

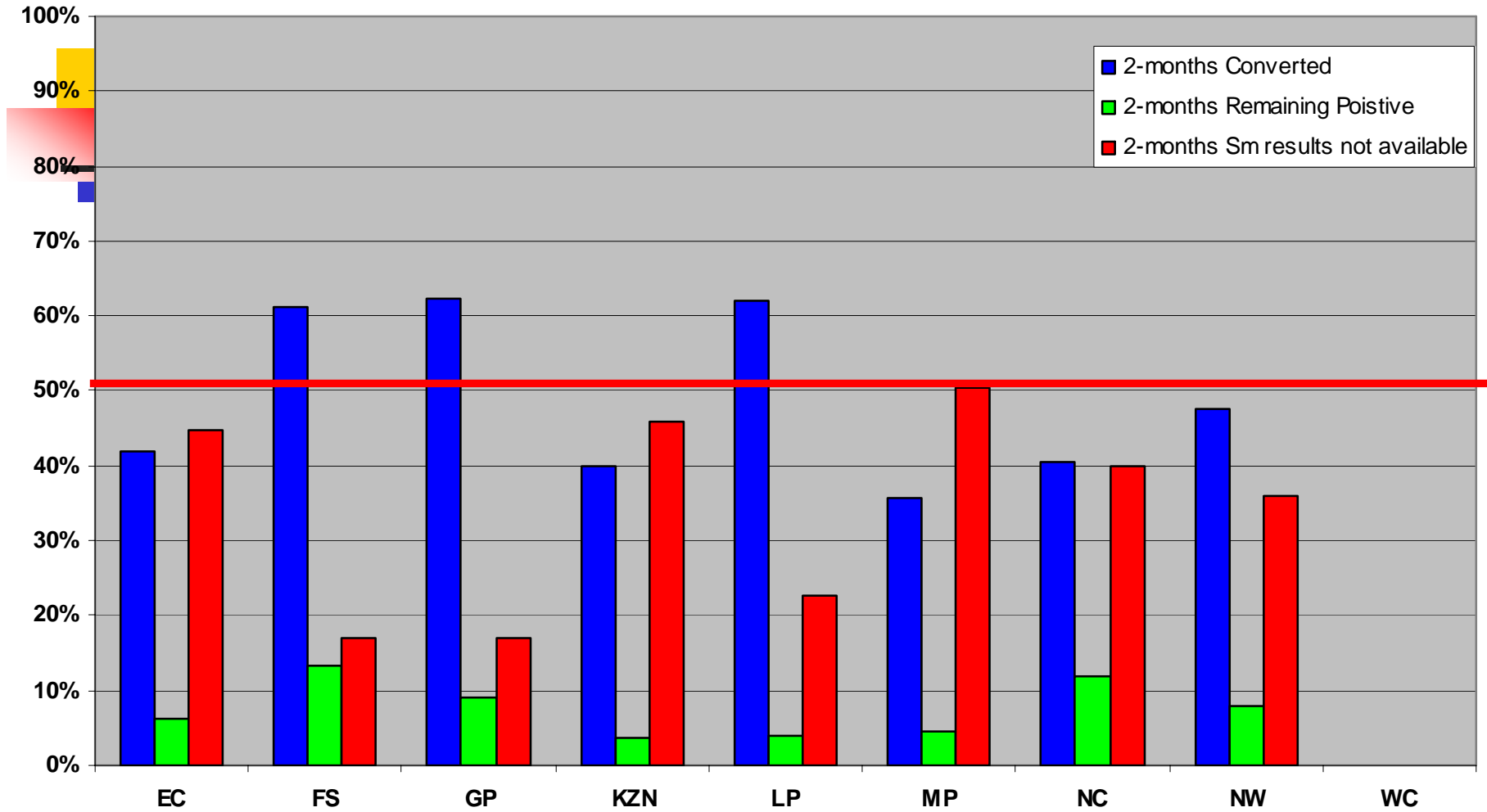


MDR-TB and XDR-TB

NDOH

4th October 2006

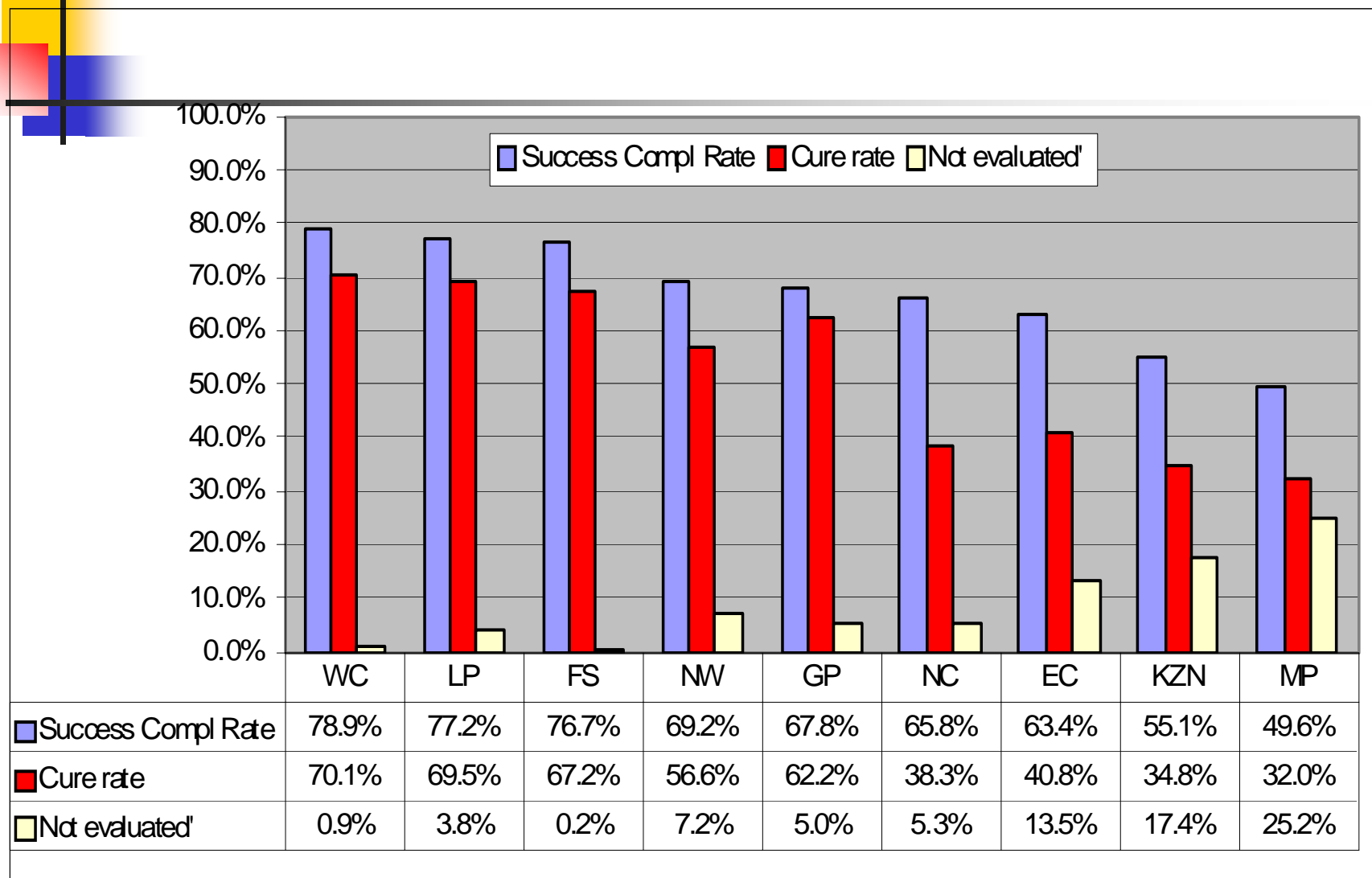
Smear Conversion Rate 2005



Treatment Outcomes

	2000	2001	2002	2003	2004
Successful Rx Completion	63.0%	60.5%	63.0%	62.9%	65.5%
Cure rate	53.8%	49.7%	50.0%	50.1%	50.8%
Defaulter Rate	12.7%	11.1%	11.9%	10.1%	10.3%
Not evaluated		7.5%	7.5%	9.8%	9.9%

Treatment Outcomes 2004





Definitions

MDR-TB:

