Strategic Investments to Scale Up Shorter TB Treatment Regimens

February 22, 2022

Treatment Action Group

Socios En Salud

Partners In Health

Centro de Salud Global

Center for Global Health

Partners In Health

Dr. Lawrence Oyewusi

Dr. Lawrence Oyewusi

Currently serving as the Site Co-Principal investigator for STEM-TB and site Principal investigator for endTB clinical trials

He holds the following degrees:

BSc Botany,
Medical & surgical Degree,
Masters of Public health and
Masters in business administration

Dr. Lawrence Oyewusi is an adept DRTB/HIV clinician with an in-depth knowledge in service deliver, programmatic management of and clinical research of DRTB/HIV. He provides technical assistance to the MOH-NTLP and he has supported development of various strategic and guiding documents for The MOH. He also serves as the master trainer for the DRTB program.

Dr. Lindsay Mckenna

As Co-Director of the Tuberculosis (TB) Project at Treatment Action Group, Lindsay works with community advocates, researchers, policy makers, developers, and donors to expedite the development of and access to novel TB treatment, diagnostic, and prevention technologies. As coordinator of the Global TB Community Advisory Board—a group of research-literate activists from around the world that acts in an advisory capacity to institutions conducting TB clinical trials—she also works to ensure that research and development efforts respond to community needs and priorities.

Dr. Mohammed Yassin

Dr Mohammed Yassin (MD, MSc, PhD) is a Senior TB Advisor at the Global Fund, based Geneva where he provides technical leadership on TB/MDR-TB, TB/HIV and advises Global Fund teams and countries to ensure resources are invested to priority interventions and population and maximize impact. He is a public health physician and Infectious diseases Epidemiologist. He started his career piloting DOTS in Ethiopia over 25 years ago and later becoming a regional manager for TB and communicable disease. Before joining the Global Fund in 2010, he has worked in Liverpool School of Tropical Medicine, UK and designed, implemented, and managed several multi-country projects. He promotes innovation and partnership and has worked with national programmes in several countries in Africa, Asia, Europe and Western Pacific and with technical partners globally. He is a member of several global task forces including PPM and GDI and contributes to policy development and accelerate implementation.

Dr. Willy Morose

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Dr. Eric Wobudeya

Dr Eric Wobudeya is a senior consultant Paediatrician and epidemiologist at Mulago National referral hospital where he heads the Pediatric TB unit. He is research scientist focused on pediatric tuberculosis (TB) for over 10 years. He was the Uganda site PI for a TB treatment shortening study in children (SHINE Trial).

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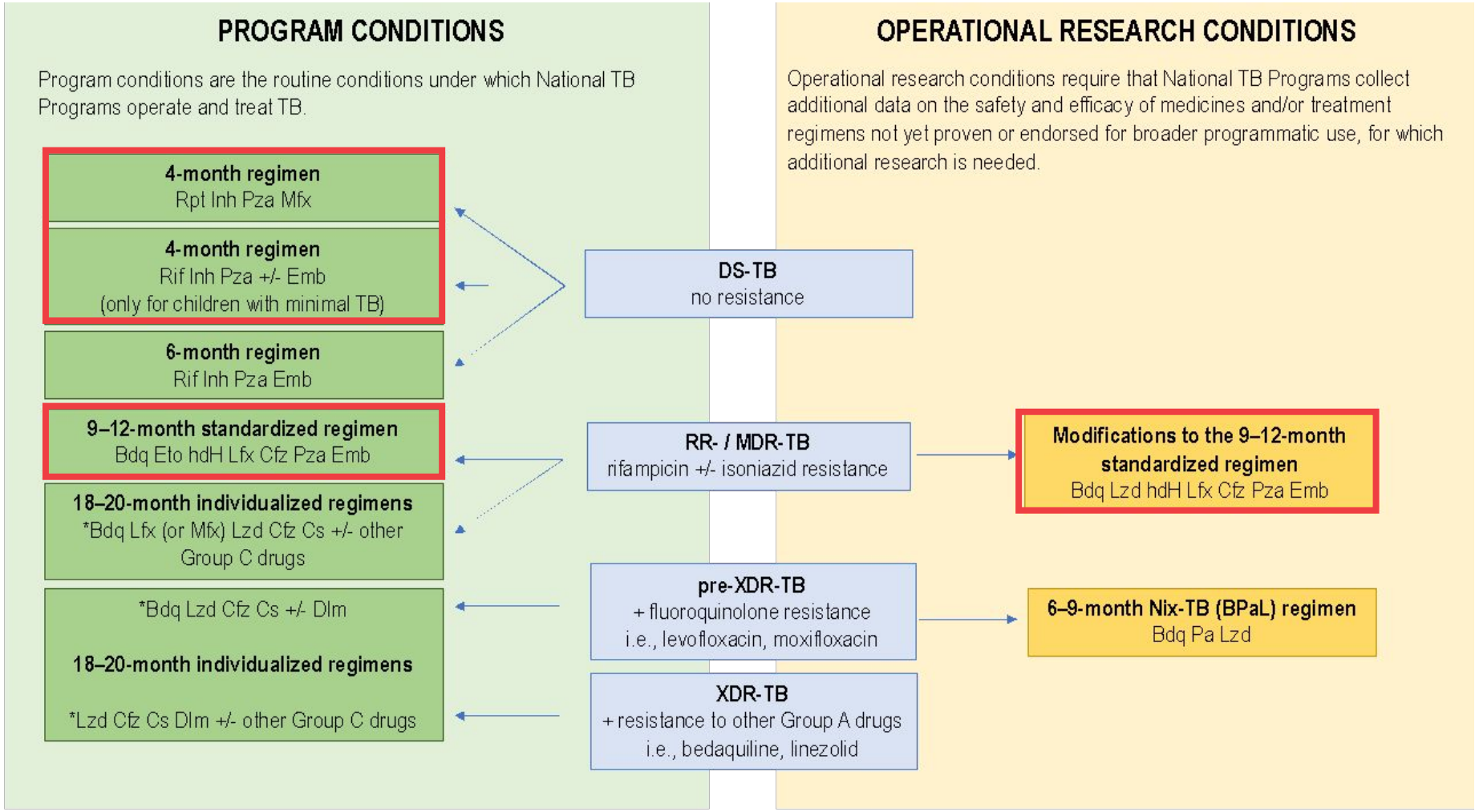
Shorter Treatment Regimens for Tuberculosis

Lindsay McKenna, MPH

Treatment Action Group

22 February 2022

Finally, Shorter Regimens for TB!



*these are examples of individualized regimens containing 4-5 medicines selected according to the WHO table of priority medicines; the composition of individualized regimens will vary depending on the individual's profile of drug-resistance and potentially other factors.

Bdq = bedaquiline Cfz = clofazimine Cs = cycloserine Dlm = delamanid Emb = ethambutol Eto = ethionamide Inh = isoniazid
hdH = high dose isoniazid (Inh) Lfx = levofloxacin Lzd = linezolid Mfx = moxifloxacin Pa = pretomanid Pza = pyrazinamide Rpt = rifapentine

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‼ Not Covered Today: BPaL(M) ‼

6-9-month BPaL (Nix-TB) regimen for adults & adolescents with pre-extensively drug-resistant TB (multidrug-resistant TB with additional fluoroquinolone-resistance):

- Nix-TB enrolled 109 participants from 3 sites in South Africa
- WHO rapid communication issued 2019; full WHO Guidance issued 2020

Given "important residual concerns about the likelihood and severity of adverse events, possible reproductive toxicity signals in the pre-clinical data, limitations in the study design, and the overall very low certainty of the evidence", the Nix-TB regimen is currently only recommended by the WHO for a limited population and under conditions of operational research.

