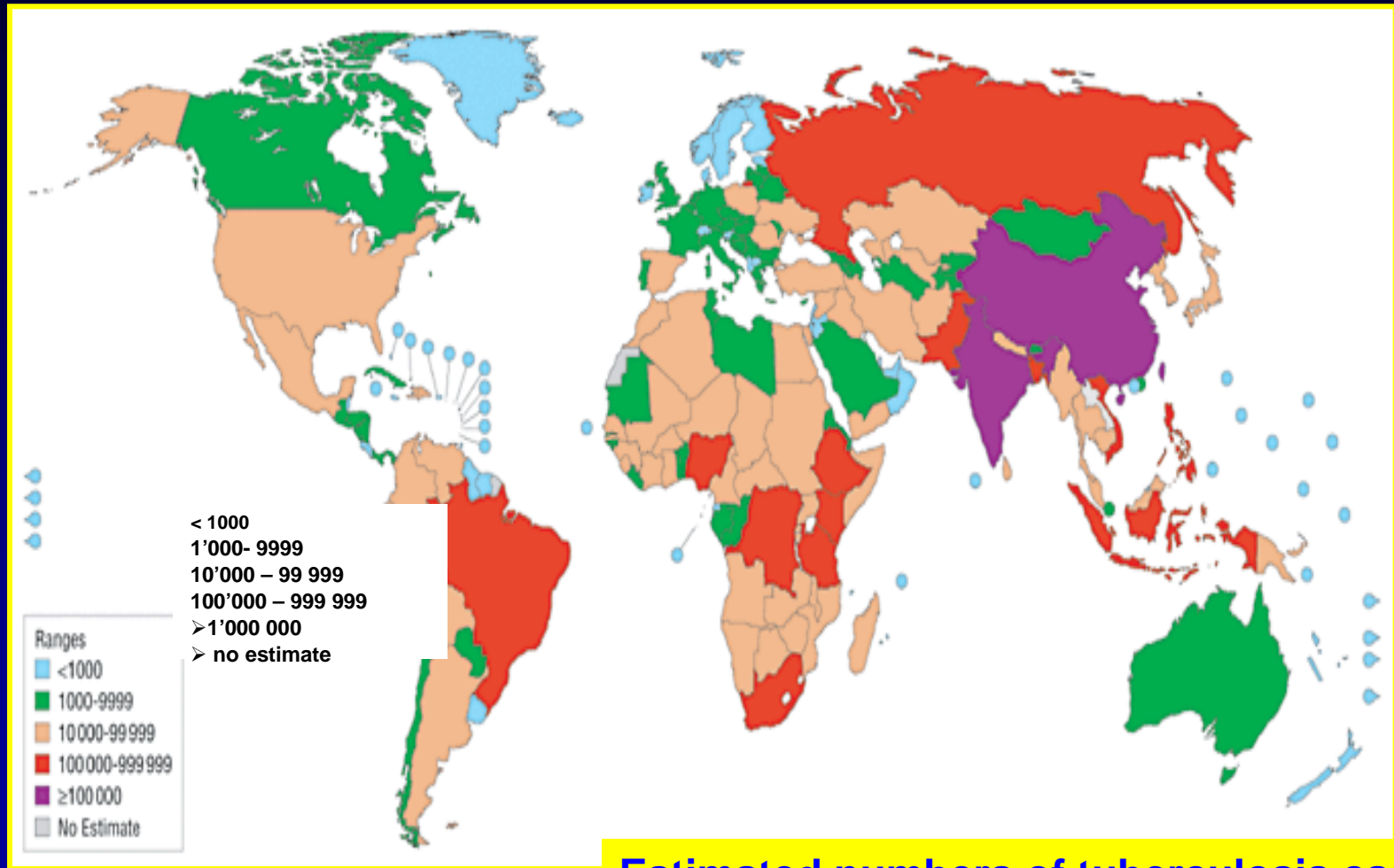


TB: a global emergency situation

- ~ one third of global population infected with MTB?
- ~ 8.3 million people/year develop active TB
- ~ 1.8 million people/year die from TB annually
- drastical rise in prevalence of infection and disease in the wake of the HIV co-pandemic
- much of the burden carried by poor countries (95 % of morbidity and 98 % of mortality)