- MDR-TB is a laboratory diagnosis of resistance mycobacterium tuberculosis to **INH** and **Rifampicin**

XDR-TB:

- *Currently* defined as **MDR-TB** with **further resistance** to at least 3 of the 6 major classes of 2d line drugs

Background



- Estimated 424,203 MDR-TB in 2004 worldwide
 - 4.3% of all TB cases are MDR
 - 11% MDR were found in Africa but
 - Low detection [under-reporting]
 - Inadequate laboratory facilities for DST
 - Survey of 49 countries
 - 20% of 17,690 isolates were MDR
 - 10% of these “MDR” were XDR
 - XDR found in 17 countries, widely distributed
 - Cluster of XDR-TB cases was reported in May 2006 in KZN



Multi-drug resistant TB

- Increase in MDR-TB cases is an indication of a poor performing TBCCP.
- MDR-TB is a man-made disease.
- Laboratory diagnosis
- Primary resistance (no history of TB Rx)
- Acquired resistance (previous ho of TB Rx)

Risk factors for development of MDR-TB



- Previously **unsuccessful TB treatment.**
- **Interruption** of TB treatment
- Inappropriate TB treatment **regimen.**
- Inappropriate TB treatment **duration**
- Previous TB **treatment in a hospital**
- High **TB prevalence.**
- HIV+ is **not an independent risk factor**



MDR-TB PREVALENCE in South Africa (2002)

- New cases: 1.7%
(range 1 – 2.4%)
- Re-treatment cases: 6.6%
(range 1.6–13.9%)

