Tuberculosis & mycobacterial infections: recent advances and research priorities

EDCTP Stakeholder Meeting

GJ Churchyard
Aurum Institute
28th October 2013

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Overview

- Background
- Tuberculosis
  - Epidemiology
  - Drugs
  - Diagnostics
  - Vaccines
  - HDT
  - Research priorities
- Buruli ulcer
- Leprosy
- Priorities for research
- Conclusion

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Mycobacterial diseases of poverty

- Tuberculosis, leprosy and buruli ulcer are
  - Infectious diseases of poverty
  - Caused by mycobacteria
  - Treatable and preventable
  - Associated with disability and stigma
  - Require further research to reduce morbidity, stigma, mortality and burden of disease

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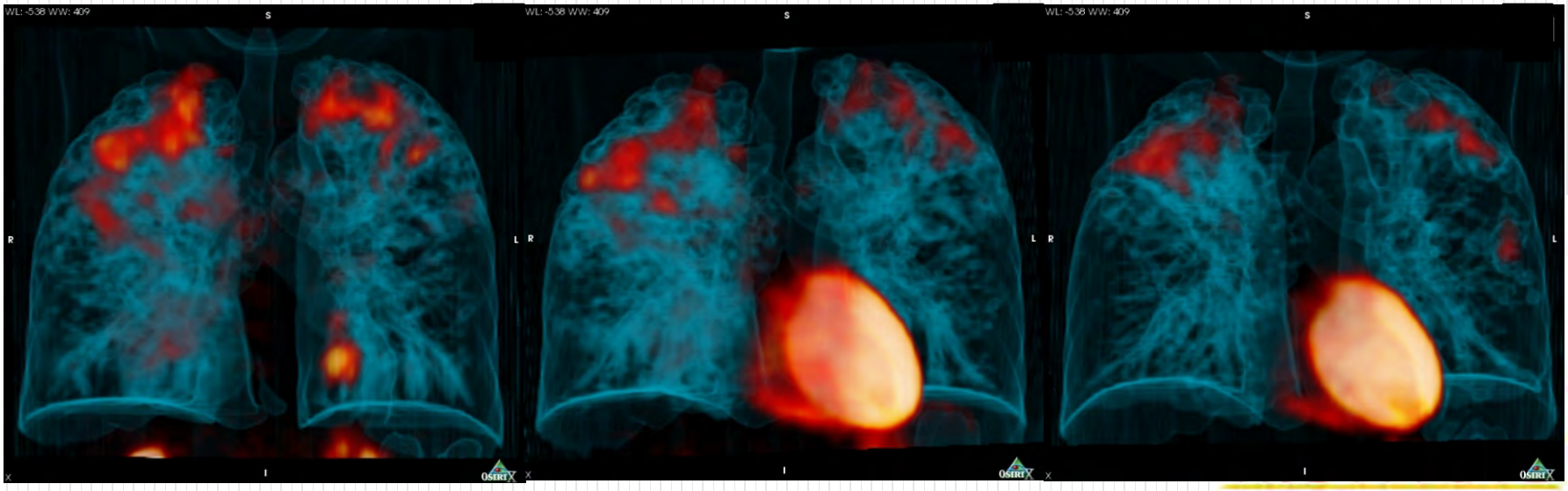
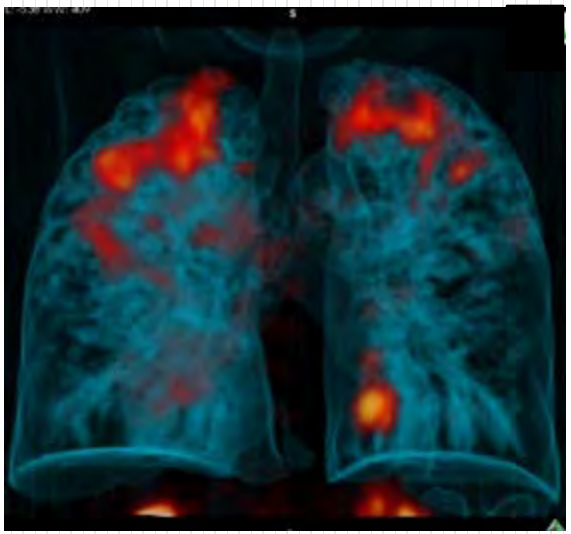
Tuberculosis



Tuberculosis



Epidemiology

Drugs

Diagnostics

Vaccines

Research priorities

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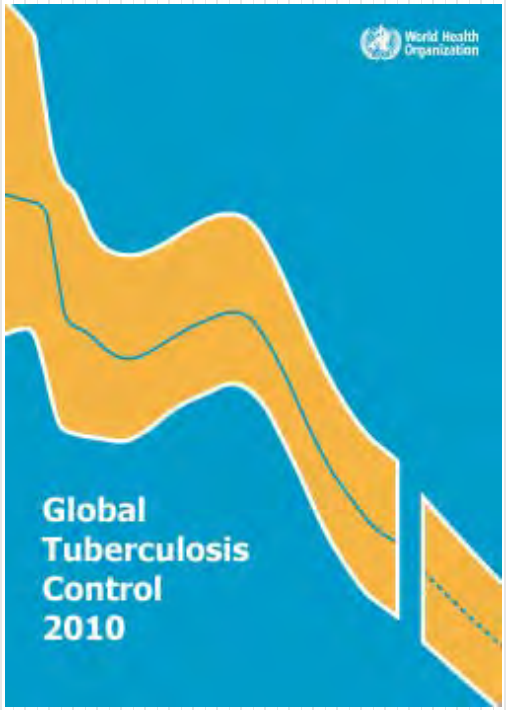
Tuberculosis



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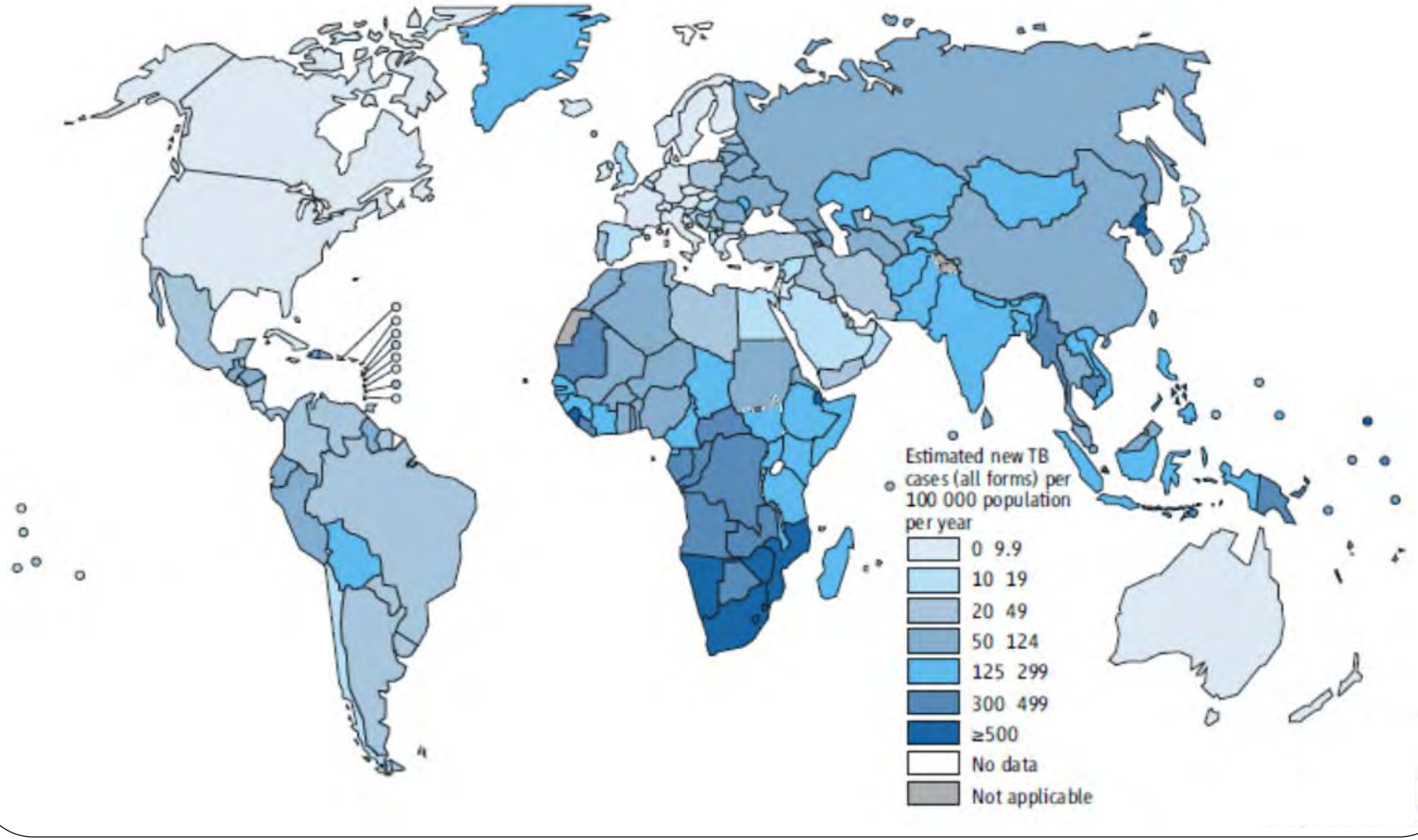
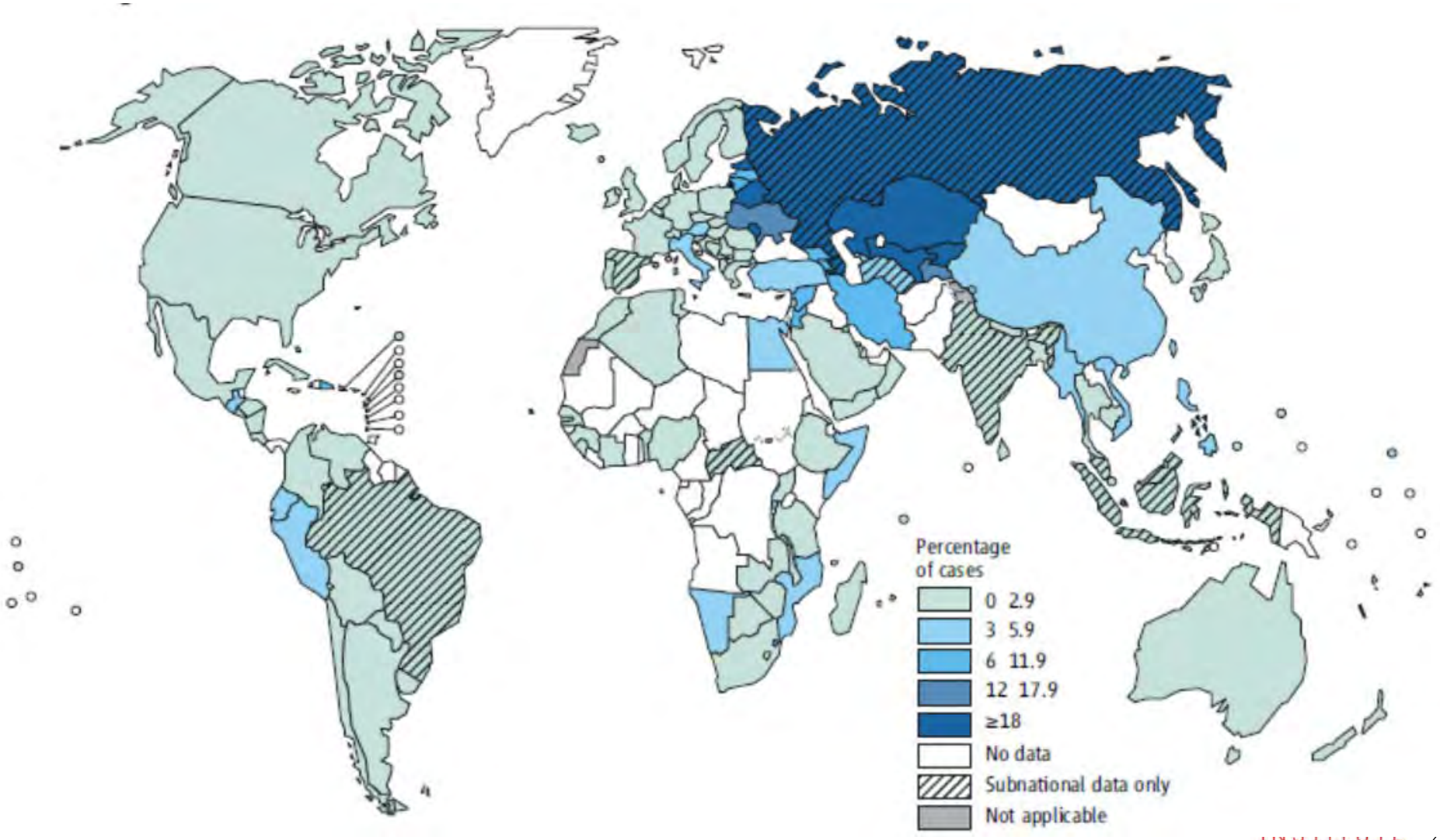
Estimated TB incidence, 2012



Proportion of new TB cases with MDR TB



MDGs and Stop TB targets

- 2015: reduce prevalence of and deaths due to TB by 50% compared to 1990 baseline

- 2050: eliminate TB as a public health problem (defined as <1 case per 1 million population per year)

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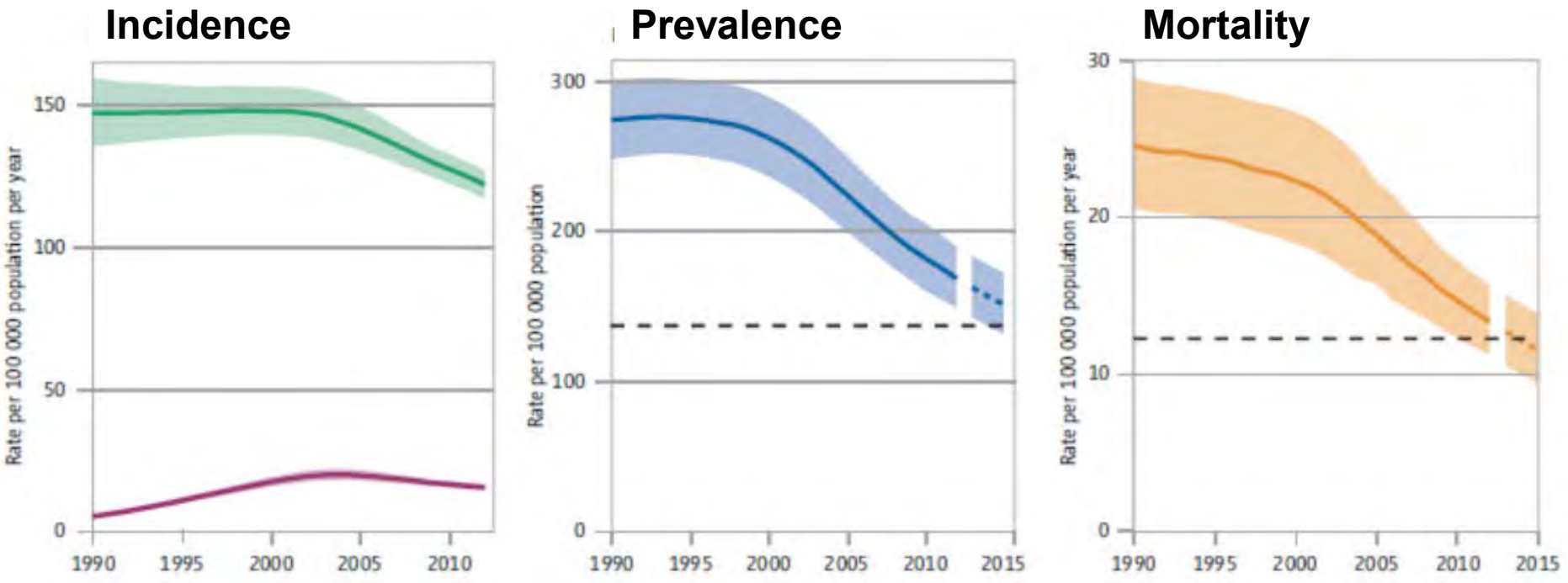
Global trends in TB



(Global TB report, 2013)

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Progress towards 2015 targets

GLOBAL	Incidence	Prevalence	Mortality
Global	Met	Not on track	On track
WHO REGION			
African (AFR)	Met	Not on track	Not on track
Americas (AMR)	Met	Met	Met
Eastern Mediterranean (EMR)	Met	Not on track	On track
European (EUR)	Met	Not on track	Not on track
South-East Asia (SEAR)	Met	On track	On track
Western Pacific (WPR)	Met	Met	Met

(Countdown to 2015. Global TB report supplement)

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- Pipeline
- Phase II studies
- Phase III studies
- PK studies
- Treatment of LTBI
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Global TB drug pipeline

Early Stage Development

- CPZEN-45
- DC-159a
- Q203
- SQ609
- SQ641
- TBI-166

GLP Tox.

- PBTZ169
- TBA-354

Phase II

- AZD5847 [N]
- Bedaquiline [N c R]
- Linezolid
- PA-824 [N c]
- Rifapentine
- SQ-109 [N]
- Sutezolid [N]

Phase III

- Delamanid [N R]
- Gatifloxacin [c]
- Moxifloxacin [c]
- Rifapentine [R]

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

[C] Drug candidate currently in combination regimen in clinical testing

[R] Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

[N] New chemical entity

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: June 2013

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TB treatment priorities

Patient Population	Vision
Drug-Susceptible TB	Shorter, simpler therapy
Drug-Resistant TB	Fully oral, shorter and safer therapy
TB/HIV co-Infection	few or no DDI with ARVs
LTBI with DS TB	Shorter, safer therapy
LTBI with DR TB	Short, efficacious & Safe

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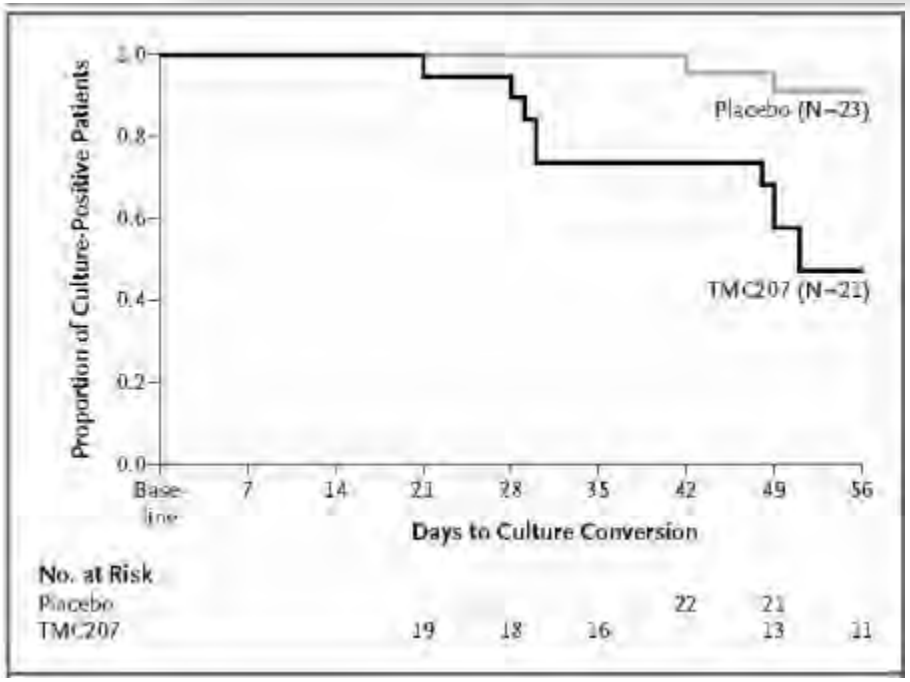
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin Grobusch, M.D., D.T.M.&H., Ramonde Patientia, M.D., Roxana Rustomjee, M.D., Ph.D., Liesl Page-Shipp, M.D., Christoffel Pistorius, M.D., Rene Krause, M.D., Mampedi Bogoshi, M.D., Gavin Churchyard, M.B., Ch.B., Amour Venter, Nat.Dip.Med.Tech.(Micro),



- Greater proportion converted their culture (48% vs 9%)
- Most AEs mild/moderate
- Unexplained deaths up to 2 years after treatment

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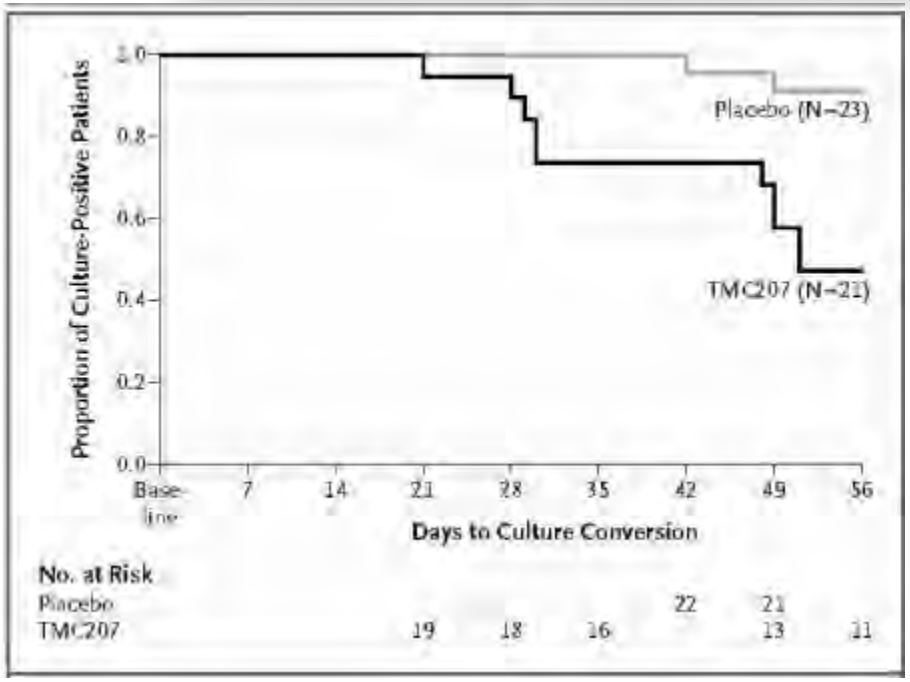

