International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB)

The Story So Far

InterTB Symposium 2015

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DENNY

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Special Mycobacterial Populations

- Model systems were set up in vitro to explore the reasons why rifampin is a better sterilizing drug than isoniazid in short-course chemotherapy of tuberculosis.

- When the growth rate of Mycobacterium tuberculosis strain H37Rv was reduced uniformly by lowering the incubation temperature or the pH of the culture medium, the bactericidal activity of rifampin and isoniazid decreased to a similar extent.

- However, when a culture was maintained at 8 degrees C and incubated for daily periods of 1 or 6 h at 37 degrees C, rifampin killed more rapidly than isoniazid.

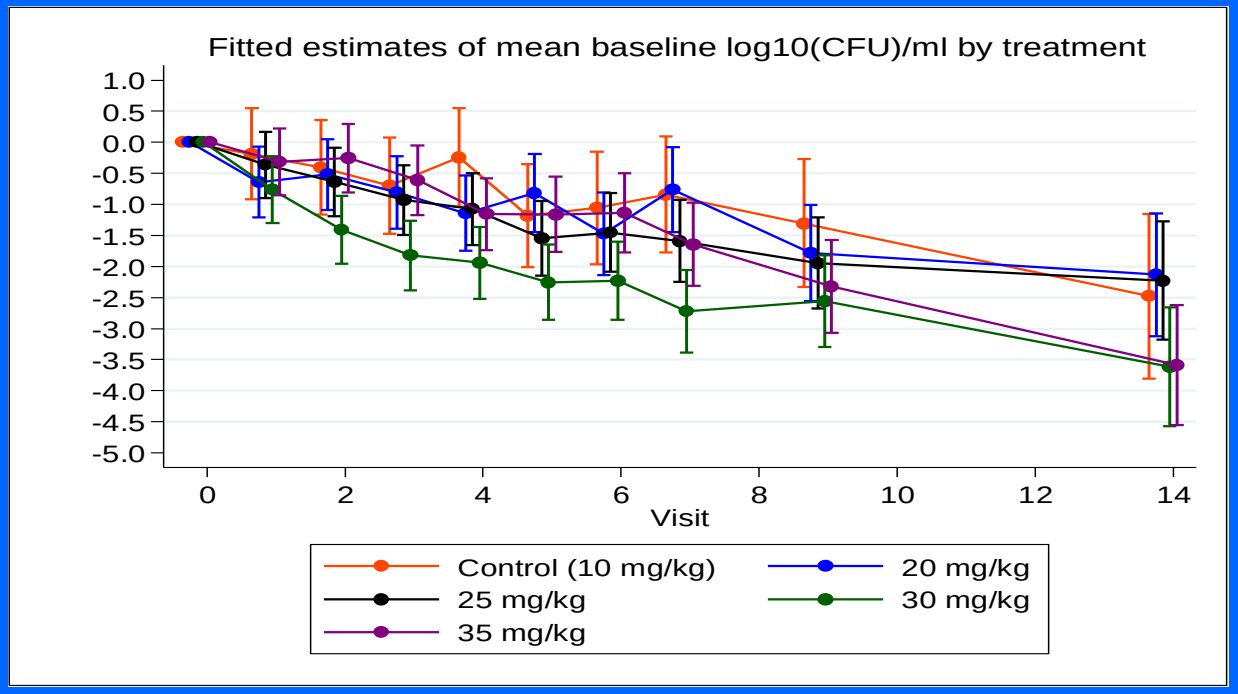
- These experiments supported the view that the special part of the bacterial population that is killed more rapidly by rifampin than by isoniazid during short-course chemotherapy consists of bacilli dormant much of the time but occasionally metabolising for short periods

Am Rev Respir Dis. 1981 Apr;123(4 Pt 1):367-71.
Experimental models to explain the high sterilizing activity of rifampin in the chemotherapy of tuberculosis.
Dickinson JM, Mitchison DA.

