

Impact of COVID-19 on TB Drug Development

Stephanie Seidel, TB Alliance
TBEC Webinar Series
October 7, 2020



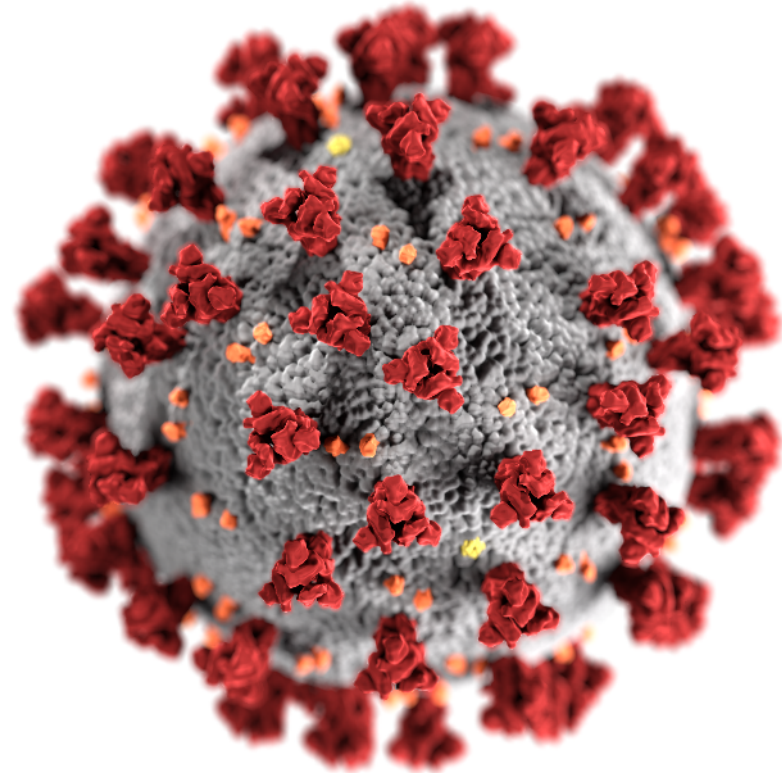
TB Alliance is a not-for-profit organization dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those in need.



Navigating COVID-19

A New Pandemic Threatens Progress - Hard-won Gains May Be Erased

- By disrupting the testing and treatment of TB and HIV, the COVID-19 pandemic could cause an additional 6.3 million TB cases and 1.4 million additional TB deaths through 2025
- Global TB incidence and deaths in 2021 could increase to levels last seen between 2013 and 2016 respectively – a setback of at least 5 to 8 years in the fight against TB



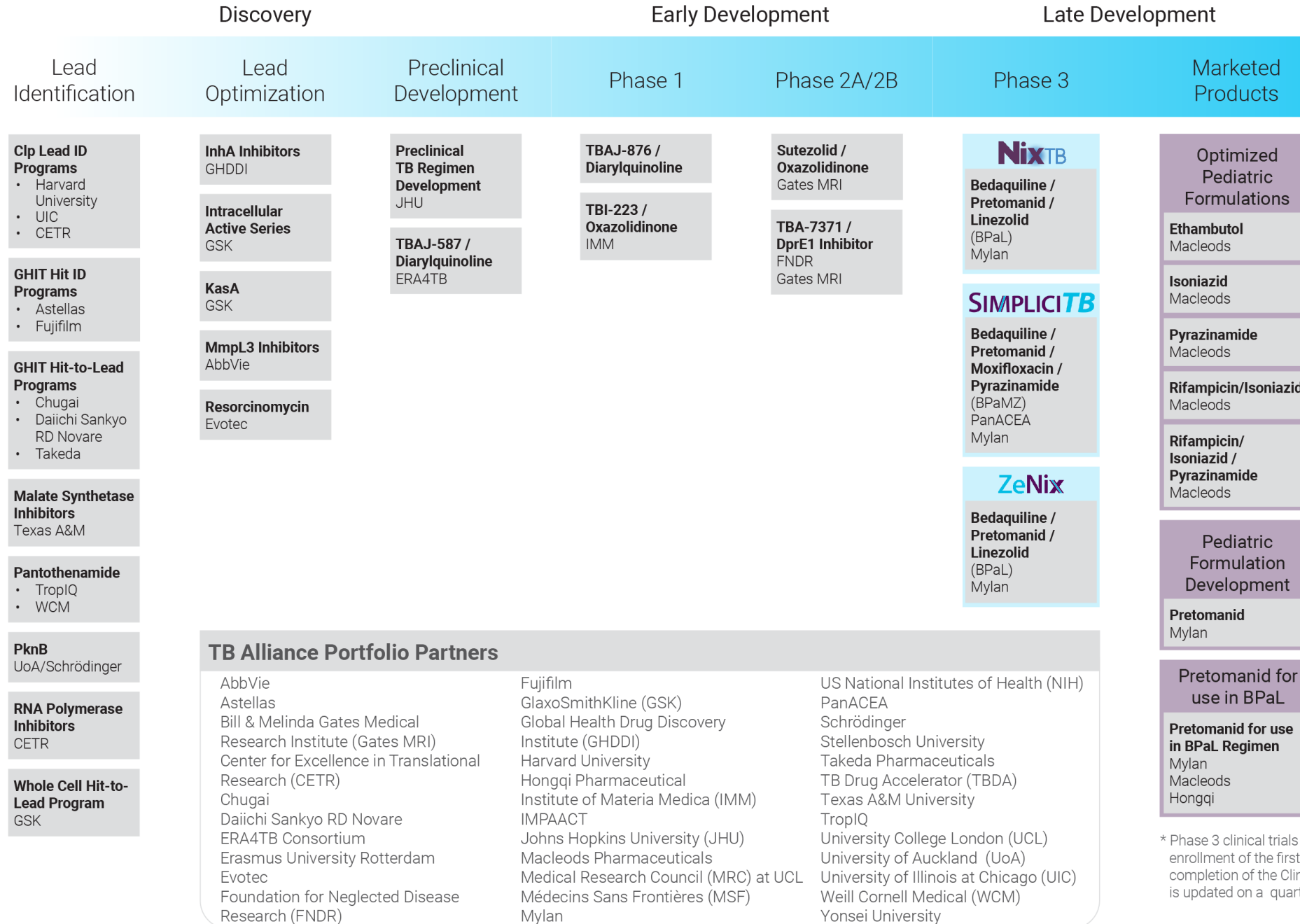
Putting science to work for better, faster TB cures

