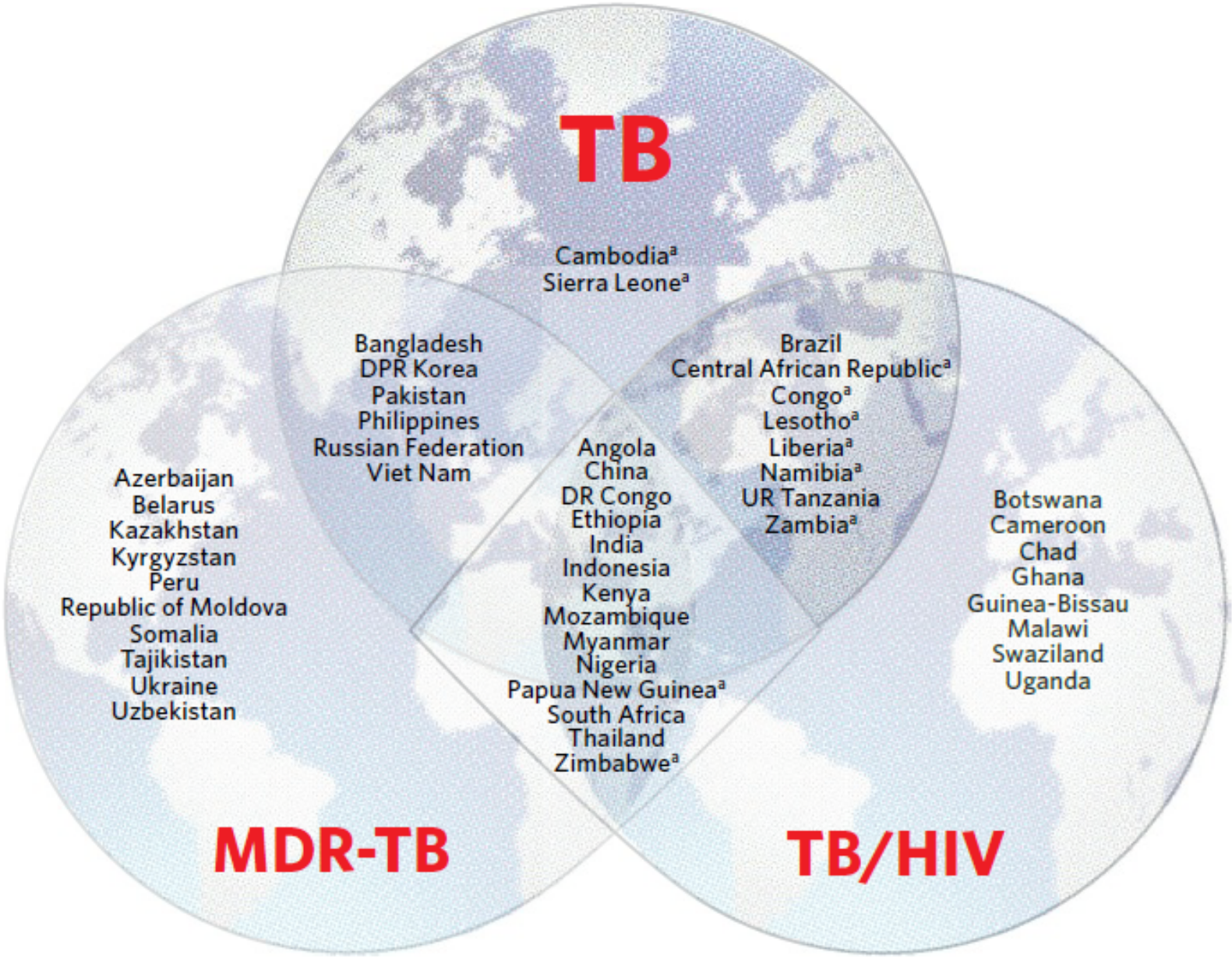
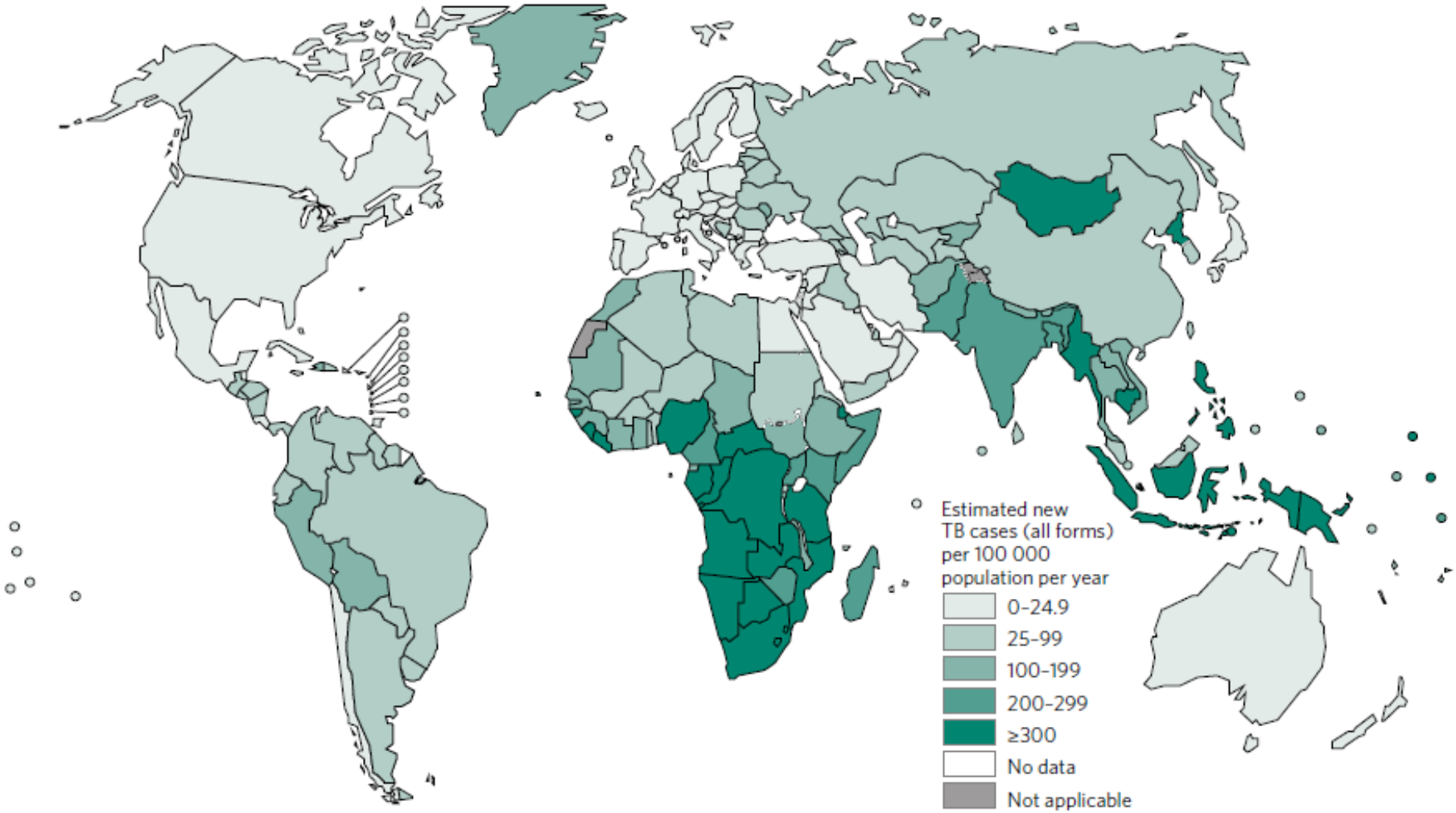
TB – Local epidemiology and clinical challenges

Dr John Black

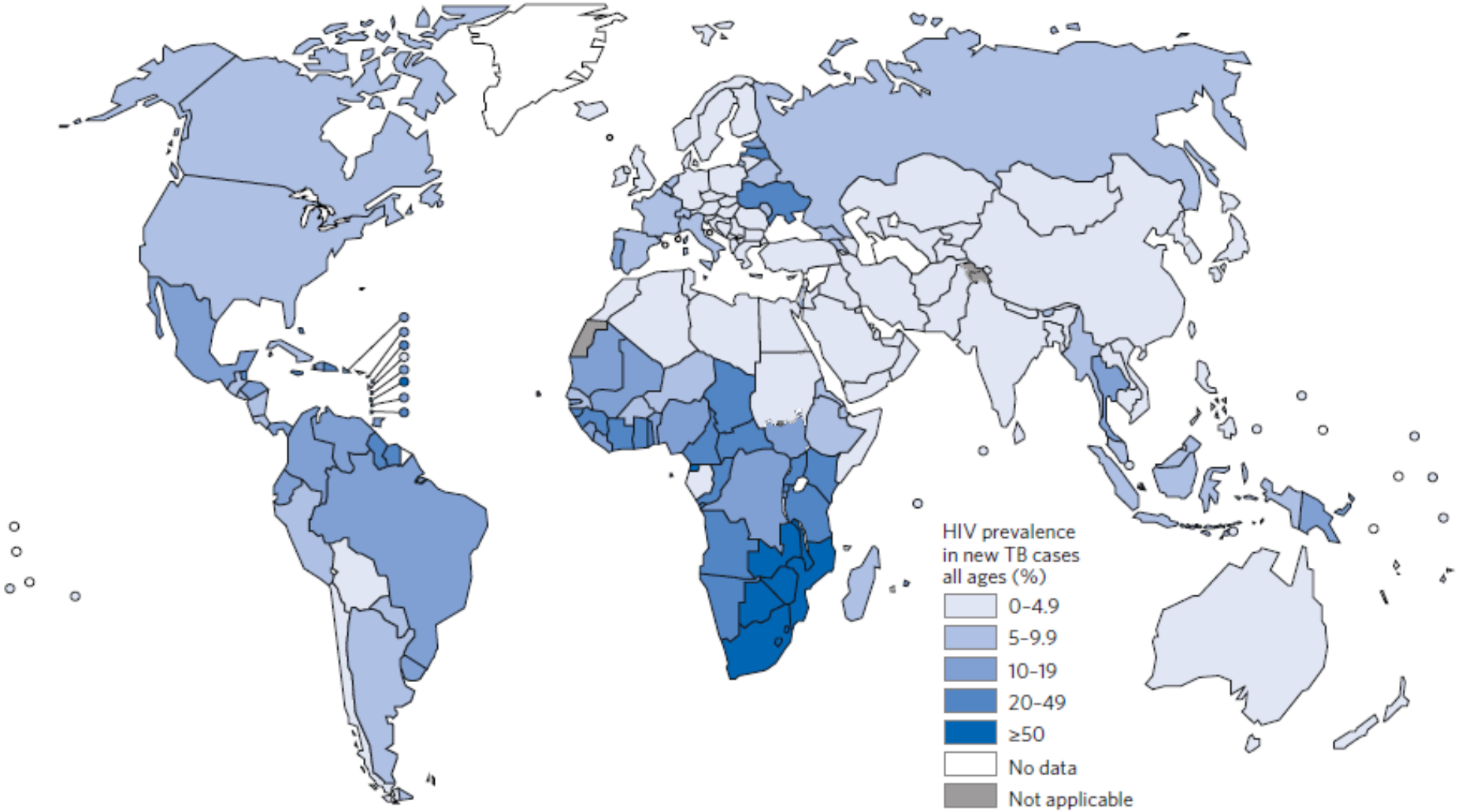
Livingstone Hospital


TB
Cambodia[a]
Sierra Leone[a]
Bangladesh
DPR Korea
Pakistan
Philippines
Russian Federation
Viet Nam
Brazil
Central African Republic[a]
Congo[a]
Lesotho[a]
Liberia[a]
Namibia[a]
UR Tanzania
Zambia[a]
Azerbaijan
Belarus
Kazakhstan
Kyrgyzstan
Peru
Republic of Moldova
Somalia
Tajikistan
Ukraine
Uzbekistan
Angola
China
DR Congo
Ethiopia
India
Indonesia
Kenya
Mozambique
Myanmar
Nigeria
Papua New Guinea[a]
South Africa
Thailand
Zimbabwe[a]
Botswana
Cameroon
Chad
Ghana
Guinea-Bissau
Malawi
Swaziland
Uganda
MDR-TB
TB/HIV

Estimated TB incidence rates, 2015



Estimated HIV prevalence in new and relapse TB cases, 2015



:: TABLE 3.3

Estimated epidemiological burden of TB in 2015 for 30 high TB burden countries, WHO regions and globally. Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval. Rates per 100 000 population except where indicated.[a]

	HIV-NEGATIVE TB MORTALITY		HIV-POSITIVE TB MORTALITY		TOTAL TB INCIDENCE		HIV PREVALENCE IN INCIDENT TB %	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL
Angola	45	27–67	29	6.5–67	370	240–529	30	24–36
Bangladesh[b]	45	27–68	0.14	0.12–0.18	225	146–321	0.18	0.14–0.21
Brazil	2.7	2.5–2.8	1.1	0.56–1.7	41	35–47	15	14–16
Cambodia	55	39–74	2.8	1.2–5.0	380	246–543	2.4	2.2–2.7
Central African Republic	45	26–70	55	20–107	391	253–558	45	36–54
China	2.6	2.5–2.7	0.19	0.09–0.33	67	57–77	1.7	1.4–2.0
Congo	49	29–75	53	44–63	379	246–542	36	29–44
DPR Korea	61	40–87	0.15	0.07–0.26	561	432–706	0.31	0.26–0.38
DR Congo	66	39–99	21	17–26	324	210–463	15	13–19
Ethiopia	26	15–38	4.0	1.6–7.4	192	142–250	8.3	7.6–9.1
India[c]	32	29–35	2.8	1.6–4.3	217	112–355	4.0	3.6–4.4
Indonesia	40	26–57	10	7.6–13	395	255–564	7.7	6.2–9.3
Kenya	20	13–27	16	1.5–45	233	189–281	33	32–35
Lesotho	55	29–89	223	139–328	788	510–1125	72	63–80
Liberia	70	41–107	19	16–22	308	199–440	13	11–15
Mozambique	74	43–115	120	73–178	551	356–787	52	45–58
Myanmar	49	30–74	9.0	6.4–12	365	267–479	8.9	7.9–9.8
Namibia	32	21–45	36	2.5–112	489	376–616	41	39–43
Nigeria	99	53–160	31	24–40	322	189–488	17	14–20
Pakistan	23	4.9–56	0.83	0.60–1.1	270	175–386	1.7	1.4–2.1
Papua New Guinea	41	24–61	8.8	5.2–13	432	352–521	15	12–18
Philippines	13	8.7–19	0.44	0.24–0.70	322	277–370	1.3	1.1–1.6
Russian Federation	11	10–11	1.0	0–5.2	80	69–92	9.9	8.8–11
Sierra Leone	51	30–76	13	6.2–21	307	198–438	13.3	12–15
South Africa	44	39–50	133	50–256	834	539–1190	57	52–61
Thailand	12	10–15	8.0	4.9–12	172	102–259	13	12–14
UR Tanzania	56	25–99	47	31–66	306	146–525	35	31–40
Viet Nam	17	12–23	1.1	0.21–2.8	137	110–166	4.3	4.0–4.6
Zambia	31	18–47	77	42–121	391	253–558	60	54–66
Zimbabwe	11	6.3–16	40	14–81	242	179–314	69	64–74