ZeNix (NCT03086486)

- enrolled 181 participants from 11 sites across South Africa, Georgia, Moldova, and Russia
- designed to improve Nix-TB regimen safety by optimizing linezolid -- the "L" in BPaL – dose and duration (600 mg vs. 1,200 mg given for two vs. six months)
- results presented at IAS 2021 -- not powered to directly compare the four different linezolid dosing strategies evaluated in the study; however, the findings suggest a better safety profile can be achieved with reduced doses and/or shorter durations of linezolid with limited effect on the efficacy of the BPaL regimen.

TB-PRACTECAL (NCT02589782)

- enrolled 552 participants from seven sites across Belarus, South Africa, and Uzbekistan
- designed to evaluate modifications to BPaL for RR-/MDR-TB (i.e., BPaL, BPaLM, BPaLC vs. standard of care)
- results comparing outcomes among BPaLM participants (N=72/151) and control participants (N=73/152) that reached primary endpoint (week 72) presented at Union 2021
- standard of care* resulted in more treatment discontinuations and deaths compared with the BPaLM regimen; BPaLM appeared to be safer. *Important to note in the control, some participants received longer, injectable-containing or injectable-sparing regimens; others received shortened injectable-containing or all-oral regimens (13 [19%] participants received a nine-month, bedaquiline-based, all-oral regimen)

Findings summarized in greater depth in TAG's ***2021 TB Treatment Pipeline Report***:
https://www.treatmentactiongroup.org/wp-content/uploads/2021/11/pipeline_TB_Treatment_2021_final.pdf

****WHO Guideline update based on these & operational research data expected later this year!**

Uptake of Shorter Regimens

4-month regimen for adults & adolescents with drug-susceptible TB (Study 31):

- Trial enrolled 2,516 participants from sites in Brazil, China (Hong Kong), Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the United States, Vietnam, and Zimbabwe
- WHO rapid communication issued June 2021; full WHO Guidance expected soon

"The available evidence reviewed by the GDG on the 4-month regimen for treatment of drug-susceptible pulmonary TB supports the use of this regimen as a possible alternative to the current standard 6-month regimen. The shorter regimen has showed similar performance to the current standard regimen, both in terms of efficacy and safety. […]"

4-month regimen for children with minimal drug-susceptible TB (SHINE):

- Trial enrolled 1,204 children from sites in South Africa, Uganda, Zambia, and India
- WHO rapid communication issued August 2021; full WHO Guidance expected soon

"In children and adolescents under 16 years of age with non-severe, presumed drug-susceptible TB, a 4-month regimen (2HRZ(E)/2HR) should be used rather than the standard 6-month regimen (2HRZ(E)/4HR). […]"

9-12-month all-oral, bedaquiline-based regimen for adults, adolescents & children with RR-/MDR-TB:

- WHO rapid communication issued 2019; full WHO Guidance issued 2020
- 2020 MSF/STBP Step Up for TB Report: **22/36 (61%) countries have national policies** [...] that include a shorter all-oral regimen either for routine use or operational research. Among these 22 countries, **10 (45%) have implemented** the regimen

"A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second- line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. (Conditional recommendation, very low certainty in the evidence)"

Benefits of Shorter Regimens

For drug-susceptible TB (DS-TB):

- We have been trying to shorten treatment for 40 years! Finally, we did it, with medicines that are off-patent, widely available, and familiar to TB programs
- 4 months vs. 6 months -- treatment duration **2 months shorter**! People can get back to their lives 60 days sooner
- For adults and adolescents, **drug costs are higher, but this is temporary** – increased volumes and competition expected to bring down the price of rifapentine – and potentially **offset by shorter duration (human resource and other savings)** -- formal economic analysis is underway
- For children with minimal TB, the tools used in the SHINE trial to diagnose non-severe TB **(smear microscopy and X-ray) and pediatric medicines** are already **widely accessible** and available to TB programs.

For rifampicin-/ multidrug-resistant TB (RR-/MDR-TB):

- 9-12 months vs. 18-20 months - treatment duration cut in half; **8–11 months shorter**!
- People can get back to their lives 250+ days sooner
- **All-oral and safer**! No more painful daily injections with medicines that can cause permanent disability (e.g., hearing loss)
- **Less expensive** than longer, older regimens **even with the inclusion of bedaquiline** (total drug costs for 9-12-month regimen is US$560)

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Helpful Resources

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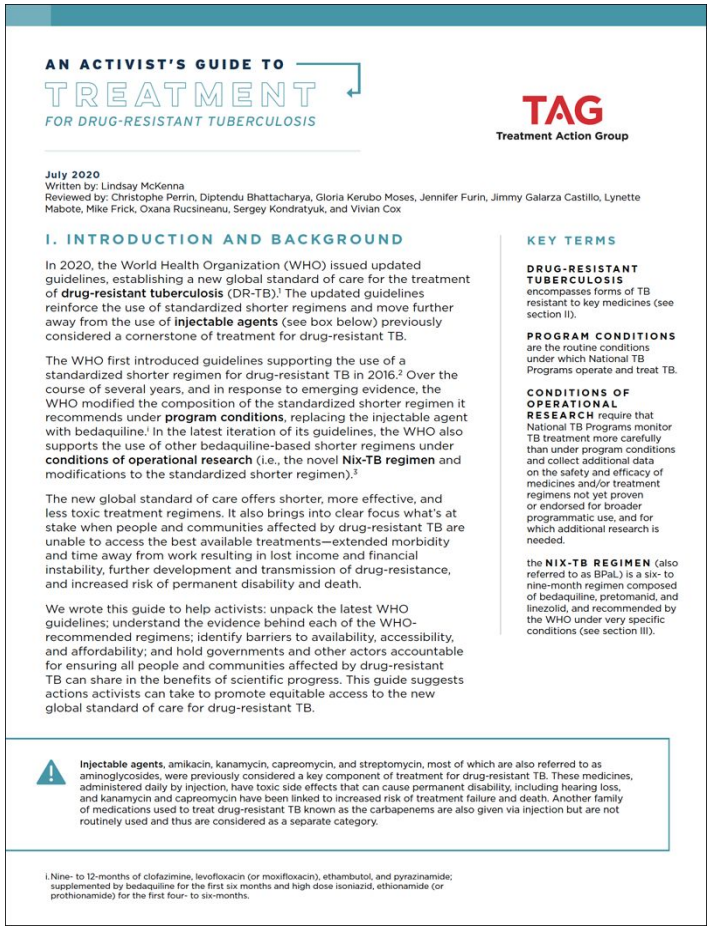

AN ACTIVIST'S GUIDE TO
TREATMENT
FOR DRUG-RESISTANT TUBERCULOSIS

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July 2020
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I. INTRODUCTION AND BACKGROUND

In 2020, the World Health Organization (WHO) issued updated guidelines, establishing a new global standard of care for the treatment of **drug-resistant tuberculosis** (DR-TB).[1] The updated guidelines reinforce the use of standardized shorter regimens and move further away from the use of **injectable agents** (see box below) previously considered a cornerstone of treatment for drug-resistant TB.

The WHO first introduced guidelines supporting the use of a standardized shorter regimen for drug-resistant TB in 2016.[2] Over the course of several years, and in response to emerging evidence, the WHO modified the composition of the standardized shorter regimen it recommends under **program conditions**, replacing the injectable agent with bedaquiline.[i] In the latest iteration of its guidelines, the WHO also supports the use of other bedaquiline-based shorter regimens under **conditions of operational research** (i.e., the novel **Nix-TB regimen** and modifications to the standardized shorter regimen).[3]

The new global standard of care offers shorter, more effective, and less toxic treatment regimens. It also brings into clear focus what's at stake when people and communities affected by drug-resistant TB are unable to access the best available treatments—extended morbidity and time away from work resulting in lost income and financial instability, further development and transmission of drug-resistance, and increased risk of permanent disability and death.

