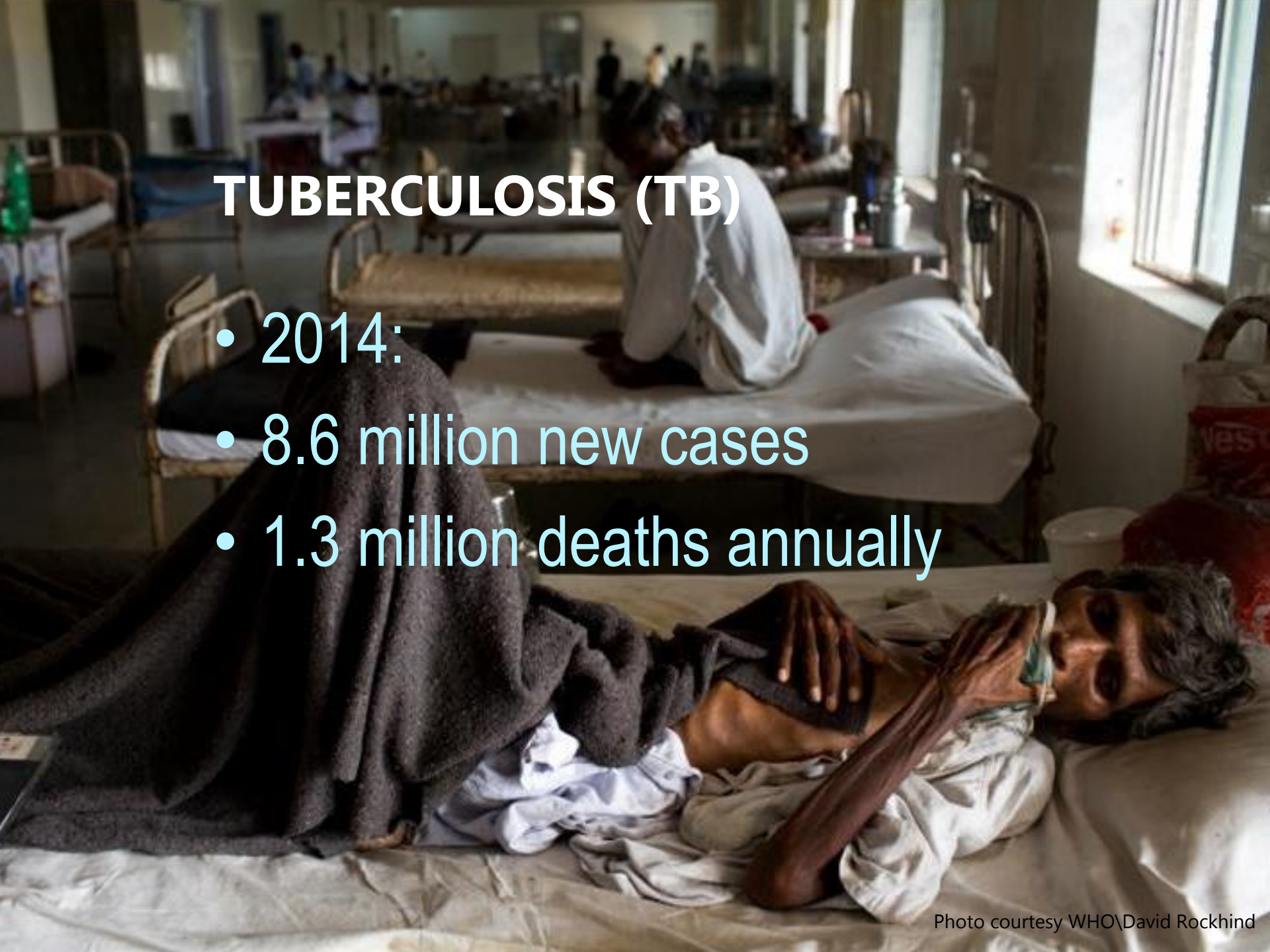
Challenges in finding new treatments for TB

Nick Paton MD FRCP

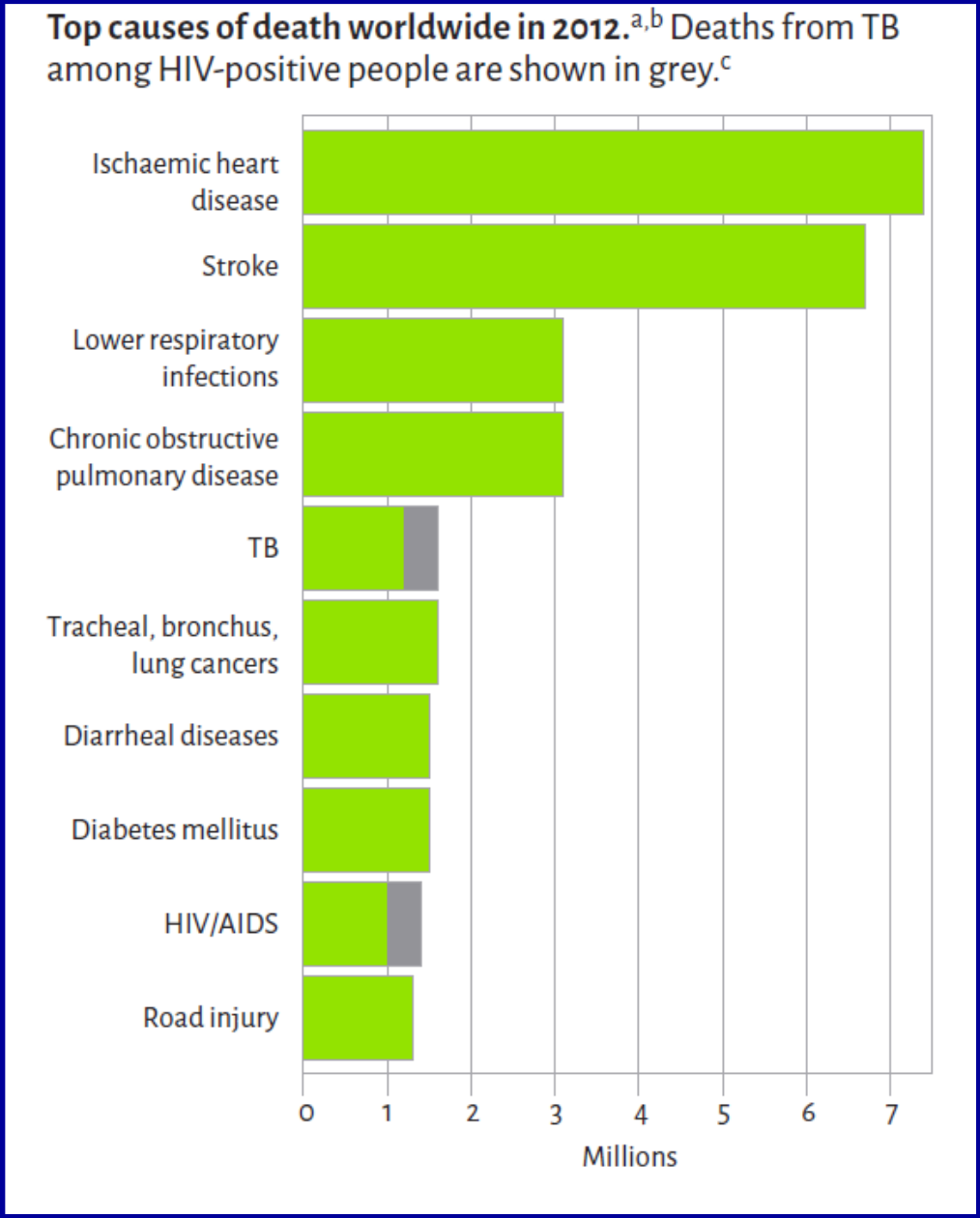
Professor of Infectious Diseases
National University of Singapore



TUBERCULOSIS (TB)