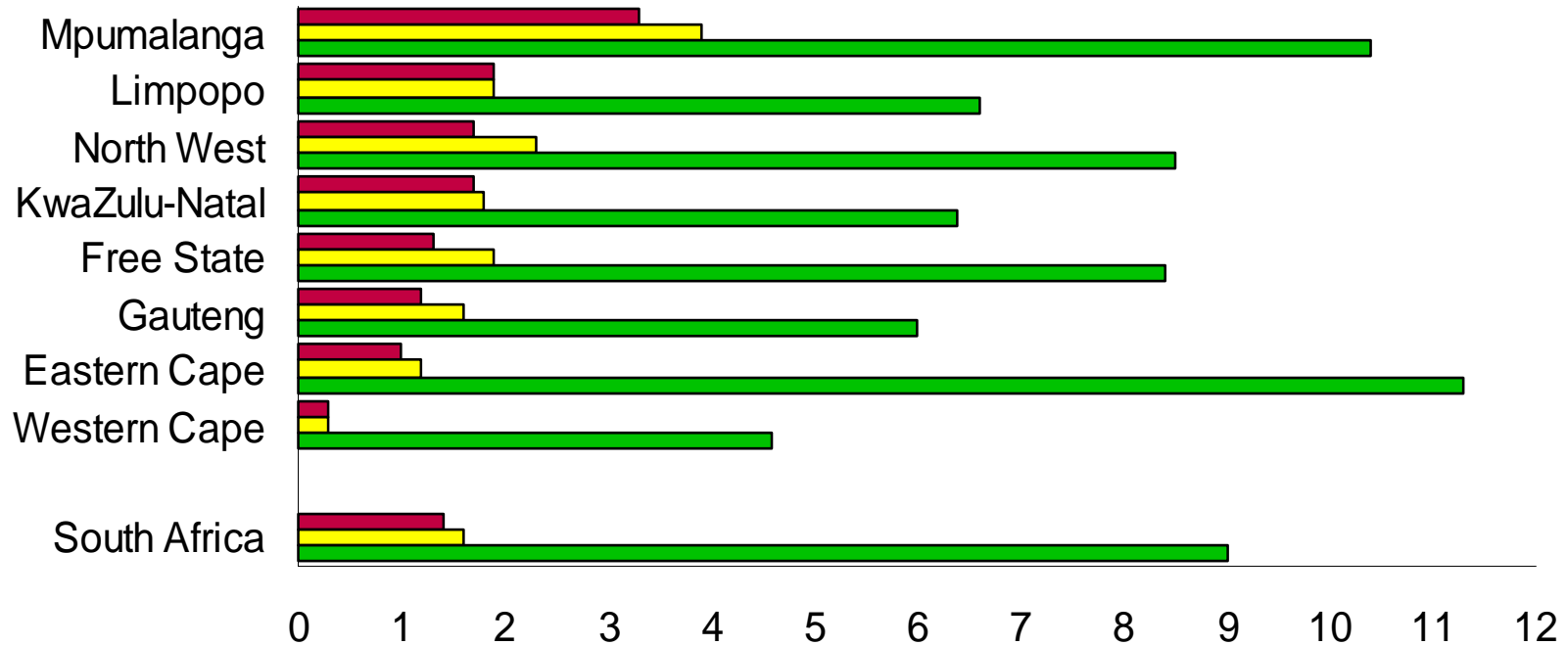
XDR-TB prevalence not known

Estimated MDR-TB burden



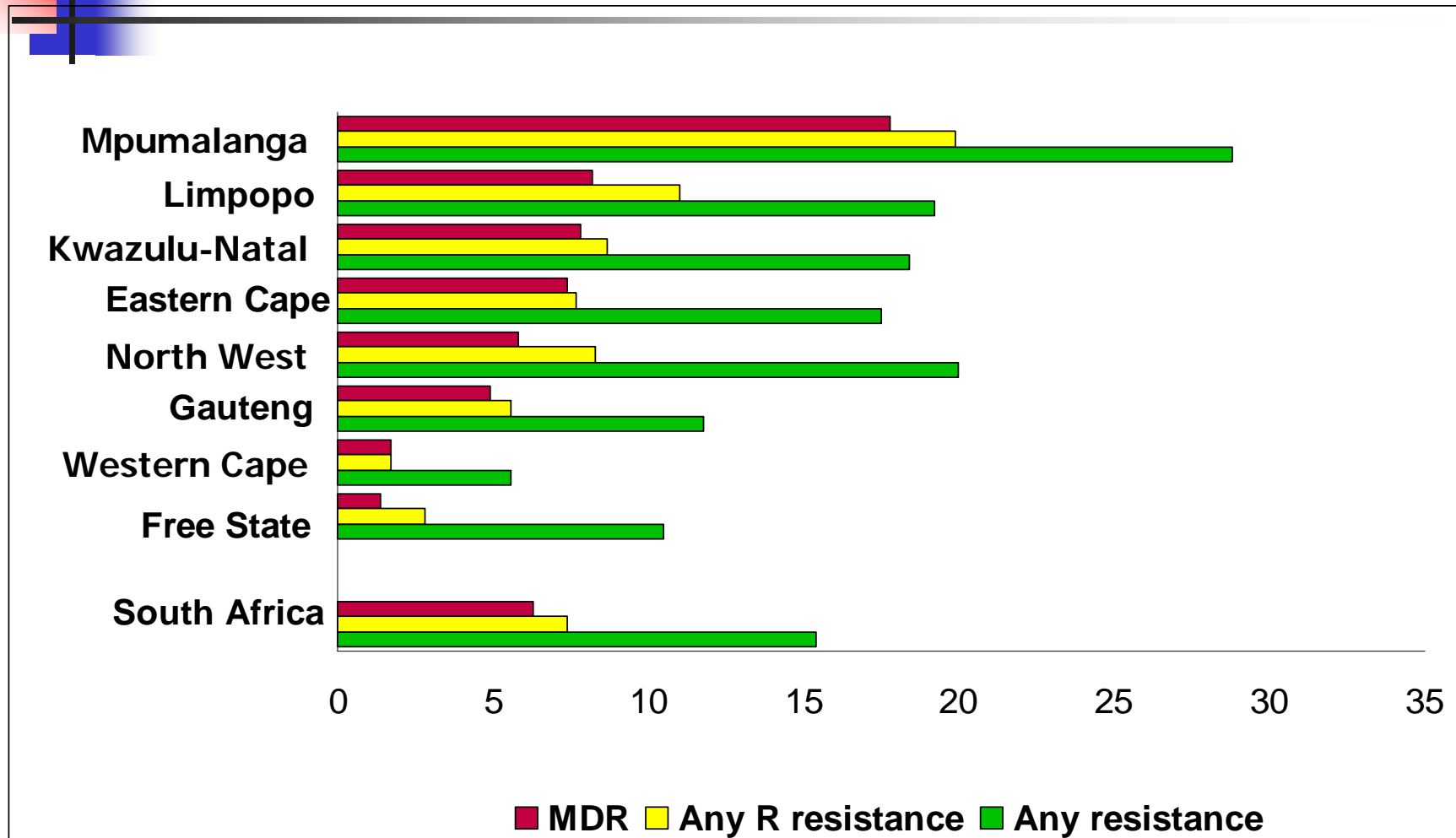
Province	Worst	Best
KZN	2 561	1 356
EC	2 181	1 190
Gauteng	1 239	673
Mpumalanga	928	496
Limpopo	779	426
WC	696	382
NW	511	278
FS	281	195
SA	9 727	5 196

