Tuberculosis, Drug Resistance & Global Health

BSc Global Health
19th October, 2012

Overview of talk

Outline of definitions

Global distribution of disease burden

Biomedical tools for control of TB

Tools to control MDR-TB

Tuberculosis is heterogenous – there are very different epidemiological settings with different challenges

The HIV epidemic is a key driver to the problems of HIV and MDR-TB

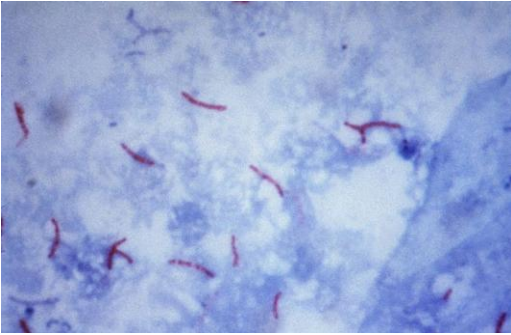Diagnostics are improving but still limited by costs and need for lab infrastructure

Treatment availability slowing expanding

XDR remains an increasing challenge

Tuberculosis

The organism: MTB

The disease

Antigen Presenting Cell (APC)

Antigen specific T cell

Antigen

APC processes Antigen

APC presents Antigen to antigen specific T cell

Antigen - specific T cell produces IFN-γ

IFN-γ
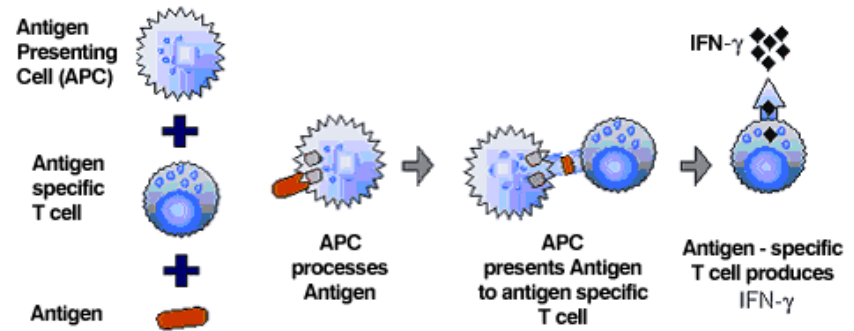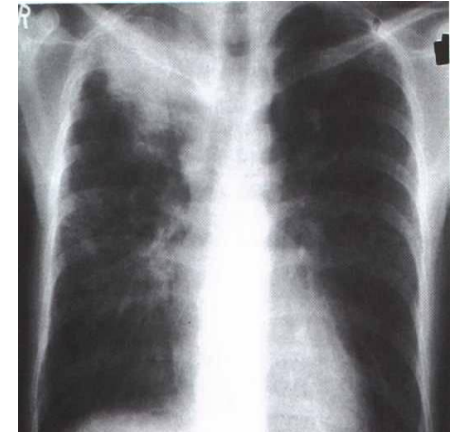
Infection with MTB

2008 Best estimates

9.4 million cases incident TB
11.1 million cases prevalent TB

1.8 million TB deaths
      1.3 million without HIV
      0.52 million with HIV

Approximately 61% cases notified and on treatment
87% successfully completed treatment

Global budget for TB control $4.1bn

Incidence of All New TB (WHO, 2008)

Estimated new TB cases (all forms) per 100 000 population
- 0–24
- 25–49
- 50–99
- 100–299
- ≥300
- No estimate
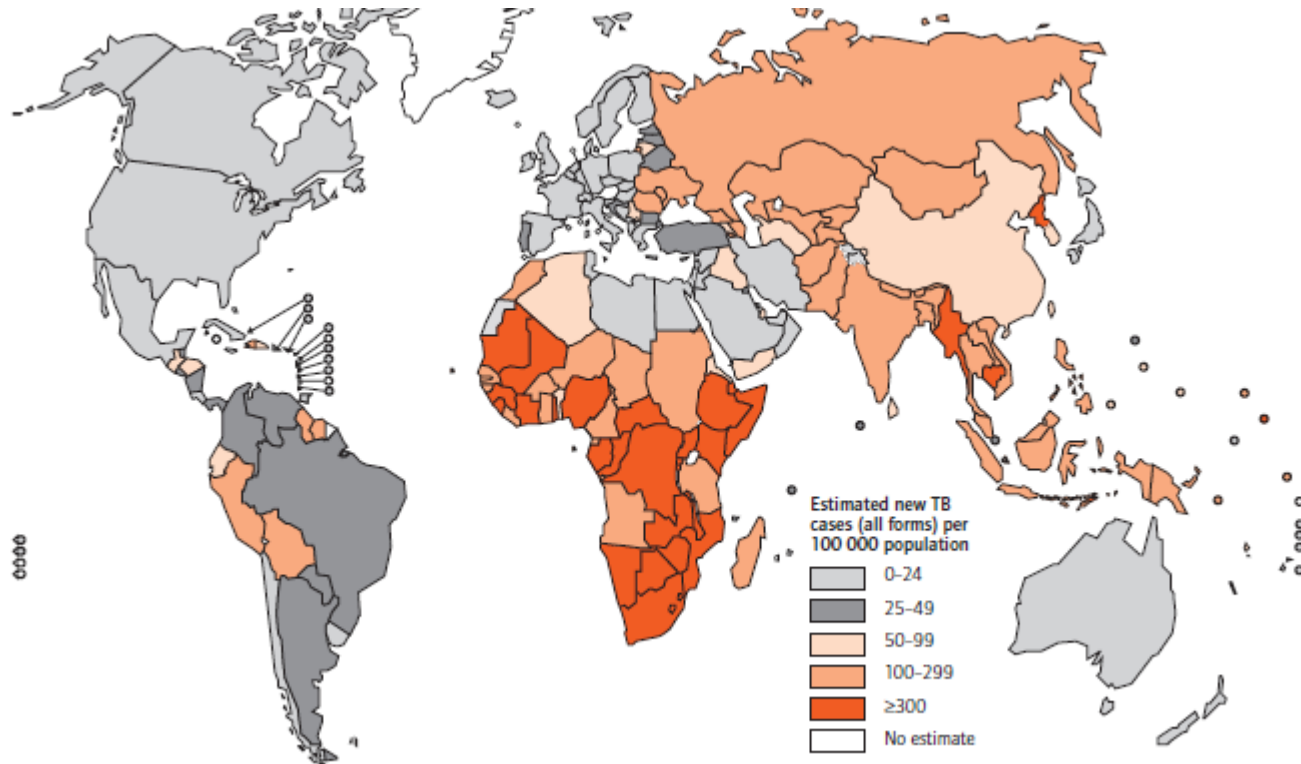
TB incidence increasing 1.8% pa

Proportion of TB with drug resistance

Median Prevalence MDR approx 5%

Median Prevalence of resistance to any drug 11.1% (IQR 7.0- 22.3)

Some basics

First line medications

Rifampicin	(R)
Isoniazid	(H)
Pyrazinamide	(Z)
Ethambutol	(E)

MDR-TB

Some basics

First line medications

Rifampicin	(R)
Isoniazid	(H)
Pyrazinamide	(Z)
Ethambutol	(E)

R, H → MDR-TB+

6/12 months minimum

Second line medications

Quinolones
Injectables (kana, ami) → XDR-TB
Ethionamide/Prothionamide
Cycloserine
PAS
Linezolid
Clofazamine

Typically 18/12 or longer

The big challenges

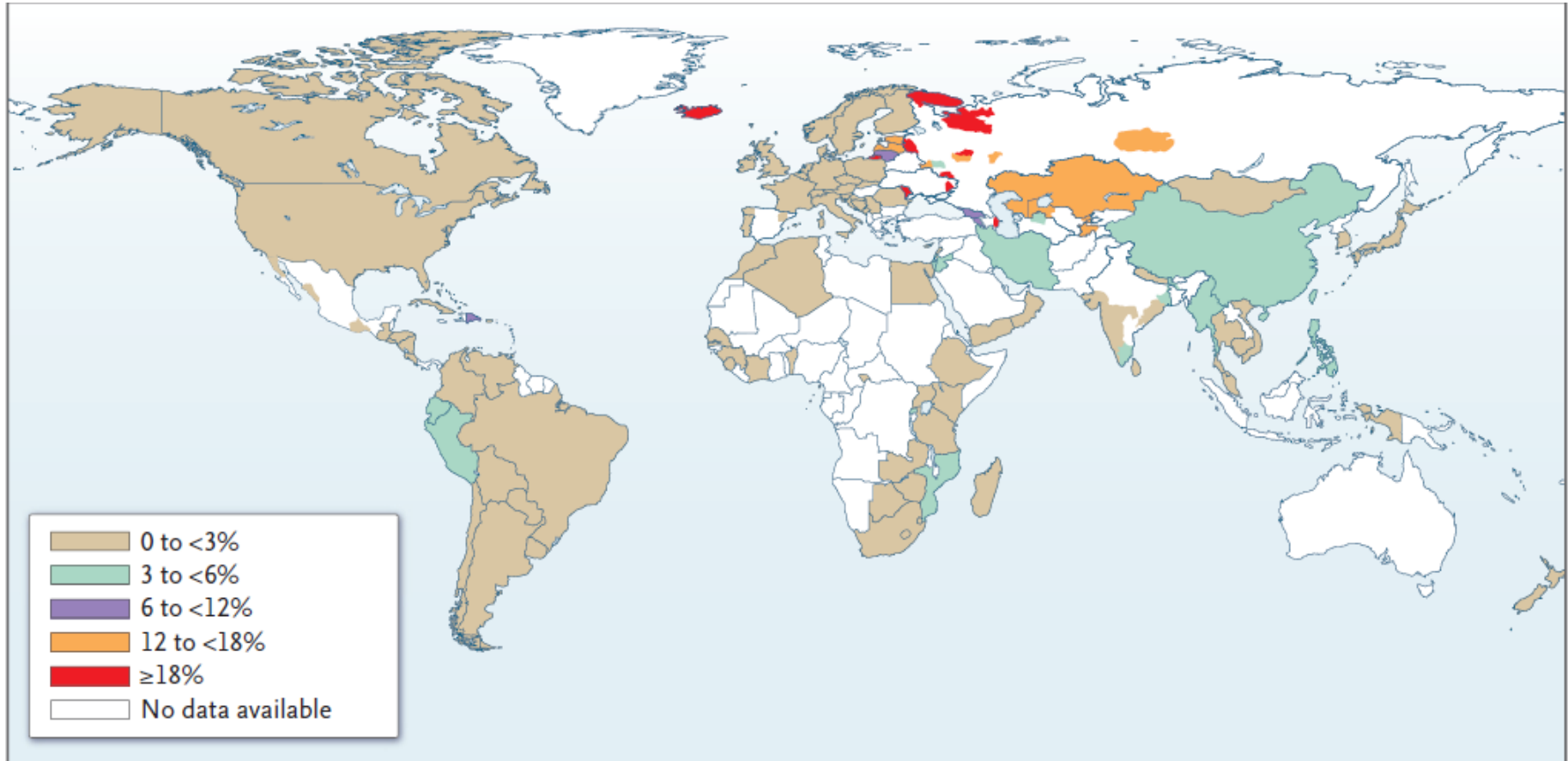First line treatment

6/12 therapy

Second line treatment

18/12 therapy or more
Poor outcomes
Toxicity – esp aminoglycosides

Proportion of new TB cases with any MDR-TB 1994-2007 (WHO, 2008)

