New Tools in the Post-UNHLM

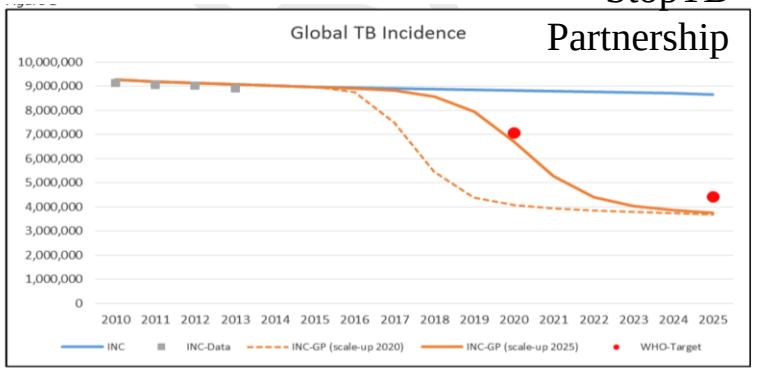
David Lewinsohn
StopTB Partnership New Tools Working Groups

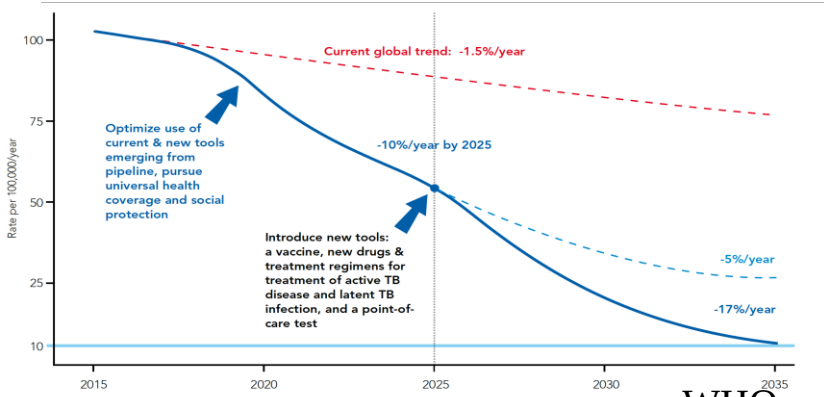
Stop TB Partnership
The Global Plan to Stop TB 2016-2020

Ending TB

- Guiding Principles
  - TB elimination **not** achievable without new tools
  - While tools not widely available in next 5 years, investments NOW is key

StopTB Partnership



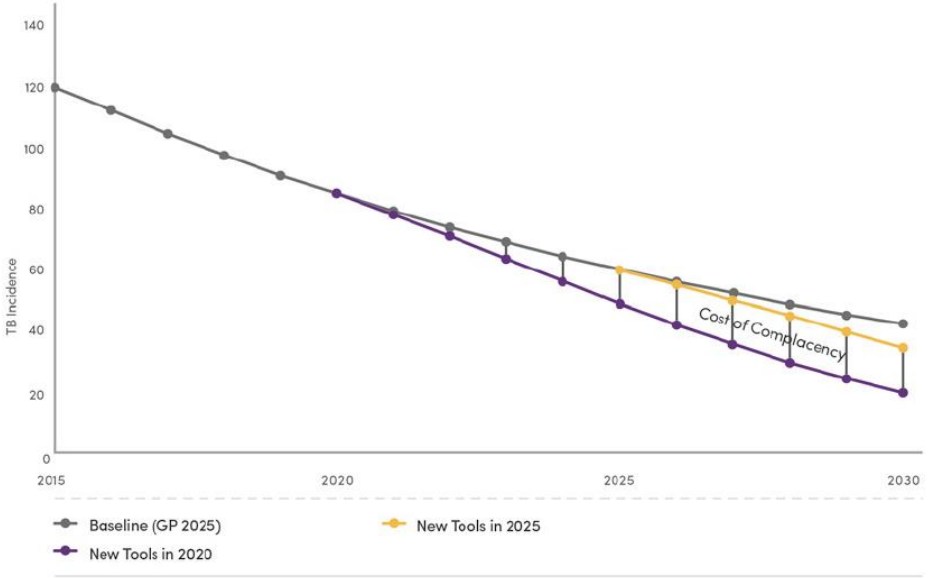


WHO

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



END TB

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 2018':

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 affected 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 to US$2 billion, in order to close the estimated US$1.3 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 sociocultural 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-centred, 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 people-centred prevention, diagnosis, treatment and care of tuberculosis.

9. REQUEST THE DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION TO **CONTINUE TO DEVELOP THE MULTISECTORAL ACCOUNTABILITY FRAMEWORK** and ensure its timely implementation no later than 2019.

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

Stop TB Partnership

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**

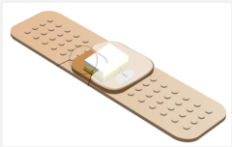
2. Highly sensitive stand-alone detection test

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



FIND

	Early development	Late or completed development	On pathway to WHO evaluation
High complexity assays	**Molecular – Detection/DST**		
	Hain – FluoroType MTBXDR Ver 1.0- Several acad./comp. – Low-cost Easy to Use NGS EMPE Dx – mfloDx MDR/XDR-TB LifeArc/Univ. St Andrews – Molecular Bacterial Load Assay	Akonni – TruArray/TruDx2000 MDR/XDR-TB Veredus Laboratories – VereMTB - CapitalBio – Mycobacteria RT PCR QuanDx – MTB drug-resistant mutation test kits Seegene – Anyplex assays for MDR/XDR series Zeesan – MeltPro MTB (MDR-TB, XDR-TB) AutoGenomics – INFINITI MDR-TB Longhorn Vaccines & Diagnostics – PrimeSuite TB - Autoimmun Diagnostika – TB Resistance Module YD Diagnostics – MolecuTech REBA MDR/XDR FujiRebio – INNO-LiPA Rif.TB LG LifeSciences – AdvanSure MDR-TB GenoBlot	Abbott – RealTime MTB RIF/INH Becton-Dickinson – BD MAX MDR-TB Hain – FluoroType MTBDR Ver 1.0 Roche – cobas MTB-RIF/INH Bioneer – AccuPower TB&MDR RT PCR
	Culture-based – Detection/DST		
	BNP Middlebrook (NanoLogix) MYCOLOR TK BNP (Salubris, USA)	QuantaMatrix – QMAC DST Thermo Fisher – TREK Sensitive MYCOTB Thermo Fisher – Sensititre System	
Moderate complexity assays	**Molecular – Detection/DST**		
	Akonni – TruArray/TruDx3000 MDR/XDR-TB FRIZ Biochem – MDR-TB Bioneer – POC for MDR/XDR-TB MicoBiomed – Rapid POCT for MDR-TB QuantuMDx – Q-POC TB/MDR TB Genedrive – MTB/RIF InSilixa – HYDRA-1k Blink – BLINK ONE SelfDiagnostics Deutschland – TB MultiTest Mobidiag - Novodiag	Cepheid – Xpert XDR Cepheid – OMNI Several groups – Preprocessing molecular stool Univ. of Washington – Sample collection molecular buccal swab	Molbio – Truenat MTB / MTB Plus
	Cellular Response/Transcriptomic – Detection/Latent and latent to active progression		
	Abbott – Incipient TB Assay Becton-Dickinson – T-cell Immune Profiling Qiagen – QFT-Predict Qiagen – QIA-TB Signature Biomérieux/Bioaster – Host signature	Lophius Biosciences – RTT TB	
	Automated Microscopy & Imaging – Detection		
	Advenio TecnoSys – RiView-TB	ID-FISH Technology – ID-FISH assay	Delft Imaging Systems – CAD4TB Qure.ai – Qure Chest X-rays for TB
	Breath Biomarker – Detection		
Low complexity assays	Menssana – BreathLink Avisa – BreathTest Technion – Breath analysis instrument	Rapid Biosensor Systems – TB Breathalyser The eNose Company – Aeonose	
	Antigen, Antibody and Biomarker detection – Detection		
	E.g. TransDot, Precision Bio – Host markers in blood E.g. NanoPin – MTB-antigens in blood Several acad./comp. – cfDNA in blood/urine E.g. Omunis, AppGenex – Antibody tests	Salus Discovery – TB Flow Global Good – High sensitivity TB rapid Dx Unima – TB Dx	Fujifilm – Sensitive LAM

