Tuberculosis: Drug Resistance & Global Health

BSc Global Health
14th October , 2011

Graham Cooke

Overview of talk

Outline of definitions

Global distribution of disease burden

Brief case presentation and discussion

Tools to control MDR-TB

Key messages

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

MDR emerging in both HIV negative and HIV positive populations (probably increased in HIV positive populations)
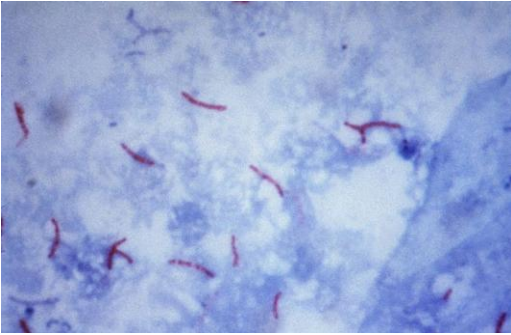
Diagnostics are improving but still limited by costs and need for lab infrastructure
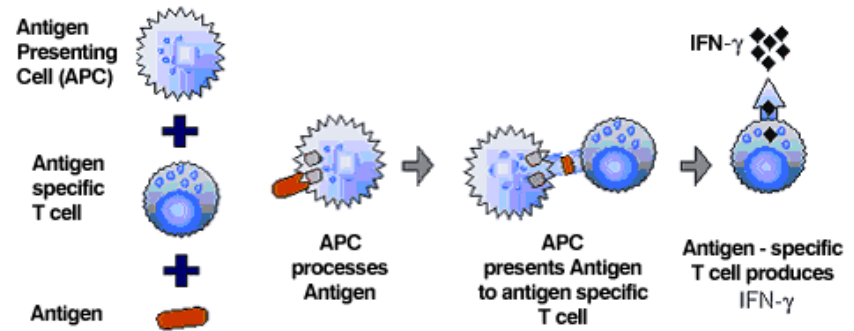
Treatment availability slowing expanding

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

IFN-γ

Antigen - specific T cell produces IFN-γ
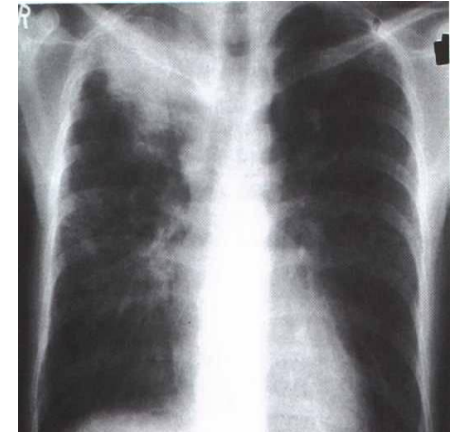
Infection with MTB

Some basics

First line medications

Rifampicin   (R)   ⎤
Isoniazid   (H)   ⎦ MDR-TB
Pyrazinamide   (Z)
Ethambutol   (E)

Some basics

First line medications

Rifampicin	(R)	⎤
Isoniazid	(H)	⎦ MDR-TB+
Pyrazinamide	(Z)	
Ethambutol	(E)	

Second line medications

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

2008 Best estimates

9.4 million cases incident TB
11.1 million cases prevalent TB

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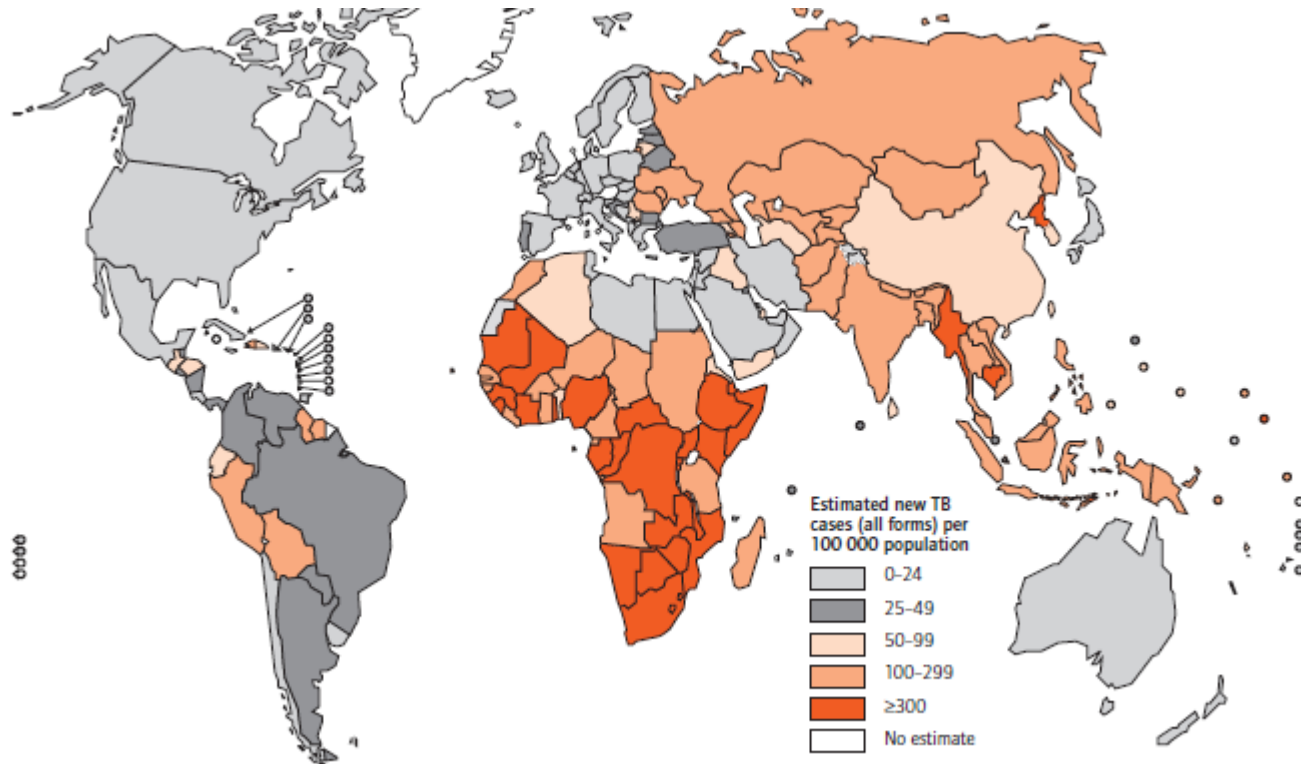   1.3 million without HIV
     0.52 million with HIV

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
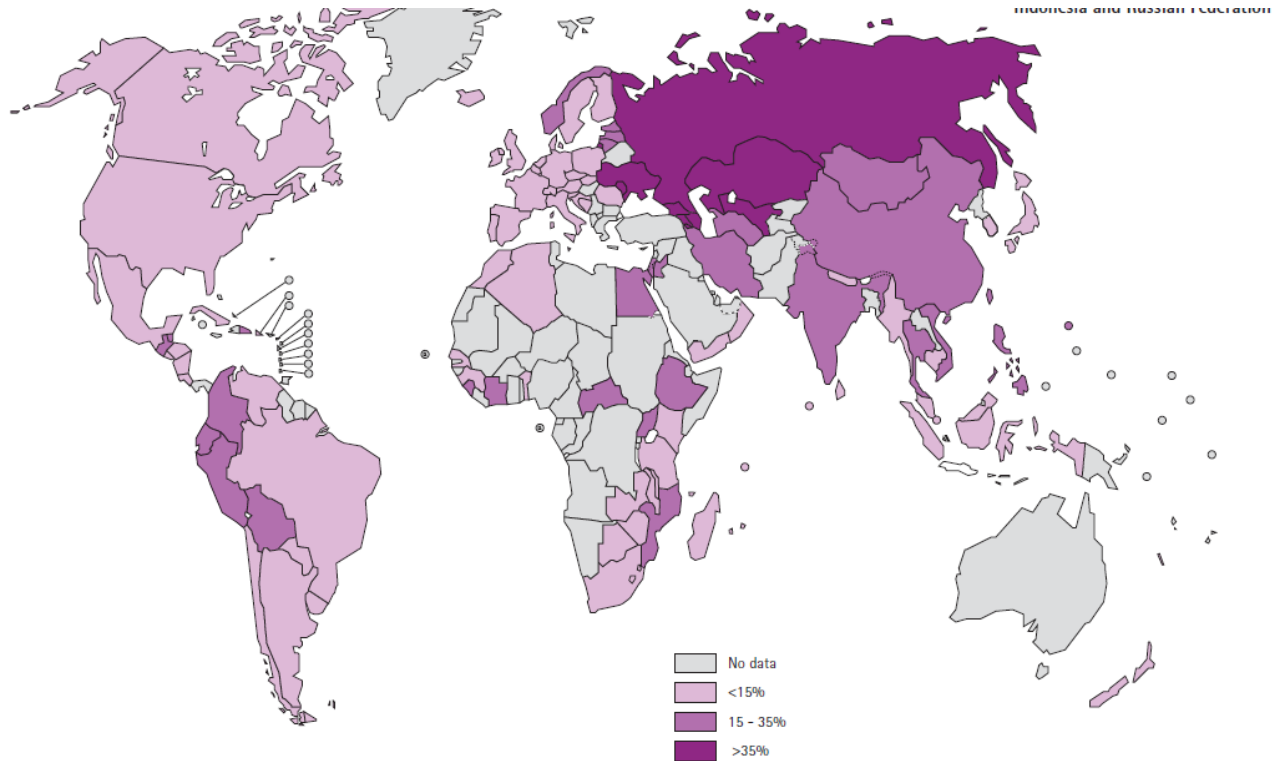- 25–49
- 50–99
- 100–299
- ≥300
- No estimate