Legend:
- 0 to <3%
- 3 to <6%
- 6 to <12%
- 12 to <18%
- ≥18%
- No data available

Numbers of newly diagnosed MDR cases (2007)

Source : Dye, WHO
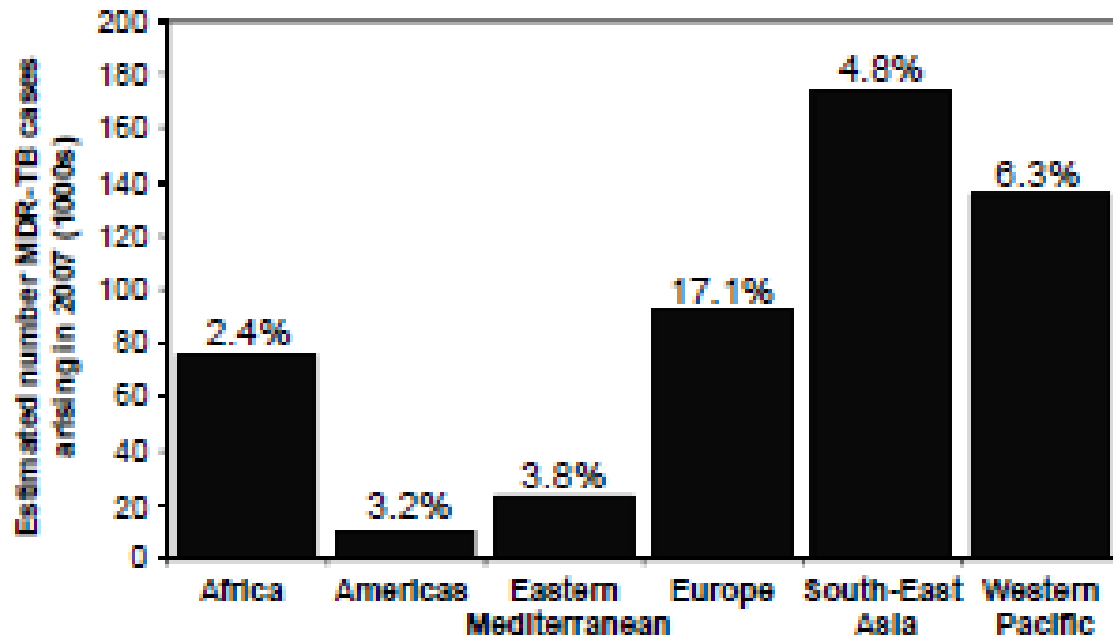
Countries with confirmed cases of XDR-TB as of November 2008
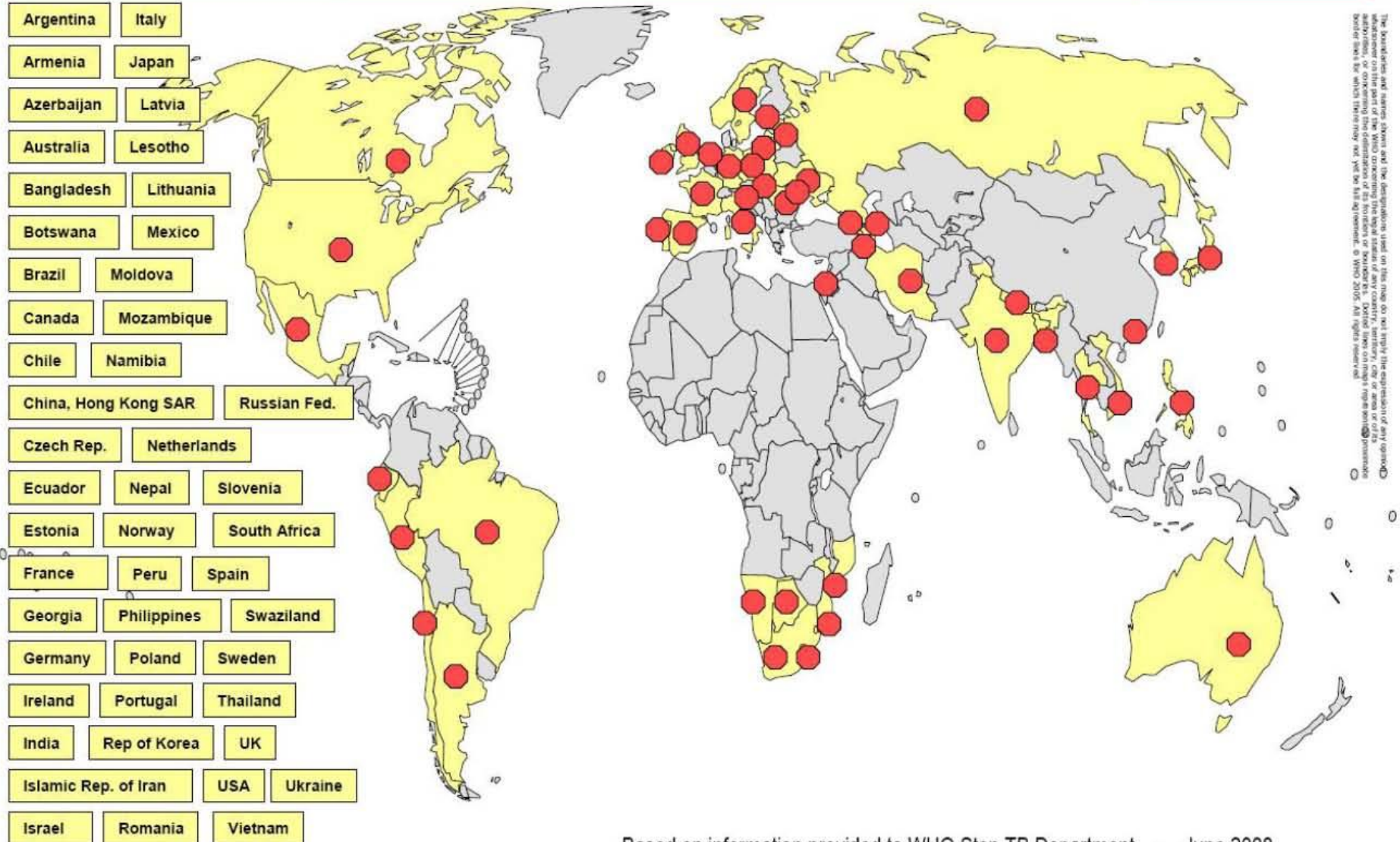
Argentina	Italy	
Armenia	Japan	
Azerbaijan	Latvia	
Australia	Lesotho	
Bangladesh	Lithuania	
Botswana	Mexico	
Brazil	Moldova	
Canada	Mozambique	
Chile	Namibia	
China, Hong Kong SAR	Russian Fed.	
Czech Rep.	Netherlands	
Ecuador	Nepal	Slovenia
Estonia	Norway	South Africa
France	Peru	Spain
Georgia	Philippines	Swaziland
Germany	Poland	Sweden
Ireland	Portugal	Thailand
India	Rep of Korea	UK
Islamic Rep. of Iran	USA	Ukraine
Israel	Romania	Vietnam

Based on information provided to WHO Stop TB Department - June 2008

HIV and TB:
A global perspective

HIV and TB in the world

A global view of HIV infection
39.5 million people [34.1-47.1] living with HIV in 2006
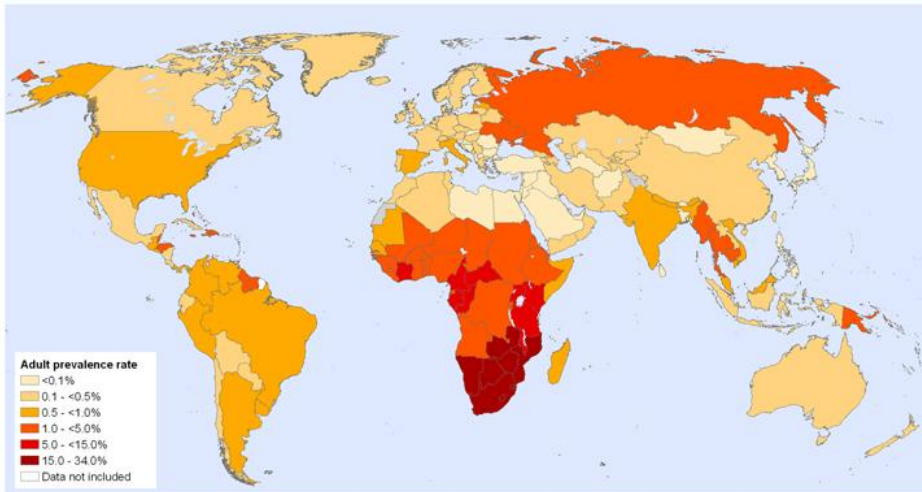
Adult prevalence rate
- <0.1%
- 0.1 - <0.5%
- 0.5 - <1.0%
- 1.0 - <5.0%
- 5.0 - <15.0%
- 15.0 - 34.0%
- Data not included