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)

Stop TB Partnership
New Diagnostics Working Group

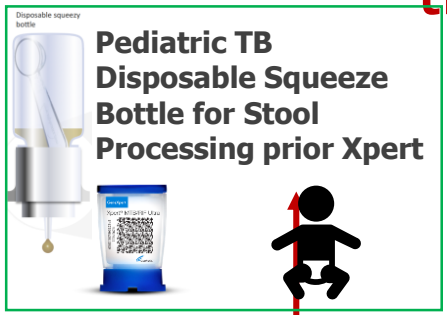
Task Force on Biomarkers for POC tests
Coordinator: Tobias Broger, FIND

Bm2Dx
from biomarker to diagnostics

Database of biomarker evidence in a standardized format to support diagnostic innovation

Non-sputum based tests for diagnosis or triage

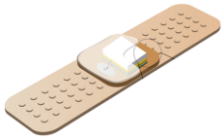
Early identification of patients with TB or at high-risk of TB on easy to access samples ideally at POC level



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

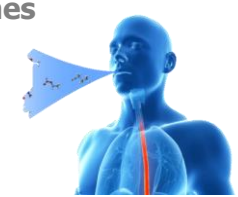
Active TB

Latent TB



Incipient TB tests (blood)

Breath Tests and Skin Patches

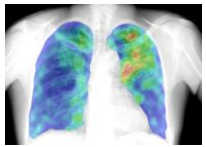


2017 | **2018** | **2019** | **2020 - 2025**

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

Negative recommendation for Serological assays by the WHO

Computer-aided detection (X-ray)

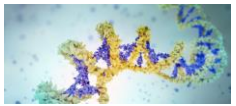


Next-generation LAM POC assays (urine, blood)

Blood host marker POC tests

TB antigen POC assays (blood)

cfDNA in blood or urine



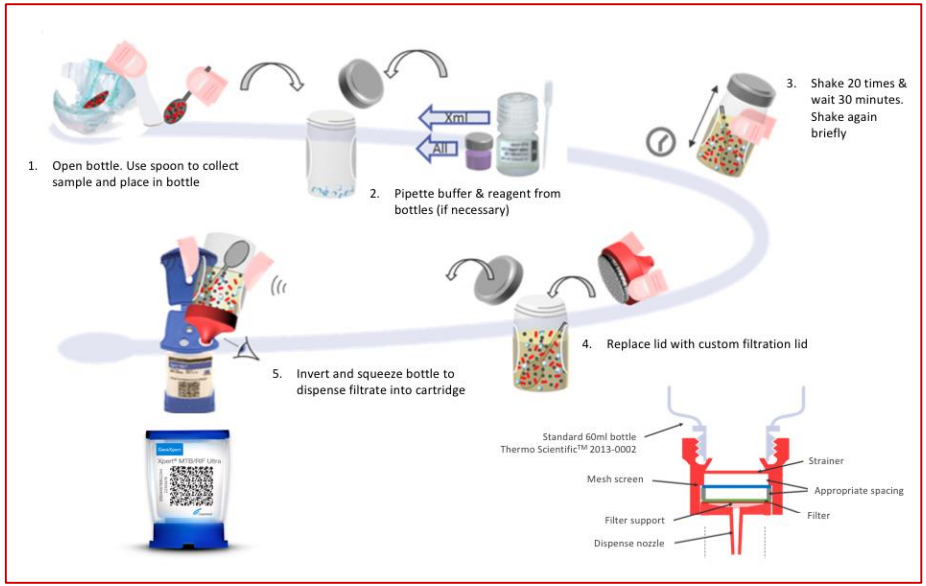
Source: http://precision-bio.com/en/images/sub/sub2_1_3.jpg

Adapted from FIND

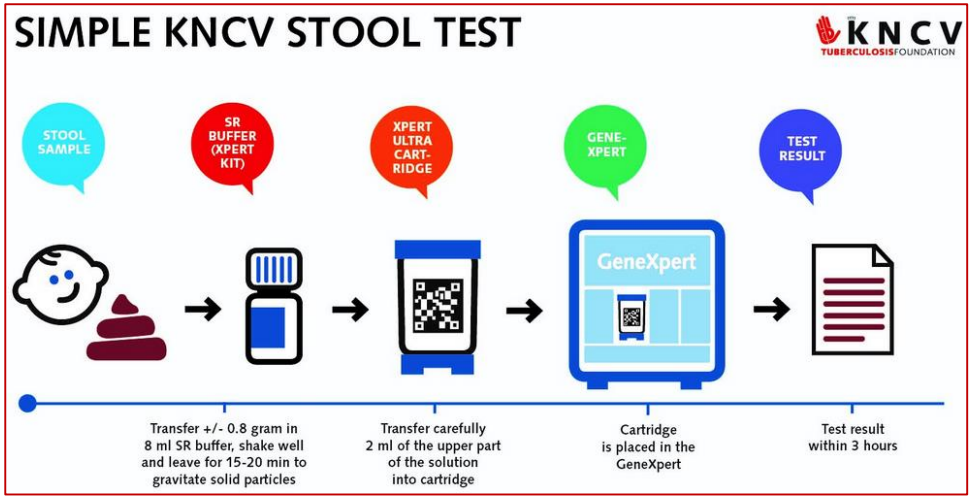
Simple solutions to improve diagnosis in children

Moving from tests to solutions

With a device

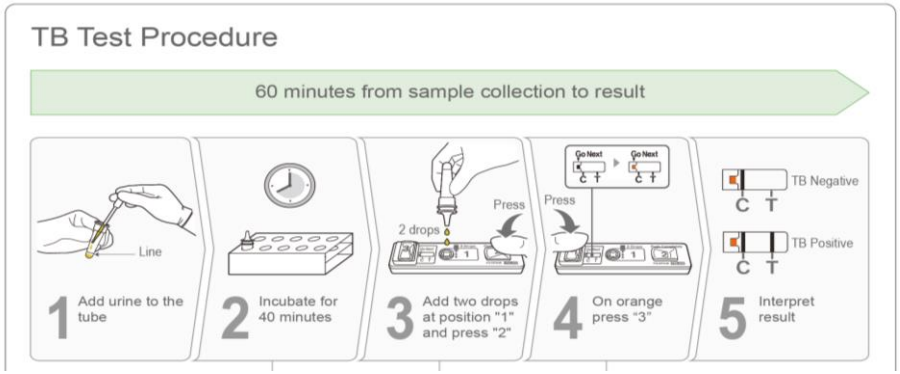


Without a device



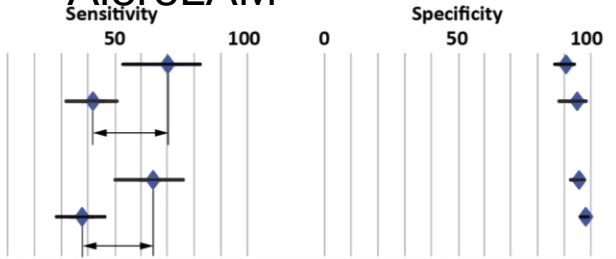
POC tests to improve diagnosis in HIV+

Emerging Bacterial Pathogens Unit
OSPEDALE SAN RAFFAELE



- 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

MRS	Test	N	TP	FP	FN	TN	Sensitivity [95% CI]*	Specificity [95% CI]*
All HIV+	FujiLAM	968	455	33	145	335	70.4% [53.0 - 83.1]	90.8% [86.0 - 94.4]
	AlereLAM	968	268	18	332	350	42.3% [31.7 - 51.8]	95.0% [87.7 - 98.8]
	ΔSn and ΔSp						28.1% [21.5 - 34.4]	-4.1% [-12.7 - 4.4]
CRS								
All HIV+	FujiLAM	968	477	11	214	266	64.9% [50.1 - 76.7]	95.7% [92.0 - 98.0]
	AlereLAM	968	281	5	410	272	38.2% [28.1 - 47.3]	98.2% [95.7 - 99.6]
	ΔSn and ΔSp						26.7% [20.4 - 32.7]	-2.4% [-11.2 - 6.3]



