Shifting the Paradigm in Anti-TB Drug Development

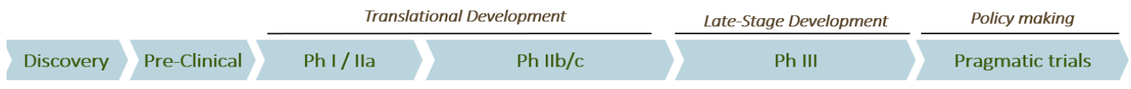
- Andrea Muscetti, Francesca Saluzzo, Arash Ghodousi, Christina Kallenberg, Quang Nguyen Le, Eva Terschlusen, Jodie A. Schildkraut, Derek J. Sloan, Daniela M. Cirillo on behalf of the UNITE4TB consortium.

FACTS & FIGURES

Start date:	01/06/2021
End date:	31/05/2028
IMI funding:	92,500,000 €
EFPIA in kind:	62,364,744 €
Other:	30,135,256 €
Total Cost:	185,000,000 €
Project website:	unite4tb.org
Social media:	linkedin/company/unite4tb

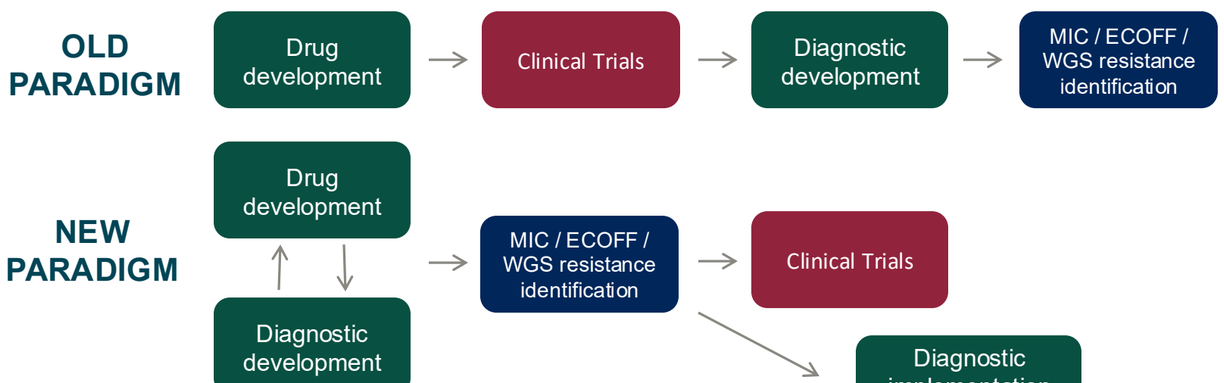
CHALLENGE

- Tuberculosis (TB) caused an estimated 1.3 million deaths in 2024
- New regimens are urgently needed to ensure effective treatment for all people living with TB

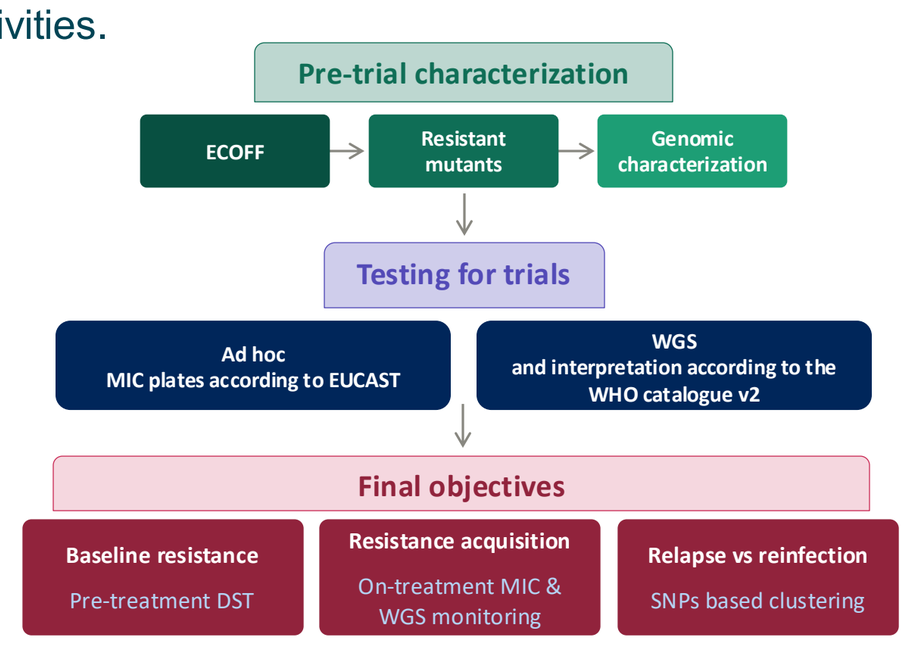


Accelerate and improve	Clinical evaluation of novel drugs and combinations of drugs for susceptible strains and resistant Tuberculosis (TB) strains
Deliver	An efficient global clinical trials network to implement phase 2° and 2B/C trials that conform with the highest regulatory standards
Integrate	Adaptive trial design with biomarkers of tratment success
Employ	Advanced PK and PD models and AI/ML techniques to select, test, and deliver these novel combinations with a high probability of success in phase 3
Set	A new standard for anti-TB regimen development, upgrading current trial methodology, and enhancing the efficiency with which new regimens are delivered to the world

