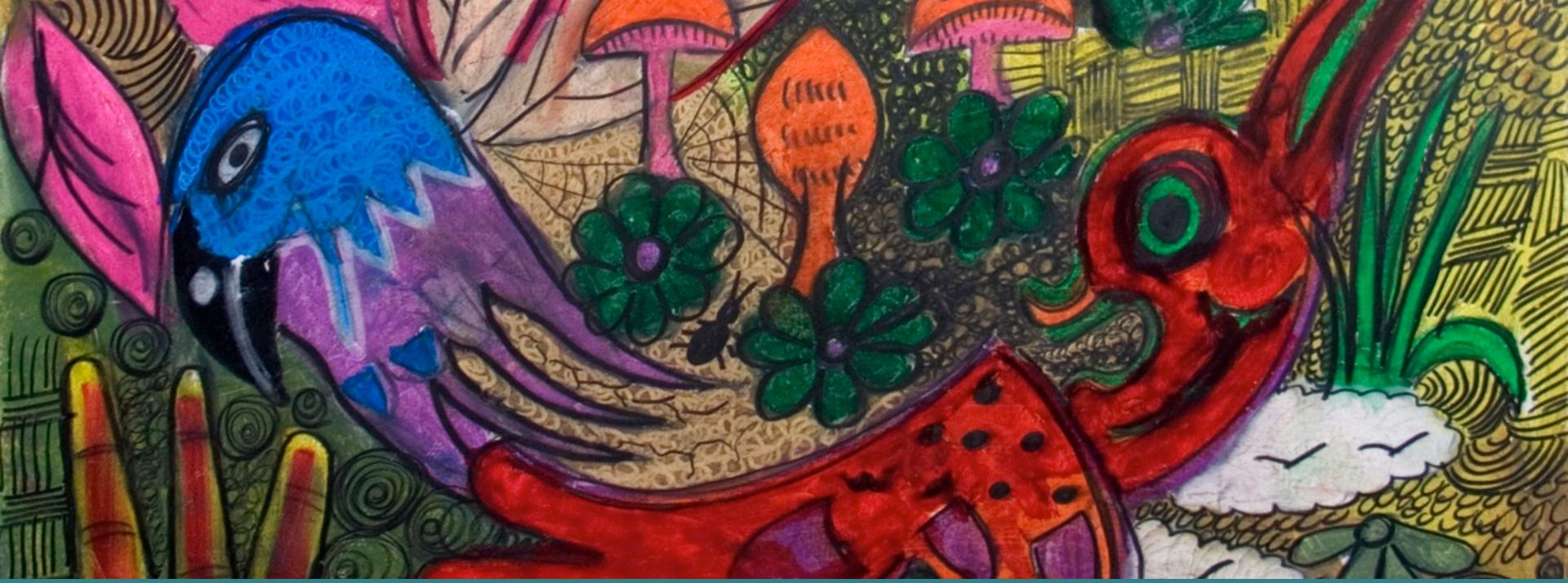

Clinical development strategies and trial designs for new TB treatment regimens: Bedaquiline case study

Myriam Theeuwes, Compound Development Team Leader

Workshop on Update of TB guideline
November 25, 2016

Julius Caesar Bustamante – *Pajaros*
Artwork from Healing Arts Initiative, a nonprofit organization that inspires healing, growth and learning through access to the arts for the culturally underserved.

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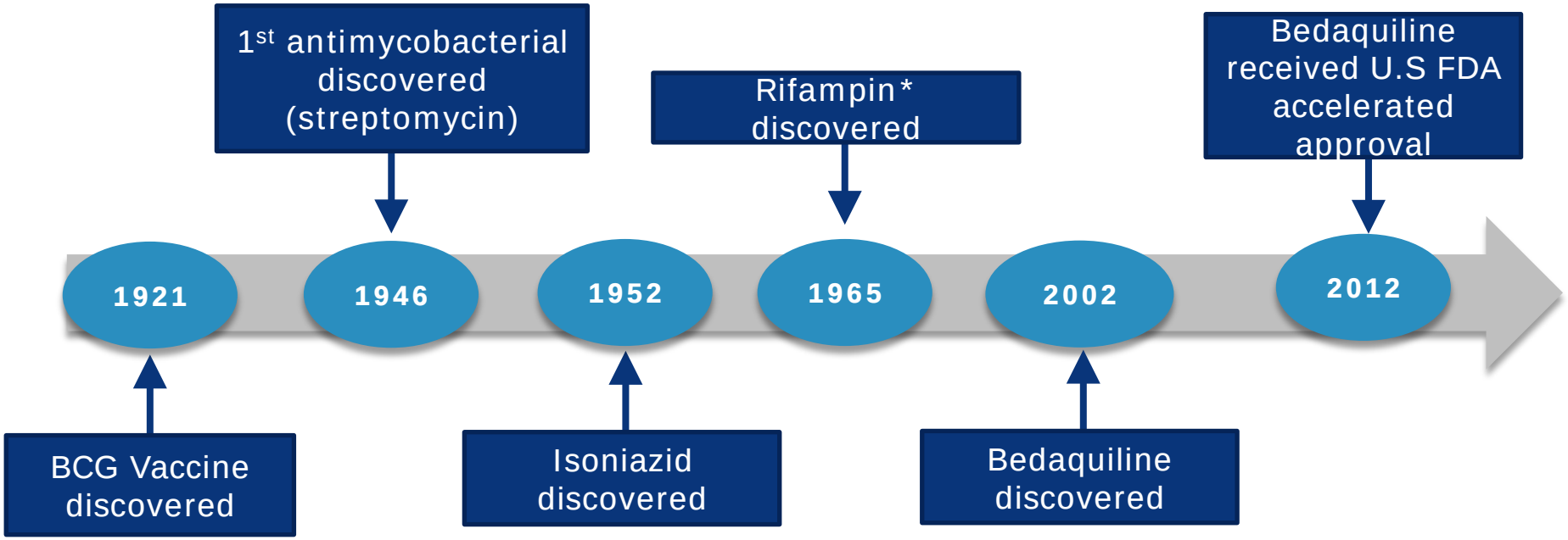
Discovery Timeline for TB Drugs:

Before antibiotics, TB was most often a death sentence



- For drug-resistant TB there are few treatment options, and when left untreated or inadequately treated, the risk of spreading additional drug-resistant strains increases
- Antibiotic resistance in healthcare settings is a significant threat to public health. By preventing antibiotic resistance in healthcare settings, transmission risk is reduced.

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** Until bedaquiline, no new TB drugs with a new mechanism of action had been introduced since Rifampin*

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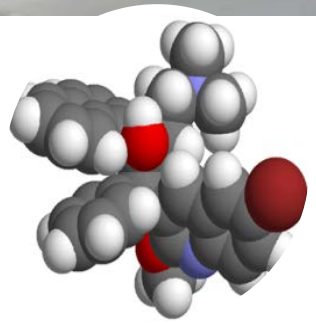
Superiority Trial design thanks to unmet need



Bedaquiline

- BDQ inhibits ATP synthase, an enzyme essential for generation of energy in Mycobacterium TB, defining a new mode of action

- Based on the huge unmet need, superiority “add on” design was feasible: The objective of C208 is to demonstrate superiority in antibacterial activity of 24 weeks of TMC207 treatment compared to placebo in addition to a BR. A sample size of 75 subjects per group (i.e., a total of 150 subjects) achieves 80% power to detect a difference of 22% in the6-month (24 weeks) conversion rates between the placebo group (50%) and the TMC207 group(72%) at a 5% level of significance (2-sided).

How was the 20% Improvement in determined?

