New Tools in the Post-UNHLM

David Lewinsohn
StopTB Partnership New Tools Working Groups
Ending TB

- Guiding Principles
  - TB elimination **not** achievable without new tools
  - While tools not widely available in next 5 years, investments NOW is key
BY 2030, A FIVE-YEAR DELAY IN INVESTMENT FOR NEW TOOLS IS ESTIMATED TO RESULT IN:

1. **8.4 MILLION ADDITIONAL TB CASES**
2. **1.4 MILLION ADDITIONAL TB DEATHS**
3. **39.8 MILLION DALYs SUFFERED** (56.1 million without discounting)
4. **US$ 5.3 BILLION IN ADDITIONAL COSTS FOR TB TREATMENTS** (US$ 7.5 billion without discounting)
5. **US$ 181 BILLION IN LOST PRODUCTIVITY** (US$ 318 billion without discounting), valuing each DALY at per-capita GNI.

THE COST OF FAILING TO INVEST IN NEW TOOLS
UNHLM ON TB KEY TARGETS FOR 2022

WE, HEADS OF STATE AND GOVERNMENT AND REPRESENTATIVES OF STATES AND GOVERNMENTS ASSEMBLED AT THE UNITED NATIONS IN NEW YORK ON 26 SEPTEMBER 2019:

1. COMMIT TO PROVIDE DIAGNOSIS AND TREATMENT with the aim of successfully treating 40 million people with tuberculosis by 2022.

2. COMMIT TO PROVIDE DIAGNOSIS AND TREATMENT with the aim of successfully treating 3.5 million children with tuberculosis by 2022.

3. COMMIT TO PROVIDE DIAGNOSIS AND TREATMENT with the aim of successfully treating 1.5 million people with drug-resistant tuberculosis, including 115,000 children with drug-resistant tuberculosis, by 2022.

4. COMMIT TO PREVENT TUBERCULOSIS for those most at risk of falling ill so that at least 30 million people, including 4 million children under five years of age, 20 million other household contacts of people infected by tuberculosis, and 6 million people living with HIV, receive preventive treatment by 2022.

5. COMMIT TO MOBILIZE SUFFICIENT AND SUSTAINABLE FINANCING for universal access to quality prevention, diagnosis, treatment and care of tuberculosis from all sources, with the aim of increasing overall global investments for ending tuberculosis reaching at least US$13 billion a year by 2022.

6. COMMIT TO MOBILIZE SUFFICIENT AND SUSTAINABLE FINANCING FOR R&D with the aim of increasing overall global investments in US$2 billion, in order to close the estimated US$3 billion gap in funding annually for tuberculosis research, ensuring all countries contribute appropriately to research and development.

7. PROMOTE AND SUPPORT AN END TO STIGMA AND ALL FORMS OF DISCRIMINATION, including by removing discriminatory laws, policies and programmes against people with tuberculosis, and through the protection and promotion of human rights and dignity. Recognize the various social, cultural and structural barriers to tuberculosis prevention, diagnosis and treatment services, especially for those who are vulnerable or in vulnerable situations, and the need to develop integrated, people-centered, community-based and gender-responsive health services based on human rights.

8. COMMIT TO DELIVERING, AS SOON AS POSSIBLE, NEW, SAFE, EFFECTIVE, EQUITABLE, AFFORDABLE, AVAILABLE VACCINES, point-of-care and child-friendly diagnostics, drug susceptibility tests and safer and more effective drugs and shorter treatment regimens for adults, adolescents and children for all forms of tuberculosis and infection, as well as innovation to strengthen health systems such as information and communication tools and delivery systems for new and existing technologies, to enable integrated preventive, diagnostic, treatment and care of tuberculosis.


10. FURTHER REQUEST THE SECRETARY GENERAL, WITH THE SUPPORT OF THE WORLD HEALTH ORGANIZATION, TO PROVIDE A PROGRESS REPORT IN 2020 on global and national progress, across sectors, in accelerating efforts to achieve agreed tuberculosis goals, which will serve to inform preparations for a comprehensive review by Heads of State and Government at a high-level meeting in 2023.
ACCELERATE DEVELOPMENT OF ESSENTIAL NEW TOOLS TO END TB

P42: ‘Commit to advancing research for basic science, public health research and the development of innovative products and approaches... including towards delivering, as soon as possible, new, safe, effective, equitable, affordable, available vaccines, point-of-care and child-friendly diagnostics, drug susceptibility tests and safer and more effective drugs and shorter treatment regimens for adults, adolescents and children for all forms of tuberculosis and infection...’