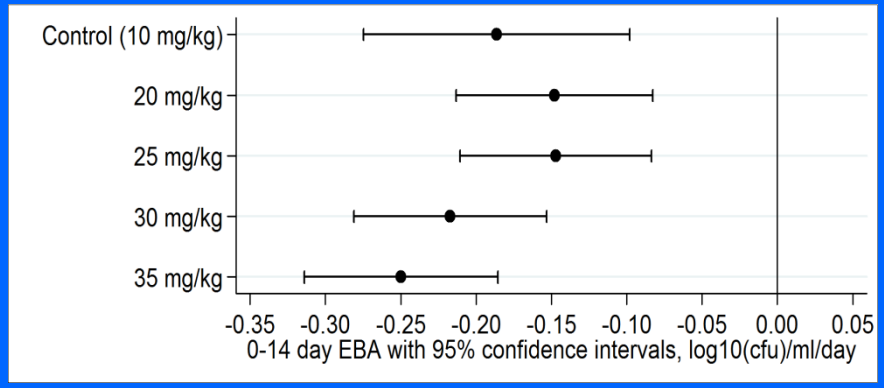
Jindani EBA Study

Mean Fall in Sputum Colony Counts					
Regimen		Number	Fall in colony count (log10 cfu/day) Days		
Drug	Dosage		0 to 2	2 to 14	0 to 14
No drug		4	-0.024	-0.023	-0.024
T	150 mg	8	0.067	1.037	0.037
P	15 g	4	0.259	0.076	0.096
Z	2 g	9	0.044	0.113	0.110
R	10 mg/kg	8	0.187	0.096	0.113
S	1 g	4	0.094	0.128	0.119
M	25 mg/kg	4	0.246	0.160	0.177
H	300 mg	4	0.722	0.113	0.192
SH		4	0.510	0.066	0.123
HM		4	0.702	0.051	0.140
HZ		4	0.494	0.098	0.155
RM		4	0.558	0.124	0.174
SZ		4	0.118	0.176	0.199
SR		4	0.325	0.210	0.230
HR		4	0.714	0.227	0.287
SHR		4	0.321	0.146	0.168
HRM		4	0.487	0.121	0.178
SHZ		4	0.799	0.153	0.246
SHRZ		4	0.685	0.161	0.232
SHRZM		4	0.686	0.200	0.273
Mean of drug containing regimens			0.422	0.129	0.171