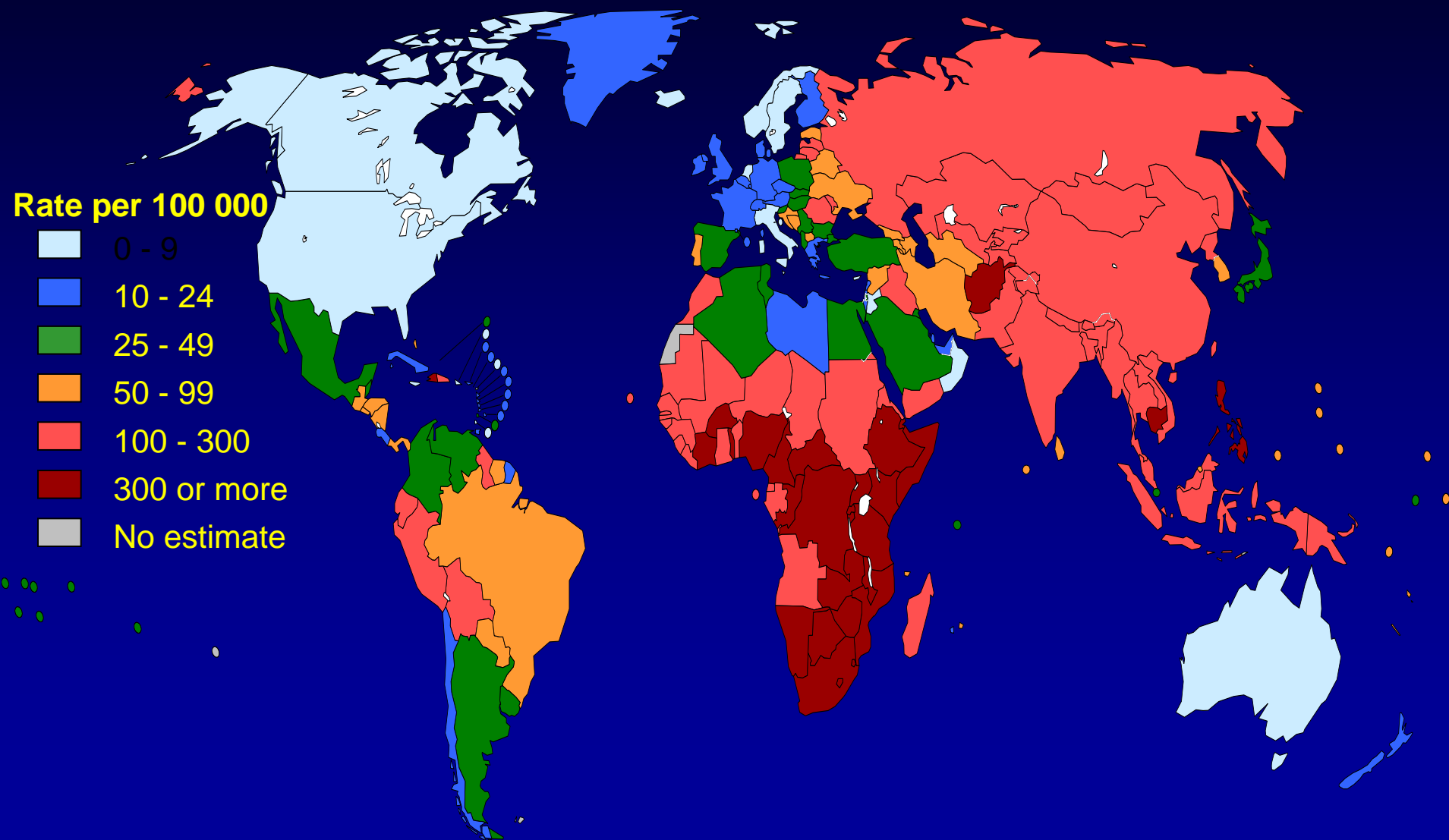


Tuberculosis Prevalence



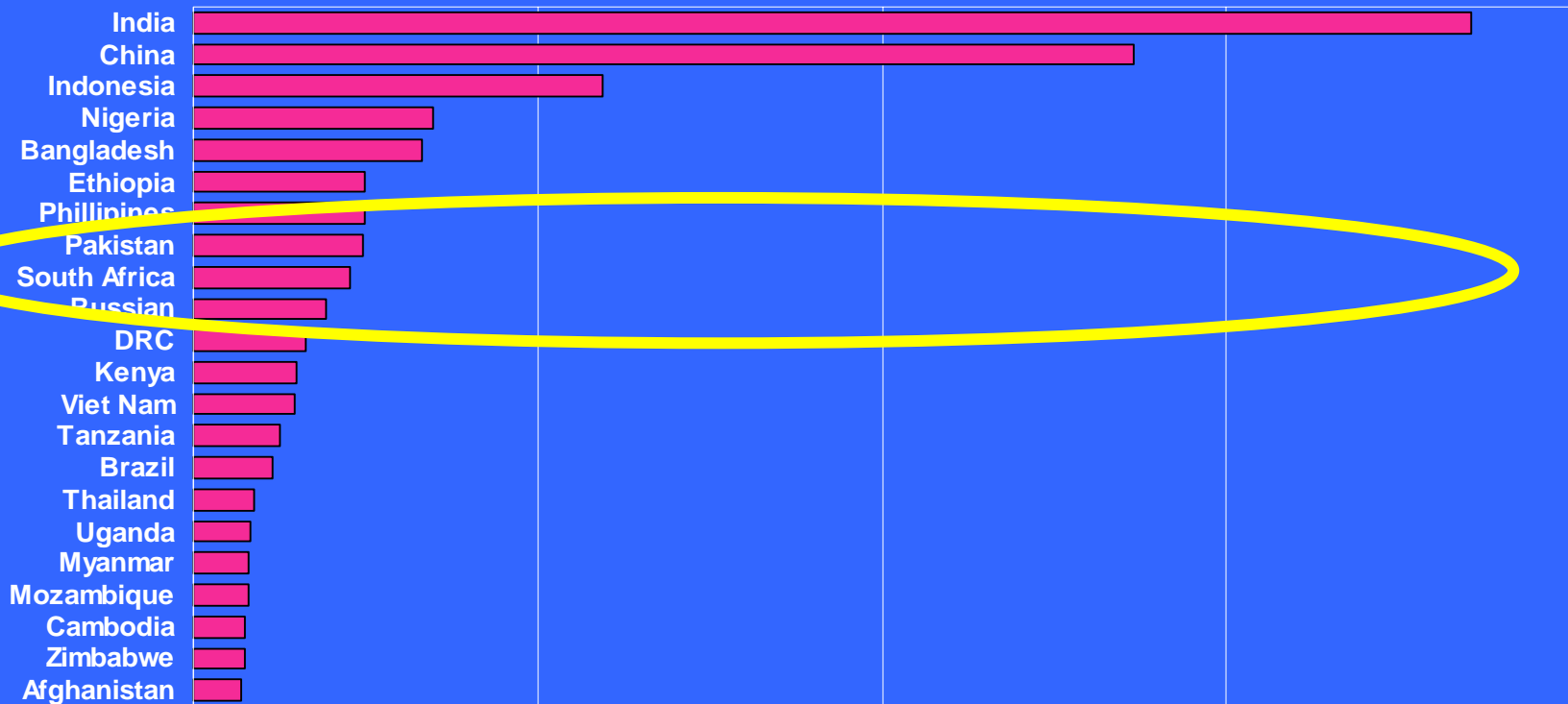
Estimated numbers of tuberculosis cases by country in 2000