P43: ‘Commit to create an environment conducive to research and development of new tools for tuberculosis, and to enable timely and effective innovation and affordable and available access to existing and new tools and delivery strategies and promote their proper use, by promoting competition and collaboration...’
Speakers

**Diagnostics**
Daniella Cirrillo, Co Chair NDWG

**Drugs**
Ann Ginsberg, IAVI

**Vaccines**
Dave Lewinsohn, Chair NVWG
Ann Ginsberg, Co-Chair NVWG
New Diagnostics Working Group

Daniela Maria Cirillo
San Raffaele Scientific Institute, NDWG Co-Chair
The roadmap to new TB diagnostics to achieve End TB and Global Plan targets

**Improve TB case detection**
1. Triage test (high NPV)
   Or **ideally**
2. Highly sensitive stand-alone detection test

**Universal access to DST**
1. TB confirmation with rapid integrated DST for critical drugs
2. Test for cure
3. Comprehensive DST to cover the extended portfolio of drugs
4. DR surveillance
5. Control transmission

**Support TB elimination**
1. LTBI: Test to identify high risk of progression to active disease
2. Incipient TB test: to identify early subclinical TB

New Diagnostics Working Group
## Early development

<table>
<thead>
<tr>
<th>Molecular – Detection/DST</th>
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<tbody>
<tr>
<td>Hain – FluoroType MTBxDR Ver 1.0</td>
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<tr>
<td>Several acad./comp. – Low cost Easy to Use NGS</td>
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<tr>
<td>EMPE Dx – mfo Dx MDR/XDR-TB</td>
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<tr>
<td>LifeArc/Univ. St Andrews – Molecular Bacterial Load Assay</td>
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## Late or completed development

<table>
<thead>
<tr>
<th>Molecular – Detection/DST</th>
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<tbody>
<tr>
<td>Akonni – TruArray/TruDx2000 MDR/XDR-TB</td>
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<tr>
<td>Veredus Laboratories – VeroMTB</td>
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<tr>
<td>CapitalBio – Mycobacteria RT PCR</td>
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<tr>
<td>QuanDx – MTB drug-resistant mutation test kits</td>
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<tr>
<td>Seegene – Amplicron assays for MDR/XDR series</td>
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<tr>
<td>Zoeean – IsolPro MTB (MDR-TB, XDR-TB)</td>
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<tr>
<td>AutoGenomics – INFINITI MDR-TB</td>
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<tr>
<td>Longhorn Vaccines &amp; Diagnostics – PrimeSuite TB</td>
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<tr>
<td>Autodigm – TB Resistance Module</td>
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<tr>
<td>YD Diagnostics – MolecuTech REBA MDR/XDR</td>
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<tr>
<td>FujiRebio – INNO-LIPA Rif.TB</td>
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<td>LG LifeSciences – AdvantSure MDR-TB GenoBlot</td>
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<tr>
<th>Culture-based – Detection/DST</th>
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<tbody>
<tr>
<td>BNP Middlebrook (NanoLogix)</td>
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<td>Mycolor TK BNP (Salubris, USA)</td>
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<tr>
<td>Quantamatrix – CMAC DST</td>
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<tr>
<td>Thermo Fisher – TREK Sensitive MYCOTB</td>
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<td>Thermo Fisher – Sensititre System</td>
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<td>FR12 Blochem – MDR-TB</td>
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<td>Bioneer – POC for MDR/XDR-TB</td>
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<td>Microlbiomed – Rapid POC for MDR-TB</td>
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<tr>
<td>QuantumMDx – Q-POC TB/MDR TB</td>
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<td>GeneDiag – MTB/RIF</td>
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<td>InSilika – HYDRA-1k</td>
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<td>Blink – BLINK ONE</td>
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<td>SelDiagnostics Deutschland – TB MultiTest</td>
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<td>Mobidiag – Novodiag</td>
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<th>Celluar Response/Transcriptomic – Detection/Latent and latent to active progression</th>
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<tr>
<td>Abbott – Incipient TB Assay</td>
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<tr>
<td>Becton Dickinson – T-cell Immune Profiling</td>
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<tr>
<td>Qiagen – QFT Predict</td>
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<tr>
<td>Qiagen – QIA TB signature</td>
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<tr>
<td>Biomérieux/Booster – Host signature</td>
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<tr>
<th>Automated Microscopy &amp; Imaging – Detection</th>
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<tr>
<td>Advemia TechnoSys – RView TB</td>
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<tr>
<th>Breath Biomarker – Detection</th>
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<tr>
<td>Mensana – BreathLink</td>
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<tr>
<td>Avisa – BreathTest</td>
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<td>Technion – Breath analysis instrument</td>
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## On pathway to WHO evaluation

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<td>Abbott – RealTime MTB Rif/INH</td>
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<td>Hain – FluoroType MTBDR Ver 1.0</td>
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<td>Roche – cobas MTB-RIF/INH</td>
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<td>Bioneer – AccuPower TB/MDR RT PCR</td>
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<th>Low complexity assays</th>
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<tbody>
<tr>
<td>Breathalyser – Rapid Biosensor Systems TB Breathalyser</td>
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<tr>
<td>The eNose Company – Aeonose</td>
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<tr>
<td>Aeonose</td>
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<td>Omsense Discovery – TB Flow</td>
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<th>Moderate complexity assays</th>
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<tr>
<td>E.g. NanoPin – MTB antigens in blood</td>
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<tr>
<td>Several acad./comp. – cfDNA in blood/urine</td>
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<th>High complexity assays</th>
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<tbody>
<tr>
<td>Fujifilm – Sensitive LAM</td>
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<tr>
<td>Global Good – High sensitivity TB rapid Dx</td>
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<tr>
<td>Salus Discovery – TB Flow</td>
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<th>E.g. TransDot, Precision Bio – Host markers in blood</th>
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<tr>
<td>Salus Discovery – TB Prow</td>
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Improve case detection: non-sputum based tests

- Triage test: decentralized, low cost, self administered test for case finding and referral to confirmatory level (digital Xray?)
- Stand alone test for TB: high PPV, easy to perform, universal (all age, all immunological status)