Per 100,000 population

0-99 100-199 200-299 300-399 400-499 500-599 600-699 700-899 900+

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Source: WHO
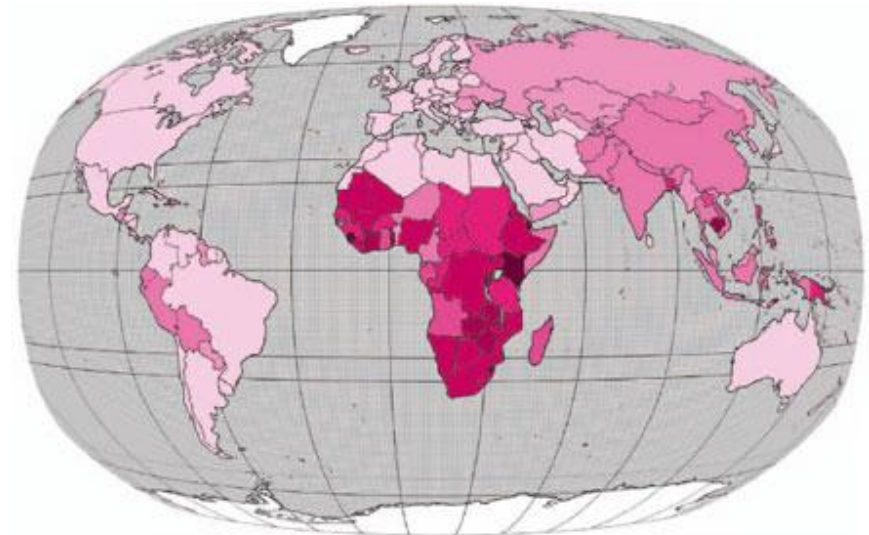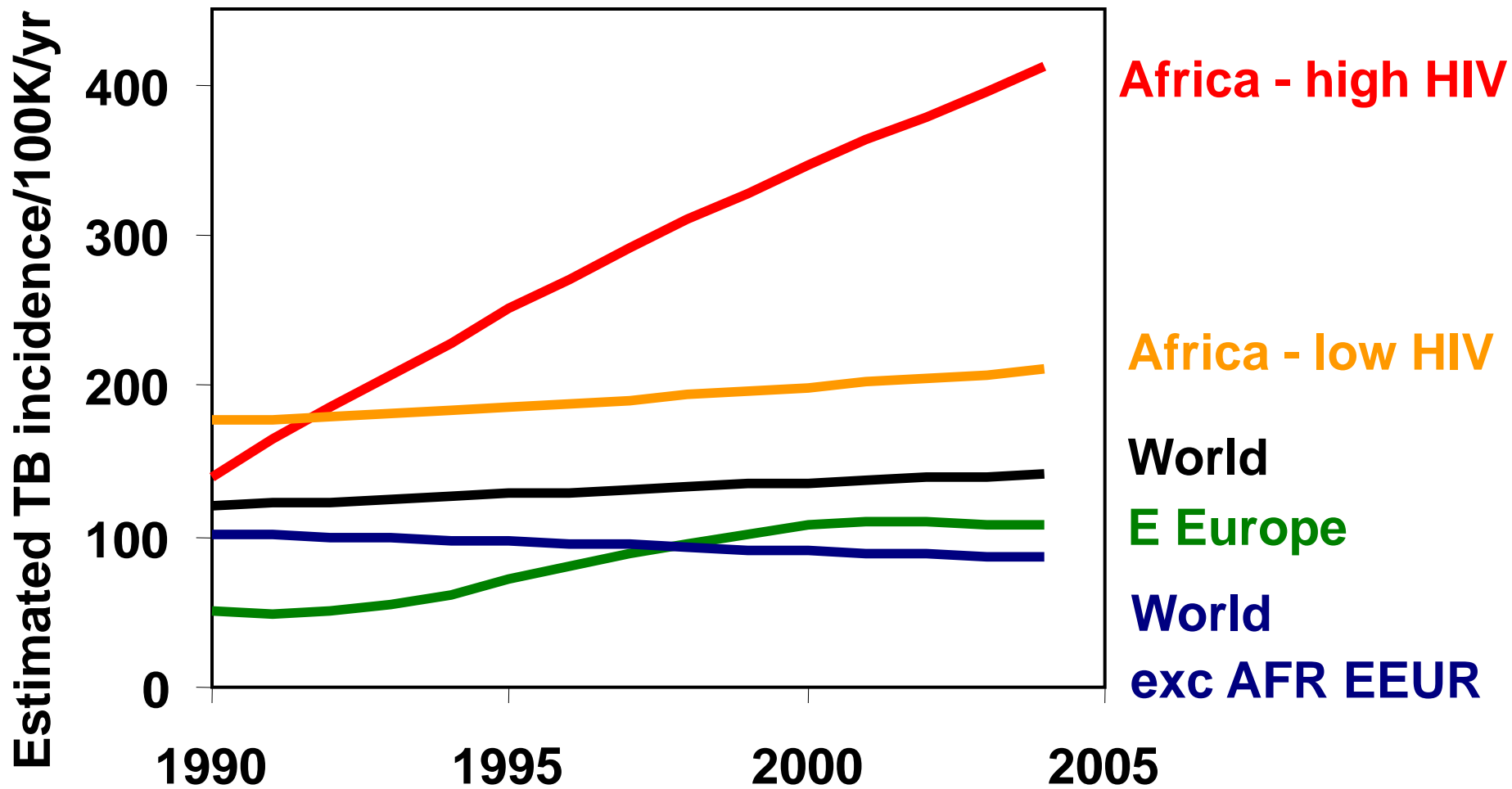
How common is co-infection?

FIGURE 1.3
Estimated HIV prevalence in new TB cases, 2007

HIV prevalence in new
TB cases, all ages (%)

- 0–4
- 5–19
- 20–49
- ≥50
- No estimate

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London

Source: Stop TB
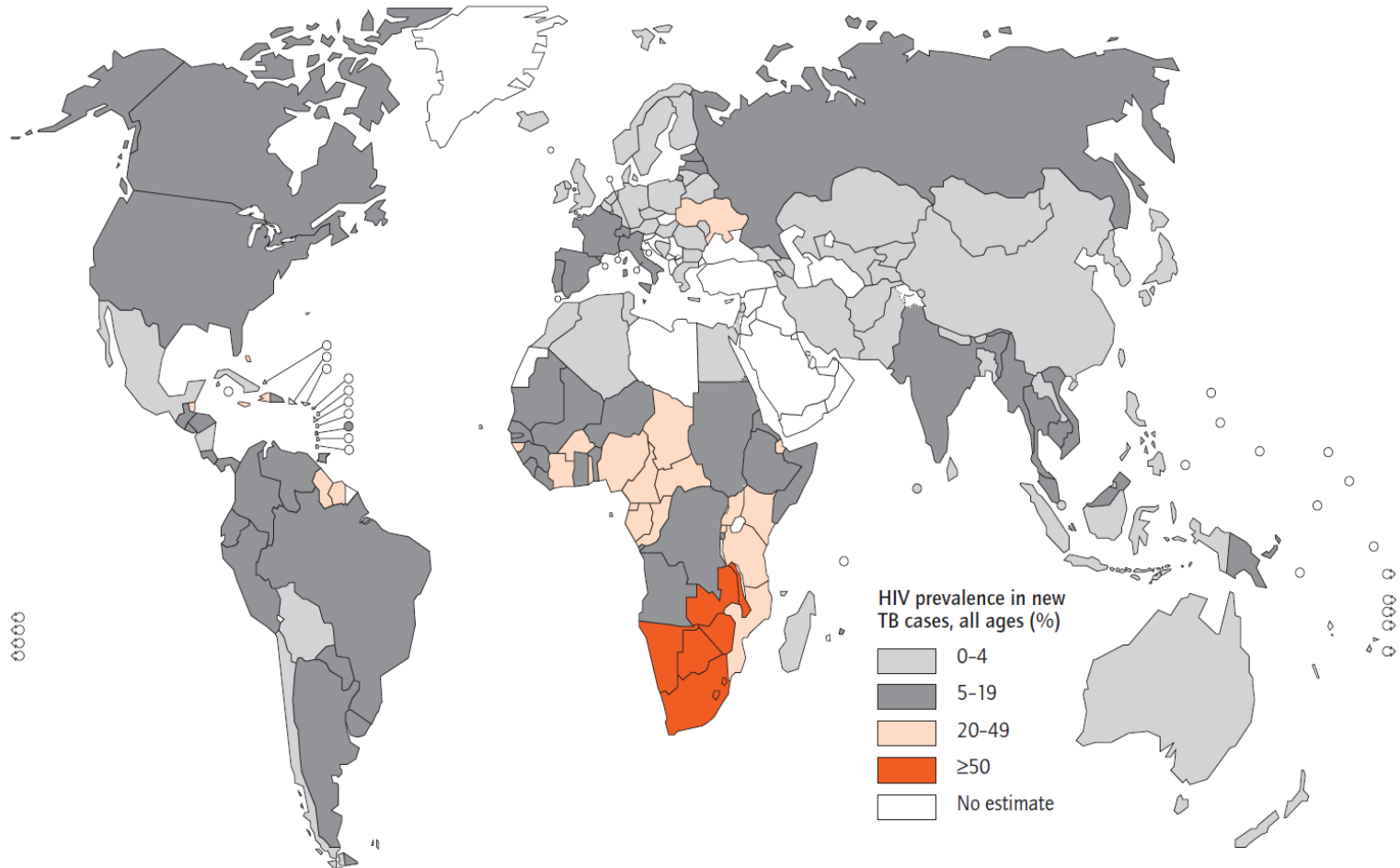
Interventions required to control MDR/XDR TB

Invest in R&D for new vaccines, drugs and diagnostics

Optimize MDR and XDR TB management

Engage all providers in MDR/XDR care

Address laboratory costs

Ensure access to high quality drugs

Improve surveillance

Prioritise infection control

Address global workforce crisis

Finance the response to MDR/XDR TB

Abolish financial barriers to care/treatment

Restrict availability of anti-TB drugs

Nathanson NEJM 2010

Biomedical Interventions for TB diagnosis and treatment

Vaccines
IPT
New diagnostics
New drugs

You wait for ages for a bus…..

New Diagnostics

Tests of immune response to TB

Quantiferon

T-spot

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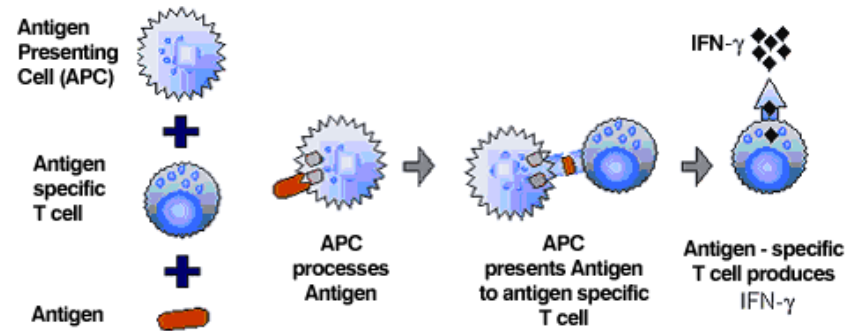
IGRAs have limited sensitivity for active TB
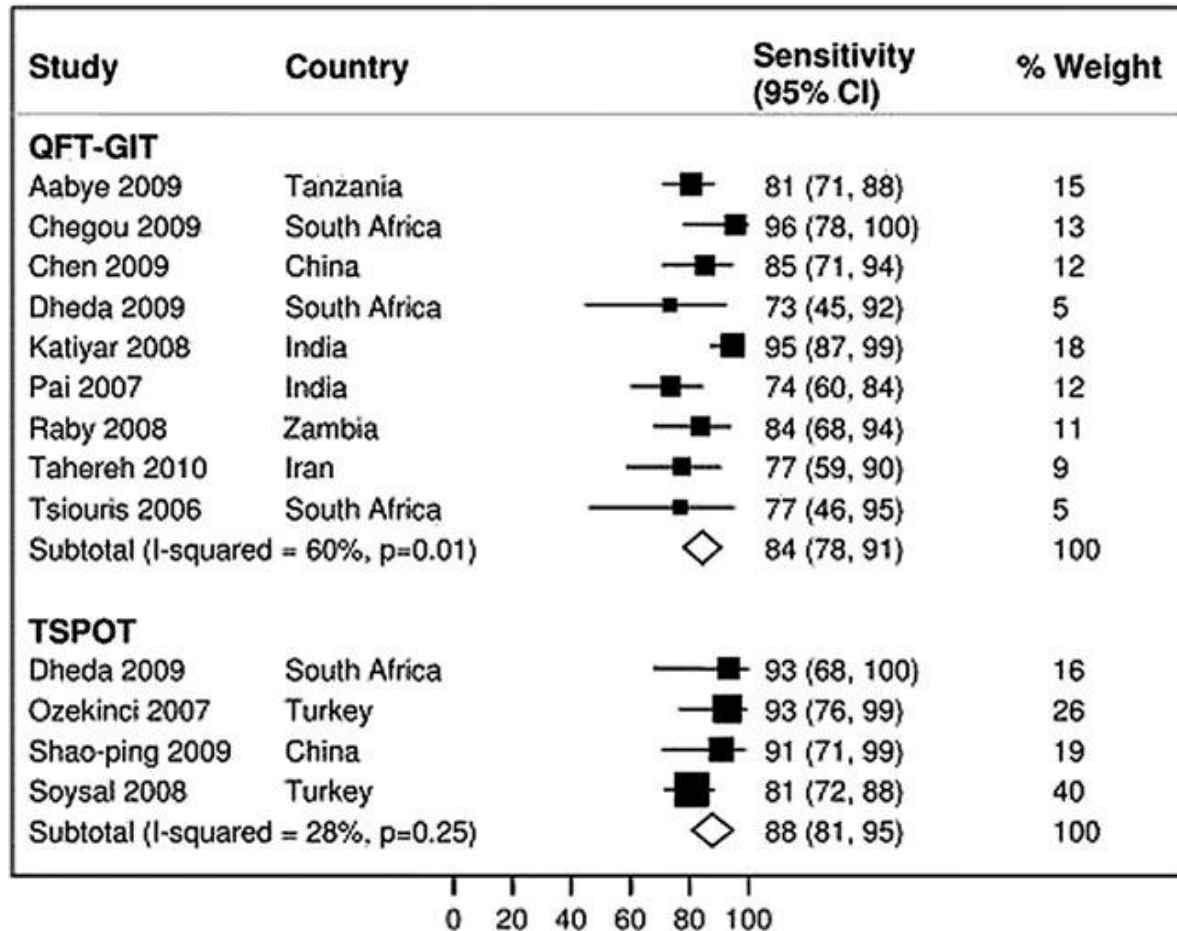
And perform less well with HIV