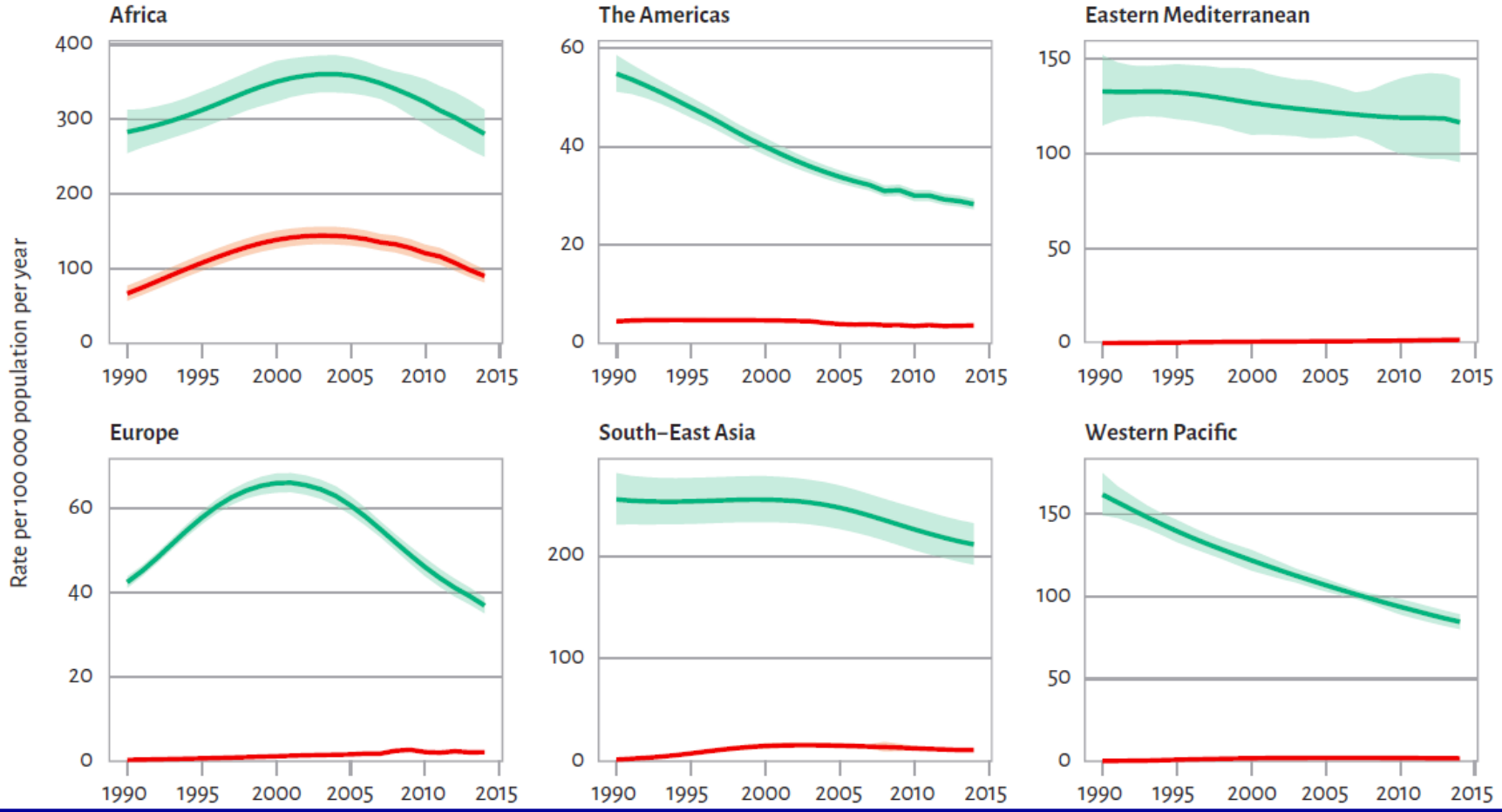
- 2014:
- 8.6 million new cases
- 1.3 million deaths annually

Photo courtesy WHO\David Rockhind

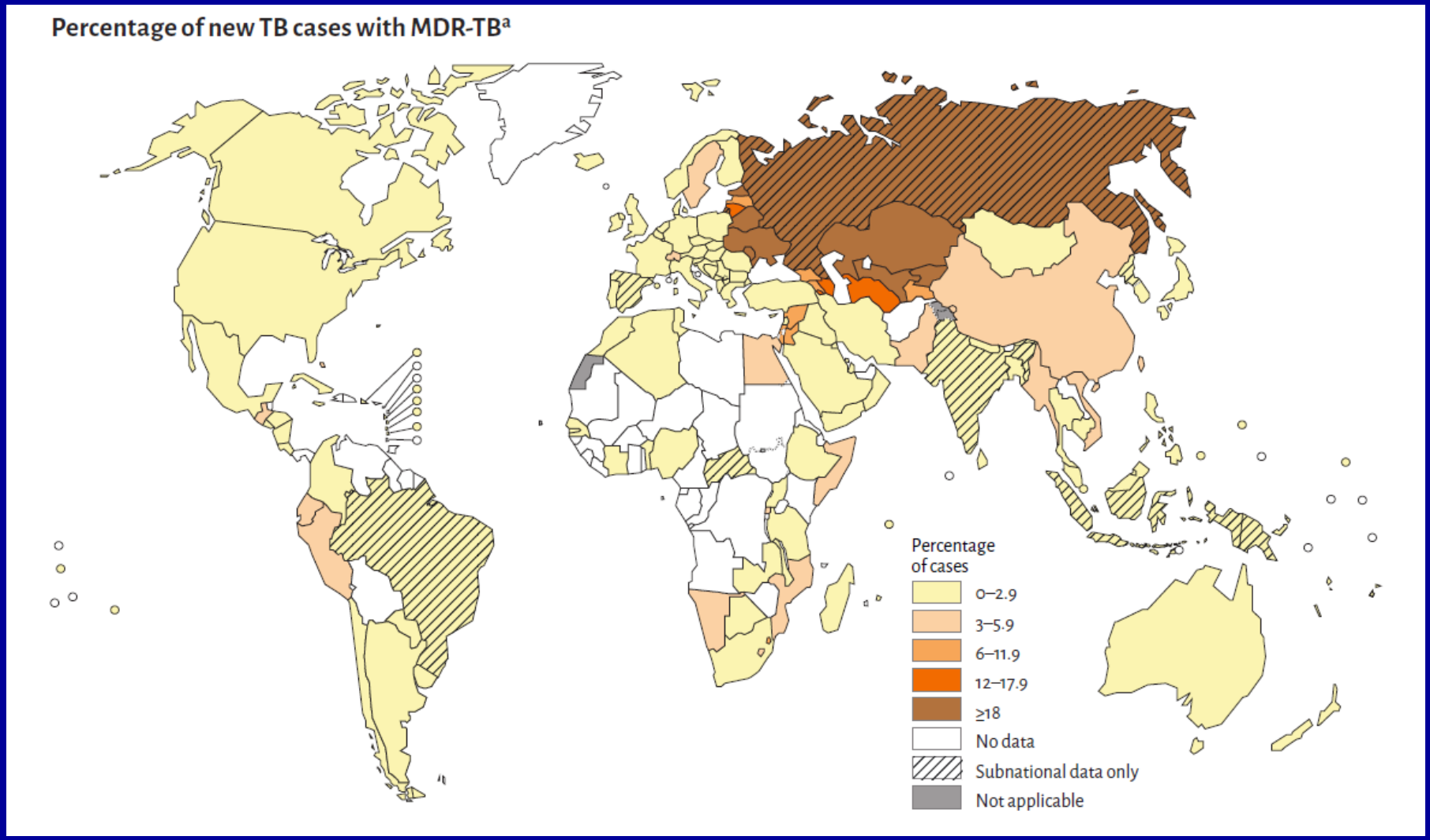


WHO TB report 2015

Estimated TB incidence rates by WHO region, 1990–2014. Estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands.