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interim policy guidance

World Health Organization

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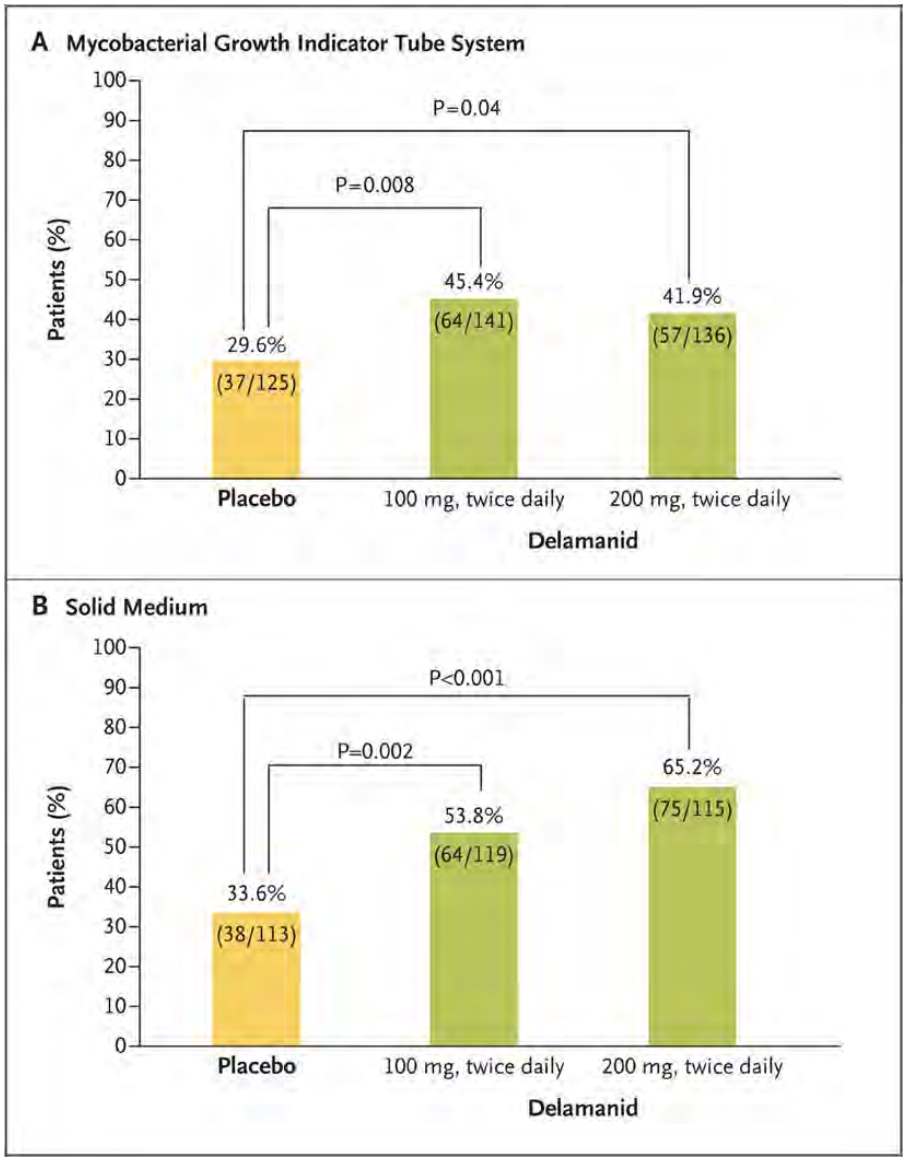
Delamanid: 8 week culture conversion rate



(Gler, NEJM, 2012)

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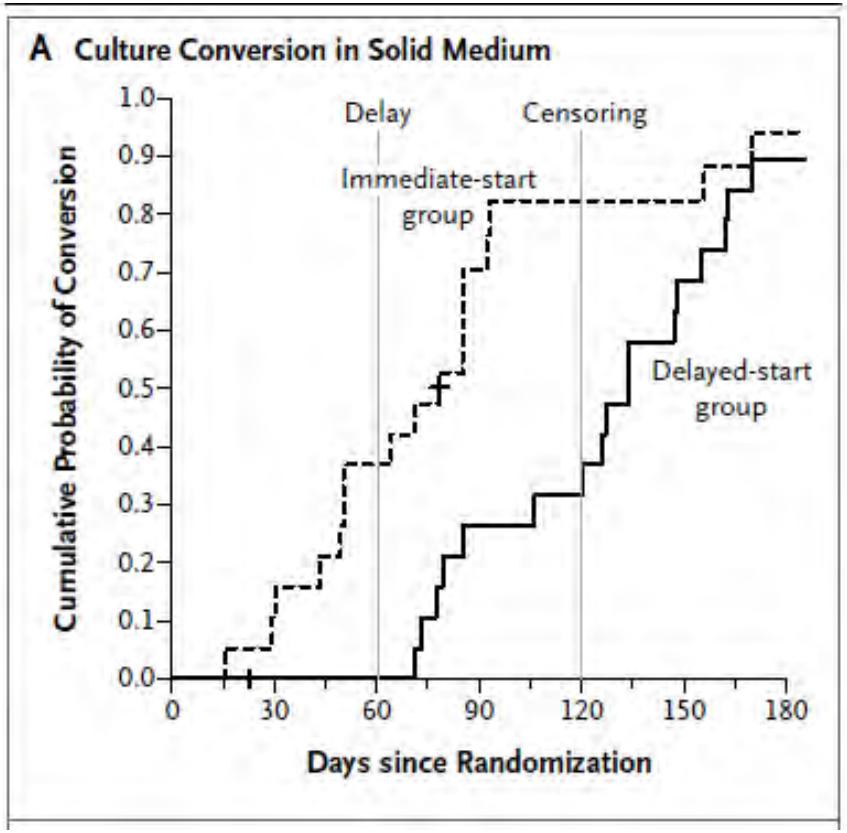
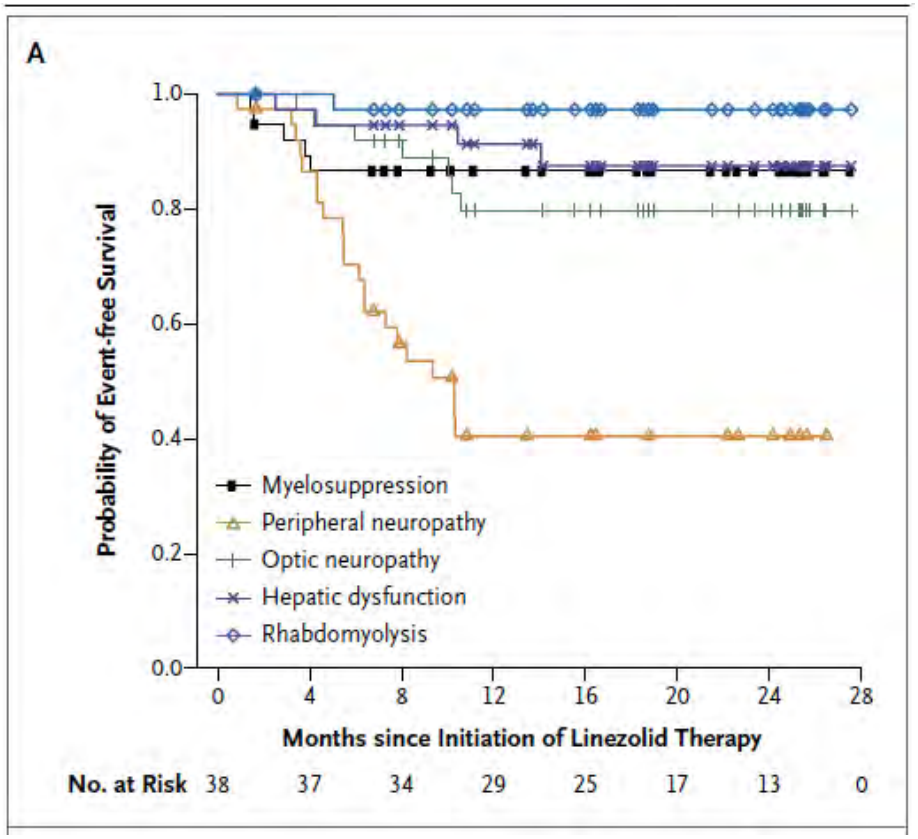
Linezolid for XDR TB





Culture conversion:
immediate vs delayed start group
79% vs 35% respectively

Clinically significant AEs observed in 82%

Lee et al. NEJM. 2012

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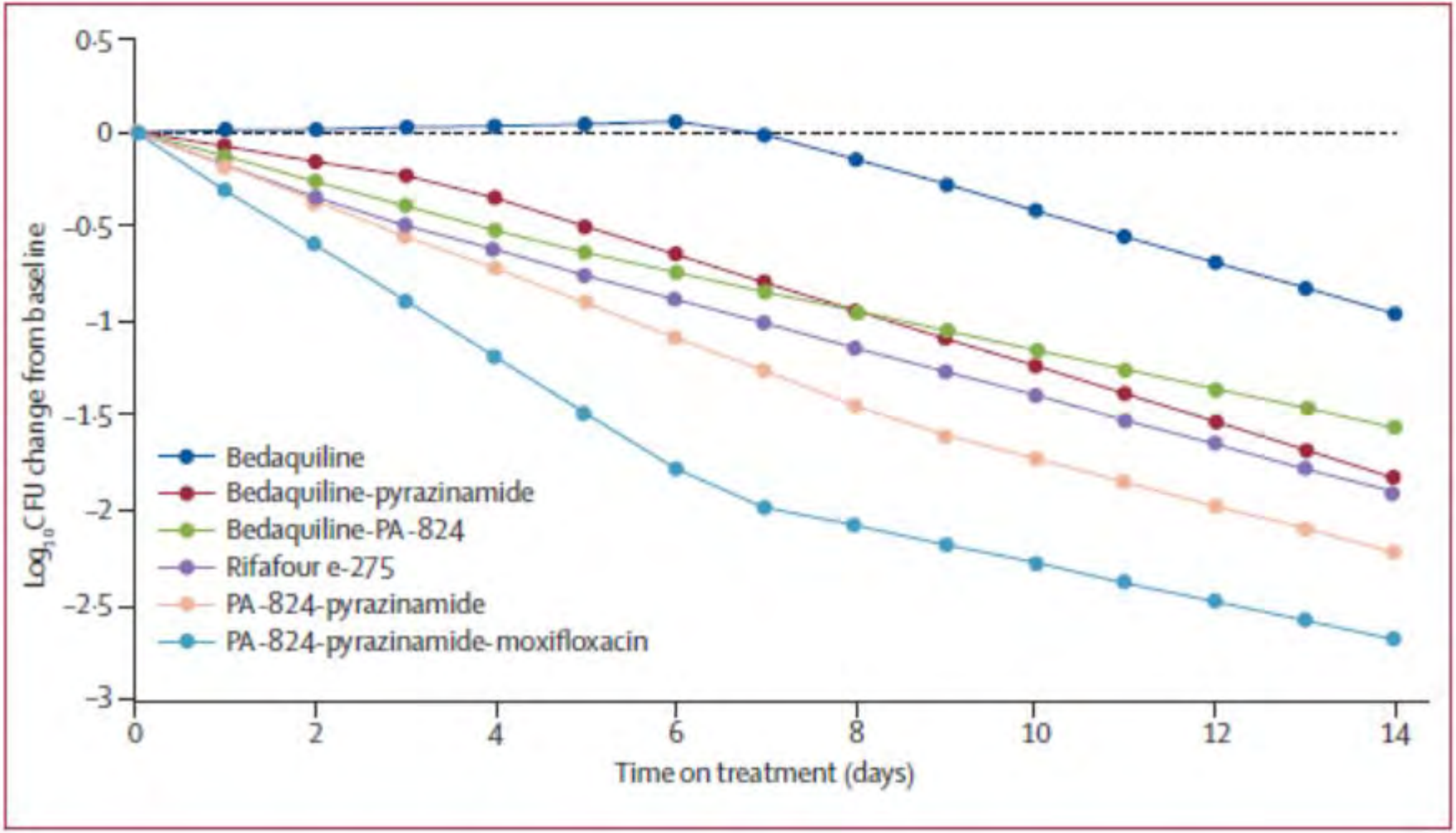
NC001: 14 day EBA of PA824, bedaquiline, pyrazinamide & moxifloxacin



(Diacon et al. Lancet. 2012)

Phase II trials

Drug	Regimen	Comment
High dose RPT (TBTC29X)	10mg, 15mg, 20mg in S+ TB patients	Safe. At highest dose 100% C- at 8 weeks Phase III trial indicated
High dose rifampicin EBA	10, 20, 25, 30 mg/kg	Well tolerated & trend towards reduced CFUs with higher doses
NC002 (8wk SSCC)	M, PA200,Z-DS TB M, PA100,Z-DS-TB M, PA200,Z-DR TB	Results will be available soon
NC003 (EBA)	Combinations of Clofazamine, bedaquiline, PA824, PZA	***Results to be presented at Union Conference***
AZD-5847	EBA	Evaluating 4 doses
MAMS-TB-01	$HRZQ_{low}$, $HRZQ_{high}$ $HR_{20}ZQ_{high}$, $HR_{20}ZM$	Enrolling

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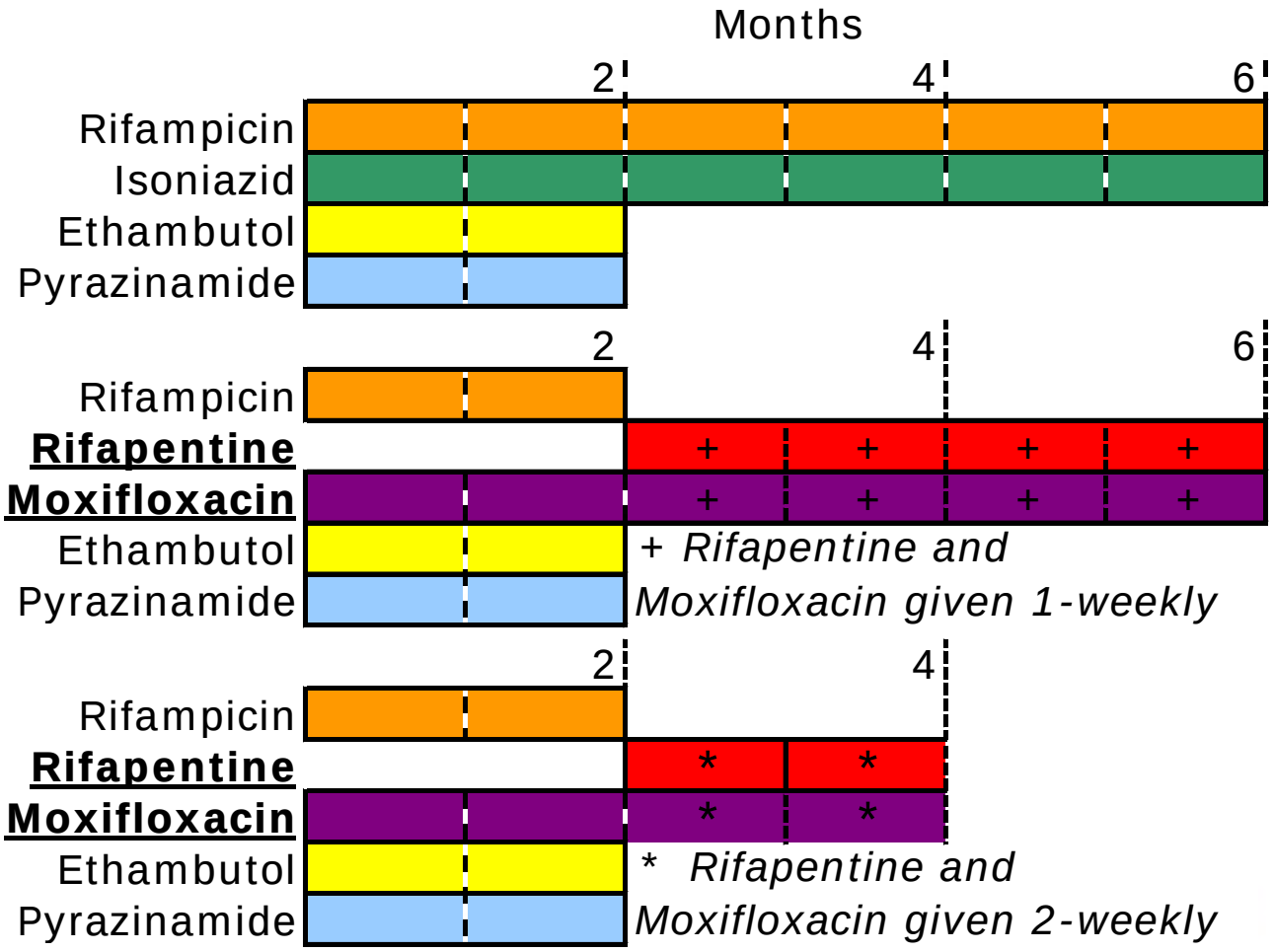
Rifaquine: study regimens



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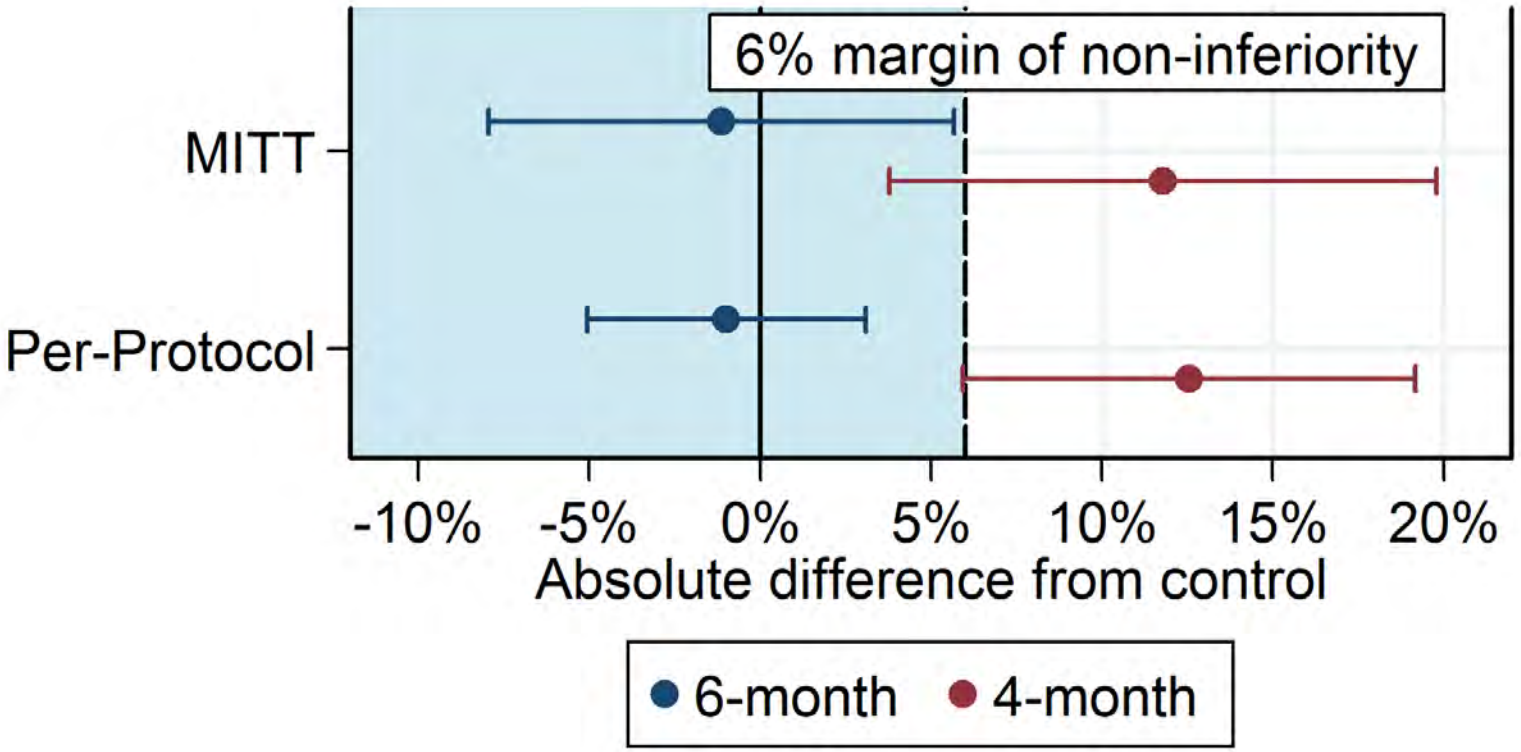
Rifaquine trial: proportion unfavourable



Phase III trials

Trial	Regimen	Comment
Oflotub DS TB	2RHGZ/HR	***LB presentation at Union conference***
ReMOX DS TB	2RMEZ/4HR 2RHMZ/4HR	*Results soon*
Delamanid MDR TB	OBR+OPC-67683/placebo (6m)	MDR TB Enrolling
Bedaquiline MDR TB	Short BR + TMC207 /placebo	Entire Rx duration
STREAM MDR TB	Mox, CLO, Eb, PZA, INH, Prot, Kanamcyin	Compared to standard Enrolling

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Nelson Mandela

"Today we are calling on the world to recognize that we can't fight AIDS unless we do **much more to fight TB as well**"

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Drug interactions with ART

- **Delamanid** has lower DDI risk
  - must be taken twice a day
- Sutezolid: not tested with ART
- EFV ↓ BDQ conc. by > 20%
- EFV ↓ PA-824 conc.by ~30%
- Enzyme induction by high-dose rifampin or rifapentine may be similar to standard-dose rifampin

(Source: Kelly Dooley)