<table>
<thead>
<tr>
<th>StopTB Partnership</th>
<th>New Diagnostics Working Group</th>
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<tbody>
<tr>
<td>Task Force on Biomarkers for POC tests</td>
<td>Coordinator: Tobias Broger, FIND</td>
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<tr>
<td>Bm2Dx</td>
<td>Database of biomarker evidence in a standardized format to support diagnostic innovation</td>
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</table>
Non-sputum based tests for diagnosis or triage

Early identification of patients with TB or at high-risk of TB on easy to access samples ideally at POC level

Pediatric TB
Disposable Squeeze Bottle for Stool
Processing prior Xpert

Active TB

Next-generation LAM POC assays
(urine, blood)

Incipient TB tests
(blood)

Breath Tests and Skin Patches

Latent TB

Blood host marker
POC tests

TB antigen POC
assays (blood)

cfDNA in blood
or urine

Determine TB LAM Ag
(urine) for HIV co-infected
with low CD4 counts

Computer-aided
detection (X-ray)

2017

2018

2019

2020 - 2025

Negative recommendation for
Serological assays by the WHO

Adapted from FIND

Source: http://lnbd.technion.ac.il

Simple solutions to improve diagnosis in children

Moving from tests to solutions

With a device

1. Open bottle. Use spoon to collect sample and place in bottle.
2. Pipette buffer & reagent from bottles (if necessary).
3. Shake 20 times & wait 30 minutes. Shake again briefly.
4. Replace lid with custom filtration lid.
5. Invert and squeeze bottle to dispense filtrate into cartridge.

SIMPLE KNCV STOOL TEST

- Transfer +/- 0.8 grams in 8 ml SR buffer, shake well and leave for 15-20 min to gravitate solid particles.
- Transfer carefully 2 ml of the upper part of the solution into cartridge.
- Cartridge is placed in the GeneXpert.
- Test result within 3 hours.

Without a device
POC tests to improve diagnosis in HIV+

- 70.4% sensitivity in HIV+ inpatients across CD4 strata
- 28.1% higher than AlereLAM and superior
- 95.7% specificity against the Composite Reference Standard
- Specificity: no significant difference to AlereLAM

Accuracy of FujiLAM is superior to Alere LAM in HIV+
In development: Non sputum based triage testing on POC platform

Goal
- Non-sputum based
- Rule-out TB
- Independent of HIV status
- Children?

Status
- Non-biased proteomic approach
- Biomarker discovered & tested
- Suitable industry partner with POC identified & Reagents developed

On-going
- Development on lateral flow platform
- Feasibility study ongoing
  - Prototype: 2019Q3
  - Design locked: 2020Q1
  - Validation in malaria endemic areas

Target Population
- Children & adult

Setting/User
- L0/L1

Cost
- < 2 USD

Time-to-result
- < 30 min
Universal access to DST: non-culture based DST

- Molecular DST: decentralizable, few drugs, selection of determinants, low cost, portable battery operated device, simple to perform
- Next Generation Sequencing based assay: centralized, first step to personalized treatment, high number of targets, will contribute to knowledge increase, will provide drug resistance emergence surveillance for all drugs, will monitor transmission dynamics

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<th>Task Force on NGS and DST</th>
<th>Coordinator: Paolo Miotto, HSR</th>
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</table>

Consensus-based TPP for next-generation DST at microscopy centres

Update

Share data from ReSeqTB and Cryptic
Diversification of sputum-based testing and DST

**Centralized DST** (Abbott, BD, Hain, Roche, Bioneer)

**POC DST** (QuantuMDx, Bioneer, MicoBiomed, Akonni, …)

**Line probe assays:**
- MTBDRplus and sl (Hain Lifescience)
- Lipa MTBDR (Nipro)
- TBmodule (AID)

**Liquid culture:**
- MGIT (BD)
- TREK Sensitive (Thermofisher)
- Mycobacterium TR BNP (Salubris)

**NAAT:**
- Xpert MTB/RIF (Cepheid)
- TB-LAMP (Eiken)
- Mycobacteria RT PCR (CapitalBio)
- Anyplex MTB/XDR (Seegene)
- Infiniti MDR TB (Autogenomics)
- VereMTB/Inh (Veredus Laboratories)
- MiePMDR (Mie University)
- Genedrive TB/Rif (Epistem)
- AccuPower TB/MDR (Bioneer)

**DISCLAIMER:** Images & time estimates are to be taken as indicative only.

**Hybridisation** (Scanogen)
### Joining Forces to speed up results and move NGS solutions to Countries to stop pDST

#### GROUP

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
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<tbody>
<tr>
<td><strong>Group A:</strong> Include all three medicines (unless they cannot be used)</td>
<td>Levofloxacin OR Moxifloxacin</td>
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<tr>
<td></td>
<td>Bedaquiline¹,⁴</td>
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<tr>
<td></td>
<td>Linezolid²</td>
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<tr>
<td><strong>Group B:</strong> Add both medicines (unless they cannot be used)</td>
<td>Clofazimine</td>
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<tr>
<td></td>
<td>Cycloserine OR Terizidone</td>
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<tr>
<td><strong>Group C:</strong> Add to complete the regimen and when medicines from Groups A and B cannot be used</td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>Delamanid³,⁴</td>
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<td></td>
<td>Pyrazinamide⁵</td>
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<tr>
<td></td>
<td>Imipenem-cilastatin OR Meropenem⁶</td>
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<tr>
<td></td>
<td>Amikacin (OR Streptomycin)⁷</td>
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<tr>
<td></td>
<td>Ethionamide OR Prothionamide</td>
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<tr>
<td></td>
<td>p-aminosalicylic acid</td>
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Support TB elimination