1970: rifampin

- First line regimen in DS-TB
- 2 month culture conversion

  Streptomycin + INH: 49 %

  Streptomycin + INH + rifampin: 69 %

- Δ= 20 %

Rifampin revolutionized the treatment of DS-TB by shortening it from 18 to 9m.

The International Journal of Tuberculosis and Lung Disease SUPPLEMENT
VOLUME 3 NUMBER 10 OCTOBER 1999

INT J TUBERC LUNG DIS 3(10):S231–S279
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Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications

Wallace Fox,* Gordon A. Ellard,† Denis A. Mitchison†

* 28 Mount Ararat Road, Richmond, Surrey, TW10 6PG, UK, † St George's Hospital Medical School, London, SW17 0RE, UK

SUMMARY

This review describes the studies on the treatment of tuberculosis carried out by the British Medical Research Council's tuberculosis units and their many collaborators throughout the world during the period from their formation in 1946 to their closure in 1986. References to all publications on studies during the period are listed. The review also includes selected publications by members of their staff who have continued the studies since closure of the units. The review is under four main headings: 1) controlled trials of chemotherapy, 2) bacteriological studies, 3) pharmacological studies, and 4) studies of surveillance and policies relevant to the control of tuberculosis.

Major events in the development of modern chemotherapy and the control of tuberculosis are as follows:

7 1961 onwards: Exploration of intermittent regimens of chemotherapy to assist implementation of full supervision.
8 1970: The first demonstration that inclusion of rifampicin or pyrazinamide in a regimen of streptomycin and isoniazid substantially reduced the subsequent relapse rate.
9 1972–1974: Demonstration that the period of treatment could be shortened to 6 months by the inclusion of rifampicin and pyrazinamide in the regimen.
10 1976: Delineation of modern short-course chemotherapy regimens by showing that the sterilising activity of pyrazinamide was confined to the first 2 months of treatment during the intensive phase,

Significance of a 20% Improvement in Culture Conversion Rate?

1970: rifampin

- First line regimen in DS-TB
- 2 month culture conversion

  Streptomycin + INH: 49 %

  Streptomycin + INH + rifampin: 69 %

- Δ= 20 %

2012: bedaquiline

- Second line regimen in MDR-TB
- 6 month culture conversion

  5-drug background + placebo: 58 %

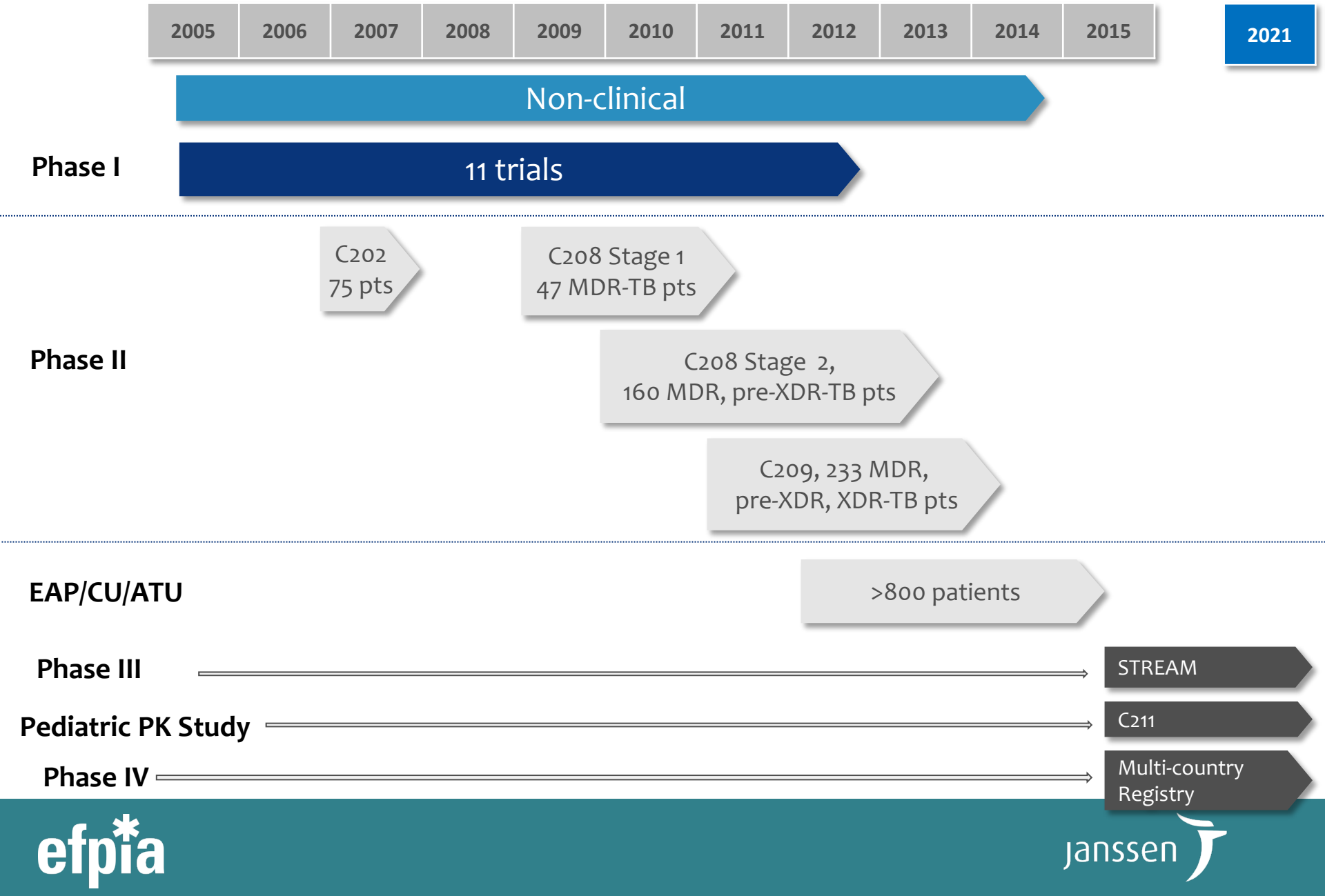
  5-drug background + BDQ: 79%

- Δ = 21 %

Rifampin revolutionized the treatment of DS-TB by shortening it from 18 to 9m.

Bedaquiline could play a significant role in MDR-TB treatment.