WHO TB report 2015



WHO TB report 2015

Standard TB treatment

2 months induction

- RIF, INH, PZA, EMB

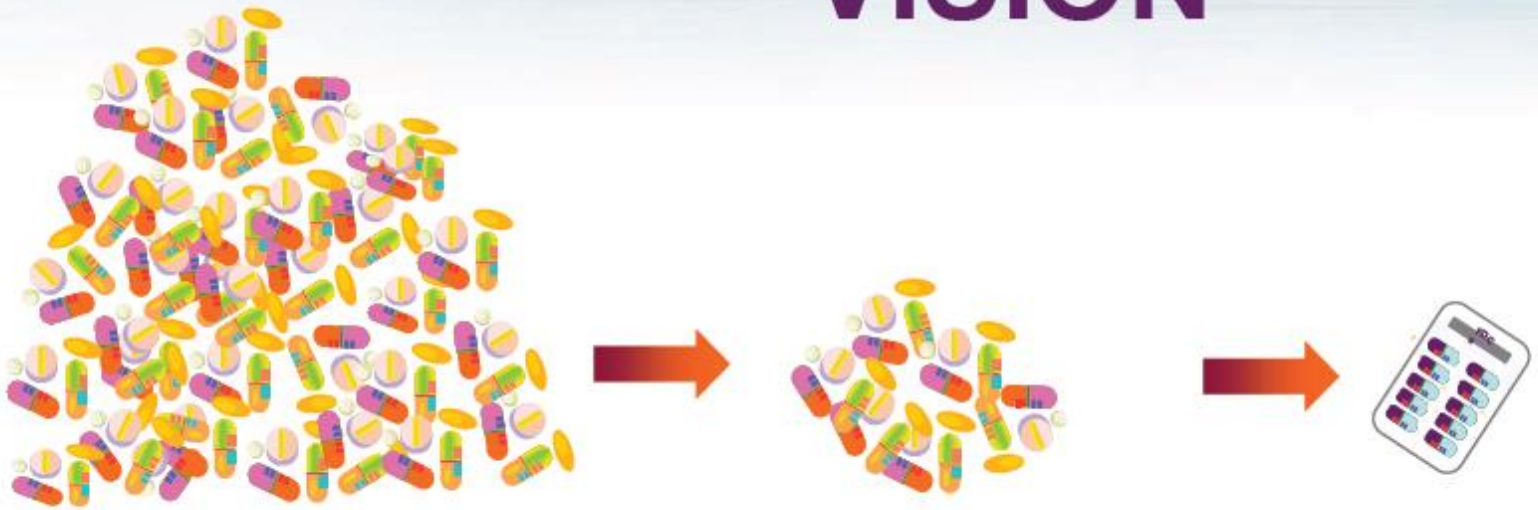
4 months continuation

- RIF & INH

*

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

VISION



6 months *2 months* *10 days*

3 approaches to shorten treatment for TB

- New drug regimens with improved activity against dormant / persistent bacteria - “sterilising activity”
- Improve the immune response to clear persistent bacteria
- Innovative treatment strategies

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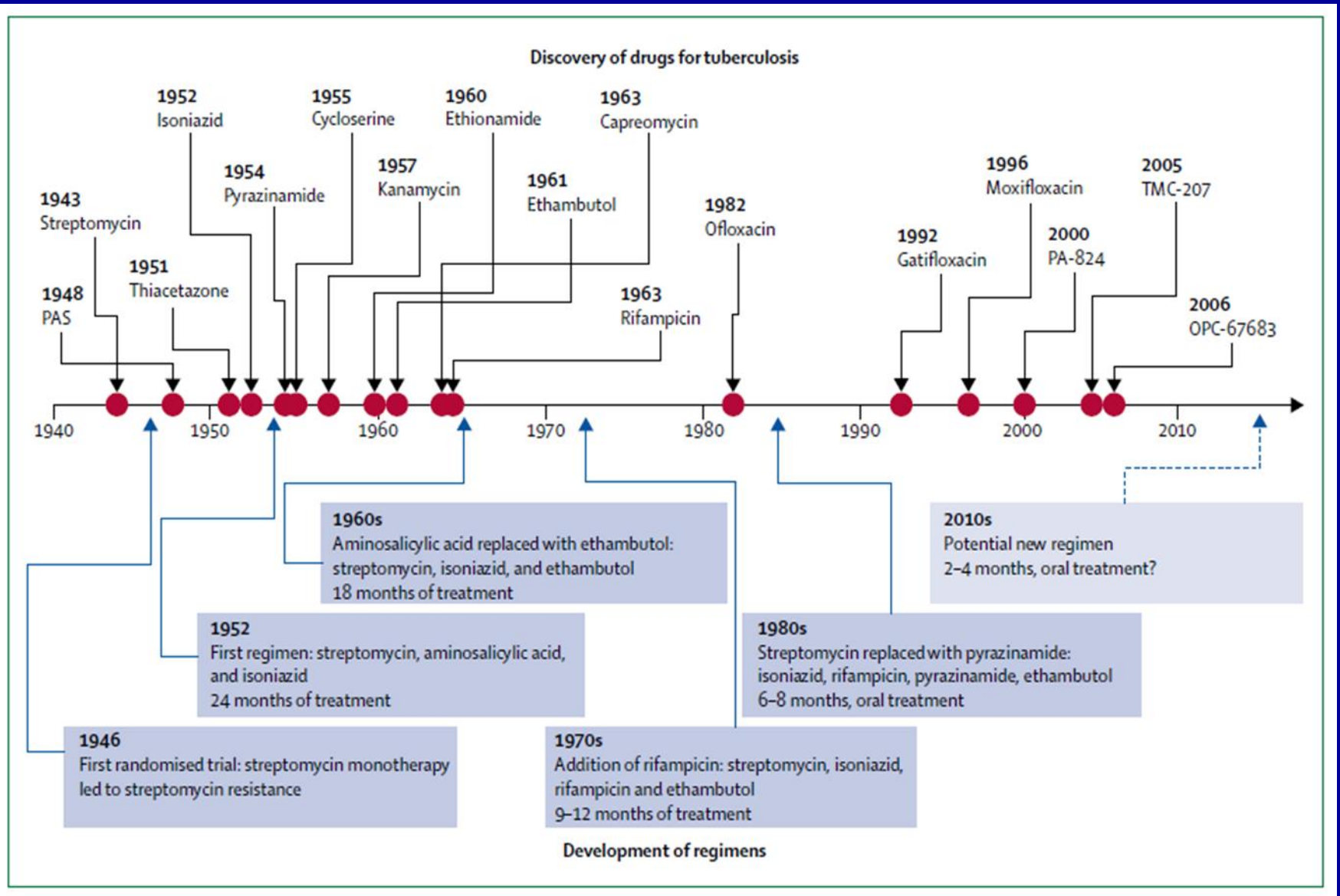

Discovery of drugs for tuberculosis
1943 Streptomycin
1948 PAS
1951 Thiacetazone
1952 Isoniazid
1954 Pyrazinamide
1955 Cycloserine
1957 Kanamycin
1960 Ethionamide
1961 Ethambutol
1963 Capreomycin
1963 Rifampicin
1982 Ofloxacin
1992 Gatifloxacin
1996 Moxifloxacin
2000 PA-824
2005 TMC-207
2006 OPC-67683
1940
1950
1960
1970
1980
1990
2000
2010
1946
First randomised trial: streptomycin monotherapy led to streptomycin resistance
1952
First regimen: streptomycin, aminosalicylic acid, and isoniazid
24 months of treatment
1960s
Aminosalicylic acid replaced with ethambutol: streptomycin, isoniazid, and ethambutol
18 months of treatment
1970s
Addition of rifampicin: streptomycin, isoniazid, rifampicin and ethambutol
9–12 months of treatment
1980s
Streptomycin replaced with pyrazinamide: isoniazid, rifampicin, pyrazinamide, ethambutol
6–8 months, oral treatment
2010s
Potential new regimen
2–4 months, oral treatment?
Development of regimens

Re-purposed drugs for TB

- Meropenem, imipenem,
- Linezolid
- Clofazimine

Testing combinations

- Many possible combinations of…..
  - old drugs
  - old drugs with modified doses
  - re-purposed drugs
  - new drugs