PanACEA Study

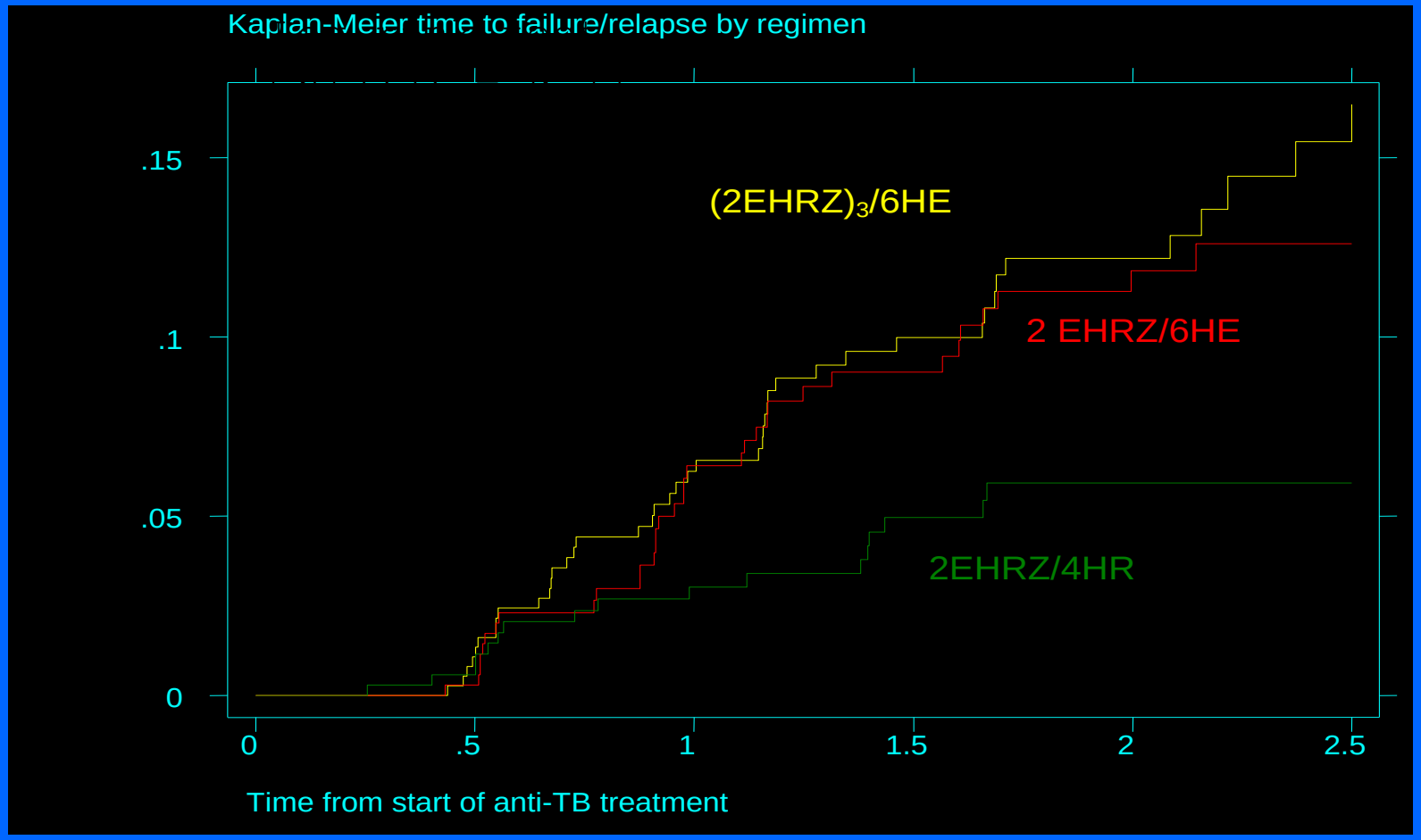


Martin J. Boeree, Andreas H. Diacon, Rodney Dawson, Kim Narunsky, Jeannine du Bois, Amour Venter,Patrick P. J. Phillips, Stephen H. Gillespie, Timothy D. McHugh, Michael Hoelscher, Norbert Heinrich, Sunita Rehal, Dick van Soolingen, Jakko van Ingen, Cecile Magis-Escurra, David Burger, Georgette Plemper van Balen, and Rob E. Aarnoutse; on behalf of the PanACEA Consortium. A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis. American Journal of Respiratory and Critical Care Medicine 2015; 191(9): 1058-1065.