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

A reader

A kit for a rapid test

Target Population	Setting/User	Cost	Time-to-result
Children & adult	L0/L1	< 2 USD	< 30 min

FIND unpublished;
Russel T J Clin Micro 2017

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

Stop TB Partnership
New Diagnostics Working Group

Task Force on NGS and DST
Coordinator: Paolo Miotto, HSR

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

Share data from ReSeqTB and Cryptic

ReSeqTB

CRyPTIC

Diversification of sputum-based testing and DST

Xpert Ultra
(Cepheid)

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

MGIT -
Bedaquiline
Delamanid (BD)

QMAC QDST
(QuantaMatrix)

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

TruArray MDRTB /
XDRTB (Akonni)

Q-POC TB/MDR
TB (QuantuMDx)

Hybridisation
(Scanogen)

2017 | **2018** | **2019** | **2020 - 2025**

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

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

NAAT:
- Xpert MTB/RIF (Cepheid)
- TB-LAMP (Eiken)
- Mycobacteria RT PCR (CapitalBIo)
- Anyplex MTB/XDR (Seegene)
- Infiniti MDR TB (Autogenomics)
- VereMTB/Rif/Inh (Veredus Laboratorie
- MeltPro MDR (Zeesan Biotech)
- Genedrive TB/Rif (Epistem)
- AccuPower TB/MDR (Bioneer)

First Xpert follower

TrueLab MDR/TB
(Molbio)

→ Enable TEST & TREAT
→ Match the regimen

Omni Platform (Cepheid)

Expanded DST
(Cepheid, Hain, Bioneer)

Whole genome Sequencing from sputum

End-to-End NGS targeted sequencing solutions from sputum

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

Adapted from FIND

Joining Forces to speed up results and move NGS solutions to Countries to stop pDST

GROUP	MEDICINE
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin
	Bedaquiline[1,4]
	Linezolid[2]
Group B: Add both medicines (unless they cannot be used)	Clofazimine
	Cycloserine OR Terizidone
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol
	Delamanid[3,4]
	Pyrazinamide[5]
	Imipenem-cilastatin OR Meropenem[6]
	Amikacin (OR Streptomycin)[7]
	Ethionamide OR Prothionamide
	p-aminosalicylic acid

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

Stop TB Partnership
New Diagnostics Working Group

Task Force on LTBI and test of progression
Alberto Matteelli, University of Brescia

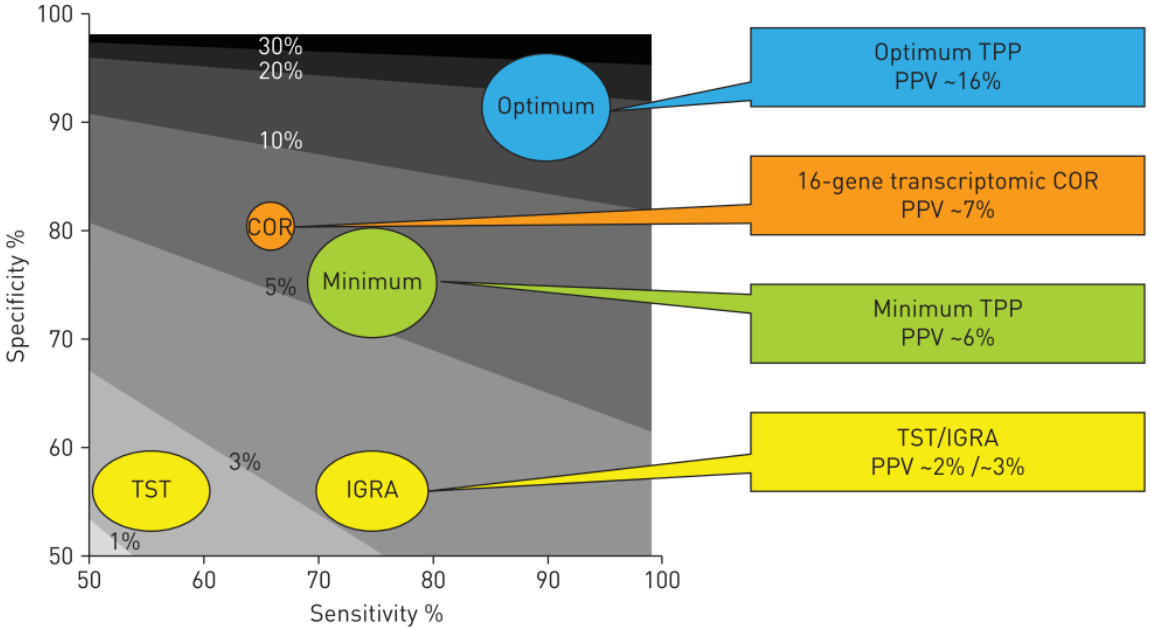
TPP and Framework for evaluation for a test of progression

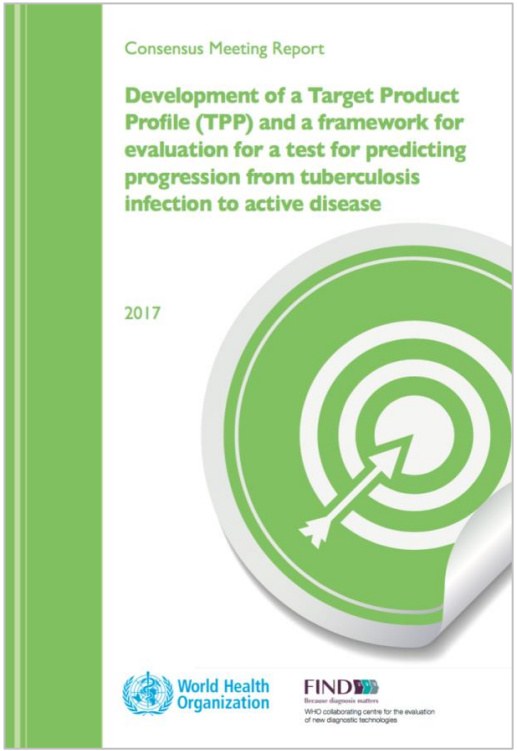
Viewpoint Paper *From latent to patent: rethinking prediction of tuberculosis*

Model to evaluate the impact of a test for incipient TB

Incipient TB - risk of progression

Current products (IGRA and TST):
2-3% PPV of existing products to detect latent TB





Incipient TB - risk of progression

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

- trascriptomic signatures
- IFN-γ release after T-cell stimulation with new antigens
- Cell differentiation markers (eg. CD27)
- Cytokine profiles (eg. IP-10)

Precision medicine approach: Merging precise individual care and large-scale programmatic functions