Drug Resistance in new patients.



■ MDR ■ Any R resistance ■ Any resistance

Drug resistance in re-treatment patients



When should MDR-TB be suspected?



- No clinical signs indicative of MDR-TB
- Suspect MDR-TB during treatment of TB patients when smear/culture results positive at
 - end of intensive phase (2/3 months)
 - end of continuation phase
- When clinical response to treatment is poor despite good patient adherence
- **Note:** exclude NTM – Non TB Mycobacteria (Niacin and Nitrate tests) and other conditions



MDR-TB treatment concerns

- Difficult and expensive to treat.
[R28,000 vs R400 ppatient]
- Intensive phase of 4 months,
continuation phase 12 months or more
- Second-line TB drugs cause more side effects.
- Less effective: Only 50% cure rate.
- Some cases never convert to negative.

Second-line TB drugs

Category (6)	Drug(s)
Aminoglycosides	Kanamycin Amikacin
Thioamides	Ethionamide Prothionamide
Polypeptides	Capreomycin
Fluoroquinolones	Ofloxacin Ciprofloxacin
Cycloserine / Terizidone	Cycloserine / Terizidone
PAS	PAS

Classification of drugs available for treatment of MDR-TB

Activity	Drug/Category
Moderate bactericidal	Aminoglycosides Thioamides Pyrazinamide (acid pH)
Low bactericidal	Fluoroquinolones
Bacteriostatic	Ethambutol Cycloserine / Terizidone PAS

Designing MDR-TB Treatment Regimens

- Minimum of four drugs necessary during intensive phase
- At least three drugs not administered previously for more than three months
- One drug option per category due to cross-resistance
- Drugs selected from highest ranking categories
- Aminoglycoside must be included during the intensive phase
- Fluoroquinolone must be included throughout



General Treatment Principles

- Provide 18-24 months' treatment, always with intensive phase of at least 4 months
- PROVIDE DOT THROUGHOUT
- Warn patients about side-effects
- Manage side-effects appropriately
- Perform cultures monthly



Treatment Approaches

- Standardised
 - All patients on the same regimen, irrespective of drug susceptibility results
 - NTP policy in South Africa since 2000
- Individualised
 - Regimen tailor-made according to drug susceptibility pattern of strain

Standardised Regimen



- According to ethambutol resistance
 - *Intensive phase (4 months)*
 - kanamycin, ofloxacin, ethionamide, pyrazinamide, ethambutol or terizidone
 - *Continuation phase (12 – 18 months)**
 - ofloxacin, ethionamide, ethambutol or terizidone

* (Shortened to 12 months following culture conversion)
 - Dose standardised according to three weight bands (<50kg, 50-65kg, >65kg)

What to do with non converters at 9 months?



Value of second-line testing (suspect XDR-TB)

1. Continue treating up to month 22
2. Restart intensive phase
3. Terminate treatment at month 9

Long term outcome of #1, 2 ?



Susceptibility Testing

- When and who to Test for DST?
 - Clinical failure
 - Bacteriological failure
 - Known MDR contact
 - Health care workers
 - Prisoners
 - Follow up of patients on MDR-TB treatment



Susceptibility Testing

- Direct and indirect testing
 - Primary Drugs testing
 - Isoniazid
 - Rifampicin
 - Ethambutol (*)
 - Pyrizinamide (*)
 - Secondary Drugs testing:[lack of standardized methods!]
 - Ofloxacin, quinolones
 - Ethionamide
 - Kanamycin
 - Capreomycin
- ! Ensure quality control and quality assurance !