We wrote this guide to help activists: unpack the latest WHO guidelines; understand the evidence behind each of the WHO-recommended regimens; identify barriers to availability, accessibility, and affordability; and hold governments and other actors accountable for ensuring all people and communities affected by drug-resistant TB can share in the benefits of scientific progress. This guide suggests actions activists can take to promote equitable access to the new global standard of care for drug-resistant TB.

KEY TERMS

DRUG-RESISTANT TUBERCULOSIS encompasses forms of TB resistant to key medicines (see section II).

PROGRAM CONDITIONS are the routine conditions under which National TB Programs operate and treat TB.

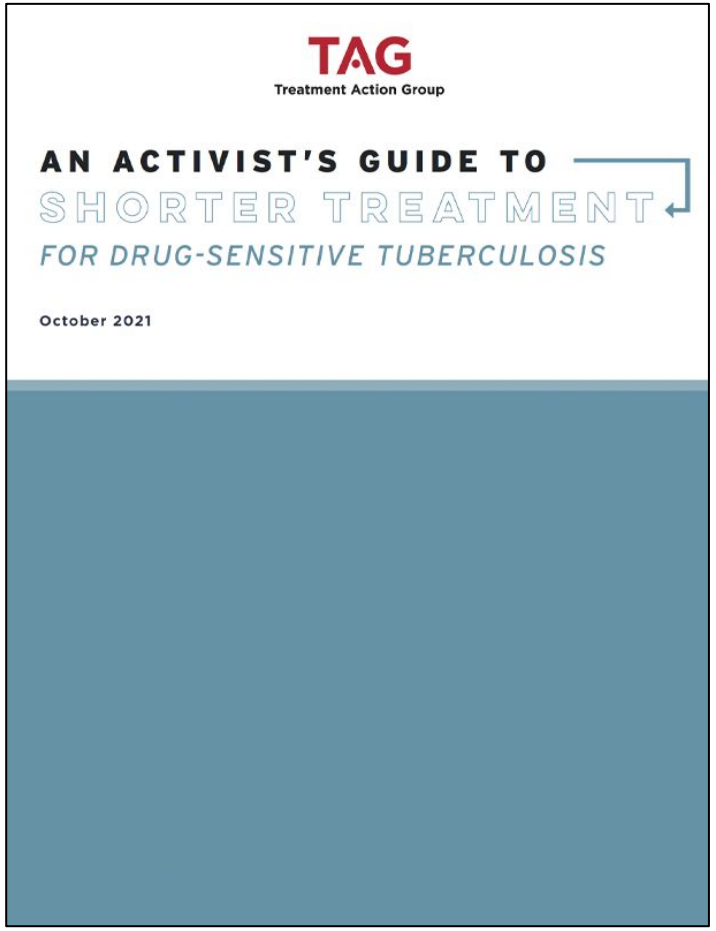
CONDITIONS OF OPERATIONAL RESEARCH require that National TB Programs monitor TB treatment more carefully than under program conditions and collect additional data on the safety and efficacy of medicines and/or treatment regimens not yet proven or endorsed for broader programmatic use, and for which additional research is needed.

the **NIX-TB REGIMEN** (also referred to as BPaL) is a six- to nine-month regimen composed of bedaquiline, pretomanid, and linezolid, and recommended by the WHO under very specific conditions (see section III).

Injectable agents, amikacin, kanamycin, capreomycin, and streptomycin, most of which are also referred to as aminoglycosides, were previously considered a key component of treatment for drug-resistant TB. These medicines, administered daily by injection, have toxic side effects that can cause permanent disability, including hearing loss, and kanamycin and capreomycin have been linked to increased risk of treatment failure and death. Another family of medications used to treat drug-resistant TB known as the carbapenems are also given via injection but are not routinely used and thus are considered as a separate category.

i. Nine- to 12-months of clofazimine, levofloxacin (or moxifloxacin), ethambutol, and pyrazinamide; supplemented by bedaquiline for the first six months and high dose isoniazid, ethionamide (or prothionamide) for the first four- to six-months.

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-treatment-for-drug-resistant-tuberculosis/.



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AN ACTIVIST'S GUIDE TO
SHORTER TREATMENT
FOR DRUG-SENSITIVE TUBERCULOSIS

October 2021

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/.

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THANK YOU!

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EXTRA SLIDES – REGIMEN SNAPSHOTS

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DS-TB (S31/A5349)

Regimen	4 months total **2 H P M Z / 2 H P M** H=isoniazid P=rifapentine M=moxifloxacin Z=pyrazinamide
Dosing	H:300mg P:1200mg M:400mg Z:1500mg
Pill Burden	With Sanofi 150mg P tablet:10–13 pills per day With near future 300mg P tablet: 6–9 pills per day With future fixed-dose combination: 4 pills per day
Price	US $235–265 per treatment course
WHO Guidance	*"The available evidence reviewed by the GDG on the 4-month regimen for treatment of drug-susceptible pulmonary TB* ***supports the use of this regimen as a possible alternative to the current standard 6-month regimen****. The shorter regimen has showed* ***similar performance*** *to the current standard regimen,* ***both in terms of efficacy and safety****. The 4-month regimen, which is* ***shorter, effective and all-oral, would be a preference for many patients and also national TB programmes, allowing faster cure and easing the burden on both patients and the healthcare system****. However, implementation and uptake of the new regimen in the short to medium term will be* ***more feasible if the cost of rifapentine is reduced and availability improved****. It will also require rigorous antibacterial* ***stewardship to ensure the appropriate use*** *of the first-line regimen given that it contains* ***moxifloxacin****, an antibiotic usually used for the treatment of drug-resistant TB."*
References	WHO Rapid Communication: https://www.who.int/publications/i/item/9789240028678 NEJM Article: https://www.nejm.org/doi/full/10.1056/NEJMoa2033400

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DS-TB (SHINE)

Regimen	4 months total **2 H R Z [E] / 2 H R** H = isoniazid R = rifampicin Z = pyrazinamide E = ethambutol
Dosing	Weight-based
Pill Burden	With 50/75/150mg and 50/75mg fixed dose combinations: 1–4 pills per day (dispersible)
Price	US $10 per treatment course
WHO Guidance	*"In children and adolescents under 16 years of age with **non-severe, presumed drug-susceptible TB, a 4-month regimen (2HRZ(E)/2HR) should be used rather than the standard 6-month regimen (2HRZ(E)/4HR).** Important implementation considerations were noted to determine eligibility for the shorter treatment regimen and will be described in the consolidated guidelines and in the operational handbook."*
References	WHO Rapid Communication: https://www.who.int/publications/i/item/9789240033450

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RR-/MDR-TB (9–12-month all-oral BDQ-based)

Regimen	9–12 months total **6 Bdq + 4–6 Eto hdH Lfx Cfz Z E / 5–6 Lfx Cfz Z E** Bdq = bedaquiline Eto = ethionamide hdH = high dose isoniazid Lfx = levofloxacin (or Mfx = moxifloxacin) Cfz = clofazimine Z = pyrazinamide E = ethambutol
Dosing	All oral, no injections! Standardized and weight-based dosing depending on medicine. Pediatric-specific dosing + formulations available.
Pill Burden	7 drugs; number of pills per day varies depending on patient weight and dosage strength of available formulations
Price	US $560 per treatment course
WHO Guidance	*"A shorter **all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis** (MDR/RR-TB) who have not been exposed to treatment with second- line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. (Conditional recommendation, very low certainty in the evidence)"*
References	WHO Guidelines, Module 4: https://www.who.int/publications/i/item/9789240007048

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Overview of opportunities to leverage Global Fund funding to support shorter regimens

Dr Mohammed Yassin
Senior TB Advisor

Global Fund investment, results and impact

The Global Fund invests US$4 billion a year to defeat HIV, TB and malaria and ensure a healthier, safer, equitable future for all.