Study	Country	Sensitivity (95% CI)	% Weight
QFT-GIT			
Aabye 2009	Tanzania	65 (52, 76)	16
Kabeer 2009	India	66 (50, 80)	15
Leidl 2009	Uganda	74 (49, 91)	12
Markova 2009	Bulgaria	92 (64, 100)	14
Raby 2008	Zambia	63 (49, 75)	16
Tsiouris 2006	South Africa	65 (44, 83)	13
Veldsman 2009	South Africa	30 (15, 49)	14
Subtotal (I-squared=76%, p<0.001)		65 (52, 77)	100
TSPOT			
Cattamanchi 2010	Uganda	54 (45, 64)	25
Jiang 2009	China	66 (47, 81)	19
Leidl 2009	Uganda	89 (67, 99)	20
Markova 2009	Bulgaria	62 (32, 86)	12
Oni 2010	South Africa	68 (57, 78)	25
Subtotal (I-squared=72%, p<0.01)		68 (56, 80)	100

0 20 40 60 80 100

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Metcalfe JID 11

New molecular diagnostics

Current interest in applicability of new molecular technologies to bring diagnosis closer to point of care

Substantial increase in sensitivity within smear negative (Boehme, NEJM 2010)

Source : Cepheid

New molecular diagnostics: rpoB target
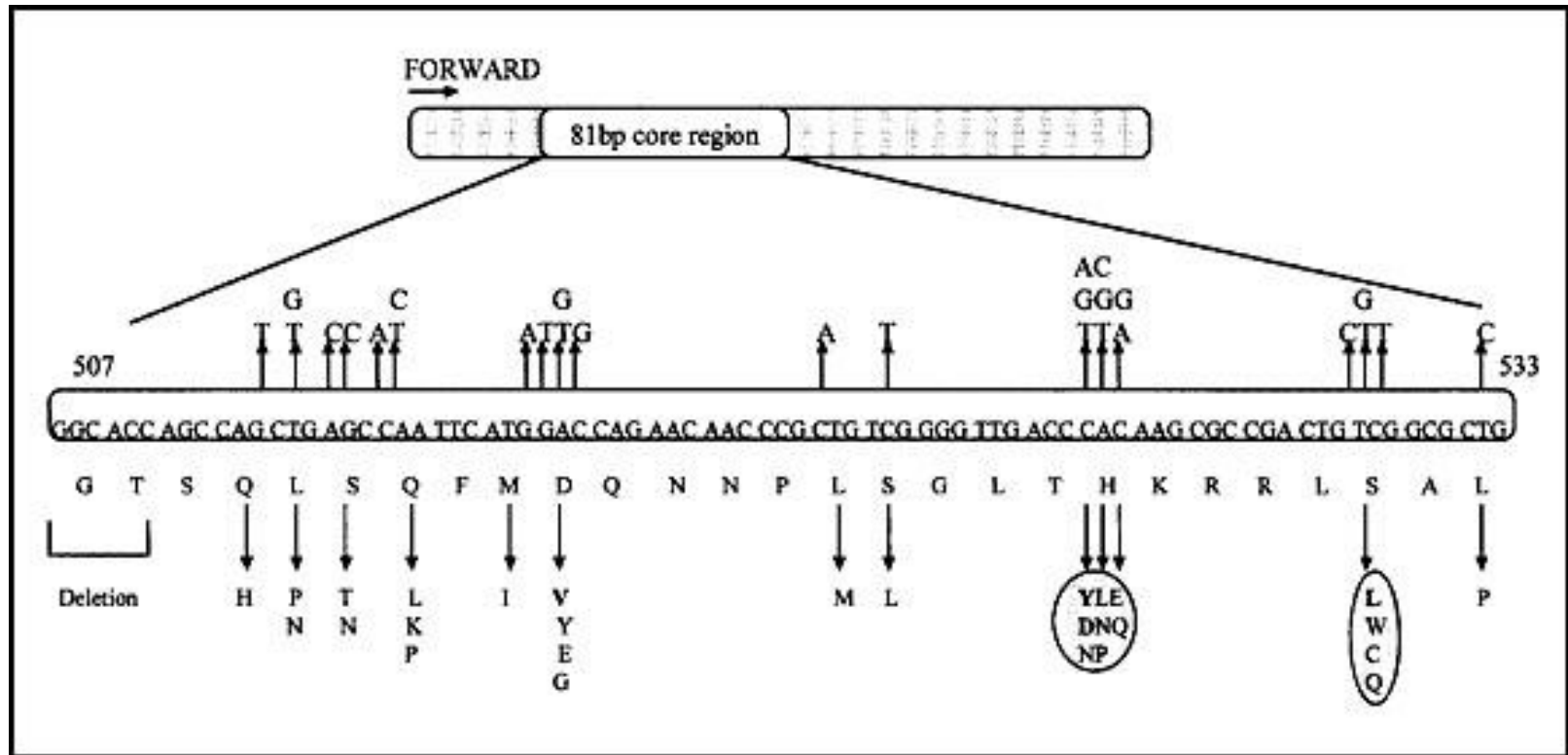
Xpert MTB/RIF

Diagnostic performance of single Xpert for detecting *M. tuberculosis* in sputum

Location	N	Reference	Sensitivity			Specificity
			Overall	Smear pos	Smear neg	
Vietnam	107	Liquid or solid culture	81.7% (67/82)	100% (29/29)	72% (38/53)	100% (25/25)
Multicentre	1462	4 x cultures	92.2% (675/732)	98.2% (551/561)	72.5%* (124/171)	99.2% (614/609)
Spain	105	Liquid or solid culture	78.2% (61/78)	-	-	100% (27/27)
France	18	Liquid or solid culture	100% (5/5)	100% (4/4)	100% (1/1)	100% (13/13)
US	216	Culture	89.2% (116/130)	97.7% (85/87)	72.1% (31/43)	95.3% (82/86)
Multicentre	6069	Culture	90.3% (933/1033)	98.3% (637/648)	76.9% (296/385)	99.0% (2846/2876)
South Africa	480	Liquid culture	78.7% (111/141)	94.7% (89/94)	46.8% (22/47)	94.4% (320/339)

* Incremental yield in smear-negative TB of second and third Xpert MTB/RIF was 12.6% and 5.1% respectively

Helb JCM 2010; Boehme NEJM 2010; Moure JCM 2011; Malbruny IJTLD 2011; Marlowe JCM 2011; Boehme Lancet 2011; Theron AJRCCM 2011

Slide: Richard Lessells

Source: Richard Lessells, Africa Centre

New Drugs

Outcomes for MDR Treatment in adults

	Success (95% CI)	Failure (%)	Default (%)	Death (%)
Individualised treatment				
Goble et al[19]	48 (41–55)	14	13	20
Burgos et al[20]	67 (55–78)	5	5	22
Olle-Goig and Sandy[21]	36 (28–44)	1	52	13
Geerlings et al[22]	72 (60–82)	10	4	13
Kim et al[23]	48 (44–51)	8	43	1
Yew et al[24]	68 (58–77)	14	9	8
Chiang et al[25]	52 (46–57)	10	9	29
Munsiff et al[26]	40 (36–44)	0	13	47
Tahaoğlu et al[9]	76 (69–82)	8	11	4
Narita et al[27]	67 (57–76)	12	3	20
Kwon et al[28]	68 (61–75)	14	10	7
Mitnick et al[4]	79 (70–87)	2	9	8
Palmero et al[29]	53 (45–61)	9	19	19
Kim et al[30]	65 (58–72)	19	8	8
Saravia et al[15]	75 (64–84)	4	9	10
Uffredi et al[31]	59 (47–71)	2	15	24
Nathanson et al[32]	68 (64–71)	7	11	14
Mitnick et al[33]	66 (62–70)	2	10	20
Tupasi et al[34]	67 (58–76)	9	12	11
Holtz et al[35]	62 (55–69)	16	11	8
Leimane et al[36]	66 (60–72)	14	13	7
Mirsaeidi et al[37]	64 (47–79)	23	6	9
Shin et al[38]	76 (70–81)	7	12	5
Kim et al[39]	45 (43–48)	5	40	7
Keshavjee et al[10]	67 (63–70)	8	20	5
Bartu[40]	68 (55–79)	2	5	25
Riekstina et al[41]	71 (62–80)	6	15	6
Cox et al[42]	62 (53–71)	9	14	15
Eker et al[43]	71 (64–78)	2	17	10
Summary	64 (59–68) I²=88 (p<0·001)	6 (3–9) I²=94 (p<0·001)	12 (8–16) I²=99 (p<0·001)	11 (7–15) I²=98 (p<0·001)
Standardised treatment				
Van Deun et al[7]	63 (50–76)	8	12	12
Suárez et al[44]	49 (44–53)	28	12	12
Saravia et al[15]	51 (43–59)	30	13	11
Park et al[8]	49 (35–60)	15	32	6
Masjedi et al[45]	61 (49–75)	15	3	15
Summary	54 (43–68) I²=52 (p=0·08)	18 (7–35) I²=89 (p<0·001)	12 (1–36) I²=91 (p<0·001)	11 (5–19) I²=62 (p=0·03)

Treatment success (%)

Individualised (64%)

Standardised (54%)

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Source: Orenstein LID (2009)

CLINICAL DEVELOPMENT

| PRECLINICAL DEVELOPMENT | PHASE I | PHASE II | PHASE III |

PRECLINICAL DEVELOPMENT

TBA-354
Nitroimidazoles
TB Alliance, University of Auckland, University of Ilinois

CPZEN-45
Caprazene nucleoside
Microbial Chemistry Research Foundation, Tokyo, Japan, Lilly TB Drug Discovery Initiative, NIAID, IDRI, Lilly, YourEncore

Quinolone DC-159a
Fluoroquinolone Antibiotics
Japan Anti-Tuberculosis Association, JATA, Daiichi-Sankyo Pharmaceutical Co.