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

DIAGNOSIS

TB-POSITIVE
Rif-S

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

TB-POSITIVE
Rif-R

LPA-SL

PATIENT DATA
FOR DOSAGE PRECISION

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

CLINICAL
DECISION
SUPPORT SYSTEM
ARTIFICIAL
INTELLIGENCE

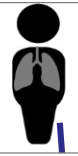
STANDARDIZED SHORTER MDR-TB REGIMEN
4-6 Amk-M-Pto-Cfz-Z-Hhd-E / 5 M-Cfz-Z-E

MDR-TB

(PRE-XDR-TB or XDR-TB)

PRECISION TREATMENT
(FOLLOWING WHO
STANDARDS)

SOCIAL SUPPORT &
COUNSELLING



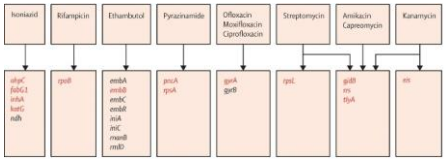
LONGER MDR-TB REGIMEN
SOCIAL SUPPORT & COUNSELLING

DR- Surveillance system
Precision measurement

DRUG PROCUREMENT SYSTEM
PRECISION SUPPLY

PHARMACOVIGILANCE
SYSTEM
BIOMARKERS TO
PERSONALISE DURATION

TARGETED NEXT GENERATION
SEQUENCING AND MIC



CENTRAL DATABASE

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

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

An Urgent Need for Improved Treatment of Active TB

Treatments are too long:

6-24

MONTHS

By 2030, five-year investment delay in R&D could result in:

8 million

MORE TB CASES

1.4 million

MORE TB DEATHS

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

WORKING GROUP ON NEW TB DRUGS

Stop TB Partnership

2018 Global TB Drug Discovery Pipeline [1]

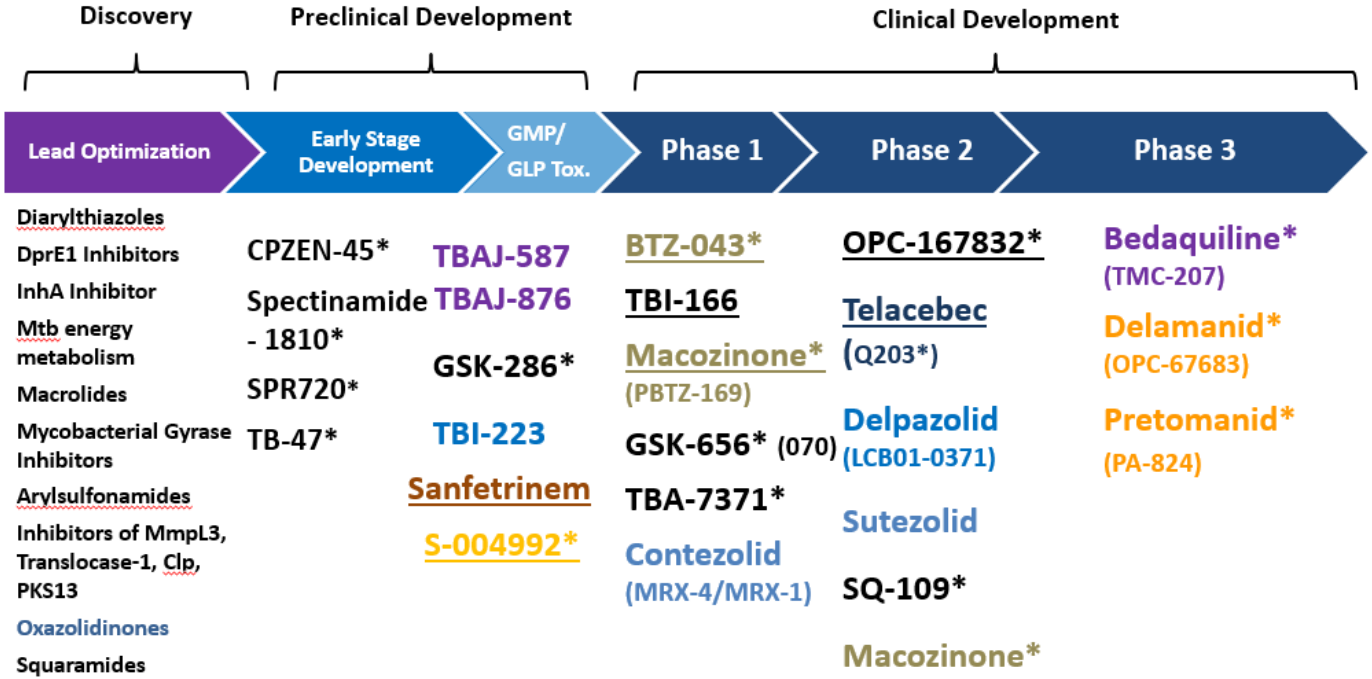
Hit-to-Lead	Lead Optimization
Actinomycete Metabolites (U ILL Chicago, Myongii U)	**Diarylthiazoles** (TBDA)
Novel Hit-to-Lead Programs (Lilly DDI) GATB	**InhA Inhibitors (**GATB/GHDDI)
Adamantanids (U ILL Chicago)	**Spectinamides** (St. Jude, U Tenn, CSU, UZ, Microbiotix)
Whole-Cell Hit-to-Lead (GSK, GATB)	**Macrolides** (GATB, Evotec)
Menaquinone Synthase Inhibitors (CSU)	**Clp** (SPRINT TB / A* Star)
M. tb Energy Metabolism Inhibitors (GATB, TBDA, J&J/CSIR-Imtech, Univ. of Notre Dame	**Indolcarboxamides / MmpL3 inhibitors** (GATB, TBDA)
Isoprenoid Biosynthesis Inhibitors (Lilly DDI)	**Oxazolidinones** (IMM)
Whole-Cell Hit-to-Lead (GATB, Evotec)	**Aryl Sulfonamides** (GATB, GSK, TBDA)
RNA Polymerase Inhibitors (GATB)	**PKS13 inhibitors** (GATB, DDU, TAMU, GSK, TBDA)
ClpC/P1P2 (GATB)	**Squaramides** (GATB, TBDA, Evotec)

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline-discovery.php and clinical development projects can be viewed at http://www.newtbdrugs.org/pipeline.php.

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

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org
Updated: October 2018

2018 Global New TB Drug Pipeline [1]



*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

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

Underline = new to Phase since March 2018

WORKING GROUP ON NEW TB DRUGS

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2018 Global TB Drug and Regimen Clinical Research [1]

Ongoing Clinical Development Research: Strategy / Optimization / Regimen Development

Phase 2	Phase 3 Regimens	Optimization/Post Market
OPC-167832*	Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)	Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)
Bedaquiline-Delamanid (ACTG 5343)	Bedaquiline-Pretomanid-Linezolid (NiX-TB)	endTB 5-Regimen Trial for MDR TB
Bedaquiline-Pretomanid-Moxifloxacin-PZA (SimpliciTB Trial, NC-008)	Delamanid with OBR for MDR-TB	PredictTB – PET/CT, biomarkers DS-TB, 4 mo
Bedaquiline - Pretomanid – Moxifloxacin - Pyrazinamide (BPaMZ) (NC-005)	High Dose Rifampicin for DS-TB (RIFASHORT)	TRUNCATE-TB Trial, 2 mo
Levofloxacin with OBR for MDR-TB (OPTI-Q)	Rifapentine - Moxifloxacin for DS-TB (CDC TBTC 31, ACTG 5349)	
Linezolid Dose-Ranging	Pretomanid-Moxifloxacin-Pyrazinamide (STAND)	
Beta-Lactams; Nitazoxanide		
High Dose Rifampicin (PANACEA)		
TB PRACTECAL - regimens with Bedaquiline-Pretomanid-Linezolid		

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.newtbdrugs.org/pipeline/clinical

[2] OBR = Optimized Background Regimen

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ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

Brief Rifapentine-Isoniazid Efficacy for TB Prevention

NCT01404312

Susan Swindells[1], Ritesh Ramchandani[2], Amita Gupta[3], Constance Benson[4], Jorge Leon-Cruz[2], Ayotunde Omoz-Oarhe[5], Marc Antoine Jean Juste[6], Javier Lama[6], Javier Valencia[6], Sharlaa Badal-Faesen[7], Laura Moran[9], Courtney V. Fletcher[1], Eric Nuermberger[3], Richard E. Chaisson[3], 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.