As an NIH-assigned Center of Excellence, we are a nonprofit R&D organization that has:

- Developed a **new treatment** for highly drug-resistant TB
- Launched **improved treatments** for children with TB
- **Transformed** how TB treatments are developed
- **Revived** the pipeline for new TB drugs
- **Mobilized** a global network of partners



AAA Mandate: Ensuring TB Alliance products are accessible to every person who needs them



* Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.

Nix-TB Results

New England Journal of Medicine, March 2020

PARTICIPANT STATS

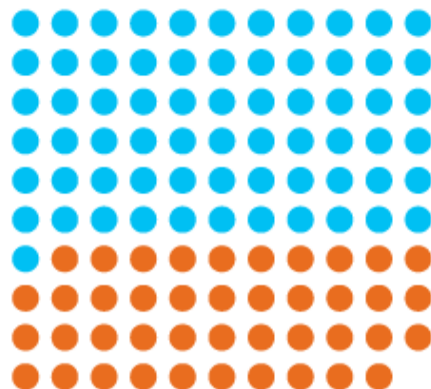
109 participants with confirmed TB

71 with XDR TB

65%

38 with MDR TB*

34%



THE RESULTS

Favourable outcomes

with XDR TB

89%

79-95 (95% CI)

with MDR TB*

92%

79-98 (95% CI)

90% of all participants had favourable outcomes

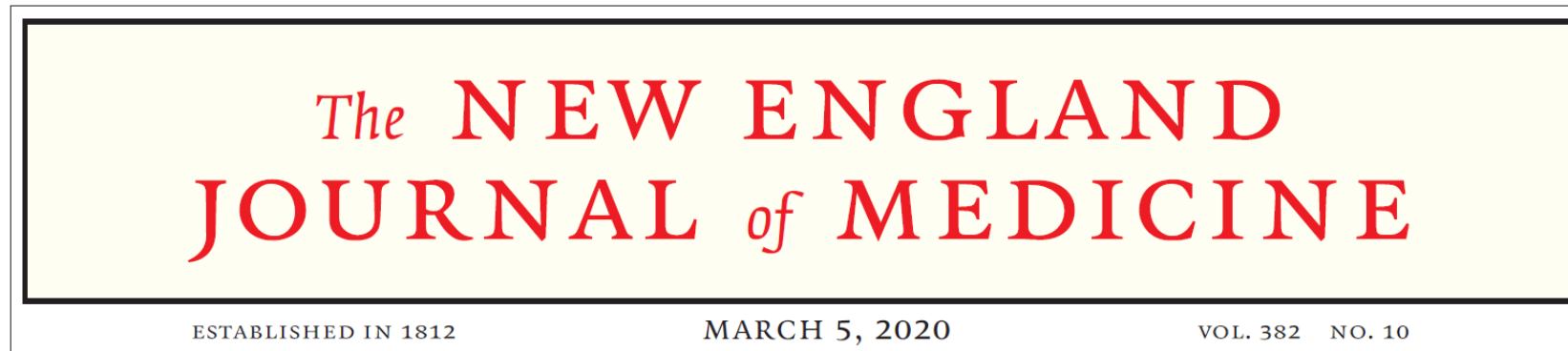


Clinical resolution
6 months after therapy

*Treatment intolerant or non-responsive MDR-TB

Pretomanid and the BPaL Regimen

- Full publication in the New England Journal of Medicine
<https://www.nejm.org/doi/full/10.1056/NEJMoa1901814>



Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch.,
Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D.,
Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D.,
Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D.,
Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Spotlight on BPaL: Accelerating Product Access

One Year Since US Approval, Rapid Progress Toward Uptake

- Pretomanid was made available for **150 low and middle-income countries** through Stop TB Partnership's Global Drug Facility (GDF) at a price of **\$364** for a six-month treatment course.
- Commercialization agreements with additional manufacturing partners: **Macleods**, and **Hongqi Pharma**.
- Global commercialization partner **Mylan** established a Named Patient Access Program
- **The World Health Organization** recommended the BPaL regimen under operational research conditions.
- Enrollment was completed in TB Alliance's phase 3 **ZeNix** and **SimpliciTB**, with results expected in 2021. The 24-month follow-up on all patients in the pivotal **Nix-TB** trial was also completed.
- **DCGI** approval for conditional access under the National Tuberculosis Elimination Program.
- Conditional **European Commission** marketing authorization as part of BPaL regimen