We unite the world to find solutions that have the most impact, and we take them to scale worldwide. It's working. We won't stop until the job is finished.

44m

lives saved through the Global Fund partnership

RESULTS

21.9m

people on antiretroviral therapy for HIV in 2020

HIV AND AIDS

4.7m

people with TB treated in 2020

TUBERCULOSIS

188m

mosquito nets distributed in 2020

MALARIA

Global Fund provides 77% of international financing for TB - UD$7.8b as of June 2021

Key results in countries where the Global Fund invests:

4.7m

people treated for TB in 2020. TB treatment coverage increased from 47% in 2010 to 69% in 2019, and the TB treatment success rate reached 85% for the 2018 cohort. Global targets for coverage and treatment success rates: 90% by 2025.

194k

children in contact with TB patients received preventative therapy in 2020.

101k

people on treatment for DR-TB in 2020; treatment coverage reached 36% in 2019 and DR-TB treatment success rate increased from 48% in 2009 to 58% for the 2017 cohort. Global targets: 90% MDR-TB treatment coverage and success by 2025.

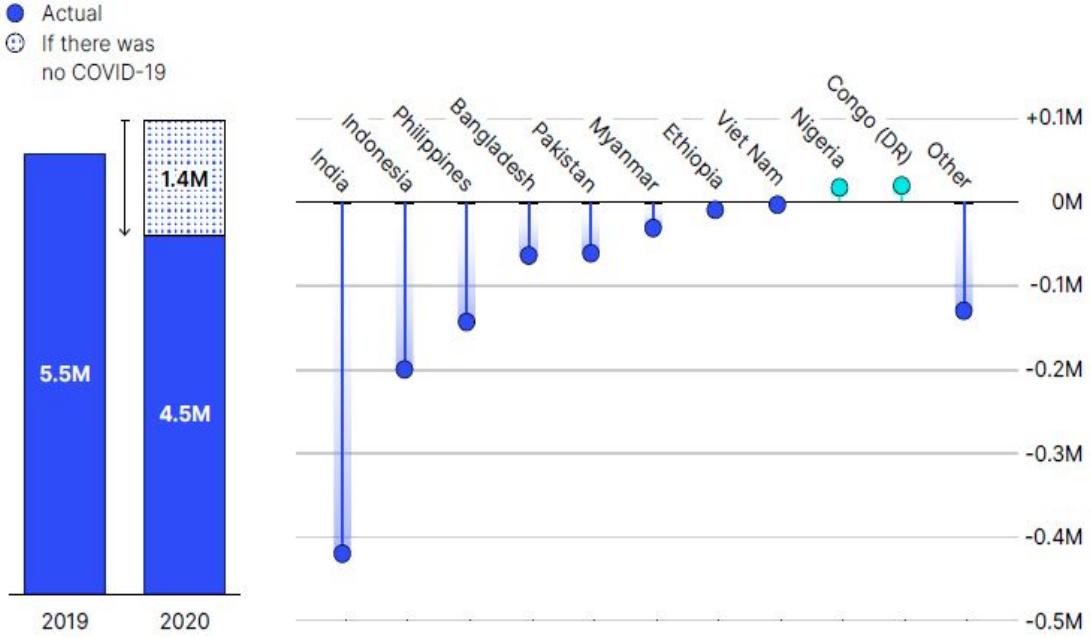
But disruptions due to COVID-19

People treated for TB

Change, 2019-2020

By **portfolio**

By **country** (10 countries with largest share of results in 2019)



The 'If there was no COVID-19' estimates are based on grant targets adjusted by grant performance prior to COVID-19. The country graphs include countries with comparable results in both years, therefore, the total results in 2019 and 2020 might be slightly lower than the total number of services seen in the other parts of this report and in the online platform.

Opportunities to scale up new recommendations –

Lessons learned from Global Fund Support to transition to new DR-TB treatment regimens

Participated in WHO GDG meeting as observer → Rapid Communication on DR-TB regimen → Internal communication and advice on immediate steps → Participated in Global Taskforce and FAQs development → Training sessions to update the GF teams

DR-TB regimen transition identified as a priority area for support through **Savings** and **portfolio optimization**

Countries willing/ready to transition patient to the new regimen & required additional resources were identified

TRP approved a waiver and provided guidance.

Additional resources provided through grants and TB Portfolio Optimization (**US$ 54 million)**

GF's flexibility and rapid response to support adoption of new guidelines and tools

Ongoing discussion with stakeholders and countries about implementation and market shaping

Opportunities to scale up shorter regimens for TB

- Global Fund encourages countries to use grants to implement and scale-up new tools, shorter regimens, innovations and new recommendations
  - Through grants, savings/efficiencies, reprogramming, **portfolio optimization**
- Countries are encouraged to incorporate scale up of new tools/regimens in their upcoming funding requests – See TB Information Note at https://www.theglobalfund.org/media/4762/core_tuberculosis_infonote_en.pdf
- TA support available through grants, TB SI, GLC and other partners
- Additional resources through C19RM
- The Global Fund New Strategy – promotes innovations and people-centered programming
- Engage with Global Fund Country Teams and explore for further opportunities

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Short regimen MDRTB Treatment Experience in HAITI

NTP

Dr Willy Morose

Feb 2022

Outline

- Context
- Haiti's experience in short regimen treatment
- Challenges
- Interventions needed to implement short regimen treatment in the country
- Constraints
- Opportunity
- Conclusion

Context

- TB including MDRTB is still a big threat in Haiti despite effort to fight it
- Estimated incidence rate has very slowly decline during the last five years (188/100000 in 2017 to 168/100000 in 2021
- Number of MDR TB cases detected has increased, but the coverage rate is about 20% only during the last five years
- Lab capacity has been reinforced with extension of geneXpert as first method for TB and MDRTB diagnosis
- Impressive improvement in the coinfection TB/HIV management during the last decade (up to 95% TB patients know their HIV status)

Context, cont

- Decentralization of the MDRTB management with the addition of 8 new sites for Ambulatory MDRTB care
- Introduction of the full ambulatory MDRTB management at the main regional hospitals
- Introduction of full oral regimen including new and repurposed drugs approved by WHO (Bedaquillin-Linezolide-Clofazimine)
- Long regimen only is in used actually in the actually (BDQ-Lfx-LNZ-CFZ) for 18 month

Context, cont

- 2 BSL3 are available and operational for culture and DST
- Sample are to be transported to Port-au-Prince for culture and DST
- Delay in treatment start has been observed because of availability of second line DST making ambulatory Short regimen treatment difficult to be implemented in country at larger scale
- Social supports are available but limited

Haiti experience in short MDRTB regimen treatment

- Implemented with the support of EndTB initiative in 2018 jointly by GHESKIO-ZL/PIH-NTP with 5 patients treated at GHESKIO on the EndTB regimen (Bedaquillin-Linezolide-Levofloxacin-Clofazimine-Pyrazinamide) for 39 weeks
- All the patients completed their treatment; until now there is no relapse among them, either invalidity
- Haiti has planned to continue the experience with the support of PAHO but, political situation, covid-19 and reinforcement of the lab network provoke delay in the process