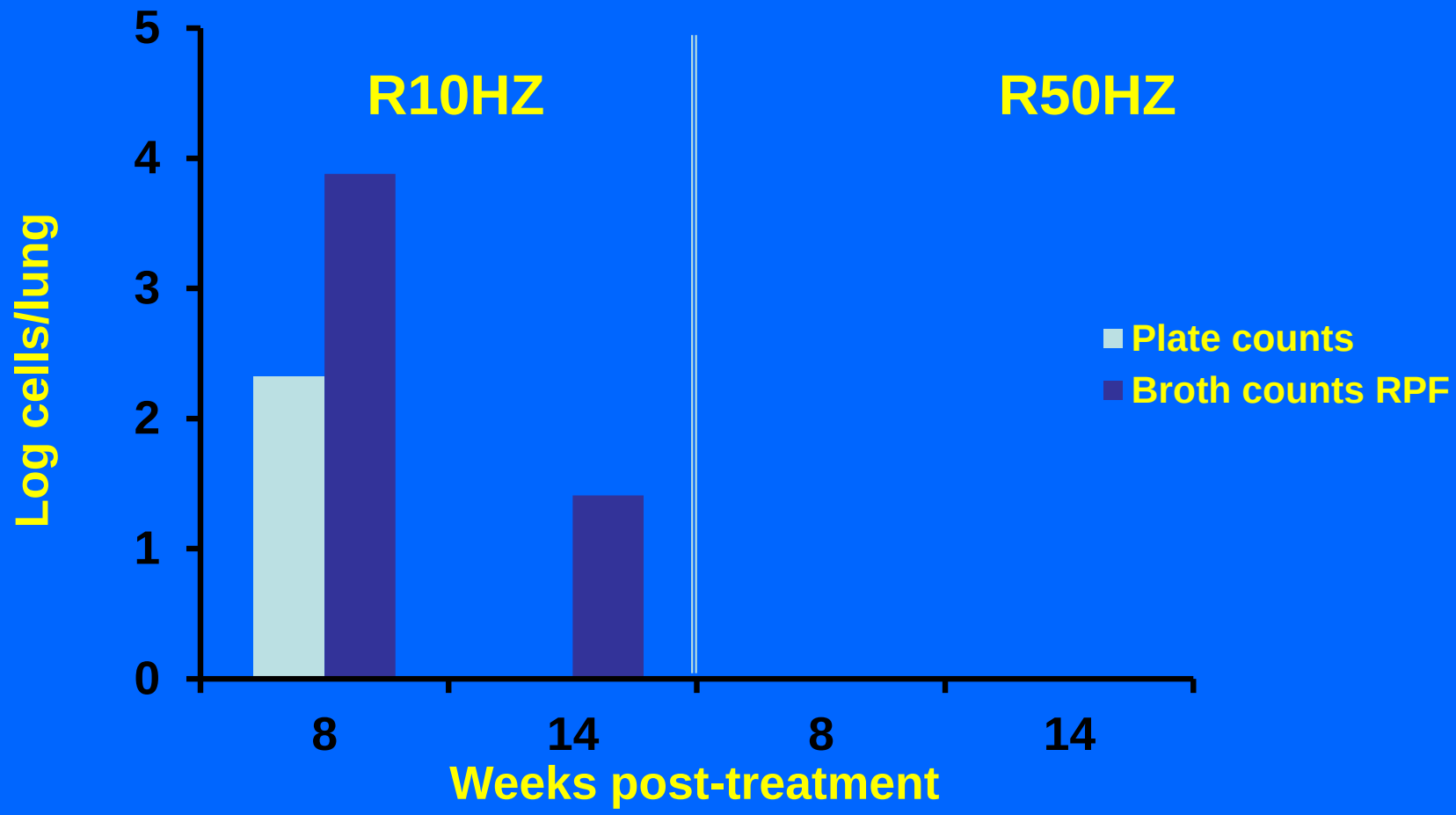
IUATLD Study A

Jindani A, Nunn AJ, Enarson DA. 2004. Lancet;364:1244-1251



N at risk (range)	365-395	346-367	265-302	217-240	162-175

No RPF-dependent persisters after treatment with high dose rifampicin regimen



Hu Y, Liu A, Ortega-Muro F, Alameda-Martin L, Mitchison D and Coates A.
High-dose rifampicin kills persisters, shortens treatment duration, and reduces relapse rates *in vitro* and *in vivo*.
Frontiers in Microbiology. 2015.6:1-10.