ACTG AIDS CLINICAL TRIALS GROUP

CROI.2018.37LB. Boston

Primary Endpoints

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

	9H	1HP	IRR Difference
Events/PY of follow up	33/4896	32/4926	0.023
Incidence per 100 PY	0.67	0.65	(95% CI -0.30-0.35)

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

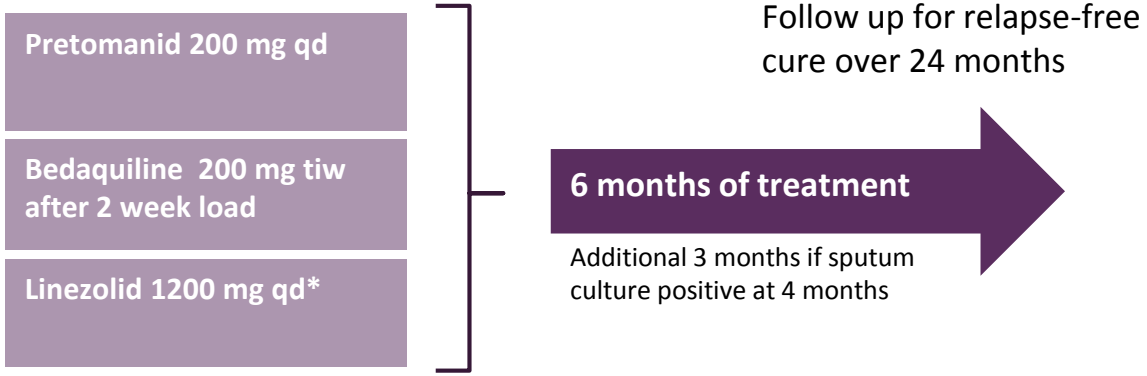
Sustained high rate of successful treatment outcomes:

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

Nix-TB Trial Design

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)



*Amended from 600 mg bid strategy

mITT (Primary Analysis)

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

*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

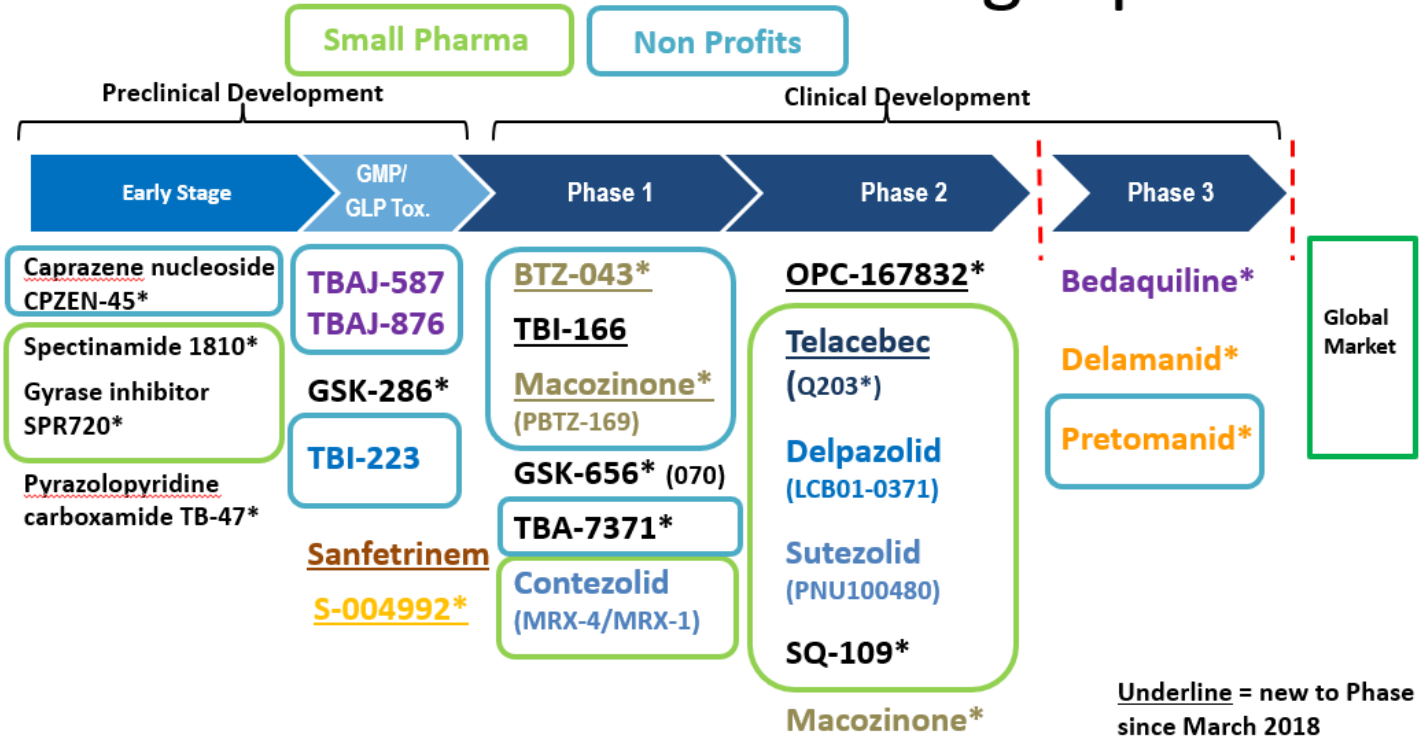
THANK YOU

Explore. Learn. Join the conversation.

www.newtbdrugs.org

Additional slides

2018 Global New TB Drug Pipeline [1]



Underline = new to Phase since March 2018

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

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

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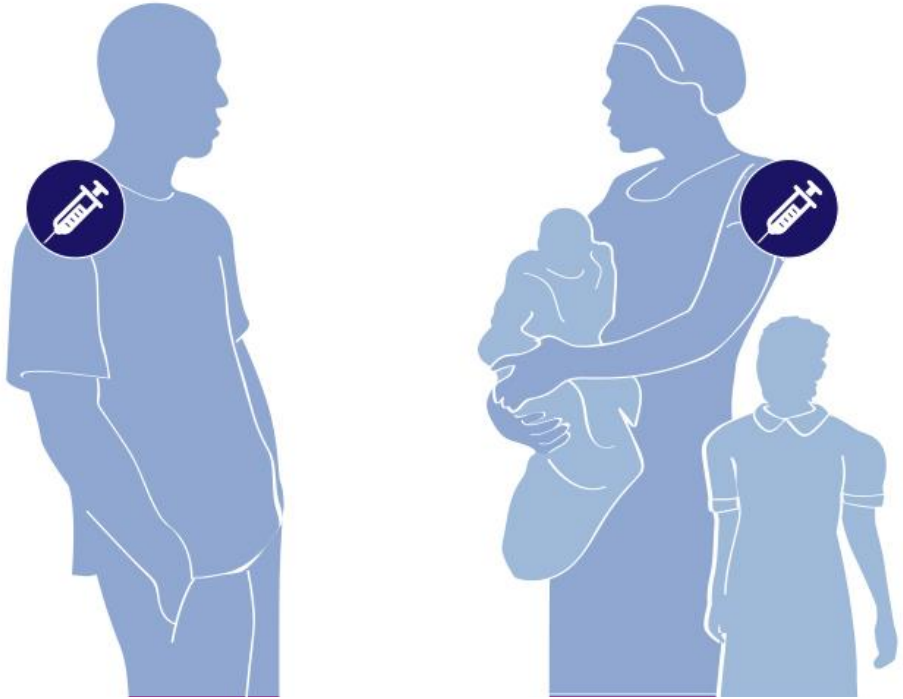
Updated: October 2018