Operations Research

- Recent TB Alliance groundwork in several countries & Mylan support in key countries has helped progress on ORs
 - 2 early movers – Ukraine & Tajikistan, funded by TB REACH [Stop-TB, TBA effort]
 - Nigeria, Kyrgyzstan, Indonesia: value proposition work by TB Alliance
 - South Africa: advocacy with DOH, local TBA & Mylan teams' support, Nix-TB trial site
 - India: local Mylan team, TB Alliance HQ missions, NTP on TB Alliance AAC
 - Philippines, Myanmar, Uzbekistan, Kazakhstan: direct engagement by us and through technical partners
- Mylan team and technical partners working in close coordination with us

Mylan Named Patient Access Program (NPAP)



- The NPAP is a means of providing access to pretomanid as part of the three-drug, all-oral BPaL regimen to patients in countries where the drug is not currently approved by a national regulatory authority.
- NPAP is designed specifically for patients who live in countries where regulatory approval for pretomanid is not yet available to help ensure that physicians can consider pretomanid as a viable treatment option for patients regardless of where they live.
- To learn more about this program and apply, please visit www.accesspretomanid.com.

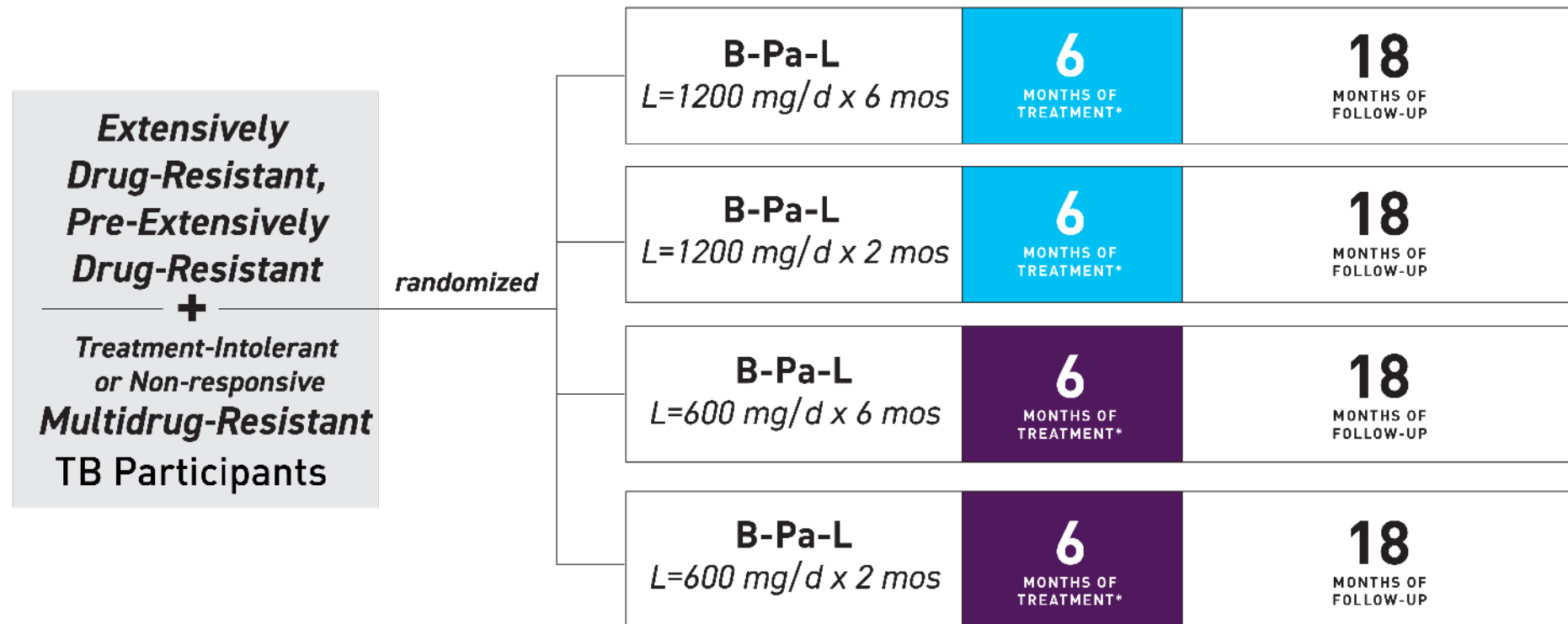
Trial Rationale

- Provide a 3-drug regimen where there is no expected resistance in the community for patients with limited treatment options
- Gather important efficacy and safety data on a regimen that could potentially treat all strains of TB
- Shorten treatment in patients who are susceptible to all drugs with Combination of B-Pa which is well tolerated
- **Nix-TB**- showed manageable toxicity and efficacy of an all oral 6-month regimen to patients with XDR. (Nix-TB all patients started with 1200 mg linezolid and Investigators could pause or adjust dose in response to toxicity.
- **ZeNix**-Blinded linezolid dose and duration differences to optimize dosing scheme for best efficacy to toxicity balance (risk/benefit) .

ZeNix: Linezolid Optimization Trial



Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment



*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

Pa pretomanid dose = 200 mg daily

B bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

ZeNix Trial Population

Expanded, just XDR and MDR intolerant and non-responsive in Nix-TB.