Estimated TB incidence rates, 2004



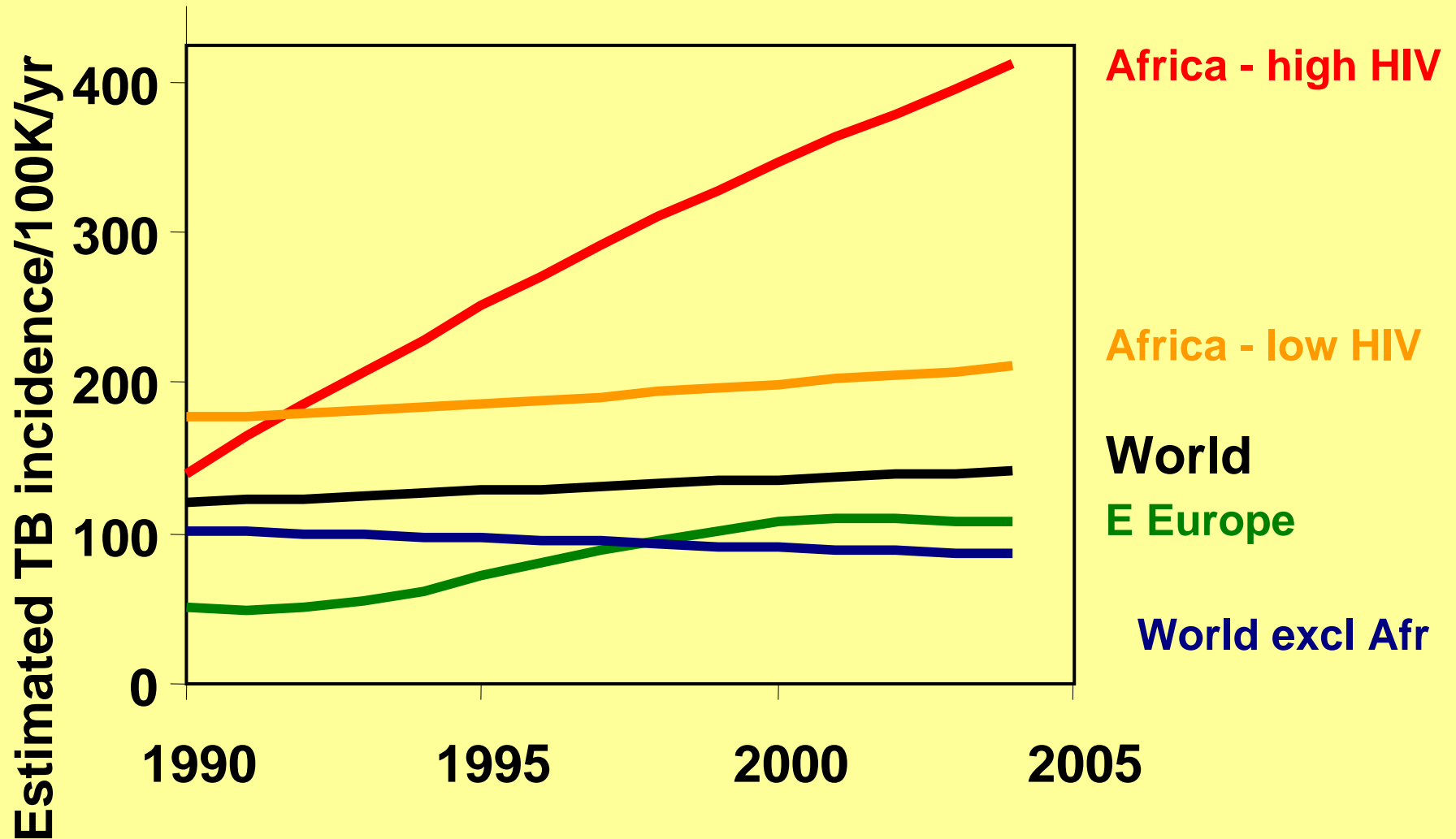
Tuberculosis in countries accounting for 80% of the global burden (T80 countries)

