WHO catalogue of mutations in *Mycobacterium tuberculosis* and associated drug resistance. The what, when and how?

**Date:** Tuesday, 30 November 2021  
**Time:** 14:00 to 17:00 CET  
**Registration link for course:**  
[https://us06web.zoom.us/meeting/register/tZcvduqvpj gvE9yCn3EBFUnZGhiqvDxgebCe](https://us06web.zoom.us/meeting/register/tZcvduqvpjgvE9yCn3EBFUnZGhiqvDxgebCe)

**Background:** The use of molecular tools for the diagnosis of TB and drug-resistant TB has had a significant impact on the management of TB globally. The use of more advanced technologies such as next-generation sequencing (NGS) is at the cusp of taking the current successes to the next level. However, a major hindrance has been the lack of a standardized single reference catalogue of mutations and their association with drug resistance. This is important for surveillance activities that already use such technologies, for manufacturers undertaking research and development and in preparation for the future programmatic use of these technologies.

**Expected outputs/outcomes:**  
1. Improved understanding of the use and special considerations when using NGS  
2. Proficiency in using the WHO Catalogue of Mutations  
3. Advanced knowledge on genotypic-phenotypic association studies

**Session sponsor:** Unitaid  
**Chairs:** Timothy Rodwell (University of California San Diego); Matteo Zignol (WHO)  
**Coordinators:** Carl-Michael Nathanson (WHO); Nazir Ismail (WHO)  
**Target audience:** Researchers, Developers, Laboratory experts, Bioinformaticians, Public Health Specialist, Epidemiologist, Programme Managers  
**Speakers:**  
Anita Suresh (FIND): Understanding the role of Next Generation Sequencing for diagnosis of drug resistant TB

Next-generation sequencing (NGS) has revolutionized our understanding, diagnosis, and management of complex diseases from antimicrobial resistance to COVID-19. An overview of the landscape and the critical strengths and
limitations of NGS will be discussed. The WHO-endorsed, standardized reference catalogue of mutations will contextualised. We will also discuss ongoing efforts to evaluate commercial targeted NGS (tNGS) solutions for clinical diagnosis of drug-resistant TB from direct clinical samples as part of the Unitaid funded Seq & Treat Project. The topic will be concluded with a rapid poll on the values and perspectives of the audience on the technology.

Nazir Ismail (WHO): Use of NGS for surveillance of drug resistant TB
The WHO has recently provided guidance on the use of NGS for surveillance of drug-resistant TB. An overview of the current drug resistance surveys that have been conducted using sequencing will be presented. Important lessons from its use will be shared. Finally, key highlights from the new guidance will be provided. The topic will be concluded with a brief Q&A session.

Timothy Walker (Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam): Genotype and phenotype association studies for drug resistance determination
The basis of the catalogue of mutations for interpretation rests on associating sequencing data with phenotypes. This is not a straightforward exercise as associating a single mutation with a phenotype is challenged by several factors. Identifying a mutation as a “SOLO” as well as issues around epistasis and heteroresistance. The phenotypic reference standard to be used and quality of data (genotype and phenotype) is another important consideration. Lastly, any association would require a statistical basis and here the issue of analysis of rare events needs to be considered. The topic will be concluded with a short quiz.

Claudio Köser (Department of Genetics, University of Cambridge): Considerations and application of expert rules in the Catalogue of mutations
The catalogue of mutations is based on association studies of empiric data. However, there are several considerations requiring expert rules to be applied. For some drugs and methods, the phenotype can result in false resistance and susceptibility and the quantity of data is unlikely to resolve such issues. Some drugs require additional considerations such as the pncA gene for pyrazinamide. Additionally, there may be convincing data on specific mutations which would need to be contextualized against the mutation catalogue. The presentation explains the considerations and decisions applied to the catalogue. The topic will be concluded with a short quiz.