Interventions needed to implement short regimen

- Availability of the automated X-ray machine in the main regional sites
- Availability of automated EKG machine in the main sites
- Availability of Xpert MTBRIF/XDR machine at the sites
- Improvement of the social support package
- Rehabilitation of the quarantine room at the main sites
- Reinforcement of the lab biochemistry unit of the main regional sites
- Extension of the MDRTB short treatment training to all TB sites since cases come from everywhere in the country
- Updating of the MDRTB register for the short regimen

Contraints

- No digital Xray machine; conventional xray reading often challenging at peripheral level
- No EKG in the Peripheral site; so that the patients have to walk for a couple of days to get the results for the clinic
- Waiting time relatively long for confirmation of MDRTB in the intermediate and low level of detection of MTB at the National lab
- Transfer of patient to GHESKIO and ZL are getting difficult because of block roads and security issues

Opportunity

- Willingness of Implementation of the short oral MDRTB treatment at peripheral level
- Support of the key implementing partners (ZL/PIH, GHESKIO, HTW
- Support of international partners : GF, WHO, CDC
- Experiences of the providers in the ambulatory TB care management
- Good coordination between NTP and the implementing partners

Conclusion

Short ambulatory MDRTB care could be an important pathway to increase MDRTB case detection and guarantee better outcome for the patients with the substantial reduction of duration of treatment in addition to the cost reduction for the entire treatment.

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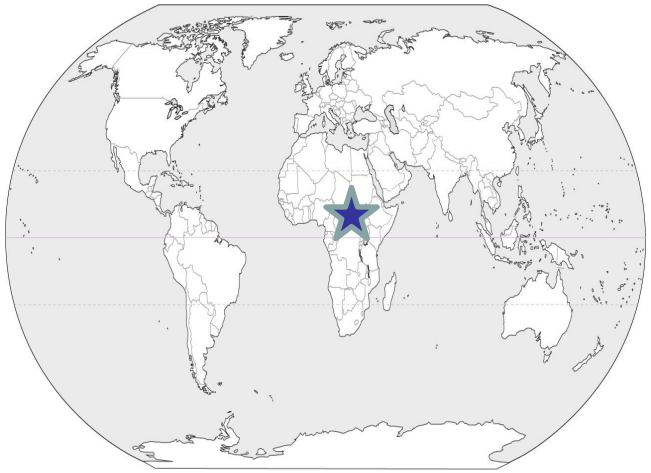
Experience and key investments to introduce shorter DS-TB regimen for adults and adolescents (Study31 four-month regimen)- **a Ugandan experience**

Grace Muzanyi, MBChB, MSc

TBTC Site 30 - Uganda-Case Western Reserve Univ Research Collaboration, Kampala Uganda

Uganda



Population 42 million (1.5 million in Kampala; 50%less than 15 years old, adult literacy rate 70%).

TB incidence - 250/100,000 population/yr (1.5% primary MDR-TB;TB/HIV co-infection at 40%)

Uganda's Past TB Regimen Experience

- Before 1995, 2STH/10TH was the standard regimen for treatment of pts with drug-susceptible TB (12 mo duration)
- From 1995-2003, the std regimen was 2ERHZ/6EH (8 mo duration).
- In 2003 with new knowledge about the efficacy of regimens using an EMB-containing continuation phase &funding from PEPFAR+Global fund, there was a shift to 2ERHZ/4RH for treating HIV+ TB patients.
- In 2015, the NTP replaced 2ERHZ/6EH (8 months) with 2ERHZ/4RH (6 mo) for all pts with drug-sensitive TB.

The Uganda Medical Community Perspective and Expectations

- DOT mostly feasible for inpatients, and a short efficacious regimen would ease both in and outpatient antiTB Rx
- With the country's limited NTP DOT implementation, shorter regimens would improve compliance, increase cure rates and mitigate the development of acquired drug resistance.
- Expected drop in the community TB transmission rates and a reduction in the overall TB burden in the country

comments by Dr. Stavia Turyahabwe, Head, NTP Uganda

Ugandan Patient Community Perspective and expectations on Shorter Treatment Regimens

- Adherence to the current 6 months regimen is difficult but would improve if shortened to 4 months; it will be exciting news for the patient community.
- Patients would prefer a shorter regimen with fewer side effects.
- Intermittent regimens are still of interest to patients.
- Shortened regimens result in faster cure and earlier return to work, providing economic benefit.
- Shortened treatment implies shorter duration of TB disease, less stigma and a quicker return to normal life in the community.

Dorothy Namutamba, Community Advisory Board, TBTC Site 30

Anticipated challenges with Shorter Regimens

- **Acceptability** – Uganda enrolled 20% of the participants in Study 31; the 2HPZM/2HPM regimen was shown to be efficacious, safe & acceptable in Uganda& across the consortium.
- **Cost** - Will the regimen be affordable in our setting?
- **Availability** - How quickly can this regimen available?(3HP part of LTBI policy in Uganda but drugs not available)
- **Policy change** - How quickly can the Country TB management guidelines be changed to integrate this regimen ?(Data dissemination complete to key stake holders)

Key investments to facilitate TB shorter regimen roll out.

- Funding workshops/conferences of key stake holders(Ministries, drug authorities,NTPs,regulatory bodies etc) where A31/ACTG5349 results could be presented.
- Invest time in discussions on fast-tracking a policy change.
- Invest time in pushing for registration of the shorter regimen for TB treatment .
- Cost and availability – request Country government s to tax-exempt the new regimen.
- Governments and Global development partners to provide a fund to subsidize on the regimen cost.
- Buy out of the Rifapentine+Moxifloxacin patency rights to facilitate global manufacture of these key drugs.

Thank you for your attention

As together, we work towards a healthier future for the next generation

Dr. Grace Muzanye

Dr Grace Muzanyi is the senior clinical Coordinator for the TB trials consortium (TBTC studies) at TBTC Site 30 and has served in this role for the past 16 years. He is a physician with a M.Sc. in clinical trials and currently pursuing a PhD in therapeutic drug monitoring. Dr Muzanyi has served as TBTC Site 30 clinical coordinator for TBTC Studies 27, 28, 28PK, 29, 29PK, 29x, 29xPK, NAA2M, and 31 and the STEP-EXPRESS 31 sputum transcriptomics study. He as well served a clinical trial consultant on TBTC study 31 for ACTG and TBTC Sites.

Dr. Eric Wobudeya

Dr Eric Wobudeya is a senior consultant Paediatrician and epidemiologist at Mulago National referral hospital where he heads the Pediatric TB unit. He is research scientist focused on pediatric tuberculosis (TB) for over 10 years. He was the Uganda site PI for a TB treatment shortening study in children (SHINE Trial).