(Source: WHO report 2002: global tuberculosis control)



Estimated number of new tuberculosis cases per annum (millions)

TB: Global incidence is rising at 1%



High tuberculosis and HIV coinfection rate, Johannesburg

MA John, CN Menezes, G Chita, I Sanne, MP Grobusch
Emerging Infectious Diseases, 2007; 13:795-796

- patients at Helen Joseph Hospital in Johannesburg, SA
- academic teaching hospital with a > 500 k catchment area of predominantly poor people
- **270 (95 %) of 284 TB patients HIV coinfect**

Tuberculosis in South Africa

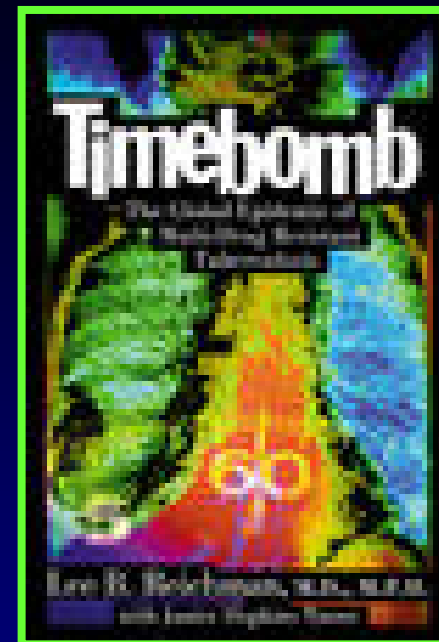
- global incidence 229/100.000
- South Africa 600/100.000
- Western Cape 1.000/100.000
- SA gold mines 2.500/100.000
- reported/registered cases
~ 307.000/2006
- 80% of all cases in KZN, WC, EC,
Gauteng



TB control in South Africa – challenges

- massive number of cases
 - inadequate DOTS implementation 70 % tx completion
 - incorrect tx regimes
 - incorrect duration of tx
 - high tx failure rates 14 % defaulters
 - low cure rates 54 %
 - inadequate infection control measures
 - patient migration between provinces
 - influx of patients without access to health care facilities
 - poverty
 - HIV/AIDS
- **huge drive of resistance!**

multi drug-resistant tuberculosis (MDR-TB)