Figure 2: Incidence of TB (all types) by district, 2015

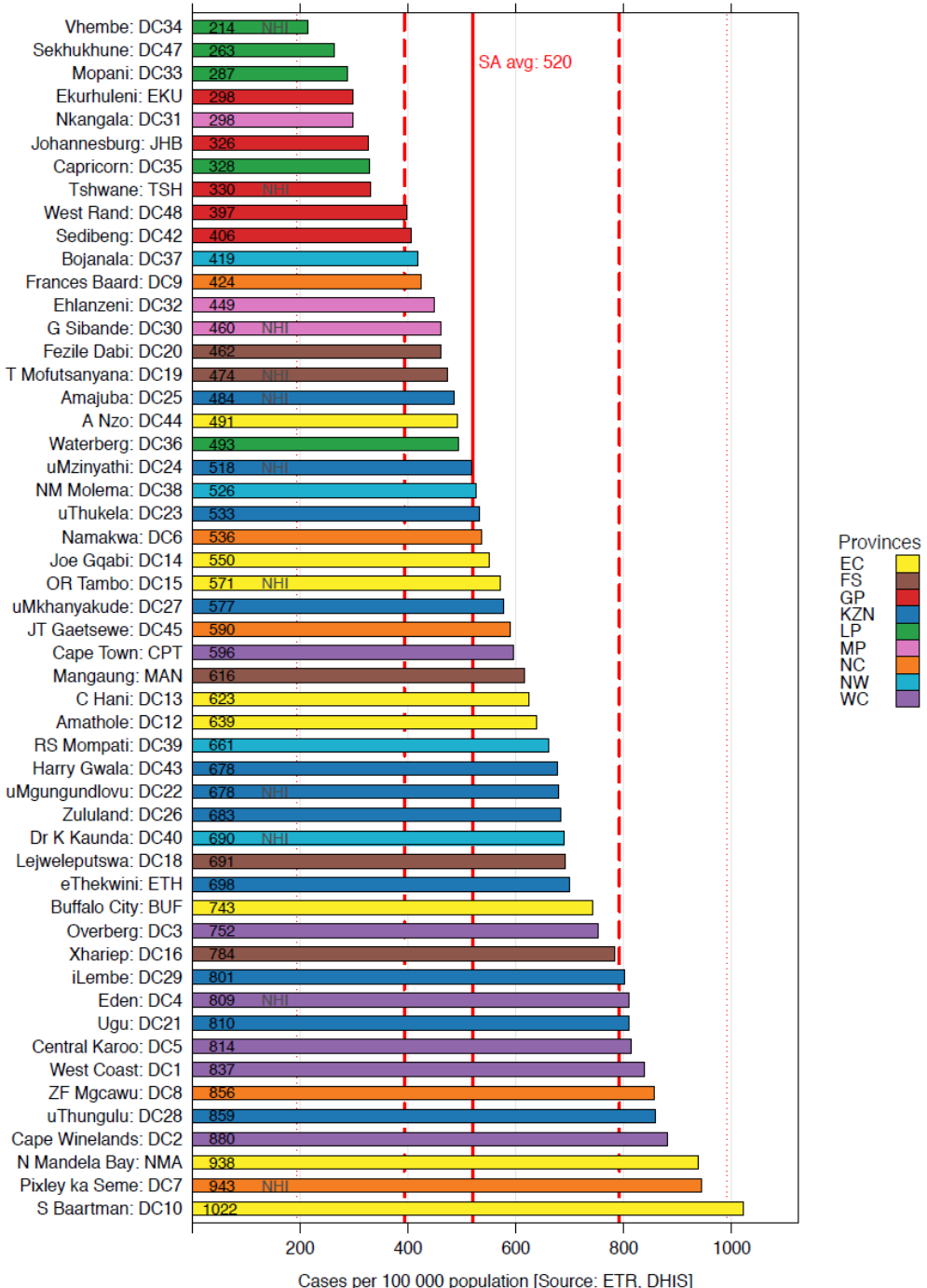
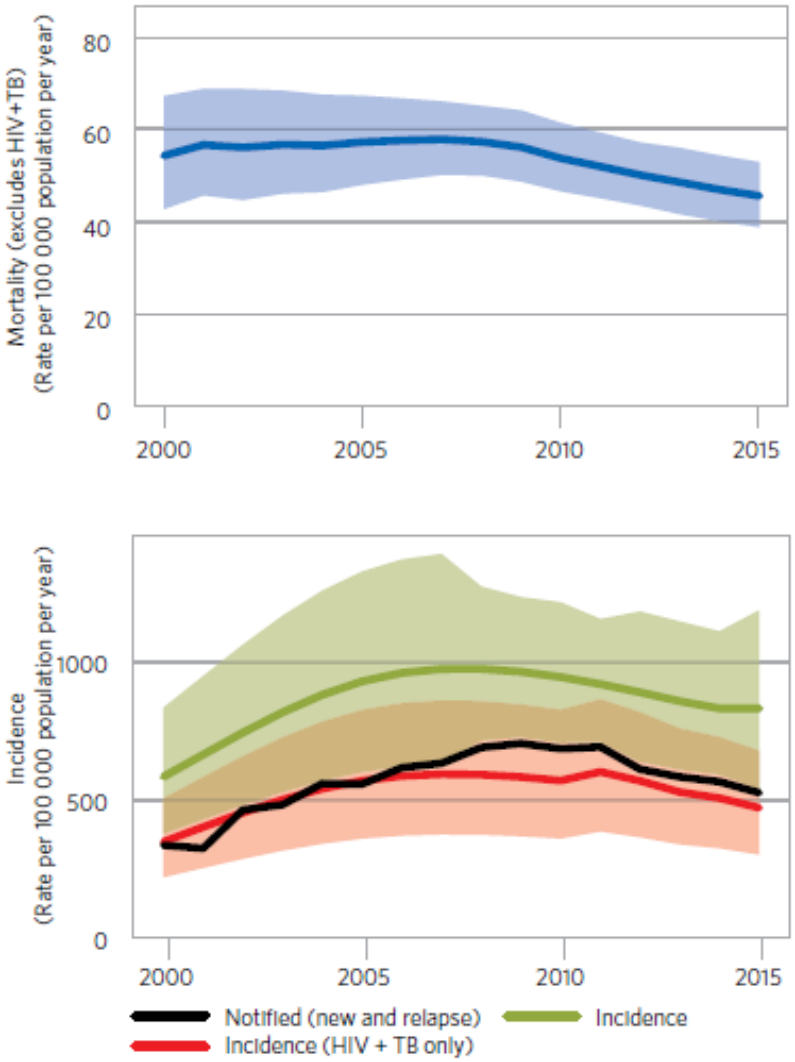


Table 4: TB as cause of natural death by province, 2011–2014

	SA		WC		EC		NC		FS		KZN		NW		GP		MP		LP	
Year	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%
2014	1	8.4	4	5.6	1	9.0	2	7.4	1	8.4	1	11.2	1	8.9	1	6.7	1	9.8	2	7.4
2013	1	8.8	4	5.7	1	9.8	2	7.7	1	8.5	1	11.9	1	8.7	1	7.3	1	10.6	2	7.7
2012	1	9.9	2	6.4	1	10.8	1	8.8	1	9.3	1	13.3	1	10.4	1	7.7	1	12.0	2	8.5
2011	1	10.7	1	7.1	1	11.4	1	8.5	2	9.6	1	14.4	1	11.3	1	8.4	1	13.4	2	9.1
2010	1	11.6	1	7.8	1	12.7	1	9.2	2	11.1	1	15.7	1	12.3	1	8.8	1	13.4	1	8.4

Source: StatsSA.[a]


Mortality (excludes HIV+TB)
(Rate per 100 000 population per year)
80
60
40
20
0
2000
2005
2010
2015
Incidence
(Rate per 100 000 population per year)
1000
500
0
2000
2005
2010
2015
Notified (new and relapse)
Incidence
Incidence (HIV + TB only)

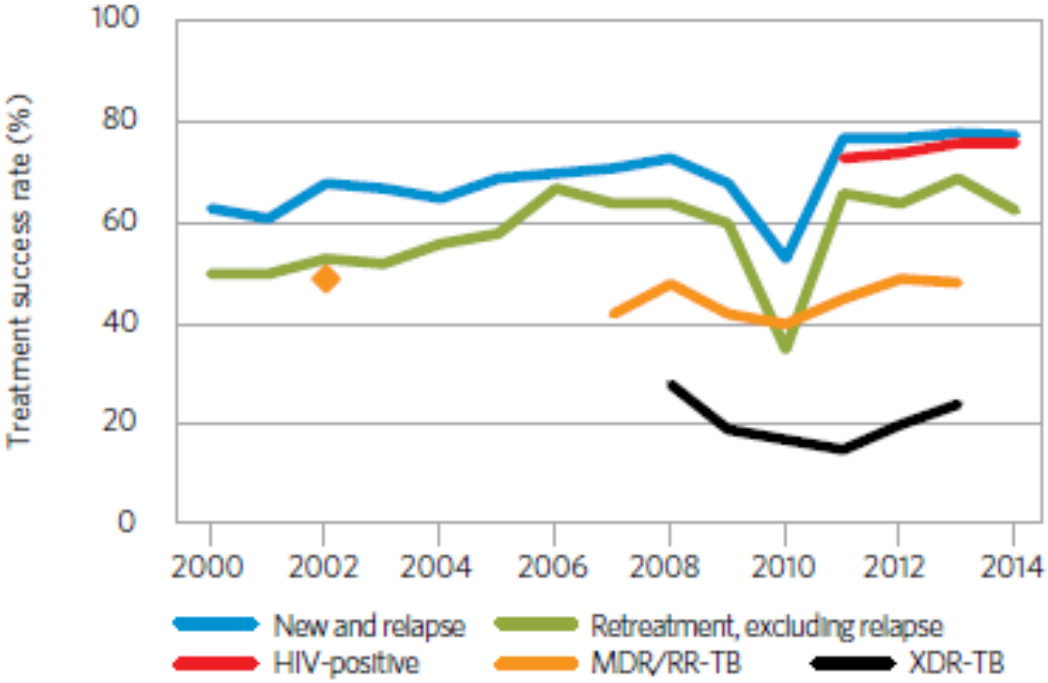

Treatment success rate (%)
100
80
60
40
20
0
2000
2002
2004
2006
2008
2010
2012
2014
New and relapse
Retreatment, excluding relapse
HIV-positive
MDR/RR-TB
XDR-TB

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Table 2: mPTB case burden and incidence rates by year, South Africa: 2004-2015

Year	n	Incidence/100000 (95% CI)	Annual change in cases (n)	Annual change in incidence (%)
2004	214 166	572(569-574)	-	-
2005	260 855	687(685-690)	46 689	20.1
2006	269 197	700(697-702)	8 342	1.9
2007	260 406	668(665-670)	-8 791	-4.6
2008	272 702	689(687-692)	12 296	3.1
2009	252 467	629(627-632)	-20 235	-8.7
2010	251 951	619(616-621)	-516	-1.6
2011*	343 960	667(665-669)	-$	-$
2012*	317 439	606(604-609)	-26 521	-9.1
2013*	309 088	581(579-584)	-8 351	-4.1
2014*	294 590	546(544-548)	-14 498	-6.0
2015*	281 055	520(519-522)	-13 535	-4.8

*includes data for KwaZulu-Natal

$ Annual change restarted with addition of KwaZulu-Natal data

- 3 327 876 mPTB patient episodes (2004-2015)
- Reduction in mPTB incidence 4%-6% pa (last 3 years) – required=10% p.a., current global average=1-2% p.a

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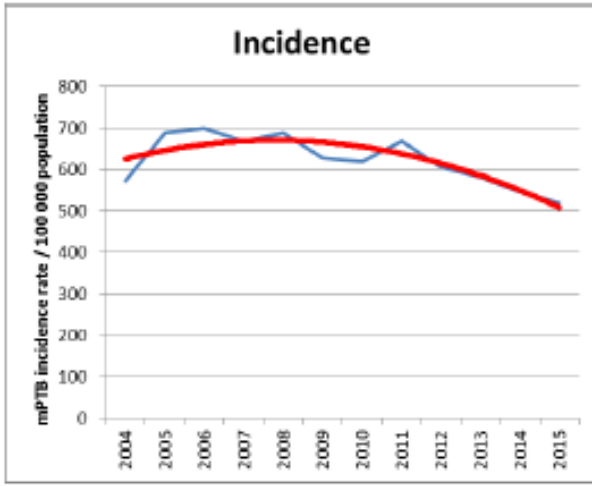
Incidence Trends