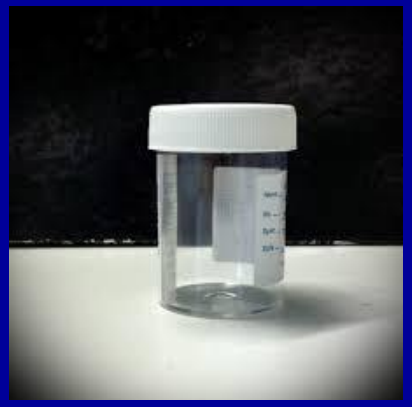
Testing new drugs / combinations

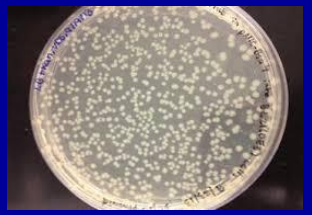
Phase I (healthy volunteers)
Dose finding / tolerability
PK / Drug interactions

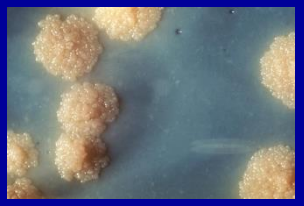
Phase II (TB patients)
EBA (2 wks.) and SSCC (8 wks.)
Quantitative Cultures / time to conversion + PK/PD

Phase III (TB patients)
Large scale clinical trials
Treatment failure / relapse
Tolerability / safety

Phase IIa: Early Bactericidal Activity (EBA) trials







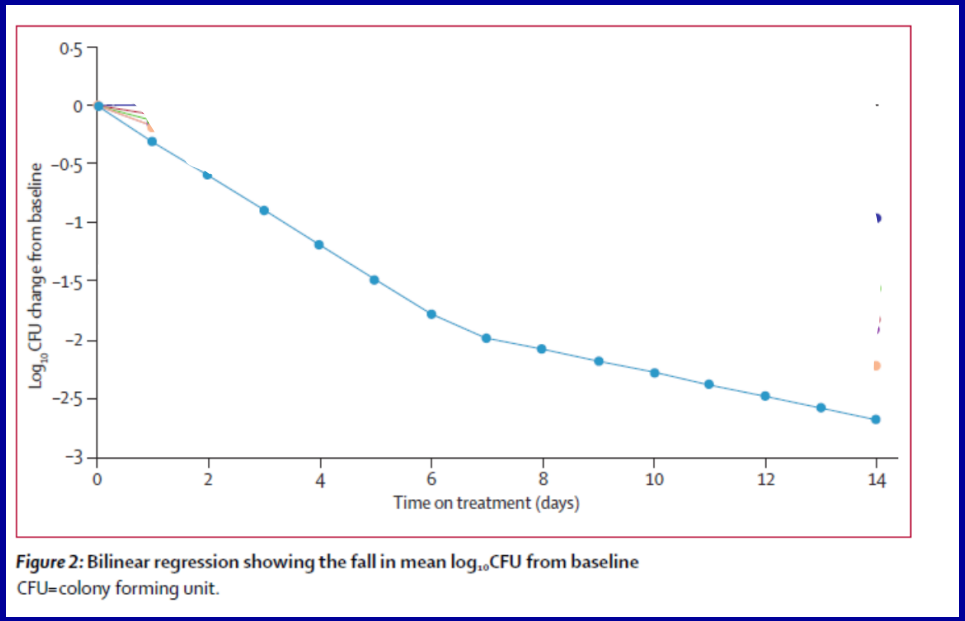
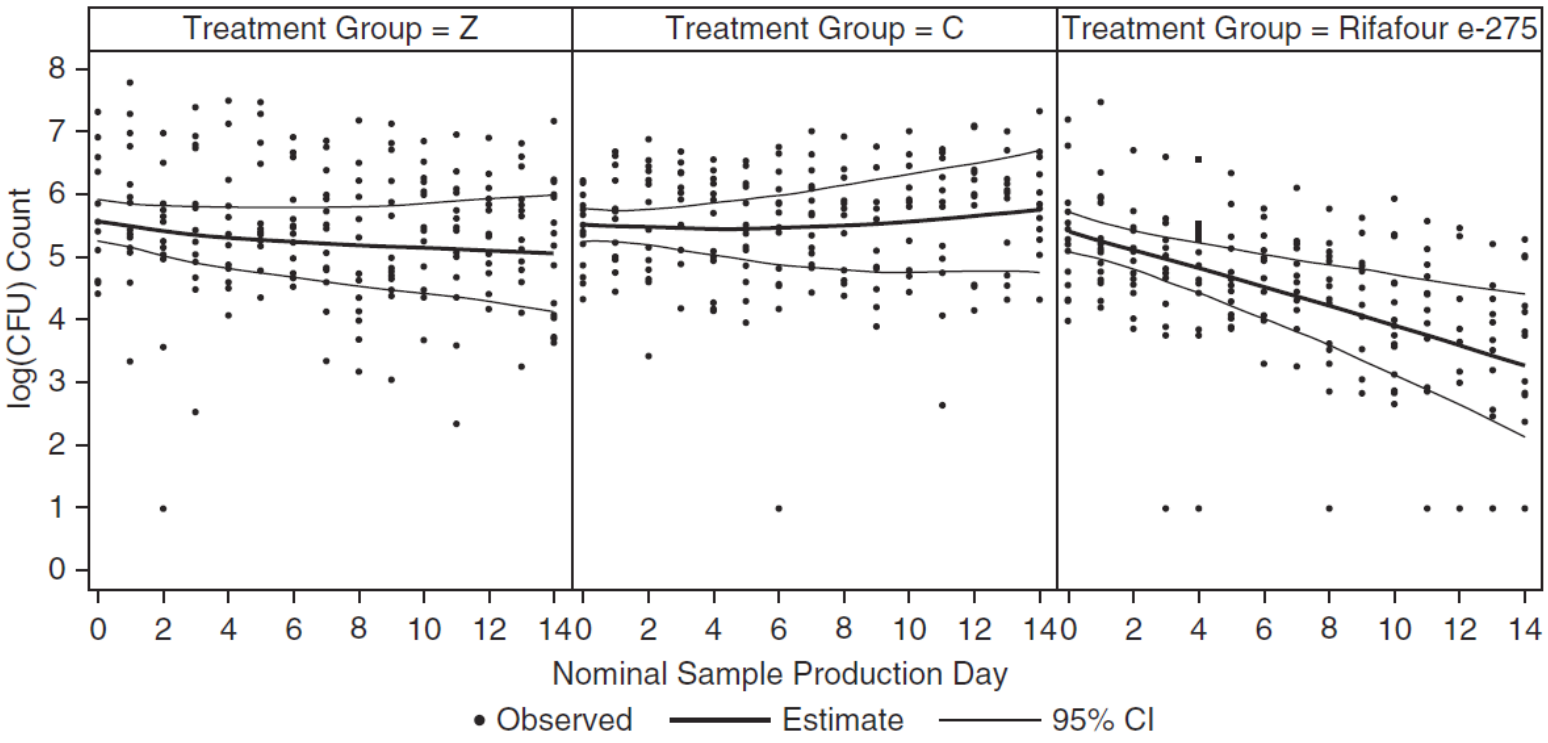


Figure 2: **Bilinear regression showing the fall in mean log_{10}CFU from baseline**
CFU=colony forming unit.