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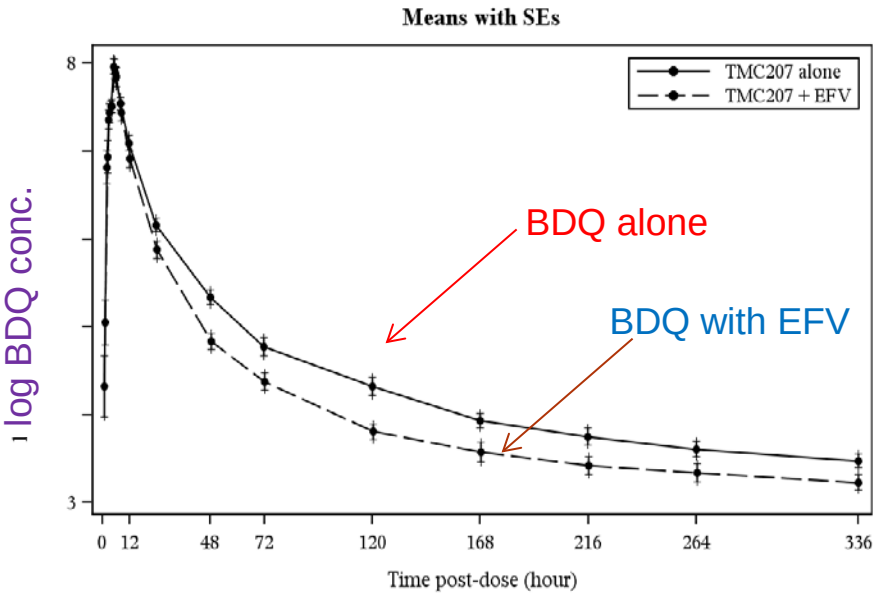

Time after dose (hours)

(Source: Kelly Dooley)

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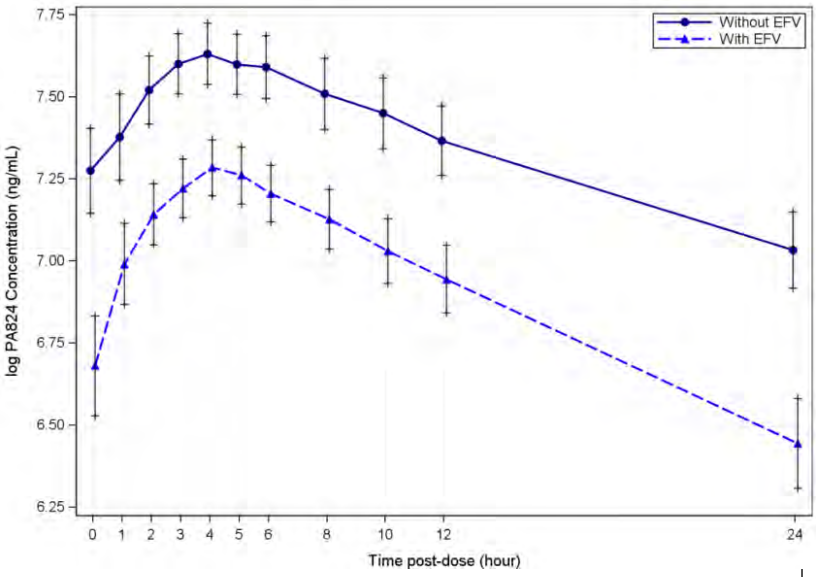
CROI2013, Poster 188LB



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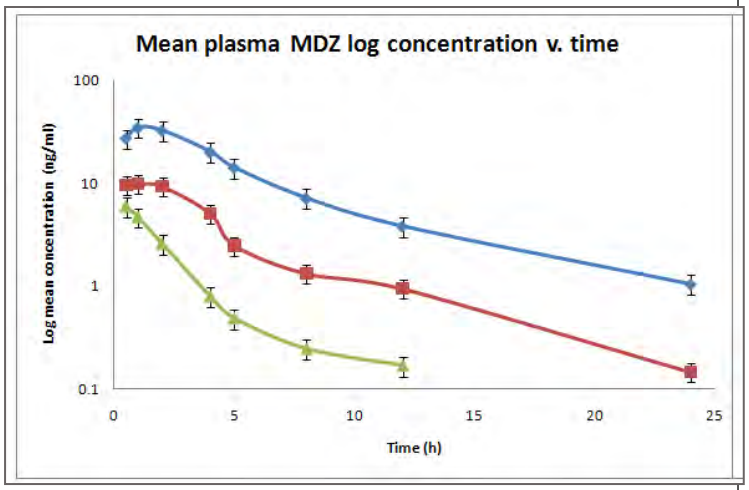
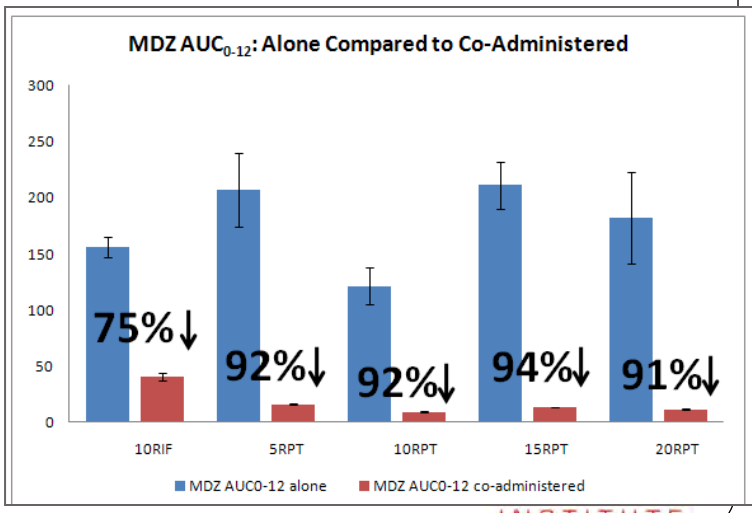


TBTC Study 29B: Dooley *et al.* (2012)



(Source: Kelly Dooley)

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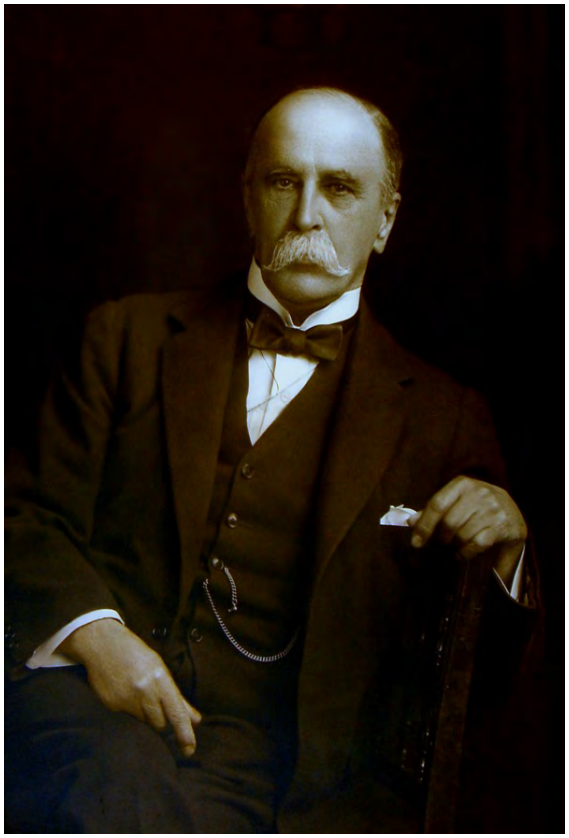
William Osler
A Canadian Physician in the 1800



“All who mix with tuberculosis patients got infected, but remained well so long as they took care of themselves and kept the soil in a condition unfavourable for the growth of the seed.”

Continuous IPT results in durable reduction in TB risk, while taking it

Author	Location	Intention to treat	Per Protocol
Martinson	S. Africa		
TST+		26%	58%*
Samandari	Botswana		
All		43%	
TST+		74%	100%
TST-		25%	

(Martinson NEJM. 2011; * Reduction for TB & deaths) (Samandari Lancet. 2011)

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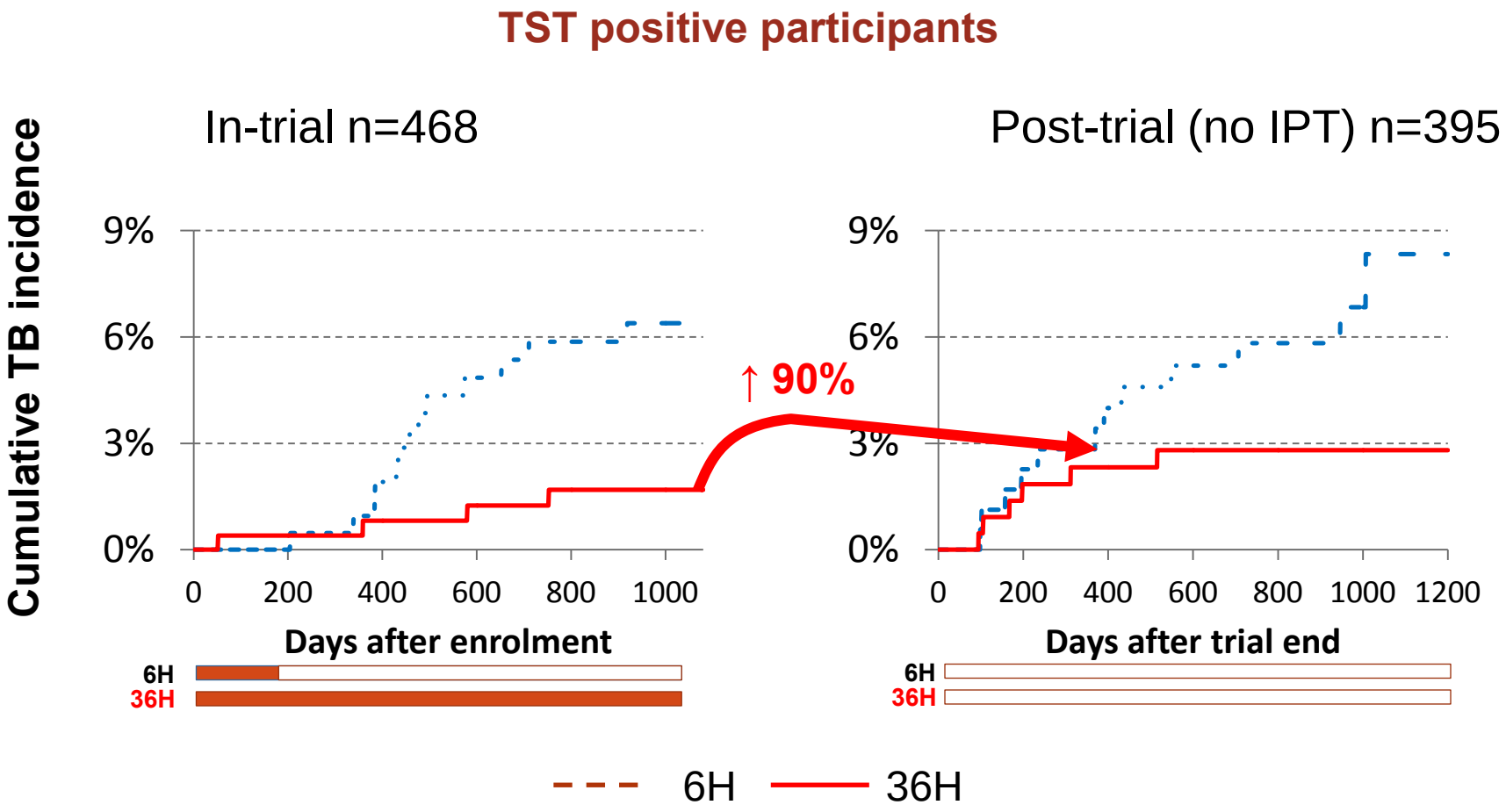
(Martinson NEJM. 2011; * Reduction for TB & deaths) (Samandari Lancet. 2011)

TB rates increase soon after stopping IPT

6H vs 36H in PWHIV in Botswana



(Samandari, CROI2012)

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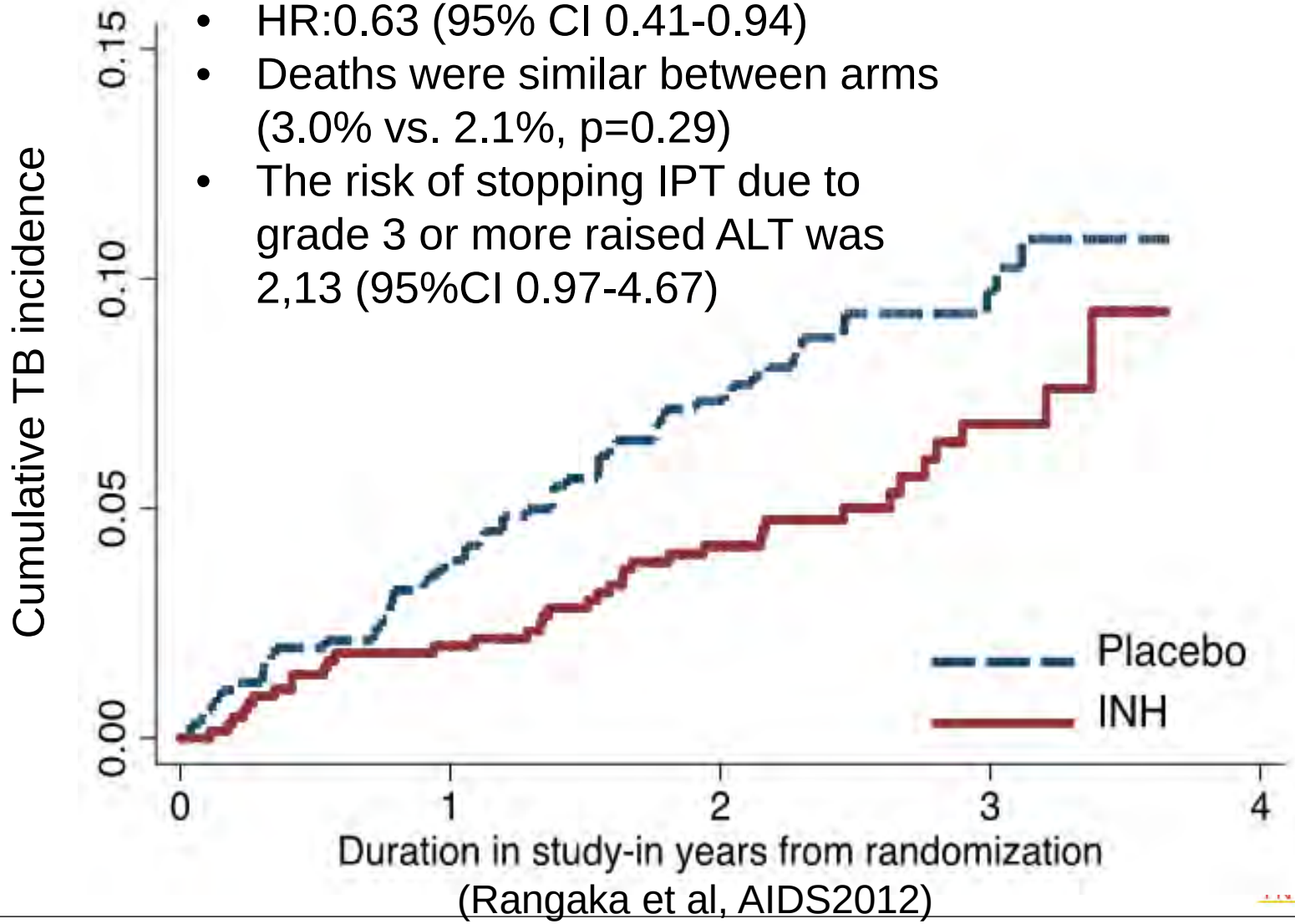
IPT with ART: a randomised controlled trial

South Africa

- HR:0.63 (95% CI 0.41-0.94)
- Deaths were similar between arms (3.0% vs. 2.1%, p=0.29)
- The risk of stopping IPT due to grade 3 or more raised ALT was 2,13 (95%CI 0.97-4.67)



(Rangaka et al, AIDS2012)

IPT with ART: a randomised controlled trial in South Africa

Effect of IPT with ART by TST or IGRA status

	TB rates (100 person years)		Adjusted HR
	Placebo	INH	(95% CI)
TST positive	2.8	2.6	0.86 (0.37-2.0)
TST negative	4.1	1.7	0.43 (0.2-0.86)
IGRA positive	3.9	3.0	0.55 (0.26-1.24)
IGRA negative	3.4	1.7	0.43 (0.2-0.96)

(Rangaka. Poster 189LB)

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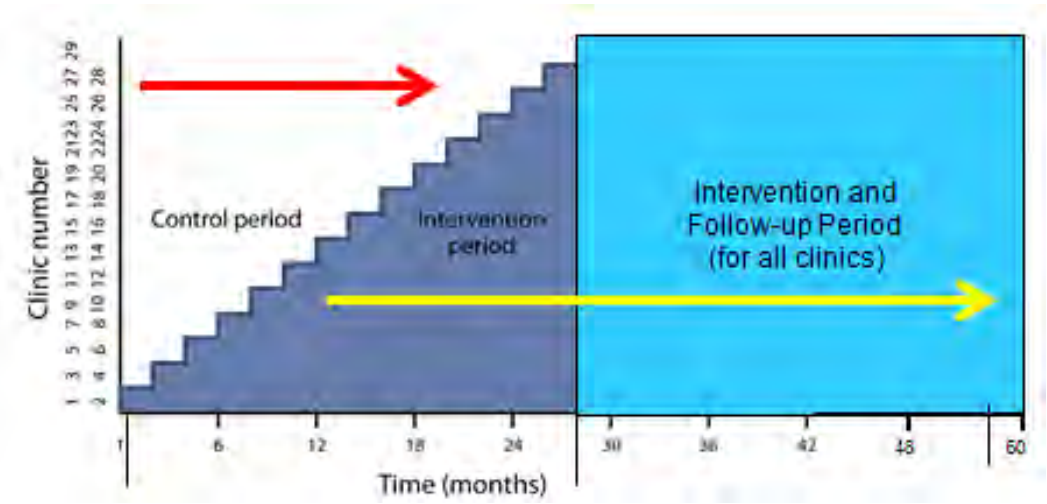
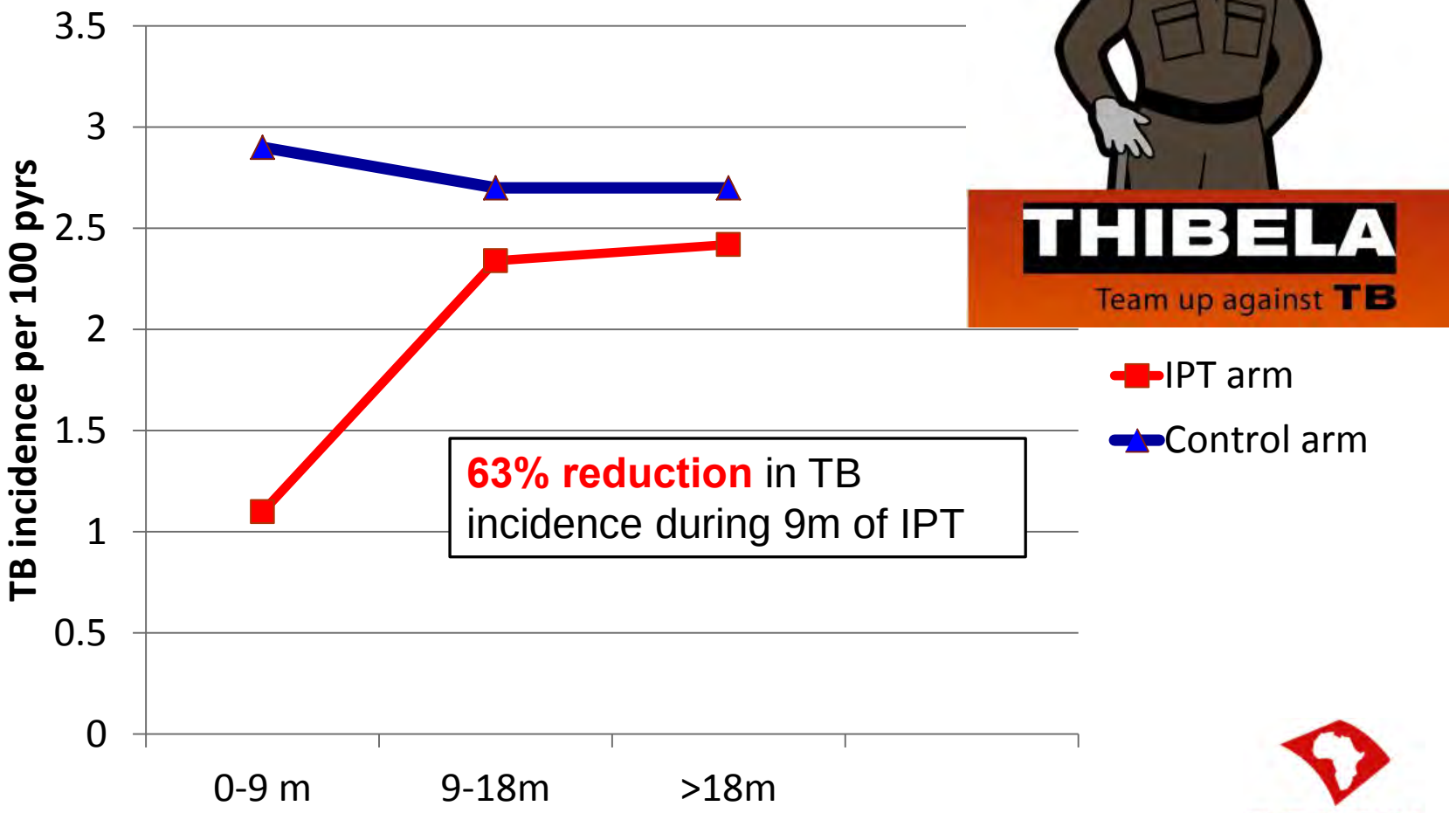
IPT promotion in 29 HIV clinics in Rio de Janeiro, Brazil reduced TB incidence/death at a clinic-level

		% reduction	HR (95% CI)	p-value
Primary Analysis	TB	475	0.87 (0.69-1.10)	0.24
	TB/Death	1313	0.74 (0.64-0.85)	< 0.001



Thibela TB: duration of IPT effect at individual level



(Fielding CROI 2012)