TB incidence increasing 1.8% pa

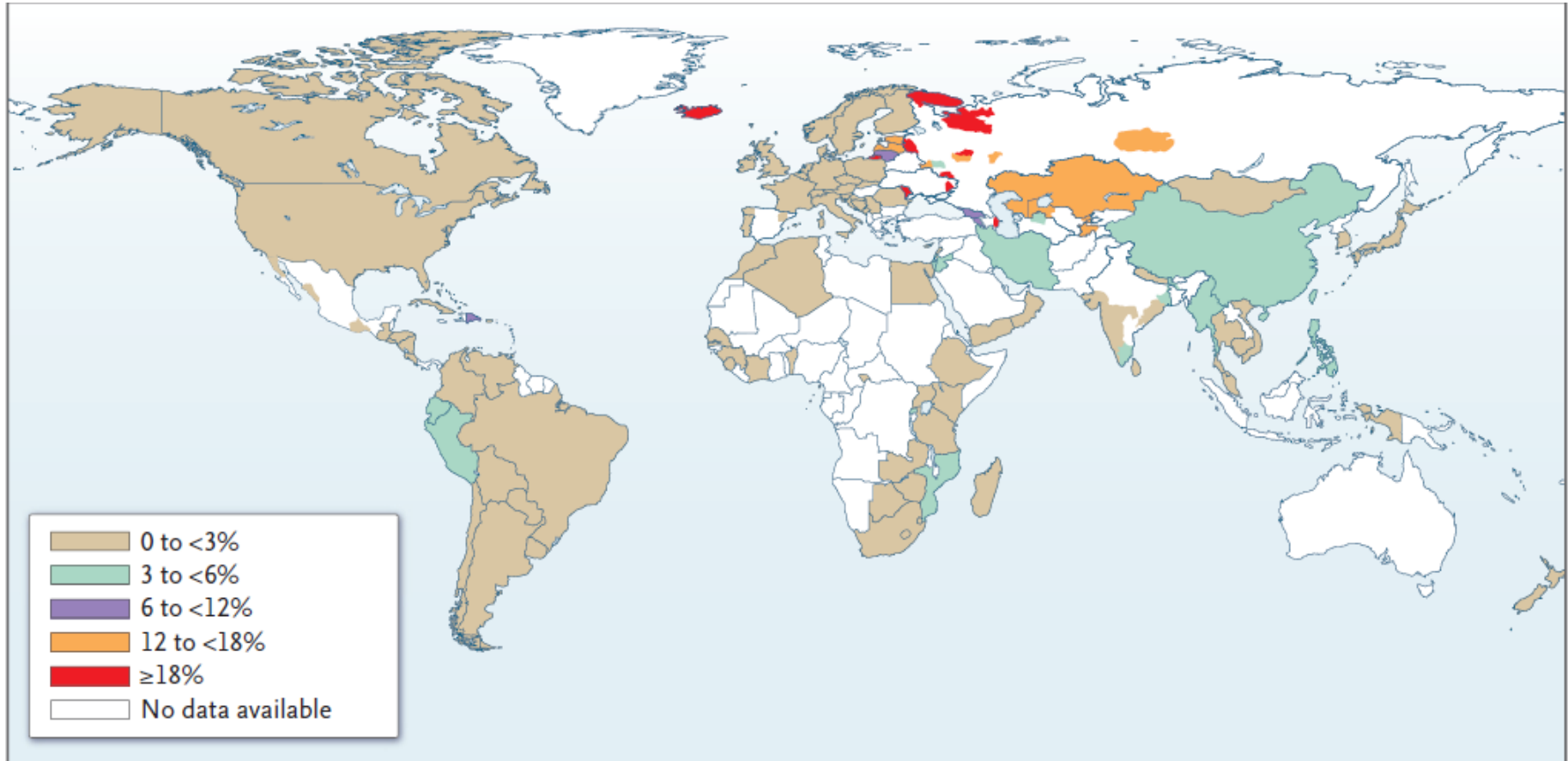# Proportion of TB with drug resistance

Median Prevalence MDR approx 5%

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

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

Indonesia and Russian Federation

No data
<15%
15 – 35%
>35%

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

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

MDR is predicted to become more common: notifications
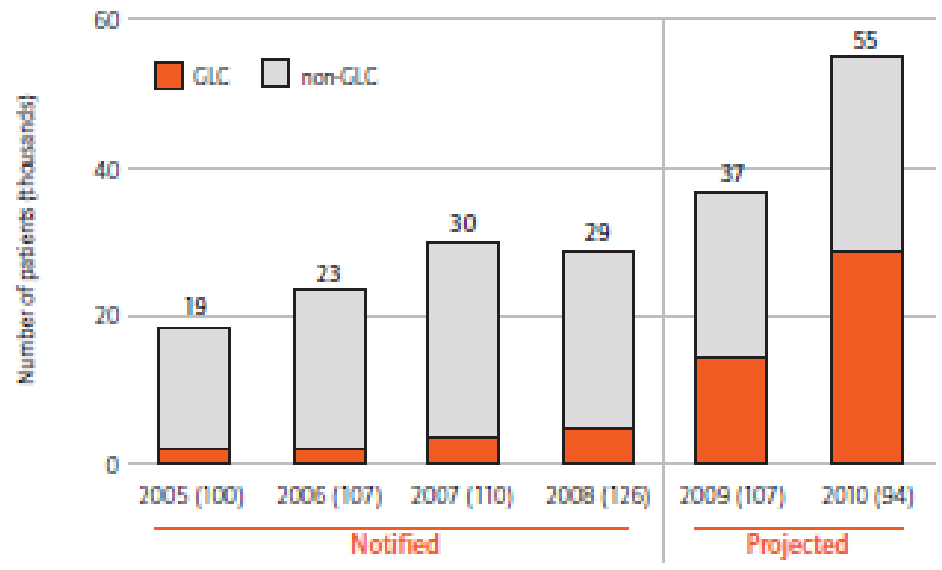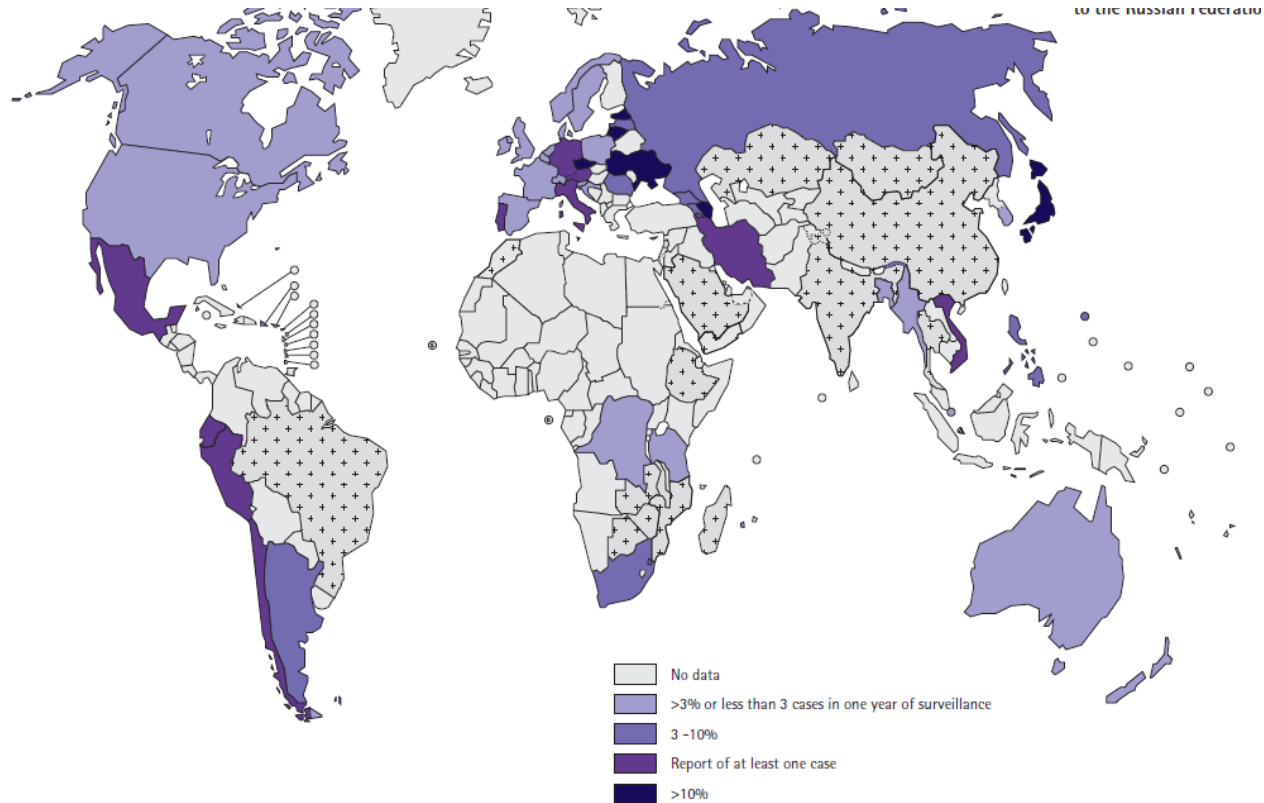
And will (probably) continue to increase
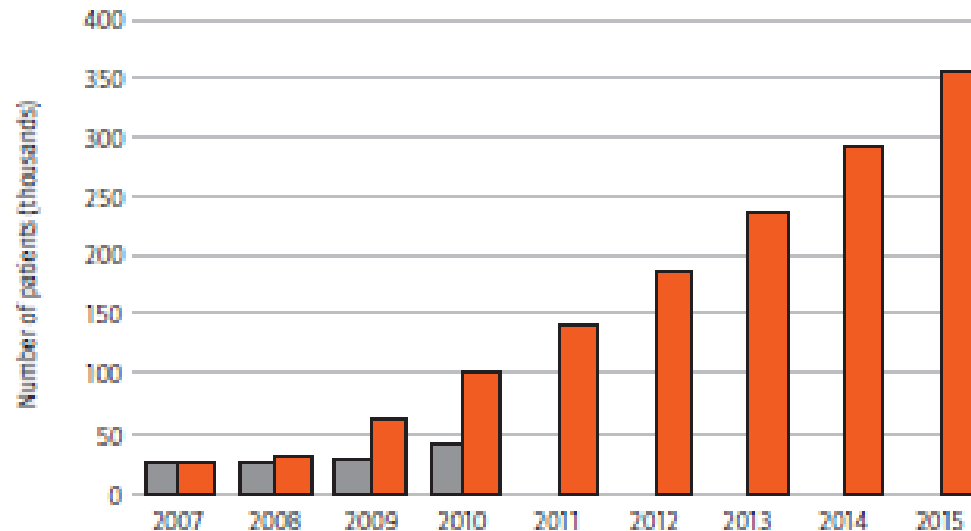
- The targets/milestones for scaling-up treatment of MDR-TB in the Global Plan are based on updated projections produced in March 2009, in preparation for a ministerial meeting on MDR/XDR-TB held in Beijing, China in April 2009.