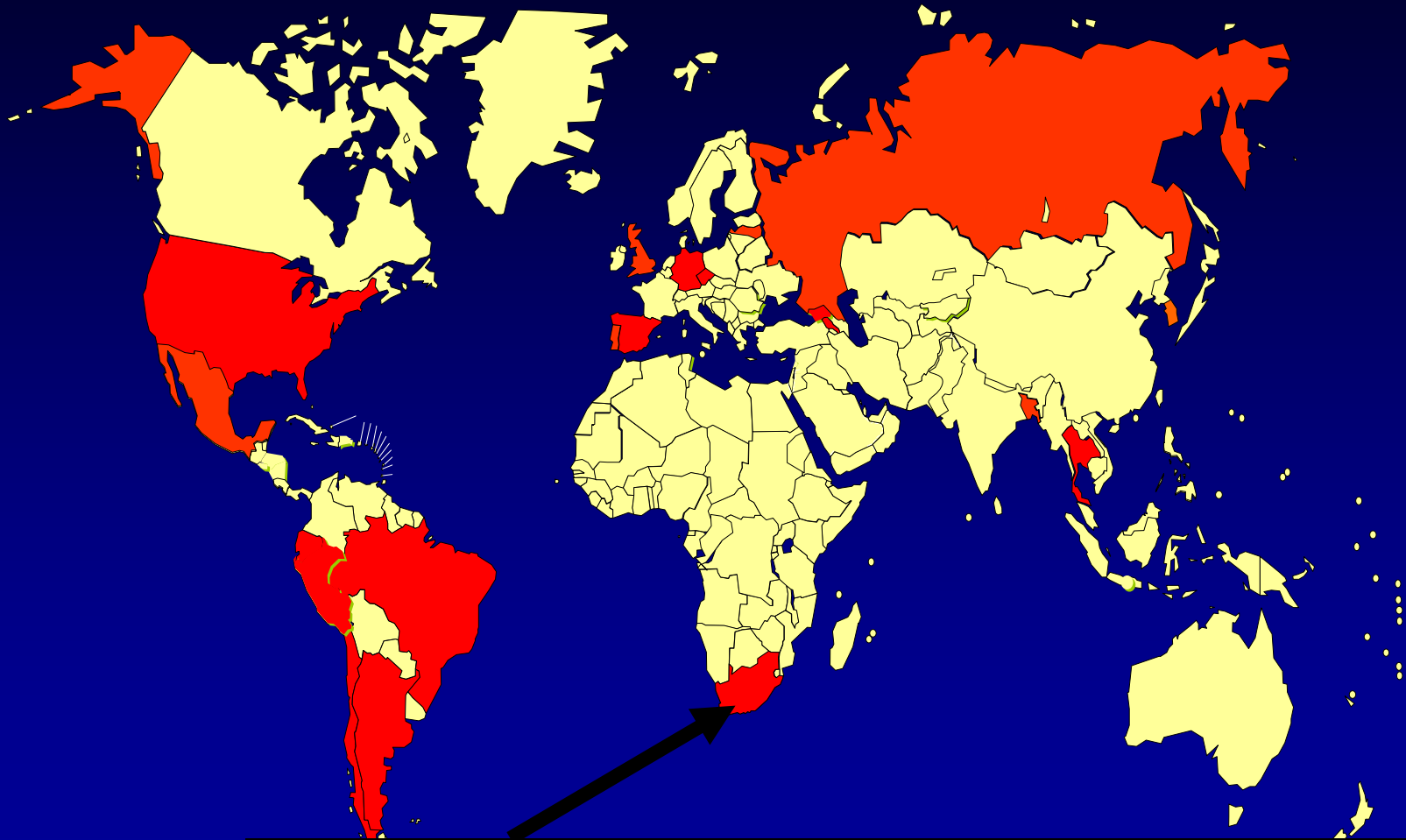
- **MDR TB: defined as MTB resistant against**
 - **isoniazide (INH)**
 - **rifampicin (RIF)**
- **WHO/IUATLD – Anti TB Drug Resistance Surveillance 1994-1997:**

prevalence 2.2%
- **CDC/WHO Global Survey 2000 – 2004:**

estimated 425.000 MDR TB cases (Africa – 11 %) = 4.5% of all TB cases

The threat of XDR-TB

Countries reporting at least one case of XDR-TB



SA in early 21st century: 6000 cases/annum
> 3% of new patients, or total cases > 500

Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Neel R Gandhi, Anthony Mall, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zeller, Jason A and PWS, Gerald Friedland

Summary

Background The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

Methods We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

Results From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR tuberculosis had never been previously treated for tuberculosis; 67% (28 of 42) had a recent hospital admission. All 44 patients with XDR tuberculosis who were tested for HIV were co-infected. 52 of 53 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis (IQR 6–37) among the 42 patients with confirmed dates of death. Genotyping of isolates showed that 39 of 46 (85%, 95% CI 74–95) patients with XDR tuberculosis had similar strains.

Conclusions MDR tuberculosis is more prevalent than previously realized in this setting. XDR tuberculosis has been transmitted to HIV co-infected patients and is associated with high mortality. These observations warrant urgent intervention and threaten the success of treatment programmes for tuberculosis and HIV.

XDR-TB ,outbreak' in South Africa

- **background:**
 - Rural area in KwaZulu Natal, South Africa
- **methods:**
 - sensitivity testing of patient isolates
 - genotyping of DR isolates
- **results:**
 - 542/1539 tested isolates were culture-positive
 - 221 MDR-TB (incl. XDR-TB cases)
 - 53 XDR-TB cases (24% of MDR-TB cases)

XDR-TB 'outbreak' in South Africa

- **results (cont.):**
 - only 45% (26/47) patients with XDR-TB were treated before against TB
 - all 44 XDR-TB patients were HIV+
 - 52/53 XDR-TB patients died within days (median survival time of 16 days after dx in 42 cases analysed)
 - genotyping: 39/46 XDR-TB patients had a similar strain.