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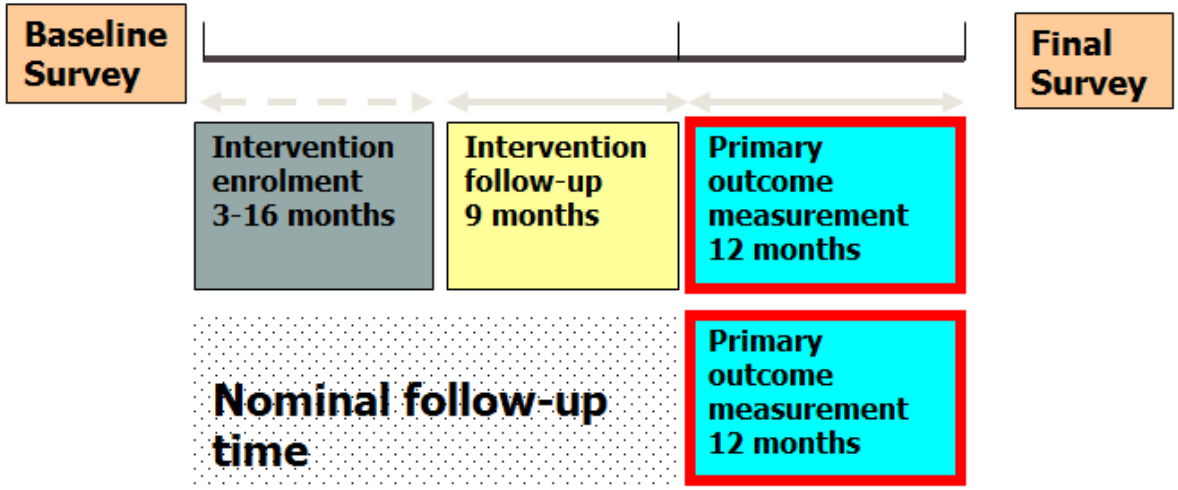


Effectiveness

TB incidence

Among <u>employees</u> in the primary outcome measurement

	TB	Person years	Rate/100 pyo
Intervention	887	29,352	3.02
Control	856	29,015	2.95

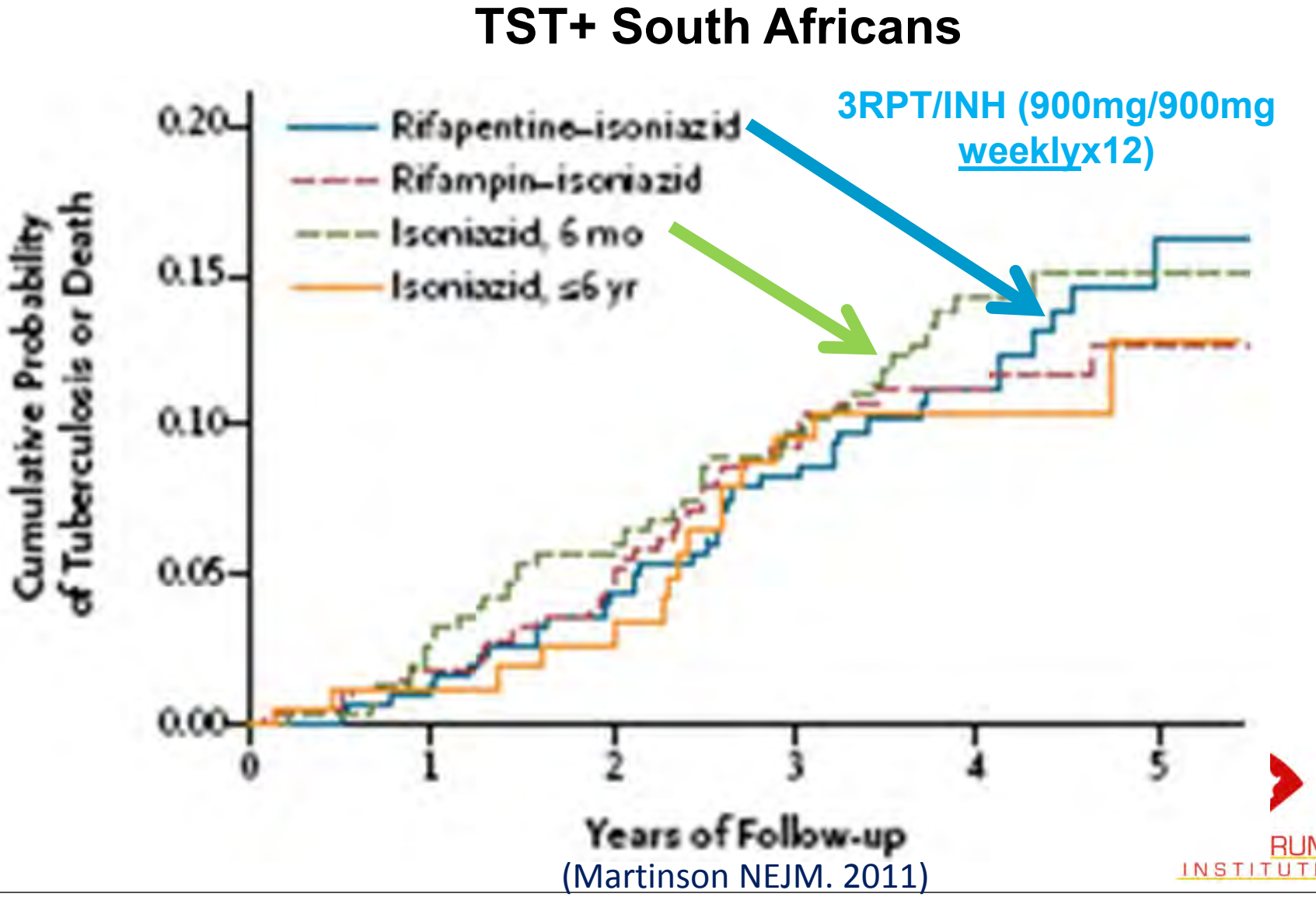
Incidence rate ratio

Unadjusted 1.00 (95% CI 0.75-1.34)

Adjusted* 0.96 (95% CI 0.76-1.21)

*Adjusted for individual level variables gender, age, surface/underground work, and cluster level variables of silicosis and ART prevalences TB case notification rate 12-months prior to cluster enrolment and pre-randomisation strata

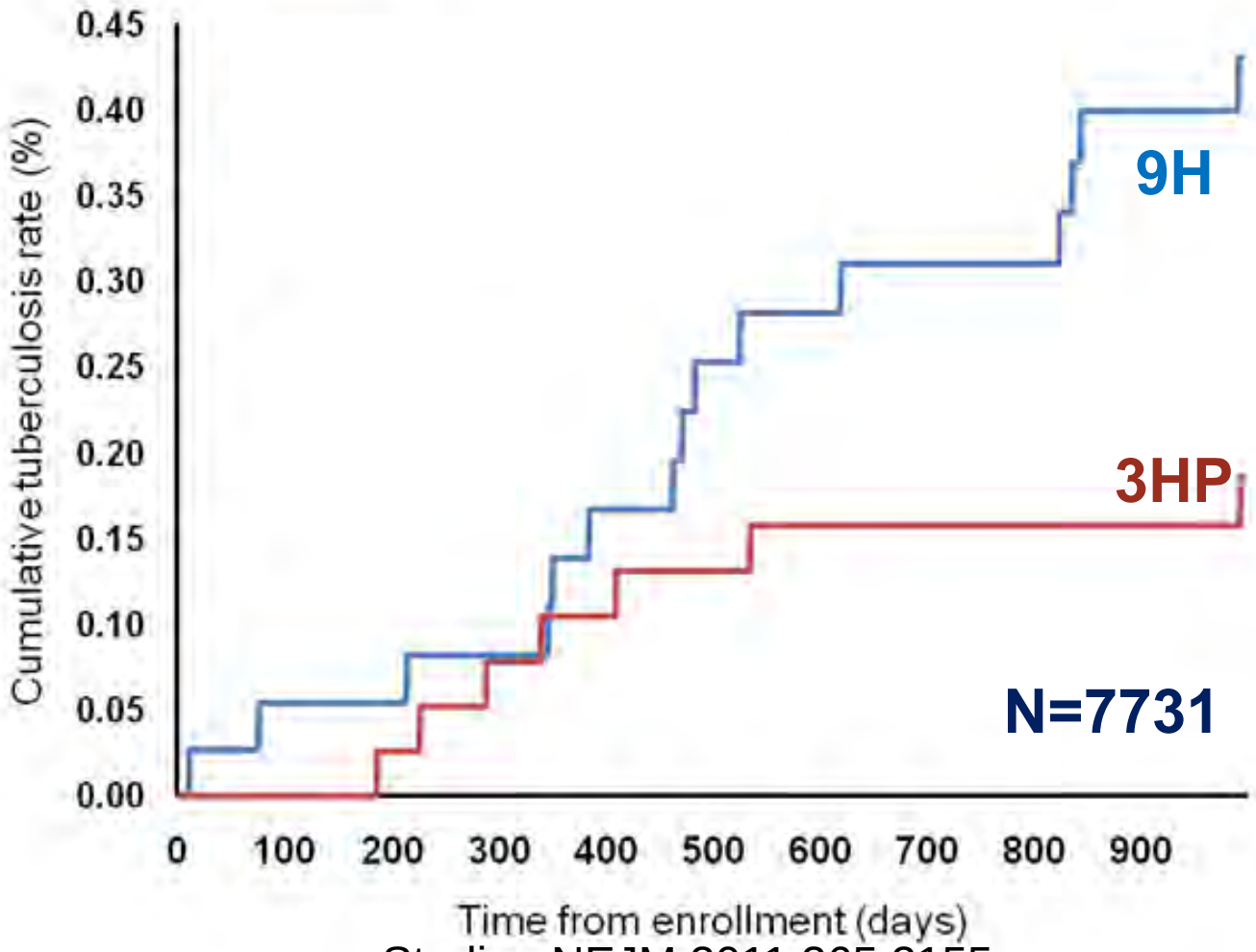
Short course rifamycin based regimens have similar efficacy as 6-months IPT in PWHIV



(Martinson NEJM. 2011)

Weekly high dose 3HP is non-inferior to 9H

Study 26: High risk persons in US, Canada, Brazil & Spain



Sterling NEJM 2011;365:2155

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Weekly high dose 3HP vs. 9H in HIV-infected persons not on ART

(N=393)

- In study 26, only 3% of participants were HIV+
- Enrolment of HIV+s extended to assess tolerability
- In MITT analysis, participants receiving 3HP
  - Had higher completion rates (89% vs 65%, p=0,04)
  - Fewer AEs (≥1) (22 vs. 40%; p=0.004)
  - Less hepatotoxicity (2% vs. 6%; p=0.03)

(Sterling et al, AIDS2012, MOAB0302)

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Rifapentine preventive therapy trials

- Study 33 (iAdhere) 3HP given by DOTS, Self-administered, self-administered with SMS reminder
- A5279.
  - A phase III trial of daily RPT and INH for one month among PWHIV and LTBI in HBCs
  - No PK issues noted with concomitant RPT & EFV
- Sanofi (NCT01690403)
  - PK study of rifapentine on Atripla in HIV+s

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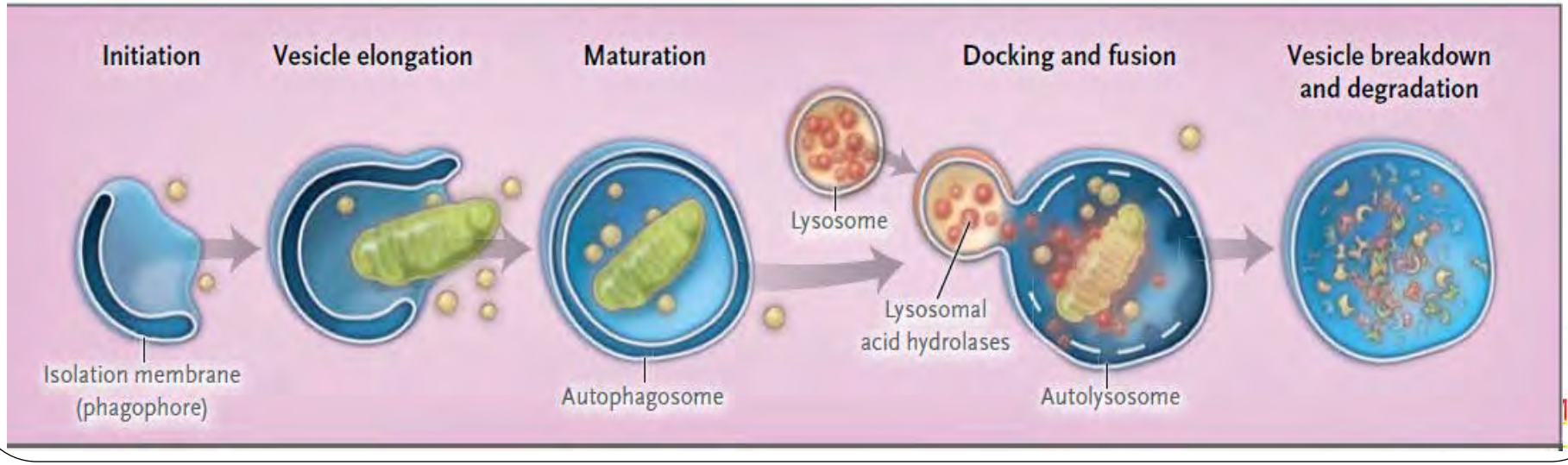
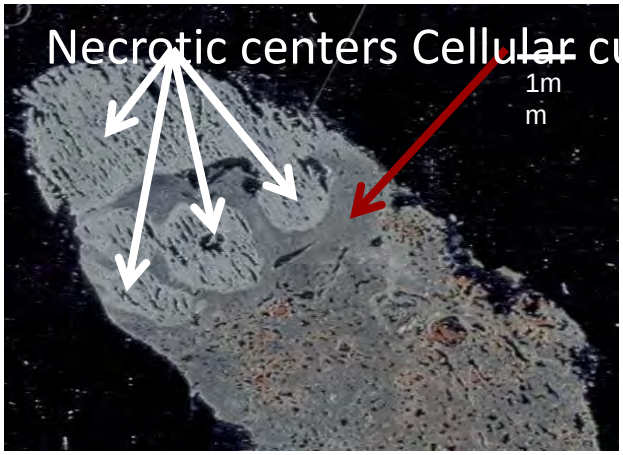
HDT: mechanisms of actions

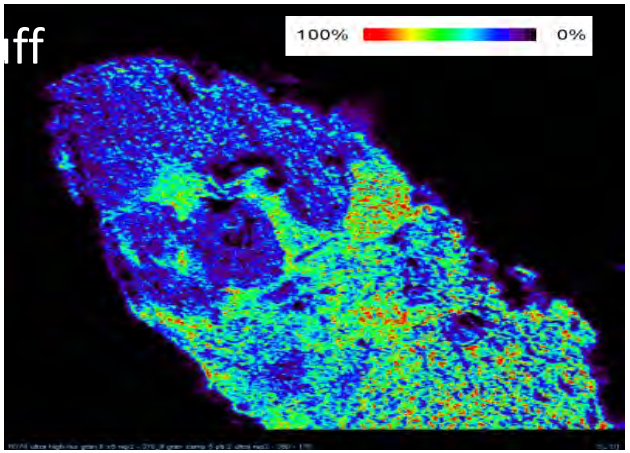
- Enhance protective immunity
- Facilitate access or activity of chemotherapeutic agents to the bacilli, by disrupting bacteriostatic pathways or fibrosis
- Enhance autophagy



Role of adjunctive HDT

- Shortening the duration of TB treatment
- Improving treatment success of DS & DR TB
- Reducing clinical complications
- Reducing rate of recurrent TB





(Source: R Wallis)

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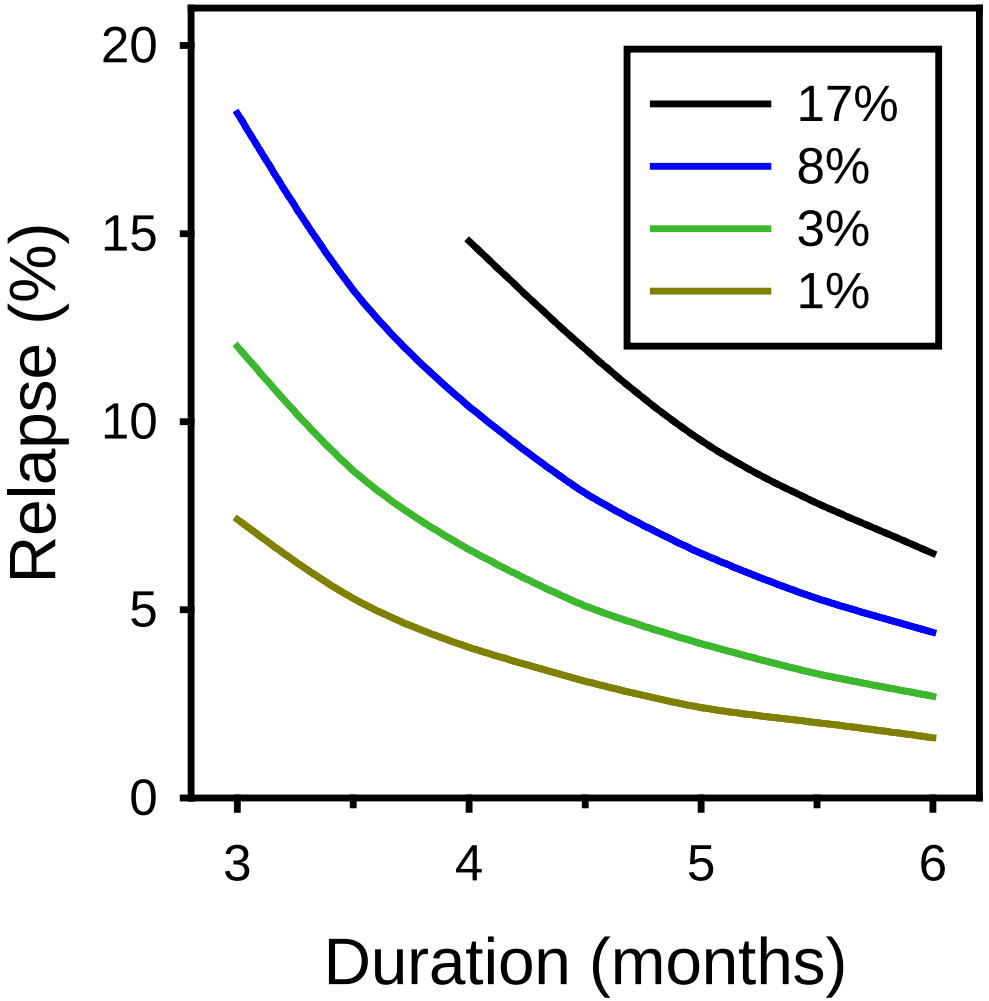
Month 2 culture status and duration
as predictors of relapse



Wallis, ***PLoS ONE*** 2013

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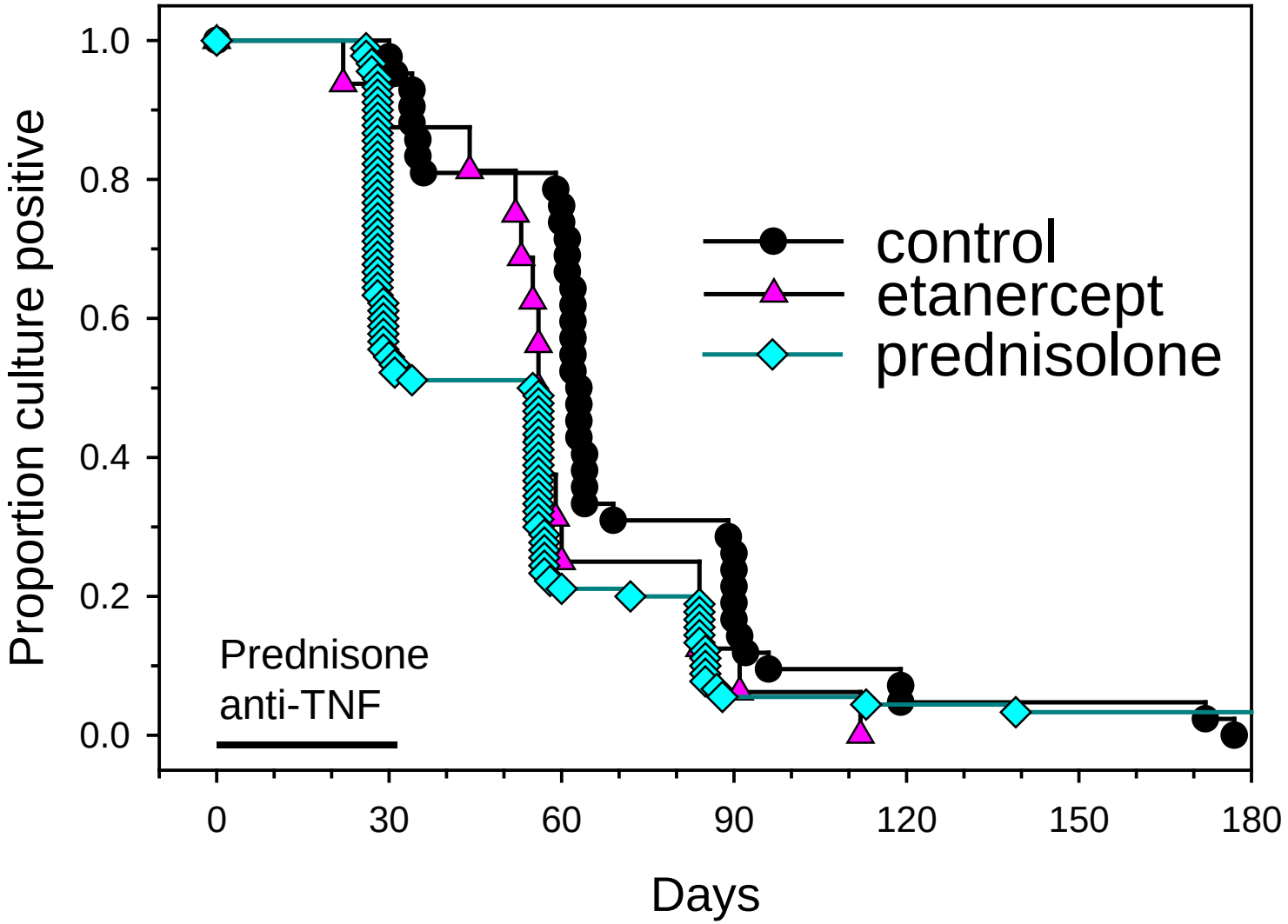
Acceleration of TB culture conversion by anti-TNF therapy