WHO (2009)

XDR-TB

Prevalence of XDR amongst MDR (WHO 2009)

Countries with confirmed cases of XDR-TB as of November 2008
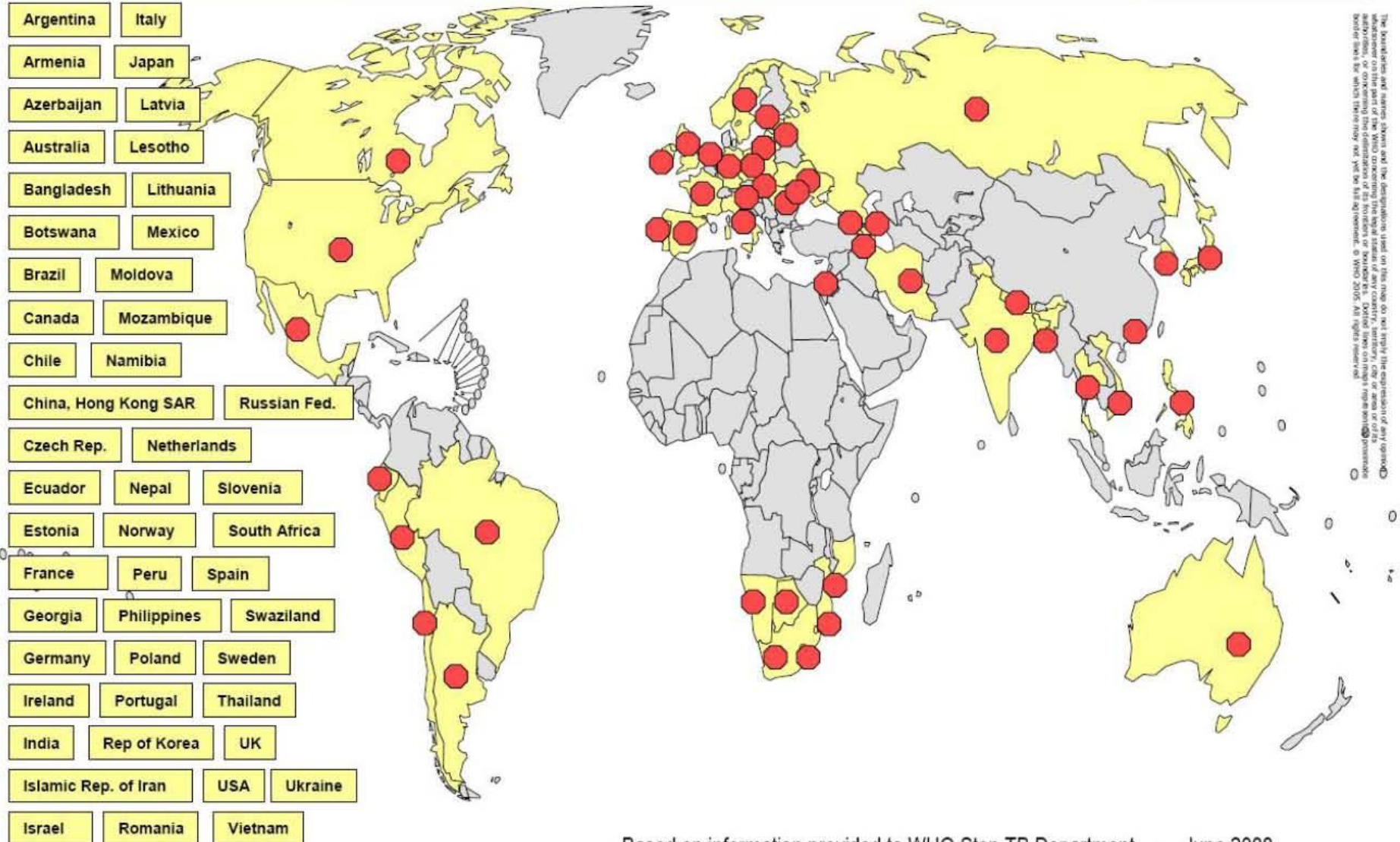
Argentina	Italy	
Armenia	Japan	
Azerbaijan	Latvia	
Australia	Lesotho	
Bangladesh	Lithuania	
Botswana	Mexico	
Brazil	Moldova	
Canada	Mozambique	
Chile	Namibia	
China, Hong Kong SAR	Russian Fed.	
Czech Rep.	Netherlands	
Ecuador	Nepal	Slovenia
Estonia	Norway	South Africa
France	Peru	Spain
Georgia	Philippines	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

A Need for Better Information: Accredited Labs

A Need for Better Information: Surveillance
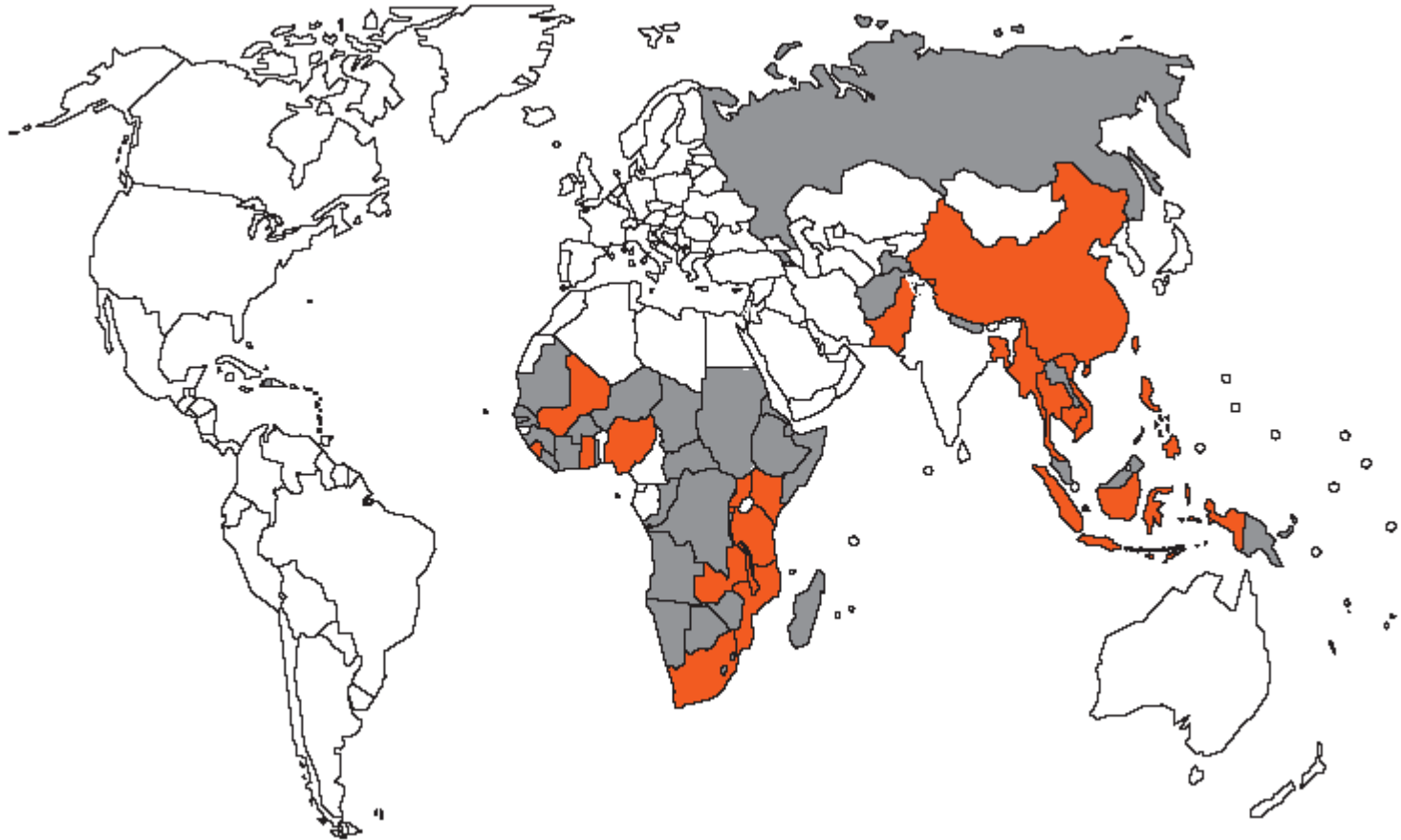
The 21 global focus countries where a national survey of the prevalence of TB disease is recommended in the period 2008–2015 (red), and extended list of countries meeting the criteria (grey) for implementing such surveys

Regions of difference

Global figures have limited applicability to interventions

- Different challenges in different regions
- Different tools in different regions
- Political and economic setting crucial

Three case examples

	No.cases TB	% MDR	Est total MDR
Russia	150,898	13%	19,616
India	1,982,628	3%	59,478
South Africa	476,732	4%	19,069

M/XDR-TB in Eastern Europe

Case Study: Tomsk, Russia

2000-2004
636 patients

Keshavjee, Lancet 08

Tomsk, Russia

	XDR TB (N=29)	Non-XDR TB (N=579)	p value
Female	5 (17%)	97 (17%)	1·00
Age (years)*	33·9 (11·1)	35·9 (11·3)	0·33
Treatment initiation site			0·17
Civilian	20 (69%)	398 (69%)	
TB hospital	17 (59%)	278 (48%)	
Day hospital or polyclinic in Tomsk	1 (3%)	96 (17%)	
Sites outside of Tomsk	2 (7%)	24 (4%)	
Prison	9 (31%)	181 (31%)	
Any disability	20 (69%)	239 (41%)	0·003
Homeless	1 (3%)	23 (4%)	1·00
Number of previous treatments against TB (median [first and third quartiles])	3·0 [2·0, 4·0]	2 [1·0, 3·0]	0·0005
New patients (no previous treatment against TB)	0 (0%)	3 (0·5%)	1·00
Previous default	0 (0%)	3 (4%)	0·62
Previous parenteral exposure (n=597)†	17 (59%)	177 (31%)	0·002
Previous fluoroquinolone exposure (n=597)†	15 (52%)	79 (14%)	<0·0001
Previous or present incarceration (n=605)	21 (72%)	320 (56%)	0·07
Low body-mass index (n=607)	18 (62%)	240 (41%)	0·03
HIV (n=604)	0 (0%)	5 (0·9%)	1·00
Alcoholism‡	9 (31%)	252 (43%)	0·19
Illegal drug use‡	7 (24%)	106 (18%)	0·46
Previous surgery for TB (n=605)	6 (21%)	5 (10%)	0·06
Baseline respiratory insufficiency (n=600)‡	17 (59%)	299 (52%)	0·51
Fibrotic or cavitary lesions on chest X-ray (n=605)	10 (34%)	92 (16%)	0·009