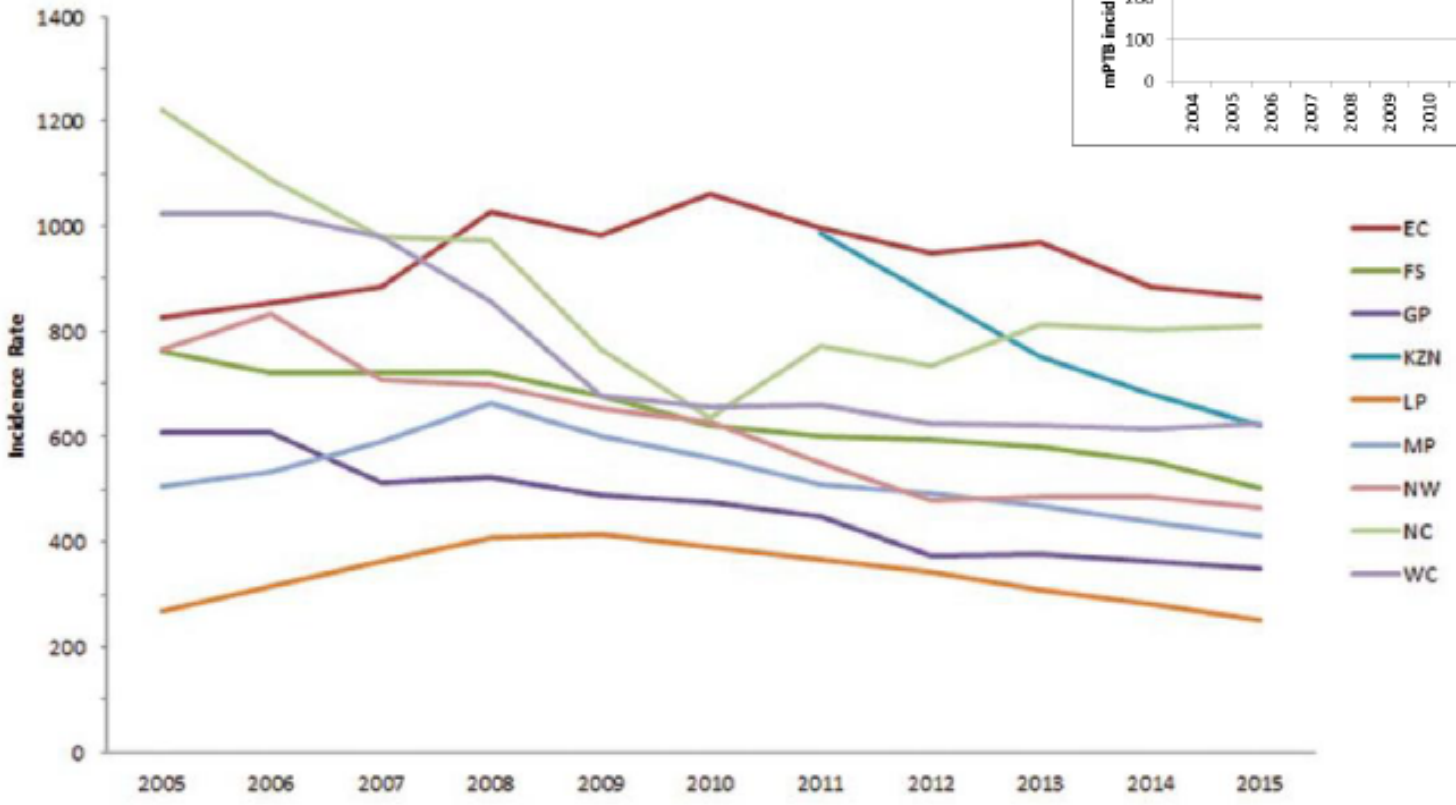
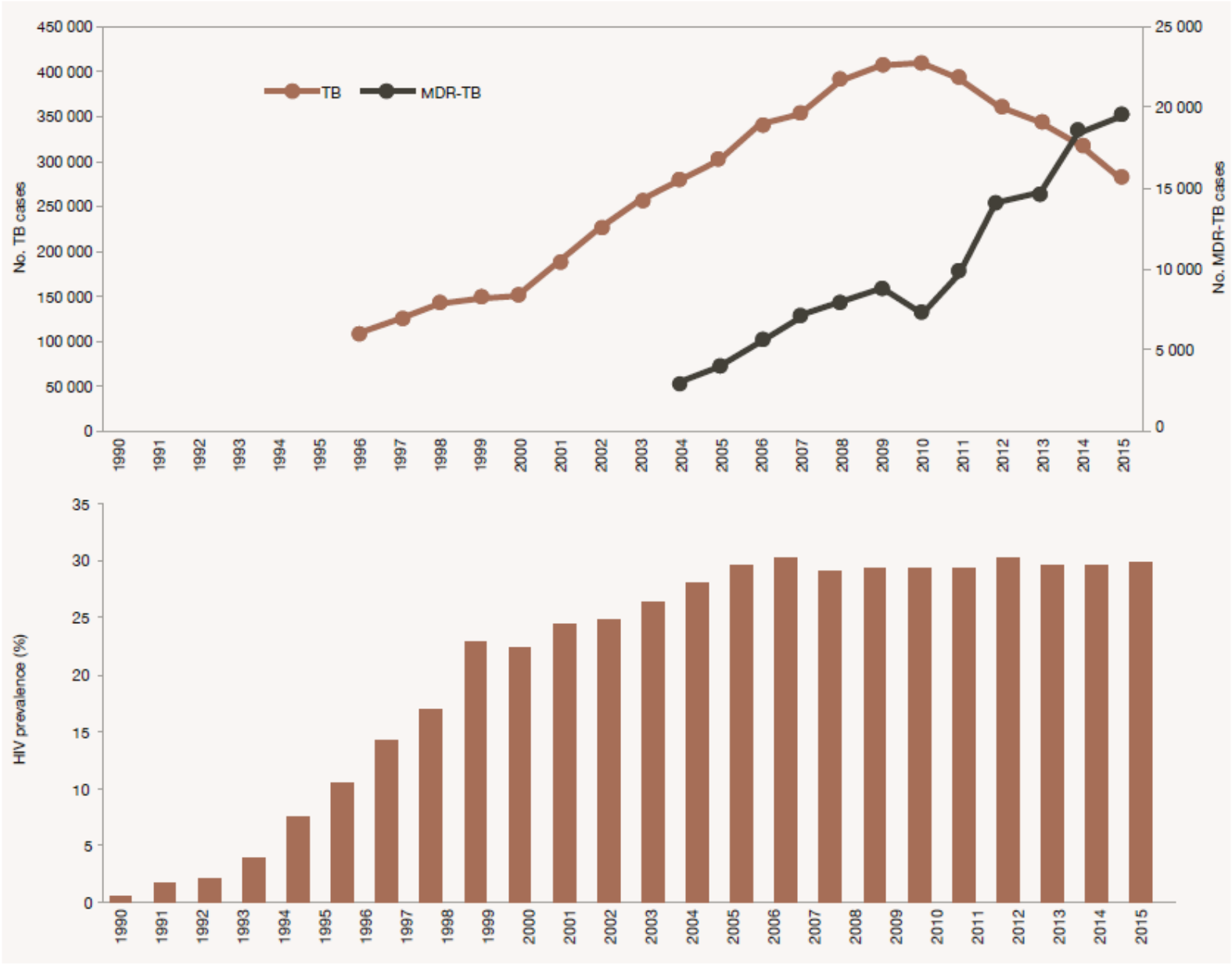
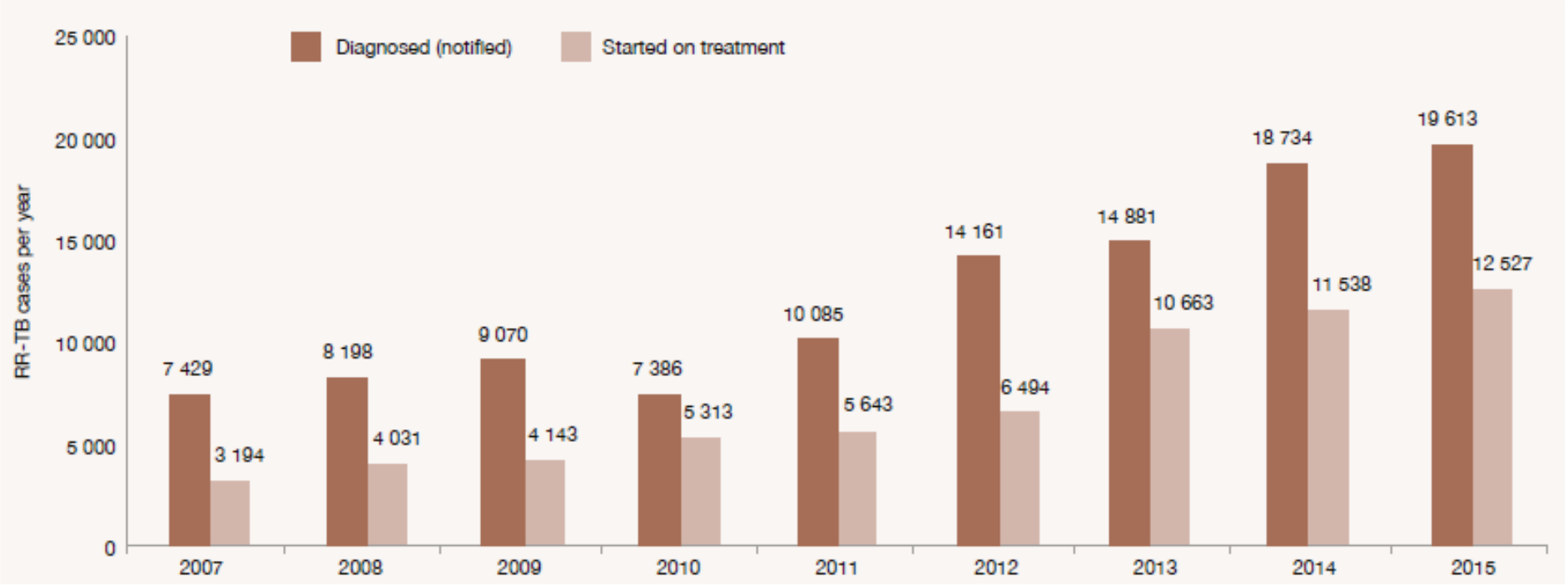


Figure 1: Reported cases of TB and laboratory-diagnosed cases of MDR-TB (top panel, note different axes), and national antenatal care HIV prevalence rate (lower panel) between 1990 and 2015



Source: WHO 2016;[4] NDoH 2011;[23] WHO 2015;[24] NDoH 2007;[25] Ndjeka 2014.[26]

Figure 2: Numbers of RR/MDR-TB patients diagnosed and reported to have started on second-line treatment, by year, in South Africa



Source: WHO 2016;[4] NDoH 2011;[23] Ndjeka, 2014.[26]

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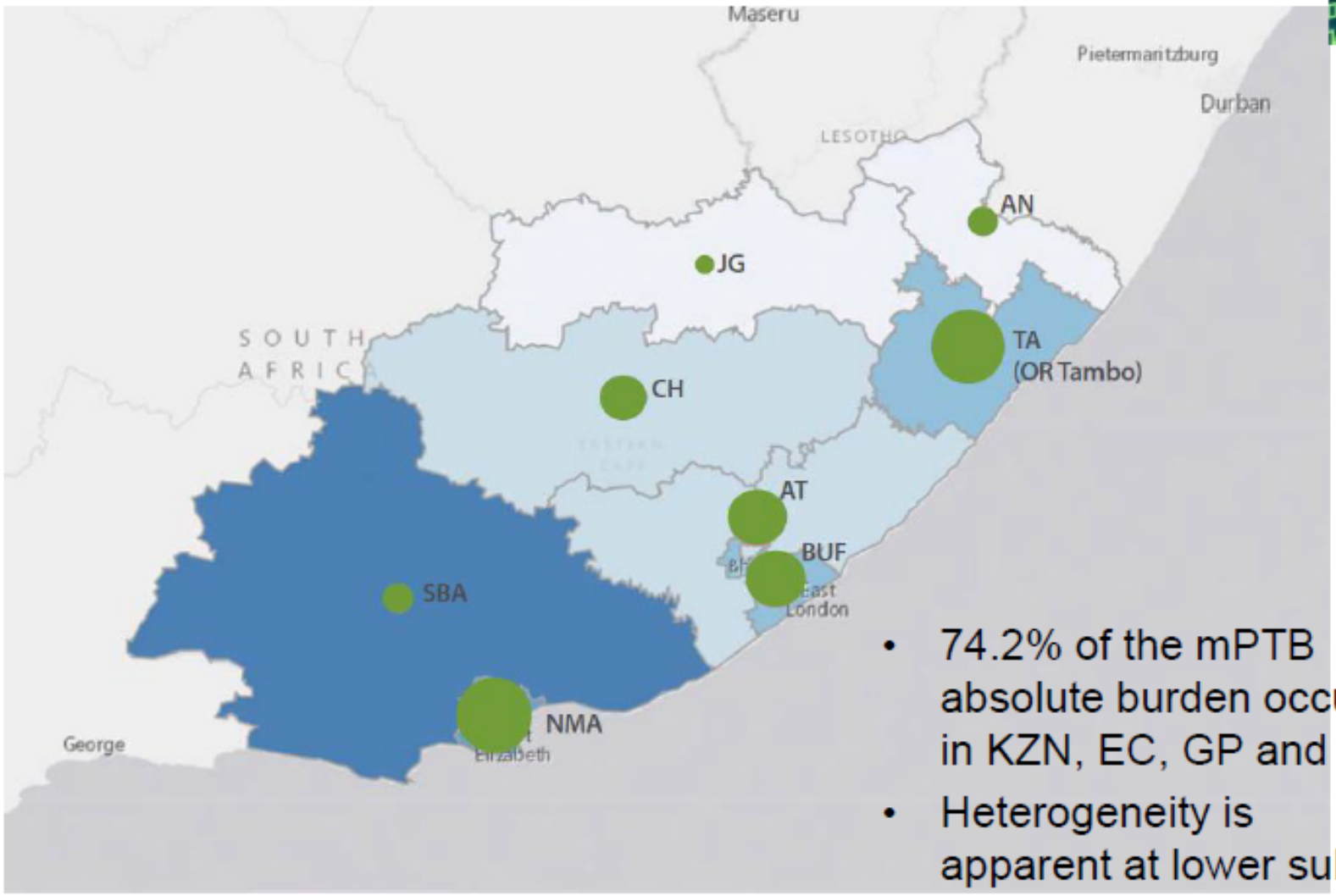
GEOSPATIAL DISTRIBUTION



- 74.2% of the mPTB absolute burden occurs in KZN, EC, GP and WC
- Heterogeneity is apparent at lower sub-national levels

2015 NHLS de-duplicated data

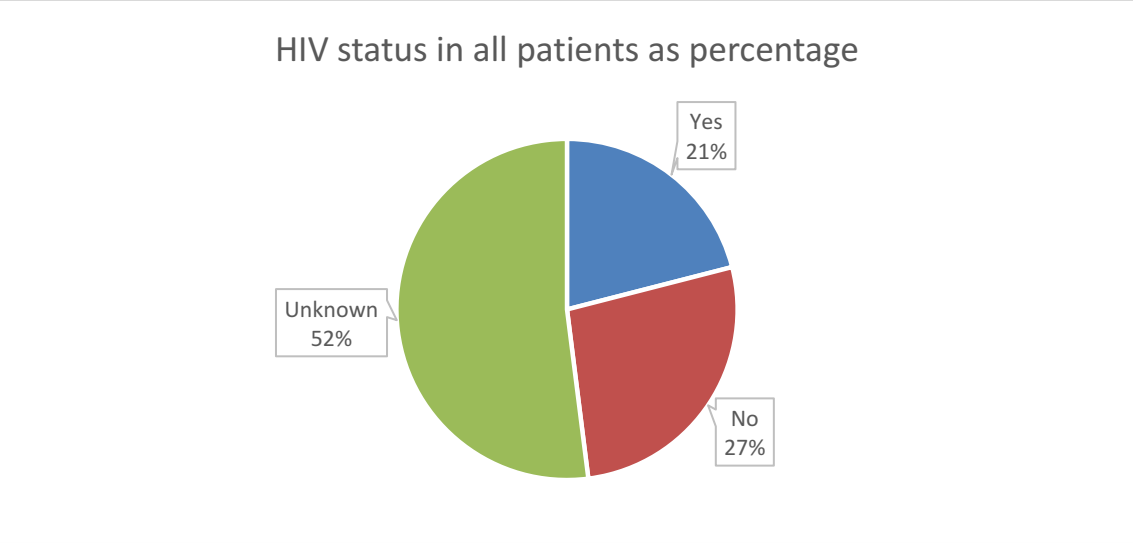
DISTRICT/SUB-DISTRICT	TOTAL PTB CASES	No. TESTED NEGATIVE	TOTAL TESTED	POSITIVITY RATE	MDR	XDR
ALFRED NZO	**5500**	**44126**	49626	11.1	**145**	**14**
AMATHOLE	**7834**	**92527**	100361	7.8	**167**	17
BUFFALO CITY	**10670**	**65764**	76434	14	**546**	**125**
SARAH BAARTMAN	**6591**	**37488**	44079	15	**215**	**54**
CHRIS HANI	**7753**	**68044**	75797	10.2	**133**	**19**
JOE GQABI	**2913**	**29940**	32853	8.9	**48**	**5**
NELSON MANDELA BAY METRO	**15234**	**63043**	78277	19.5	**580**	**182**
O R TAMBO	**13858**	**77077**	90935	15.2	**357**	**49**
COLUMN TOTAL	**70353**	**478009**	**548362**	**12.8**	**2191**	**465**