Wallis, ***CID*** 2005;41:201

Tuberculosis

Epidemiology

Drugs

Diagnostics

Vaccines

Research priorities

- Pipeline
- WHO endorsed
- WHO not endorsed
- Early development
- Point of care

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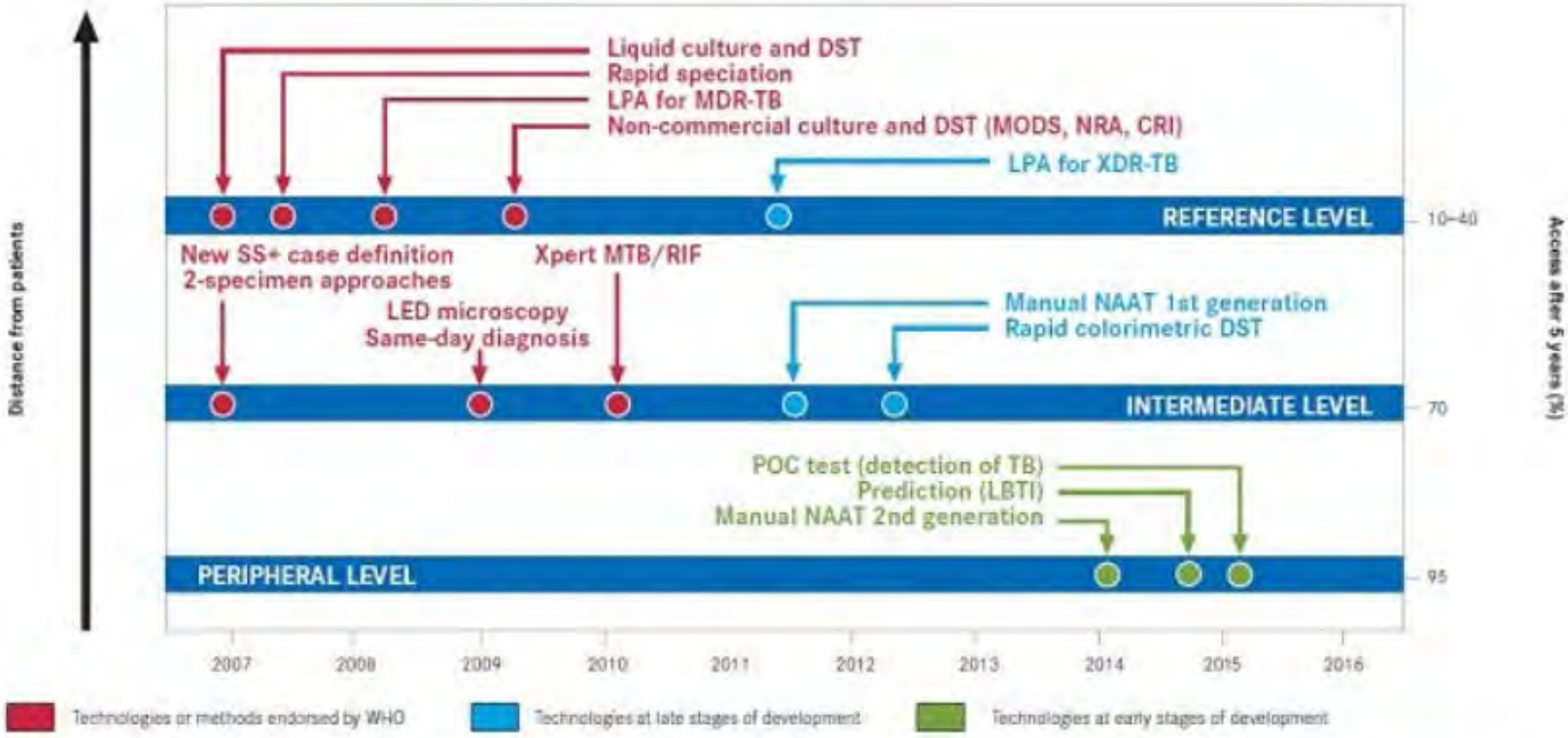
Global TB diagnostics pipeline



Abbreviations: **DST** Drug susceptibility test; **NAAT** Nucleic acid amplification test; **LTBI** Latent TB infection; **POC** Point of care; **MODS** Microscopic observation drug-susceptibility; **NRA** Nitrate reductase assay; **CRI** Colorimetric redox indicator assay; **LED** Light-emitting diode; **LPA** Line probe assay

Source: WHO Global TB Report 2011

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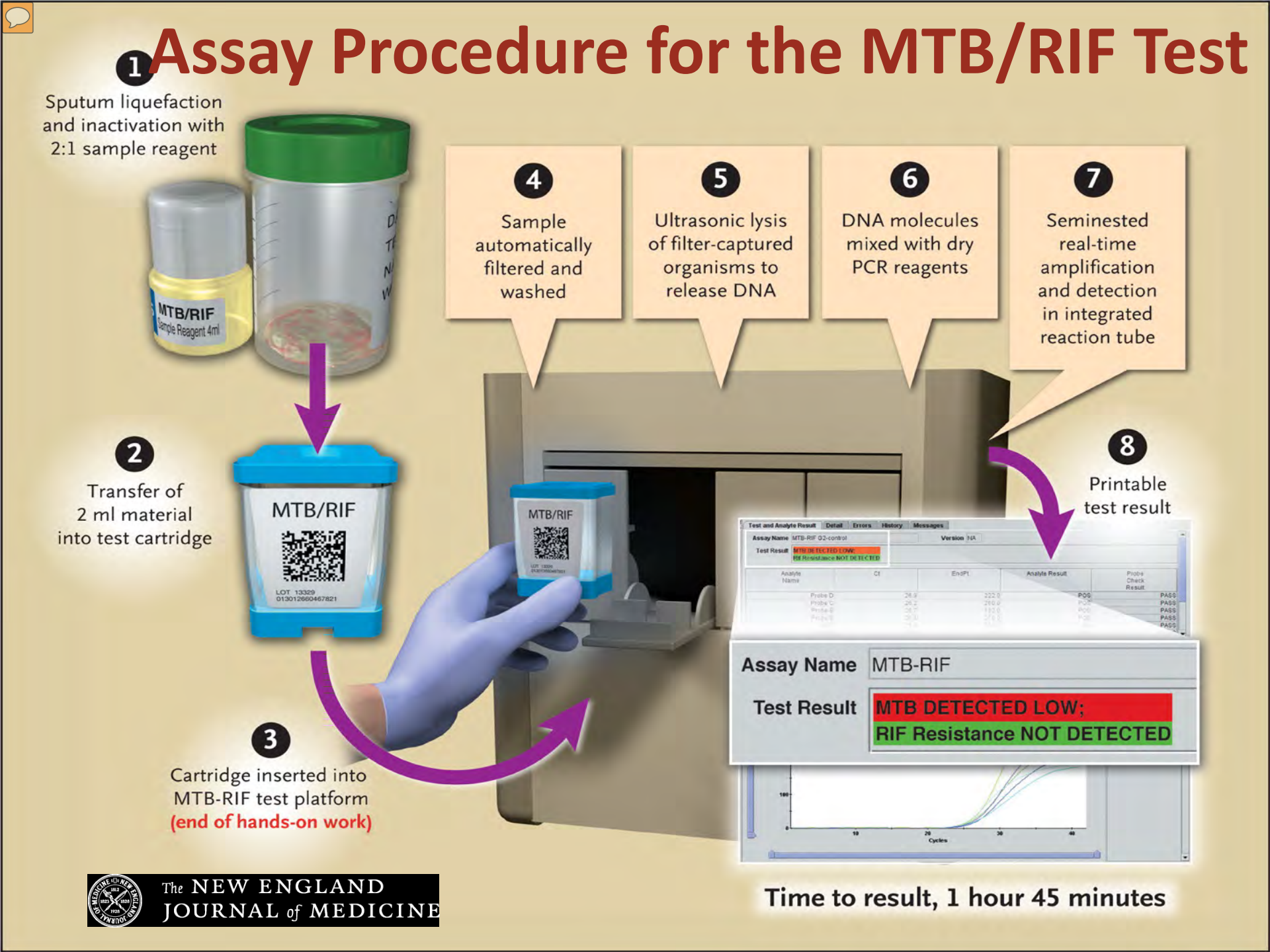
Assay Procedure for the MTB/RIF Test



Time to result, 1 hour 45 minutes

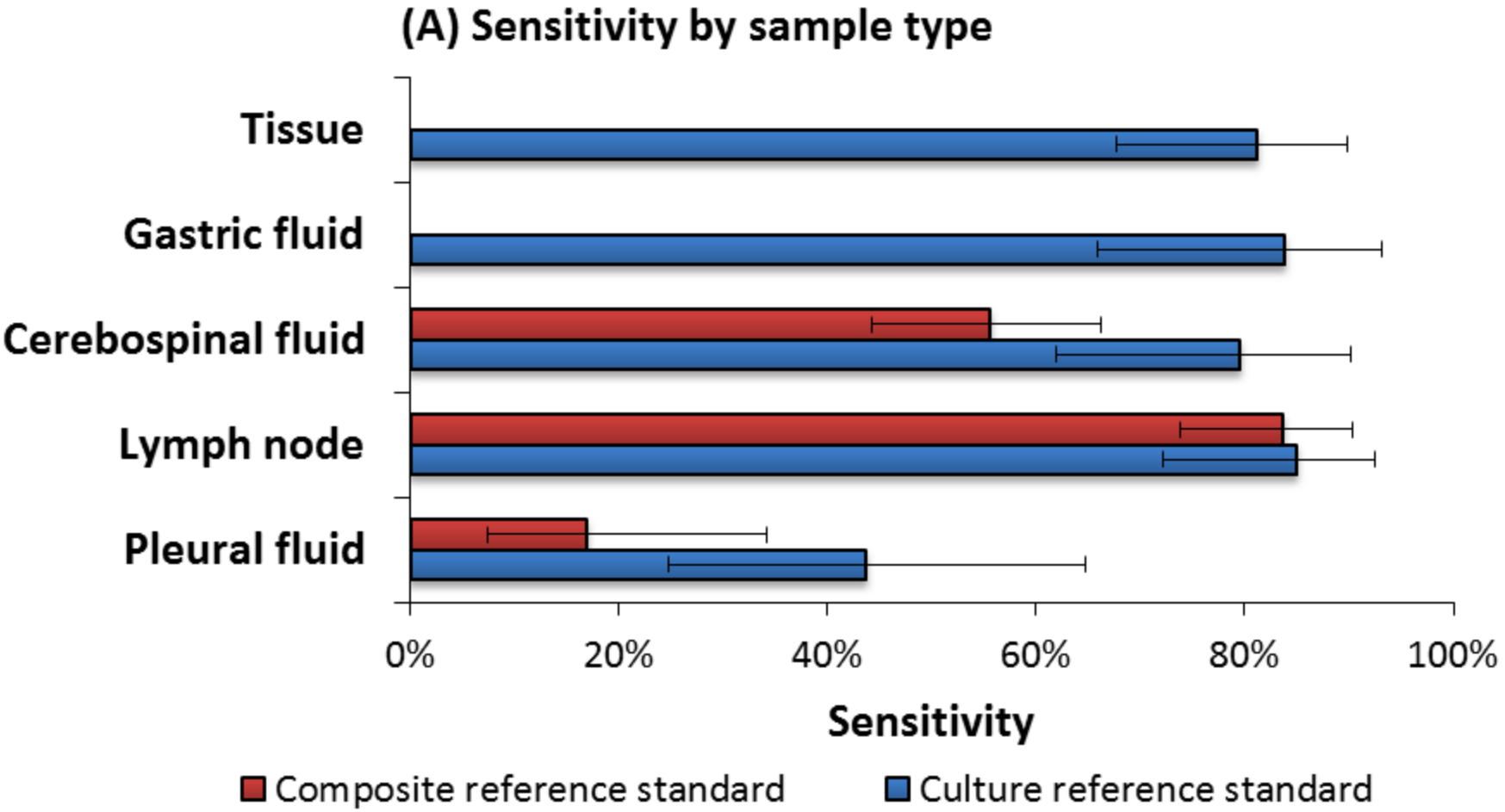
The NEW ENGLAND JOURNAL of MEDICINE

Xpert MTB/RIF for detection of TB and rifampicin resistance

(WHO Expert meeting report for use of Xpert MTB/RIF, 2013)

	Sensitivity	Specificity
Replacing microscopy as initial test for TB	88%	99%
Add on following negative microscopy	68%	99%
Rifampicin resistance	95%	98%
HIV-associated TB	79%	98%
Children	66%	98%
Extrapulmonary TB	81%	98%

Xpert sensitivity for ETB



(WHO Expert meeting report for use of Xpert MTB/RIF, 2013)

WHO recommendations for Xpert

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults presumed to have MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence).

- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults presumed to have TB. (Conditional recommendation acknowledging resource implications, high-quality evidence).

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Xpert for TB- Evaluating a New Diagnostic

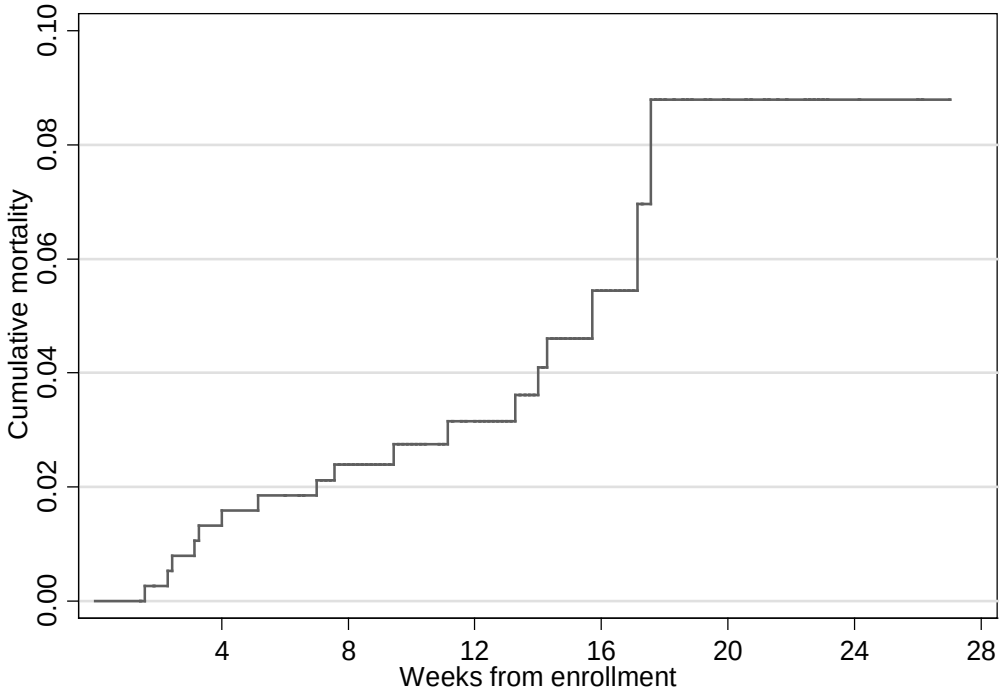
A cluster randomised trial evaluating patient, programme & population level impact of Xpert

XTEND

XTEND: early mortality

- Median follow-up: 3.3 months (IQR 2.1 - 3.7)
- During follow-up: 17 deaths, 97.2 person-years (py)
- Overall mortality rate: 17.5 per 100py

Kaplan-Meier mortality plot, among clinic attendees suspected of TB (n=380)



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Genotype MTBDR*plus 2.0* vs MGIT & clinical TB

Crudu. JCM, 2012	Sensitivity	Specificity
MTB		
Overall	87.6%	99.2%
Smear negative	79.8%	99.2%
Rifampicin resistance		
Overall	94.3%	96.0%
Smear negative	90.7%	96.0%
Isoniazid resistance		
Overall	95.8%	88.9%
Smear negative	93.5%	82.3%

GenoType MTBDRsl

Drug	Sensitivity	Specificity
Kontsevaya,I. JCM. 2011		
Fluoroquinolone	86.2%	100%
Kiet,V.S. JCM. 2010		
Fluoroquinolone	75.6%	100%
kanamycin	100%	100%
Ethambutol	64.2%	100%
Hillemann,D. JCM. 2009		
Fluoroquinolone	88.9%	
Amikacin	75.0%	
Ethambutol	38.5%	

GenoType MTBDRsl

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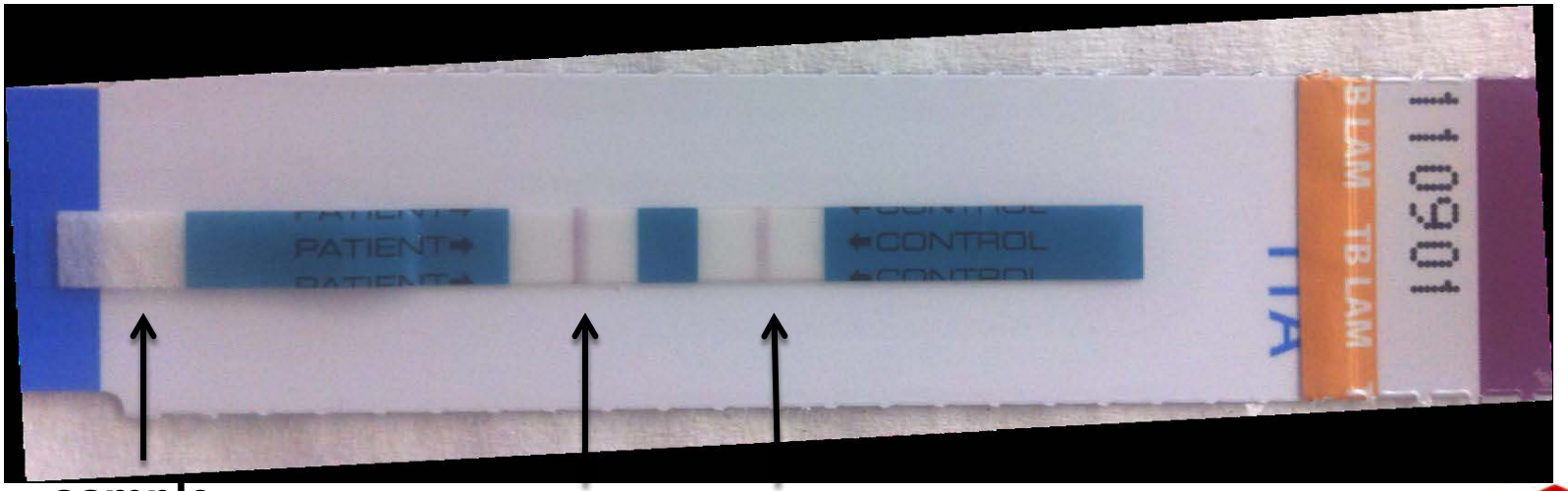
Ethambutol	38.5%	

Determine LAM lateral flow assay (Alere)

- uses Determine testing platform
- No sample processing; results in 25 minutes
- Analytical sensitivity reported to be 0.25 ng/ml
- Reporting scale: no band (neg), 1+ to 5+ (pos)



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Determine TB-LAM

Author/ Year	N	Setting	Sensitivity		Specificity
			Overall	**CD4<100**	
Peter, 2012	335	Inpatients	45%		96%
Lawn, 2012	516	ART clinic	28%	52%	99%
Dorman S, 2012	561	Outpatients Inpatients	45%	80%	90%

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- WHO not endorsed
- **Early development**
- Point of care

TB diagnostics: early development

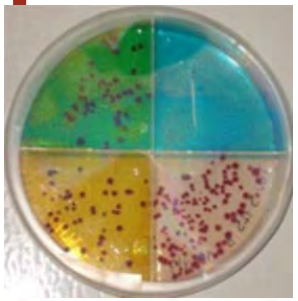
Volatile organic compounds

- BreathLink, Menssana Research, USA
- Prototype breath analyzer device, Next Dimensions Technology, USA

Molecular technologies

- Alere Q, Alere, USA
- B-SMART, LabCorp, USA
- Gendrive MTB/RIF ID, Epistem, UK
- LATE-PCR, Brandeis University, USA
- GeneXpert XDR cartridge, Cepheid, USA
- TruArray MDR-TB, Akkoni, USA
- INFINITIMTB Assay, AutoGenomics, USA

TB diagnostics: early development



Culture-based technologies

- BNP Middlebrook, NanoLogix, USA
- MDR-XDR TB Color Test, FIND, Switzerland/Imperial College, UK
- TREK Sensititre MYCOTB MIC plate, Trek Diagnostic Systems/Thermo Fisher Scientific, USA

Other technologies

- TB Rapid Screen, Global BioDiagnostics, USA
- TBDx, Signature Mapping Medical Sciences, USA

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Rationalizing the use of Xpert: the role of automated microscopy

TBDx: automated smear microscopy

- automatically loads slides
- conventional fluorescence microscope
- Autofocuses and digitally captures images
- Reads 300 fields of view
- Computerised algorithms classifies slides as +ve/–ve