Bedaquiline Development Program



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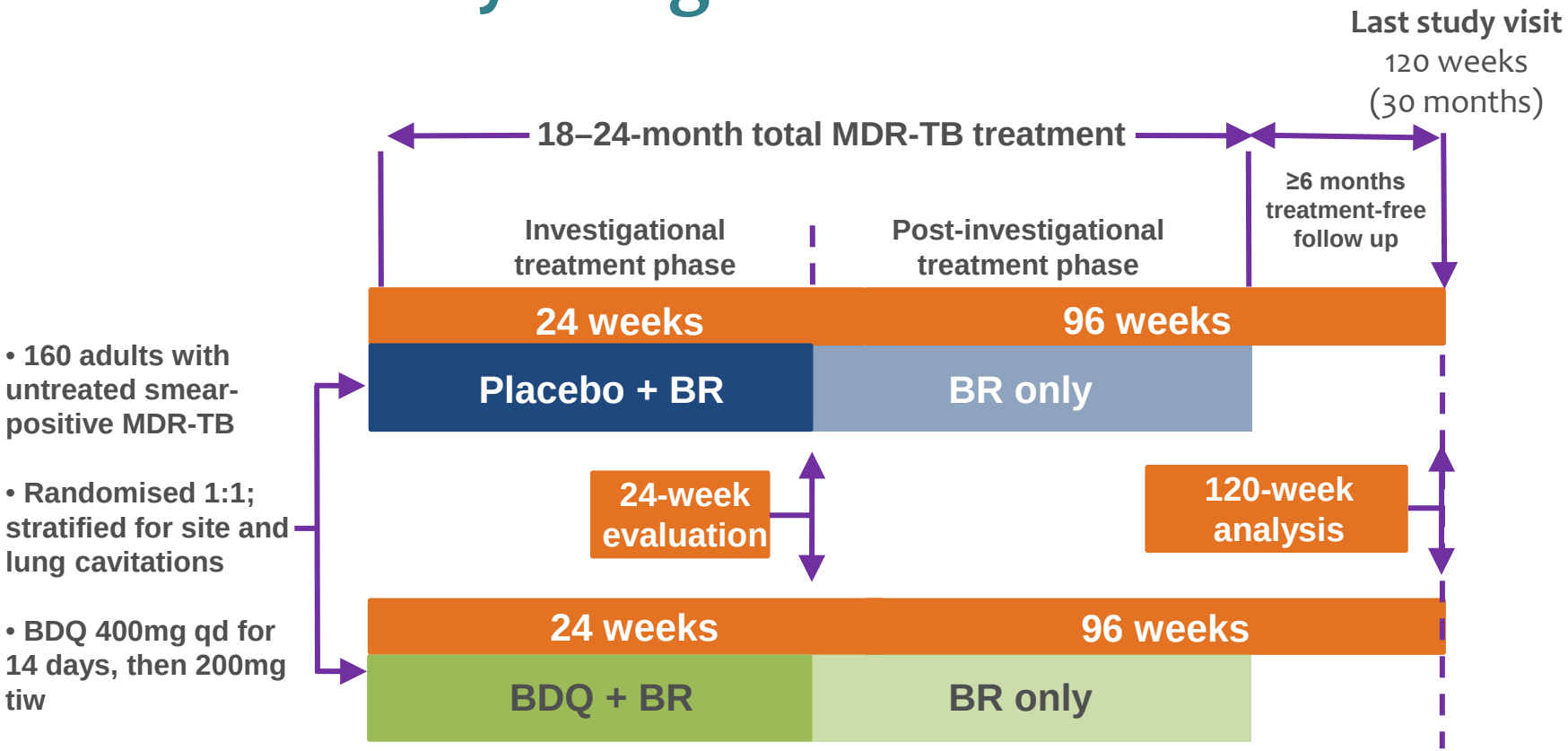
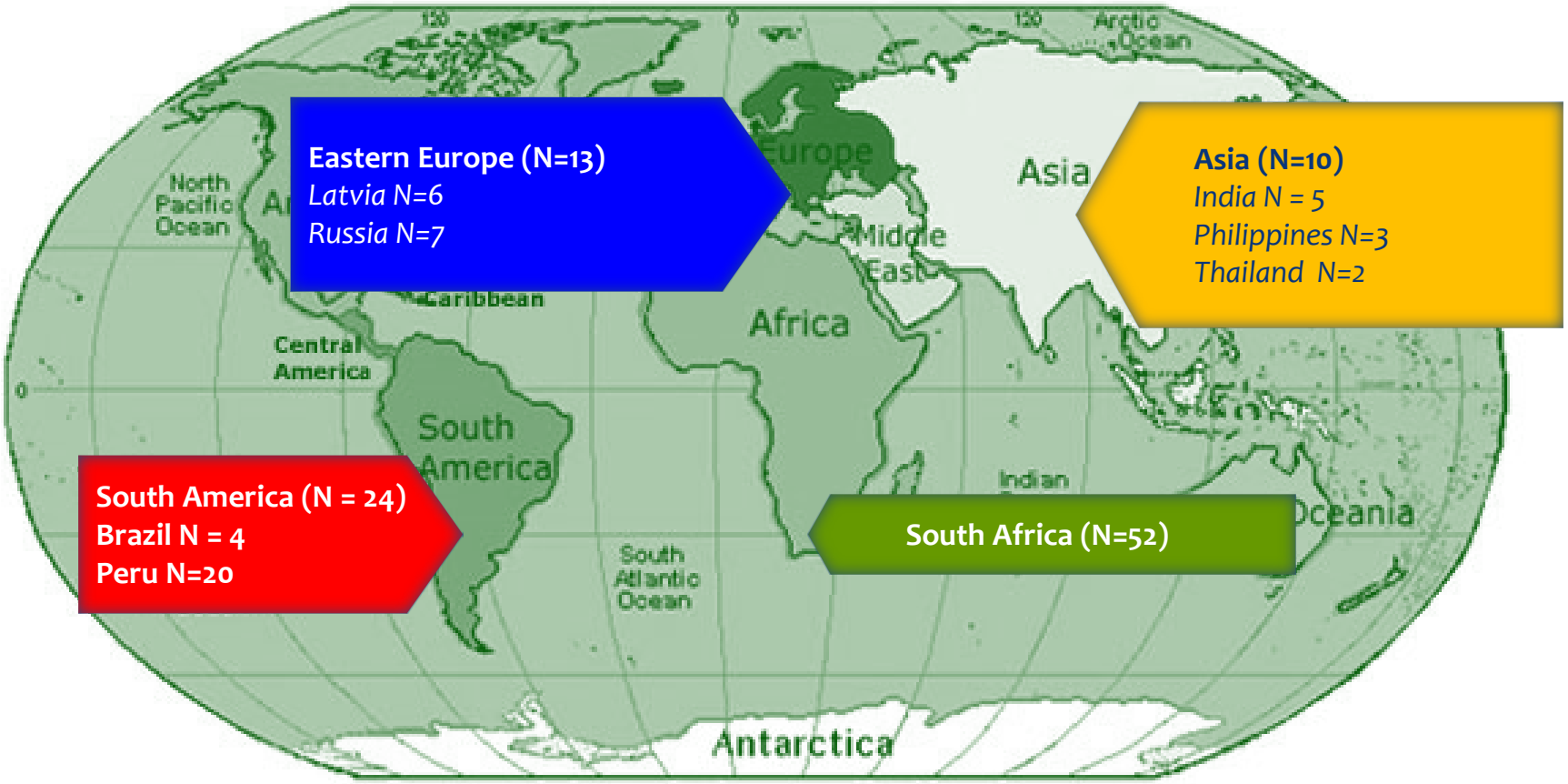
Development activities (trials) with bedaquiline