SHINE Experience

Eric Wobudeya

MUJHU Care Ltd

On behalf of the SHINE trial team

Treatment Action Group

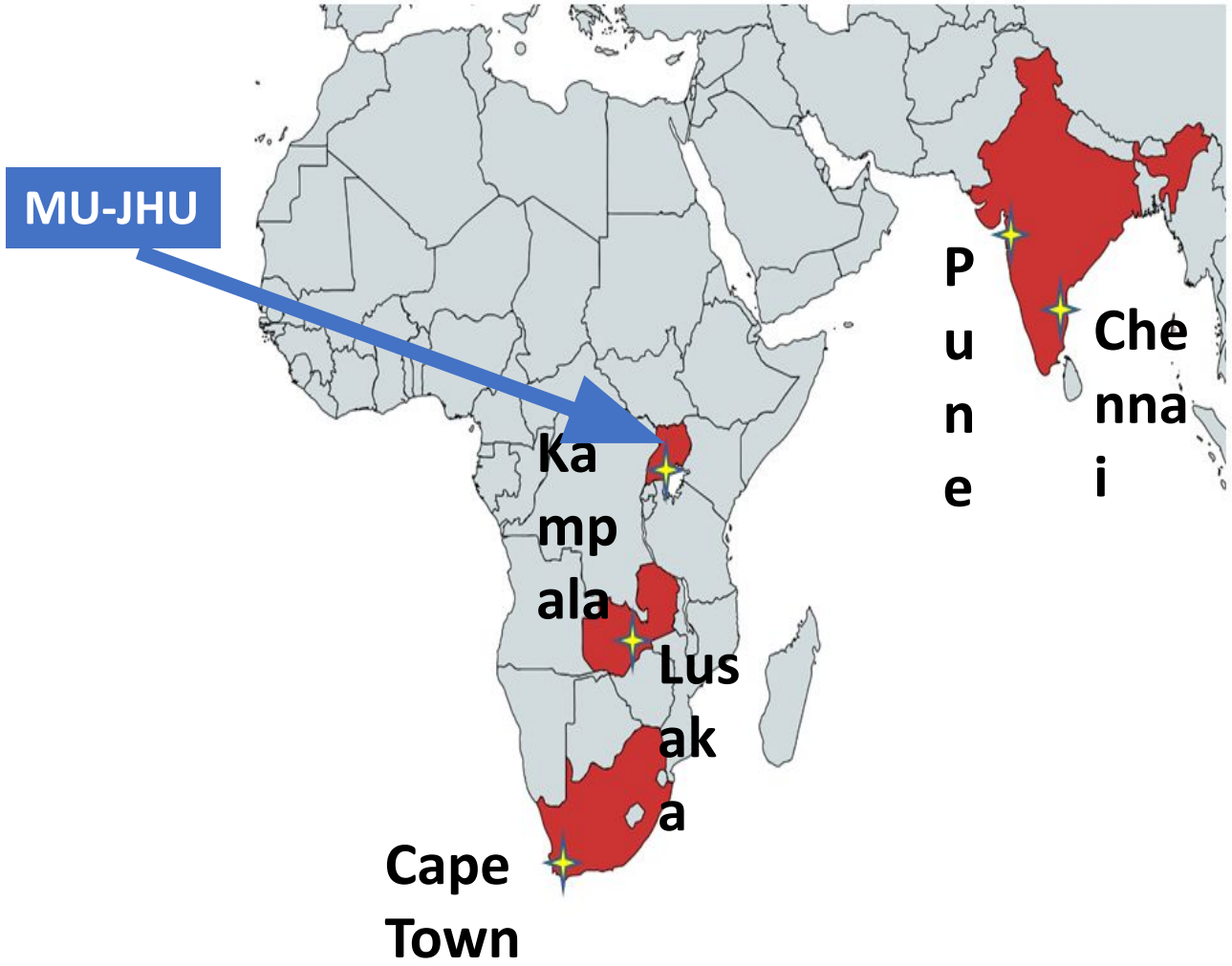
22 Feb 2022

Partners

Funders:

The SHINE trial

4 countries:
South Africa, Uganda, Zambia and India



1204 children
with 'minimal TB' randomised to receive either 6 months or 4 months of treatment

SHINE included children with **'minimal TB'**, which was defined as **both smear-negative and non-severe**

The SHINE trial found **no difference between the groups**: children who had only 4 months of treatment did as well as those who had 6 months of treatment

MUJHU research site

- A total of 376 (31%) were from MUJHU research site
- Received most referrals from nearby Mulago hospital TB clinic and then other 6 nearby Health centres
- The Mulago TB clinic registers 200 children with TB per year.
- All follow up done at the research site

Implementation experience – gastric aspirates

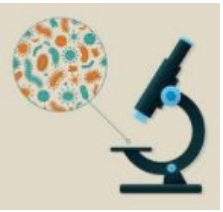
- We were required to obtain 2 respiratory samples from children
  - SHINE enrolment criteria included smear-negative respiratory samples
  - The samples were also processed for Xpert testing (children with Xpert M.Tb positive, Rif resistance negative respiratory samples were eligible)
- Nearly all children were seen in Outpatients
- Two early morning GA samples were collected with 2-3 hours between the collections
- Nurses were trained on an GA SOP, it was a single 1 hour session. GA was obtained from all the children
- Parents advised to fast children overnight and those with malnutrition were advised to have last meal at least 4 hours prior. This is feasible for non-research clinics

Implementation - respiratory samples

Smear microscopy

- Quality **sputum sample** collection or **gastric aspirates** can be challenging, particularly in young children
  - **Implementation solution:**
  - Simpler respiratory sample collection could be used, including nasopharyngeal aspiration with battery operated suction machines

- At our site **concentrated smear microscopy** was used – the equipment (e.g. centrifuge) may not be readily available for other clinics
  - **Implementation solution:**
  - Roll out of Xpert testing instead of smear microscopy (?)



- Smear grade is highly correlated with Xpert cycle threshold values
- In SHINE, children had **negative semiquantitative Xpert results** (majority) or **low-positive Xpert** results, which suggests that the SHINE results can be applied to children with these Xpert values

Implementation Experience – CXR reading

- Site clinicians had 2-3-hour training on reading of paediatric CXRs, including recognition of CXR changes typical and not typical for TB and what CXR changes should be considered as **severe and non-severe**
- Clinicians were comfortable interpreting and easily distinguished severe from non-severe CXRs. Second opinions and discussion were not frequent.
- Agreement between local and central reads in terms of severity was 94%
- A small number of children (71/1204 (6%) in all sites) were considered non-severe locally and severe by the SHINE radiology expert group
    - The outcomes in this group were consistent with the main trial

Non-severe pulmonary TB includes:
Confined to less than one lobe with no cavities and
no significant airway narrowing /no bilateral airway narrowing

CXR reading

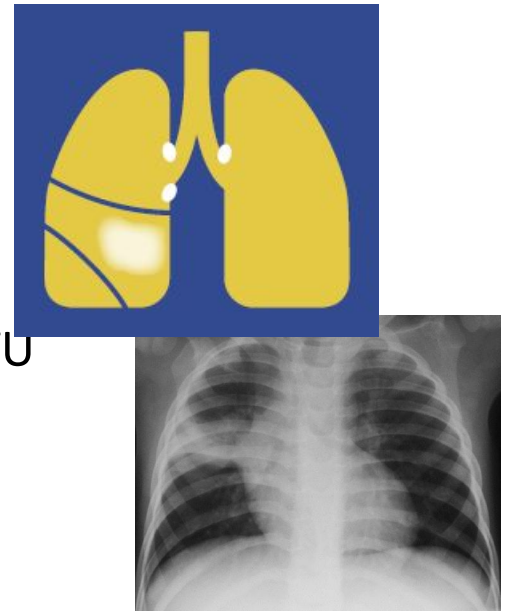
- **Implementation solutions:**

  <u>Settings with CXRs available:</u>

  - The UNION Diagnostic CXR Atlas for Paediatric TB with infographics
    - Will be available online very soon – watch the space!
  - Computer-aided detection (CAD) for paediatric CXR reading
    - In progress (collaborative work between Stellenbosch University, MRC CTU at UCL and FIND is ongoing)

  <u>Settings with CXRs NOT widely available:</u>

  - Consider referring children to health centres where CXRs are available
  - Investments to improve access to portable, digital CXRs