- LTBI: ESAT6/ CFP10 based IGRAs and Skin tests
- Test to identify high risk of progression to active disease
- Incipient TB test: to identify early subclinical TB
Incipient TB - risk of progression

Current products (IGRA and TST):
2-3% PPV of existing products to detect latent TB
Several companies are working on products with higher PPV

**Market Entry ≥2020**

**Automatization of QT-Plus (diaSorin)**

**Products in the pipeline**
- QFT-Predict (Qiagen)
- QIA-TB Signature (Qiagen)
- T-cell Immune Profiling (BD)
- RTT TB (Lophius)
- Incipient TB Assay (Abbott)
- and others

**Principle of the test**
- transcriptomic signatures
- IFN-γ release after T-cell stimulation with new antigens
- Cell differentiation markers (eg. CD27)
- Cytokine profiles (eg. IP-10)

Incipient TB - risk of progression
Precision medicine approach: Merging precise individual care and large-scale programmatic functions

Consider: DST, preference for oral route, DR prevalence, h/o previous treatment, tolerability, drug-drug interactions, severe forms

STANDARDIZED SHORTER MDR-TB REGIMEN
4-6 Amk-M-Pto-Cfz-Z-Hhd-E / 5 M-Cfz-Z-E

LONGER MDR-TB REGIMEN
SOCIAL SUPPORT & COUNSELLING

(PRE-XDR-TB or XDR-TB)
PRECISION TREATMENT
(FOLLOWING WHO STANDARDS)

TREATMENT FOR DRUG SUSCEPTIBLE TB
(2HRZE/4HR)

TB-POSITIVE Rif-R

LPA-SL

TARGETED NEXT GENERATION SEQUENCING AND MIC

CLINICAL DECISION SUPPORT SYSTEM
ARTIFICIAL INTELLIGENCE

CENTRAL DATABASE
FEED-BACK LEARNING LOOP FOR ADJUSTMENT OF DX, RX, APPROACHES

DRUG PROCUREMENT SYSTEM
PRECISION SUPPLY

PHARMACOVIGILANCE SYSTEM
BIOMARKERS TO PERSONALISE DURATION

SOCIAL SUPPORT & COUNSELLING

FIRST-LINE RAPID DIAGNOSTIC
XPERT MTB/RIF
(FOLLOWED BY CULTURE)

Adapted from M Raviglione UNIMI
Moving from tests to solutions, keeping in mind that “one size doesn’t fit all”

Thank you

Claudia Denkinger
Catharina Boehme
Tobias Broger
Alessandra Varga
NDWG core group members and TF leaders
Working Group on New TB Drugs
Update

Stop TB Coordinating Board Meeting
January 28, 2019

www.newtbdrugs.org
An Urgent Need for Improved Treatment of Active TB

<table>
<thead>
<tr>
<th>Treatments are too long:</th>
<th>By 2030, five-year investment delay in R&amp;D could result in:</th>
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<tr>
<td>6-24 MONTHS</td>
<td>8 million MORE TB CASES</td>
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<td>1.4 million MORE TB DEATHS</td>
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Cost of 1-Year Delay in Investment: $1.3 Billion USD

"Only in providing the funding needed can we hope to transform the promise in the pipeline to millions of lives saved."

--Melvin Spigelman, Co-chair, WGND

"The pipeline of new drugs is increasing and advancing. We are making progress. To combat drug resistance, even more compounds are needed."

--Barbara Laughon, Co-chair, WGND
2018 Global TB Drug Discovery Pipeline

**Hit-to-Lead**

- **Actinomycete Metabolites** (U ILL Chicago, Myongii U)
- **Novel Hit-to-Lead Programs** (Lilly DDI) GATB
- **Adamantanids** (U ILL Chicago)
- **Whole-Cell Hit-to-Lead** (GSK, GATB)
- **Menaquinone Synthase Inhibitors** (CSU)
- **M. tb Energy Metabolism Inhibitors** (GATB, TBDA, J&J/CSIR-Imtech, Univ. of Notre Dame
- **Isoprenoid Biosynthesis Inhibitors** (Lilly DDI)
- **Whole-Cell Hit-to-Lead** (GATB, Evotec)
- **RNA Polymerase Inhibitors** (GATB)
- **CtpC/P1P2** (GATB)

**Lead Optimization**

- **Diarlythiazoles** (TBDA)
- **InhA Inhibitors** (GATB/GHDDI)
- **Spectinamides** (St. Jude, U Tenn, CSU, UZ, Microbitionx)
- **Macrolides** (GATB, Evotec)
- **Cip** (SPRINT TB / A* Star)
- **Indolcarboxamides / MmpL3 inhibitors** (GATB, TBDA)
- **Oxazolidinones** (IMM)
- **Aryl Sulphonamides** (GATB, GSK, TBDA)
- **PKS13 Inhibitors** (GATB, DDU, TAMU, GSK, TBDA)
- **Squaramides** (GATB, TBDA, Evotec)