Outcomes in Tomsk

Favourable
- Completion
- Cure　　　　　(completion with micro support)

Unfavourable
- Default
- Failure
- Death

Time to culture conversion

Time from treatment to date of first of two consecutive negative cultures

Outcomes in Tomsk

	XDR TB (N=29)	Non-XDR TB (N=579)	Total number	p value
Favourable outcome	14 (48%)	386 (67%)	400 (66%)	0·04*
Cured	13 (45%)	366 (63%)	379 (62%)	
Treatment completed	1 (3·%)	20 (3%)	21 (3%)	
Poor outcome				
Failure	9 (31%)	49 (8%)	58 (9%)	0·0008†
Death	2 (7%)	29 (5%)	31 (5%)	0·65†
Default	4 (14%)	115 (20%)	119 (20%)	0·42†

Total number of patients=608. Data are numbers (%). MDR=multidrug resistant. XDR TB=extensively drug-resistant tuberculosis. Non-XDR TB=non-extensively drug-resistant tuberculosis. *This value refers to the comparison between favourable and poor outcome. †This value refers to the comparison between each outcome (ie, failure, death, or default) and all other outcomes.

Table 2: Treatment outcomes of patients with MDR tuberculosis

Imperial College London

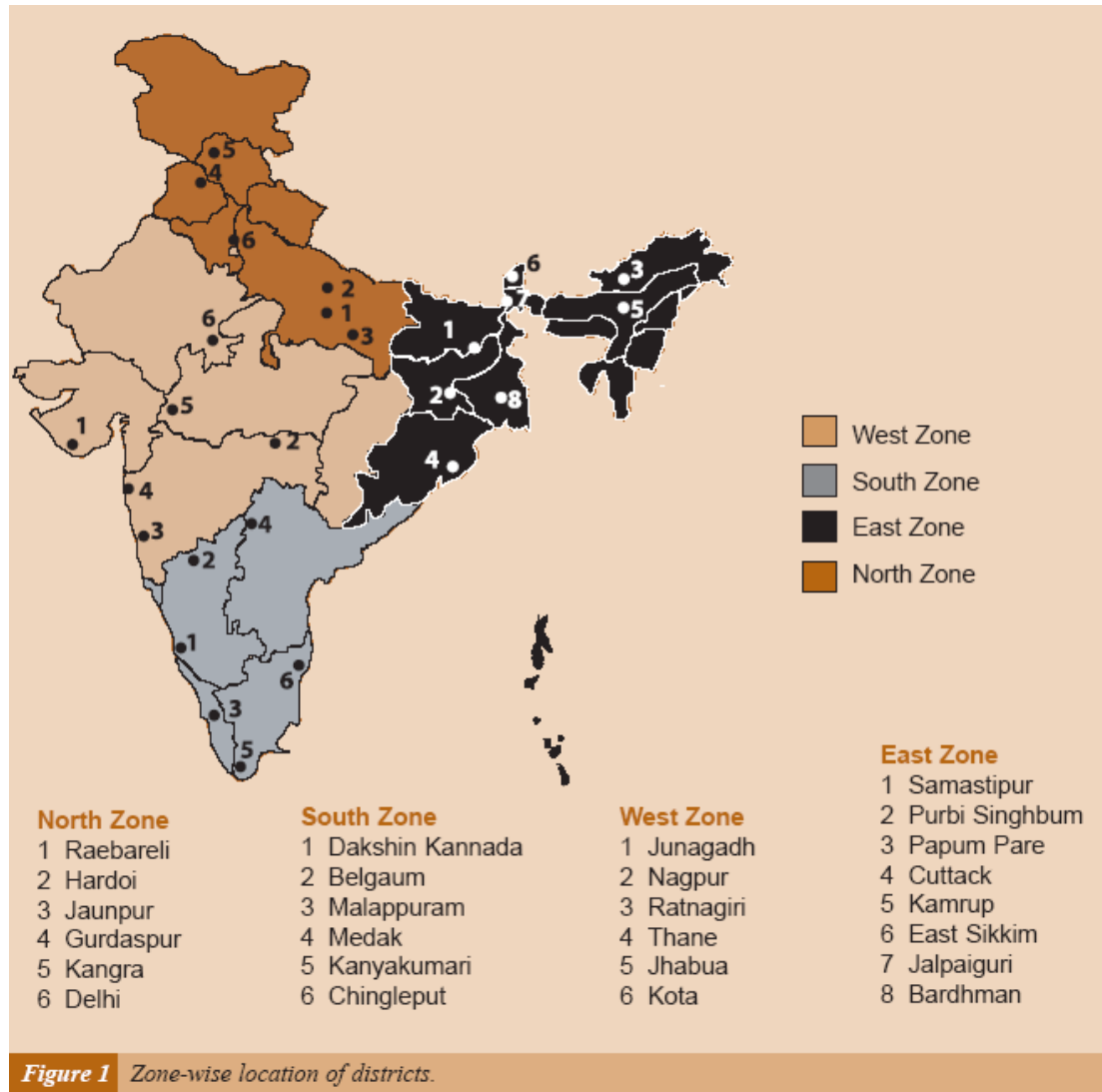# Baseline resistance to 1ˢᵗ and 2ⁿᵈ line agents in M/XDR isolates
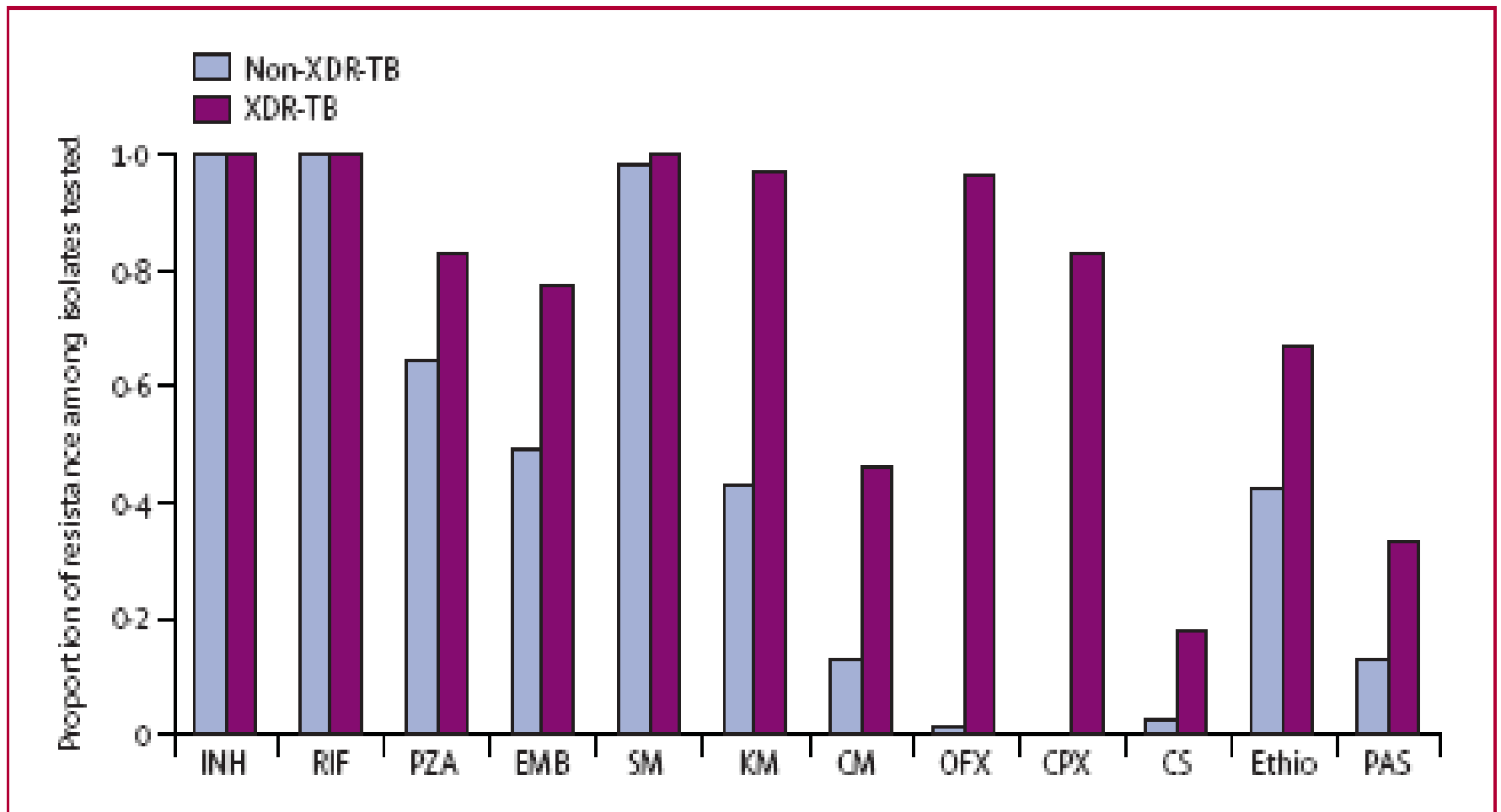
2nd line drugs are toxic and adverse events common

	Frequency during treatment for MDR TB (N=608)		Adverse event needing change in treatment against MDR TB (N=608)	
	XDR TB	Non-XDR TB	XDR TB	Non-XDR TB
Nausea, vomiting	22 (76%)	405 (70%)	11 (50%)	189 (47%)
Arthralgia	9 (31%)	289 (50%)	1 (11·%)	55 (19%)
Depression	2 (7%)	47 (8%)	1 (50%)	21 (45%)
Diarrhoea	10 (34%)	228 (39%)	4 (40%)	60 (26%)
Hepatitis	5 (17%)	89 (15%)	1 (20%)	21 (24%)
Hypokalaemia	11 (38%)	220 (38%)	0 (0%)	21 (9%)
Hypothyroidism	2 (7%)	59 (10%)	0 (0%)	8 (14%)
Nephrotoxicity	1 (3%)	38 (7%)	0 (0%)	4 (10%)
Neuropathy	1 (3%)	41 (7%)	0 (0%)	9 (22%)
Ototoxicity	3 (10%)	75 (13%)	0 (0%)	31 (41%)
Psychosis	3 (10%)	50 (9%)	2 (67%)	40 (80%)
Rash	3 (10%)	82 (14%)	0 (0%)	16 (19%)
Seizure	2 (7%)	55 (9%)	2 (100%)	32 (58%)

Data are n (%). MDR TB= multidrug resistant tuberculosis.