Vaccines

Stopping the cycle of transmission in adults will prevent the spread of TB to children as well



International AIDS Vaccine Initiative

Target Patient Populations

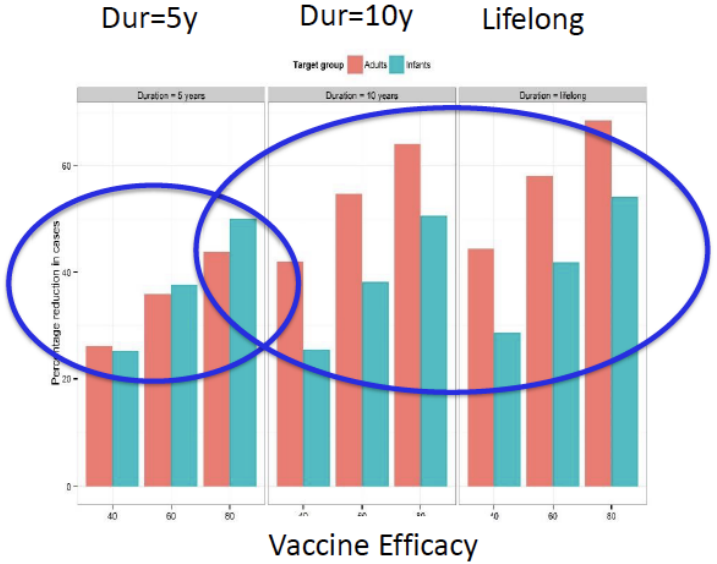
- Adolescents and adults
  - healthy
  - TB patients

- Infants
  - healthy

iavi International AIDS Vaccine Initiative

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

World Health Organization

Pre-Clinical

IV BCG

William Barclay
Sally Sharpe
Frank Verreck
Bob Seder and
JoAnne Flynn

Pulmonary BCG

Frank Verreck

CMV

Louis Picker

Tuberculosis
Volume 101, December 2016, Pages 174-190

Model Systems

Alternative BCG delivery strategies improve protection against *Mycobacterium tuberculosis* in non-human primates: Protection associated with mycobacterial antigen-specific CD4 effector memory T-cell populations

S. Sharpe [a], A. White [a], C. Sarfas [a], L. Sibley [a], F. Gleeson [b], A. McIntyre [b], R. Basaraba [c], S. Clark [a], G. Hall [a], E. Rayner [a], A. Williams [a], P.D. Marsh [a], M. Dennis [a]

nature medicine

Article | Published: 15 January 2018

Prevention of tuberculosis in rhesus macaques by a cytomegalovirus-based vaccine

Scott G Hansen, Daniel E Zak [...] Louis J Picker

Nature Medicine **24**, 130–143 (2018) | Download Citation

nature medicine

Letter | Published: 21 January 2019

Prevention of tuberculosis infection and disease by local BCG in repeatedly exposed rhesus macaques

Karin Dijkman, Claudia C. Sombroek, Richard A. W. Vervenne, Sam O. Hofman, Charelle Boot, Edmond J. Remarque, Clemens H. M. Kocken, Tom H. M. Ottenhoff, Ivanela Kondova, Mohammed A. Khayum, Krista G. Haanstra, Michel P. M. Vierboom & Frank A. W. Verreck

Nature Medicine (2019) | Download Citation

Turning a Corner: recent and upcoming data in TB vaccine efficacy trials

	PHASE	PARTICIPANTS	EFFICACY	LOCATION	RESULTS
Vaccae TM Anhui Zhifei Longcom	Phase III	10000 PPD+ 15-65y	Prevention of disease	China	2-3Q2018
★ H4:IC31/BCG revacc SP, SSI, Aeras	Phase II	990 Q- 12-17y	Prevention of infection	South Africa	1Q2018
★ M72/AS01E GSK, Aeras	Phase IIb	3573 Q+ 18-50y	Prevention of disease	South Africa, Kenya, Zambia	2Q2018
DAR-901 Dartmouth Medical School, GHIT	Phase IIb	650 Q- 13-15y	Prevention of infection	Tanzania	4Q2019
VPM1002 Max Planck, VPM, SII	Phase II/III	2000 TB+ 18-65y	Prevention of recurrence	India	4Q2019

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

Nemes et al, NEJM 2018; Van Der Meeren et al, NEJM 2018

Modified from M-A Demoitie, GSK

Recent Results are Game-Changing

TB vaccines are achievable

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE JUL 12, 2018

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

Nemes E., Geldenhuys H., Rozot V., et al. | N Engl J Med 2018; 379:138-149

...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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE
SEP 25, 2018

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

Van Der Meeren 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,...

FREE

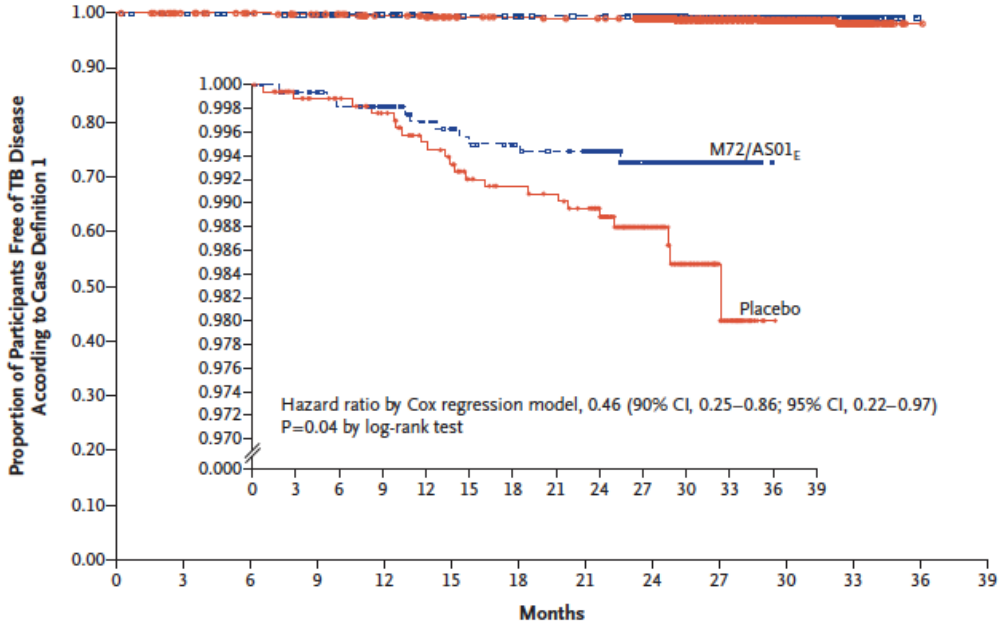
EDITORIAL
SEP 25, 2018

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...