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**Abbreviations of Developers:** A* Star - Agency for Science Technology and Research, CSU - Colorado State University; FAPESP - São Paulo Research Foundation; GATB - Global Alliance for TB Drug Development (TB Alliance); GSK - GlaxoSmithKline; Lilly DDI - Lilly TB Drug Discovery Initiative; RI - Research Institute; SPRINT TB - Singapore Programme of Research Investigating New Approaches to Treatment of TB; St. Jude - St. Jude Children's Research Hospital; TAMU - Texas A&M University; TBDA - TB Drug Accelerator; U-University; U ILL - University of Illinois; UPenn - University of Pennsylvania; U Tenn - University of Tennessee; UZ - University of Zurich

**www.newtbdrugs.org**

Updated: October 2018
2018 Global New TB Drug Pipeline

**Discovery**
- Lead Optimization
  - Diarylthiazoles
  - DprE1 Inhibitors
  - InhA Inhibitor
  - Mtb energy metabolism
  - Macrolides
  - Mycobacterial Gyrase Inhibitors
  - Arylsulfonamides
  - Inhibitors of MmpL3, Translocase-1, Clp, PKS13
  - Oxazolidinones
  - Squaramides

**Preclinical Development**
- Early Stage Development
  - CPZEN-45*
  - Spectinamide - 1810*
  - SPR720*
  - TB-47*
- GMP/ GLP Tox.
  - TBAJ-587
  - TBAJ-876
  - GSK-286*
  - TBI-223
  - Sanfetrinem
  - S-004992*

**Clinical Development**
- Phase 1
  - BTZ-043*
  - TBL-166
  - Macozinone*
  - GSK-656* (PBTZ-169)
  - TBA-7371*
  - Contezolid (MRX-4/MRX-1)
  - Sanfetrinem
  - S-004992*

- Phase 2
  - OPC-167832*
  - Telacebec
  - Delpazolid (LCB01-0371)
  - Sutezolid
  - SQ-109*

- Phase 3
  - Bedaquiline* (TMC-207)
  - Delamanid* (OPC-67683)
  - Pretomanid* (PA-824)

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

1 New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline/clinical](http://www.newtbdrugs.org/pipeline/clinical)

Ongoing projects without a lead compound series identified: [http://www.newtbdrugs.org/pipeline/discovery](http://www.newtbdrugs.org/pipeline/discovery)

**Underline = new to Phase since March 2018**

[www.newtbdrugs.org](http://www.newtbdrugs.org)

Updated: October 2018
2018 Global TB Drug and Regimen Clinical Research

Ongoing Clinical Development Research: Strategy / Optimization / Regimen Development

**Phase 2**
- OPC-167832*
- **Bedaquiline-Delamanid** (ACTG 5343)
- **Bedaquiline-Pretomanid-Moxifloxacin-PZA** (SimpliciTB Trial, NC-008)
- **Bedaquiline - Pretomanid – Moxifloxacin - Pyrazinamide (BPamZ)** (NC-005)
- **Levofloxacin** with OBR for MDR-TB (OPTI-Q)
- **Linezolid** Dose-Ranging
- **Beta-Lactams; Nitazoxanide**
- **High Dose Rifampicin** (PANACEA)
- **TB PRACTECAL - regimens with Bedaquiline-Pretomanid-Linezolid**

**Phase 3 Regimens**
- **Bedaquiline-STREAM MDR-TB**
  - Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)
- **Bedaquiline-Pretomanid-Linezolid** (NIX-TB)
- **Delamanid** with OBR for MDR-TB
- **High Dose Rifampicin** for DS-TB (RIFASHORT)
- **Rifapentine - Moxifloxacin** for DS-TB (CDC TBTC 31, ACTG 5349)
- **Pretomanid-Moxifloxacin-Pyrazinamide (STAND)**

**Optimization/Post Market**
- **Bedaquiline-Linezolid** with OBR for MDR-TB (NeXt Trial)
- endTB 5-Regimen Trial for MDR TB
- PredictTB – PET/CT, biomarkers DS-TB, 4 mo
- TRUNCATE-TB Trial, 2 mo

Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

1 Strategy trials, regimen development, open label, repurposed drug studies. Details for projects listed can be found at [http://www.newtbdugs.org/pipeline/clinical](http://www.newtbdugs.org/pipeline/clinical)

2 OBR = Optimized Background Regimen

www.newtbdugs.org

Updated: October 2018
ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB
IN PEOPLE WITH HIV: BRIEF-TB/A5279
Brief Rifapentine-Isoniazid Efficacy for TB Prevention
NCT01404312

Susan Swindells1, Ritesh Ramchandani2, Amita Gupta3, Constance Benson4, Jorge Leon-Cruz2, Ayotunde Omoz-Oarhe5, Marc Antoine Jean Juste6, Javier Lama6, Javier Valencia6,
Sharlaa Badal-Faesen7, Laura Moran9, Courtney V. Fletcher1, Eric Nuermberger3,
Richard E. Chaisson3, and the AIDS Clinical Trials Group A5279/BRIEF TB Study Team

1 University of Nebraska Medical Center, Omaha, NE; 2 Harvard University TH Chan School of Public Health, Boston, MA; 3 Johns Hopkins
University School of Medicine, Baltimore, MD; 4 University of California, San Diego, CA; 5 Botswana-Harvard AIDS Partnership,
Gaborone, Botswana; 6 GHESKIO, Port-au-Prince, Haiti; 7 IMPACTA, Lima, Peru; 8 Helen Joseph Hospital, Johannesburg, South Africa; 9
Social and Scientific Systems, Silver Spring, MD.