ZeNix trial included patients with:

- XDR-TB
- Pre-XDR-TB or
- MDR-TB who have failed or are intolerant to treatment

ZeNix Timelines

- First Patient Randomized **November 2017**
- Last Patient completed treatment **June 2020**
- Last Patient to complete 6-month follow-up (Primary Endpoint) **December 2020**
- Primary Endpoint Analysis Complete/Available **September 2021**
- Last Patient to complete trial **December 2021**

COVID-19 Issues and Actions

- Working with sites to ensure participants supported in Follow up:
 - Encourage documentation of missed visits, assessments and out of window visits due to COVID-19
 - Instruct sites to perform telephone visits where on-site visits not possible, on-site visit to be scheduled as soon as possible to ensure sputum sample collection
 - On-site monitoring visits were suspended and have started again
 - TB Alliance emailing monthly reminders of upcoming visits for primary and secondary endpoints (Follow-up week 26 and 78)

All ZeNix patients in follow-up

Important for patients to return for follow up visits to provide sputum
6 months after treatment completion (primary endpoint) and at the end
of the trial, **18 months after treatment completion**.

BPaMZ Regimen

SimpliciTB Clinical Trial

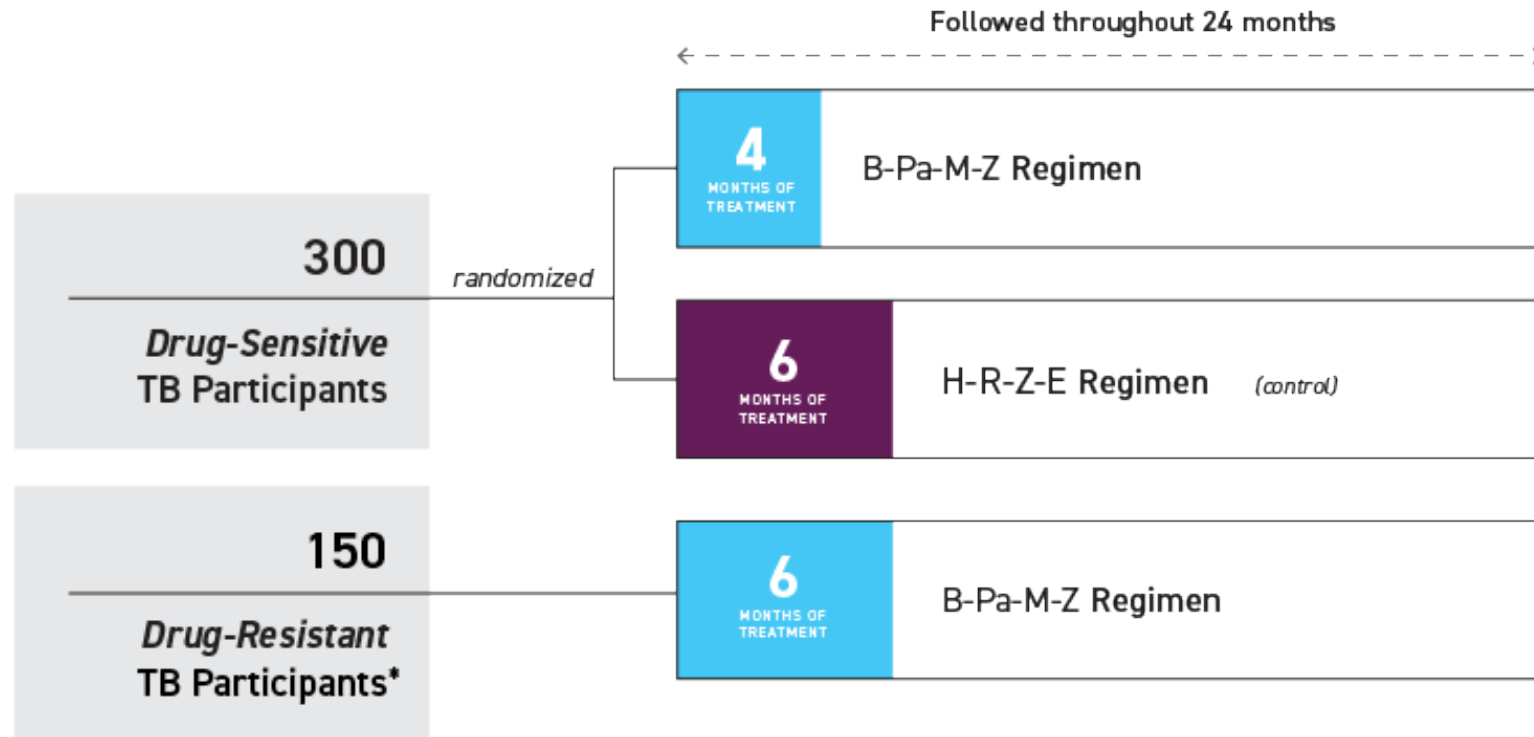
- The SimpliciTB clinical trial seeks to test a novel regimen consisting of bedaquiline (B), pretomanid (Pa), moxifloxacin (M) and pyrazinamide (Z) (BPaMZ)
- This trial evaluates
 - The effectiveness of a 4-month regimen of BPaMZ in people with DS-TB versus six months of HRZE (control/standard of care)
 - The safety, tolerability and efficacy of a 6-month BPaMZ regimen for patients with DR-TB
- Enrollment commenced on 30 July 2018
 - Enrollment completed on 2 March 2020
 - Patients enrolled in 27 sites in 8 countries on 4 continents



SimpliciTB Trial: BPaMZ



Participants with newly diagnosed DS- and MDR-TB



*Specifically MDR-TB and mono-resistance to isoniazid or rifampicin.