TAG. An activist guide to shorter treatment for drug-sensitive TB. 2021
https://www.treatmentactiongroup.org/wp-content/uploads/2021/10/activists_guide_shorter_treatment_ds_tb_final.pdf

Implementation experience – feedback from the families

- Quotes from families:
  - "it is convenient to the parents, it is convenient to the children…"
  - "four months is better because it is not good for children to take medicines for a long time…"
  - "it was better to have 4 months and my child recovered well…"

More on patient experiences see the SHINE film:
https://vimeo.com/645164426/251c376917

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SHINE study participants and their families

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Endpoint Review Committee: S. Welch, S. Graham, J. Seddon, E. Whittaker, S. Anderson, L. Grandjean

Independent Data Monitoring Committee: T. Peto, A. Mwinga, K. Fielding

Trial Steering Committee: P. Mugyenyi, J. Darbyshire, P. Clayden, P. Donald, V. Singh, M. Grzemska, S. Swaminathan

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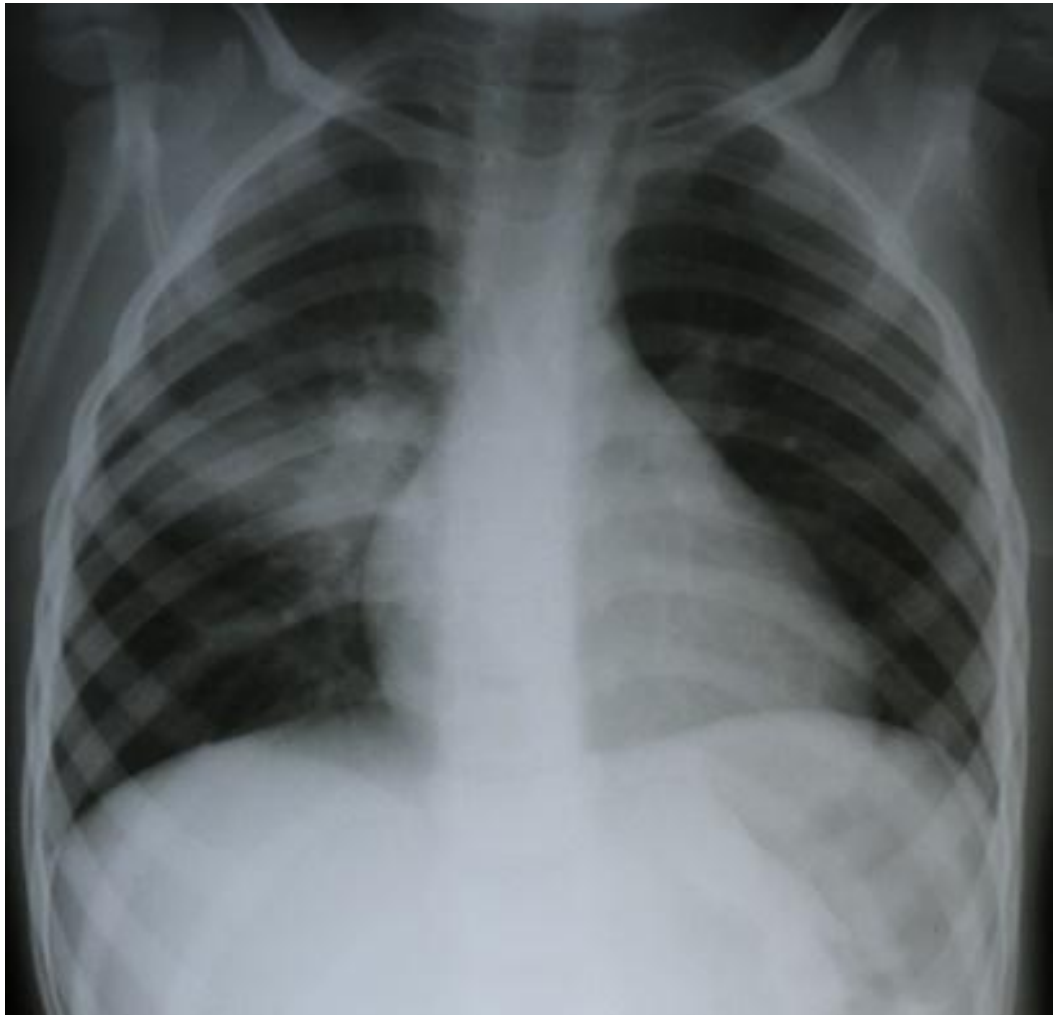
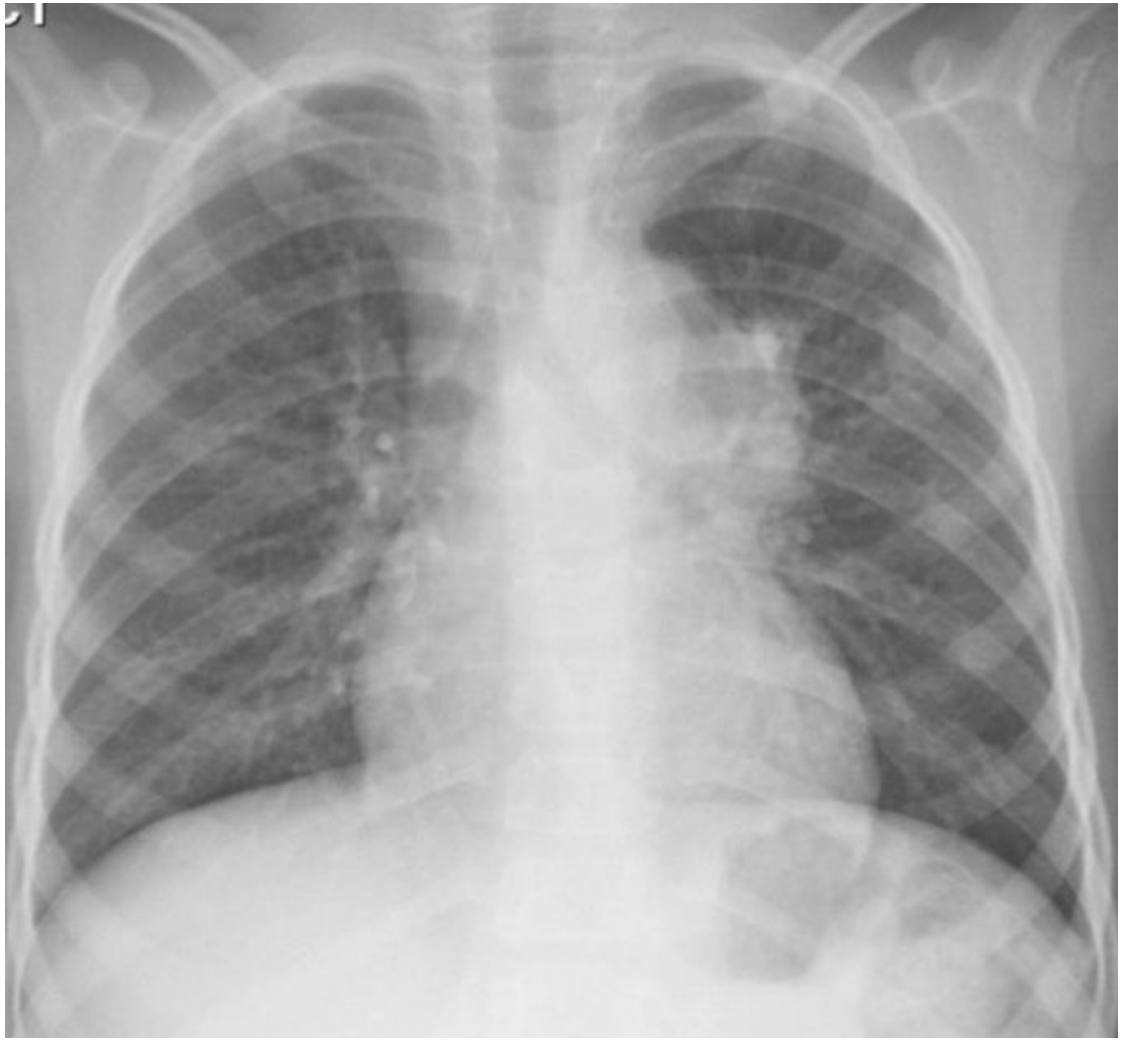
Trial drugs**:** Manufactured by Macleods Pharmaceuticals Ltd.