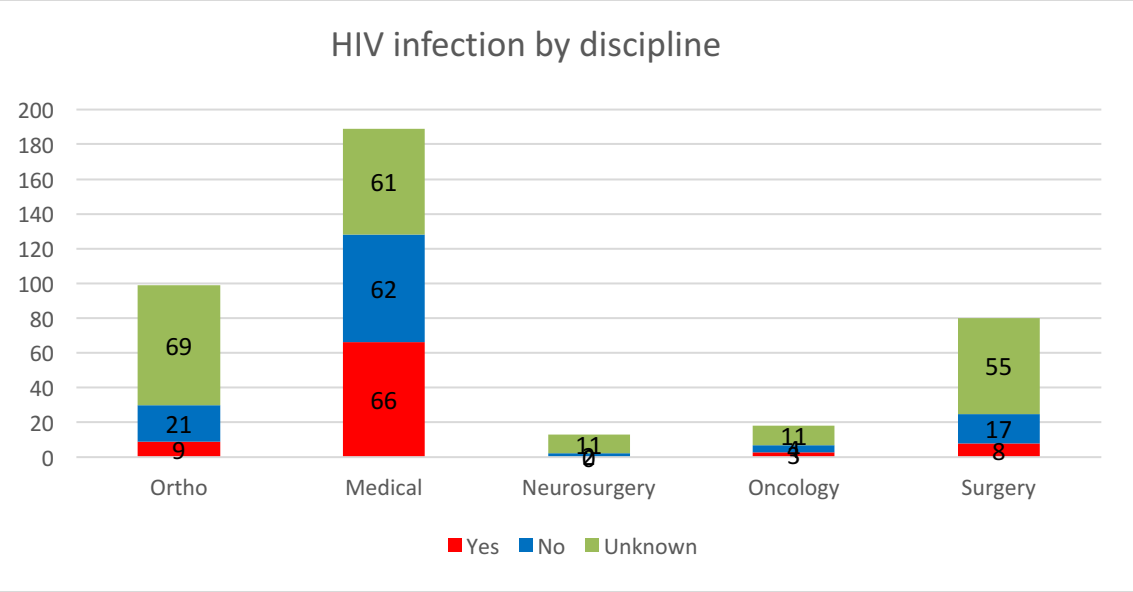
Tuberculosis in EC and NMB 2015

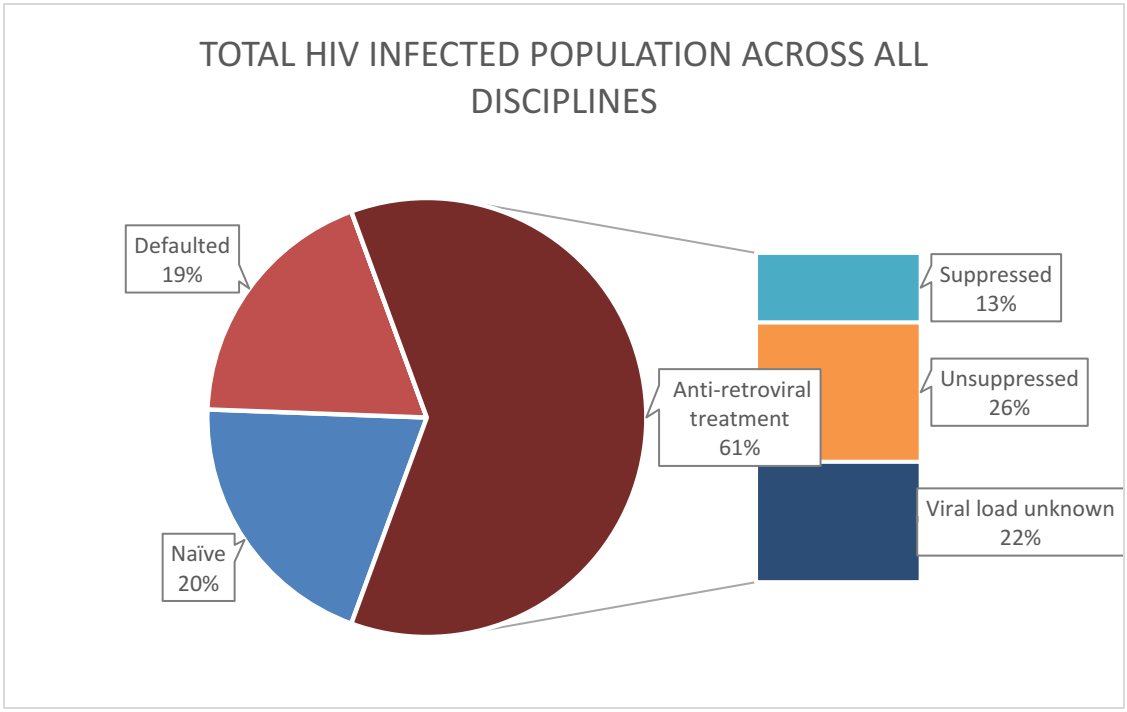
	DSTB	MDR	XDR
Eastern Cape	70353	2191	465
NMB	15234	580	182

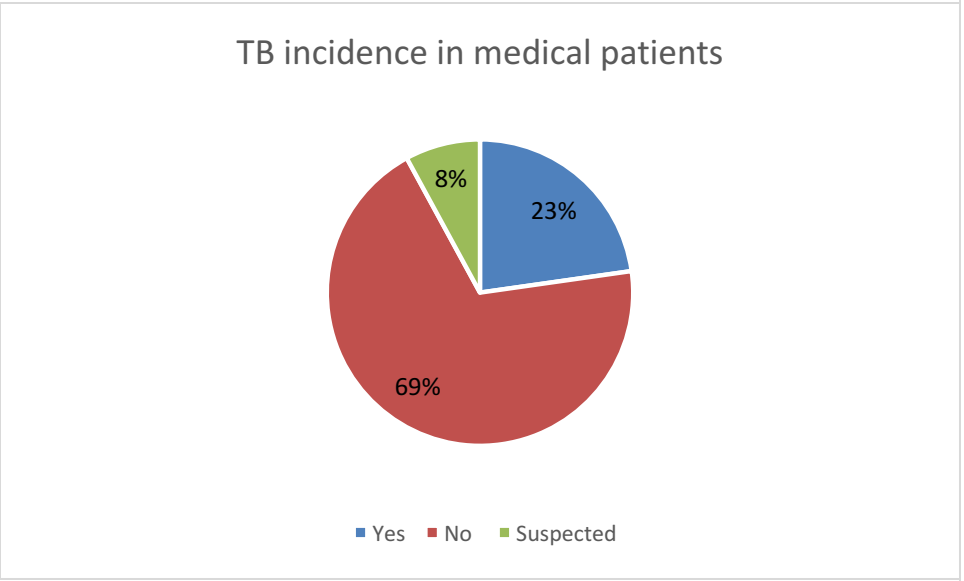
	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec		Total	Resistant	%
DORA NGINZA HOSPITAL	34	38	61	46	58	54	49	57	56	64	39	60		616	49	7.954545
LIVINGSTONE HOSPITAL	47	43	39	42	30	42	29	28	58	53	32	46		489	36	7.361963
UITENHAGE HOSPITAL	17	7	13	11	11	12	21	22	30	21	9	15		189	15	7.936508

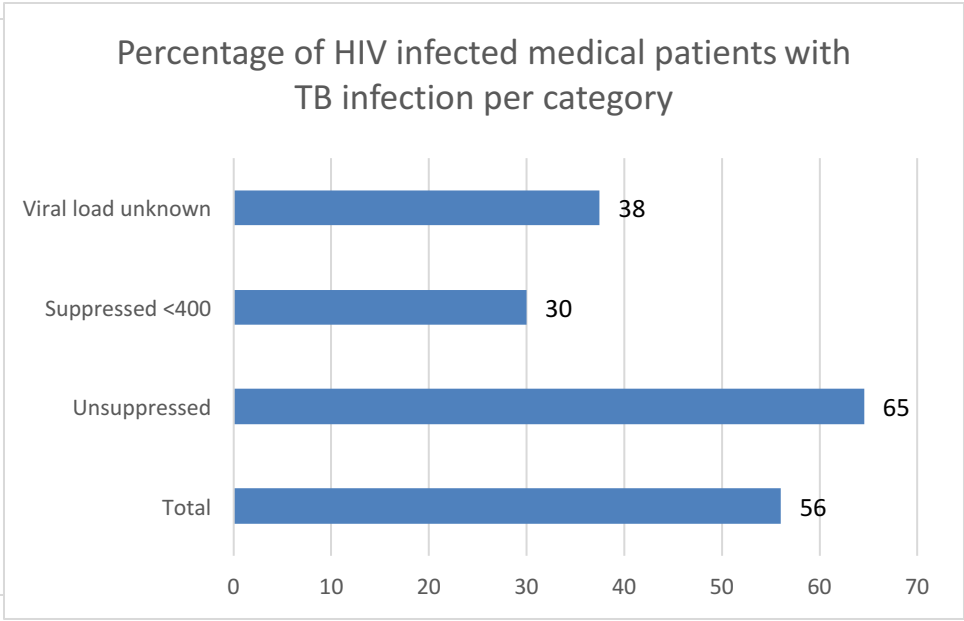
HIV in the hospitals






TOTAL HIV INFECTED POPULATION ACROSS ALL DISCIPLINES
Defaulted 19%
Naïve 20%
Anti-retroviral treatment 61%
Suppressed 13%
Unsuppressed 26%
Viral load unknown 22%


TB incidence in medical patients
8%
23%
69%
Yes
No
Suspected

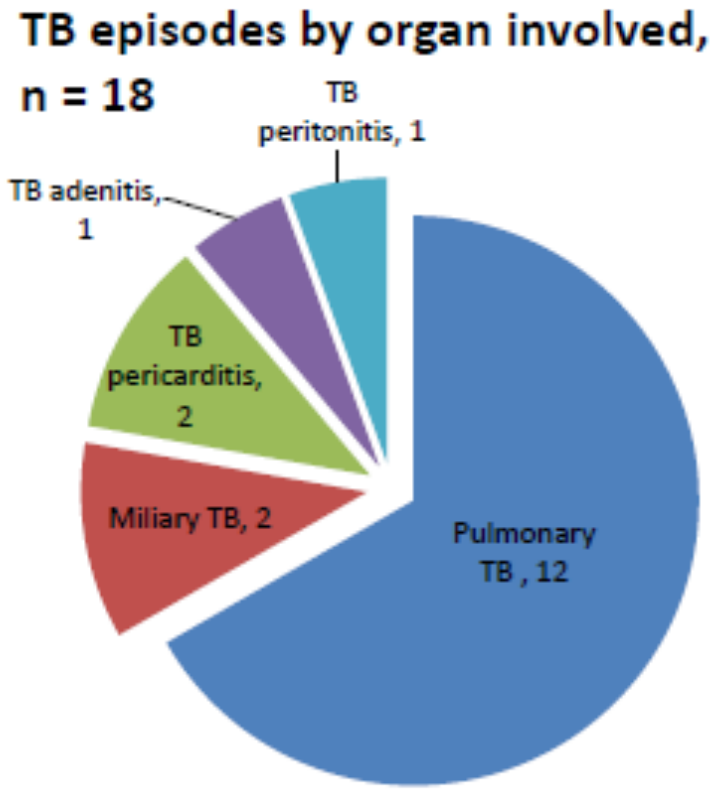

Percentage of HIV infected medical patients with TB infection per category
Viral load unknown
38
Suppressed <400
30
Unsuppressed
65
Total
56
0
10
20
30
40
50
60
70

HIGH BURDEN OF TUBERCULOSIS IN SOUTH AFRICAN DIALYSIS PATIENTS: THE REPORT OF A SINGLE CENTRE IN THE EASTERN CAPE, SOUTH AFRICA.

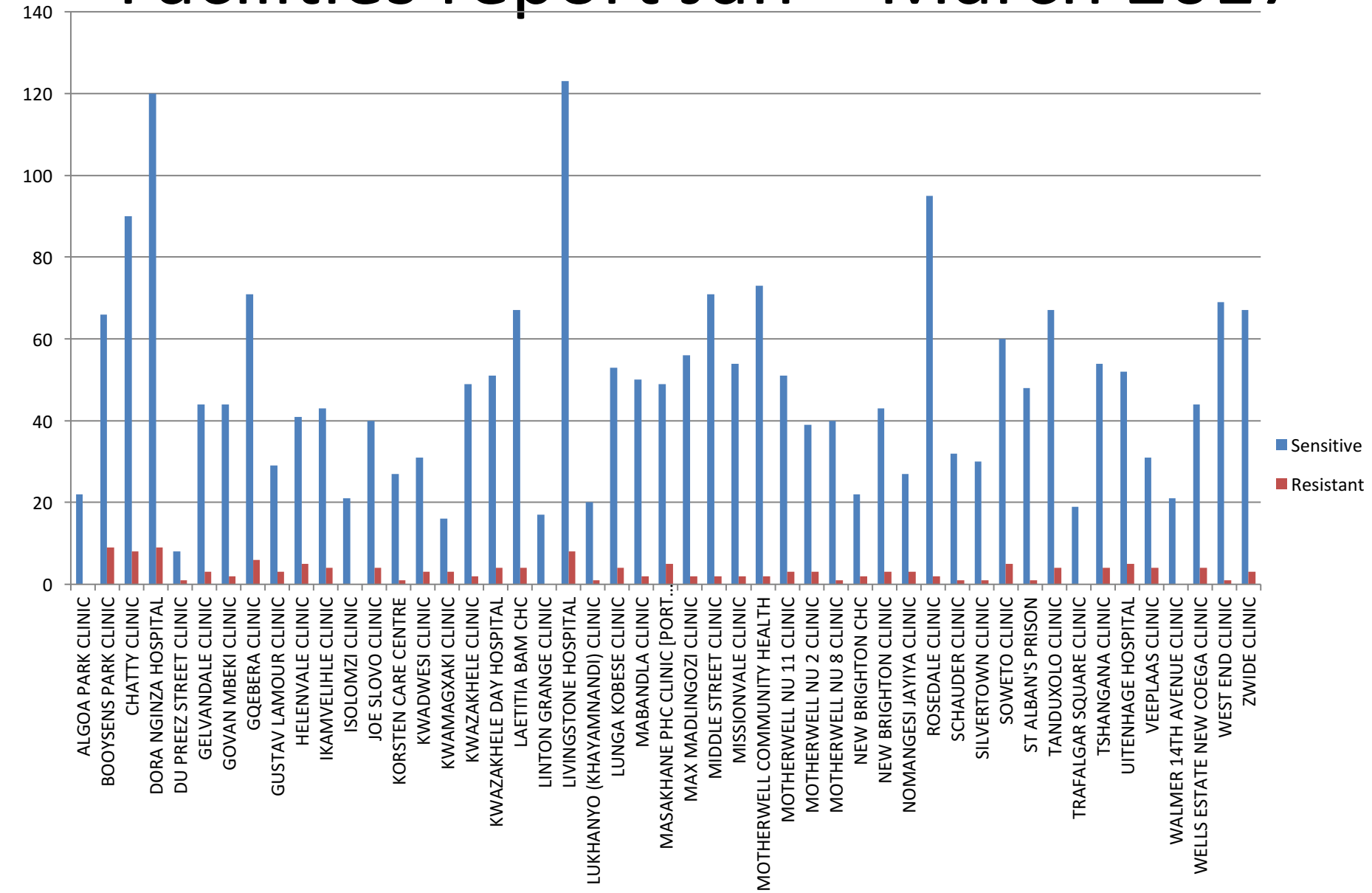
Siviwe Ndamase[1], John Black[1, 2], Gregory Calligaro[2], Henri Carrara[3], Robert Freercks.[1, 2]
[1]Livingstone Hospital, Division of Nephrology, Port Elizabeth, South Africa,[2] University of Cape Town, Department of Medicine, South Africa, [3] University of Cape Town, School of Public Health and Family Medicine, South Africa