Table 5: Occurrence and management of adverse events

Imperial College
London

MDR-TB in South East Asia

Figure 1 *Zone-wise location of districts.*

North Zone
1 Raebareli
2 Hardoi
3 Jaunpur
4 Gurdaspur
5 Kangra
6 Delhi

South Zone
1 Dakshin Kannada
2 Belgaum
3 Malappuram
4 Medak
5 Kanyakumari
6 Chingleput

West Zone
1 Junagadh
2 Nagpur
3 Ratnagiri
4 Thane
5 Jhabua
6 Kota

East Zone
1 Samastipur
2 Purbi Singhbum
3 Papum Pare
4 Cuttack
5 Kamrup
6 East Sikkim
7 Jalpaiguri
8 Bardhman

West Zone
South Zone
East Zone
North Zone

Figure 2 *Annual risk of tuberculous infection (ARTI) by zone and stratum - Method I*

Hungary	1.904	25	4	169	1,3	0,2	8,7
Iceland	13	0	0	4	0,0	0,0	34,8
India	1.932.852	54.806	33.723	78.291	2,8	2,3	3,4
Indonesia	534.439	10.583	0	28.811	2,0	0,2	7,0
Iran	15.678	777	428	1.204	5,0	3,4	6,9
Iraq	15.968	478	68	2.729	3,0	0,5	16,6
Ireland	555	3	0	10	0,5	0,0	2,8

India

Low HIV prevalence

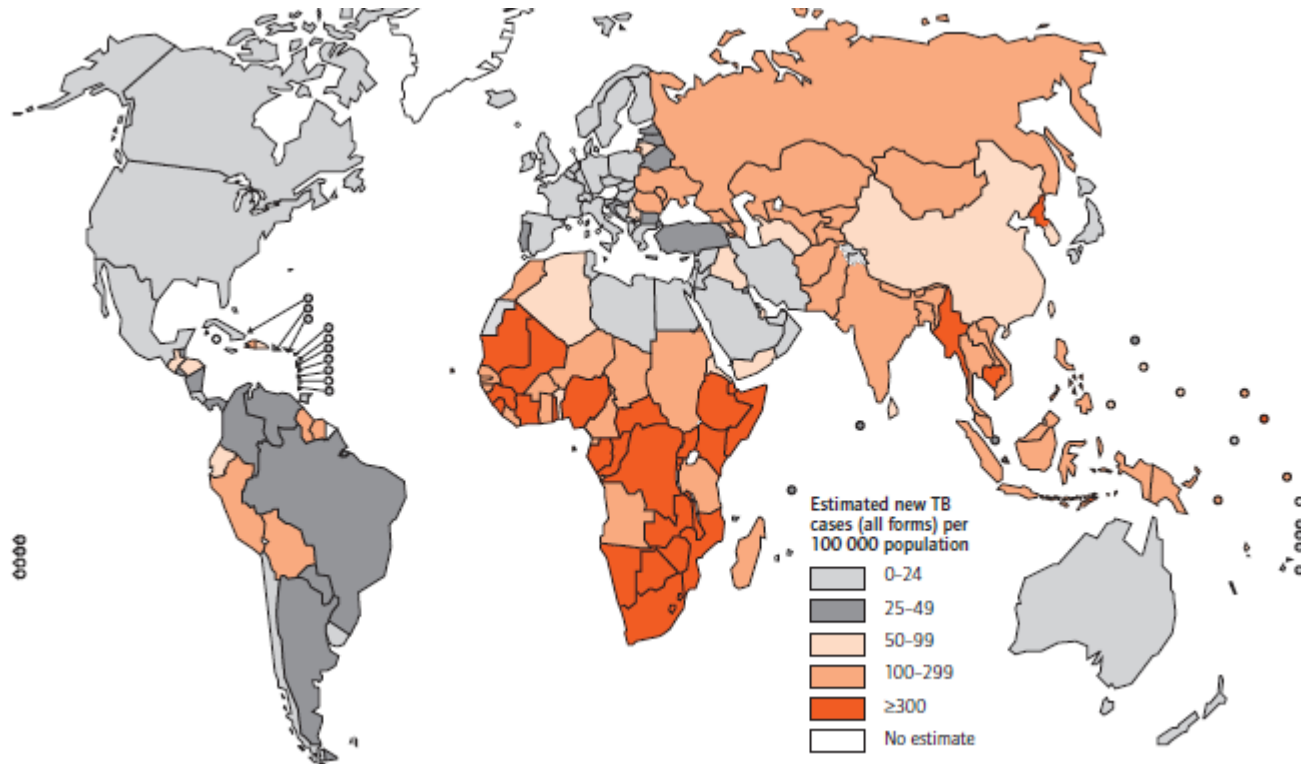Very high rates of TB notification

MDR prevalence relatively low

Very active private sector, probably contributing to
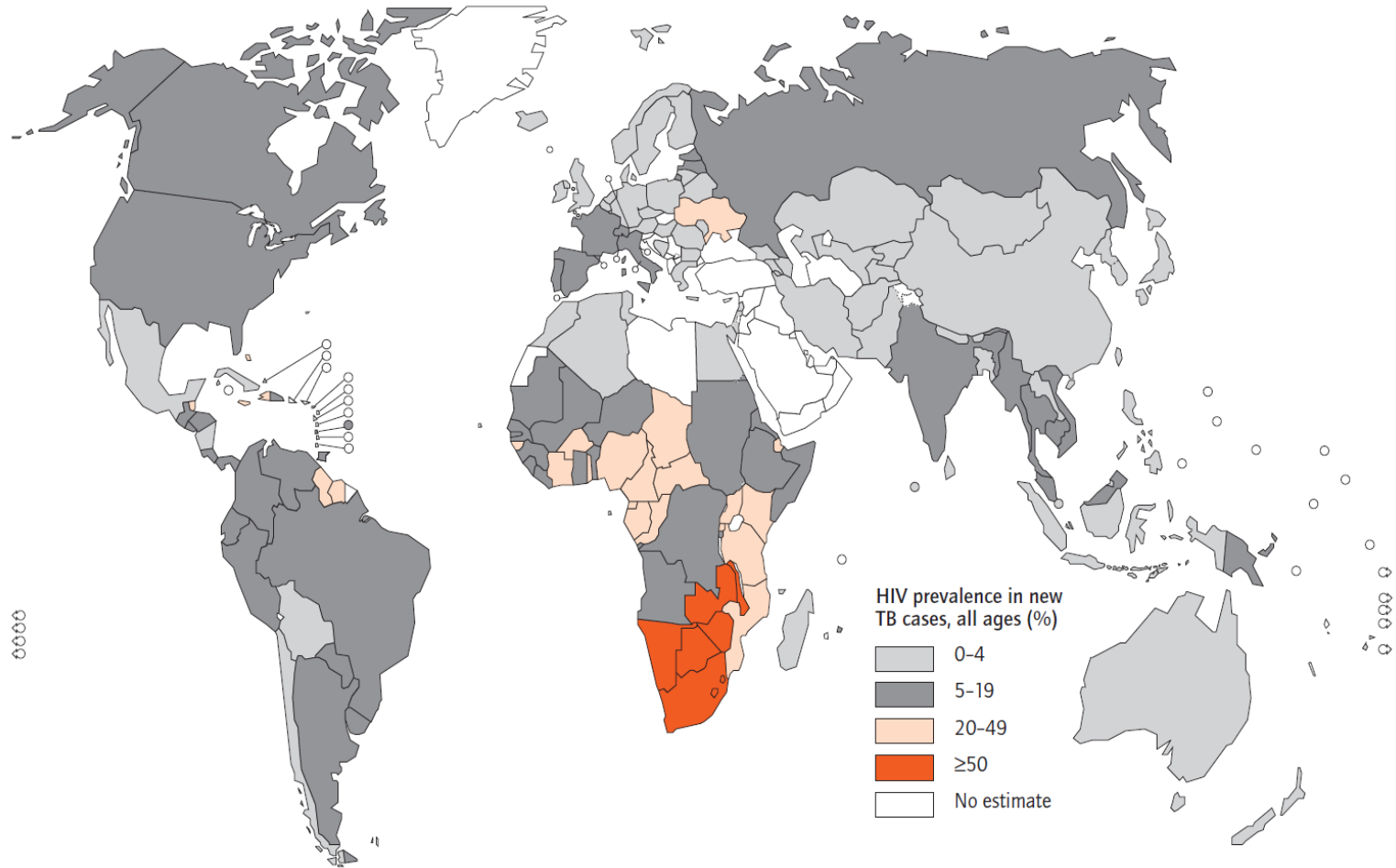 resistance burden

M/XDR-TB in Sub-Saharan Africa

HIV

A recap

Estimated new TB
cases (all forms) per
100 000 population

- 0–24
- 25–49
- 50–99
- 100–299
- ≥300
- No estimate

Incidence of New TB (WHO, 2008)

■ 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

Percentage of notified
TB cases with known
HIV status

- 0–14
- 15–49
- 50–74
- ≥75
- No data

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.