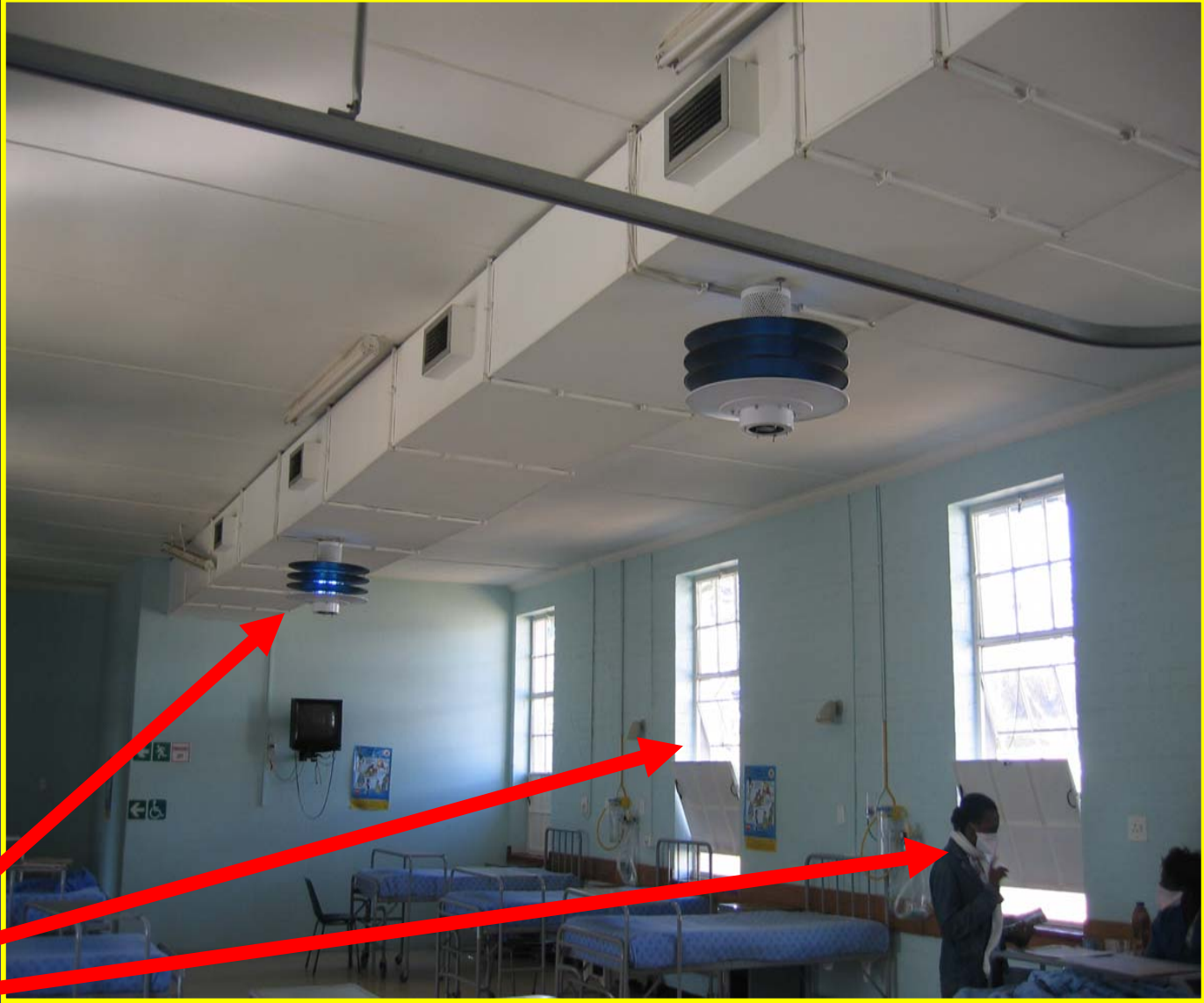


**SIZWE
TROPICAL
DISEASES
HOSPITAL**



M/XDR-TB TB control in Gauteng, SA - challenges

- **Systems**
- **Ineffective planning and management**
- **Communication and information systems**
- **Lack of performance management and support**
- **Poor and inappropriate infrastructure conditions , re-isolation**
- **Inadequate cross ventilation**
- **Infection control measures insufficient**
- **Inadequate facilities for hand washing**
- **Wearing of appropriate N95 masks**
- **Long period of hospitalisation of patients**
- **Non-separation of patients re drug sensitivity**
- **Prolonged laboratory results turn around time (TAT)**
- **Referral and transportation of patients**
- **Non-effective defaulter tracing**



Principles for designing individually tailored drug regimens

- drug choice based on individual DST profile and
- on Hx of previous drug regimen(s)
- inclusion of at least two bactericidal drugs
- \geq five drugs