SQ609
Dipiperidines
Sequella

SQ641
Capuramycins
Sequella

BTZ043   GLP
Benzothiazinones
New Medicines For Tuberculosis (NM4TB)

Q201-Novel anti-TB agent
Imidazopyridine
Quro Science, Inc.

PHASE I

AZD5847   NCE
Oxazolidinone
Astrazeneca

PHASE II

PA-824   REG   NCE
Nitroimidazol-oxazine
TB Alliance

Novel Combinations/Regimens   NCE
Nitroimidazol-oxazine, diarylquinoline, fluoroquinolone, Nicotinic acid derivative
TB Alliance

PNU-100480 (Sutezolid)   NCE
Oxazolidinone
Pfizer

TMC207 (Bedaquiline) for MDR-TB   NCE
Diarylquinoline
Tibotec BVBA

SQ109   NCE
Ethylenediamines
Sequella,NIH

TMC207(Bedaquiline) for DS-TB   NCE
Diarylquinoline
TB Alliance, Janssen Pharmaceutica N.V.

Linezolid for MDR-TB
Oxazolidinones
TBTC, Pfizer

Rifapentine (TBTC study 29)
Rifamycin
CDC, Sanofi-aventis

Oral M. vaccae (V7)   REG
adjunct immunotherapy, therapeutic vaccine
Immunitor Inc.

PHASE III

Gatifloxacin
Fluoroquinolones
Information provided by WGND

Moxifloxacin for Drug-Sensitive TB
Fluoroquinolones
TB Alliance

OPC-67683 (Delamanid)   NCE
Nitro-dihydro-imidazooxazole
Otsuka Pharmaceutical Co., Ltd.

Rifapentine (TBTC Study 26)
Rifamycin
CDC, Sanofi-aventis

TB	1	8	4
HCV	14	19	4

Phase 2 Trial of TMC207 C208 Pt1 (Bedaquiline)

Multi-centre, placebo controlled trial

1 week lead in (TB treatment stopped)
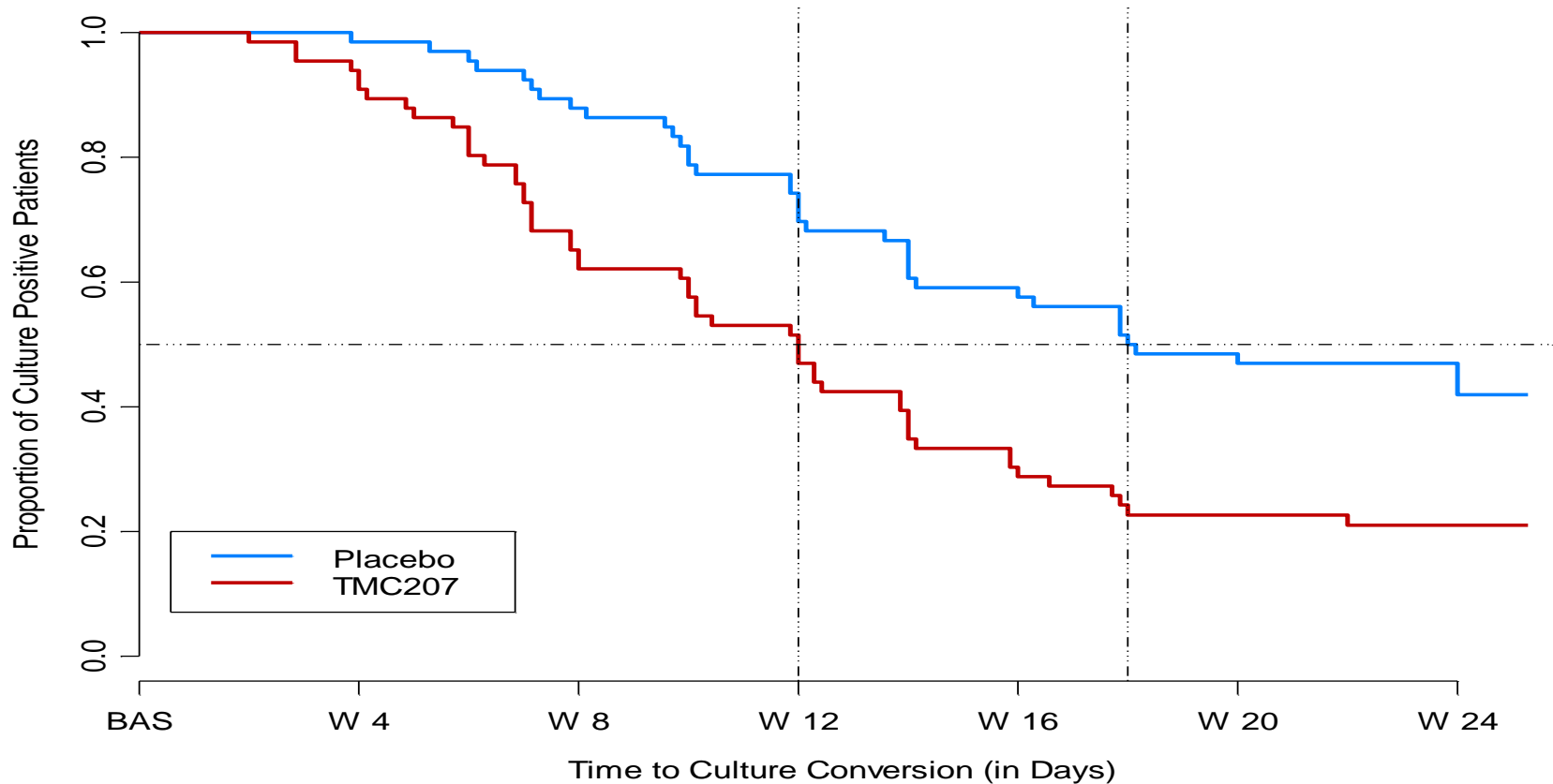
Stratified by centre and extent of lung disease

Arm 1: TMC207 400mg od for 14/7, then 200mg 3/week
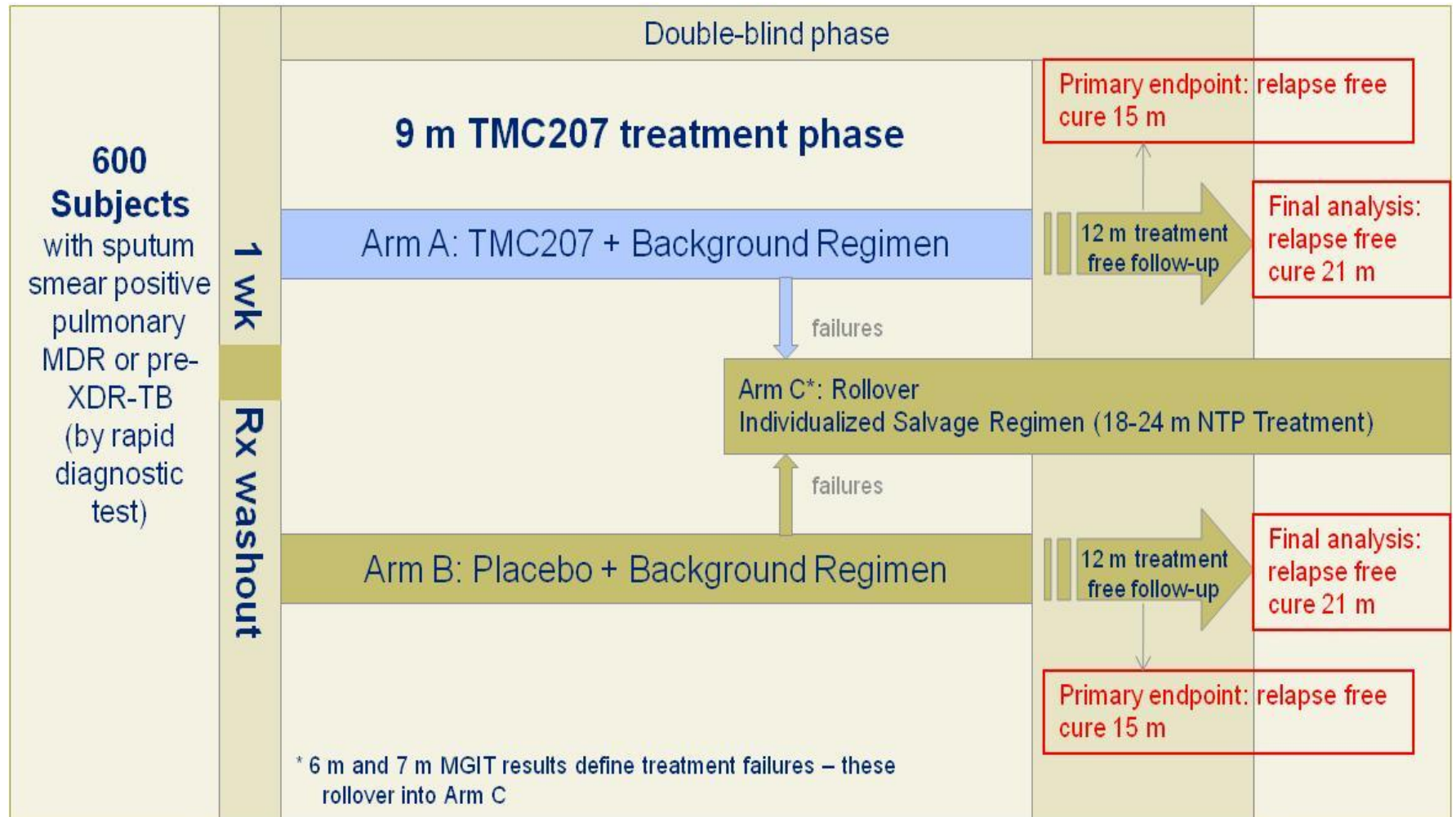Arm 2: Placebo

Preferred background: kanamycin, ofloxacin, ethionamide, pyrazinamide and cycloserine or terizidone modified by DST