FREE



No. at Risk													
M72/AS01$_E$	1623	1618	1612	1607	1593	1584	1580	1576	1354	847	500	166	0
Placebo	1660	1648	1640	1630	1613	1594	1587	1584	1347	849	509	170	1

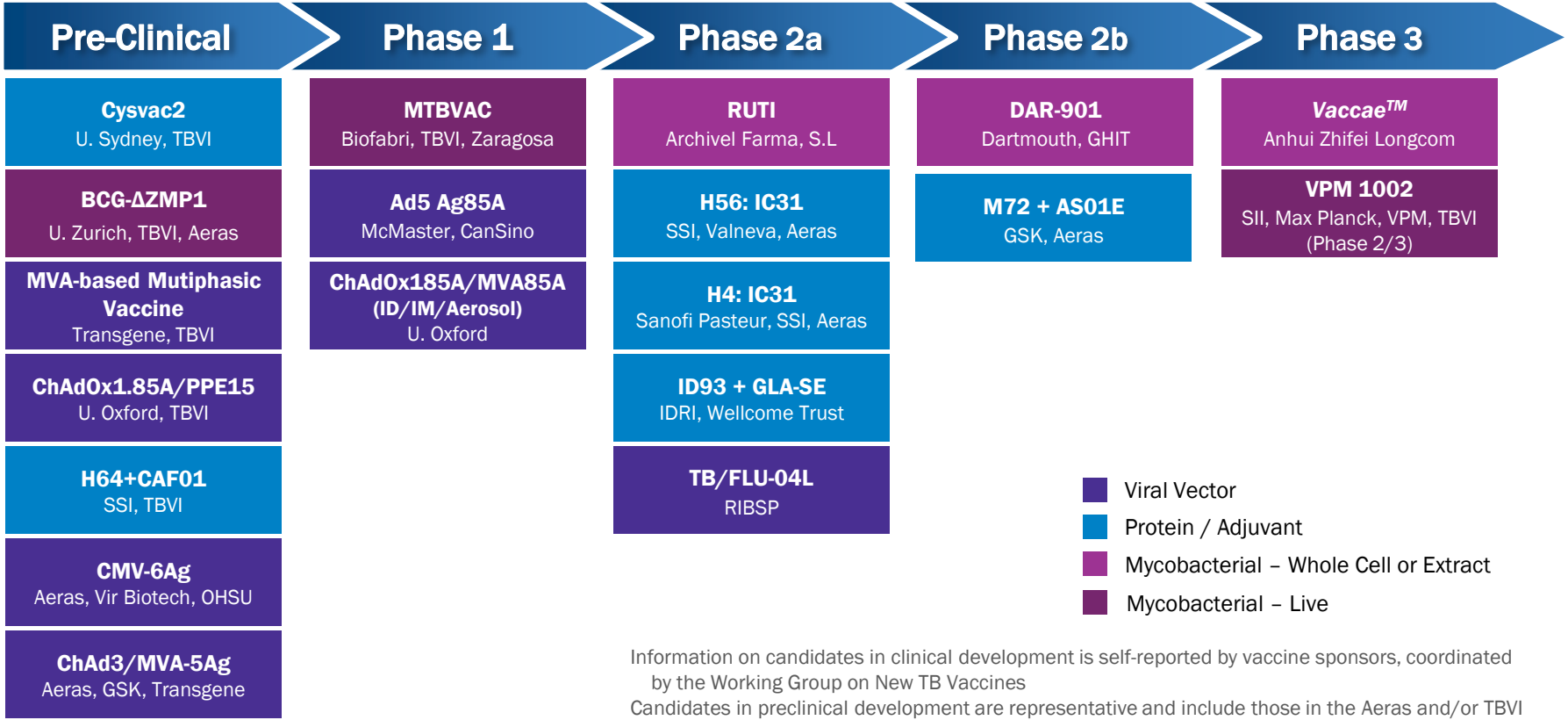
Figure 2. Kaplan–Meier Estimate of Definite Pulmonary Tuberculosis (TB) Disease Not Associated with HIV Infection (First Case Definition).

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%

Global Pipeline of TB Vaccine Candidates



Information on candidates in clinical development is self-reported by vaccine sponsors, coordinated by the Working Group on New TB Vaccines

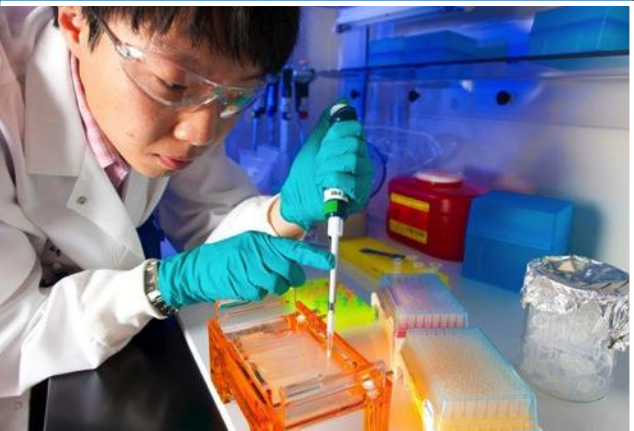
Candidates in preclinical development are representative and include those in the Aeras and/or TBVI portfolios that have completed Gate 1 as published in Barker L, Hessel L, Walker B, *Tuberculosis,* 92S1 (2012) S25–S29

IAVI

Ann Ginsberg

28 January 2019

Stop TB Partnership Coordinating Board pre-meeting



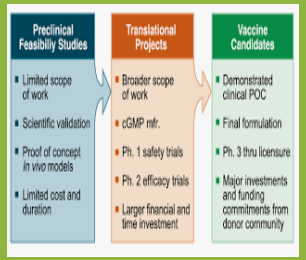
IAVI

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

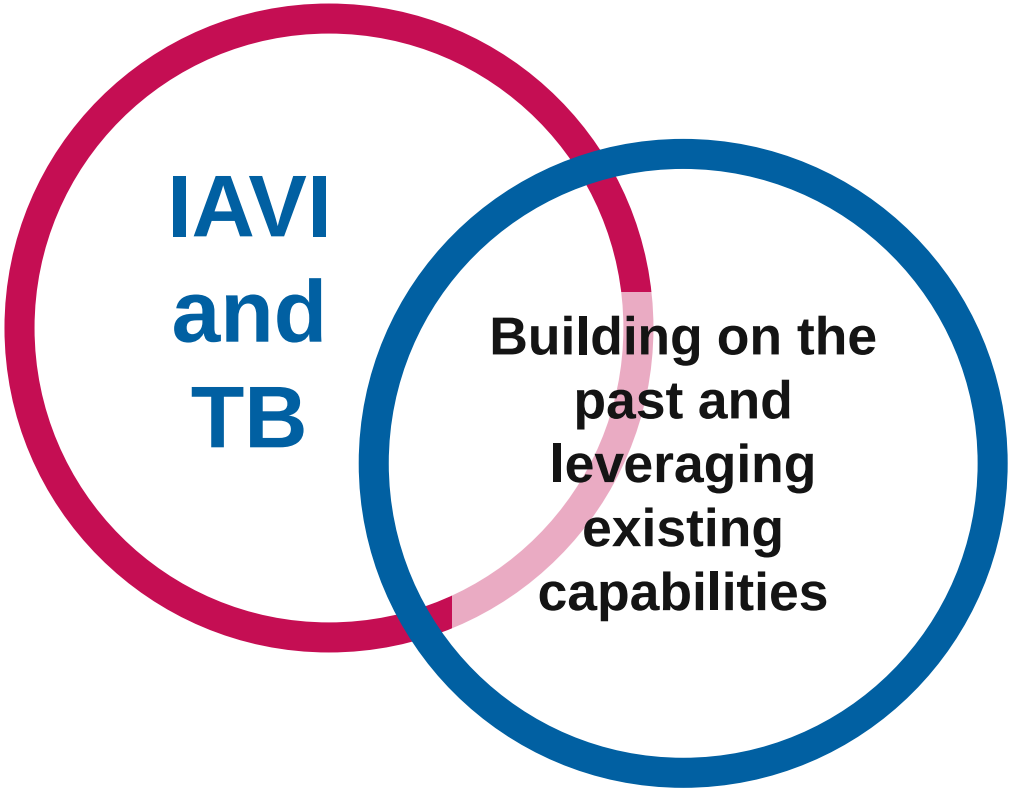
Vision and commitment required for end to end product development