B bedaquiline 200 mg x 8 weeks, then 100 mg | Pa pretomanid 200 mg | M moxifloxacin 400 mg | Z pyrazinamide 1500 mg

H isoniazid | R rifampin | Z pyrazinamide | E ethambutol

- Immediate Intervention from TB Alliance
 - Weekly, then bi-weekly, internal TC's and tracking
 - No changes since August 2020
 - Direct communication with all sites and vendors
 - Weekly monitoring of safety and IMP supplies, proactive ordering etc
 - Participant visits – telephonic, remote and EDC completion instructions
 - Support for COVID-19 testing and reimbursement
 - Regular newsletters to sites

COVID-19 Impact on Community Engagement

- All site programs have transitioned to using virtual platforms and tools to communicate with Community Advisory Boards and affected communities
- Site-level CE programs are now including COVID-19 prevention and safety in their educational programs, in addition to TB disease and research education
- CE teams have reported general difficulty with supporting patients in for their treatments and follow ups.
- Ongoing survey of TB Alliance site-level CE and research teams, CABs and communities to understand overall impact of COVID-19.
- Early responses are consistent with published reports on impact at the community-level.



The impact of COVID-19 on the TB epidemic: A community perspective

https://drive.google.com/file/d/1rxREVzu_K-5EYNqLahMmTnKHJSaff0-Q/view



Upcoming Event

Stakeholders Association Annual Meeting

**November
2020**

20
**YEARS OF
IMPACT**

TB Alliance Donors

20 YEARS OF
IMPACT



Indonesia
Health Fund



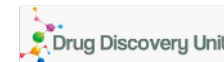
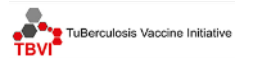
TB Alliance Stakeholders



Community Representative,
Maurine Murenga



Community Representative,
Sarah Mulera

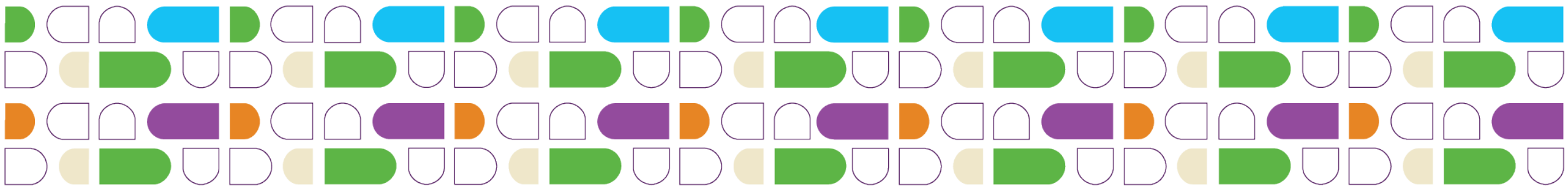


Louder Than TB: Coalition of Partners

More than 50 organizations have joined the campaign



Thank you!