APPROACH & METHODOLOGY



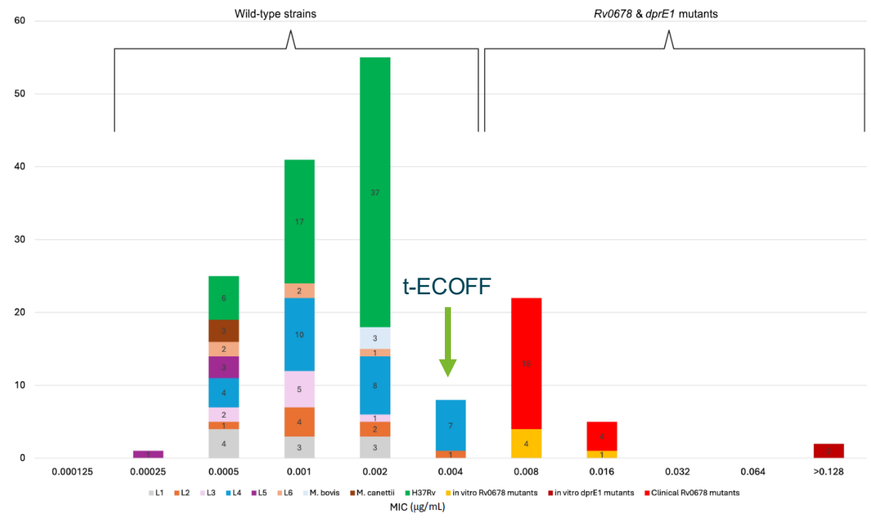
We aim to integrate Minimum Inhibitory Concentration (MIC) testing, Epidemiological Cut-Off Value (ECOFF) definition, Whole Genome Sequencing (WGS) resistance identification into the drug-development pathway, supporting clinical trials and future IMI activities.



EUCAST: European Committee on Antimicrobial Susceptibility Testing; WHO: World Health Organization; DST: Drug Susceptibility Testing; SNPs: Single Nucleotide Polymorphisms

RESULTS

1. EUCAST-based ECOFF determination
Establishment of MIC distributions for Wild Type (WT) strains and preliminary ECOFFs for novel compounds.



(Ghodousi A. et al. 2025)

2. Characterization of resistance determinants
Generation of drug-resistant mutants under selective pressure and characterization of resistance-associated mutations to support ECOFF definition

3. Tentative ECOFF establishment
Integration of WT MIC distributions and resistant mutant data to define tentative ECOFFs for novel compounds

4. Development of a comprehensive MIC testing plate
Integration of newly generated, literature and EUCAST data to define specific dilution ranges for compounds tested in UNITE4TB DECISION and PARADIGM4TB trials.

	1	2	3	4	5	6	7	8	9	10	11	12
A	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O
B	neg control w/ DMSO	LEVO 2	BDQ 1	BDQ 0.5	BDQ 0.25	BDQ 0.125	BDQ 0.06	BDQ 0.03	BDQ 0.016	BDQ 0.008	BDQ 0.004	H2O
C	neg control w/ DMSO	LEVO 1	GAN 0.5	GAN 0.25	GAN 0.125	GAN 0.06	GAN 0.03	GAN 0.016	GAN 0.008	GAN 0.004	GAN 0.002	H2O
D	neg control w/ DMSO	LEVO 0.5	Pa 4	Pa 2	Pa 1	Pa 0.5	Pa 0.25	Pa 0.125	Pa 0.06	Pa 0.03	Pa 0.016	H2O
E	neg control w/ DMSO	LEVO 0.25	BTZ-043 0.016	BTZ-043 0.008	BTZ-043 0.004	BTZ-043 0.002	BTZ-043 0.001	BTZ-043 0.0005	BTZ-043 0.0002	BTZ-043 0.0001	GC 100%	H2O
F	neg control w/ DMSO	LEVO 0.125	DLM 0.125	DLM 0.06	DLM 0.03	DLM 0.016	DLM 0.008	DLM 0.004	DLM 0.002	DLM 0.001	GC 100% w/ DMSO	H2O
G	neg control w/ DMSO	LEVO 0.06	LZD 4	LZD 2	LZD 1	LZD 0.5	LZD 0.25	LZD 0.125	LZD 0.06	GC 1%	GC 1% w/ DMSO	H2O
H	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O	H2O

LEVO	Levofloxacin
BDQ	Bedaquiline
GAN	Ganfeborole
Pa	Pretomanid
BTZ-043	BTZ-043
DLM	Delamanid
LZD	Linezolid

Standardized MIC testing for clinical trial sites
A standardized approach enabling harmonized susceptibility testing across trial-testing laboratories.

VALUE OF IMI COLLABORATION

- The public–private partnership provides access to novel compounds, enabling their early evaluation alongside a strong academic network of experienced laboratories with the expertise and capacity to establish ECOFFs.
- This collaborative framework facilitates the translation of pre-clinical findings into clinical and trial research, supporting the co-development of resistance monitoring strategies alongside novel treatment regimens.

CAREER IMPACT

- The UNITE4TB consortium and the projects has connected my research with a broader international and interdisciplinary trial network, fostering collaboration, knowledge exchange and new research ideas.
- Working alongside researchers from different academic, clinical and industry backgrounds, together with mentorship and exposure to diverse expertise, has supported my scientific and professional development.
- The multi-site collaborative environment has also strengthened my skills in coordination, data sharing, scientific communication and collaborative problem-solving, while providing opportunities to build a broad professional network.

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