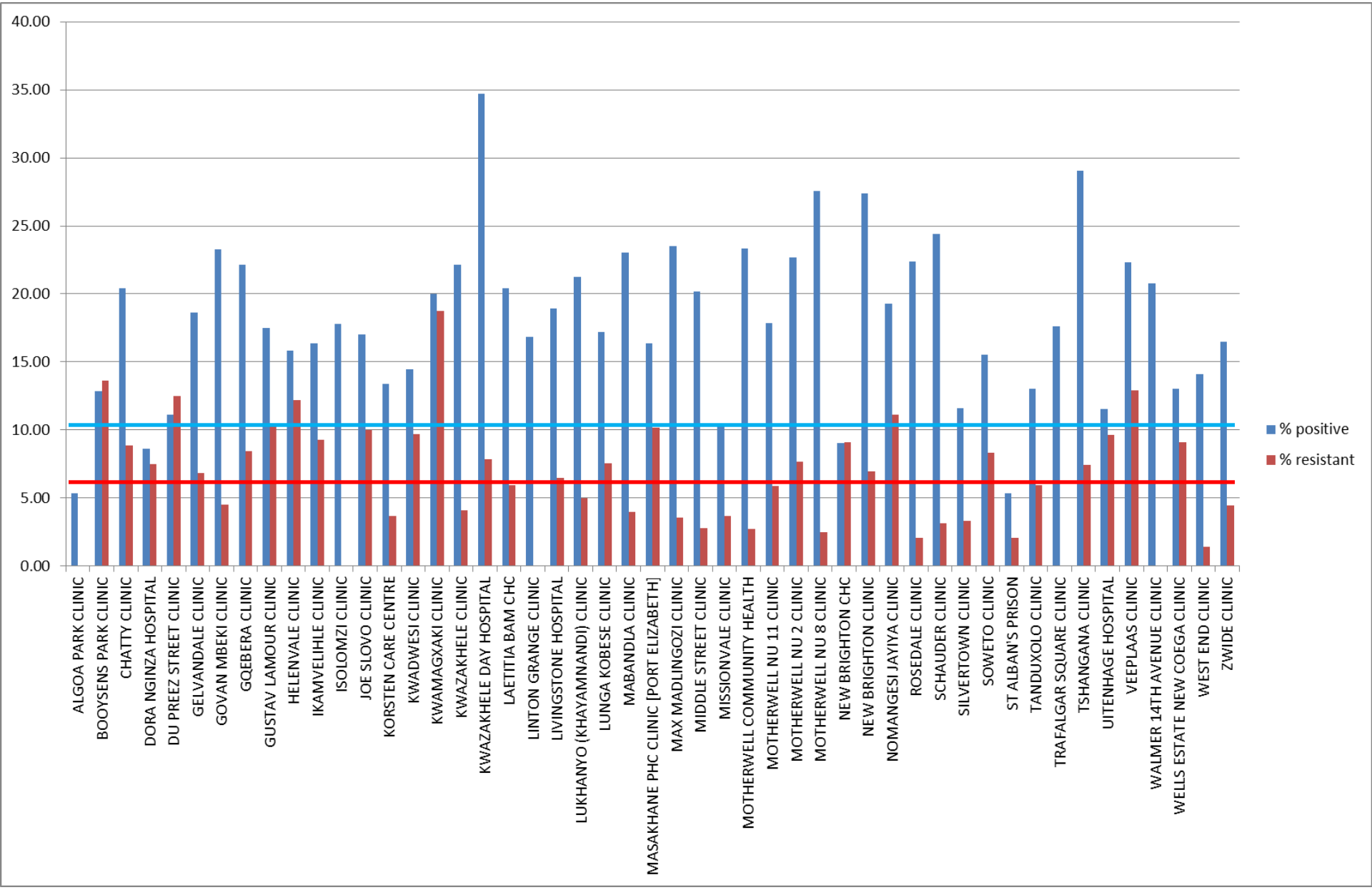
RESULTS

The study participants were predominantly black African (75%) and female (55%); mean age was 42.6 (SD ± 9.4). Sixty patients were on haemodialysis and 38 were on peritoneal dialysis. There were 18 TB infections in the study period, giving an incidence rate of 4592 per 100 000 person years. Recent hospitalization and poorer housing were more prevalent in those with TB, but there was no difference by HIV status.



Facilities report Jan – March 2017



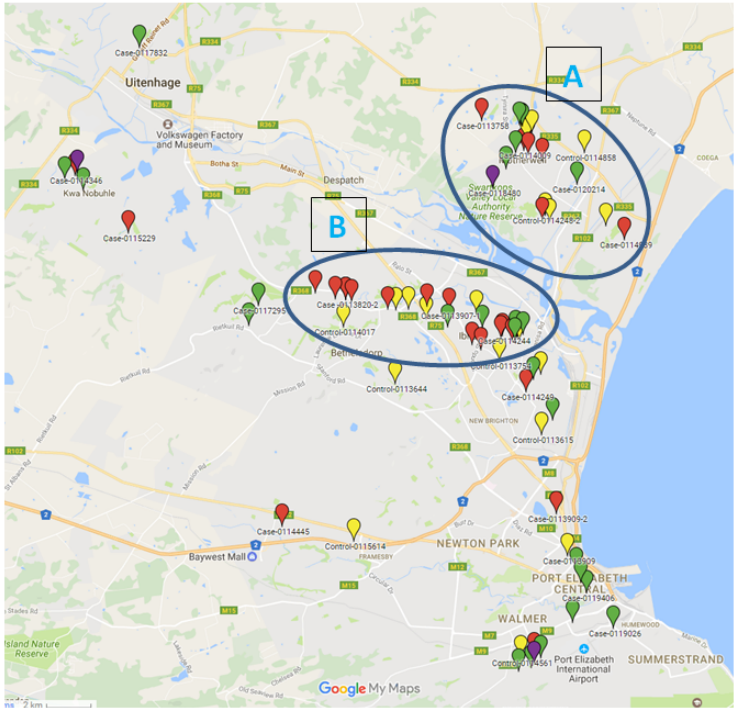

40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
% positive
% resistant
ALGOA PARK CLINIC
BOOYSENS PARK CLINIC
CHATTY CLINIC
DORA NGINZA HOSPITAL
DU PREEZ STREET CLINIC
GELVANDALE CLINIC
GOVAN MBEKI CLINIC
GQEBERA CLINIC
GUSTAV LAMOUR CLINIC
HELENVALE CLINIC
IKAMVELIHLE CLINIC
ISOLOMZI CLINIC
JOE SLOVO CLINIC
KORSTEN CARE CENTRE
KWADWESI CLINIC
KWAMAGXAKI CLINIC
KWAZAKHELE CLINIC
KWAZAKHELE DAY HOSPITAL
LAETITIA BAM CHC
LINTON GRANGE CLINIC
LIVINGSTONE HOSPITAL
LUKHANYO (KHAYAMNANDI) CLINIC
LUNGA KOBESE CLINIC
MABANDLA CLINIC
MASAKHANE PHC CLINIC [PORT ELIZABETH]
MAX MADLINGOZI CLINIC
MIDDLE STREET CLINIC
MISSIONVALE CLINIC
MOTHERWELL COMMUNITY HEALTH
MOTHERWELL NU 11 CLINIC
MOTHERWELL NU 2 CLINIC
MOTHERWELL NU 8 CLINIC
NEW BRIGHTON CHC
NEW BRIGHTON CLINIC
NOMANGESI JAYIYA CLINIC
ROSEDALE CLINIC
SCHAUDER CLINIC
SILVERTOWN CLINIC
SOWETO CLINIC
ST ALBAN'S PRISON
TANDUXOLO CLINIC
TRAFALGAR SQUARE CLINIC
TSHANGANA CLINIC
UITENHAGE HOSPITAL
VEEPLAAS CLINIC
WALMER 14TH AVENUE CLINIC
WELLS ESTATE NEW COEGA CLINIC
WEST END CLINIC
ZWIDE CLINIC

Investigation of a cluster of genotypically identical rifampicin resistant TB cases in the Nelson Mandela Bay Metropolitan Municipality

Preliminary Results:
Social network analysis

- Amongst 30 persons with genotypically identical TB
  - 21 interviews done
  - No person voluntarily reported knowing another member of the cluster
  - 9/21 had no known TB contact
  - Of 12 who had a TB contact, 10 shared their home with a TB contact.
  - 8 employed until admission (domestic worker, factory/general worker, cashier, hair stylist, waitress)

- 15/21 cases clustered in 2 geographical areas

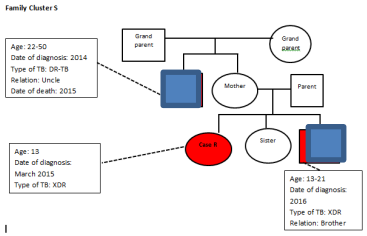


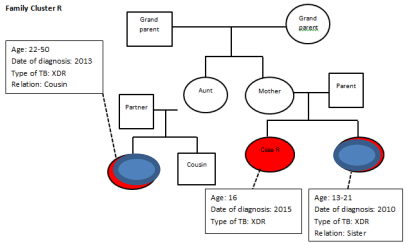
Legend: Controls, Cases (current address), Cases (new address), post investigation cases

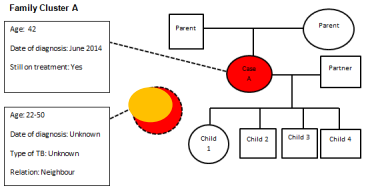
Data/slide courtesy R Mapuroma, N Ismail

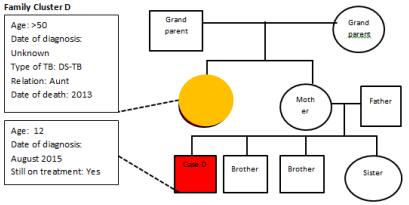
Preliminary Results:
Social network analysis

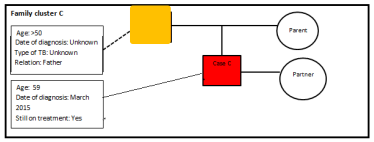
Amongst 12 persons with TB contact in place of residence, 7 contacts had known DR-TB

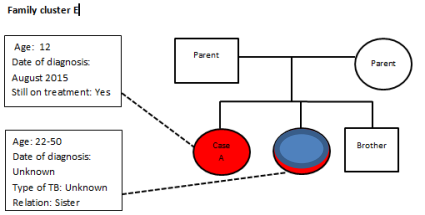


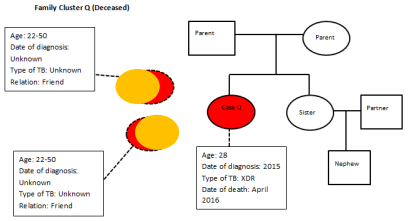


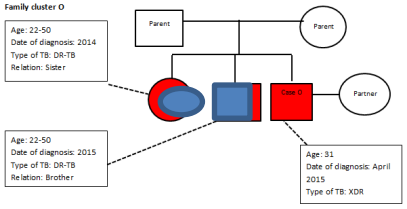


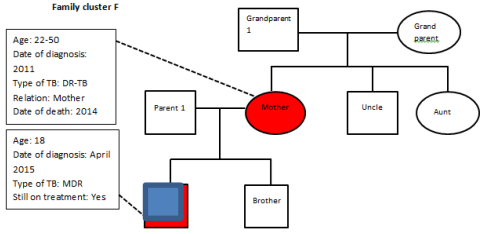


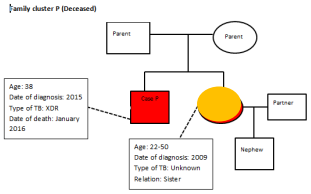


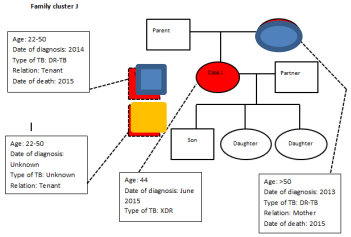


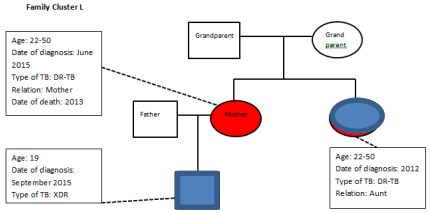












Female/male index case with DR-TB

Female/male DR-TB

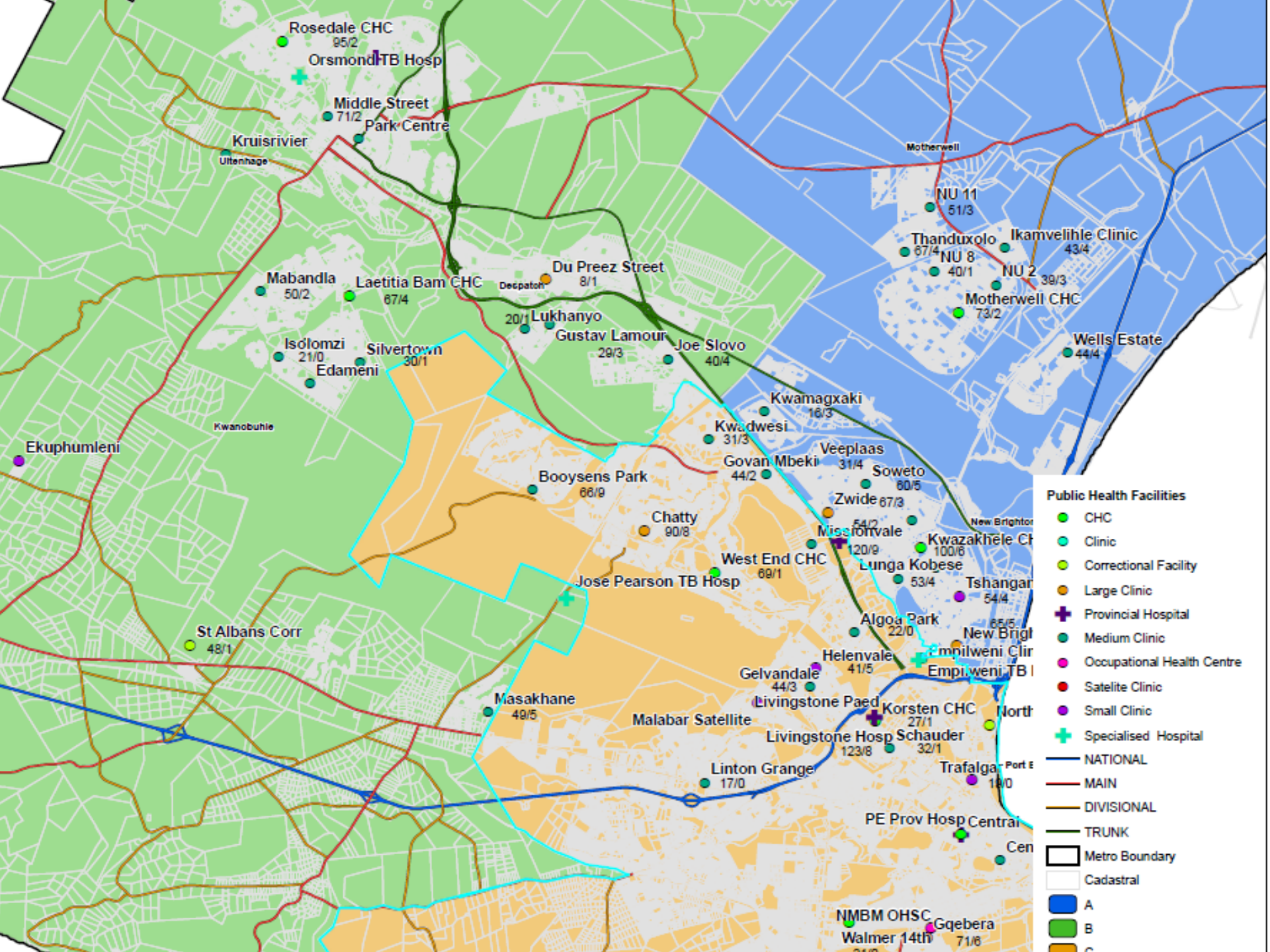
Female/male DS-TB or susceptibility profile unknown