Schedule of Investigations for the Persister and TranscriptomeStudy

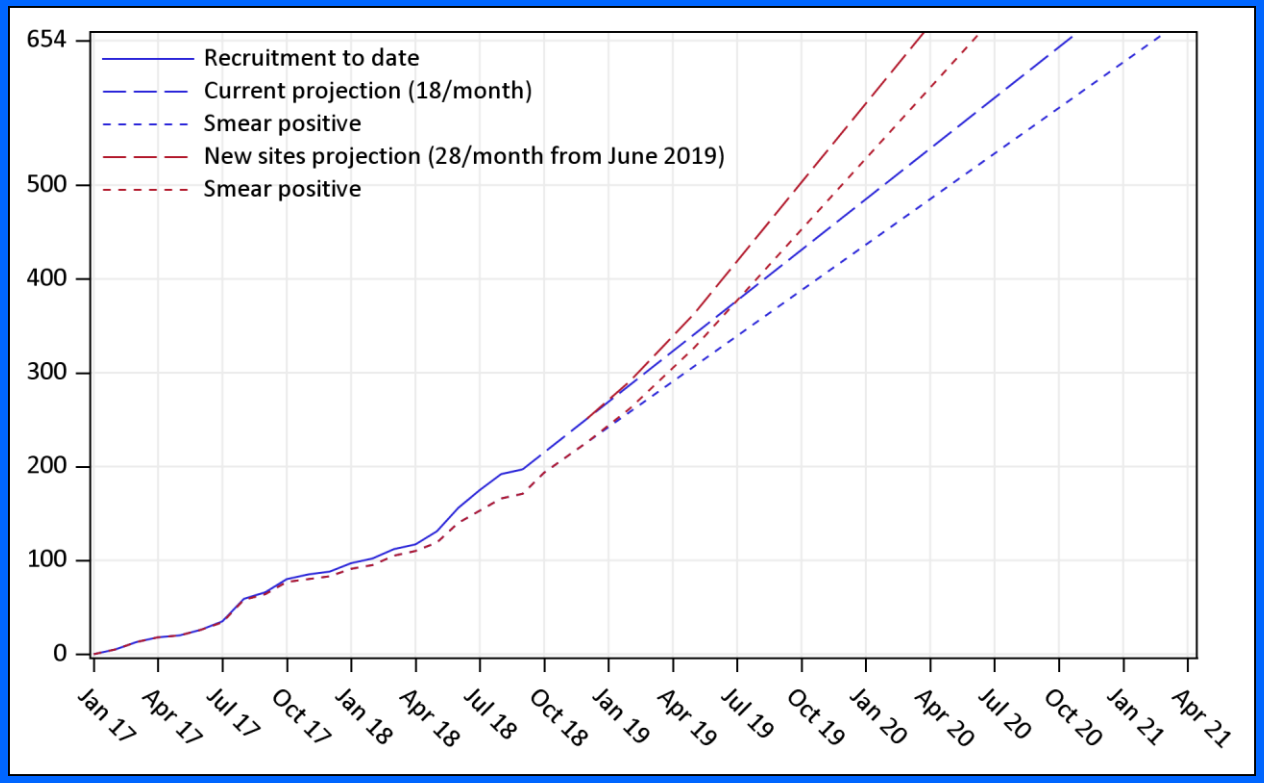
Study	(Patient no.)	Consent	Sputum
RIFASHORT Trial • **Gaborone** • **Mbarara**	n=214** 100 114	S, E	S, E, m2-18 inclusive
Case-Control	n=195 (95 +100) 65 in each arm	S, E	W0, **w2**, **w4,** w8
Transcriptome	n=60 (30 +30) 20 in each arm	S, E	W0, **d3,** **w2**, **w4**, w8
Validation	n=300*** (including SA sites) 100 in each arm		w4 (smear only)

n – no. patients; S- screening visit; E- Enrolment visit (t=0); m – month; w – week; d – day; # Bold indicates extra visit; Underline indicates extra sample; **African Sites only. * Extra smears will be obtained from the South American sites (n= >600) to achieve these numbers. Note that clinical metadata will be collected at enrolment and progress monitored by repeat chest X-rays together with blood and urine samples at appropriate intervals.**

Current Phase III Trials

- Alliance SimpliciTB Trial
- TBTC Study 31
- INTERTB RIFASHORT Trial

Projected Recruitment



Advances in Clinical Trial design

Report of the Technical Consultation

on

Advances in Clinical Trial Design for Development of New TB Treatments

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Glion-sur-Montreux, Switzerland

14-16 March 2018

DRUG SELECTION

- How do we select the drug combinations?