EBA ≠ sterilizing activity



Diacon et al, Am J Respir Crit Care Med 2015

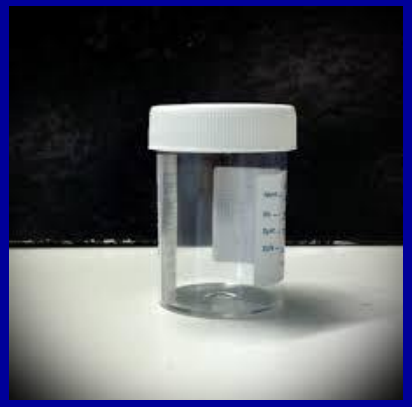
Testing new drugs / combinations

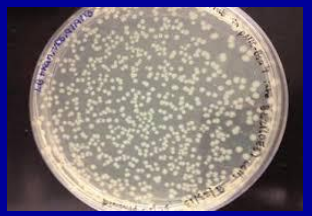
Phase I (healthy volunteers)
Dose finding / tolerability
PK / Drug interactions

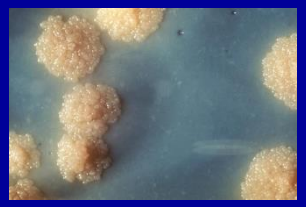
Phase II (TB patients)
EBA (2 wks.) and SSCC (8 wks.)
Quantitative Cultures / time to conversion + PK/PD

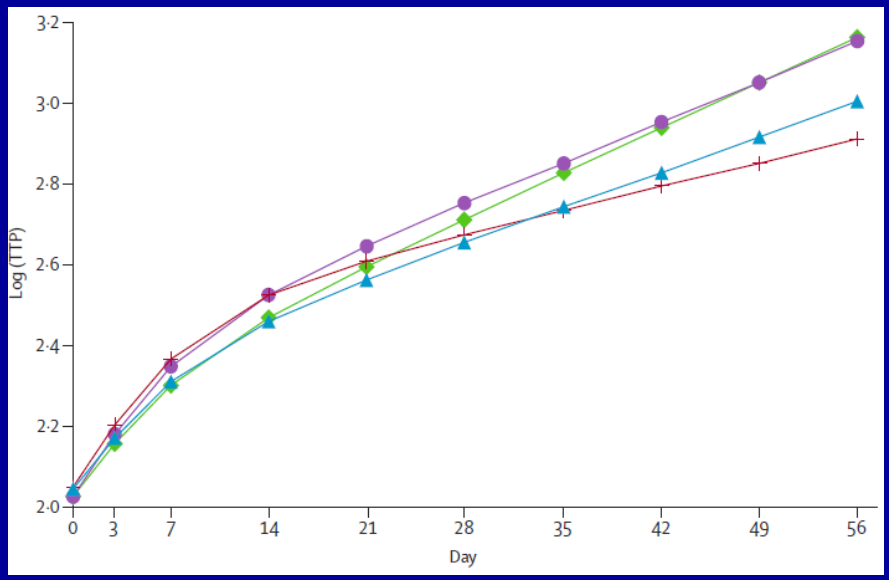
Phase III (TB patients)
Large scale clinical trials
Treatment failure / relapse
Tolerability / safety

Phase IIb: Serial sputum colony count (SSCC) trial

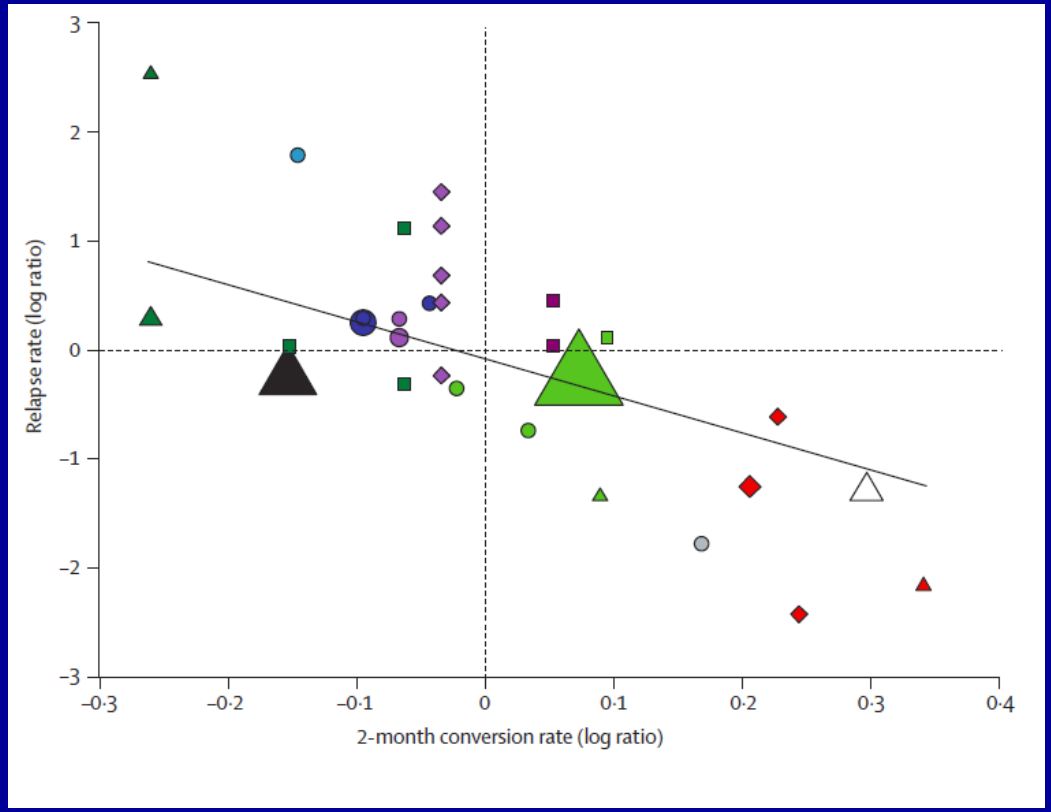








2m culture conversion ….prediction of relapse



2m culture conversion is a “reasonable predictor of sterilization in trials” but not individuals