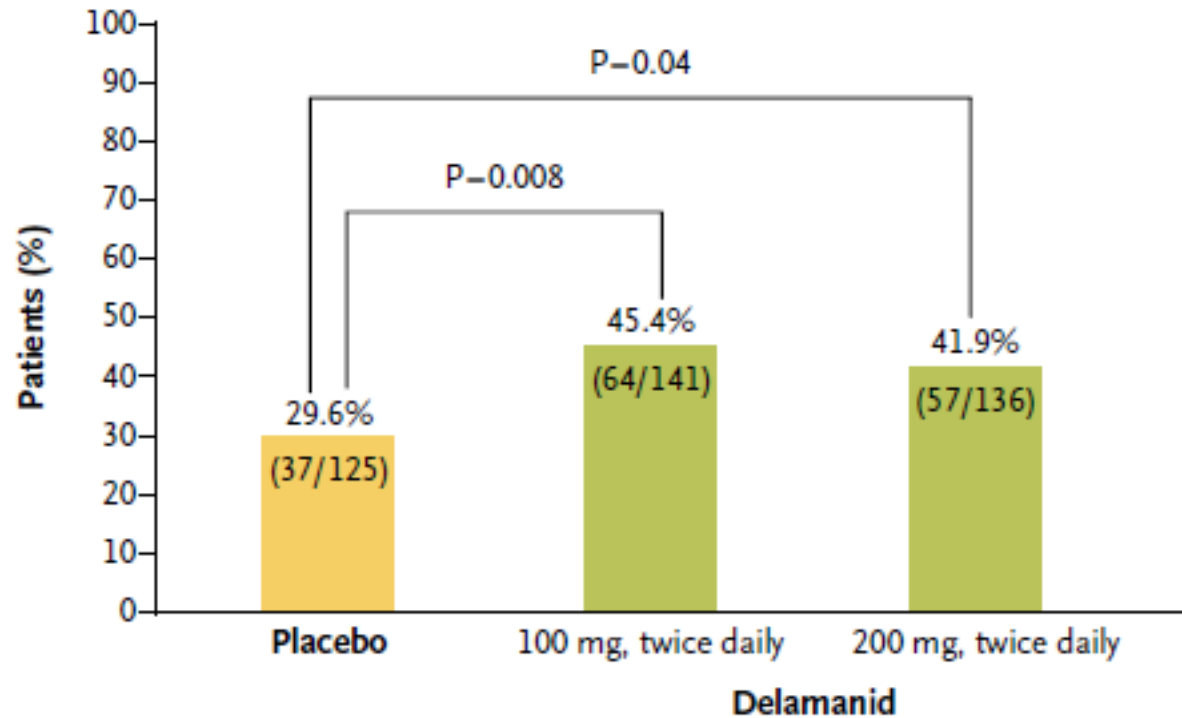At 8 weeks, 48% v 9% culture conversion

Source : Diacon et al (2009)

Phase 2 Trial of TMC207 Pt 2 (Bedaquiline, C208)

TMC207 (bedaquiline) Phase III underway

Source: Tibotec

Even newer drugs

New challenges in combinations

Cher NEJM 2012

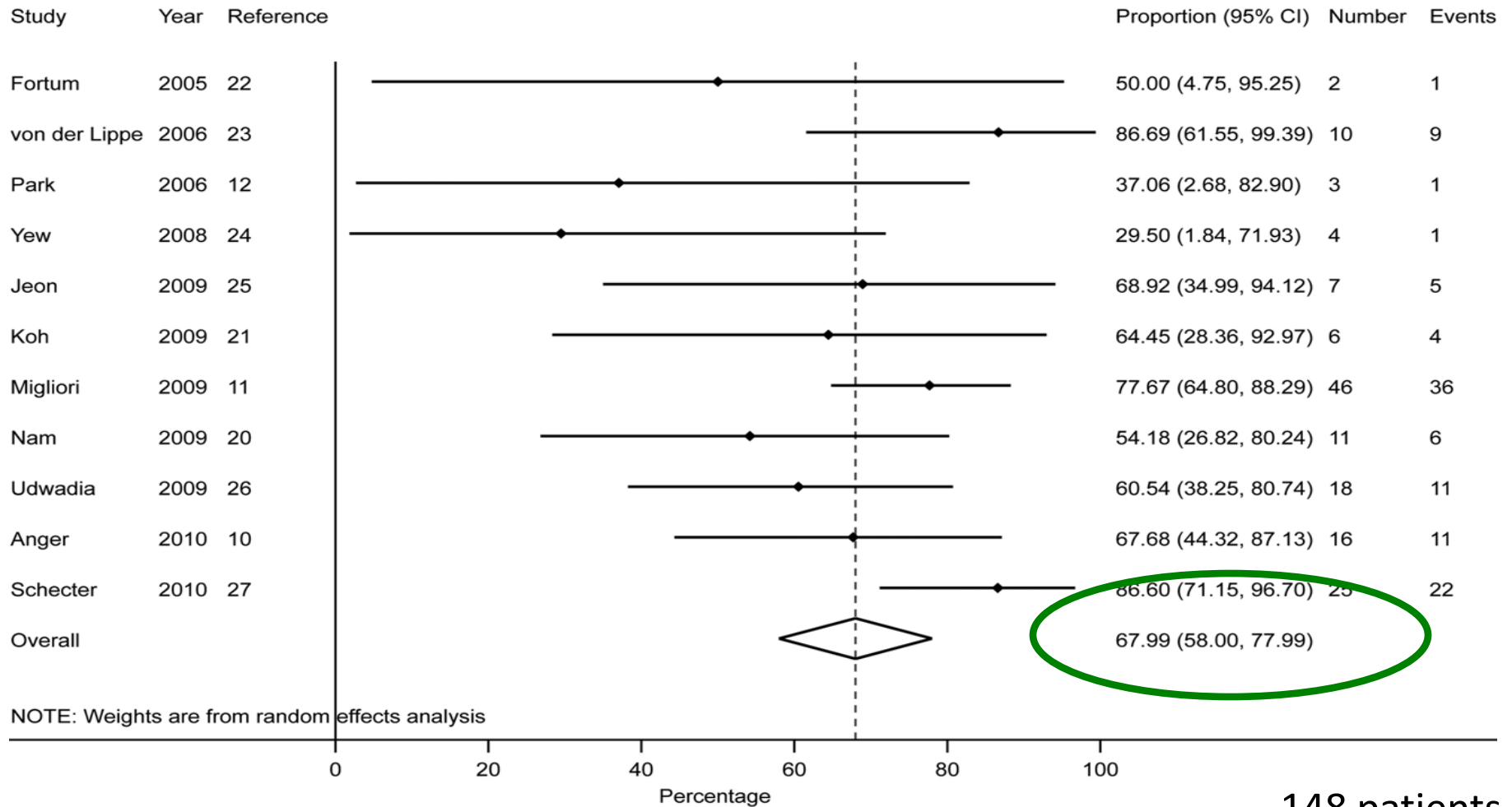# Repurposing Existing drugs

Repurposing Old drugs

Carbapenems - Imipenem and Meropenem (Hugonnet 09, Veziris 11)

Oxazolidinones - Linezolid   (Alcala 03, Fortun 05)

Tetracyclines – Doxycycline (Walker, 12)

Non anti-infectives

Linezolid – treatment success

Study	Year	Reference	Proportion (95% CI)	Number	Events
Fortum	2005	22	50.00 (4.75, 95.25)	2	1
von der Lippe	2006	23	86.69 (61.55, 99.39)	10	9
Park	2006	12	37.06 (2.68, 82.90)	3	1
Yew	2008	24	29.50 (1.84, 71.93)	4	1
Jeon	2009	25	68.92 (34.99, 94.12)	7	5
Koh	2009	21	64.45 (28.36, 92.97)	6	4
Migliori	2009	11	77.67 (64.80, 88.29)	46	36
Nam	2009	20	54.18 (26.82, 80.24)	11	6
Udwadia	2009	26	60.54 (38.25, 80.74)	18	11
Anger	2010	10	67.68 (44.32, 87.13)	16	11
Schecter	2010	27	86.60 (71.15, 96.70)	25	22
Overall			67.99 (58.00, 77.99)		

NOTE: Weights are from random effects analysis

Percentage

148 patients

Imperial College London

Cox & Ford *Int J Tuberc Lung Dis*. (2012)

Preventative therapy

Isoniazid Preventative therapy (IPT)

Debate over best way to implement IPT in both resource rich and resource poor settings

Effort to prevent a single case of TB quite substantial

Needs exclusion of subclinical/active TB to prevent delivery of isoniazid to patients with disease…… that's a problem where the problem is worst

Two most popular regimens
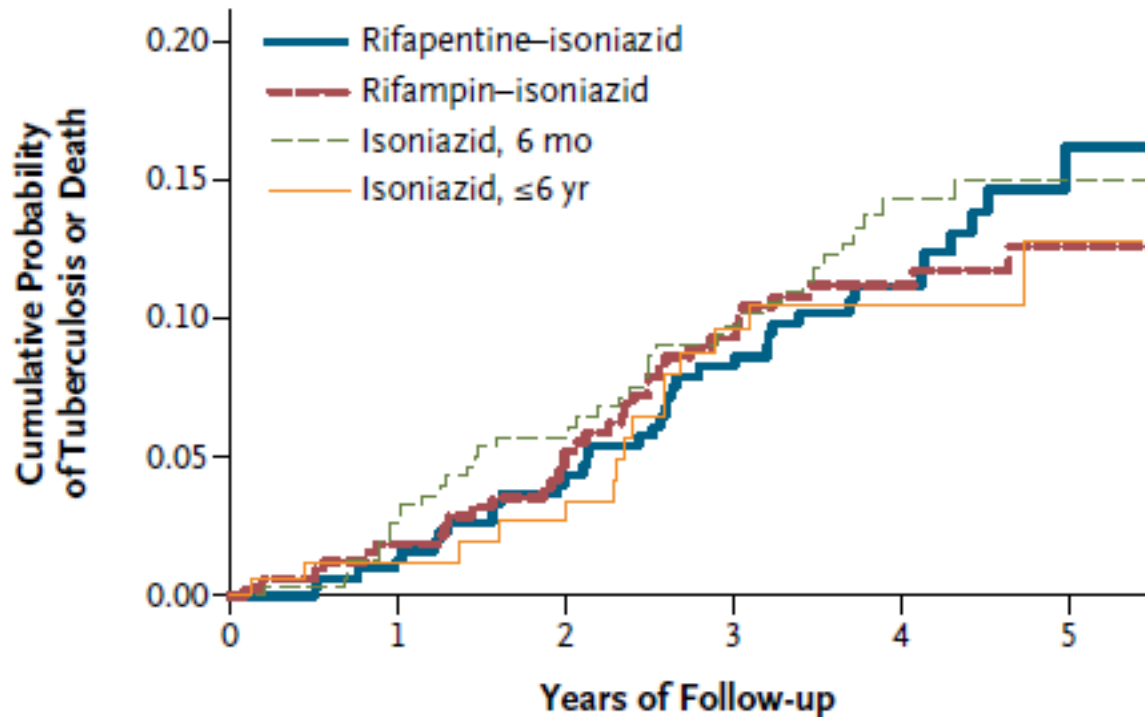
Isoniazid for 6/12

Rifampicin and Isoniazid for 3/12

PPD +ve

PPD -ve

Study or subgroup	Treatment (INH) n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 PPD+					
Hawken 1997	5/67	8/69		6.3 %	0.64 [0.22, 1.87]
Mwinga 1998	4/52	11/60		8.2 %	0.42 [0.14, 1.24]
Pape 1993	2/38	6/25		5.8 %	0.22 [0.05, 1.00]
Whalen 1997	7/536	21/464		18.0 %	0.29 [0.12, 0.67]
Subtotal (95% CI)	**693**	**618**		**38.3 %**	**0.36 [0.22, 0.61]**

Total events: 18 (Treatment (INH)), 46 (Control)
Heterogeneity: Chi² = 1.88, df = 3 (P = 0.60); I² = 0.0%
Test for overall effect: Z = 3.78 (P = 0.00015)

2 PPD-					
Fitzgerald 2001	6/126	4/111		3.4 %	1.32 [0.38, 4.56]
Gordin 1997	4/260	6/257		4.8 %	0.66 [0.19, 2.31]
Hawken 1997	11/235	8/224		6.6 %	1.31 [0.54, 3.20]
Mwinga 1998	14/178	17/166		14.1 %	0.77 [0.39, 1.51]
Pape 1993	2/20	5/35		2.9 %	0.70 [0.15, 3.28]
Rivero 2003	3/83	4/77		3.3 %	0.70 [0.16, 3.01]
Whalen 1997-anergy	9/395	10/323		8.8 %	0.74 [0.30, 1.79]
Subtotal (95% CI)	**1297**	**1193**		**43.9 %**	**0.86 [0.59, 1.26]**

Akolo et al Cochrane

Isoniazid Preventative therapy (IPT) – what?