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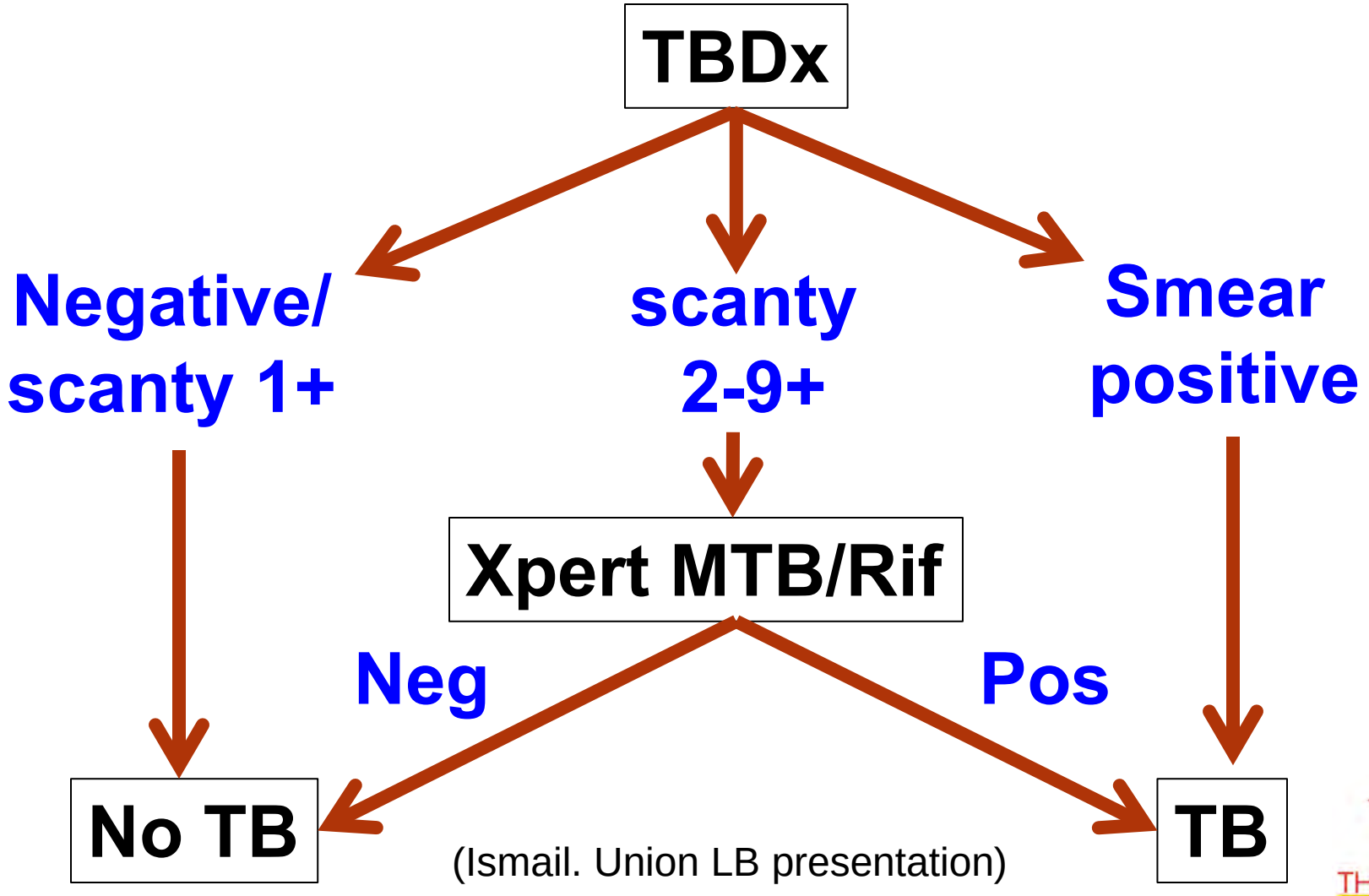
Rationalizing the use of Xpert: the role of automated microscopy



(Ismail. Union LB presentation)

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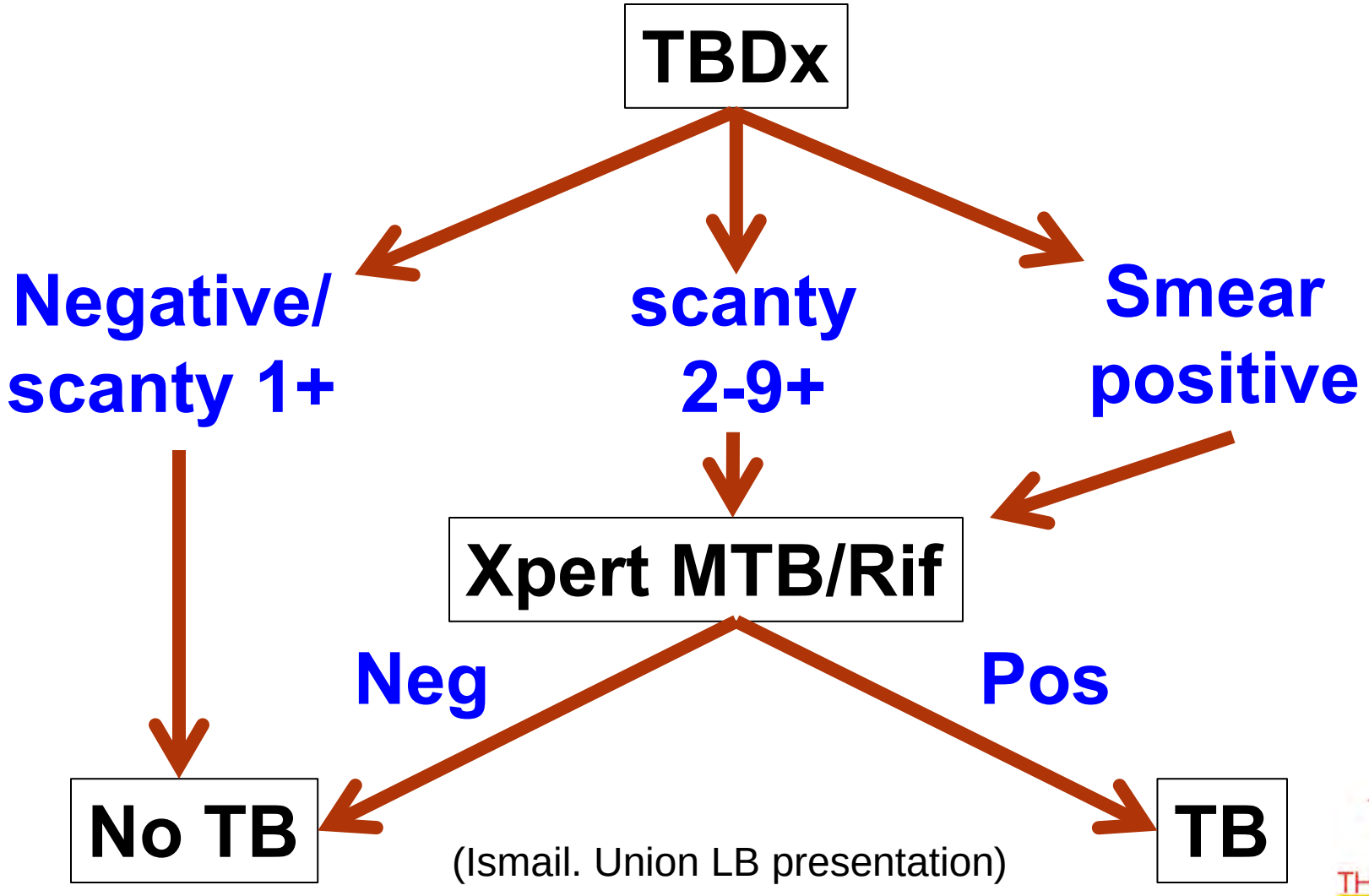
Rationalizing the use of Xpert: the role of automated microscopy



(Ismail. Union LB presentation)

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Tuberculosis

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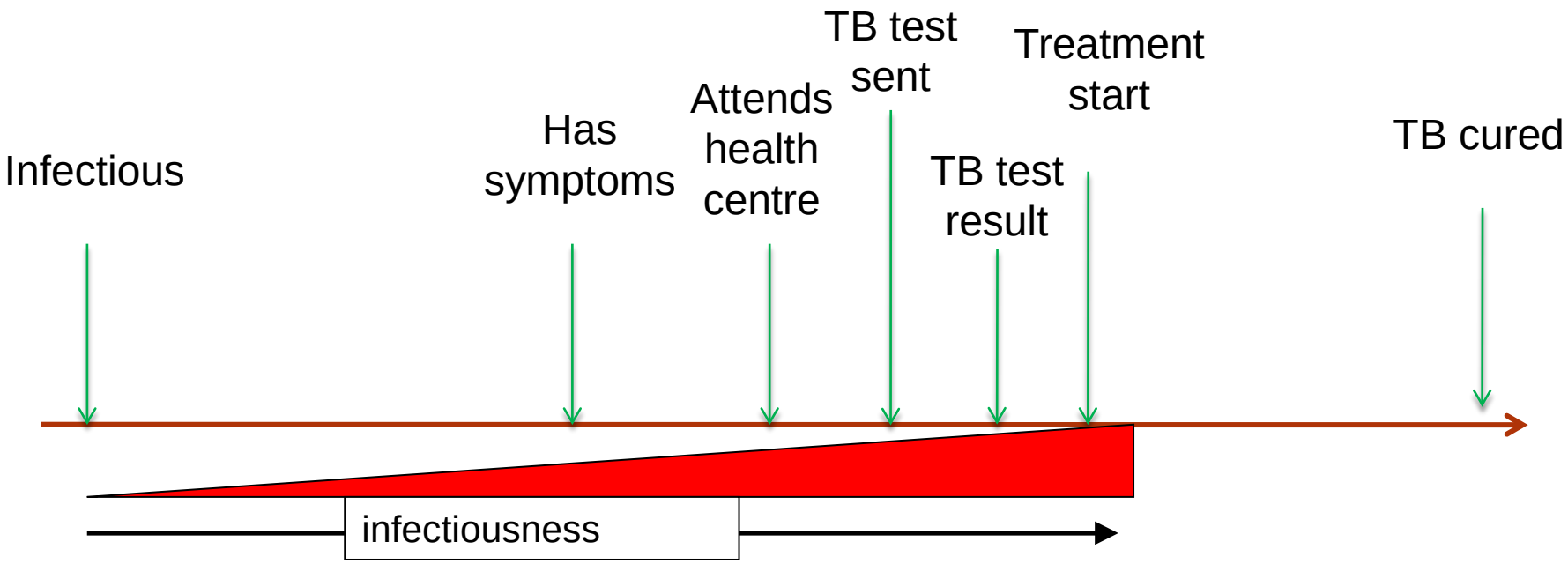
- **Point of care**

The long & winding road to TB treatment



(A Grant. AIDS2012)

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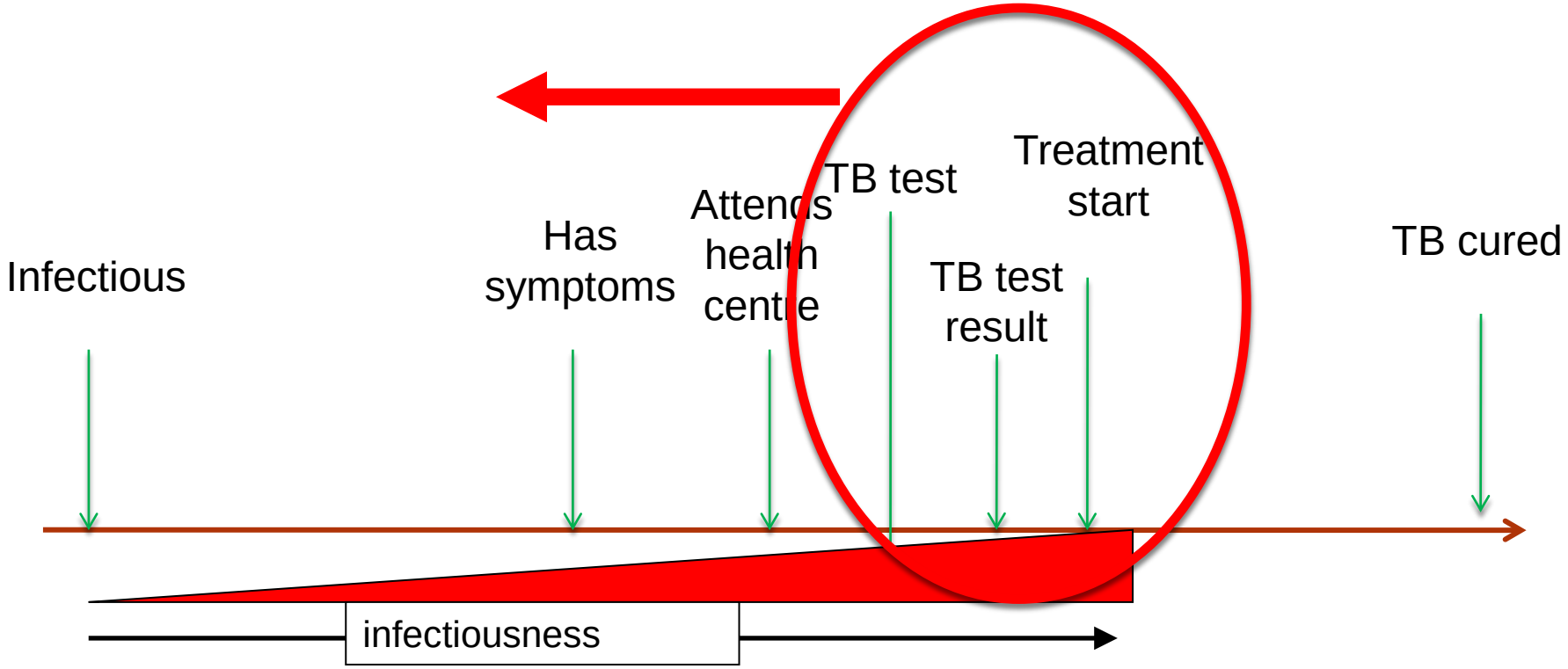
Earlier testing is TB prevention



(A Grant. AIDS2012)

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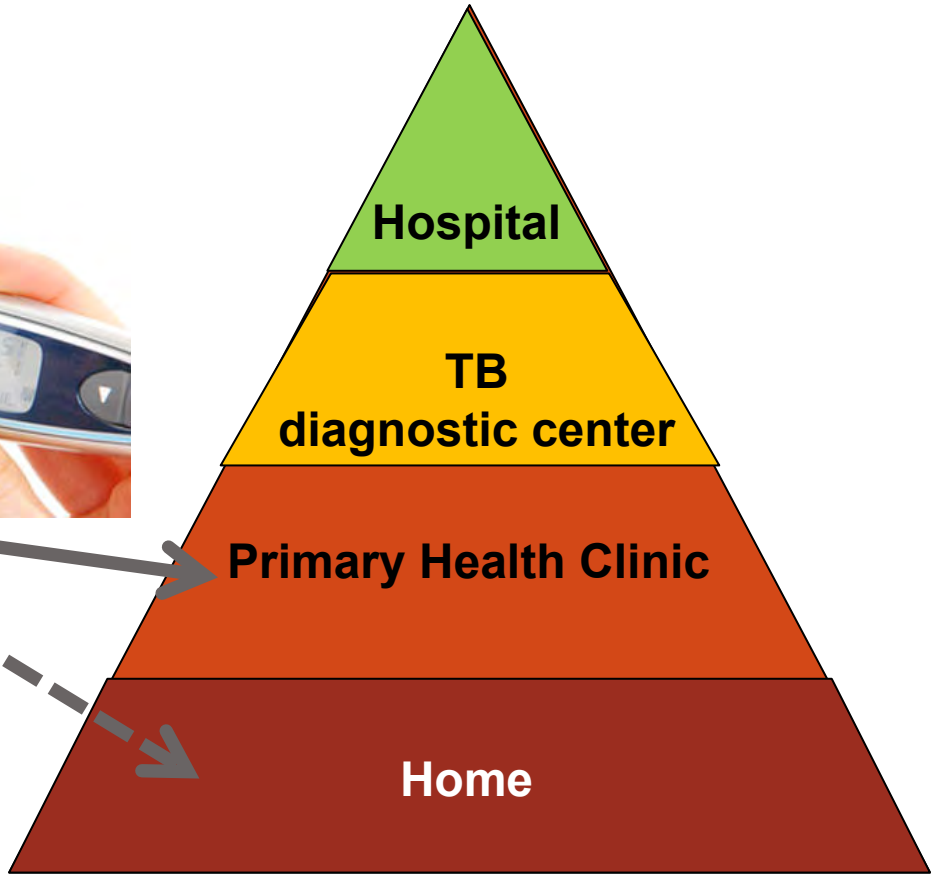
Point of care diagnostic

Point of care test



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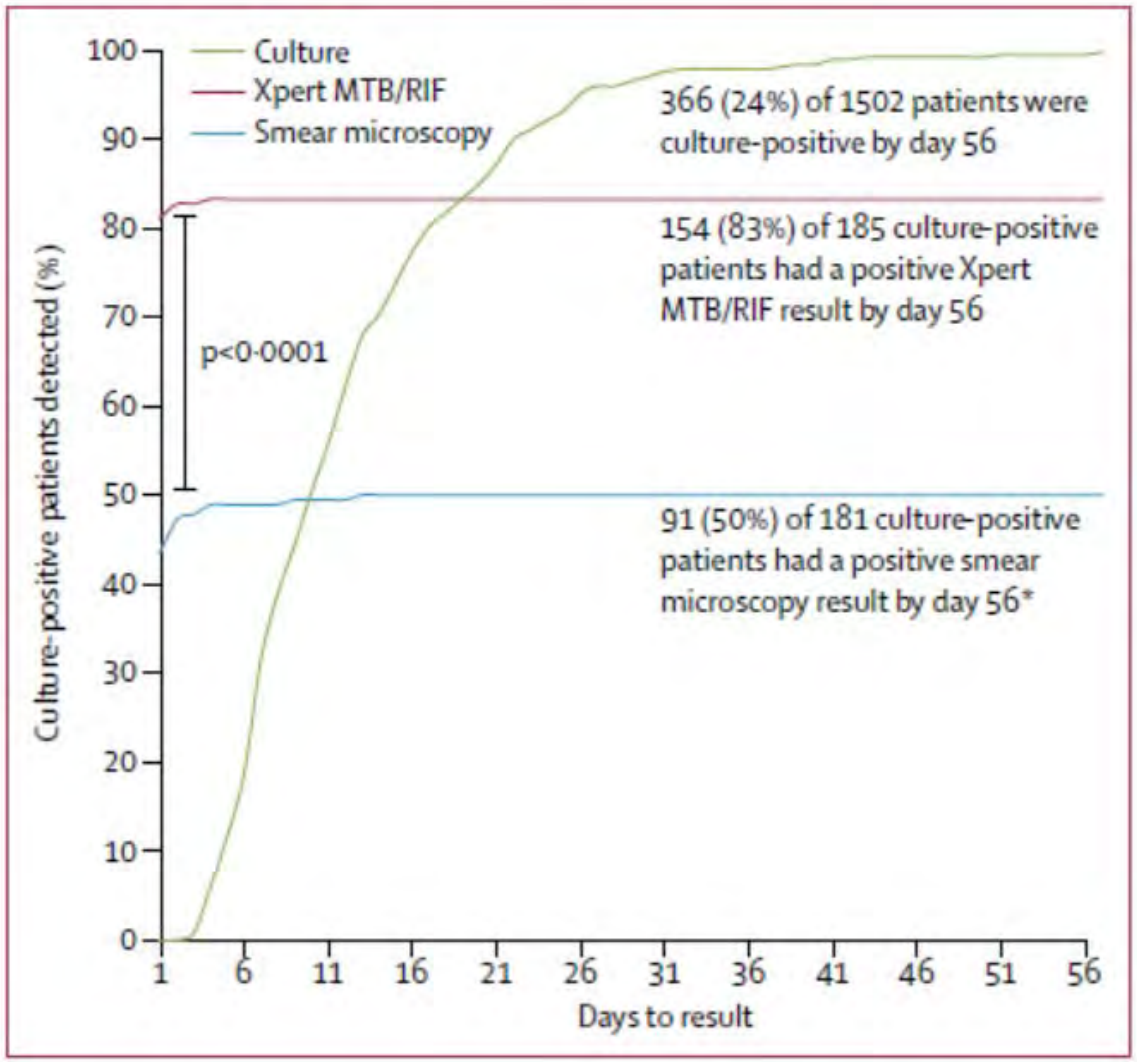
Point of care Xpert in PHCs in Africa



- 5 sites
- Randomised to
  - 758 microscopy
  - 744 Xpert
- TB related morbidity similar, due to common use of empiric treatment

(Theron et al. Lancet. 2013)

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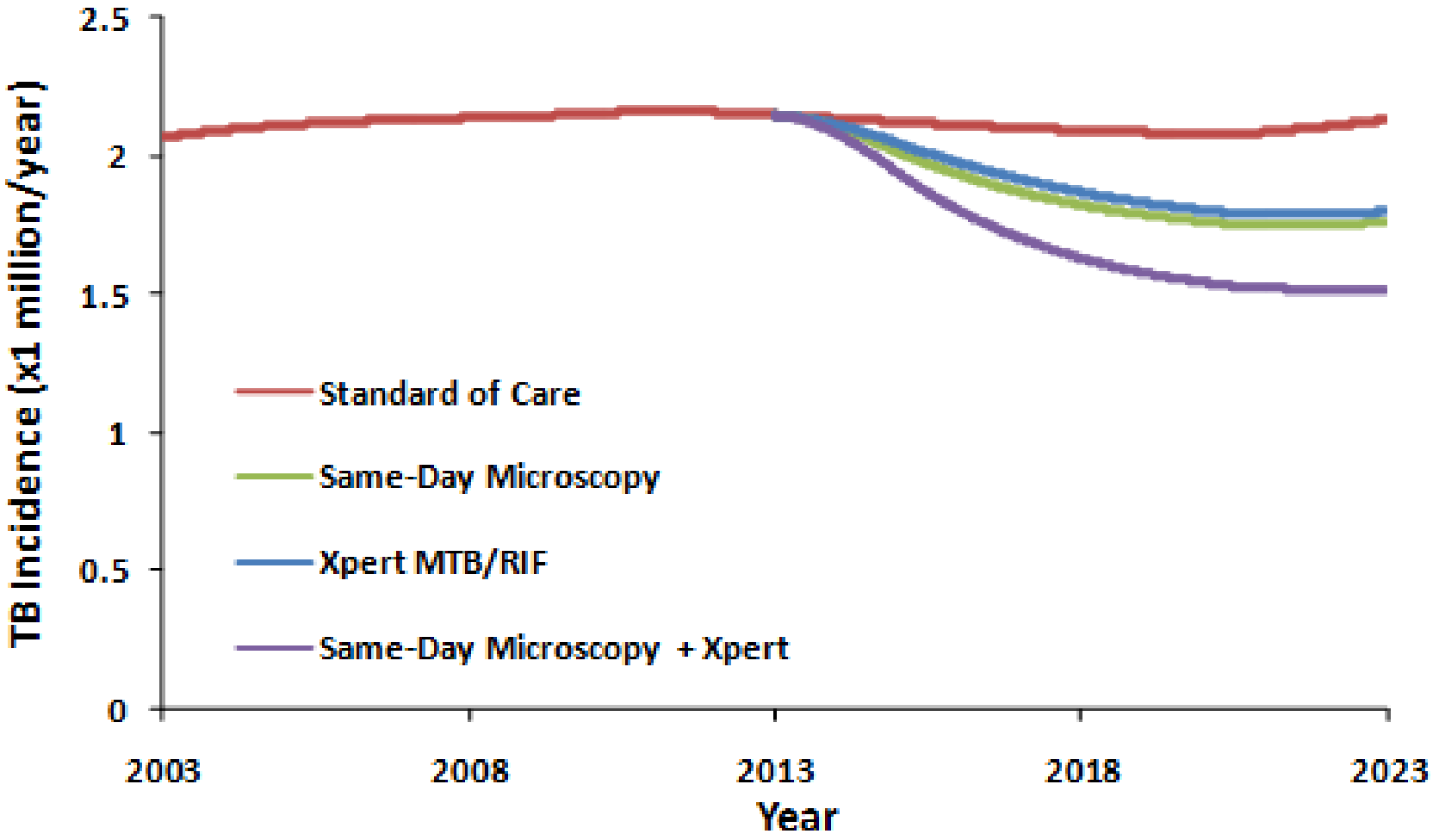
Population level impact of same-day microscopy & Xpert MTB/RIF