KwaZulu Natal experience



Tugela Ferry

- Annual mortality rate among TB and HIV co-infected patients 40% before antiretroviral (ARV) medications
- Reduced to 12% in TB/ARV integration study, but:
 - 10 of 14 (71%) deaths from multidrug-resistant TB



MDR-TB in KZN

- MDR TB rate in KwaZulu Natal in 2002
 - 1.7% of new TB cases
- 10 of 110 (9.1%) with MDR TB in TB/ARV integration study
 - 6 of 10 MDR TB patients resistant to all first and some second line TB drugs:
 - Isoniazid, rifampicin, ethambutol, streptomycin, kanamycin, ciprofloxacin



XDR-TB

- Recent CDC & WHO report described TB resistant to second line TB medications
 - Extensively Drug-Resistant (XDR) TB
 - Found in 347 isolates worldwide (over 3520 MDR identified, majority in South Korea, Eastern Europe and industrialised countries)



Methods

- Cross-sectional study of patients suspected with active TB at a rural district hospital
- Isolates collected for mycobacterial culture (MGIT) from January 2005 to March 2006



Results

- 1539 patients tested for culture
- 544 (35%) culture positive
- 221 (41%) MDR
- 53 (24% of MDR) found resistant to kanamycin and quinolones

**10% of culture positive cases had
"XDR-TB"**



Demographics of XDR TB Patients

Resistant to all drugs tested

Characteristics

(XDR)

Total N

53

Age: years: Median (range)

35 (20-75)

Sex: Female (%)

25 (49%)

Sputum Smear: Positive: n (%)

42 (79%)

Negative: n (%)

11 (21%)



Prior TB Treatment

Characteristic

XDR TB patients
n (%)

Prior TB Treatment:

No prior TB treatment

26 (51%)

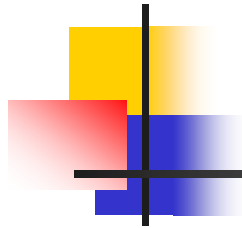
Prior TB treatment:

Cure or Completed treatment

14 (28%)

Treatment Default or Failure

7 (14%)



HIV Characteristics

Characteristic	XDR TB Patients
HIV Tested: n (%)	44 (86%)
HIV positive (if tested):	100%
Recent CD4 count: mean	72.7
median (range)	63 (9 - 283)
On Antiretroviral Therapy: n (%)	15 (34%)



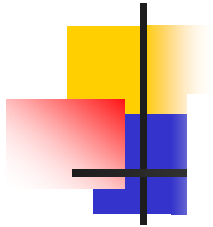
Molecular Fingerprinting

- 26 of 30 (87%) XDR TB isolates found to be genetically similar
- Majority of patients had no previous history of TB treatment
- Suggestive of recent infection with drug-resistant strain
- Additional cases identified in 28 of the 68 hospitals in KZN