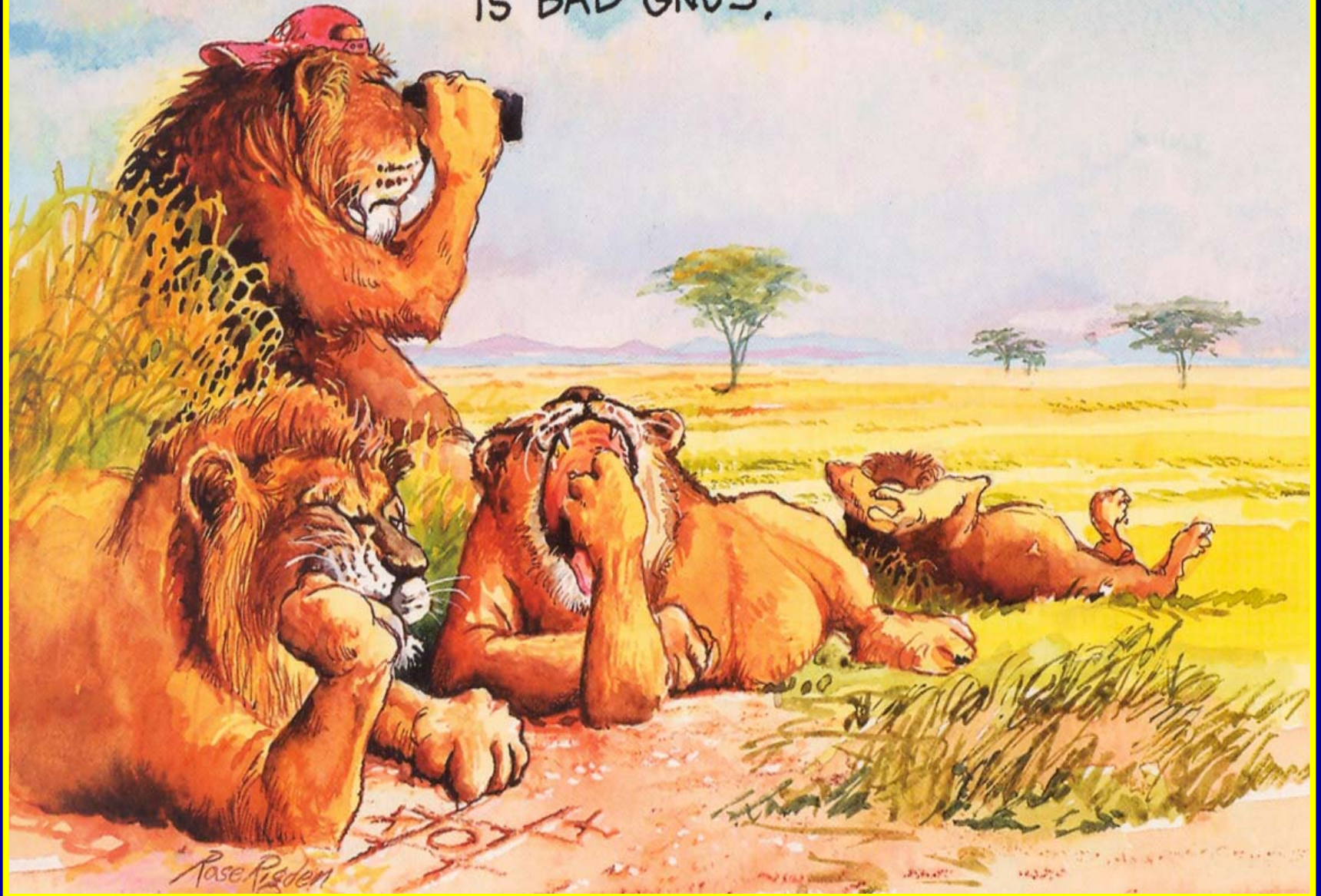
Example: J.R., male, 46 y o

- RVD negative
- on TB tx since 2005
- initially 4DR, then 7DR
- DR: INH, Rifa, Eth, Strep, Ethion, Oflox, Amik
- Tx_{alt}: INH-HD, Terizid, PZA, Clarithrom, Capreom, PAS
- 1 Nov: culture neg after 47 days (22 Dec); good correlation with clinical findings

XDR-TB patients in Gauteng/Sizwe Hospital since 9/06

- 46 patients in Gauteng identified
- 44 patients treated at SH
- 3 patients transferred
- 2 patients ,disappeared‘
- 11 deceased (25 %)
- 21 under treatment
- **7 discharged as non-infectious (15.6%)**

NO GNUS
IS BAD GNUS!