Defining new business and partnership models to enable global access

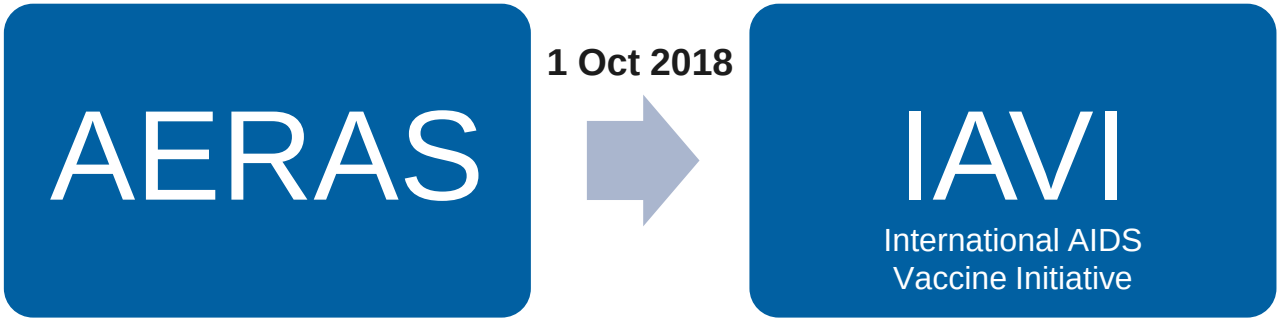
A not-for-profit product developer for global health needs

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**

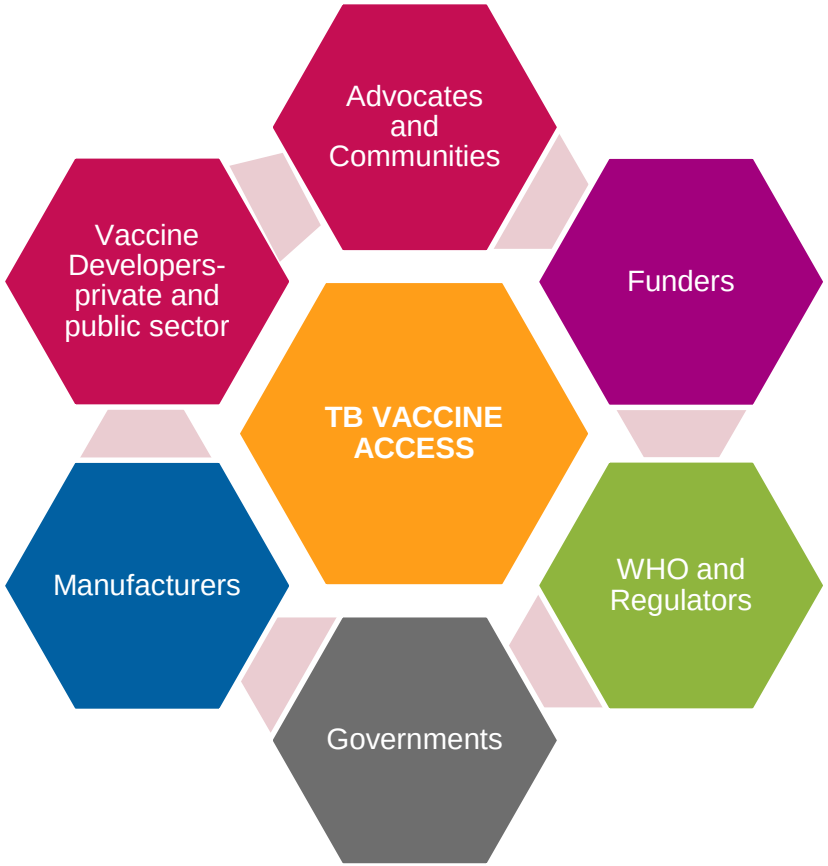
"…evaluating cost effectiveness found new TB vaccines to be an overwhelmingly cost effective intervention, whether from the health system or societal perspective."

Harris R, et al 2016, *Human Vaccines and Immunotherapeutics. 12:2813-2832.*

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

amfAR, The Foundation for AIDS Research | Bill & Melinda Gates Foundation | The Buimerc Group | Broadway Cares/Equity Fights AIDS | The City of New York, Economic Development Corporation | Coalition for Epidemic Preparedness Innovations | European & Developing Countries Clinical Trials Partnership | European Union | Foundation for the National Institutes of Health | GlaxoSmithKline | Government of Japan | The Hearst Foundations | Irish Aid, Department of Foreign Affairs and Trade | Ministry of Foreign Affairs of Denmark | Ministry of Foreign Affairs of The Netherlands | Ministry of Science & Technology, Government of India | National Institute of Allergy and Infectious Diseases | The Research Council of Norway | U.K. Department for International Development | The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development | The World Bank

And many other generous individuals and partners around the world

As of January 2019

Thank you

iavi

International AIDS
Vaccine Initiative

Concluding Remarks

TAG
Treatment Action Group

Stop TB Partnership

Tuberculosis Research Funding Trends 2005-2017

TABLE 3

Pediatric TB R&D Funders by Rank, 2017

2017 RANK	FUNDING ORGANIZATION	FUNDER TYPE	2017 PEDIATRIC TB R&D FUNDING	PERCENTAGE OF TOTAL PEDIATRIC FUNDING
1	European and Developing Countries Clinical Trials Partnership (EDCTP)	P	$10,604,544	18.8%
2	U.S. Agency for International Development (USAID)	P	$9,500,000	16.8%
3	U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID)	P	$6,886,622	12.2%
4	Unitaid	M	$6,615,400	11.7%
5	Company X	C	$5,700,000	10.1%
6	U.S. National Institutes of Health, Other Institutes and Centers (NIH Other ICs)	P	$5,562,805	9.9%
7	U.K. Medical Research Council (U.K. MRC)	P	$4,535,821	8.0%
8	Brazilian Development Bank	P	$1,814,040	3.2%
9	South African Medical Research Council (SAMRC)	P	$1,083,446	1.9%
10	World Health Organization	M	$600,000	1.1%
11	Norwegian Agency for Development Cooperation (NORAD)	P	$437,361	0.78%
12	Novartis Pharma AG	C	$320,000	0.57%
13	Australian National Health and Medical Research Council	P	$311,383	0.55%
14	Molbio Diagnostics	C	$308,600	0.55%
15	Brazilian Ministry of Health	P	$302,340	0.54%
16	Médecins Sans Frontières	F	$261,742	0.46%
17	Japan Agency for Medical Research and Development (AMED)	P	$251,544	0.45%
18	Thrasher Research Fund	F	$237,296	0.42%
19	German Federal Ministry of Education and Research (BMBF)	P	$231,310	0.41%
20	ELMA Foundation	F	$175,000	0.31%
21	Wellcome Trust	F	$171,040	0.30%
22	Swedish Research Council	P	$141,936	0.25%
23	Company V	C	$114,227	0.20%
24	Canadian Institutes of Health Research	P	$65,823	0.12%
25	Thailand Ministry of Public Health	P	$62,798	0.11%
26	Thailand Health Systems Research Institute	P	$61,993	0.11%
27	Other public funders with investments less than $50,000	P	$72,083	0.13%
	TOTAL		**$56,429,152**	

C = Corporation/Private Sector; F = Foundation/Philanthropy; M = Multilateral; P = Public-Sector R&D Agency

Otsuka Pharmaceuticals, which is close to completing its pharmacokinetic and safety study of delamanid in children, notified TAG that it cannot disaggregate pediatric expenditures from its overall investment and is therefore not listed in the table.