Data/slide courtesy R Mapuroma

Preliminary results
Contact tracing

- 39 contacts of 16 cases were identified
  - 8 had previous episode of DR-TB
  - 3 had active TB and were on Rx, 2 with DR-TB and one with DS-TB
  - 6 were never screened for TB symptoms
  - 6 had current TB symptoms and were asked to visit their clinic to give sputum; only a single contact provided sputum, and s/he tested Xpert negative.

Data/slide courtesy R Chingonzo


Rosedale CHC
95/2
Orsmond TB Hosp
Middle Street
71/2
Park Centre
Kruisrivier
Uitenhage
Motherwell
NU 11
51/3
Thanduxolo
67/4
Ikamvelihle Clinic
43/4
NU 8
40/1
NU 2
39/3
Motherwell CHC
73/2
Wells Estate
44/4
Mabandla
50/2
Laetitia Bam CHC
67/4
Decpatch
Du Preez Street
8/1
20/1
Lukhanyo
Gustav Lamour
29/3
Joe Slovo
40/4
Isolomzi
21/0
Silvertown
30/1
Edameni
Kwanobuhle
Kwamagxaki
16/3
Kwadwesi
31/3
Ekuphumleni
Veeplaas
31/4
Govan Mbeki
44/2
Soweto
60/5
Booysens Park
66/9
Zwide
67/3
Chatty
90/8
Missionvale
120/9
Kwazakhele
100/6
West End CHC
69/1
Lunga Kobese
53/4
Jose Pearson TB Hosp
Algoa Park
22/0
St Albans Corr
48/1
Helenvale
41/5
Gelvandale
44/3
Masakhane
49/5
Livingstone Paed
Korsten CHC
27/1
Malabar Satellite
Livingstone Hosp
123/8
Schauder
32/1
Linton Grange
17/0
PE Prov Hosp
NMBM OHSC
Walmer 14th
Gqebera
71/6
Public Health Facilities
CHC
Clinic
Correctional Facility
Large Clinic
Provincial Hospital
Medium Clinic
Occupational Health Centre
Satelite Clinic
Small Clinic
Specialised Hospital
NATIONAL
MAIN
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TRUNK
Metro Boundary
Cadastral
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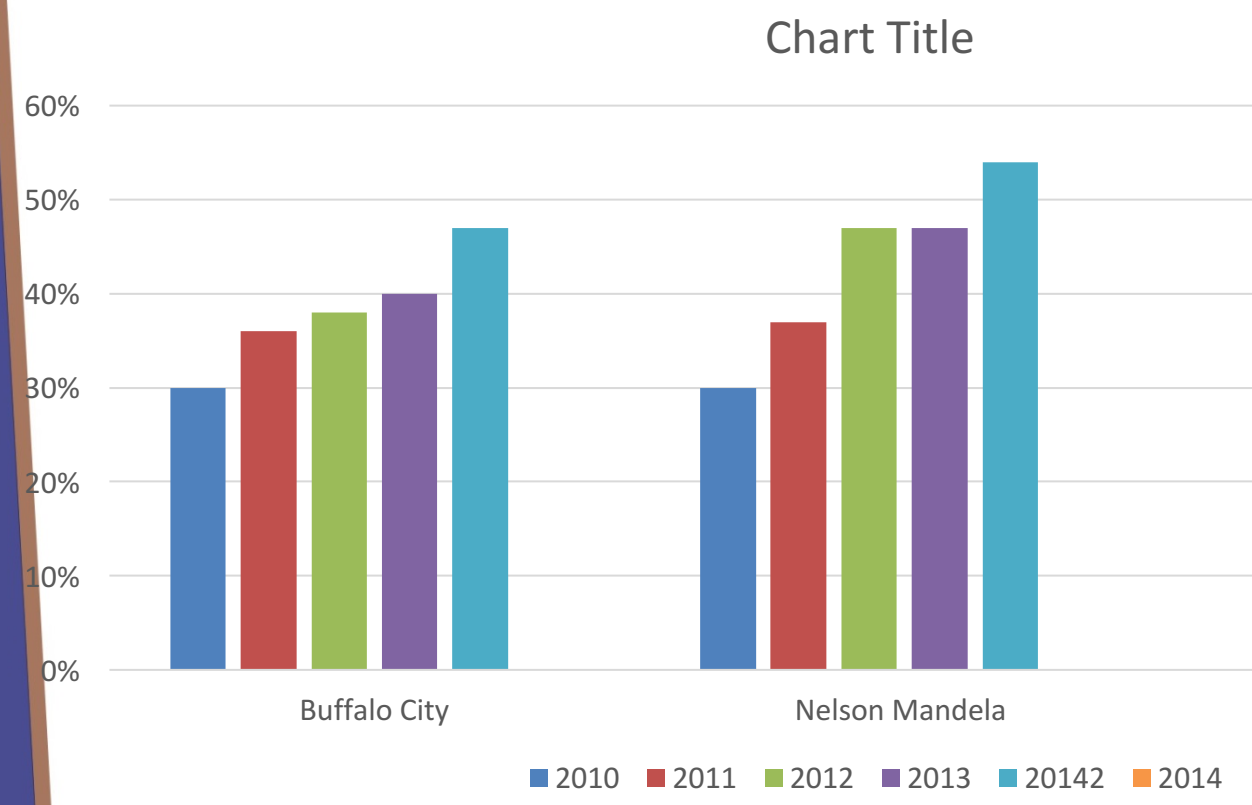
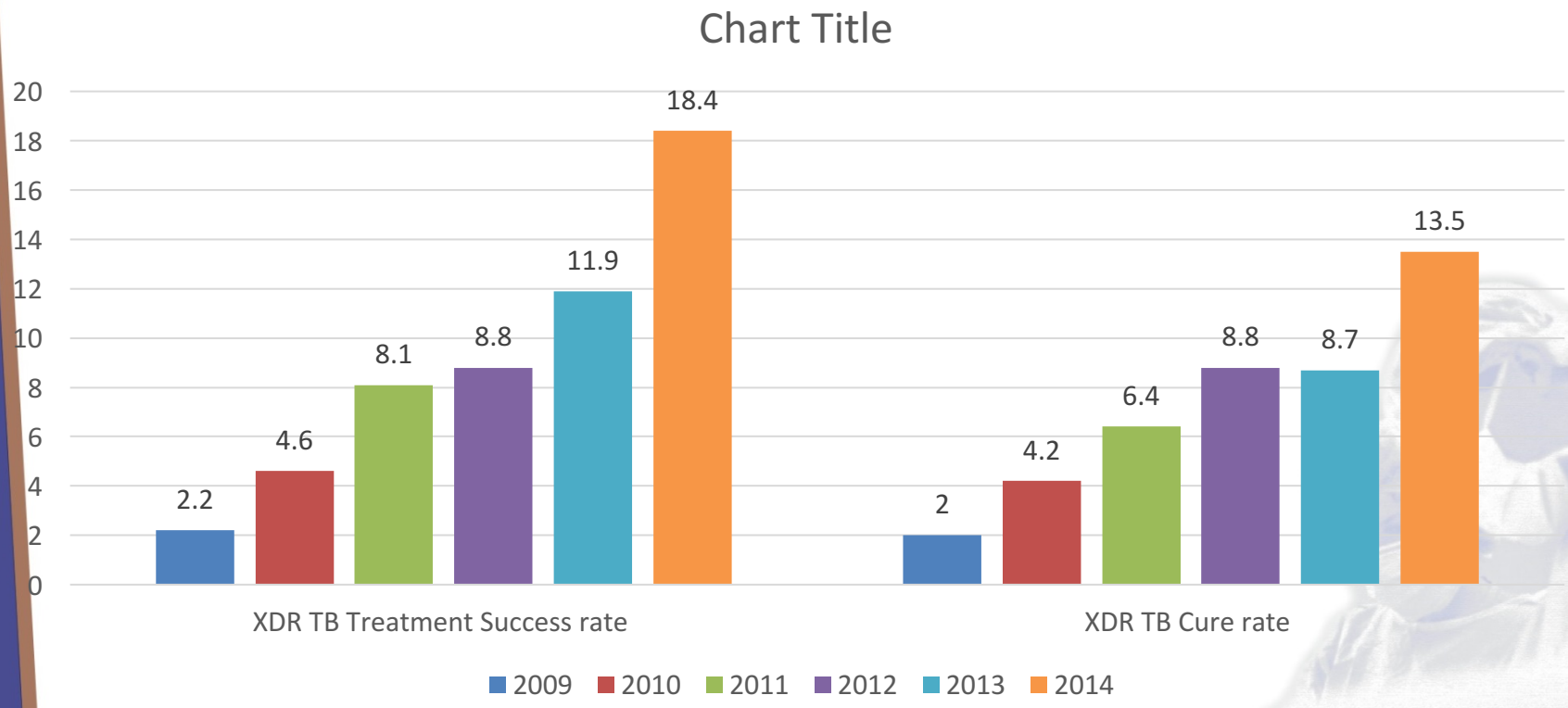
TRENDS IN DR SUCCESS RATE



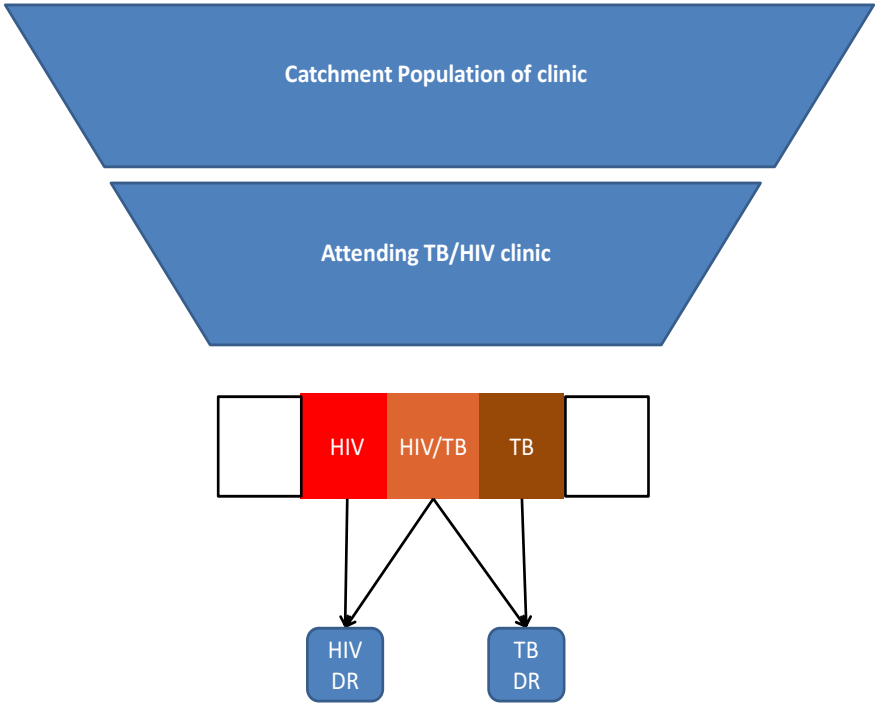
Provincial trend in XDR Success rate and cure rate



Quarter				
Province				
District	% VL <= 1000	% CD4 <= 500	% CD4 <= 350	% CD4 <= 100
Alfred Nzo	83.61%	53.93%	32.76%	6.26%
Amathole	77.58%	63.44%	43.65%	11.44%
Buffalo City Metro	79.99%	60.76%	41.74%	11.09%
Chris Hani	76.56%	64.90%	44.02%	11.24%
Joe Gqabi	76.46%	63.89%	42.44%	10.13%
Nelson Mandela Bay Metro	71.60%	66.32%	47.53%	13.04%
O R Tambo	80.06%	59.12%	39.53%	9.42%
Sarah Baartman	69.27%	62.69%	43.06%	10.57%
Total	**77.41%**	**61.45%**	**41.54%**	**10.33%**

Prospective Sentinel Surveillance of Tuberculosis and Human Immunodeficiency Virus in South Africa and Related Drug Resistance: Study design

- Sentinel site surveillance using the GERMS platform
  - 1 clinic per province
- To measure levels of HIV + TB DR at initiation of therapy
- MP, NW, EC, GP, KZN (Nov '14 – May '17)