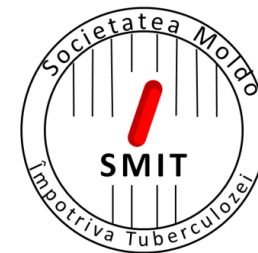


CE IN RESEARCH AND DEVELOPMENT

CAB MOLDOVA MODEL

Oxana Rucşineanu, SMIT Executive Director,
CAB Moldova Coordinator

October 07, TB Europe Coalition Webinar



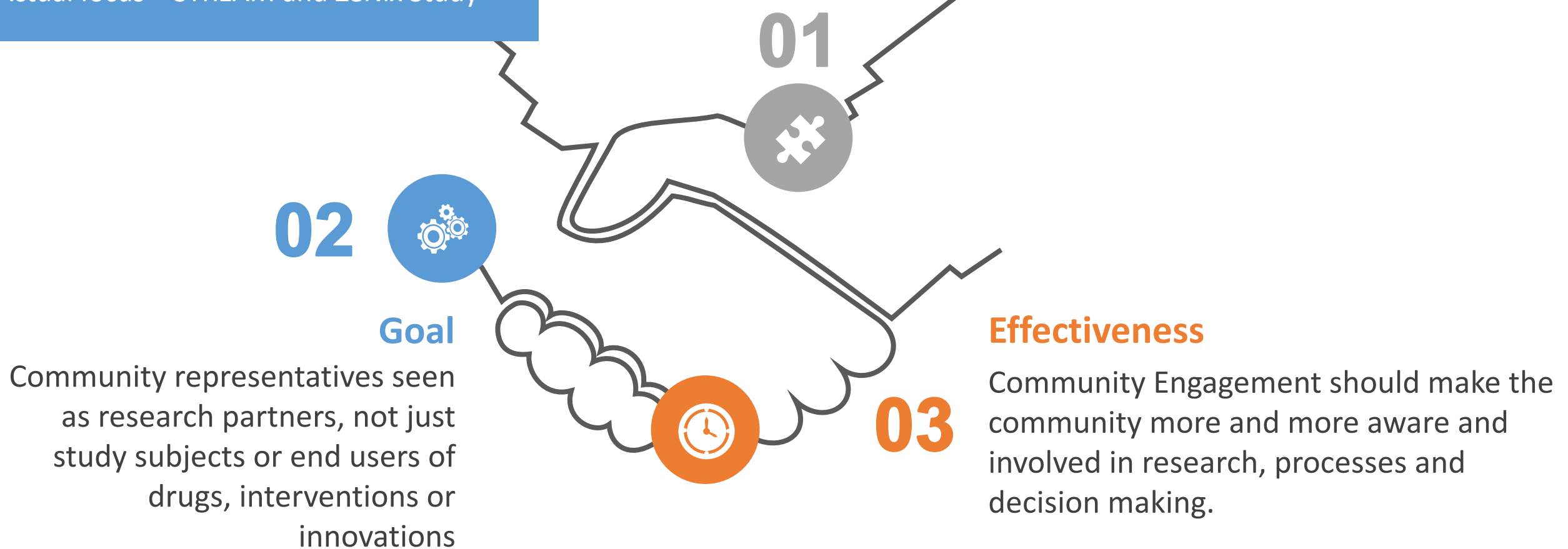
OUR PRIMARY MISSION

Where do we want to reach with the CAB Advocacy?

Actual focus – STREAM and ZeNix Study

Context

Community Engagement in research and development is a dynamic and interactive relationship among researchers, policy makers, the community/civil society

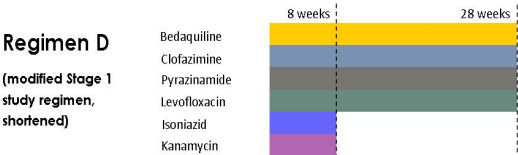
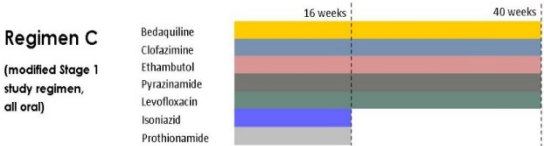


STREAM STAGE 2 study aims to generate evidence regarding the efficacy, safety and cost –effectiveness of more tolerable MDR-TB regimens, including a 9-month BQL-containing all oral-regimen

Regimen A

Locally used WHO-approved MDR-TB regimen

Total participants enroled – 588 (63 in Moldova)
Study period: 2016 – 2020



13 sites in 7 countries - Ethiopia, Georgia, India, Moldova, Mongolia, S. Africa and Uganda

ZeNix STUDY is a phase 3 partially-blinded aims to generate evidence regarding the safety and efficacy of various doses and treatment durations of the BPaL (three-drug) XDR-TB regimen in six- to nine-month regimen

Total participants enrolled – 180 (10 in Moldova)
Study period: 2017 – 2021

BPaL (three-drug) XDR-TB regimen consists of bedaquiline, pretomanid and linezolid

Participants enrolled

- XDR-TB,
- pre-XDR-TB, or
- treatment intolerant or non-responsive MDR-TB

sites in 4 countries - Georgia, Moldova, Russian Federation and South Africa



HOW DO STAKEHOLDERS SEE THE CAB

COMMUNITY

CRG (community rights & gender) GF national experts (by human rights NGO)
Liaison among TB and HIV communities (KAP) and TB Platform
Voice of those affected

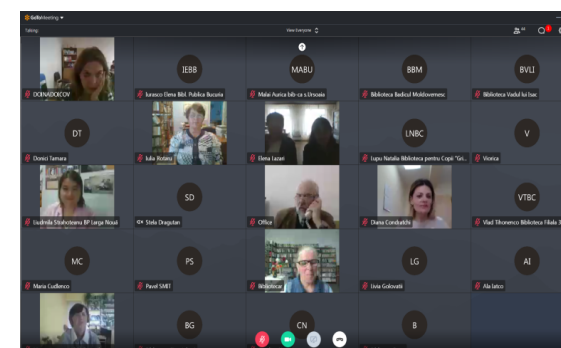
EXPERTS

Experts in community engagement and health in prisons (WHO, UNODC, UNAIDS)
Experience for community-based studies / research
TB doctor and public health expertise

PARTNER

Partner for trial implementation
Members of the TB working groups
Active participants in development of the NTP 2021-2025
Active participants in development of the application for the GF 2021-2023 or other regional funding opportunities for national TB response

IMPACT OF COVID-19 ON CE in R&D

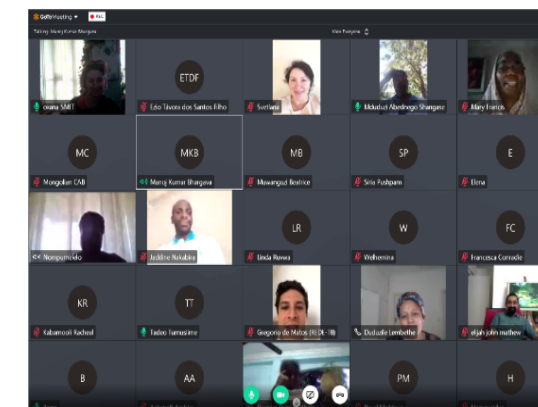


SAFETY OF STAFF AND BENEFICIARIES - Development of valuable IEC materials

ENGAGING COMMUNITIES - Advancing patient perspectives and building comprehensive care

INFORMATION AND AWARENESS EVENTS - stakeholders countrywide

TB research studies and networks from around the world have reported challenges due to COVID-19 and are adapting their research efforts and protocols to enable the continuation of critical research. Study responses to COVID-19 apparently will have budgetary implications, and additional funding will be required to cover extended timelines and unforeseen expenses (TAG TB Research Investments Provide Returns in Combating Both TB and COVID-19).