CXR examples: non-severe TB

Lymph node TB plus <1 lobe opacification

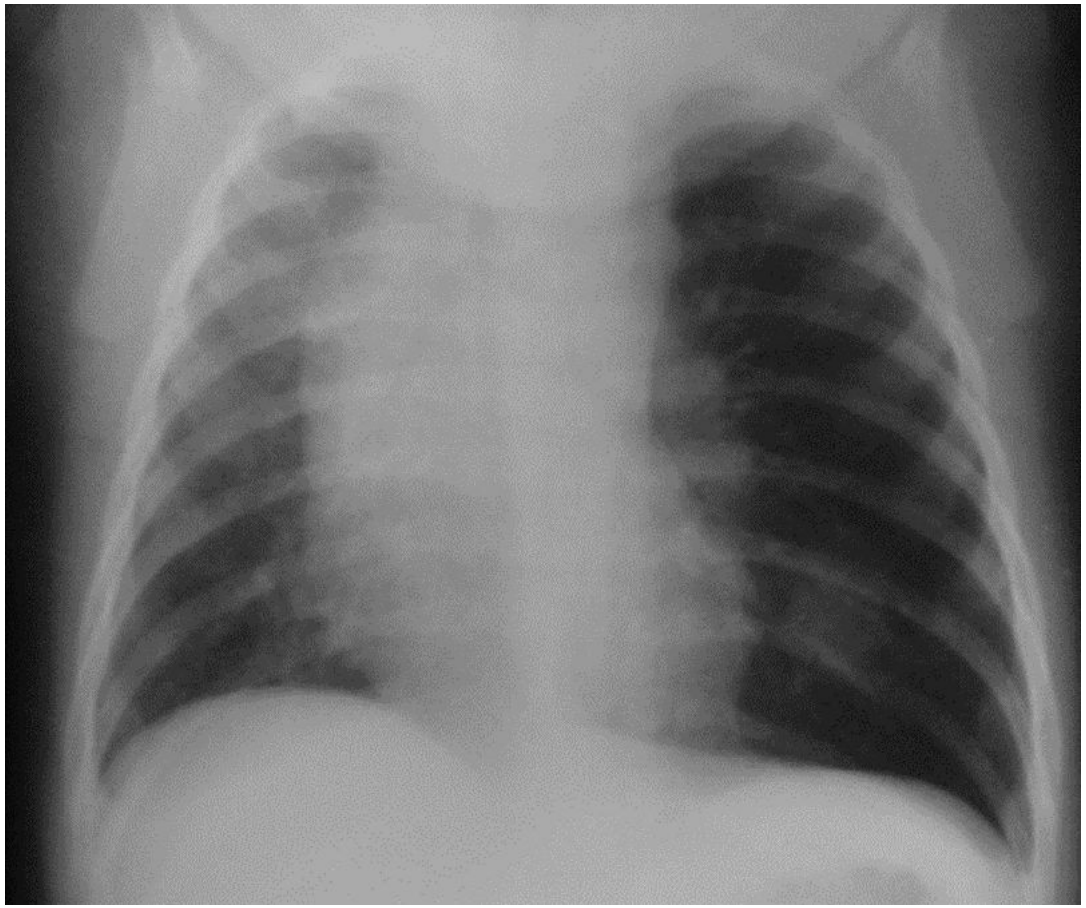


Lymph node TB

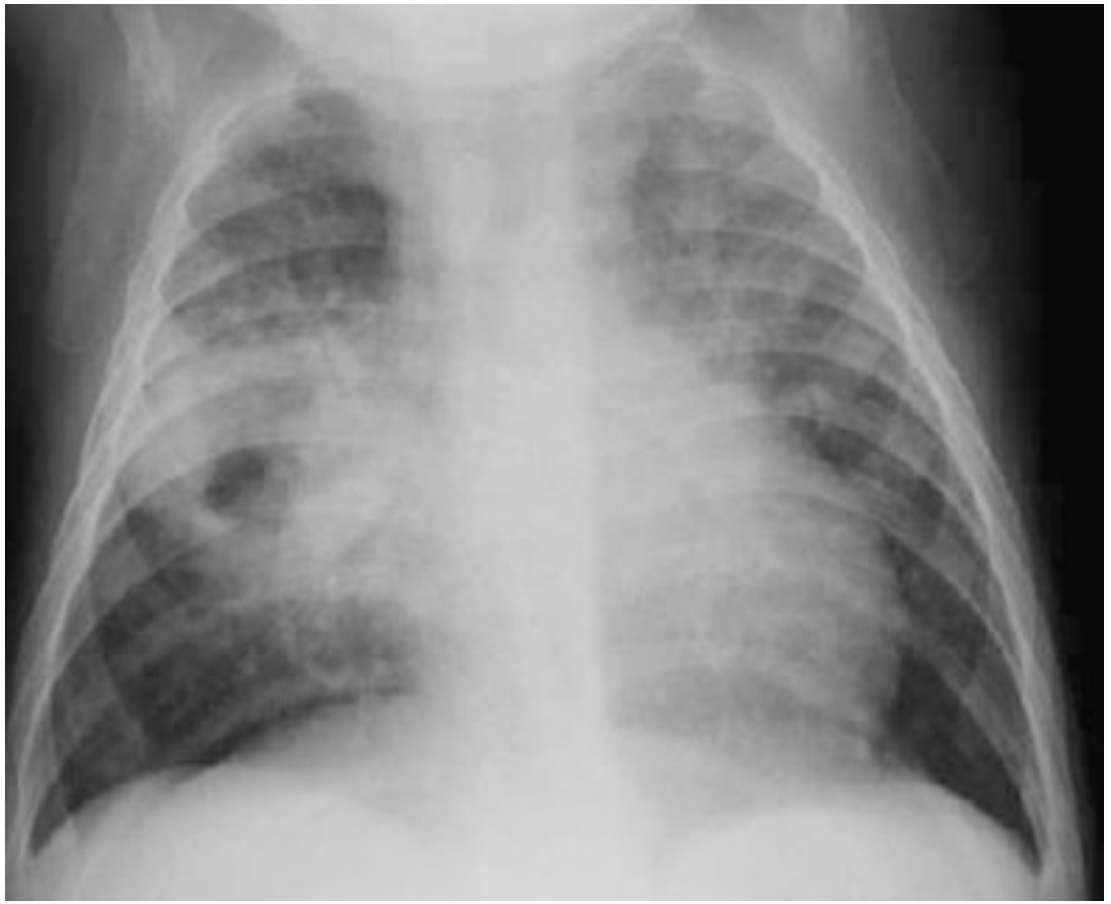


CXR examples: **severe TB**

Severe airway obstruction



Cavitary TB



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Strategic Investments to Scale Up Shorter TB Treatment Regimens

February 22, 2022

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