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

GERMS SOUTH AFRICA

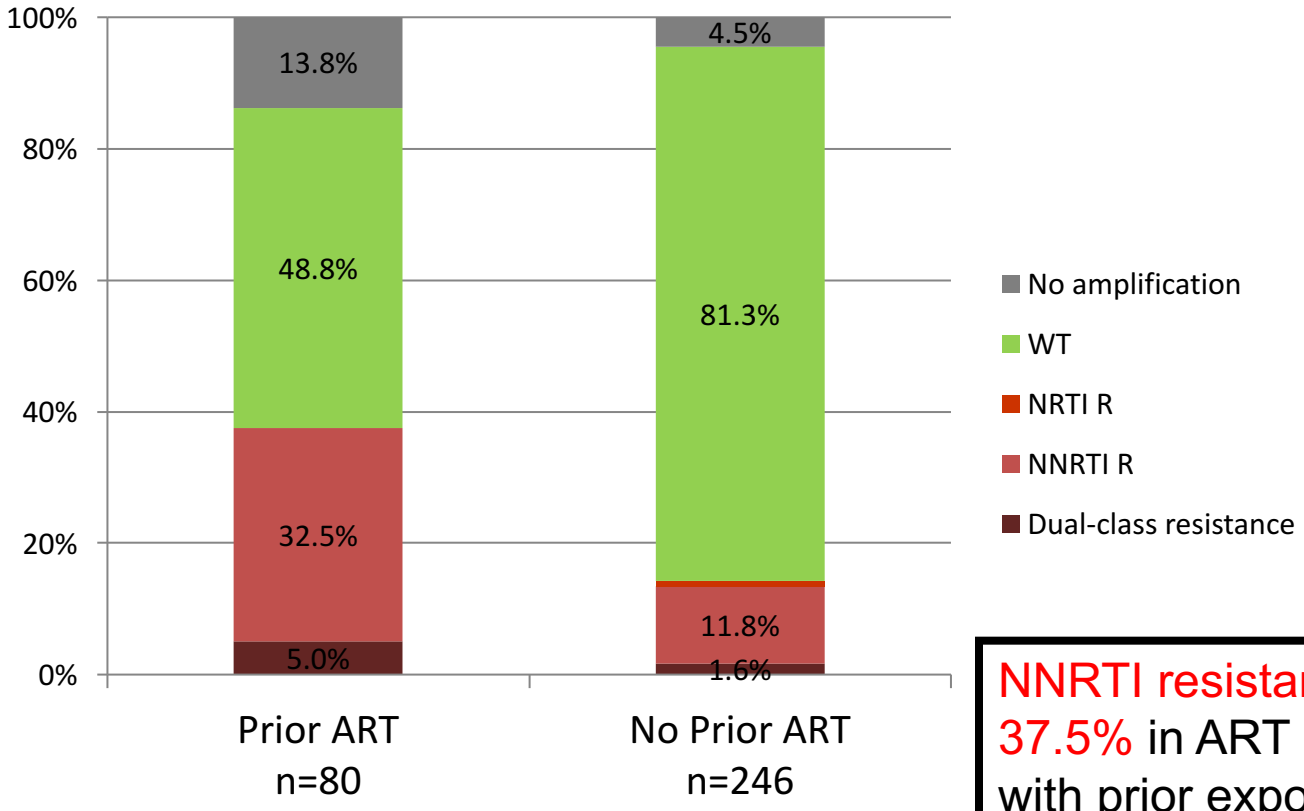
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Preliminary Data

Demographics:

- To date, n=1,139 specimens collected and tested for HIVDR
- 340 questionnaires were captured:
  - 71% of enrolled participants were female
  - median age of all participants is 32 years (IQR 26 - 40 years)
  - median recent CD4 count at time of cART initiation was 257 cells/µl (IQR 160 – 389 cells/µl).
- Prior exposure to ART (as PMTCT and/or previous cART) was reported in 80/326 (24.5%) participants
  - 14 (17.5%) reported receiving PMTCT
  - 47 (58.8%) had previously received standardized cART for clinical management
  - 19 (23.7%) participants reported receiving both PMTCT and cART.

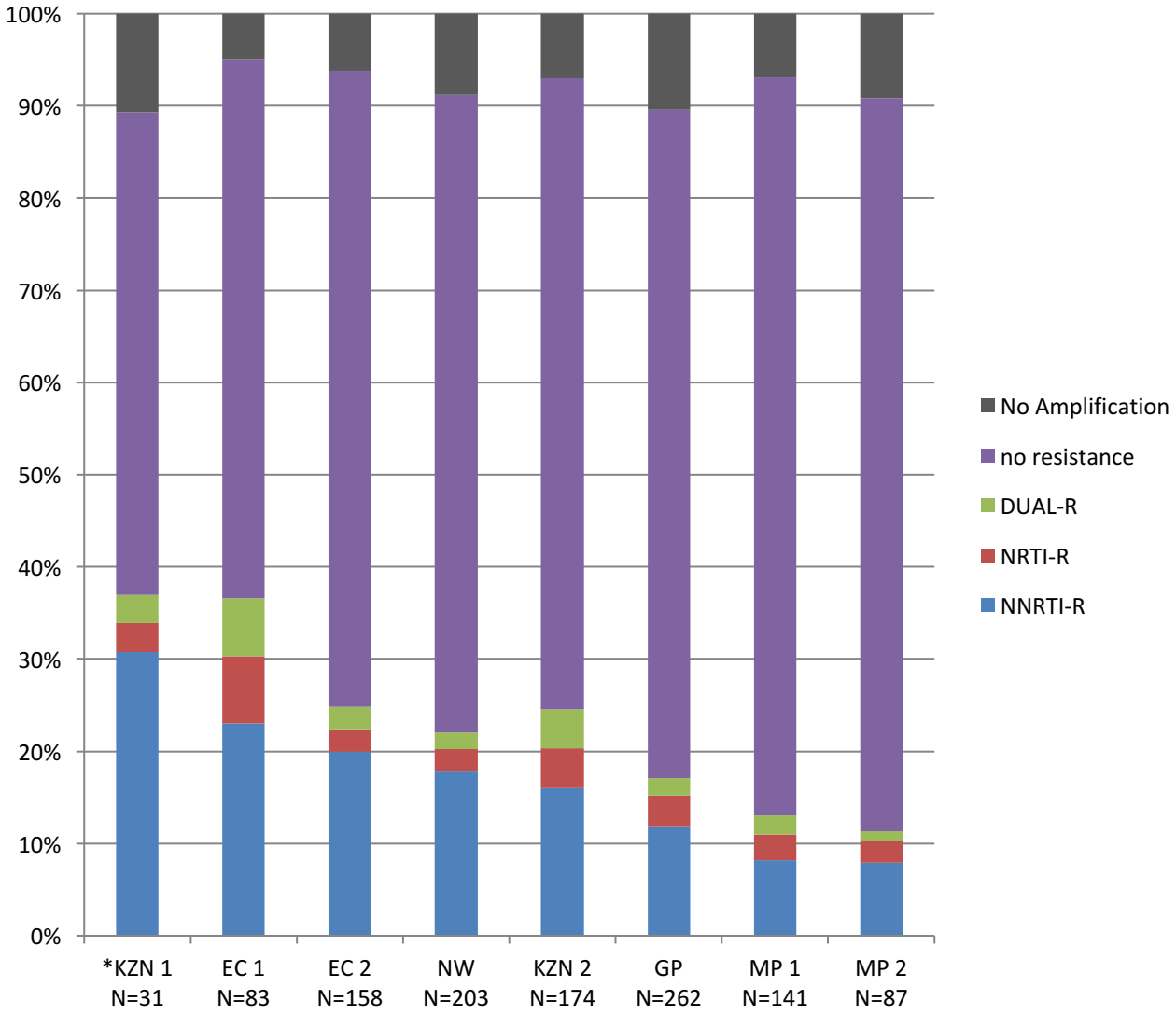
Levels of NNRTI and dual-class resistance detected amongst patients enrolled into study according to self-reported prior ART exposure



NNRTI resistance:
37.5% in ART starters with prior exposure to ARVs

13.4% in ARV-naive

Levels of NNRTI and dual-class resistance detected amongst patients enrolled into study in 8 clinics across SA (N=1,032)



Impact of HIV Infection on the Epidemiology of Tuberculosis in a Peri-Urban Community in South Africa: The Need for Age-Specific Interventions

Clinical differences in HIV

- Ongoing transmission
- Primary infection
- Less cavitation
- Smear negative
- EPTB
- Rapidly progressive
- Difficult to diagnose
  - Delay in diagnosis
  - Delay in treatment
- Drug absorption

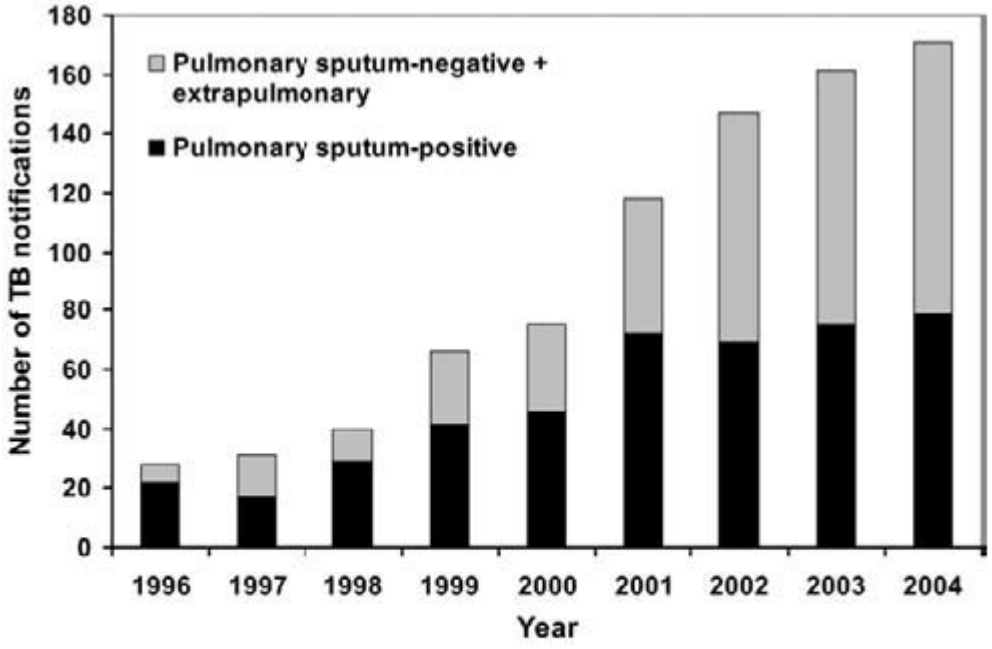
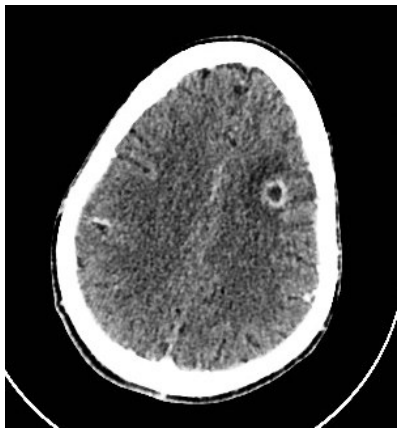


Figure 1. Annual numbers of tuberculosis (TB) notifications, stratified by site of disease and sputum microbiologic test findings. Children with diagnoses of primary TB were excluded.

Clinical Infectious Diseases 2006; 42:1040–7

Clinical challenges in HIV/TB care

- General comments:
  - When swimming in a sea of TB – everything feels like TB
  - Delay diagnosis of TB mimics (lymphoma etc)
  - Sheer volume means TB occurs in difficult populations
    - Oncology/Haematology
    - Dialysis
    - Rheumatology
    - Neurology
  - Often delays or impacts on other co-morbidities



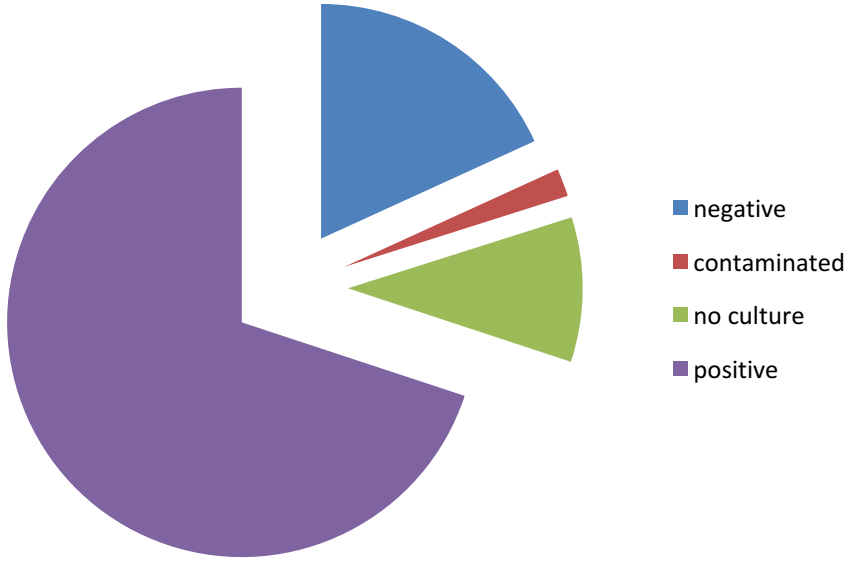
HIV/TB specific challenges

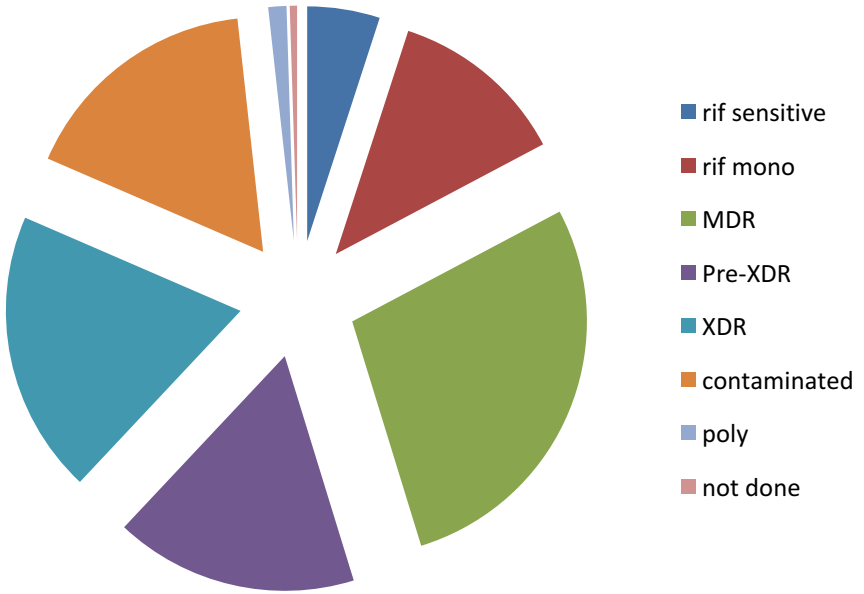
- The HIV and TB epidemic has changed
- Increasing numbers of patients with:
  - Drug resistant HIV
  - Drug resistant TB
  - Other co-morbidities
- Changing diagnostics and treatment options
  - ? Evidence for effective implementation
  - ? Generalisable

Diagnostics

- Challenges
  - Screening
  - Children
  - Advanced HIV
  - Extrapulmonary TB
  - DRTB
    - Multiple specimens for staged testing
    - Discordant /inconclusive results
    - Designing regimens
  - Introduction of new tests

total number of patients	572	
negative	104	18%
contaminated	11	2%
no culture	57	10%
positive	400	70%
positive cultures	400	
rif sensitive	20	5%
rif mono	49	12%
MDR	112	28%
Pre-XDR	67	16%
XDR	78	20%
contaminated	67	16%
poly	5	2%
not done	2	1%