PhII: C208 Study Design



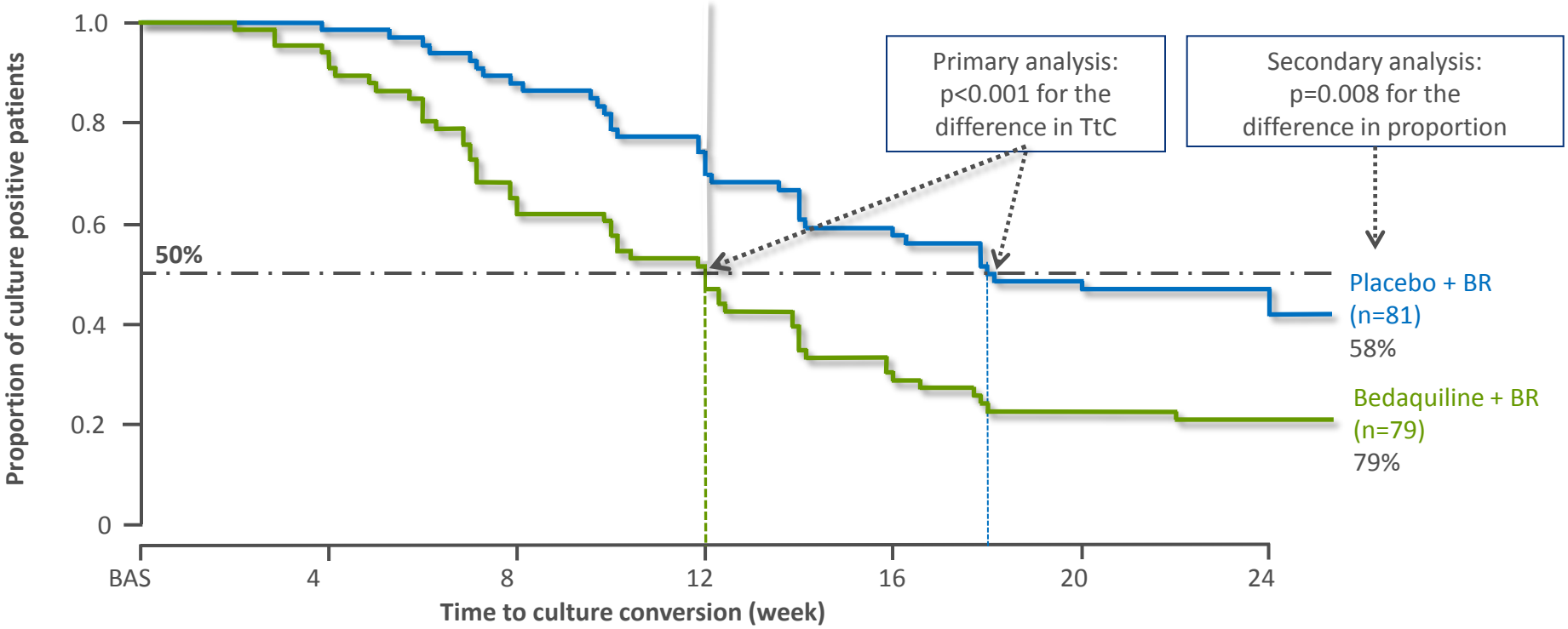
Objective: Demonstrate superiority of BDQ vs placebo at 24 weeks in the mITT population

PhII C208:
Trial sites and patient recruitment (ITT population)



Superiority based on a surrogate marker: PhII C208 Stage 2: *Significant reduction in time to conversion*

- Median time to culture conversion (mITT) = 83 days for bedaquiline versus 125 days for placebo

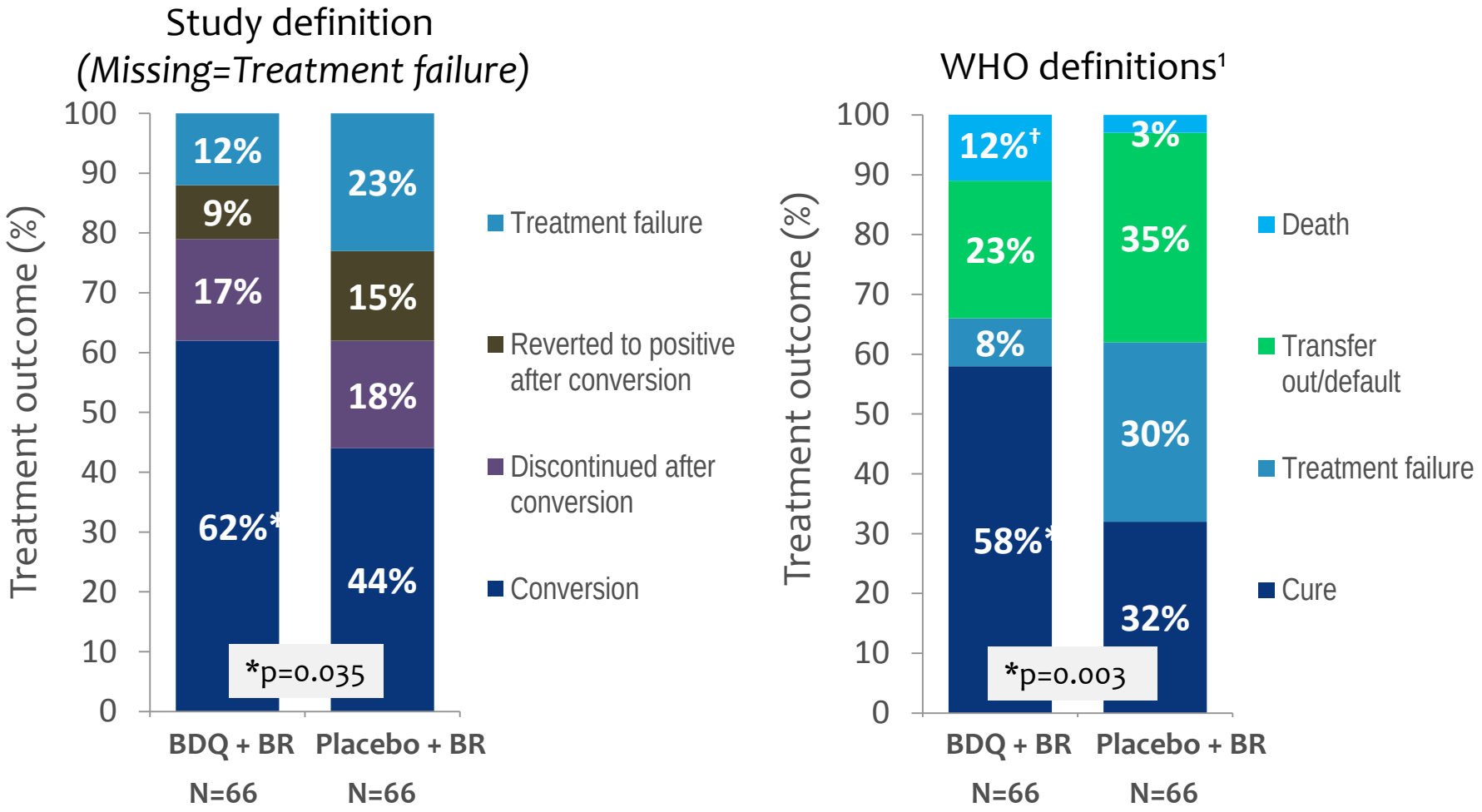


p-value from Cox proportional model adjusting for strata
The intersection of horizontal dotted line and each treatment arm represents the median time to sputum conversion