CROI.2018.37LB. Boston
## Primary Endpoints

<table>
<thead>
<tr>
<th>First Outcome</th>
<th>Randomized Treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9H</td>
<td>1HP</td>
<td>Total</td>
</tr>
<tr>
<td>All Outcomes</td>
<td>33</td>
<td>32</td>
<td>65</td>
</tr>
<tr>
<td>Active TB, Confirmed</td>
<td>14 (42%)</td>
<td>18 (56%)</td>
<td>32 (49%)</td>
</tr>
<tr>
<td>Active TB, Probable</td>
<td>10 (30%)</td>
<td>11 (34%)</td>
<td>21 (32%)</td>
</tr>
<tr>
<td>Death Related to TB</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Death from Unknown Cause</td>
<td>7 (21%)</td>
<td>3 (9%)</td>
<td>10 (15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>9H</th>
<th>1HP</th>
<th>IRR Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/PY of follow up</td>
<td>33/4896</td>
<td>32/4926</td>
<td>0.023</td>
</tr>
<tr>
<td>Incidence per 100 PY</td>
<td>0.67</td>
<td>0.65</td>
<td>(95% CI -0.30-0.35)</td>
</tr>
</tbody>
</table>

Non-Inferiority margin = 1.25 per 100 PY
Conclusions

- 1HP is non-inferior to 9H for preventing TB, TB death or death from unknown cause in adults and adolescents with HIV infection
- Rates of TB were higher in those with +TST/IGRA or CD4 <250
- Rates of endpoints were higher in 1HP recipients with CD4 <250 vs 9H
- Safety was good and similar in both arms, with more hematologic toxicity with 1HP and more liver and neuro-toxicity with 9H
- Completion of treatment was excellent in both arms but better with 1HP
- 1HP provides a highly-effective, ultra-short course regimen for the prevention of TB in people with HIV
Sustained high rate of successful treatment outcomes:
Interim results of 75 patients in the Nix-TB clinical study of pretomanid, bedaquiline and linezolid

Francesca Conradie, Andreas Diacon, Pauline Howell, Daniel Everitt, Angela Crook, Carl Mendel, Erica Egizi, Joanna Moreira, Juliano Timm, Timothy McHugh, Genevieve Wills, Christo Van Niekerk, Mengchun Li, Morounfolu Olugbosi, Melvin Spigelman
Open-label trial to assess the safety and efficacy of bedaquiline, pretomanid plus linezolid in participants with pulmonary infection with either extensively drug-resistant TB (XDR-TB) or treatment intolerant/non responsive multidrug-resistant TB (MDR-TB)

- Pretomanid 200 mg qd
- Bedaquiline 200 mg tiw after 2 week load
- Linezolid 1200 mg qd*

Follow up for relapse-free cure over 24 months

6 months of treatment

Additional 3 months if sputum culture positive at 4 months

*Amended from 600 mg bid strategy
### mITT (Primary Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>XDR</th>
<th>MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total for interim analysis</td>
<td>75</td>
<td>51</td>
<td>24</td>
</tr>
<tr>
<td>Unassessable*</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total Assessable</td>
<td>74</td>
<td>50</td>
<td>24</td>
</tr>
<tr>
<td>Favourable</td>
<td>66 (89%)</td>
<td>44 (88%)</td>
<td>22 (92%)</td>
</tr>
<tr>
<td>Unfavourable**</td>
<td>8 (11%)</td>
<td>6 (12%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>95% CI for Favourable</td>
<td>(79.8%, 95.2%)</td>
<td>(75.7%, 95.5%)</td>
<td>(73.0%, 99.0%)</td>
</tr>
</tbody>
</table>

*non TB related death in follow-up

**6 deaths and two relapse
Conclusion

• Interim results of this simplified, shortened all oral regimen for drug-resistant TB continue to be encouraging in terms of both efficacy and safety
  – All patients (other than the 6 who died) completed 26 weeks of treatment
  – No patients were withdrawn due to AE
  – No extensions of treatment for late conversion were needed
  – TEAEs were common but predictable and mostly handled at local facilities
  – Only one liver related SAE that completed drug therapy

• 89% of participant had a favourable outcome

• Previously reported rate of success has been surpassed by the first 75 patients who completed 6 months post treatment follow-up
THANK YOU

Explore. Learn. Join the conversation.

www.newtbdrugs.org
Additional slides
2018 Global New TB Drug Pipeline

Small Pharma
Non Profits

Preclinical Development
Early Stage
GMP/GLP Tox.