Drugs with anti (XDR-) TB efficacy in clinical development

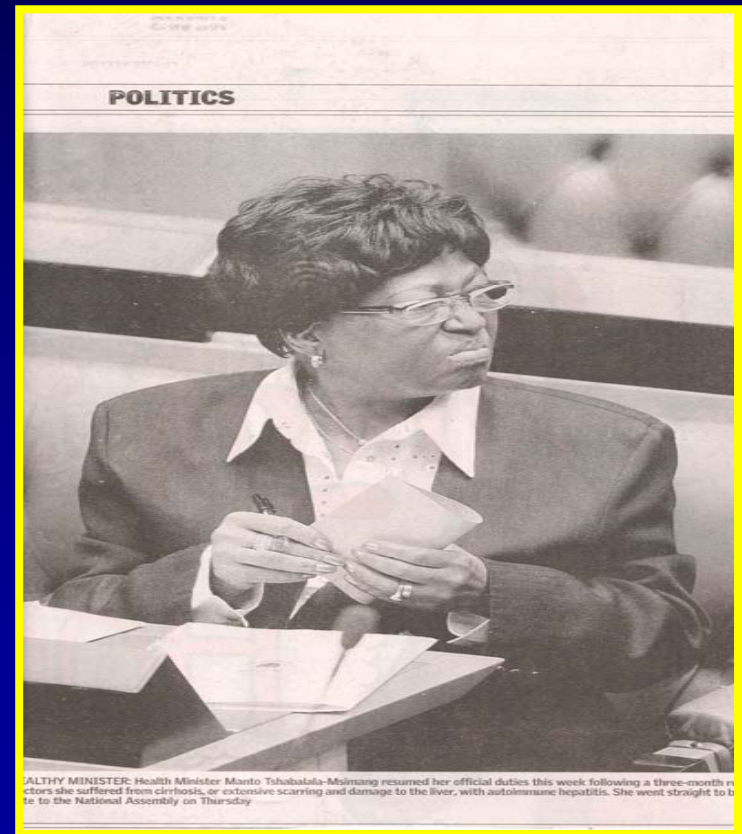
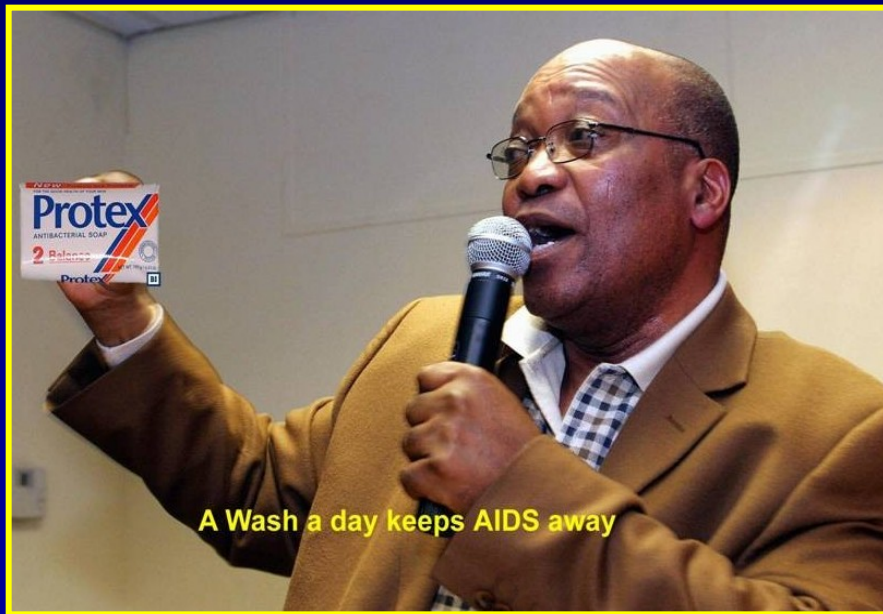
drug	mechanism of action	dev. stage
TMC 207 Diarylquinoline	PPI of MB ATP synthase	phase II
OPC 6783 Nitroimidazole	protein- and cell wall lipid synthesis inhibitor	phase II
PA 824 Nitroimidazole	protein- and cell wall lipid synthesis inhibitor	phase II
SQ 109 Diamine	cell wall synthesis inhibitor	phase I
LL 3858	?	phase I

Research questions

- I've got plenty – which ones do you have?
 - e.g. in the fields of
 - immunology
 - diagnosis
 - treatment
 - prevention
 - and else?

Research-related questions

... and what are the specific research conditions in that setting?



Conclusions

- Clinical research paralleling clinical care is a necessity in the absence
 - of well-known epidemiological features
 - reliable and swift diagnostic tools and
 - safe, effective and efficacious treatment particularly for drug-resistant TB

Key messages

- drug resistant TB is globally on the rise
- one of the hardest-hit regions is South Africa
- clinical care and clinical research must go hand in hand

Lessons learned

Clinical research can be initiated almost ,from scratch‘ within a couple of months even in a setting which was not primarily designed to facilitate research.