Diacon AH, et al. *N Engl J Med* 2014;371:723–32

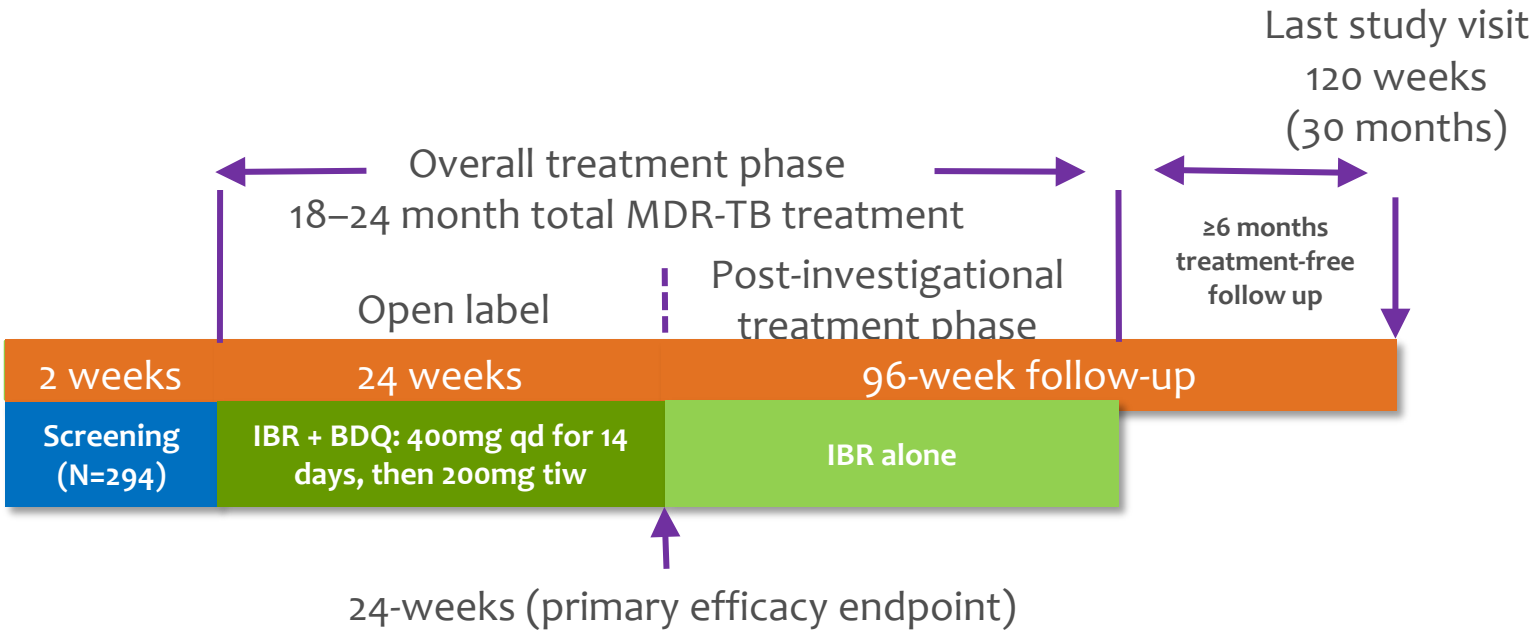
Superiority based on traditional endpoints of TB: Increased cure rate: *Outcome at study end* *(120 weeks; mITT)*

- Validation of the surrogate marker (24 w culture conversion)



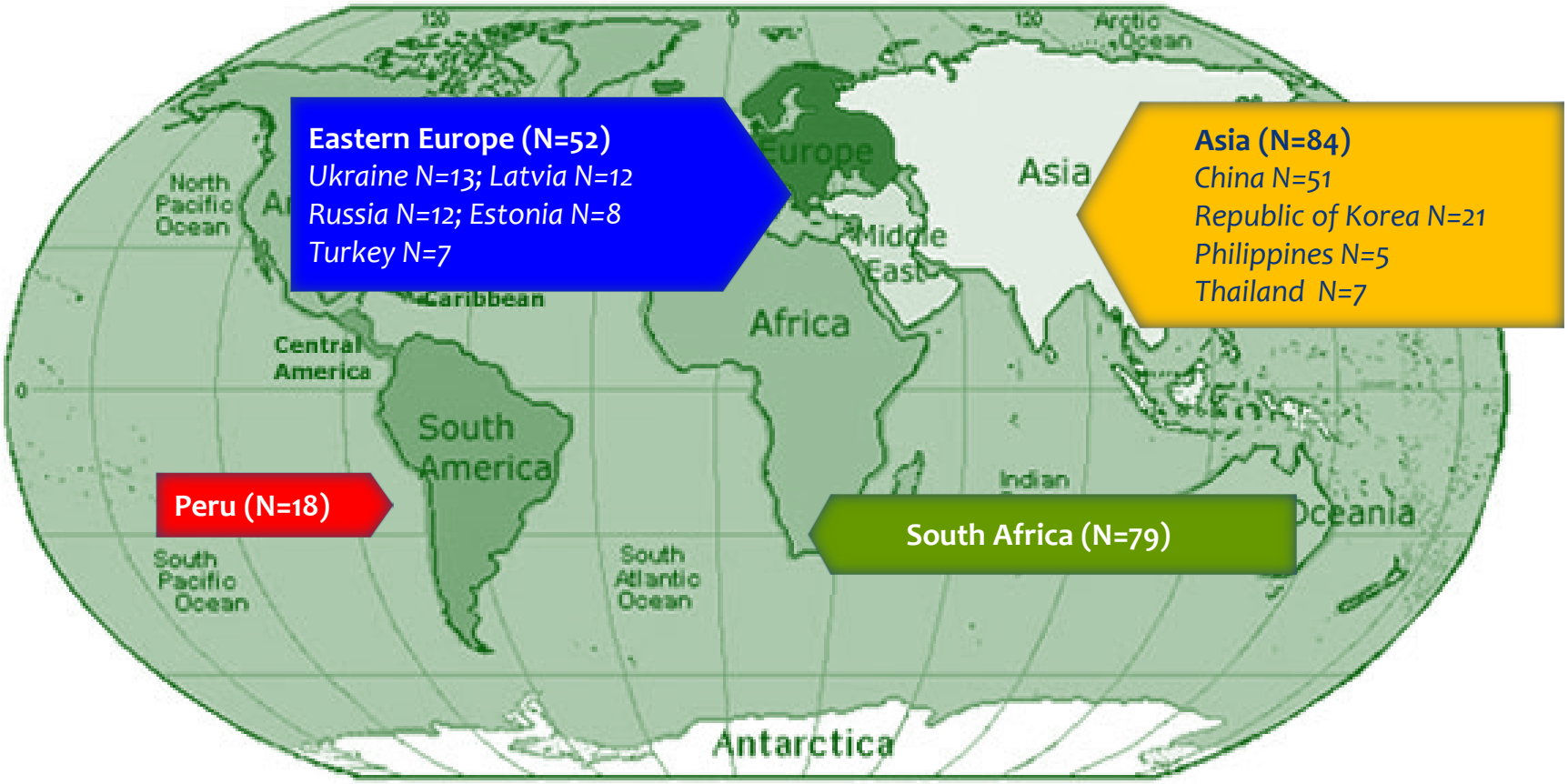
An adequate safety data-base:
PhII C209: *Single-arm, open-label, multicentre study*

- C209* included 233 adults with either newly or non-newly diagnosed confirmed smear-positive pulmonary MDR-TB disease, including pre-XDR- and XDR-TB