Rifampicin V. Rifapentine

- TBTC Study 31
- RIFASHORT Trial

BIOMARKERS

- Are biomarkers of any use?

Getting the Duration Right

- No treatment
- Indefinite treatment
- 18 months treatment
- 6 months treatment
- 4 months treatment
- One shot treatment

Getting the Economics Right

Will it?

Won't it?

Prospects for Advancing Tuberculosis Control Efforts through Novel Therapies

The introduction of new, shorter treatment regimens could dramatically accelerate the reductions in TB incidence and mortality that are expected under current regimens – with up to 2- or 3-fold increases in rates of decline if shorter regimens are accompanied by enhanced case detection.

J.A. Salomon, J.O. Lloyd-Smith, W.M. Getz, S. Resch, M.S. Sanchez, T.C. Porco, M.W. Borgdorff

PLOS Med Aug 2006, Volume 3, Issue 8.

Population-Level Impact of Short-Course Regimens for Tuberculosis: A Model-Based Analysis

These findings suggest that novel regimens that shorten treatment duration may have only a modest effect on TB transmission except in settings of very low treatment completion.

M.O. Fofana, G.M. Knight, G.B. Gomez, R.G. White, D.W. Dowdy.

PLOS One May 2014, Volume 9, Issue 5.

Cost Effectiveness

The introduction of a non-inferior 4-month first-line TB regimen into South Africa would have little impact on the TB burden.

However, under several scenarios, it is likely that the averted societal costs would make such a regimen cost-effective in South Africa.

Knight GM, Gomez GB, Dodd OJ,Dowdy D, Zwerling A, Wells WA, Cobelens F, Vassall A, White RG.

The Impact and Cost-Effectiveness of a Four-Month Regimen for First-Line Treatment of Active Tuberculosis in South Africa.

PLoS One. 2015 Dec 30;10(12):e0145796. doi: 10.1371/journal.pone.0145796. eCollection 2015

Trials in LTBI

- Peristent
- Dormant
- Latent

And What About Their Human Rights

- Addressing the Human Rights on TB Patients

UN HLM

UN HLM

- We need increased investments, especially in science and research, and we need new medicines, new vaccines, and new diagnostics." - Tedros Adhanom Ghebreyesus, Director General of the WHO.

- "We also need better tools to end the TB epidemic. Recently, we've witnessed encouraging research progress toward the development of improved TB vaccines and treatment regiments." -Bill Gates, Co-Chair of BMGF.

- "Investing in research and development is critical if we are to develop new diagnostics, vaccines, and medicines. It is only with new tools that we can achieve dramatic reduction in the incidence of tuberculosis." -Cyril Ramaphosa, President of South Africa.

Quo Vadimus

- Yet the disease does not receive anywhere near the attention it deserves. Care, treatment and diagnostics remain woefully underfunded. Despite the fact that the number of new people being diagnosed with TB every year is decreasing, the overall number of people living with TB is at an all-time high as we fail to cure people already living with the disease.

- An estimated two in every five people who fall sick with the disease are left undiagnosed and untreated.