Isoniazid Preventative therapy (IPT) – who?

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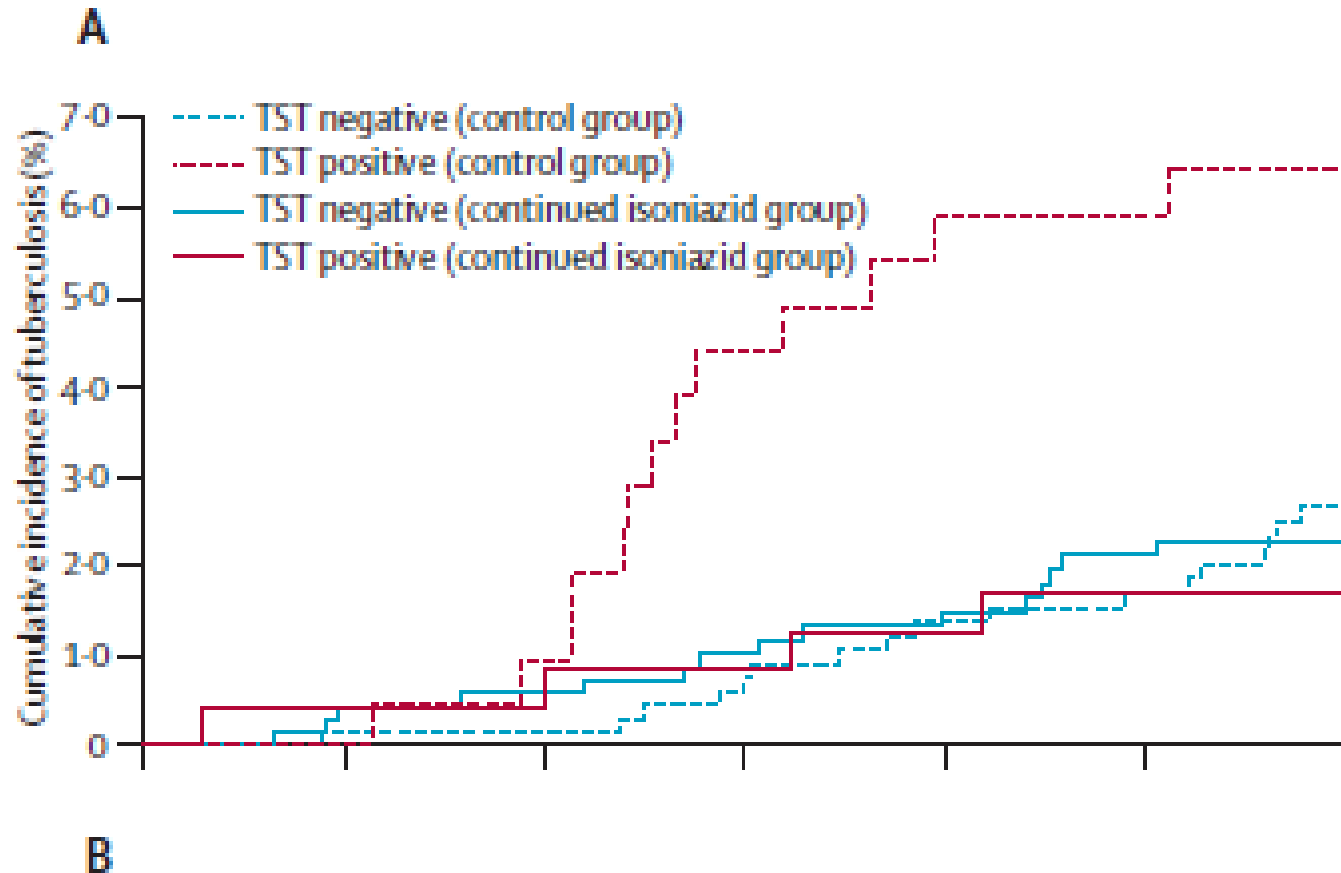
Adherence to Treatments

Intervention	Description	Studies	Patients	Defaulting (95% CI)	p
Regimen	Individualized	17	4289	9.30 (5.60, 13.00)	Ref
Regimen	Standardized	63	15003	15.60 (12.60, 18.60)	0.01
Regimen	Mixed	2	139	14.10 (8.50, 19.90)	0.16
DOT	None	10	3352	26.20 (15.50, 37.00)	Ref
DOT	Partial	25	6689	15.70 (11.00, 20.40)	0.08
DOT	Always	38	8064	11.40 (9.00, 13.90)	0.009
Dot Provider	Nurse	20	5035	18.20 (13.00, 23.30)	Ref
Dot Provider	Family member	2	38	1.30 (0.00, 4.60)	<0.001
Dot Provider	CHW	17	2687	9.10 (6.30, 11.80)	0.002
Dot Provider	Mix	14	2507	6.80 (4.60, 9.10)	<0.001
DOT provider paid	No/sometimes	12	2387	7.00 (4.20, 9.80)	Ref
DOT provider paid	Always	32	6500	14.30 (11.00, 17.70)	0.001
DOT location	Facility	39	9815	15.70 (12.00, 19.40)	Ref
DOT location	Home/mixed	23	4010	8.90 (6.40, 11.40)	0.03
Education	No/not stated	73	17976	14.80 (12.20, 17.40)	Ref
Education	Yes	10	1495	9.30 (5.20, 13.30)	0.03
Cohort size	<100	42	1704	10.10 (7.80, 12.50)	Ref
Cohort size	100-499	27	6439	14.90 (11.60, 18.20)	0.02
Cohort size	500-999	9	5528	17.70 (9.70, 25.80)	0.07
Cohort size	>1000	5	5800	24.50 (14.80, 34.20)	0.005
Counselling	No	65	15754	14.40 (11.50, 17.20)	Ref
Counselling	Yes	18	3717	13.50 (9.30, 17.70)	0.7

percentage

Toczek et al IJTLD 2012

Infection control, isolation and HCW

Routine case detection and identification

In low prevalence settings emphasis on ventilation, masks and Isolation

In high prevelance settings, such interventions not always Possible or affordable

e.g. in hyperendemic areas many hospitals with have high rates Of undiagnosed TB on wards

Natural ventilation of proven benefit

UV lights can be helpful in terms of local infection control

Rocked by Aids, Zulu kingdom now faces even worse foe: incurable TB

Doctors fear fresh fight with South African health chiefs for cash to battle new strain

Chris McGreal in Tugela Ferry
The Guardian, Wednesday 13 September 2006

A patient at Tugela Ferry hospital, where a new strain of incurable TB - with a 98% mortality rate - has been found. Photograph: Rajesh Jantilal/AFP

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 Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, 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 realised 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.

Rocked by Aids, Zulu kingdom now faces even worse foe: incurable TB

Doctors fear fresh fight with South African health chiefs for cash to battle new strain

Chris McGreal in Tugela Ferry
The Guardian, Wednesday 13 September 2006

A patient at Tugela Ferry hospital, where a new strain of incurable TB - with a 98% mortality rate - has been found. Photograph: Rajesh Jantilal/AFP

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 Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

Summary

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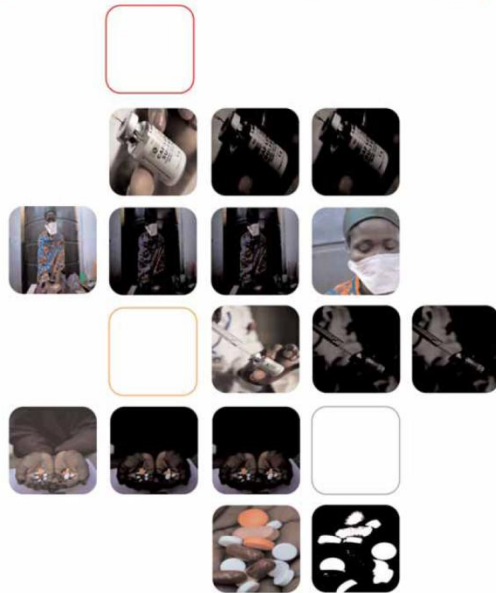
	HCWs	General Population	Incidence Rate Ratio (95% C.I.)*
Annual MDR or XDR-TB Incidence	66.8/100,000	11.7/100,000	5.71 (4.96-6.69)
Annual MDR-TB Incidence	62.3/100,000	10.7/100,000	5.82 (5.03-6.87)
Annual XDR-TB Incidence	4.5/100,000	1.04/100,000	4.33 (2.69-8.18)

O'Donnell (2010)

Access to Treatments

Evolution of DR-TB drug prices

DR-TB drugs under the microscope

SOURCES AND PRICES for drug-resistant tuberculosis medicines

International Union Against Tuberculosis and Lung Disease

MEDECINS SANS FRONTIERES

Prices available for GLC - approved programmes, in US$

Products	July 2001	March 2011 (lowest price)	% Difference 2001/2011
Amikacin 500mg	0.11	1.20	+991%
Kanamycin 1g	0.36	2.58	+617%
Cycloserine 250mg	0.14	0.59	+321%
Capreomycin 1gr	1.02	4.00	+292%
Ethionamide 250mg	0.10	0.09	Stable
Prothionamide 250mg	0.10	0.10	Stable
PAS 4g sachet	1.51	1.57	Stable

Imperial College London

Slide : Nathan Ford (MSF)