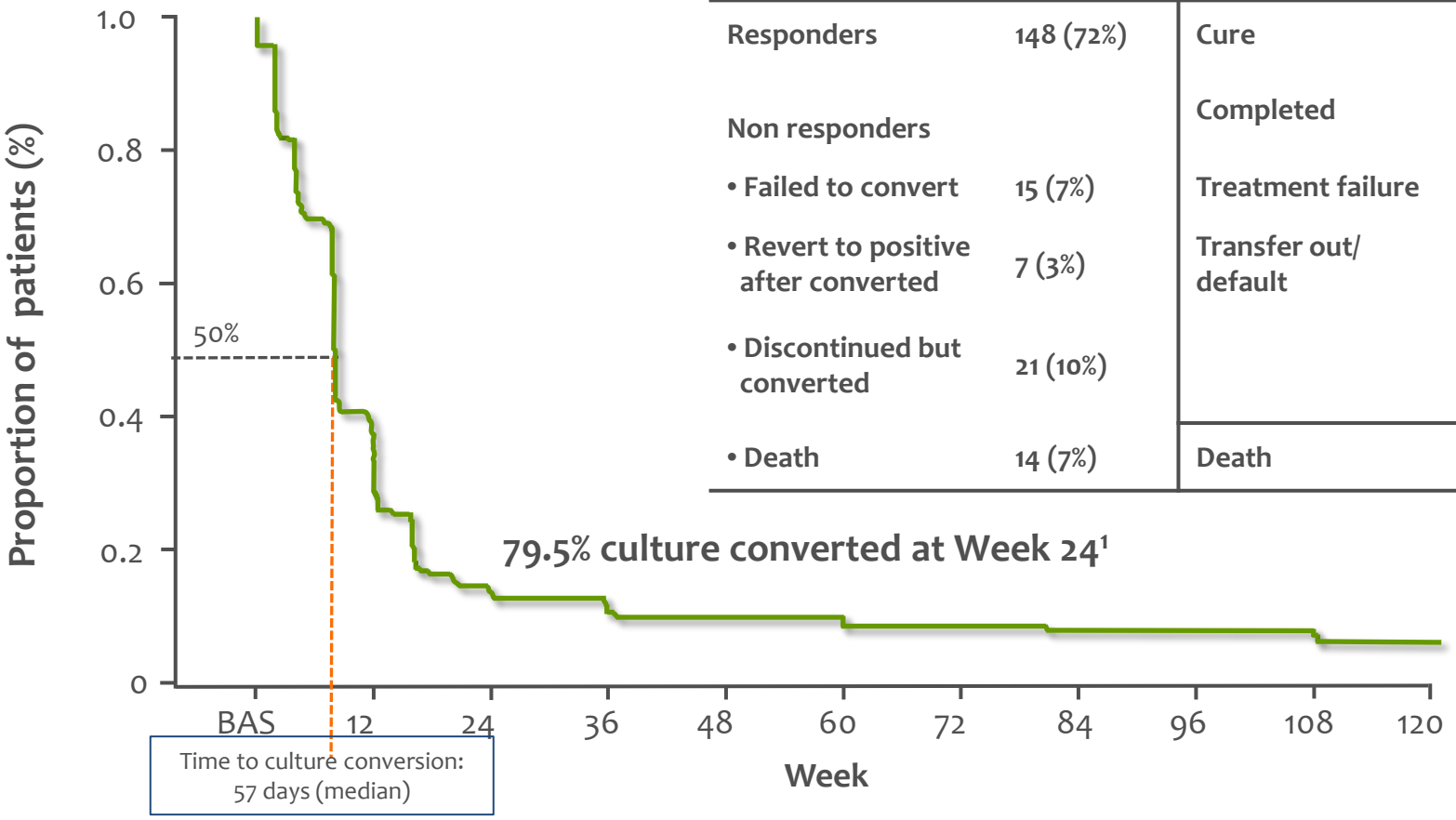


*NCT00910871

PhII C209:
Trial sites and patient recruitment (ITT population)



Efficacy results consistent with C208 for surrogate and traditional endpoints; PhII C209: Time to culture conversion (MGIT) on BDQ (mITT final analysis)



Study end (missing=failure)		WHO classification	
Responders	148 (72%)	Cure	125 (61%)
		Completed	3 (1%)
Non responders			
• Failed to convert	15 (7%)	Treatment failure	32 (16%)
• Revert to positive after converted	7 (3%)	Transfer out/ default	31 (15%)
• Discontinued but converted	21 (10%)		
• Death	14 (7%)	Death	14 (7%)

1. Haxaire M, et al. Int J Tuberc Lung Dis. 2011;14 Suppl 3:S58
2. Pym et al, ERJ Express, Dec 2015; doi: 10.1183/13993003.00724-2015:

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FDA Approval (December 2012)
EMA Approval (March 2014)

A Breakthrough, Possibly a Beginning

In Swaziland, 32-year-old mother Happiness Dlamini no longer sleeps next to her 4-year-old daughter. Happiness has multidrug-resistant tuberculosis (MDR-TB). The highly contagious infection has put a painful physical distance between Happiness and those she loves. She takes 15 pills every day and will do so for another 20 months. And while the pills may treat her MDR-TB, they have many side effects that can make her feel sick.

Happiness's story and others like hers are shared through TB+ME, a collaborative blogging project by patients being treated for MDR-TB in locations around the world who want to raise awareness of the disease and the suffering they endure.

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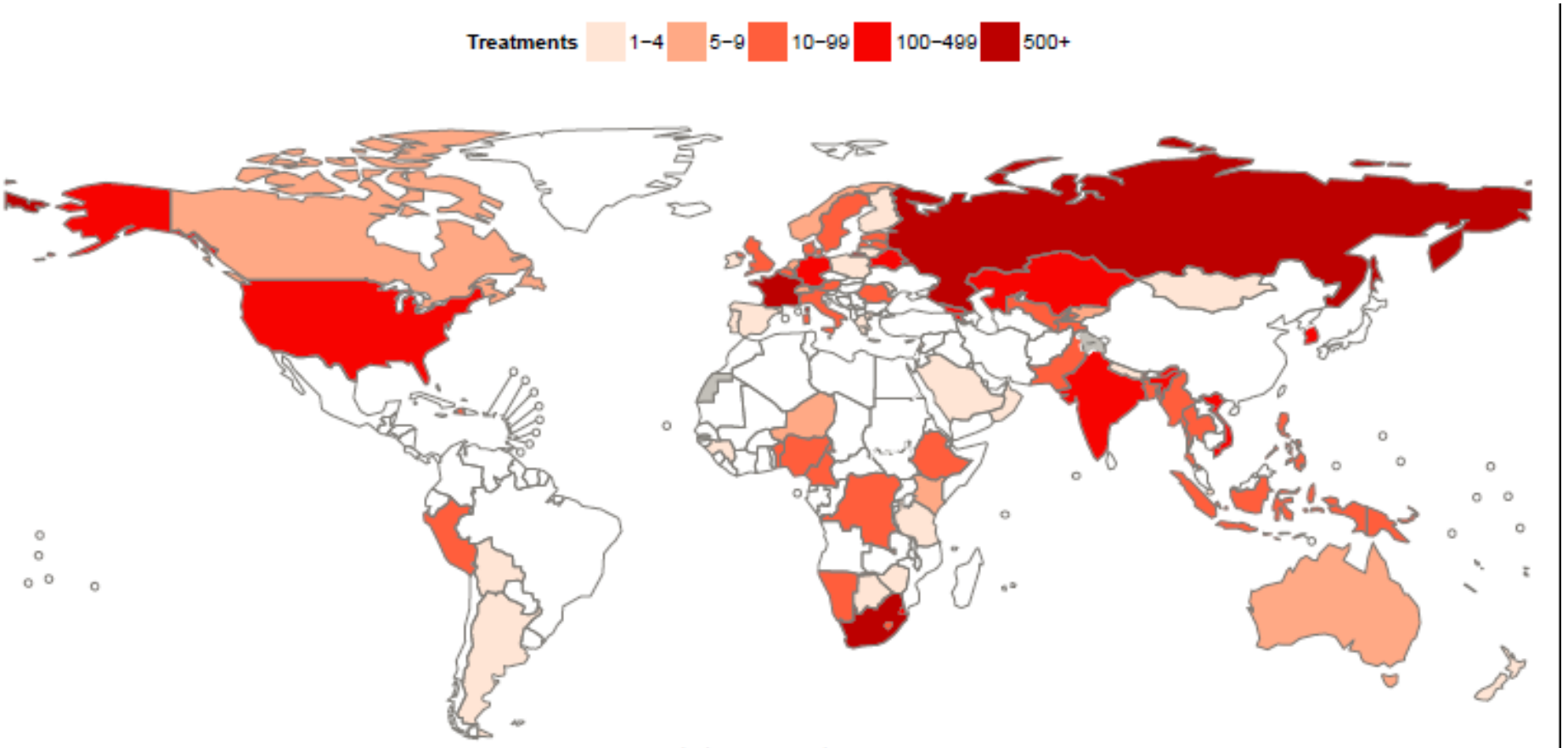
Impact of New Drugs under programmatic conditions and evolving Standard of Care

Worldwide Exposure to BDQ 10/16: 12,455 patients in 74 countries (c); >10,000 patients in 23 high MDR-TB burden c's.