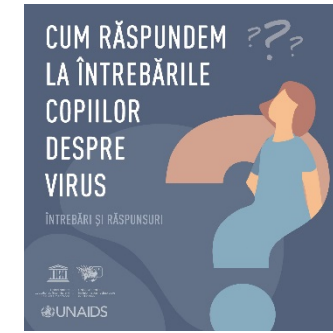


IMPACT OF COVID-19 on CE

Since its appearance, COVID-19 has spread rapidly around the globe and caused a staggering loss of life. (RM: on **March 7** COVID-19 first case detected and on **March 18** first death reported)

Safety of staff members from COVID-19 –

1. Participate in the development of valuable tools: Instructions for CSOs during COVID-19 and TB specialists - ORGANIZATIONAL POLICY in the Context of the Coronavirus Outbreak and INSTRUCTIONS for safety and health at work place in connection with the epidemiological situation in the country and the occurrence of the risk of contracting COVID-19
2. Personal protective equipment



Safety of staff and Beneficiaries

1. Information and education on preventive measures for COVID-19 through virtual trainings & meetings
2. Environmental controls (physical distancing, beneficiaries flow)
3. Working from home whenever feasible and possible

Community engagement strengthening

1. Physical distance, self care, prevention, first line support, referrals
2. Outreach and on-line worker;
3. Supporting the beneficiaries to make informed, safe decisions about their health and well-being

COMMUNITY CONTRIBUTION: RECENT UPDATES

How communities contribute to awareness, community monitoring and policy changes in Moldova?

Awareness and Community Monitoring during

1. Engage in CCM, Council of Experts, KAP Committee and TB NGOs Platform, Evaluation Committee for GF small grants for CSOs
2. Ensure and monitor continuation of TB services and awareness via phone, survey, webinars, interviews, letters, open statements
3. Monitor of drugs availability, procurement during of Covid-19, including from GF
4. Ensure continuation of country engagements in regard of CSOs (public funding for CSOs)

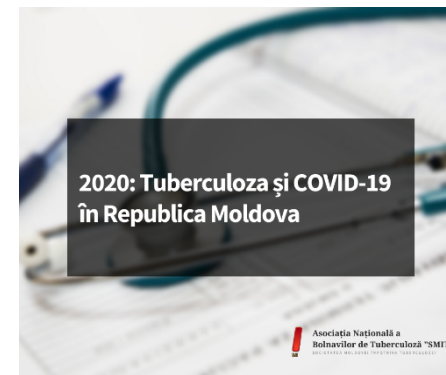
Development of the NTP 2021-2025

1. Component of the community based trials/operational research has been included
2. Communities representative will be included in the Ethics Committee

Development of the GF Application 2021-2023

1. Aspects of the community based studies, legal barriers on TB, community mobilization and organizational management for sustainability (not only service provision) have been included
2. Engage with CRG to foster community participation in Country Dialogue

IMPACT OF COVID-19 on TB: CHALLENGES



- ❑ Smaller number of consultations
- ❑ Smaller number of self-reporting
- ❑ 39,4% reduction in TB notification
- ❑ 39,4% reduction in TB enrollment in treatment
- ❑ 38,80 % reduction in RR MDR TB enrollment in treatment

| Indicator | Q1, 2019 | | | Q2, 2019 | | | Q3, 2019 | | total 8 MONTH 2019 | Q1, 2020 | | | Q 2, 2020 | | | Q3, 2020 | | total 8 luni 2020 | % |
|---------------------------------|----------|--------|--------|----------|--------|--------|----------|--------|--------------------|----------|--------|--------|-----------|--------|--------|----------|--------|-------------------|-------|
| | ian.19 | feb.19 | mar.19 | apr.19 | mai.19 | iun.19 | iul.19 | aug.19 | | ian.20 | feb.20 | mar.20 | apr.20 | mai.20 | iun.20 | iul.20 | aug.20 | | |
| NEW & RELAPSE CASES | 256 | 262 | 315 | 259 | 237 | 228 | 270 | 213 | 2040 | 223 | 238 | 204 | 112 | 99 | 130 | 126 | 105 | 1237 | 39,40 |
| INITIATED TREATMENT (ALL CASES) | 283 | 295 | 358 | 305 | 243 | 266 | 321 | 258 | 2329 | 240 | 276 | 231 | 128 | 115 | 151 | 147 | 124 | 1412 | 39,40 |
| RR MDR TB INITIATED TREATMENT | 86 | 63 | 84 | 85 | 63 | 67 | 79 | 81 | 608 | 57 | 71 | 67 | 36 | 41 | 37 | 34 | 29 | 372 | 38,80 |

IMPACT OF COVID-19 on TB: OPPORTUNITIES

CSOs engagement in TB finding

- ✓ Maintaining the most critical services, especially the detection and treatment of tuberculosis, is a priority for reducing the overall impact of the COVID-19 pandemic
- ✓ Detection and treatment of TB people - fundamental pillars in TB care
- ✓ Additional measures and resources mobilised
- ✓ Active TB case finding with the support of CSOs in a short term

Therefore:

1. June 2020 - funds identified to engage CSOs in TB detection
2. June - July 2020 Development of SOP for CSOs
3. **July 2020** - Identifying territories – 9 rayons
4. July 2020 – MHSP order issued on organizing active TB detection
5. August 2020 - Training of CSOs Staff (remotely)
6. September 2020 – Start of work
7. December 2020 – Results expected