Tugela Ferry Experience

Extensive outbreak of XDR-TB almost exclusively in HIV positive individuals, a lot of HCWs

Came to light through an evaluation programme to integrate HIV/TB programmes

Brought international attention to problem of XDR-TB

Imperial College London

The bigger problem is MDR/HIV in South Africa

	Tugela Ferry	KwaZulu Natal	South Africa
MDR	269	4,701	17,615
XDR	350	656	996
Total	619	5,357	28,611

2005-2007

Courtesy Gerry Friedland

Despite the apparent data, still great deficiencies in current surveillance systems

Part 2

Case presentation

Case presentation

Presents with 1/12 of cough, weight loss, SOBOE

Oral thrush

Previous shingles scar

4cm R supraclavicular LN
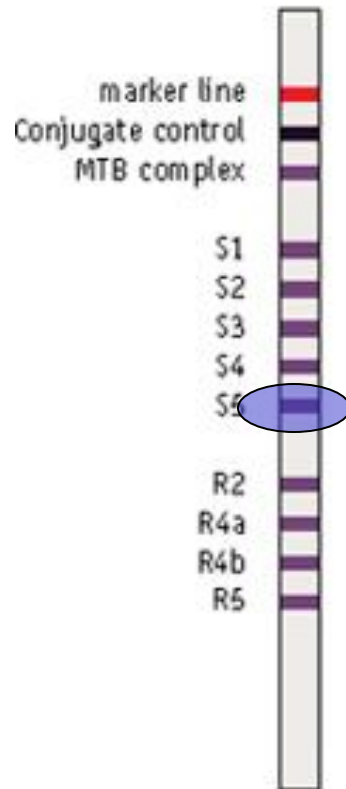
Case presentation

HIV positive, CD4 0

Lymph node aspirate AFB +++

Culture sent

Standard TB treatment started (RHZE)

Molecular testing consistent with MDR-TB

*D516V, H526Y, H26D, S531L

D516G, L533P, I1106T [KZN]

Case presentation

2nd line TB drugs added

HIV treatment added

Further deterioration (26/9/8)
Needed negative pressure ventilated room
SMH nearest available – accepted for transfer

Case presentation

Case presentation

A stormy course

-Hepatitis
   - TB Rx changed (Cycloserine replacing Pyr, Mox, Etham)
   - HAART changed (Efavirenz to Kaletra)
   - levoflox and prothionamide introduced

-Pleural effusion (likely IRIS)
   - Chest drain, subsequently removed

-Confusion (from cycloserine)

-Slowly weaned and tracheostomy inserted, woken and began to communicate

Further history

-Letter board

-Church of Scotland Hospital, Tugela Ferry until 2002

Date	Treatment	Started	Stopped	Event
16/9	R.H,Z,E	R,H,Z,E		TB diagnosis
24/9	R,H,Z,E,<u>Lfx</u>,<u>Am</u>	Lfx,Am		INNO-LIPA.rif
26/9	Z,E,<u>Cm</u>,<u>Mfx</u>,Pto	Cm,Mfx,Pto	R,H,Lfx,Am	ITU EFV/FTC/TVF
2/10	E,<u>Cm</u>,<u>Cs</u>	Cs	Z,Mfx,Pto	Hepatitis EFV>Kaletra
10/10	E,<u>Cm</u>,<u>Cs</u>,Lfx,Pto	Pto		LFT's normal
15/10	<u>Cm</u>,<u>Cs</u>,Lfx,<u>PAS</u>	PAS	E,Pto	H,E,Pto resistance
18/10	<u>Cm</u>,<u>Cs</u>,Lfx,<u>Lzd</u>	Lzd	PAS	Unable to pass PAS down NGT
2/11	<u>Cm</u>,<u>Cs</u>,<u>Mfx</u>	Mfx	Lfx,Lzd	Lfx>Mfx Pancytopenic
12/11	<u>Mfx</u>,<u>PAS</u>,<u>Lzd</u>	PAS,Lzd	Cm,Cs	ARF/conf TVF stopped

Progress

- Discharged to the ward

- Much improved – planning transfer to Bristol

- However …..

- Began to deteriorate
    - Sepsis
    - Readmitted to ITU
    - Died soon after, likely of fungal septicaemia

Molecular evidence that infection acquired in Tugela Ferry

Table. Locus typing for tuberculosis patient isolate according to standard nomenclature based on chromosomal locations*

Genotypic family and strain or isolate	Allele at MIRU-VNTR locus														
	154	577	580	802	960	1644	2059	2165	2461	2531	2687	2996	3007	3192	4348
F15/LAM4/KZN															
Patient isolate	1	4	3	4	4	3	2	2	2	6	1	5	3	3	2
605 (reference)	1	4	2	4	4	3	2	2	2	6	1	5	3	3	2
1435	1	4	2	5	4	3	2	2	2	6	1	5	3	3	2
R506	1	4	2	3	3	3	2	2	2	6	1	4	3	3	2
V2475	1	4	2	3	3	3	2	2	2	6	1	4	3	3	2
4207	1	4	2	3+4	3+4	3	2	2	2	6	1	4+5	3	3	2
F11/LAM															
F11	2	4	2	3	3	3	2	2	2	6	1	4	3	3	2

*Patient's isolate most closely matches F15/LAM4/KZN605 reference strain by a single locus variation, a genetic distance equal to or lower than that separating other known F15/LAM4/KZN strains (i.e., 1–3 locus variations). MIRU-VNTR, mycobacterial interspersed repetitive units–variable number tandem repeats.

Cooke et al EID 2011

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R506	1	4	2	3	3	3	2	2	2	6	1	4	3	3	2
V2475	1	4	2	3	3	3	2	2	2	6	1	4	3	3	2
4207	1	4	2	3+4	3+4	3	2	2	2	6	1	4+5	3	3	2
F11/LAM															
F11	2	4	2	3	3	3	2	2	2	6	1	4	3	3	2

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Cooke et al EID 2011

How could we have prevented this death?

How could we have prevented this death?

- Better medical management in UK?

- Better occupational health in UK?

- Improved implementation of HIV testing policies?

- Improved screening programmes for migrants?

- Improved infection control in SA hospitals?

- Improved public health control in SSA?

- Biomedical advances in vaccine and treatment?

- Better diagnostics?

- Greater advocacy and activism around above issues?

Part 3

Some new developments

New Vaccines

New Diagnostics

New Treatment Strategies

New Treatments

New Political will

Some new developments

~~New Vaccines~~

New Diagnostics

New Treatment Strategies

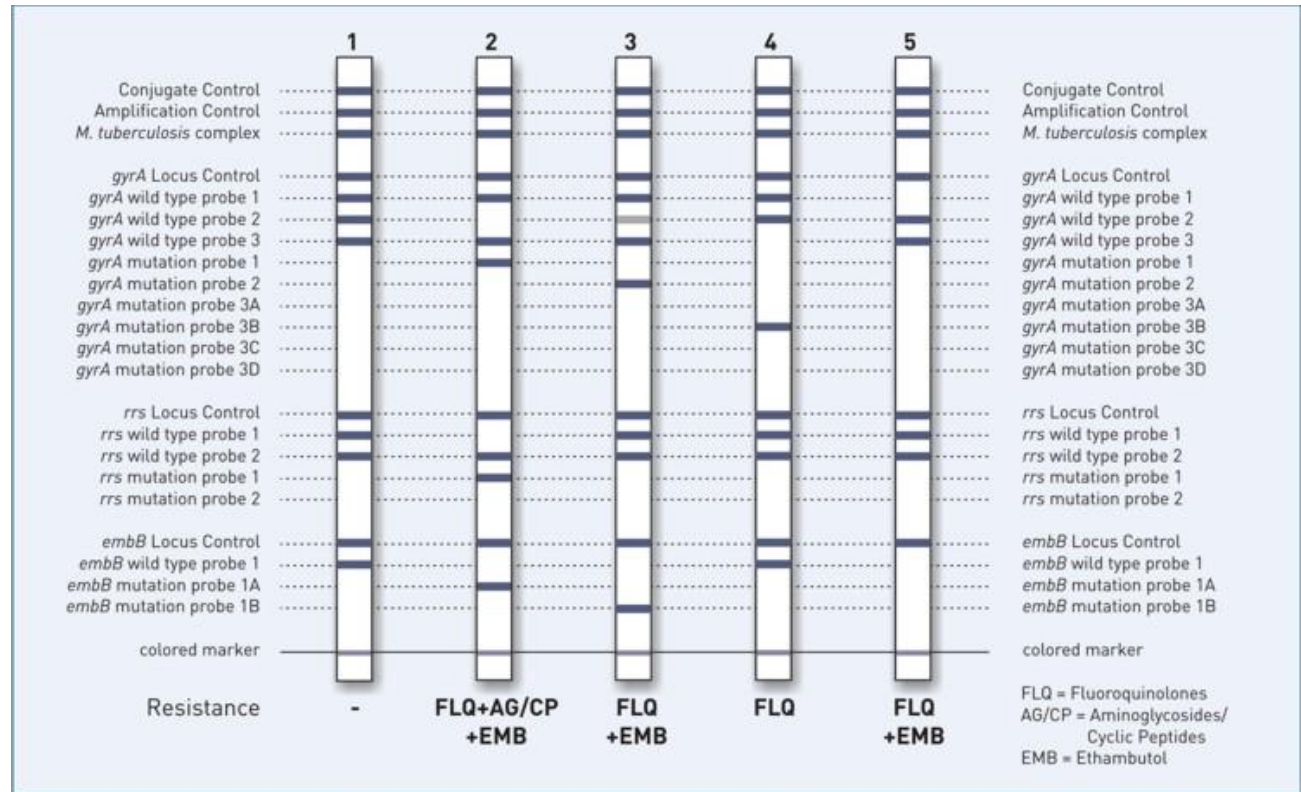New Treatments

New Political will

New Diagnostics

Some models predict the impact of an ideal new diagnostic for TB could prevent 625,000 deaths annually and have a greater impact on ID than any other single intervention

Similar impact to new vaccine or shortened course of TB therapy

Molecular diagnostics
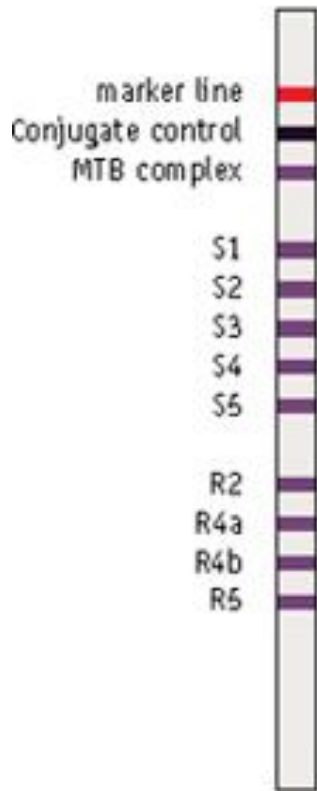


Rif.INNO.LiPa

MDR Genotyper Plus

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)