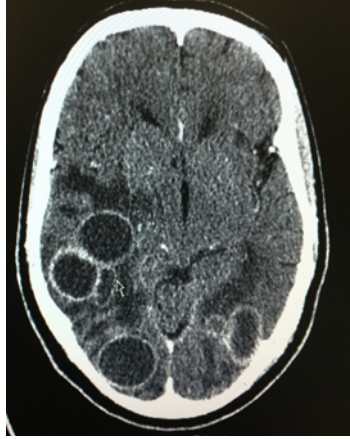


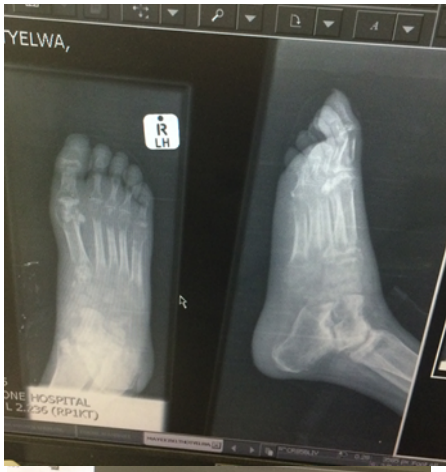
Example

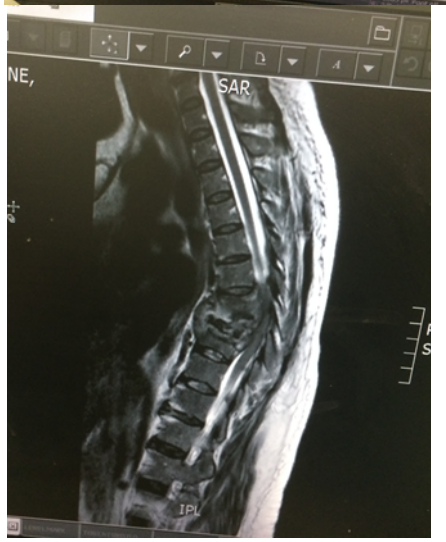
- HIV positive patient – CD4 150, previous PTB with chronic cough
- CXR: Extensive bronchiectatic changes
- GXP: MTB detected, Rif resistant
- Smear negative, culture contaminated
- ?treatment

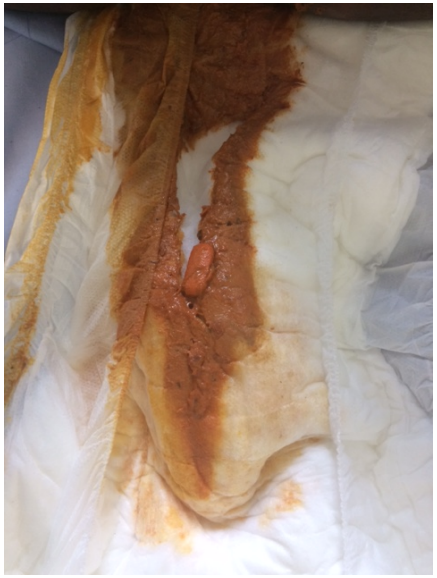
Treatment challenges

- Extrapulmonary TB
- Drug interactions
- Drug toxicity
- Co-morbidities
  - Liver/renal disease
  - ICU
  - Other opportunistic infections
- Malabsorption
- Steroids
- Pregnancy
- Children

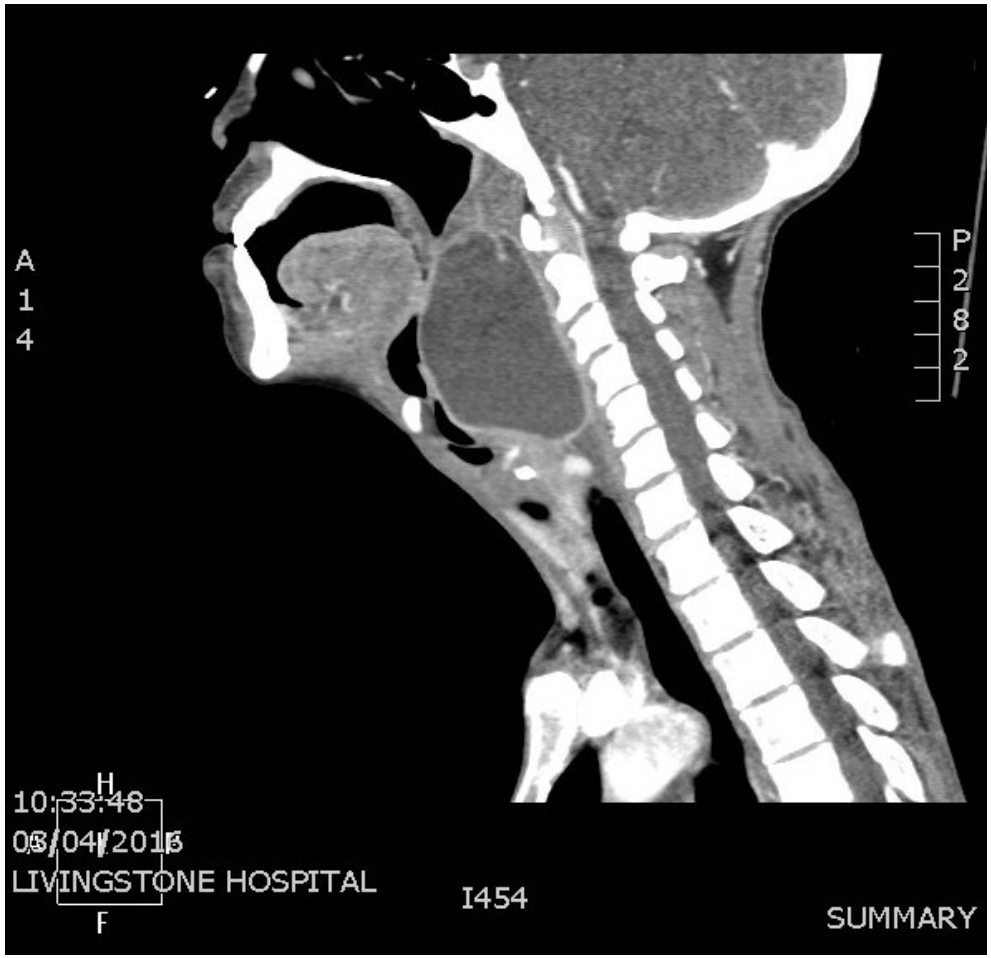








IRIS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LIVINGSTONE HOSPITAL
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SUMMARY

Example

- HIV positive lady – CD4 – 76
- Starts on TDF/FTC/EFV
- Unmasking TB IRIS, confirmed GXP positive, rifampicin sensitive. Started on RHZE
- Develops AKI following heavy analgesic use for abdominal pain, requiring dialysis.
- Subsequently develops acute abdomen following bowel perforation from TB. In ICU on TPN on dialysis. Unable to tolerate oral meds (high NGT output)
- What is the best TB and ART regimen?
- What if she had MDR TB?

GROUP A Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin
GROUP B Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)
GROUP C Other Core Second-line Agents		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine
GROUP D Add-on agents *(not core MDR-TB regimen components)*	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	*p*-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

Choosing the treatment regimen for RR-/MDR-TB

- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)?
- Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month?
- Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)?
- Pregnancy?
- Extrapulmonary disease?
- At least one medicine in the shorter MDR-TB regimen not available?

NO

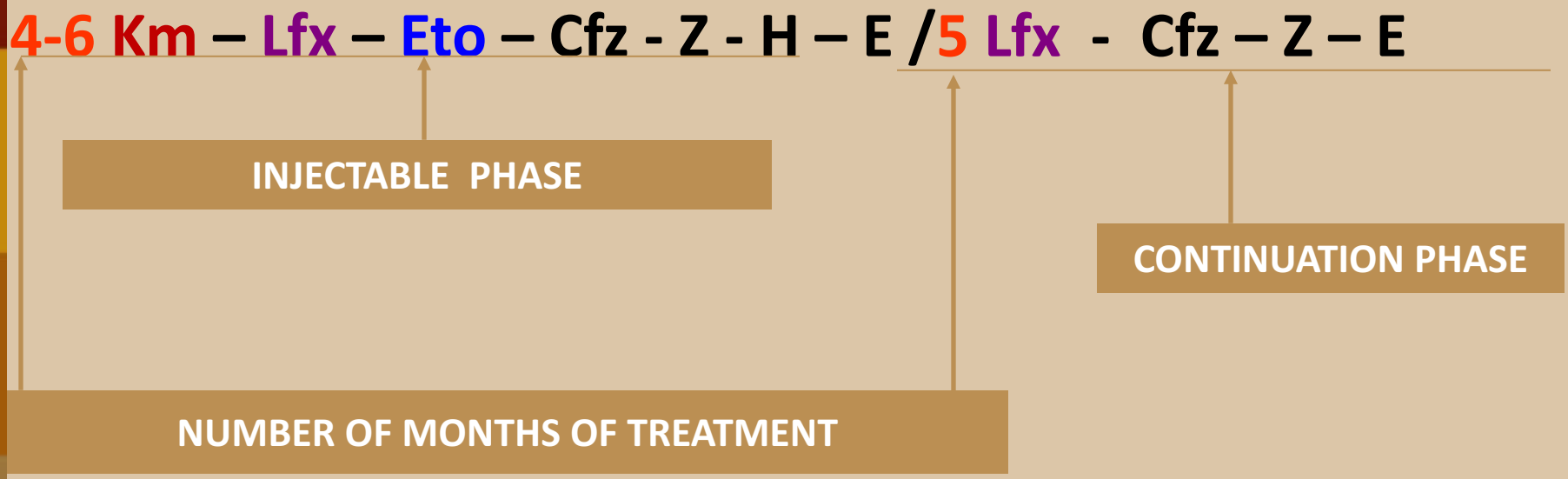
Shorter MDR-TB regimen

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

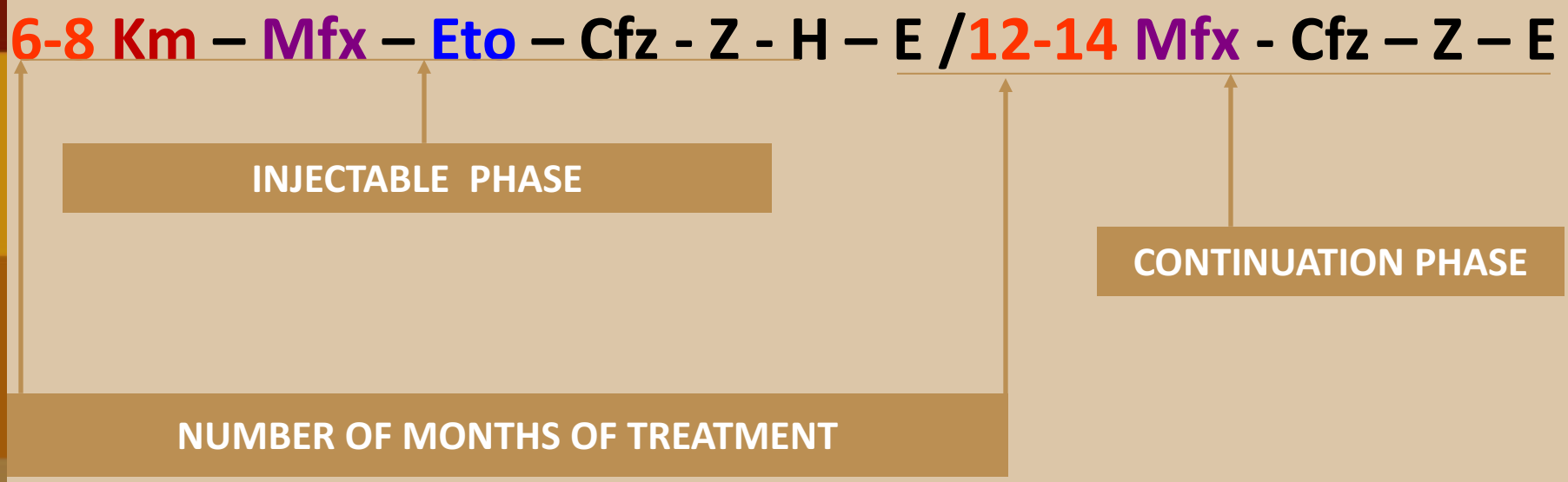
YES

Longer MDR-TB regimens

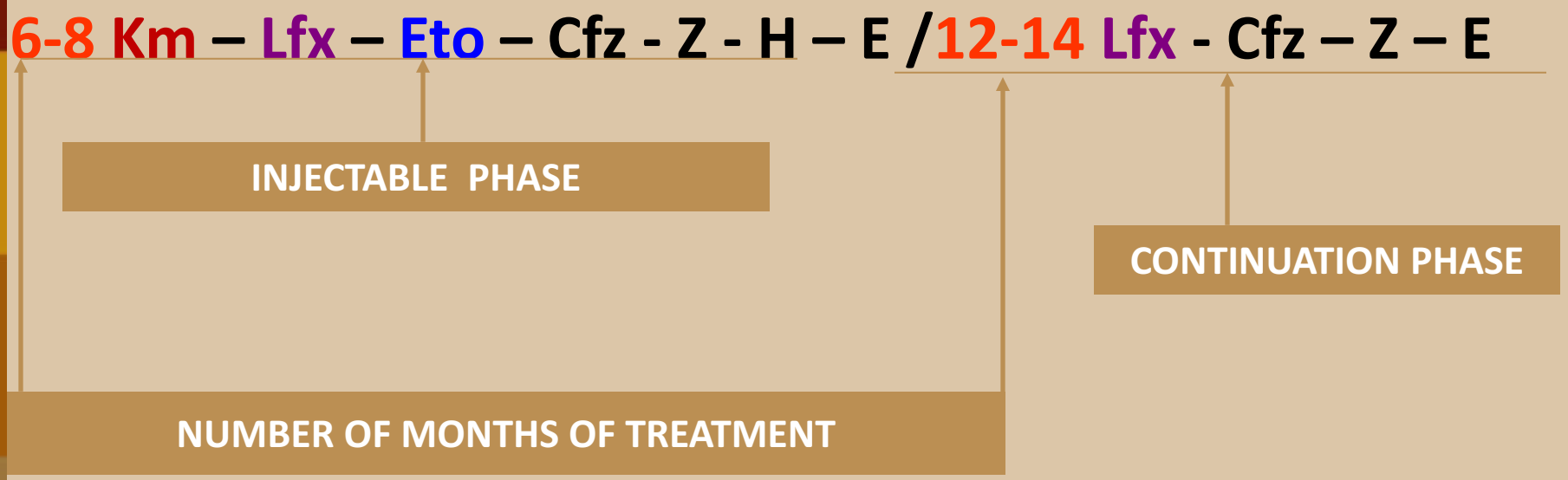
MDR-TB 9 Month Regimen (Adults &Children < 8 years)



MDR-TB Long Regimen (Adults &Children > 8 years)



MDR-TB Long Regimen (Adults &Children < 8 years)



- Defining the right treatment requires
  - Good diagnostics
  - Good clinician
  - Good understanding of the drug issues
- Standardised therapy may work for many, but there will always be exceptions
  - Be aware of common interactions and toxicities
  - Know when to refer
- There are lots of unknowns

Rapid change

A big challenge for the programme

- Diagnostics, regimens
- Responsible/monitored implementation
- Feasible and site specific to adapt to local need

BUT

We need to get the basics right to make a significant impact on the burden of disease