(Dowdy et al, PLOS One, 2013)

Tuberculosis

Epidemiology

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Research priorities

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Tuberculosis

Epidemiology

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Research priorities

- Vaccination strategies
- Pipeline
- Phase II
- Phase IIb/III
- Blueprint
- BCG revaccination

Tuberculosis

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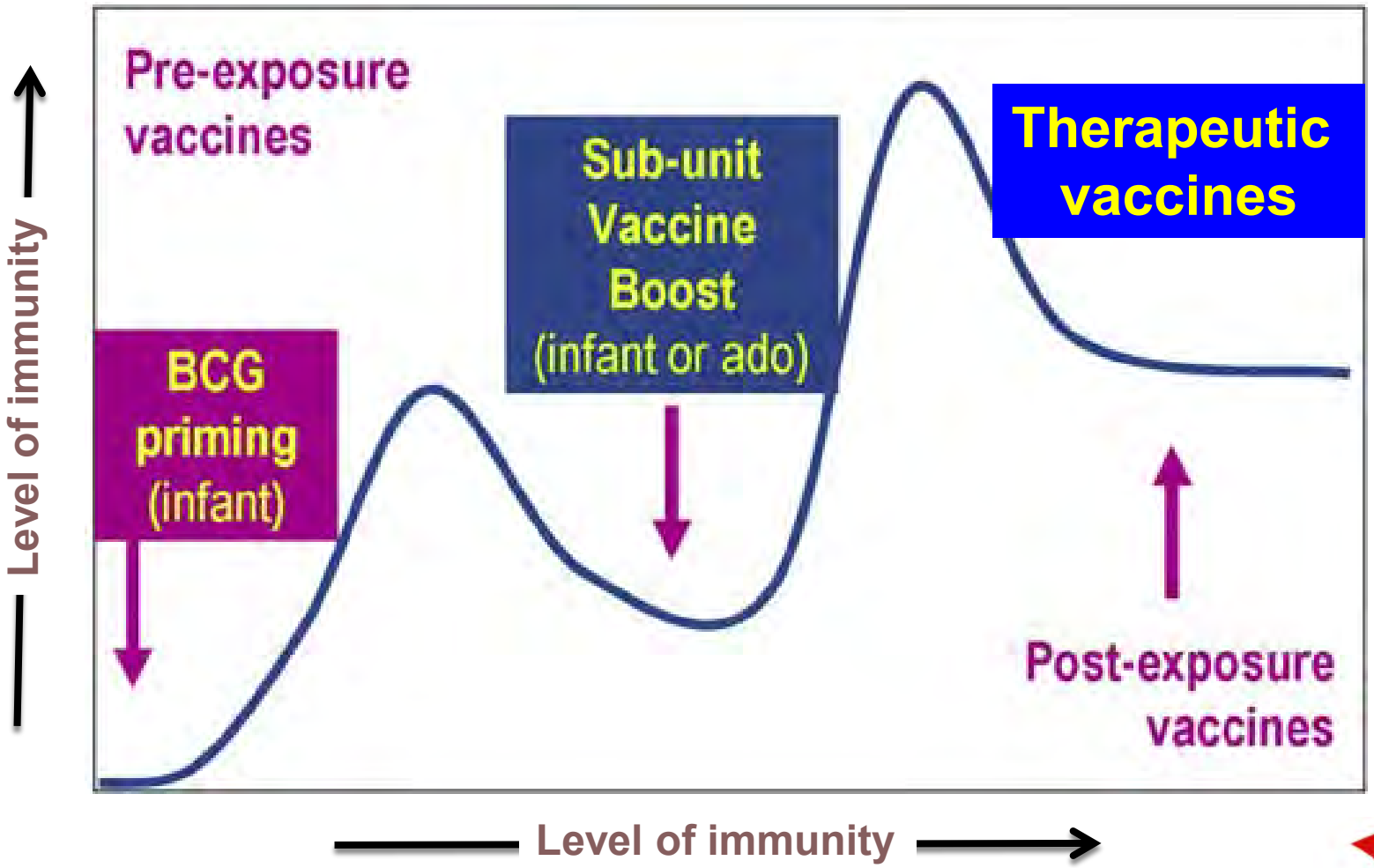
TB Vaccine strategies



(PH Lambert et al. Clin Chest Med 30. 2009;811–826)

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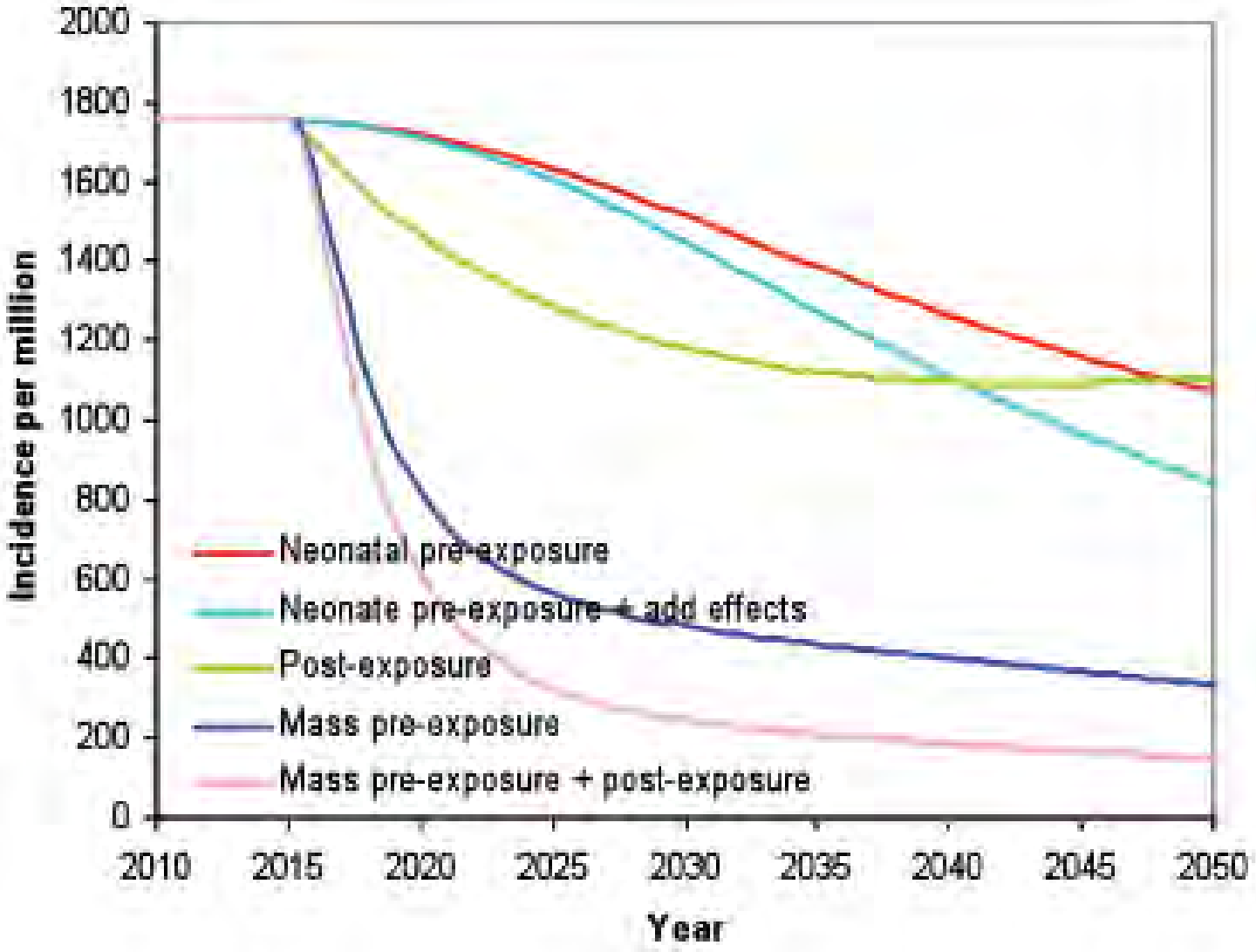
Potential impact of new TB vaccines, diagnostics and drugs in SE Asia



Source: L. Abu Raddad *et al*, PNAS 2009

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Tuberculosis

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- Phase II
- Phase IIb/III
- Blueprint

Global TB vaccine pipeline

Phase I	Phase II	Phase IIb	Phase III
AdAg85A McMaster, CanSino (P) (B) [PI]	**VPM 1002** Max Planck, VPM, TBVI, Serum Institute (P) (B)	**MVA85A/ AERAS-485** Oxford, Aeras, EDCTP (B) [PI] [IT]	***M. Vaccae*** Anhui Longcom [IT]
MTBVAC TBVI, Zaragoza, Biofabri (P)	**H1+IC31** SSI, TBVI, EDCTP, Intercell (P) (B) [PI]	**M72+AS01** GSK, Aeras (B) [PI]	
ID93+GLA-SE Infectious Disease Research Institute (IDRI), Aeras (B)	**RUTI** Archivel Farma, S.L. (B) [PI] [IT]		
Crucell Ad35/MVA85A Crucell, Oxford, Aeras (P) (B)	**H56/AERAS-456 +IC31** SSI, Aeras, Intercell (P) (B) [PI]		
	H4/AERAS-404 +IC31 SSI, sanofi-pasteur, Aeras, Intercell (B)		
	Crucell Ad35/AERAS-402 Crucell, Aeras (B)		

(P) **Prime**

(B) **Boost**

[PI] **Post-infection**

[IT] **Immunotherapy**

TB Vaccine Types
Viral-vectored: MVA85A, AERAS-402, AdAg85A
Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93
rBCG: VPM 1002
Killed WC or Extract: Mw, RUTI

June 2013

Stop TB Partnership
Working Group on New TB Vaccines

Tuberculosis

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Vaccines

Research priorities

- Vaccination strategies
- Pipeline
- **Phase II**
- Phase IIb/III
- Blueprint

VPM1002 in HIV-exposed infants

- Live recombinant rBCG
- Phase IIa:
  - HIV-uninfected newborns: safe & immunogenic
  - HIV exposed and unexposed newborns: safety and immunogenicity study planned

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Tuberculosis

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Research priorities

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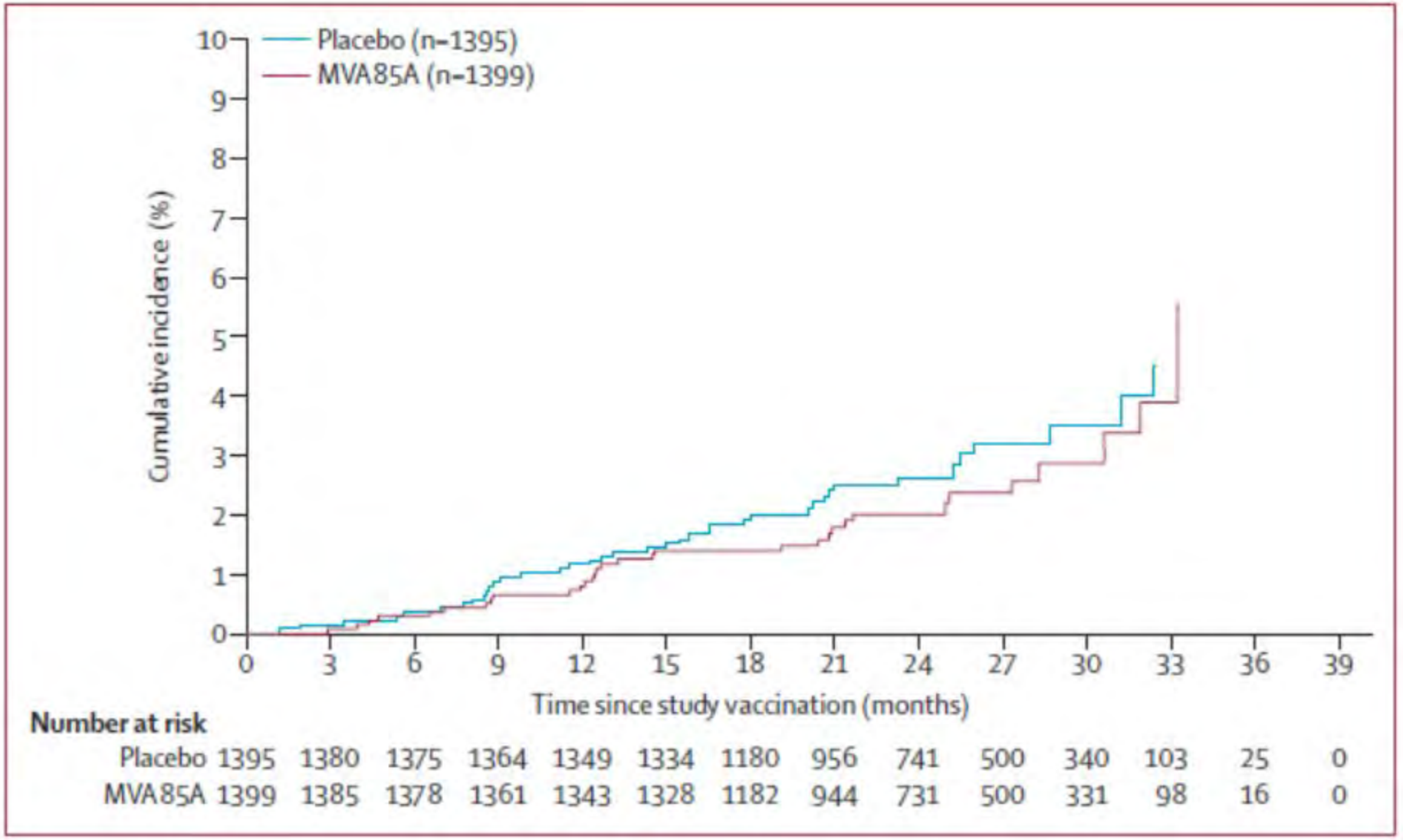
- Phase II
- **Phase IIb/III**
- Blueprint

MVA85A Efficacy in BCG vaccinate infants



(McShane, Lancet, 2013)

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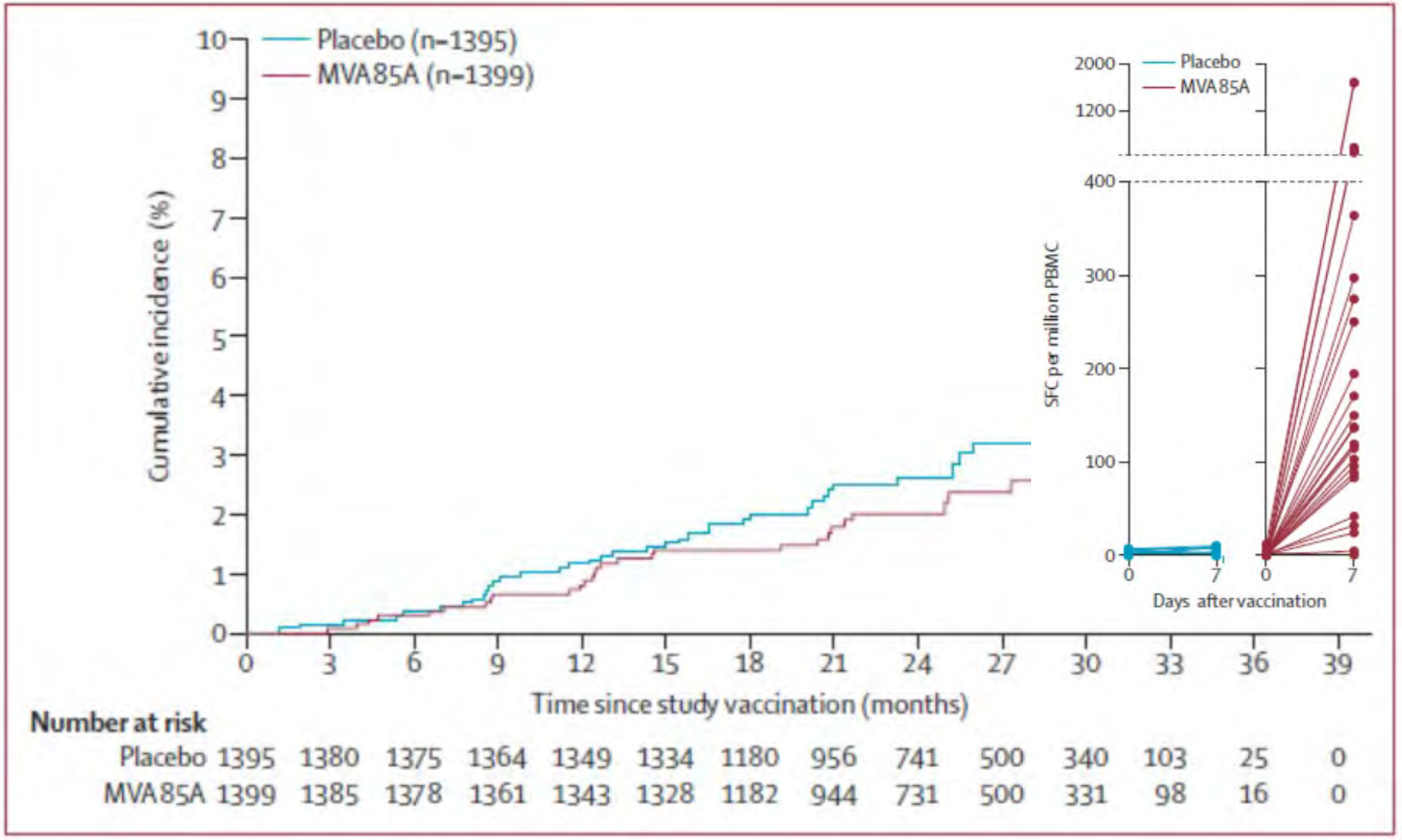
MVA85A Efficacy in BCG vaccinate infants



Number at risk

Placebo	1395	1380	1375	1364	1349	1334	1180	956	741	500	340	103	25	0
MVA85A	1399	1385	1378	1361	1343	1328	1182	944	731	500	331	98	16	0

McShane, Lancet, 2013)

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DarDar study: M vaccae in HIV-infected adults

Table 1 Protection against HIV-associated TB in the DarDar Trial

	Cases			
TB endpoints	Vaccine *n*	Placebo *n*	Hazard ratio (95%CI)	*P* value
Disseminated	7	13	0.52 (0.21–1.34)	0.16
Definite	33	52	0.61 (0.39–0.96)	0.03
Probable	48	40	1.17 (0.76–1.80)	0.46

HIV = human immunodeficiency virus; TB = tuberculosis; CI = confidence interval.

(von Reyn et al. AIDS, 2010)

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TB Vaccine efficacy trials

Agent	Strategy	Type	Sponsors	Status
M. vaccae	Immunotherapeutic	Whole-cell *M. vaccae*	AnHui Longcom	Phase III pending
MVA85A/ AERAS-485	Prime-boost	Viral vector	Oxford University, Aeras	Phase IIb in HIV+s Enrolling
M72 + AS01	Prime-boost	Adjuvanted subunit	GSK, Aeras	Phase Iib Pending

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- **Blueprint**

TB vaccine blueprint

Keys to progress

- Creativity in research & discovery
- Correlates of immunity & biomarkers for TB vaccines
- Clinical trials: harmonization and cooperation
- Rationale selection of TB vaccine candidates
- Critical need for advocacy, community acceptance & funding

(Brennan, Tuberculosis, 2012)

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TB vaccine blueprint

Keys to progress

- Creativity in research & discovery
- Correlates of immunity & biomarkers for TB vaccines
- Clinical trials: harmonization and cooperation
- Rationale selection of TB vaccine candidates
- Critical need for advocacy, community acceptance & funding

- Use out the box approaches to identify mechanisms of protection for TB
- Expand antigenic repertoire & try new combinations
- Translational research, comparative preclinical studies, animal studies that mimic human TB

(Brennan, Tuberculosis, 2012)

TB vaccine blueprint

Keys to progress

- Creativity in research & discovery
- Correlates of immunity & biomarkers for TB vaccines
- Clinical trials: harmonization and cooperation
- Rationale selection of TB vaccine candidates
- Critical need for advocacy, community acceptance & funding

- Explore novel approaches to identifying biomarkers
- Introduce novel assays
- Identify signatures of efficacy

(Brennan, Tuberculosis, 2012)