WHO Member States reporting use = 69

High MDR–TB burden countries reporting use = 23

South Africa:
Commitment and Collaboration

"…Treatment outcomes in Pre/XDR TB are now overtaking our outcomes in MDR-TB: New Drugs are the top priority."

A story of successful private public partnership

Introduction of bedaquiline into the National TB programme of South Africa

There is an urgent need to improve the outcomes of M/XDR TB treatment. For the first time in decades, there are a number of new and repurposed drugs now available that have the potential to improve the outcomes.

These include bedaquiline and linezolid. Randomised controlled clinical trial data is eagerly awaited as to how to incorporate these drugs into effective regimens.

However, there is a need to urgently provide access to these drugs, to patients with few treatment options remaining. Adequate measures need to be taken to assess both safety and efficacy. In addition, injudicious use of the new drugs without an optimised background regimen may result in resistance. With a HIV prevalent background of at least 10% in most provinces of South Africa, the new drugs would need to be combined with antiretrovirals in many patients.

Following a successful clinical access programme, with careful attention paid to the regulatory framework and ethical consideration, the National Department decided to embark on an access programme. In a collaboration led by the National Department of Health of South Africa, Janssen Pharmaceutica and other partners including Right to Care and Médecins Sans Frontiers, access was provided to bedaquiline to over 200 patients prior to registration.

Following registration in October 2014, a bold decision was made to provide access as broadly as possible within South Africa. Input from experts in South Africa was used to decide on a framework for introduction of new drug and new drug regimens, as well as the mechanism adopted to ensure the ongoing protection of the drug and monitoring for resistance.

Friday, 04 December 2015 - 7:30 to 8:45am
Session No2054

The Westin Capetown, Ballroom West
Convention Square, Lower Long Street
Capetown 8000

International Union Against Tuberculosis and Lung Disease	
07:30 - 07:35	Opening remarks - Norbert Ndjeka (South Africa)
07:35 - 07:55	Early clinical outcomes of bedaquiline patients and lessons learnt - Iqbal Master (South Africa)
07:55 - 08:15	Launch of the framework for the "Introduction of new drug and new drug regimen for the treatment of drug-resistant TB" - Yogan Pillay (South Africa)
08:15 - 08:30	Focus on patient selection for bedaquiline and other new drugs - Francesca Conradie (South Africa)
08:30 - 08:45	Bedaquiline resistance monitoring - Nazir Ismail (South Africa)

Chairs

Graeme Ayton Meintjes
(South Africa)
graemein@mweb.co.za

Rodolfo Romero Leyet
(South Africa)
romeroleyet@mweb.co.za

health
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USAID
Right to care

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Bedaquiline RWE: ***Use in Hardest-to-Treat Patients***

Description of three cohorts of patients started on bedaquiline-containing treatment regimens

Period reported	France[36]	South Africa[37]	Armenia[38]
	January 2010–July 2013	**March 2013–July 2014**	**March 2013–January 2015**
Number of patients	35[a]	91	53
XDR-TB	54.3%	37.4%	45%
Pre-XDR-TB (FQ)	28.6%	45.1%	49%
Pre-XDR-TB (Inj)	11.4%	17.6%	6%
Median age (years)	39	35	42.5
Sex, male	80%	60.4%	87%
HIV positive	0	59.3%	4%
Lzd[b]	94.3%	70.3%	100%
Imp[b]	65.7%	0%	75%
Cfz[b]	14.3%	74.7%	74%

Grania, Brigden, Hewison, Cathy, Varaine, Francis, **New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid, Doverpress,** 30 October 2015 Volume 2015:8 Pages 367—378 http://dx.doi.org/10.2147/IDR.S68351

Evidence of Impact:

*Bedaquiline regimens near outcomes in Drug Sensitive TB**

Summary of available culture conversion and safety data from three cohorts of patients given bedaquiline-containing regimens

	France[36]	South Africa[37]	Armenia[38]
Culture conversion at 6 months among patients culture positive at baseline	28/29 (97%)	33/43 (77%)	22/26 (84%)
Early mortality (<24 weeks bedaquiline)[a]	1/35 (3%)	1/63 (1.6%)	4/53 (7.5%)
Increase in QTcB/F (ms)	1.96[b]	8[c]	Not reported
QTcB/F increase	7/35 (20%) >60 ms	24/91 (26.3%) >50 ms	Not reported
QTcB/F >500 ms	3/35 (9%)	3/91 (3.2%)	Not reported
Discontinuation of bedaquiline	2/35[d] (6%)	1/91[e] (1%)	Not reported
Patients with serious adverse events reported (unrelated to bedaquiline)	1/35 (3%)	9/91 (9.9%)	4/53 (8%)

Grania, Brigden, Hewison, Cathy, Varaine, Francis, **New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid, Doverpress,** 30 October 2015 Volume 2015:8 Pages 367—378
http://dx.doi.org/10.2147/IDR.S68351

** WHO Global Average: 48%*

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Evolving SOC & Response by the field to the remaining unmet need: Treatment shortening/simplification

Simpler Regimens

Use courtesy of MSF

Simpler Regimens

Use courtesy of MSF

Bangladesh Regimen: *A treatment reality*

First results reported from 9-country observational study in francophone Africa

Researchers participating in a cohort study coordinated by the International Union Against Tuberculosis and Lung Disease (The Union) announced results from the first multi-country cohort of MDR-TB patients treated using a shortened, 9-month treatment regimen. Among a cohort of 507 adult patients, 80.9% had treatment success, 7.7% died, 6.5% were lost to follow-up and 4.9% were treatment failures. Patients participated from nine francophone countries in sub-Saharan Africa: Benin, Burkina Faso, Burundi, Cameroon, Cote d'Ivoire, Niger, Central African Republic, Democratic Republic of Congo and Rwanda.

"These preliminary results from using a 9-month MDR-TB treatment regimen are excellent," said Dr Arnaud Trebucq of The Union, a lead investigator of the study. "Implementing the shortened regimen is proving feasible and with improved outcomes compared with the standard MDR-TB treatment regimen."

Francophone African experience teaches us that policy guidance can be informed by operational research done by NTP's in a manner that is faster, more efficient, and cheaper than doing clinical trials.

http://www.medicalbrief.co.za/archives/nine-month-regimen-successful-in-treating-mdr-tb-francophone-africa-study/

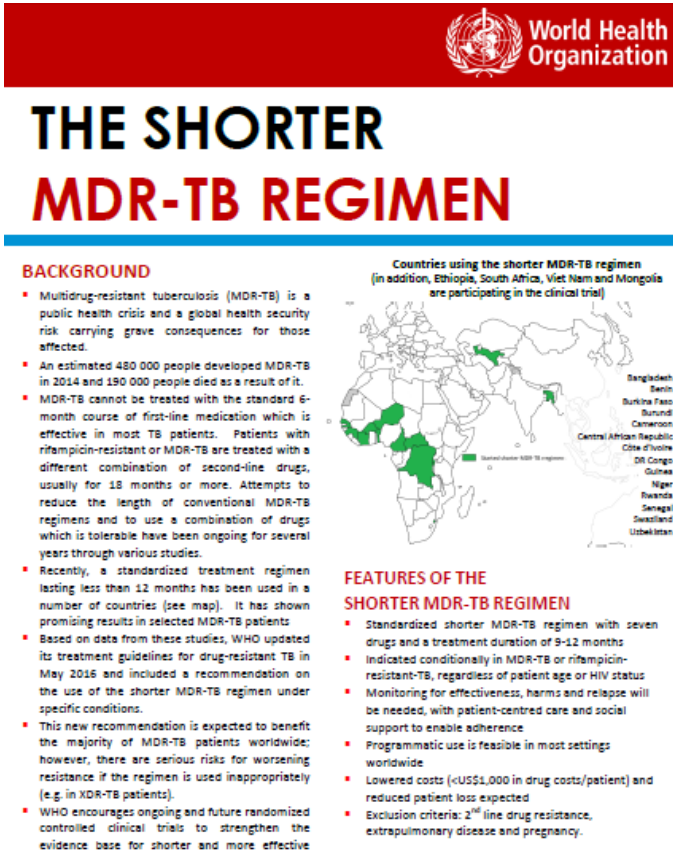
2016 Policy Updates

Bangladesh (5/12/16)