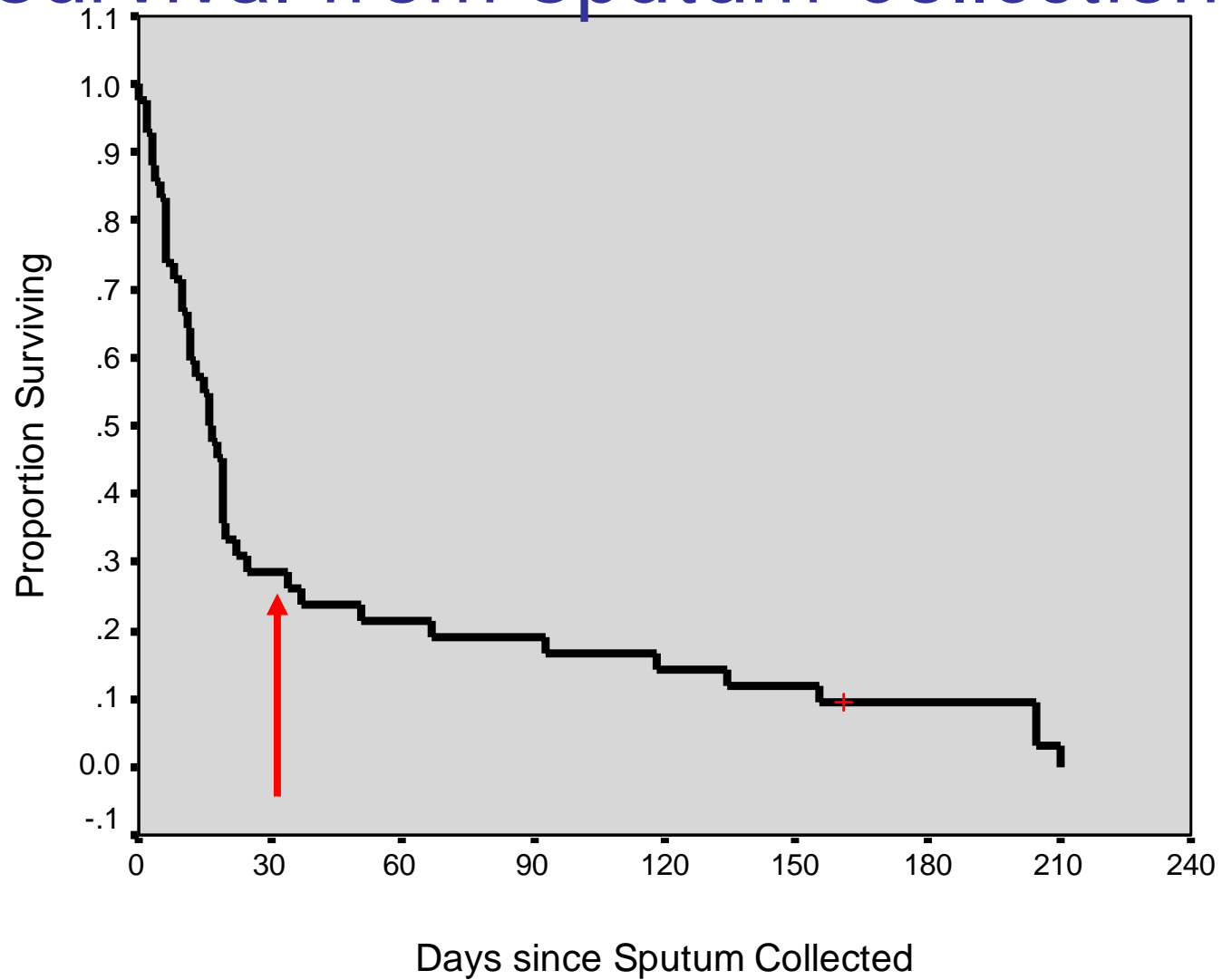


Mortality

- 52 of 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



Survival from Sputum Collection





Summary KZN report

- Multidrug-resistant TB substantially more common in a rural district of KwaZulu Natal compared with previously published rates
- An extensively drug-resistant strain of TB accounts for nearly one-quarter of all MDR TB cases found
 - Recent transmission in both hospital and community
 - All patients HIV tested were HIV-infected
 - Rapidly fatal



Recommendations (1)

- Urgently confront and correct poor TB control performance
- Ensure strict control and proper use of first and second line of anti TB drugs
- Develop national emergency response plans for MDR-TB and XDR-TB including social mobilisation and management protocols
- Conduct rapid surveys of MDR-TB and XDR-TB to assess geographic distribution and vulnerable groups



Recommendations (2)

■ Strengthen and expand laboratory capacity (including enhanced QA and QC) and provide TB culture and DST for:

- Known contacts of MDR-TB and XDR-TB
 - All retreatment cases
 - All TB patients with positive smear at 2-3 months
 - All TB failure
- Implement improved Infection Control (administrative, environmental and staff protection):
- Improved ventilation in wards
 - Isolation facilities for suspected MDR TB cases
 - Increased vigilance to identify undiagnosed TB cases (incl Contact tracing of all TB, MDR & XDR TB cases)



Recommendations (long term)

- Establish capacity for clinical and public health managers to respond effectively to MDR-TB and XDR-TB
- Promote universal access to ART for all co-infected patients
- Support further research into drug development and rapid diagnostic tests



Acknowledgements

- Gandhi, A Moll, R Pawinski, U Lalloo, AW Sturm, K Zeller, J Andrews, G Friedland
- WHO