Wallis Lancet 2010

Phase II SSCC trial: quinolones

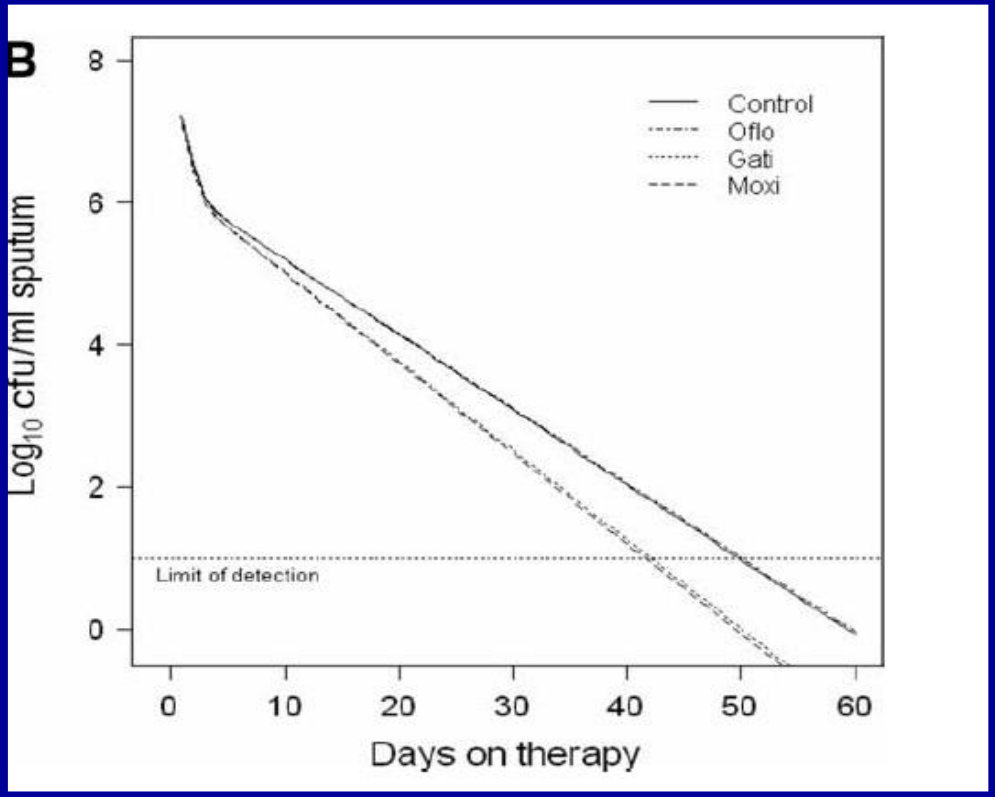


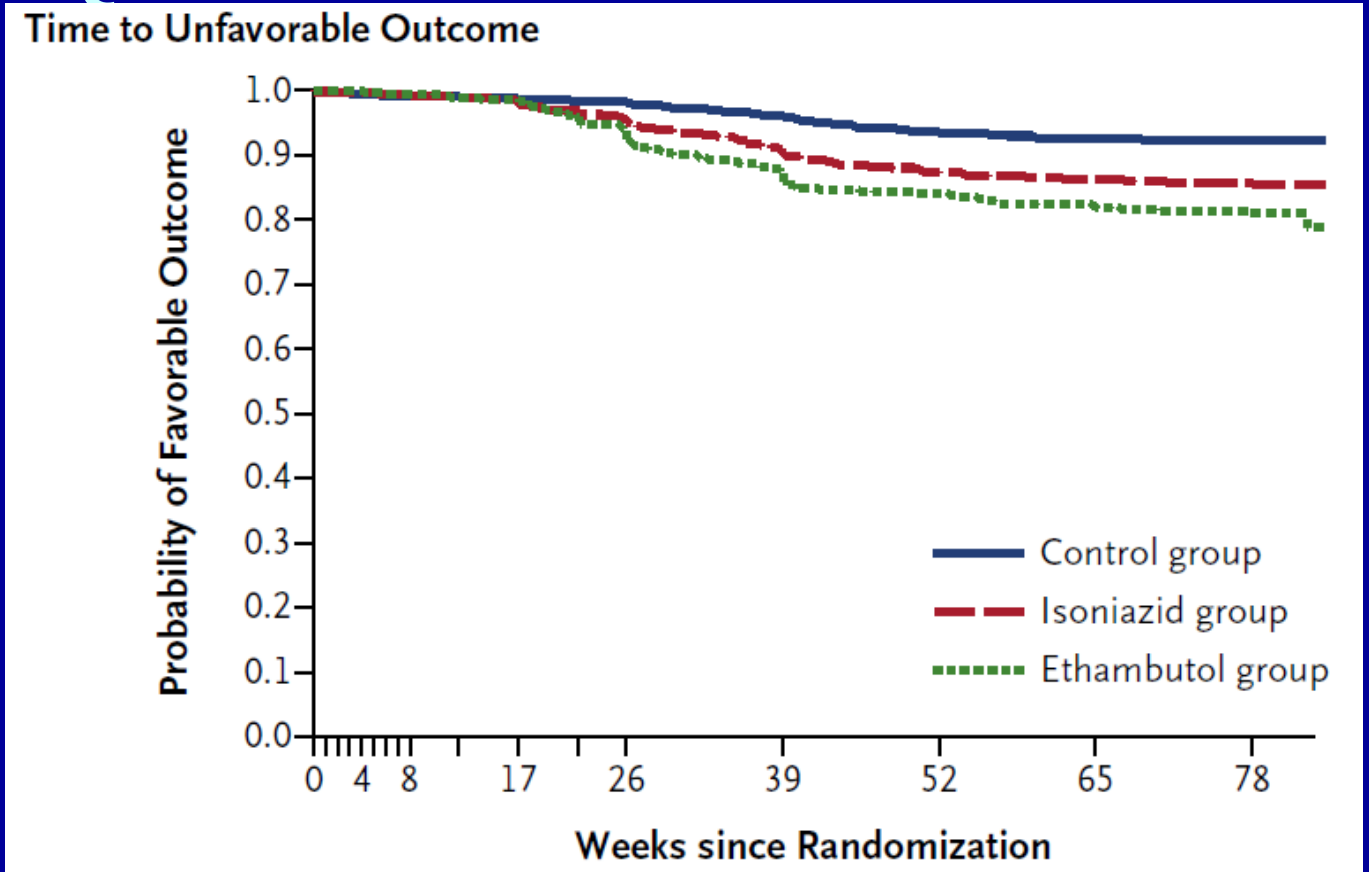
Table 5 Cox regression estimates for the speed of sputum conversion

Treatment series	Hazard ratio	*P* vs. control	95%CI
Before adjustment for covariates*			
Control	1	—	—
GFX	1.257	0.3	0.835–1.890
MXF	1.726	0.009	1.145–2.601
OFX	0.887	0.6	0.584–1.348
After adjustment for covariates*			
Control	1	—	—
GFX	1.519	0.054	0.993–2.324
MXF	1.683	0.017	1.098–2.578
OFX	0.830	0.4	0.542–1.271

* Covariates were age, sex, HIV status and radiographic extent of disease.
CI = confidence interval; GFX = gatifloxacin; MXF = moxifloxacin; OFX = ofloxacin.

Rustomjee 2008 Int. J TB Lung Dis

Quinolone trials in DS-TB

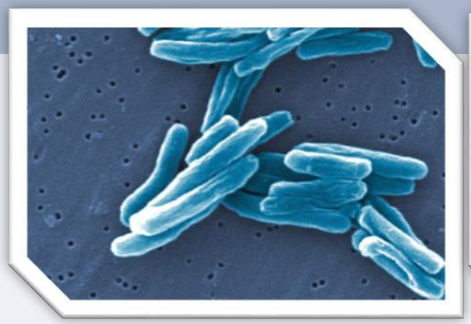


No. at Risk					
Control	600	563	533	493	472
Isoniazid	617	570	522	459	439
Ethambutol	604	568	523	445	425

Gillespie NEJM 2014

SINGAPORE
PROGRAMME OF
RESEARCH
INVESTIGATING
NEW APPROACHES TO
TREATMENT OF
TUBERCULOSIS

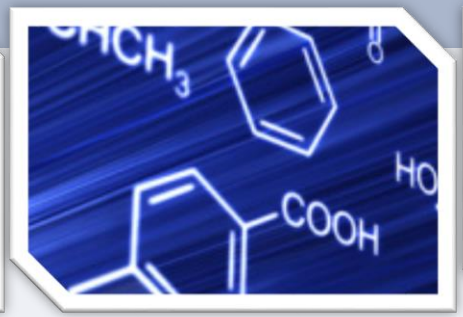
SPRINT-TB RESEARCH THEMES



Theme 1
BACTERIAL TARGET DISCOVERY

Lead: A/Prof. Thomas Dick
Department of Microbiology, NUS

Using genetic and chemical approaches to identify new mycobacterial targets.



Theme 2
DRUG DISCOVERY

Lead: Prof. Alex Matter
Experimental Therapeutics Centre, A*STAR

Screening, medicinal chemistry and pharmacology studies to develop new TB drug candidates. Preclinical devt/animal models
.

Theme 3
CLINICAL DEVELOPMENT

Lead: Prof. Nick Paton
Department of Medicine, NUS

Conducting clinical trials to evaluate safety and efficacy of new drugs with the focus on novel treatment regimens for TB.

Theme 4
TREATMENT DELIVERY

Lead: Prof. Richard Coker
School of Public Health, NUS

Studying individual and systemic barriers that hinder successful provision of effective combination therapy and develops solutions to these problems.

SPRINT TB

“Improving” Phase II TB trials

- Principle of testing drugs individually and in combination for a short period is valuable