12/10/2020

CE IN R&D: CAB MOLDOVA MODEL

MINISTERUL
SĂNĂTĂȚII, MUNCII ȘI
PROTECȚIEI SOCIALE
AL REPUBLICII MOLDOVA



MINISTRY
OF HEALTH, LABOUR AND
SOCIAL PROTECTION OF THE
REPUBLIC OF MOLDOVA

DISPOZIȚIE
mun. Chișinău

"20" iulie 2020

nr. 313-d

**Cu privire la organizarea depistării ținute
a cazurilor TB în condițiile pandemiei COVID-19**

În scopul realizării Programului Național de Control al Tuberculozei pentru anii 2016–2020 aprobat prin Hotărârea Guvernului nr. 1160/2016 în condițiile pandemiei COVID-19, și în temeiul Regulamentului privind organizarea și funcționarea Ministerului Sănătății, Muncii și Protecției Sociale, aprobat prin Hotărârea Guvernului nr. 694/2017,

DISPUN:

1. Conducătorii Direcției Sănătății a Consiliului Municipal Chișinău, Serviciului Sănătate a Primăriei mun. Bălți, Direcției generale a sănătății și protecției sociale a populației UTA Găgăuzia, instituțiilor medico-sanitare publice republicane, raionale vor asigura sub responsabilitate personală:
 - 1) examinarea persoanelor cu simptome respiratorii conform algoritmului din Anexa 1;
 - 2) organizarea depistării ținute a cazurilor TB pentru a îmbunătăți notificarea cazurilor în condițiile pandemiei COVID-19, conform Anexei 1;
 - 3) examinarea radiologică a persoanelor din grupurile țintă menționate în Anexa 1 (orice persoană care prezintă simptome respiratorii; contacții cu pacienții TB; persoanele cu sechele posttuberculoase; pacienți cu diabet zaharat; persoanele care trăiesc cu HIV; persoane cu dependențe (utilizatori de droguri, abuz de alcool) cu acoperirea costurilor din sumele contractate cu CNAM pentru anul 2020 în acest scop;
 - 4) suport organizațiilor neguvernamentale active în domeniu TB și HIV implicate în activitățile de depistare ținută TB în teritorii, conform Anexei 2.
2. Departamentul de coordonare PNCT, IMSP IFP „Chiril Draganiuc” va acorda suportul consultativ coordonatorilor teritoriali.
3. Controlul executării dispoziției se atribuie dnei Daniela Demișcan, șef Direcția politici în domeniul sănătății publice.

SECRETAR DE STAT

Constantin RÎMIȘ

IMPACT OF COVID-19 on TB: OPPORTUNITIES

CSOs engagement in VOT

- ✓ PC outpatient and community care is preferred over hospitalisation to reduce transmission
- ✓ TB treatment schemes prescriptions modified
- ✓ Alternative methods to DOTS encouraged

Therefore:

April 2020 - VOT was launched in Chisinau based on MoH disposition

Main activities:

- Distribution of equipment
- Training of medical Staff (remotely)
- training and registration of patients (remotely)

Results:

September 2020 – Over 100 TB people enrolled on VOT

MINISTERUL
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AL REPUBLICII MOLDOVA



MINISTRY
OF HEALTH, LABOUR AND
SOCIAL PROTECTION OF THE
REPUBLIC OF MOLDOVA

DISPOZIȚIE
mun. Chișinău

„30” „martie” 2020

nr. 115/20

Cu privire la organizarea implementării
tratamentului antituberculos video-observat
în condițiile epidemiei COVID – 19

În contextul situației epidemiologice create în urma răspândirii virusului COVID19, și întru asigurarea realizării continue a Programului Național de Control al Tuberculozei pentru anii 2016–2020, aprobat prin Hotărârea Guvernului nr.1160/2016, ținând cont de prevederile Regulamentului cu privire la modul de organizare a tratamentului video observat al tuberculozei (VOT), aprobat prin ordinul Ministerului Sănătății, Muncii și Protecției Sociale nr. 341/2019, în temeiul Regulamentului privind organizarea și funcționarea Ministerului Sănătății, Muncii și Protecției Sociale, aprobat prin Hotărârea Guvernului nr. 694/2017,

DISPUN:

1. Conducătorul Direcției asistență socială și sănătate a Consiliului Municipal Chișinău, va asigura organizarea implementării tratamentului video observat al tuberculozei (VOT) în condițiile epidemiei COVID – 19, luând în considerare prevederile ordinului nr. 341 din 18 martie 2019 și instrucțiunea, conform anexei.
2. Centrul pentru Politici și Analize în Sănătate (Centrul PAS), în faza de implementare a VOT va oferi spațiu hosting pentru sistemul informațional VOT al IMSP Institutul de Ftiziopneumologie ”Chiril Draganiuc” pentru asigurarea suportului tehnic continuu și transferul treptat de cunoștințe către personalul IT desemnat de IMSP IFP ”Chiril Draganiuc”.
3. Coordonatorul Programului Național de Control al Tuberculozei (Dna Valentina VILC) va acorda suportul consultativ metodic coordonatorilor teritoriali din AMT.
4. Controlul executării dispoziției se atribuie dnei Daniela Demișcan, șef Direcția politici în domeniul sănătății publice.

Secretar de stat

Constantin RÎMIȘ