Clinical Development
Phase 1
BTZ-043*
TBI-166
Macozinone* (PBTZ-169)
GSK-656* (070)
TBA-7371*
Contezolid (MRX-4/MRX-1)

Phase 2
OPC-167832*
Telacebec (Q203*)
Delpazolid (LCB01-0371)
Sutezolid (PNU100480)
SQ-109*

Phase 3
Bedaquiline*
Delamanid*
Pretomanid*

Global Market

New chemical classes* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

1 New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = new to Phase since March 2018

www.newtbdrugs.org
Updated: October 2018
Vaccines
Stopping the cycle of transmission in adults will prevent the spread of TB to children as well
Target Patient Populations

- Adolescents and adults
  - healthy
  - TB patients

- Infants
  - healthy
In LMICs, to reduce TB in 0-4 years olds, targeting adolescents/adults, may have quicker impact than targeting <1 year olds

- Extending *Knight et al*, PNAS, 2014 (pre and post efficacy, POD vaccine)
- To reduce TB in 0-4 year olds, vaccinating adolescents/adults, may be as effective, or more effective, than vaccinating neonates
- Because indirect effect of reducing the force of infection on infants, by vaccinating adolescents/adults, greater than direct effect of vaccinating infants
Being Chair of the Vaccine Working Group is Not Easy

THE PARADIGM SHIFT 2016-2020

THE END TB STRATEGY
Pre-Clinical

IV BCG
William Barclay
Sally Sharpe
Frank Verreck
Bob Seder and
JoAnne Flynn

Pulmonary BCG
Frank Verreck

CMV
Louis Picker
## Turning a Corner: recent and upcoming data in TB vaccine efficacy trials

<table>
<thead>
<tr>
<th>PHASE</th>
<th>PARTICIPANTS</th>
<th>EFFICACY</th>
<th>LOCATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td>10000 PPD+</td>
<td>Prevention of disease</td>
<td>China</td>
<td>2-3Q2018</td>
</tr>
<tr>
<td>Phase II</td>
<td>990 Q-</td>
<td>Prevention of infection</td>
<td>South Africa</td>
<td>1Q2018</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>3573 Q+</td>
<td>Prevention of disease</td>
<td>South Africa, Kenya, Zambia</td>
<td>2Q2018</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>650 Q-</td>
<td>Prevention of infection</td>
<td>Tanzania</td>
<td>4Q2019</td>
</tr>
<tr>
<td>Phase II/III</td>
<td>2000 TB+</td>
<td>Prevention of recurrence</td>
<td>India</td>
<td>4Q2019</td>
</tr>
</tbody>
</table>

PHASE PARTICIPANTS EFFICACY LOCATION RESULTS

- **Vaccae TM**
  - Anhui Zhifei Longcom

- **H4/IC31/BCG revacc SP, SSI, Aeras**

- **M72/AS01E**
  - GSK, Aeras

- **DAR-901**
  - Dartmouth Medical School, GHIT

- **VPM1002**
  - Max Planck, VPM, SII

Anhui Zhifei Longcom: AnHui Zhifei Longcom Biologic Pharmacy Co., Ltd; SSI: Statens Serum Institute; VPM: Vakzine Projekt Management GmbH;

*Vemes et al, NEJM 2018; Van Der Meeren et al, NEJM 2018*
Recent Results are Game-Changing

TB vaccines are achievable

Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination


...new tuberculosis vaccines, was the regulatory sponsor of the trial and contributed to the trial design and data analysis. The H4 antigen in the H4:IC31 vaccine was supplied by Sanofi Pasteur, and the IC31 adjuvant was supplied by Statens Serum Institut. The BCG vaccine (Statens Serum Institut)...

FREE CME
Recent Results are Game-Changing

TB vaccines are achievable.

Phase 2b Controlled Trial of M72/AS01e Vaccine to Prevent Tuberculosis
Van Der Meerren O., Hatherill M., Nduba V., et al. | 10.1056/NEJMoA1803484

...substantial protection against pulmonary tuberculosis in M. tuberculosis–infected adults. The M72/AS01E (GlaxoSmithKline) candidate vaccine contains the M72 recombinant fusion protein derived from two immunogenic M. tuberculosis antigens (Mtb32A and Mtb39A), combined with the AS01 adjuvant system...

New Promise for Vaccines against Tuberculosis
Bloom B.R. | 10.1056/NEJMe1812483

Tuberculosis has now exceeded infection with the human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) and malaria as the world's largest cause of death from an infectious disease. The World Health Organization (WHO) estimates that there are 10.4 million new cases and 1.7...
TRIAL OF M72/AS01, VACCINE TO PREVENT TUBERCULOSIS

Figure 2. Kaplan-Meier Estimate of Definite Pulmonary Tuberculosis (TB) Disease Not Associated with HIV Infection (First Case Definition).

The analysis was conducted in the according-to-protocol efficacy cohort. The time shown is the time from the beginning of follow-up (i.e., 30 days after dose 2). The inset shows the same data on an enlarged y axis. The decreased number at risk after 24 months reflects the participants for whom follow-up after this time point had not occurred at the date of data lock.

10 vs 22 cases (p=0.04)

Efficacy 54%
Information on candidates in clinical development is self-reported by vaccine sponsors, coordinated by the Working Group on New TB Vaccines. Candidates in preclinical development are representative and include those in the Aeras and/or TBVI portfolios that have completed Gate 1 as published in Barker L, Hessel L, Walker B, *Tuberculosis*, 92S1 (2012) S25–S29.
Mission: Translating scientific discoveries into affordable, accessible public health solutions

Working in LMICs to benefit underserved and at-risk populations

Translation of vaccine concepts from the “bench” into the clinic

Vision and commitment required for end to end product development

Defining new business and partnership models to enable global access

A not-for-profit product developer for global health needs
IAVI’s Commitment to Supporting TB Vaccine Development

Long-term commitment

Strategic goals include working with partners to:

- Accelerate most promising candidates through to access
- Ensure robust pipeline of vaccine candidates to meet world’s diverse needs
- Partnering with many collaborators to support the field via Stop TB WGNV, Global Forum, etc.
Aeras Asset Transfer Agreement

Goal: to support the TB vaccine field by maintaining Aeras’ TB vaccine clinical development expertise and capacity and leveraging and enhancing IAVI’s expertise and capabilities

Transferred Assets:

✓ Key clinical staff (US and South Africa)
✓ Clinical programs and committed funding
✓ Biorepository
✓ Preclinical assets
✓ Intellectual Property
✓ Policies, SOPs, access to historic data, etc.
TB Vaccine R&D Has Turned a Corner!!