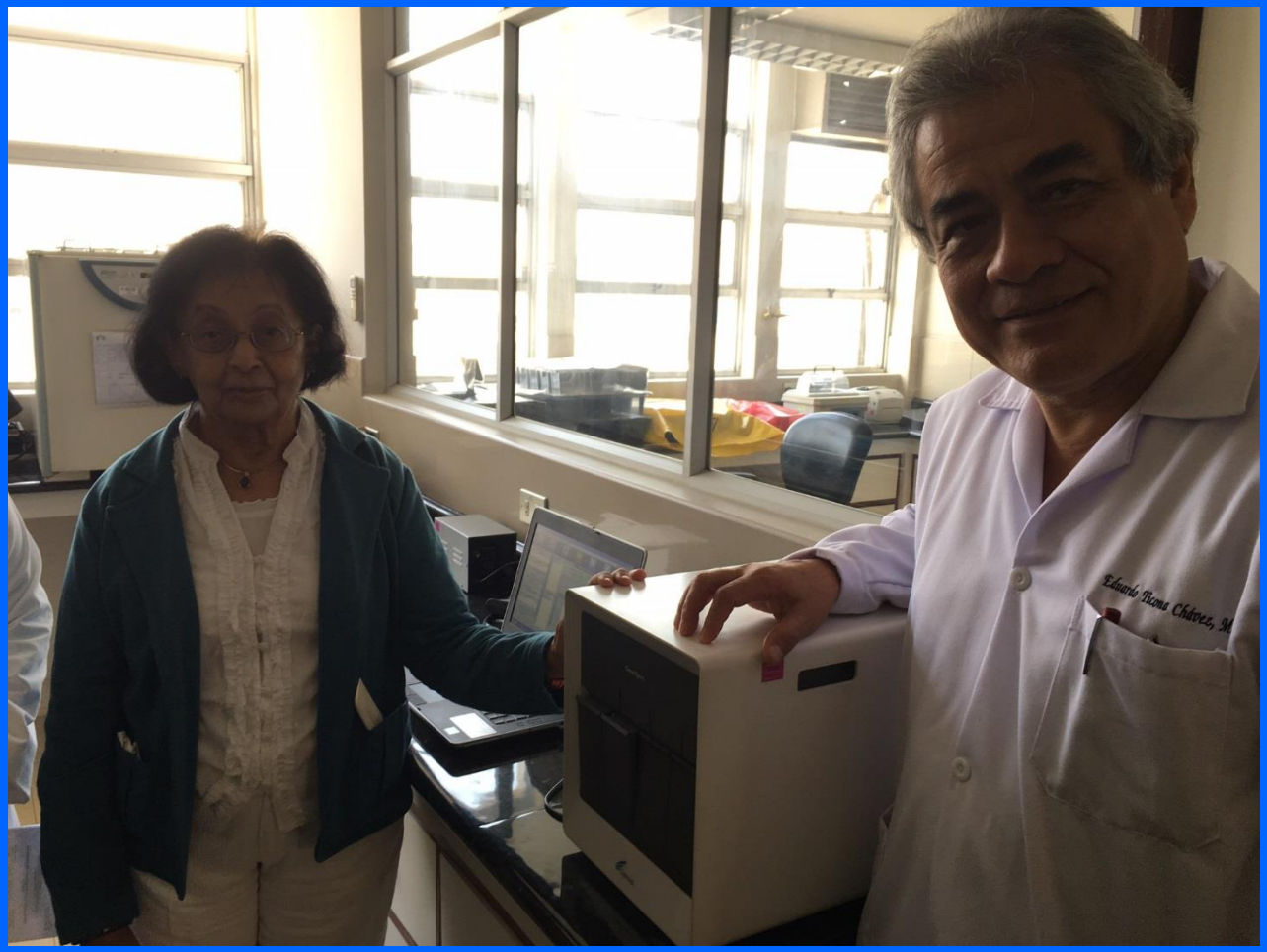
- Medicines to treat TB have barely improved in 50 years.

Dr Bern-Thomas Nyang'wa is a TB specialist at Médecins Sans Frontières/Doctors Without Borders (MSF). June 1st, 2017

World Without TB

A UK registered charity
whose mission is
the global eradication of tuberculosis.

Donating Xpert Machine to Hospital Dos de Mayo, Lima



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Centrifuge for Ignace Deen Hospital, Conakry

LEST WE FORGET

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