Paolo Miotto (Ospedale San Raffaele, Milan, Italy): Accessing and using the WHO Catalogue of Mutations in Mycobacterium tuberculosis and associated drug resistance
After understanding the generation of the catalogue of mutations and specific considerations, this session will allow users to fully maximize the use of the catalogue. Attendees will be directed to download the catalogue in advance of the session. A quick demonstration will be provided on how to navigate the catalogue, understand the data provided on a mutation and how the final interpretation was derived. Following this demonstration, a practical session will follow allowing attendees to explore the catalogue and complete specific exercises using the catalogue.
Chairs and Speaker biographies

Chair: Matteo Zignol

Dr. Matteo Zignol is an infectious disease specialist and clinical epidemiologist, who joined the World Health Organization (WHO) in 2003. At WHO he coordinated activities related to drug resistance surveillance and managed a multi-country project on the use of genetic sequencing for surveillance purposes. Currently, as the Head of the TB Prevention, Diagnosis, Treatment, Care & Innovation Unit of the WHO Global TB Programme, Dr Zignol leads the work on the development of new policies for universal access to diagnosis, treatment and care; as well as helping shape the TB research agenda and innovation.

Chair: Timothy Rodwell

Dr. Timothy Rodwell is a Professor of Medicine at University of California, San Diego, and a Senior Scientific Advisor to FIND, in Geneva, Switzerland. Dr. Rodwell’s research is primarily focused on the development of rapid diagnostics for tuberculosis (TB) and other infectious diseases, as well as the genetic basis of drug resistance in Mycobacterium tuberculosis. Dr. Rodwell is currently working with global collaborators to develop and evaluate next generation sequencing (NGS) approaches for characterizing comprehensive antimicrobial resistance profiles from direct clinical samples.

Anita Suresh

Anita Suresh is Head of Sequencing at FIND, focused on enabling next-generation sequencing for TB, AMR, COVID-19 and other infectious diseases in low- and middle-income countries. She has 15 years of experience in molecular diagnostics, bioinformatics, TB, and global health. Her research background is in molecular biology and bioinformatics.
Nazir Ismail

Dr Nazir Ismail is a Team Leader in the Unit for TB Prevention, Diagnosis, Treatment, Care and Innovation at the WHO’s Global TB Department in Geneva, Switzerland. He leads the team responsible for developing global policies, norms and standards in TB Diagnosis and Laboratory Strengthening. He is the former Head of the Centre for Tuberculosis at the National Institute of Communicable Diseases (NICD) in South Africa. A medical doctor by training that specialized in microbiological pathology passing his fellowship with distinction. He has a focus on diagnostics, epidemiology, public health responses and TB transmission.

Timothy Walker

Timothy Walker is an infectious diseases physician, clinical microbiologist, and Wellcome Trust Clinical Research Fellow based at Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam, where he is investigating how people get drug resistant tuberculosis. He also has a research interest in the application of genome sequencing technologies for TB diagnostics. He has worked with Public Health England and now with WHO to generate catalogues of mutations for molecular drug susceptibility testing.

Claudio Köser

Claudio Koser is a visiting scientist at the Department of Genetics, University of Cambridge. His main interest lies in bringing modern microbiological principles to defining susceptibility and resistance to anti-TB agents. This work revealed that the WHO breakpoints for several first- and second-line drug had been too high, resulting in the systematic misclassification of resistant strains as susceptible. He is working closely with EUCAST and drug developers to avoid these shortcomings for new agents.

Paolo Miotto

Paolo Piotto is a Research associate at the Ospedale San Raffaele, Milan, Italy. His main interest is drugs resistance genetics in *M. tuberculosis* and he is currently involved in the Seq&Treat project, a collaborative initiative leaded by FIND to support the global adoption of NGS for affordable, scalable and rapid TB DST. He is also working on the characterization of small regulatory RNAs to identify new mechanisms of drug resistance and better understand the pathogenesis of tuberculosis. As part of team of the WHO SRL for TB Control in Milan, he is involved in training and technical support to TB laboratories.