Two positive efficacy trials

- First demonstration that a vaccine can protect Mtb-infected adults from developing TB disease
- Proof of concept that a subunit vaccine (just 2 TB antigens plus adjuvant) can protect against TB disease
- New use for BCG? - protect high risk, uninfected populations from TB infection with BCG revaccination

Road to impact: access and delivery

➢ Stop TB Partnership has key roles to play in ensuring success
“...evaluating cost effectiveness found new TB vaccines to be an overwhelmingly cost effective intervention, whether from the health system or societal perspective.”


Over the first ~25 years of use, a prevention of disease vaccine could avert over 50 million cases of TB globally (Murray et al. 1998)

As low as 20% efficacy and 5 years duration of protection could be cost effective if delivered to adolescents/adults (Knight et al. 2014)
Novel Partnerships Will Be Key to Success
IAVI gratefully acknowledges the generous support provided by the following major donors:


And many other generous individuals and partners around the world.

As of January 2019
Thank you
Concluding Remarks
## Table 3

<table>
<thead>
<tr>
<th>2017 Rank</th>
<th>Funding Organization</th>
<th>Funder Type</th>
<th>2017 Pediatric TB R&amp;D Funding</th>
<th>Percentage of Total Pediatric Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP)</td>
<td>P</td>
<td>$10,604,544</td>
<td>18.8%</td>
</tr>
<tr>
<td>2</td>
<td>U.S. Agency for International Development (USAID)</td>
<td>P</td>
<td>$9,500,000</td>
<td>16.8%</td>
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<tr>
<td>3</td>
<td>U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID)</td>
<td>P</td>
<td>$6,886,622</td>
<td>12.2%</td>
</tr>
<tr>
<td>4</td>
<td>Unitaid</td>
<td>M</td>
<td>$6,615,400</td>
<td>11.7%</td>
</tr>
<tr>
<td>5</td>
<td>Company X</td>
<td>C</td>
<td>$5,700,000</td>
<td>10.1%</td>
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<tr>
<td>6</td>
<td>U.S. National Institutes of Health, Other Institutes and Centers (NIH Other ICs)</td>
<td>P</td>
<td>$5,562,805</td>
<td>9.9%</td>
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<tr>
<td>7</td>
<td>U.K. Medical Research Council (U.K. MRC)</td>
<td>P</td>
<td>$4,535,821</td>
<td>8.2%</td>
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<tr>
<td>8</td>
<td>Brazilian Development Bank</td>
<td>P</td>
<td>$1,814,040</td>
<td>3.2%</td>
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<tr>
<td>9</td>
<td>South African Medical Research Council (SAMRC)</td>
<td>P</td>
<td>$1,083,446</td>
<td>1.9%</td>
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<tr>
<td>10</td>
<td>World Health Organization</td>
<td>M</td>
<td>$600,000</td>
<td>1.1%</td>
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<tr>
<td>11</td>
<td>Norwegian Agency for Development Cooperation (NorRAD)</td>
<td>P</td>
<td>$437,361</td>
<td>0.78%</td>
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<tr>
<td>12</td>
<td>Novartis Pharma AG</td>
<td>C</td>
<td>$320,000</td>
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<td>13</td>
<td>Australian National Health and Medical Research Council</td>
<td>P</td>
<td>$311,383</td>
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<td>14</td>
<td>MitoBio Diagnostics</td>
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<td>15</td>
<td>Brazilian Ministry of Health</td>
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<td>$302,340</td>
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<td>16</td>
<td>Médecins Sans Frontières</td>
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<td>$261,742</td>
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<td>17</td>
<td>Japan Agency for Medical Research and Development (AMED)</td>
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<td>Tshwane Research Fund</td>
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<td>19</td>
<td>German Federal Ministry of Education and Research (BMBF)</td>
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<td>ELMA Foundation</td>
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<td>Welcome Trust</td>
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<td>22</td>
<td>Swedish Research Council</td>
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<td>24</td>
<td>Canadian Institutes of Health Research</td>
<td>P</td>
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<td>25</td>
<td>Thailand Ministry of Public Health</td>
<td>P</td>
<td>$62,798</td>
<td>0.11%</td>
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<td>26</td>
<td>Thailand Health Systems Research Institute</td>
<td>P</td>
<td>$61,993</td>
<td>0.11%</td>
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<tr>
<td>27</td>
<td>Other public funders with investments less than $50,000</td>
<td>P</td>
<td>$72,083</td>
<td>0.13%</td>
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<tr>
<td><strong>Total</strong></td>
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<td></td>
<td><strong>$56,428,152</strong></td>
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