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

Source: Cepheid
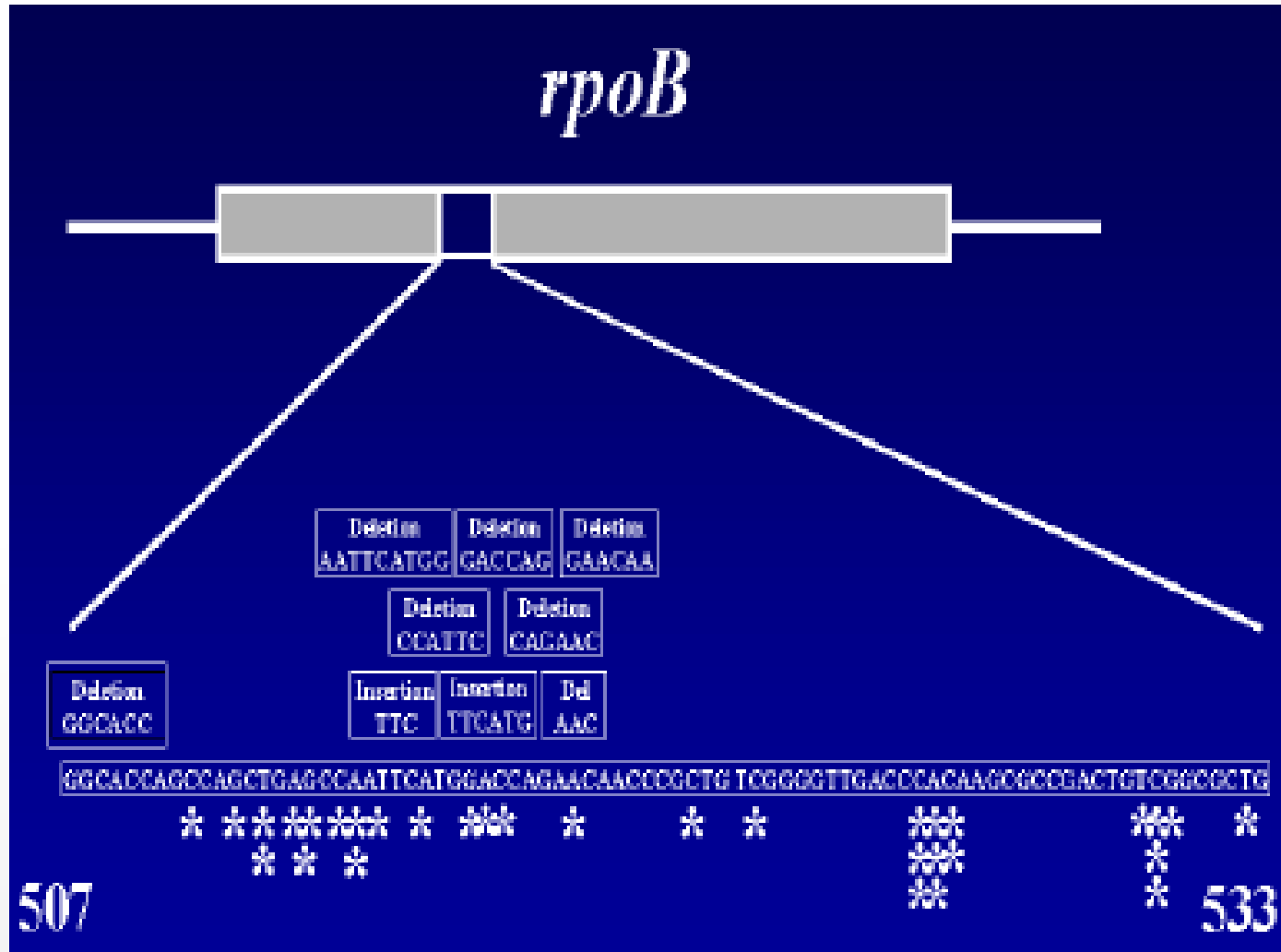
TOWARDS | LAB-FREE TUBERCULOSIS DIAGNOSIS

Hans-Georg Batz
Graham S Cooke
Steven D Reid

TAG
Treatment Action Group

TBHIV
TB/HIV Working Group
STOP TB Partnership

Imperial College London

CAMPAIGN FOR
ACCESS TO **ESSENTIAL MEDICINES**
MEDECINS SANS FRONTIERES

EXPAND-TB Initiative for laboratory infrastructure
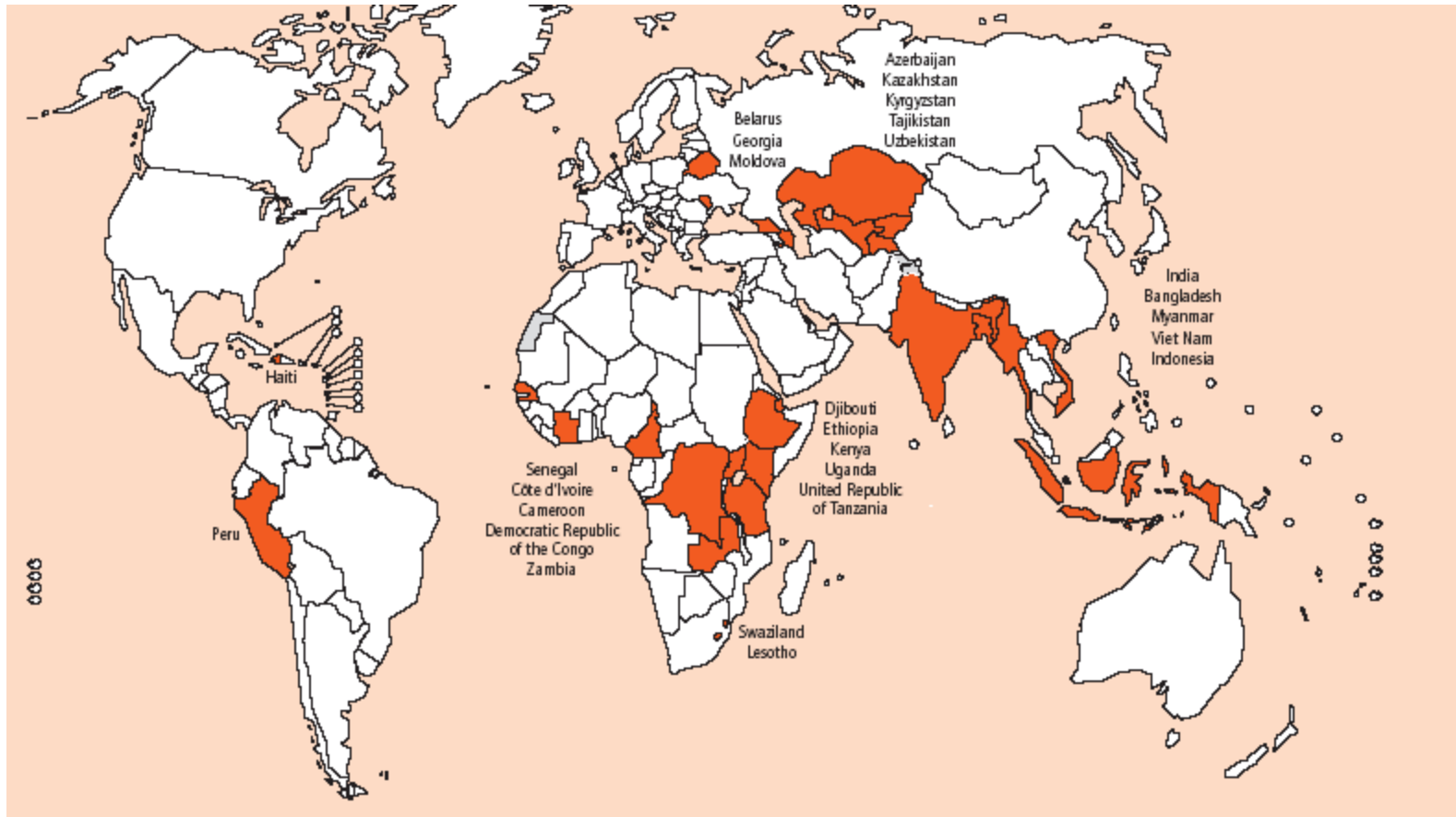
New Drugs

Drug Pipeline

Table 2
New drugs in development for treatment of TB

Stage of development	Drug candidate	Sponsor	References
Phase I clinical trials	LL-3858	Lupin Ltd.	(115, 116)
Phase I clinical trials	SQ-109	Sequella Inc.	(117–119)
Phase II clinical trials	OPC-67683	Otsuka Frankfurt Research Institute GmbH	(75, 120)
Phase II clinical trials	PA-824	Global Alliance for TB Drug Development	(121, 122)
Phase II clinical trials	TMC207	Tibotec	(84, 123)
Phase III clinical trials	Moxifloxacin	Bayer	(124, 125, 126)
		Global Alliance for TB Drug Development	
		CDC	
		University College of London	
		Johns Hopkins University	
Phase III clinical trials	Gatifloxacin	OFLOTUB	(127, 128)
		European Commission	
		WHO-TDR	
		Lupin Ltd.	

CDC, Centers for Disease Control and Prevention; WHO-TDR, WHO Special Programme for Research and Training in Tropical Diseases.