Access to New Drugs- children

Source: Ettehad et al LID (2012)
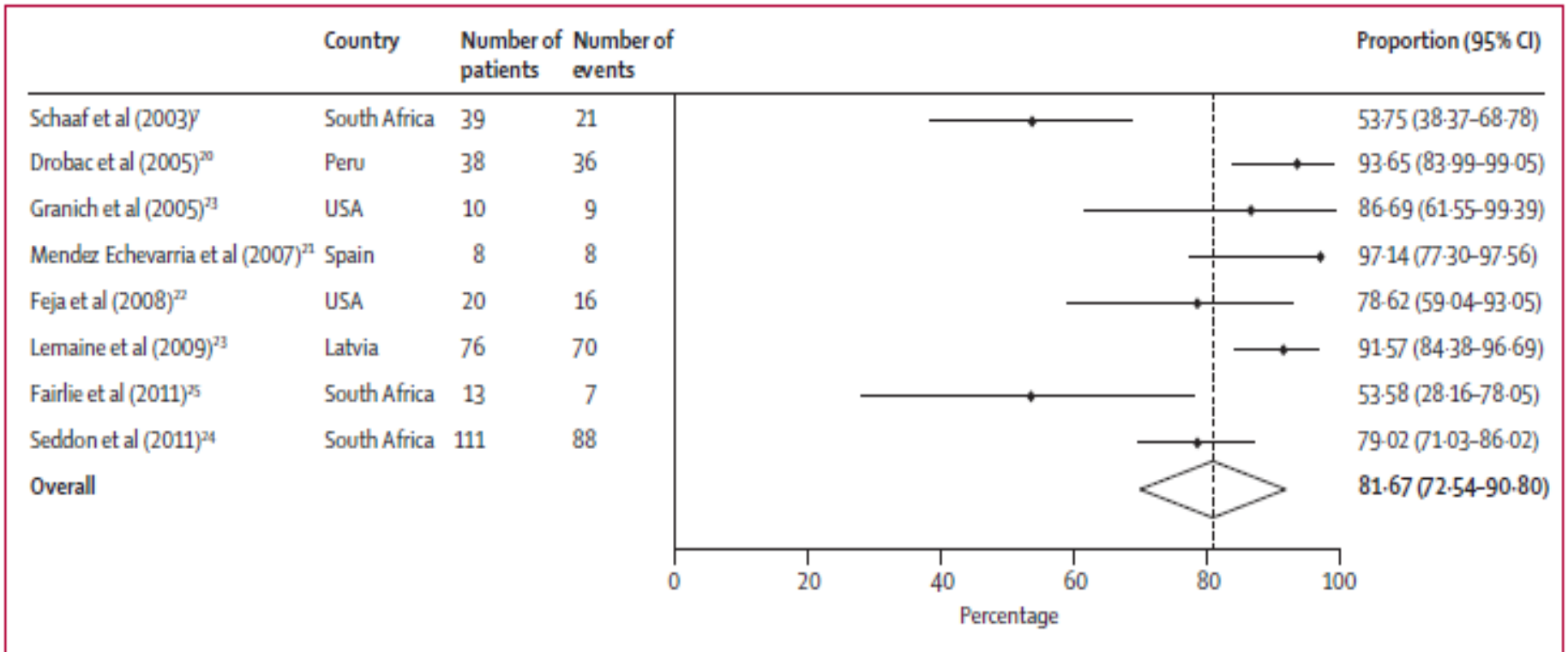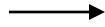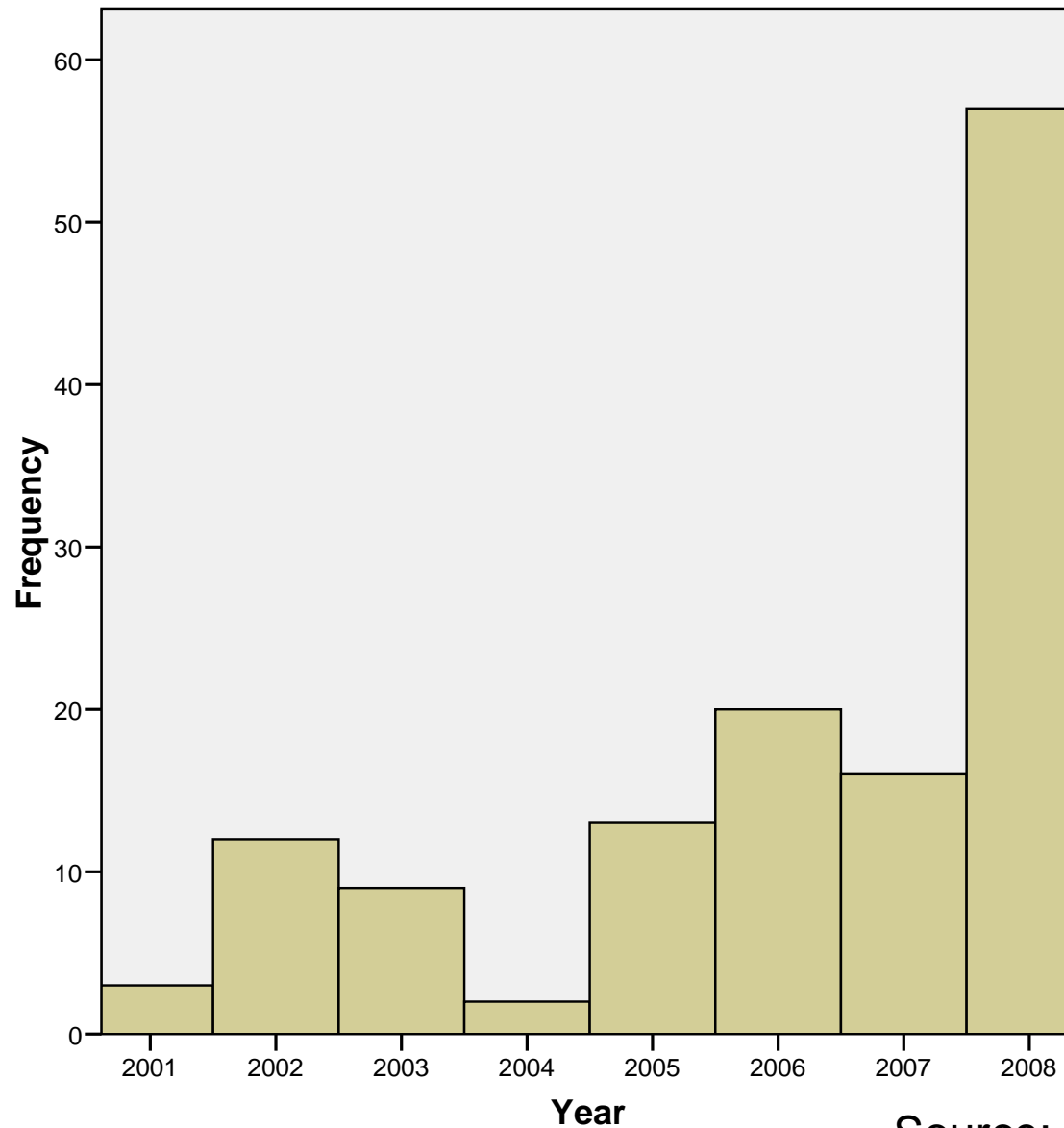
New Treatment Strategies

Renovated multi-story building
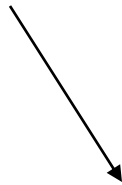
# MDR Treatment Initiations Hlabisa 2001-8

Source: Heller et al (2010)

Decentralised MDR programme

Patient characteristic		Jan 2001 – Mar 2008 (*n*=77)	Mar 2008 – Dec 2008 (*n*=57)
Age (mean, yrs)		-	36.7
Female (%)		56%	53%
Weight (mean, kg)		51kg	51kg
BMI (mean, kg/m^2)		19.4	19.0
HIV status	Positive	41.7%	81.8%
	Negative	23.6%	16.4%
	Unknown	34.7%	1.8%
CD4 count	<50 cells/mm^3	-	11.1%
	<200 cells/mm^3	-	55.6%
	<350 cells/mm^3	-	83.3%
Resistance pattern	RH	15 (19.5%)	21 (36.8%)
	RHE	6 (7.8%)	1 (1.8%)
	RHS	26 (33.8%)	31 (54.4%)
	RHES	10 (13.0%)	-
	XDR	-	1 (1.8%)
	Other	4 (5.2%)*	3 (5.3%)#
	Missing	16 (20.8%)	-

Decentralised MDR programme
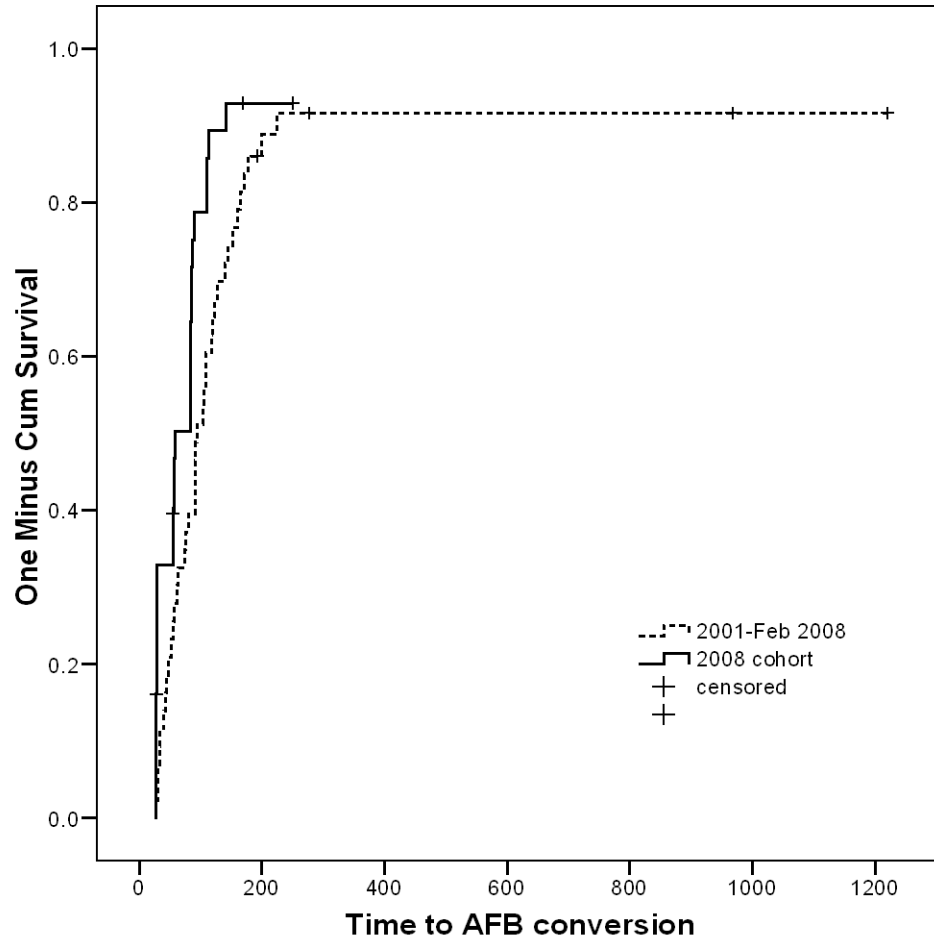
Source: Heller et al (2010)

Thank you

Questions?