- 9-month treatment regimen
- 9-country Observational Study
- >80% cure rates
- New SOC in MDR (excl: Pre/XDR)

~2000 pills

World Health Organization



World Health Organization

THE SHORTER MDR-TB REGIMEN

BACKGROUND

- Multidrug-resistant tuberculosis (MDR-TB) is a public health crisis and a global health security risk carrying grave consequences for those affected.
- An estimated 480 000 people developed MDR-TB in 2014 and 190 000 people died as a result of it.
- MDR-TB cannot be treated with the standard 6-month course of first-line medication which is effective in most TB patients. Patients with rifampicin-resistant or MDR-TB are treated with a different combination of second-line drugs, usually for 18 months or more. Attempts to reduce the length of conventional MDR-TB regimens and to use a combination of drugs which is tolerable have been ongoing for several years through various studies.
- Recently, a standardized treatment regimen lasting less than 12 months has been used in a number of countries (see map). It has shown promising results in selected MDR-TB patients
- Based on data from these studies, WHO updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation on the use of the shorter MDR-TB regimen under specific conditions.
- This new recommendation is expected to benefit the majority of MDR-TB patients worldwide; however, there are serious risks for worsening resistance if the regimen is used inappropriately (e.g. in XDR-TB patients).
- WHO encourages ongoing and future randomized controlled clinical trials to strengthen the evidence base for shorter and more effective

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

FEATURES OF THE SHORTER MDR-TB REGIMEN

- Standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-12 months
- Indicated conditionally in MDR-TB or rifampicin-resistant-TB, regardless of patient age or HIV status
- Monitoring for effectiveness, harms and relapse will be needed, with patient-centred care and social support to enable adherence
- Programmatic use is feasible in most settings worldwide
- Lowered costs (<US$1,000 in drug costs/patient) and reduced patient loss expected
- Exclusion criteria: 2nd line drug resistance, extrapulmonary disease and pregnancy.

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US Government:
A Call to Action

The goals of the *National Action Plan* are to:

1. Strengthen domestic capacity to combat MDR-TB;
2. Improve international capacity and collaboration to combat MDR-TB; and
3. Accelerate basic and applied research and development to combat MDR-TB.

NATIONAL ACTION PLAN FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS

THE WHITE HOUSE
WASHINGTON

US Government:
A Call to Action

NATIONAL ACTION PLAN FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS

MILESTONES

Within 1 year:

- USAID will work with up to 5 countries[90] to introduce a new MDR-TB drug (bedaquiline, delamanid, or both); and
- USAID will work with 1 country[91] to scale-up use of bedaquiline or delamanid.

Within 3 years:

- USAID will work with up to 10 countries[92] to introduce new MDR-TB drugs (bedaquiline, delamanid, or both);

3.3.2. Enhance knowledge to enable optimal and safe use of newly registered TB drugs

Two new drugs, bedaquiline and delamanid, have received recent approvals by regulatory authorities in the United States, FDA, and in Europe, European Medicines Agency (EMA), respectively, for treatment of drug-resistant TB when no other treatment options are available. Intensified efforts are needed to determine:

- How to integrate these new drugs into existing regimens in ways that allow safe and efficacious use; and
- Whether these two drugs can be administered at the same time without increasing the likelihood of adverse effects or adverse drug interactions.

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The field is running with shortened simplifed regimens– An Overview of Key Regimens in Development

- **Bedaquiline** for MDR-TB: (END TB programmatic use: PIH/MSF)
- Delamanid for MDR-TB: (END TB programmatic use: PIH/MSF; Phase III Otsuka)
- **Bedaquiline** + Delamanid for Pre-XDR/MDR (NIH)
- Pretomanid-**Bedaquiline**-[oxazolidinone] for XDR-TB (TBA, NiXTB)
- Delamanid-**Bedaquiline**-LZD/CFZ/ other: MDR 9m (END-TB: PIH/MSF)
- Pretomanid-**Bedaquiline**-LZD/CFZ/other: MDR 6 m (MSF TB : Practecal)
- **Bedaquiline**–LZD/PZA/LEV/ETOH/-INH for 6-9 m v- SOC w/injectable for 24 m (NeXT Study, South Africa)
- **Bedaquiline** + Delamanid for Pre-XDR/XDR 6m (USAID)

THE STOP TB PARTNERSHIP

Leading the fight against TB

Accelerating action to meet the SDG TB targets: the case for a UN High Level Meeting on TB in 2017

By Honorable Minister Aaron Motsoaledi

For the treatment of those diagnosed, we are using new drugs such as Bedaquiline and we plan to introduce the shorter MDR-TB regimens in January 2017. [U1]

Even if we have these new medicines, we must continue to push for better, shorter, less toxic MDR-TB regimens through targeted research. Our programme, in collaboration with U.S. Agency for International Development (USAID) will evaluate the efficacy, safety and tolerability of a six-month regimen (a combination of Bedaquiline and Delamanid with one to two other TB medicines) especially for patients with drug resistance to isoniazid, rifampicin and a quinolone. If successful, this could have a major impact on the MDR TB epidemic globally.

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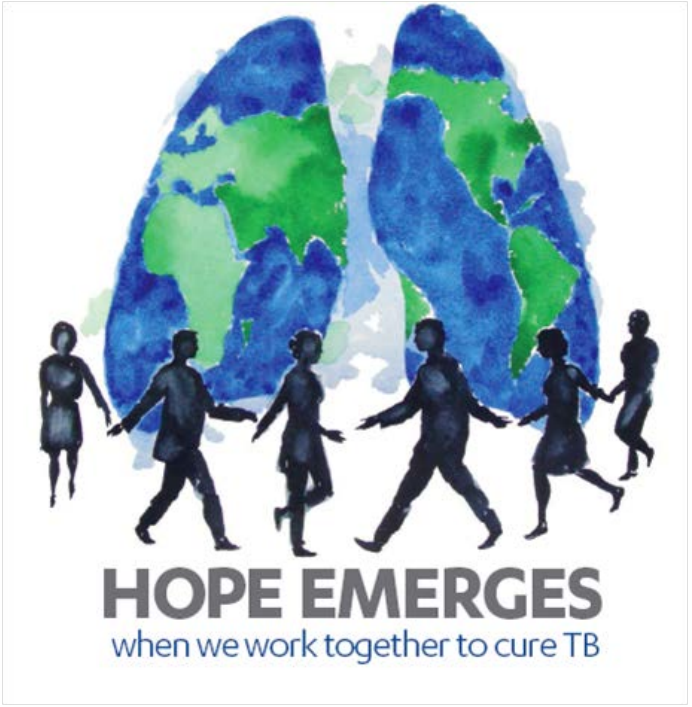
Challenge:

- With the approval of new drugs establishing high cure rates in MDR-TB
- Regimen optimization with new drugs being undertaken by the field
  - Continued research is needed for an ultra short, simple, safe universal regimen



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