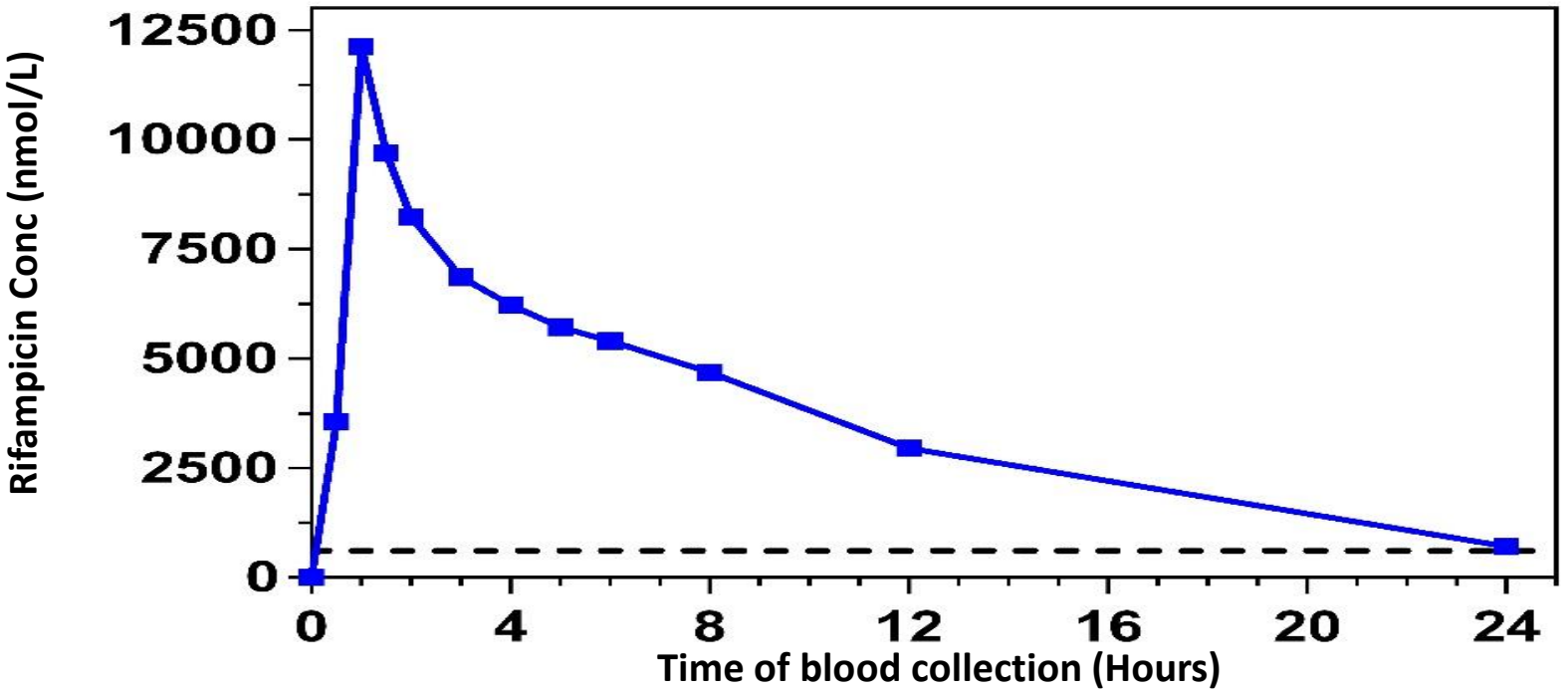
- Problem is the outcome parameters …..

New outcomes in Phase II

- Whole blood bactericidal activity
- Cultures with resuscitation promotion factors
- Transcriptomics (bacterial and host)
- Imaging

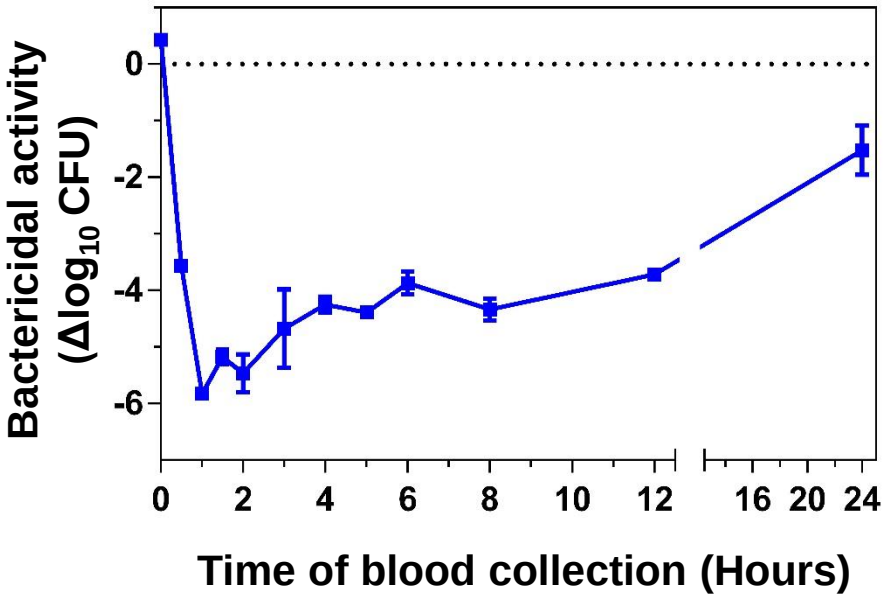
Rifampicin WBA Study

Pharmacokinetics data



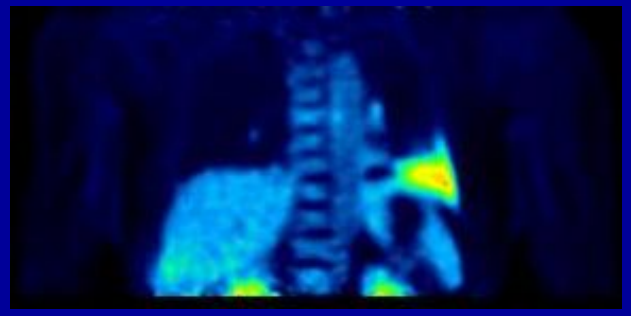
Whole Blood Bactericidal activity of Rifampicin against *M.tuberculosis* H37Rv

WBA or Bacillary Killing :
$\Delta\log_{10}$ CFU= $\log_{10}$ (*final*) - $\log_{10}$ (*initial*)