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Tuberculosis

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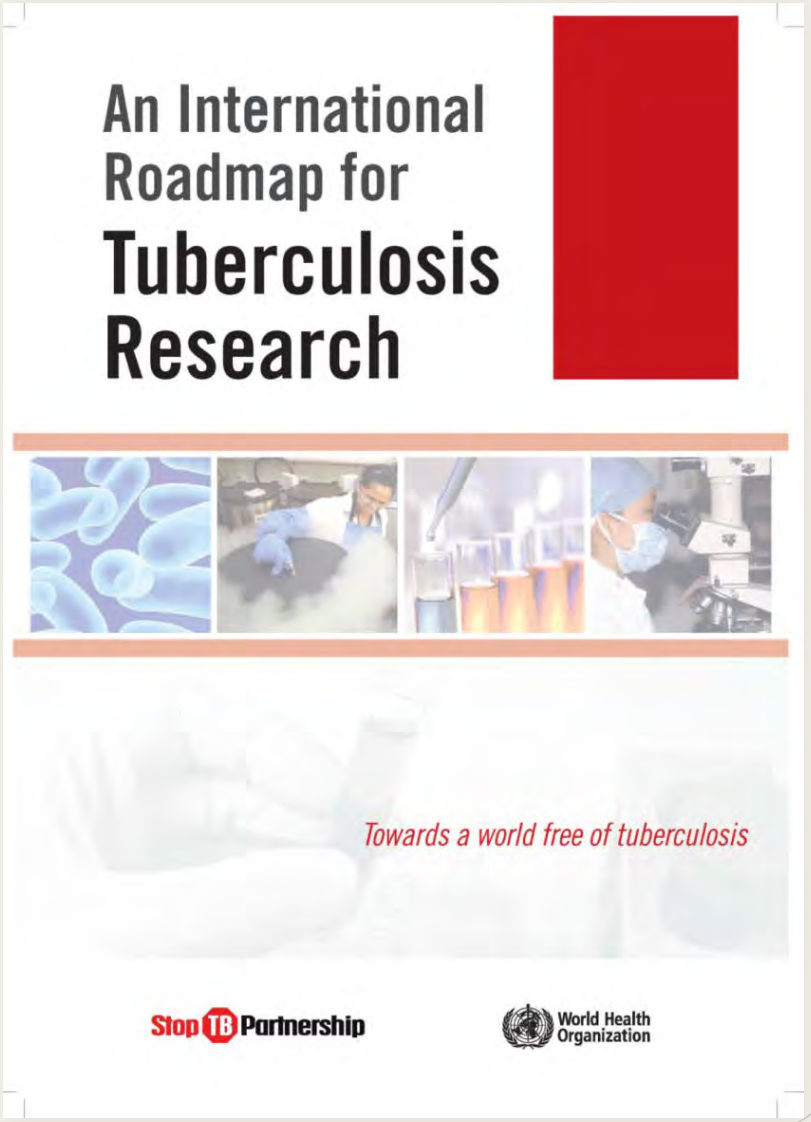
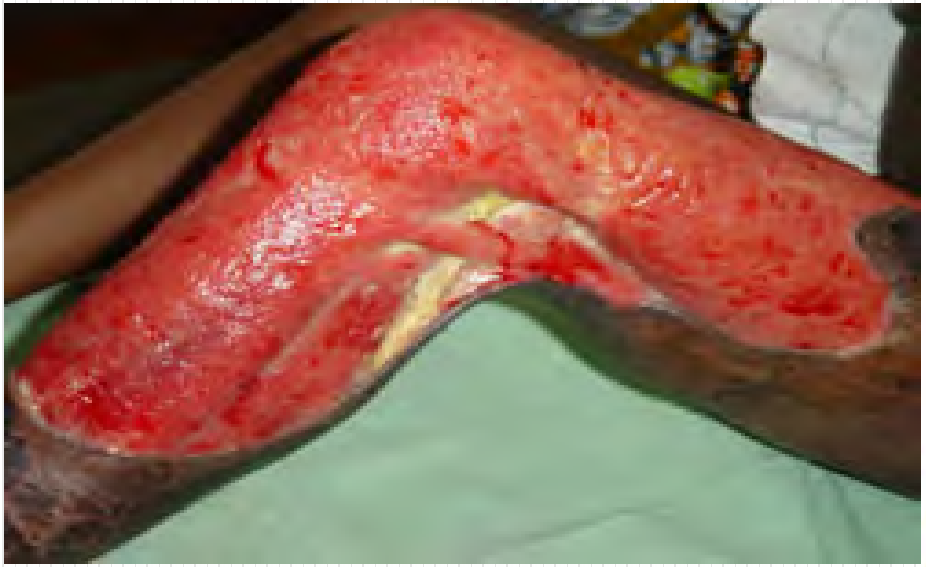
TB research priorities



Buruli Ulcer



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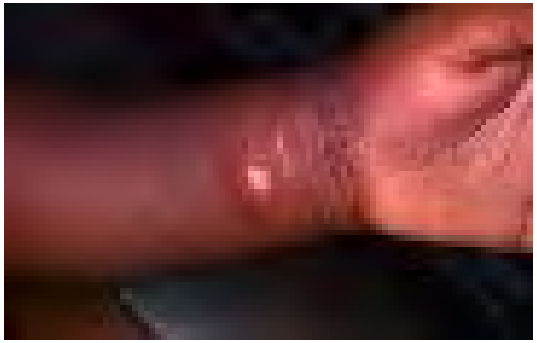
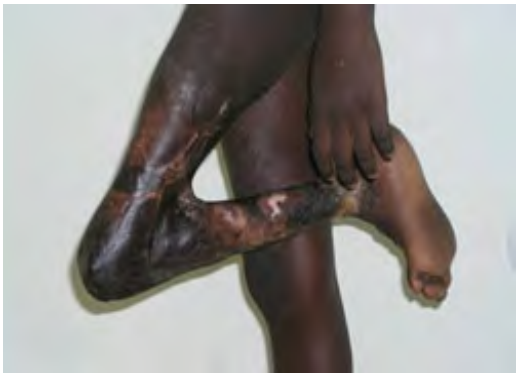
Buruli ulcer: background

- Buruli ulcer is a neglected but treatable tropical disease
- Caused by subcutaneous infection with *Mycobacterium ulcerans*
- Slowly progressing disease
  - often painless
  - begins as a nodule
  - life-long deformity may occur
- Early diagnosis and treatment are key to preventing disabilities
- Children and the elderly appear most susceptible





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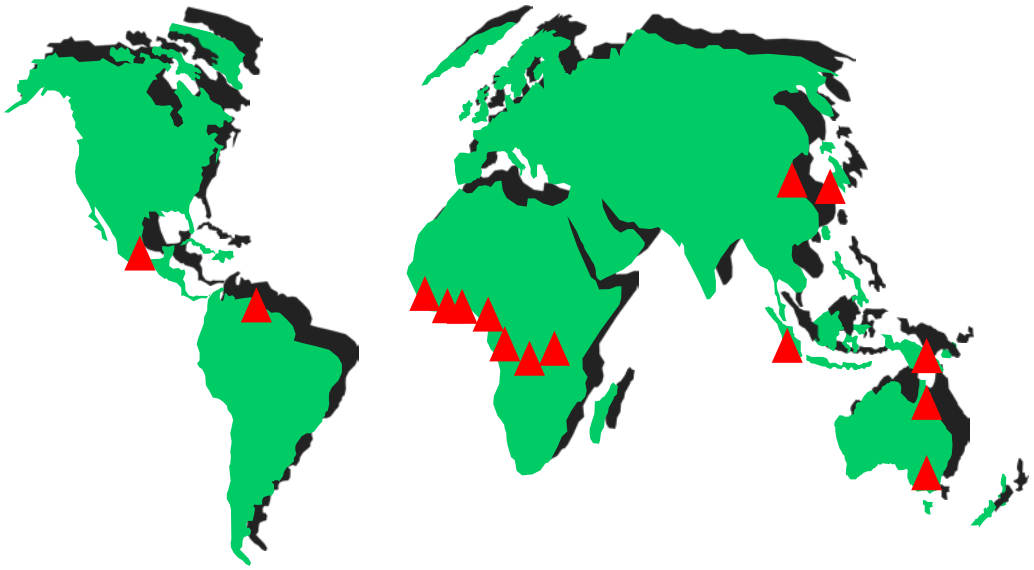
Buruli ulcer: burden of disease

- Globally, 26,000 cases recorded b/w 2004-2008
- Greatest burden in Africa
  - Primarily in remote, rural areas
  - prevalence in Ghana and Benin range from 50 - 3,500 cases per 100,000



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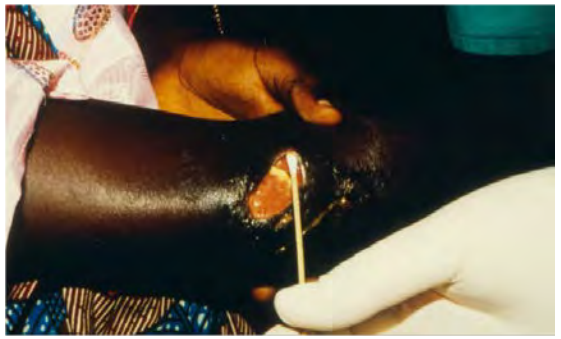
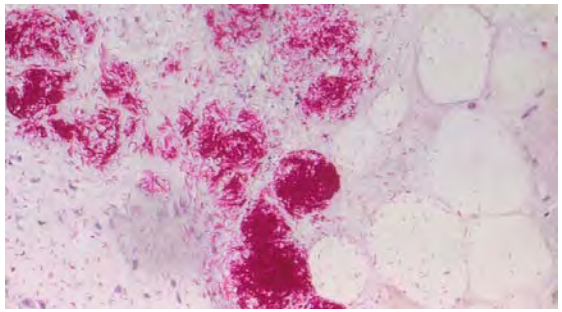
Buruli ulcer: reservoir & mode of transmission

- Although classified as an environmental mycobacterium, does not live freely in the environment
- Occupies specific (vertebrate and invertebrates) hosts
- Infection associated with swamps and slow-flowing water
- Transmitted to humans by an unknown mechanism
  - Mosquitoes may be involved in transmission (in Australia)





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Buruli ulcer: diagnosis

- Direct smear examination
- Culture
- Polymerase chain reaction
- Histopathology
- There is no rapid point-of-care test

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Buruli Ulcer: treatment and prevention

- Rifampicin & streptomycin/amikacin x 8wks
  - Oral regimen: rifampicin & clarithromycin or ciprofloxacin or moxifloxacin for 3 months
- Surgery to remove necrotic tissue, cover skin defects and correct deformities
- There is no vaccine against *BU*
  - BCG offers short-term protection

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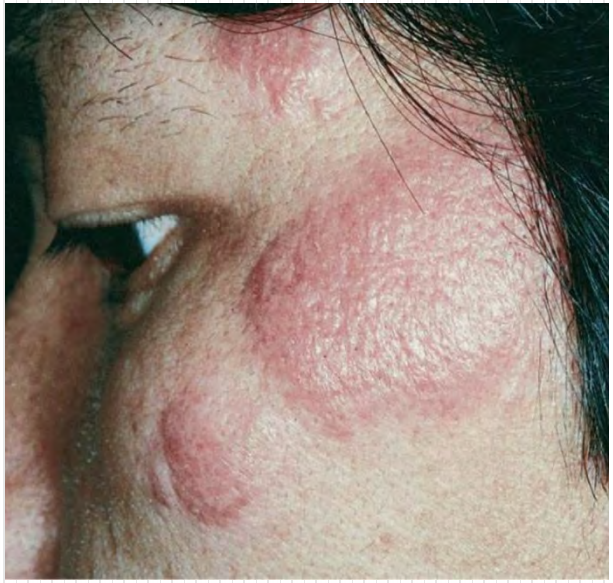
Leprosy



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Leprosy: background

- Caused by *M leprae*
- Leading infectious cause of disability
- Delayed diagnosis results in increased risk of nerve damage.
- Stigma an important feature in many cultures

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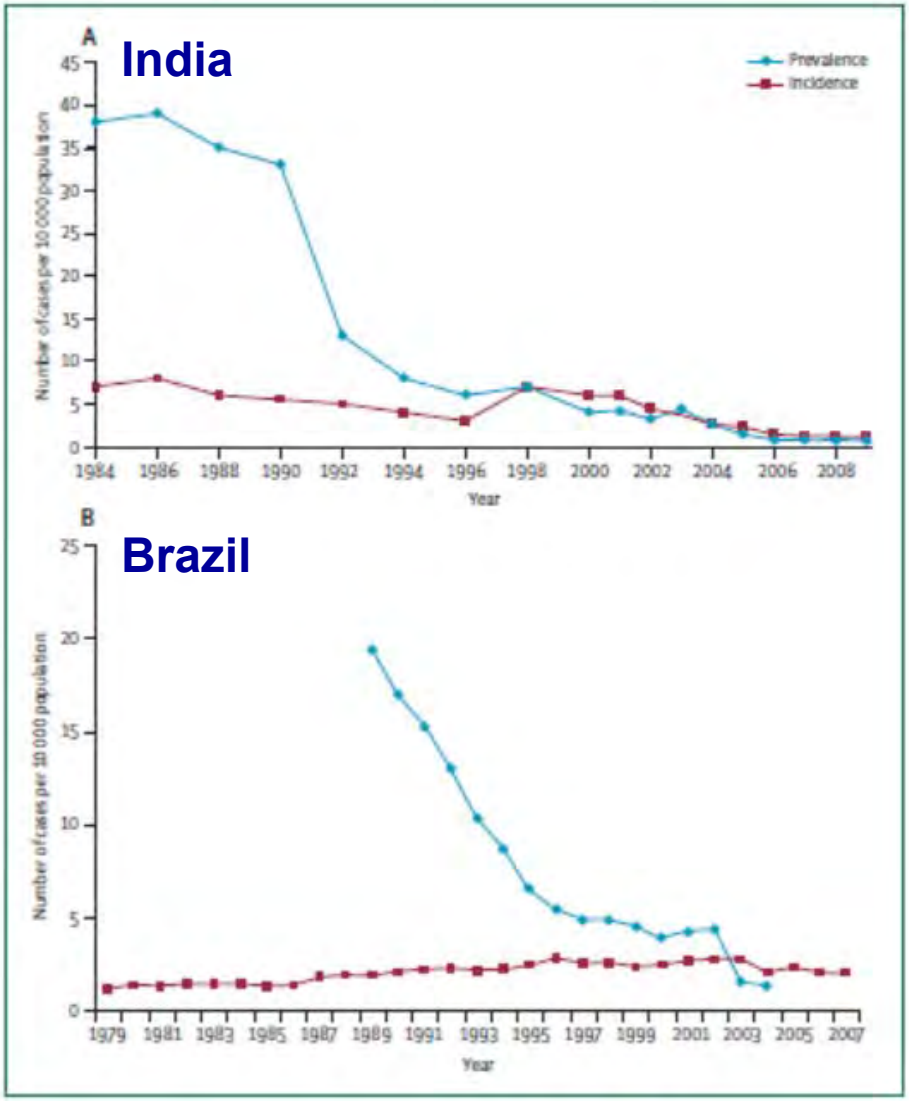
Leprosy: epidemiology

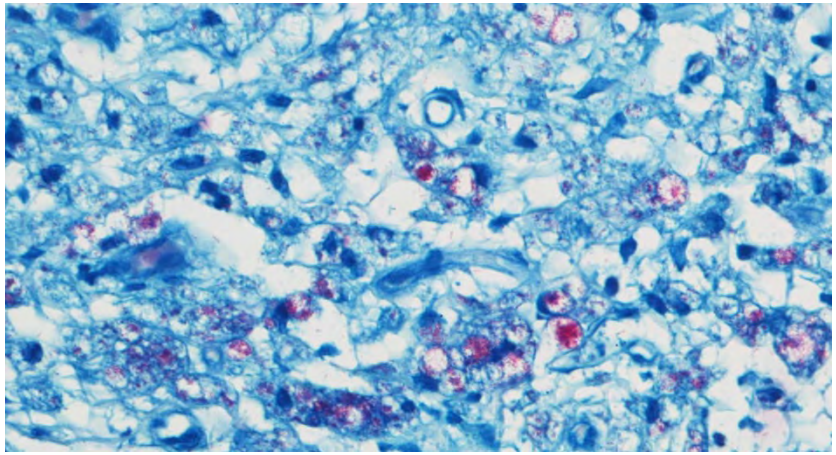
- 250 000 cases/year
- Prevalence fallen substantially
- Transmission continues



(Rodrigues, 2011, Lancet ID)

Leprosy: clinical

- Caused by chronic granulomatous inflammation in skin and peripheral nerves



Classification

- WHO (skin lessions: <6, 6+)
- Ridley-Jopling
  - Tuberculoid disease
    - good cell-mediated immune response
    - few lesions with no detectable mycobacteria
  - Lepromatous leprosy
    - anergic to *M leprae*
    - multiple lesions with mycobacteria present
  - Borderline leprosy types

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Leprosy: treatment

- Paucibacillary disease
  - rifampicin and dapsone x6m
- Multibacillary disease
  - rifampicin, dapsone, clofazimine x 12m
- Alternative regimen
  - Rifampicin, oxfloxacin and minocycline X1 month
- Infectiousness reduced after starting treatment
- Relapse rate: 2-3 per 100 person years
- Immune-mediated reactions
  - Occur in 30% of patients with multibacillary disease
  - Steroids are the main treatment

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Leprosy: prevention

- Chemoprophylaxis reduces risk in household contacts
  - Rifampicin single dose
  - Rifampicin 2 doses, ofloxacin, minocycline
- Vaccination with BCG protects people from developing leprosy
- Search for subunit protein vaccine been facilitated by the sequencing of *M leprae*
- There is no suitable animal model

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Priorities for mycobacterial research

- Integrated research priorities
- Multidisciplinary

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TDR: Global research priorities for TB, leprosy and buruli ulcer

Improve diagnostics for infection, disease and drug resistance for TB, leprosy and buruli ulcer, especially point of care tests
Develop improved treatment and prevention regimens (based on current and new drugs) for TB, leprosy and buruli ulcer
Identify and validate biomarkers that facilitate development of vaccines, diagnostics and drugs for TB, leprosy and buruli ulcer
Increase understanding of the pathogenesis of TB, leprosy and buruli ulcer to fuel discovery of drugs, vaccines and diagnostics
Increase understanding of the burden of disease, the modes of transmission and the impact of public health interventions for TB, leprosy and buruli ulcer
Develop novel vaccines and optimise current vaccines for TB, leprosy and buruli ulcer
Evaluate and optimise strategies to improve case finding and reduce barriers to treatment access for TB, leprosy and buruli ulcer
Optimise implementation of preventive therapy (for TB and leprosy), TB infection control and patient centred TB management, especially drug resistant TB
Evaluate and optimise new and current strategies to quantify, prevent and minimise disability and stigma resulting from TB, leprosy and buruli ulcer
Evaluate strategies to strengthen health systems to support control of TB, leprosy and buruli ulcer

What are the barriers?

"we ... activists recoiled from the formaldehyde-enshrouded world of TB science .... so different from the vibrant and ever forward thrusting vitality of HIV science"

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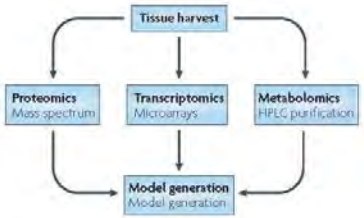
Continuum of TB research

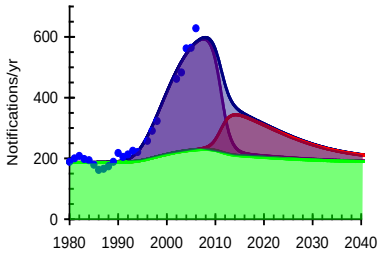
Basic research for discovery

Development of new tools (diagnostic tests, drugs, vaccines)

Implementation operational research

Monitoring Evaluation of impact Epidemiology & modelling





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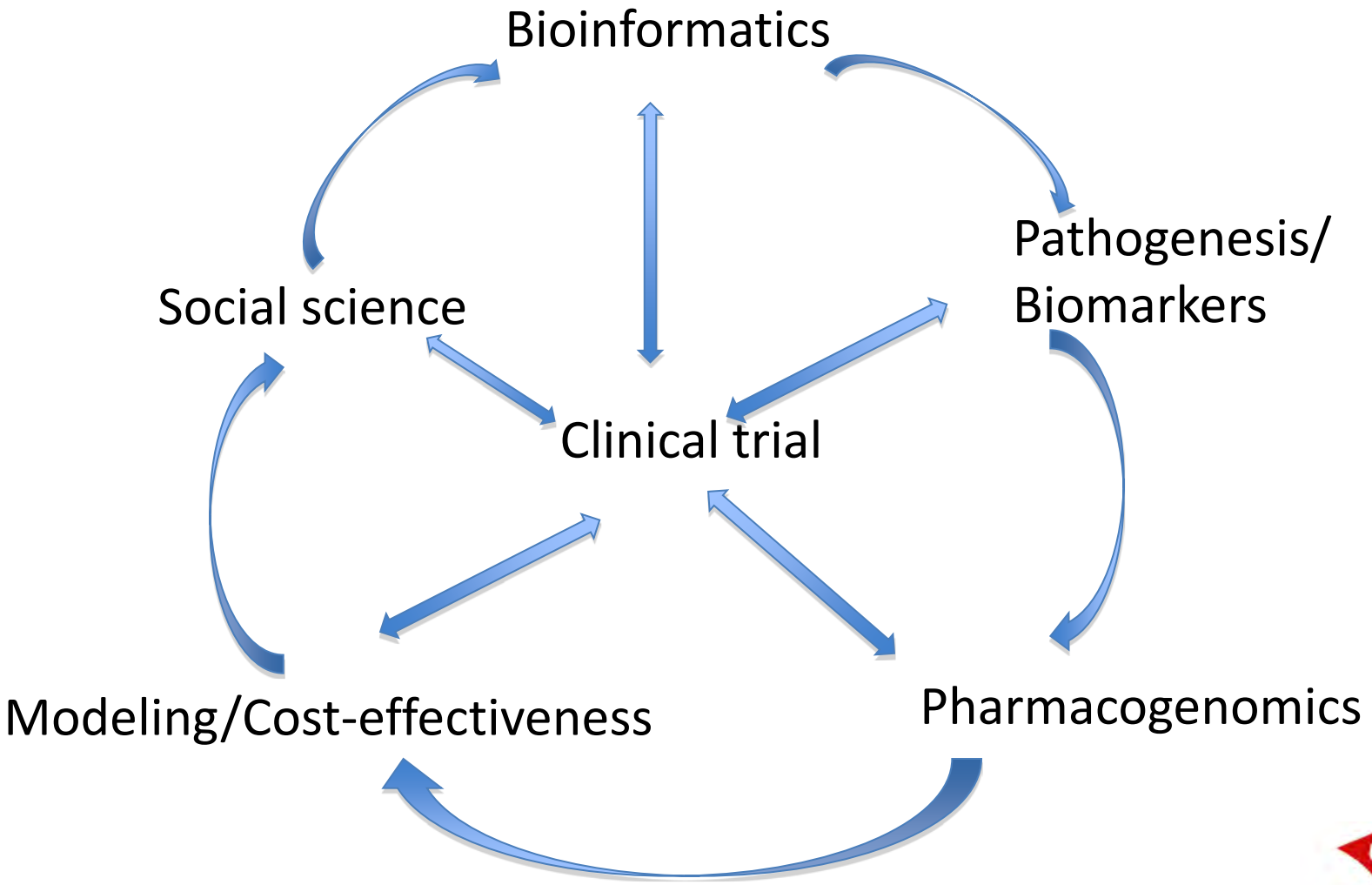
Multidisciplinary approach



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Conclusion

- TB, leprosy and buruli ulcer remain important public health problems
- Elimination of TB, leprosy and buruli ulcer is possible
- New diagnostics, drugs and vaccines are required to reduce morbidity, mortality and burden of disease

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