Drug Development

TMC 207

Imipenem / clavulanic acid

Phase 2 Trial of TMC207 (Diacon,09)

8 week, multi-centre, placebo controlled trial
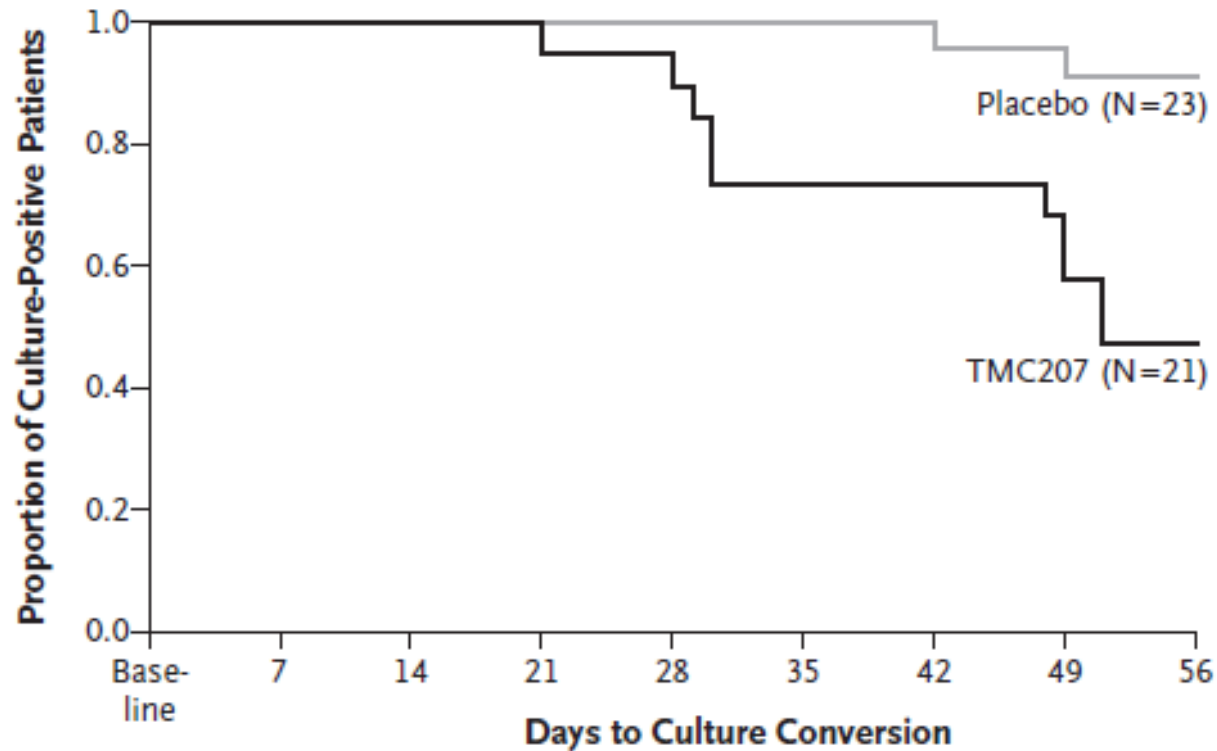
1 week lead in (TB treatment stopped)

Stratified by centre and extent of lung disease

Arm 1: TMC207 400mg od weeks 1 and 2, then 200mg 3/week
Arm 2: Placebo

Preferred background: kanamycin, ofloxacin, ethionamide, pyrazinamide and cycloserine or terizidone modified by DST
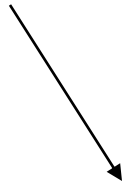
Phase 2 Trial of TMC207 (Diacon,09)
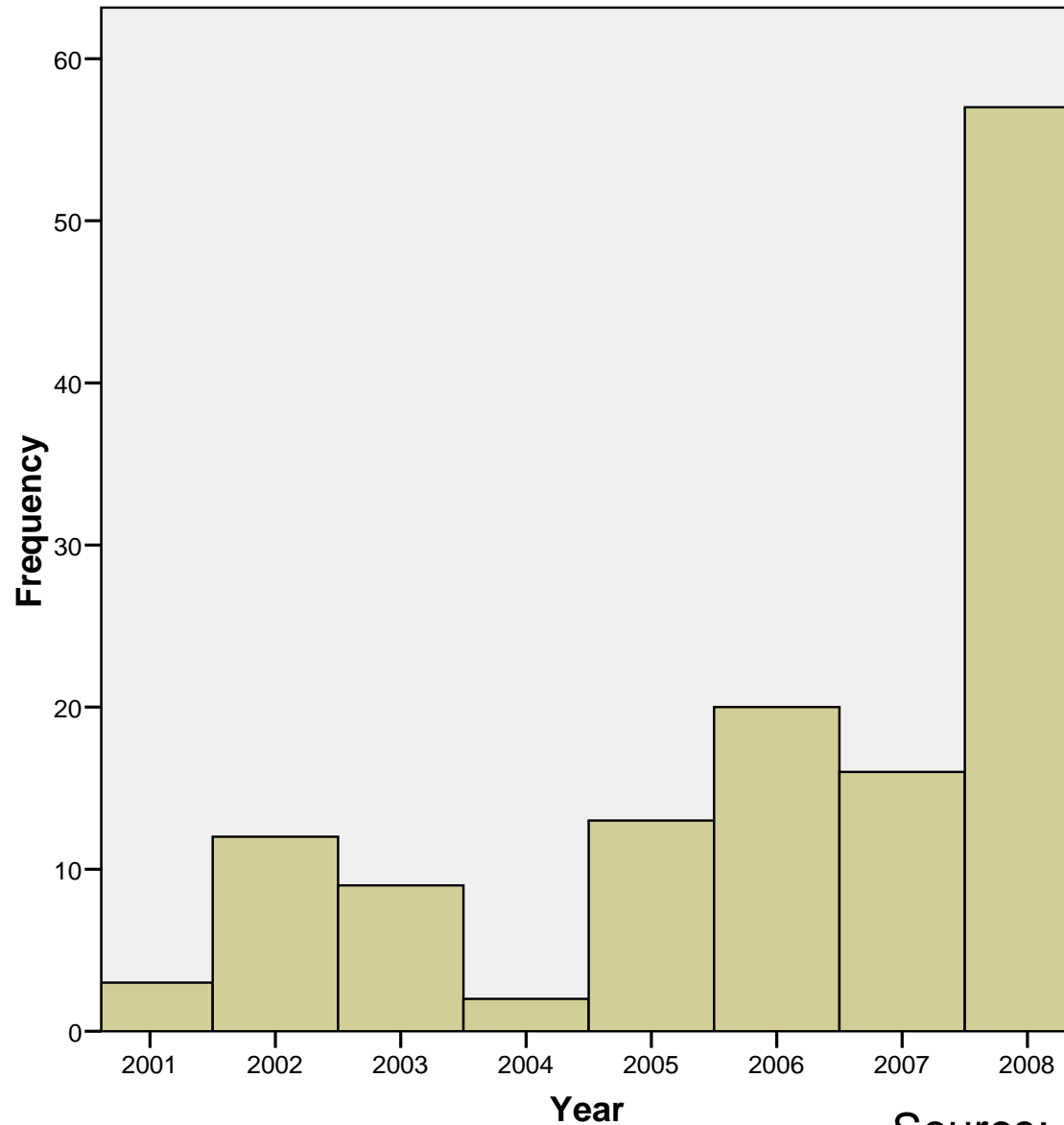

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New Treatment Strategies

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
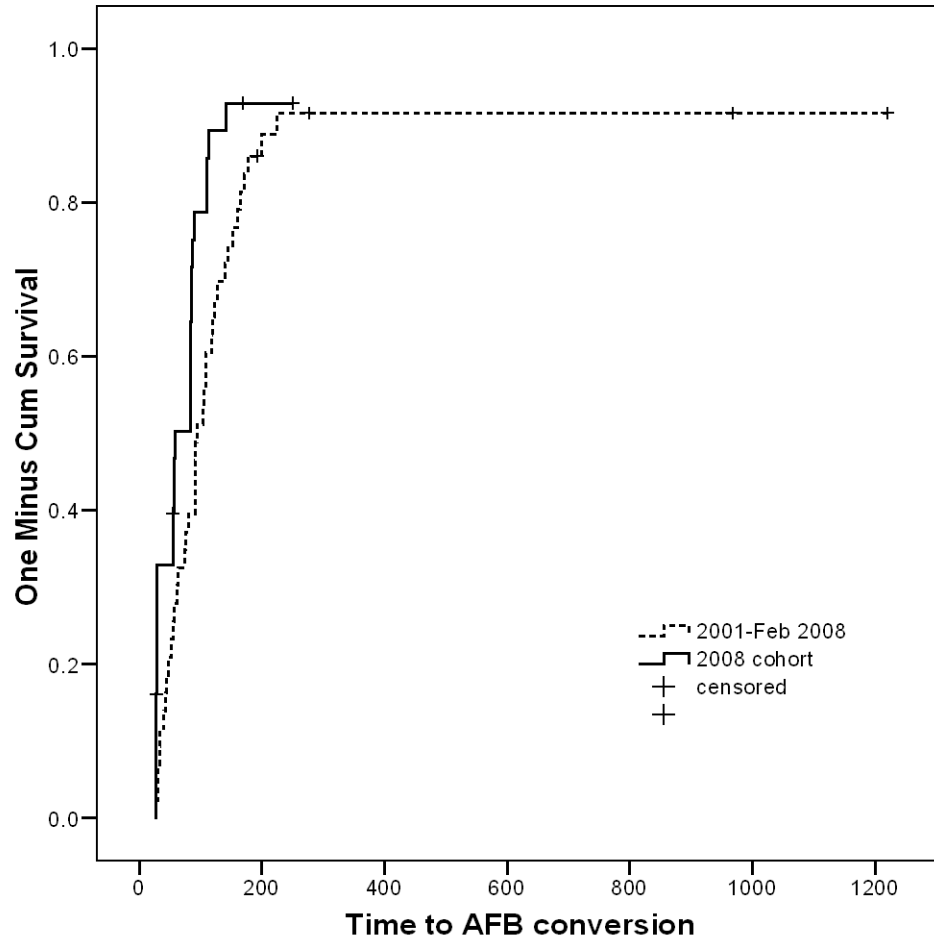
Source: Heller et al (in press)

Barriers to eliminating MDR-TB

Financing control and care

Improve financing systems to reduce costs

Improve integration with other services to implement best practice

Improve case detection and treatment

Improve TB diagnostics

Strengthen lab support for diagnosis

Restrict availability of TB drugs

Give priority to infection control, particularly in healthcare settings

Improve surveillance systems

Strengthen global health workforce

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Source Nathanson et al NEJM (2010)

Renewing Political Will

High level political meeting in Beijing (2009)

- WHO, BMGF and Chinese government

- Resolution 62.15 at WHA 2009

- 20/29 of the highest burden countries were beginning to implement new national guidelines as a result

Source Nathanson et al NEJM (2010)

Conclusions

Tuberculosis is heterogenous – there are very different epidemiological settings

MDR emerging in both HIV negative and HIV positive populations (probably increased in HIV positive populations)

Diagnostics are improving but availability still limited by costs

Treatment availability slowing expanding

XDR remains an increasing challenge

Tackling the epidemic will require new tools, more money and political motivation

Need a break?

Thank you