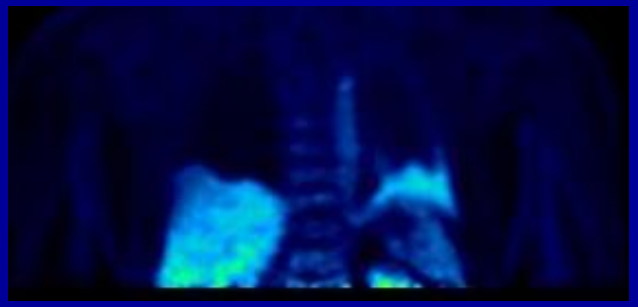


TB vs Pneumonia

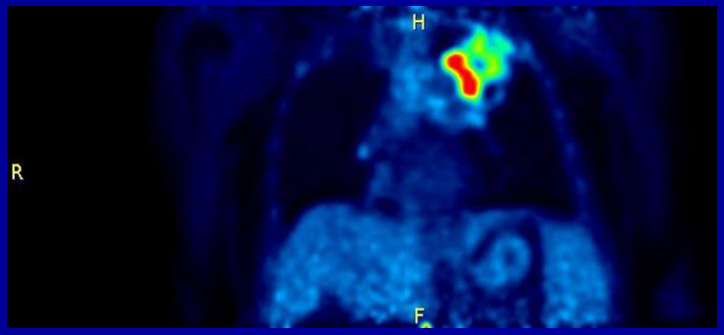
Pneumonia



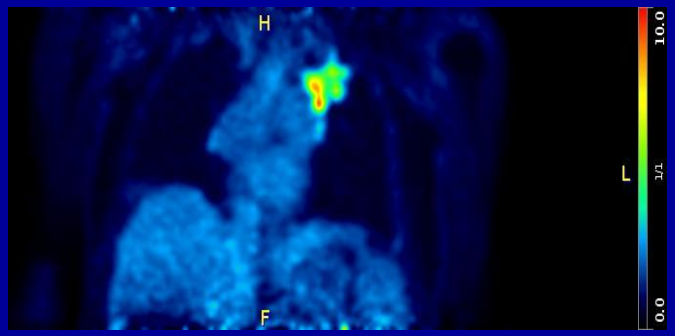
5 days



Tuberculosis



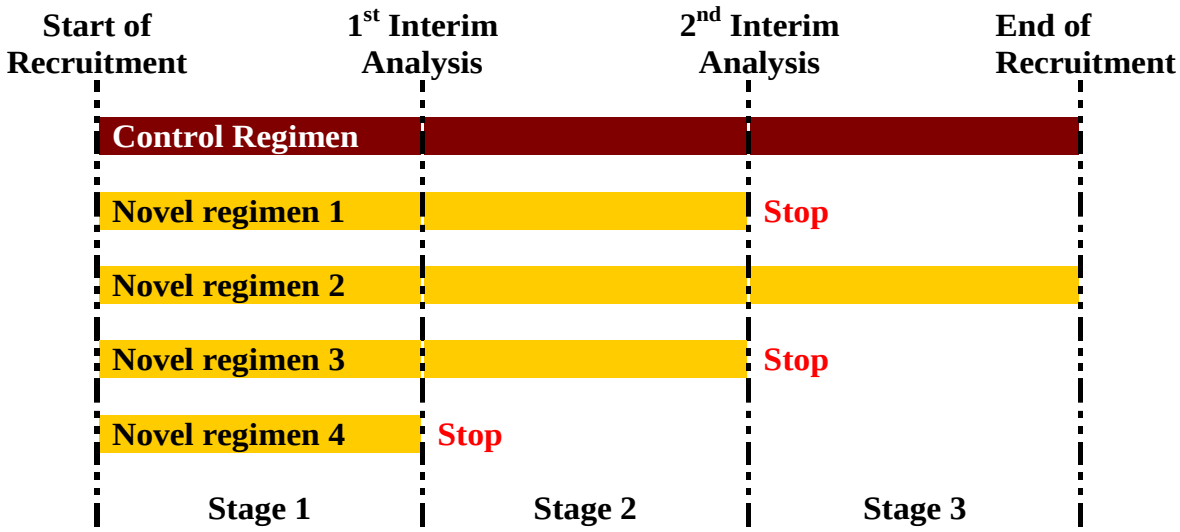
6 weeks



De-risking Phase III

- Adaptive designs
- Observational trials

Multi arm, Multi stage trial design (MAMS)



TRUNCATE-TB

CORE DELIVERABLE:
SHORTER TB TREATMENT REGIMEN

TRUNCATE-TB Trial

Standard Regimen

Arm A: 8 weeks rifampicin (10mg/kg), isoniazid, pyrazinamide, ethambutol, then 16 weeks rifampicin, isoniazid

Experimental Regimens

Arm B: 8 weeks rifampicin (35mg/kg), isoniazid, pyrazinamide, ethambutol, linezolid
Arm C: 8 weeks rifampicin (35mg/kg), isoniazid, pyrazinamide, ethambutol, clofazimine
Arm D: 8 weeks rifapentine, isoniazid, pyrazinamide, linezolid, levofloxacin
Arm E: 8 weeks isoniazid, pyrazinamide, ethambutol, linezolid, bedaquiline

Conducted in
4 countries in Asia

Recruitment starting
Q1/2017

Number of subjects
900

Design
Muti-arm, multi-stage

SPRINT TB

Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

[1]International Union Against Tuberculosis and Lung Disease, Paris, France; [2]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; [3]Damien Foundation Bangladesh, Dhaka, Bangladesh; and [4]Institute of Social and Preventive Medicine, University of Zurich, Switzerland

TABLE 1. REGIMENS SEQUENTIALLY USED IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS, BANGLADESH DAMIEN FOUNDATION PROJECTS

Regimen (sequence)	Intensive Phase	Continuation Phase 1	Continuation Phase 2	Patients Enrolled	
				Number	Col %
1	3* KCOEHZP	12 OEHZP	6 EP	59	13.8
2	3(+) KCOEHZP	12 OHEZP		44	10.3
3	3(4) KCOEZP	12 OEZP		35	8.2
4	3(+) KCOEHZP	12 OHEZ		45	10.5
5	3(+) KCOEHZP	12 OHEZC		38	8.9
6	4(+) KCGEHZP	5 GEZC		206	48.2
Total number of patients enrolled				427	100.0

Definition of abbreviations: C = clofazimine; Col % = column percent; E = ethambutol; G = gatifloxacin; H = isoniazid; K = kanamycin; O = ofloxacin; P = prothionamide; Z = pyrazinamide.

Am J Respir Crit Care Med Vol 182. pp 684–692, 2010

Results from the initial 9m regimen cohorts

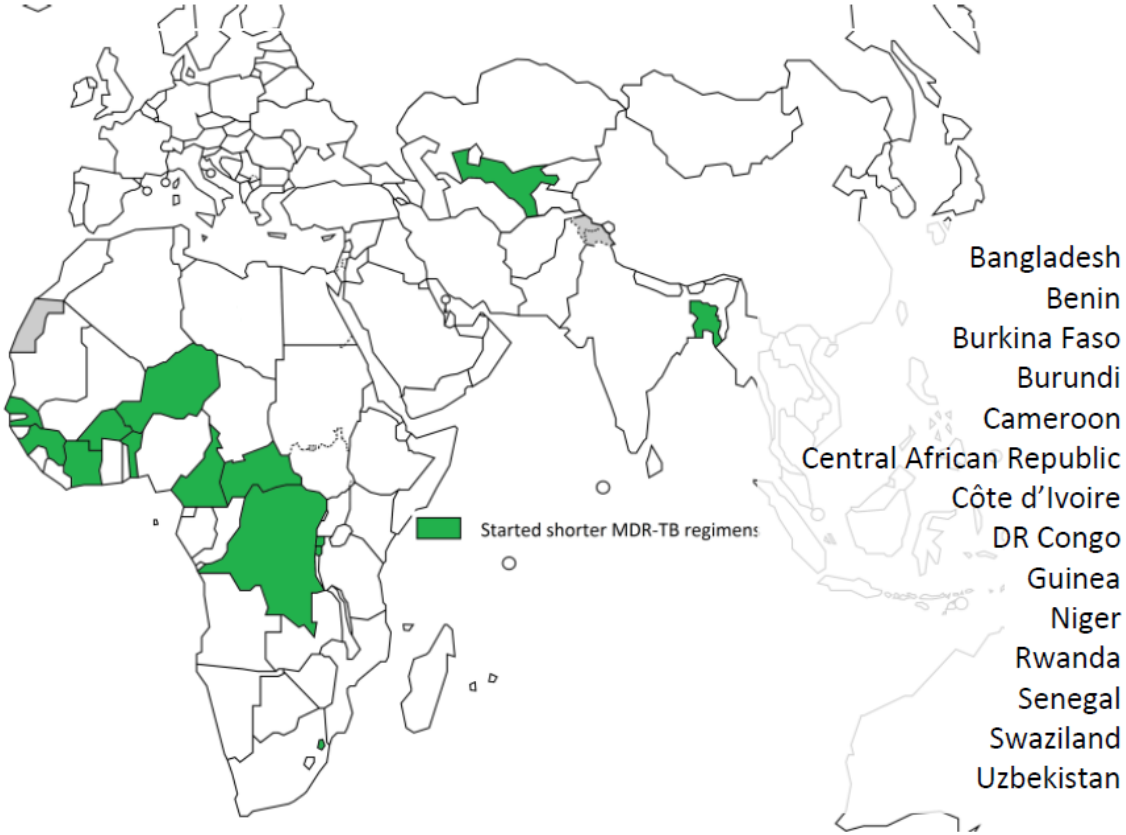
Original cohort (206 pts)		*Updated cohort (515 pts)*
Cure	82.5%	81.2%
Completion	5.3%	3.3%
Default	5.8%	7.8%
Death	5.3%	5.6%
Failure	0.5%	1.4%
Relapse	0.5%	0.8%
Overall success rate:		Overall success rate:
87.9% (95% CI 82.7, 92.6)		84.5% (95% CI 0.81, 0.88)

Am J Respir Crit Care Med Vol 182. 684–692, 2010

Aung et all, IJTLD 18(10):1180–1187, 2014

Countries using the shorter MDR-TB regimen

(in addition, Ethiopia, South Africa, Viet Nam and Mongolia are participating in the clinical trial)



Bangladesh
Benin
Burkina Faso
Burundi
Cameroon
Central African Republic
Côte d'Ivoire
DR Congo
Guinea
Niger
Rwanda
Senegal
Swaziland
Uzbekistan

WHO May 2016

World Health Organization

THE SHORTER MDR-TB REGIMEN

WHO May 2016

SINGAPORE
PROGRAMME OF
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