Author Claudia Denkinger, Head of Tuberculosis and Hepatitis Programme at FIND (Foundation for Innovation New Diagnostics)

Brief on background and needs for diagnostics that can reduce antimicrobial resistance in tuberculosis

Background:

- Every year, one in three people who fall ill with TB are left undiagnosed or not registered by health systems. **These "missing" 3.6 million people** are at the root of why TB transmission continues at high levels. The problem is lack of access to sensitive tests at the point where most patients present to care, so-called Level 1 of the health care system (see Figure 1).

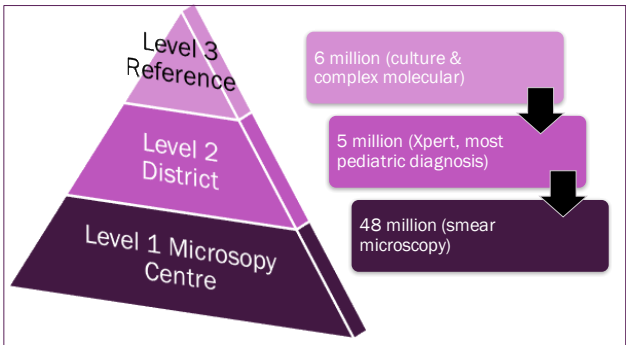

Figure 1: Where patients present? Where is testing happening?

- Culture-based tests for drug resistance take 120 days and are only available at few reference laboratories. Genotypic tests offer the opportunity for rapid drug resistance detection. However, currently available tests only test for susceptibility to the first-line drugs: rifampicin (on Xpert MTB/RIF) at Level 2 facilities, and rifampicin plus isoniazid (on Genotype MTBDRplus) at Level 3 facilities. No available rapid tests of drug susceptibility to TB can be deployed at the lowest level of the health care system.
- In order to guide therapy of patients with multi-drug resistance, drug susceptibility testing for second line drugs is necessary. Our understanding of the genotypic basis of drug resistance is evolving rapidly, and the treatment landscape is changing with the anticipated arrival of novel regimens in the coming years. Therefore, in order to be most useful, drug susceptibility tests need to be easily adaptable to new data and new drugs. Sequencing of *M. tuberculosis* genes directly from sputum is, for now, the only test method that could offer drug susceptibility information with reasonably rapid turn around and adaptability.
- Children are considered to be at low risk of drug resistance; however, one study published recently (DOI: 10.1371/journal.pone.0140375) found multi-drug resistance in 7.4% of children with TB, an extraordinarily high rate. Children are rarely able to produce sputum, and both TB diagnosis and drug susceptibility testing therefore require testing samples other than sputum. Ideally, these would be samples that are easily accessible.

Ongoing development and needs:

- **Implementation needs:** The Omni/Ultra is a new portable testing platform that will likely be available and WHO endorsed in 2017. The Omni is small and battery-operated, making it possible to use in settings where most patients present for diagnosis (Level 1). This test should make TB diagnosis more accessible, more sensitive, and faster than current methods, while identifying resistance to rifampicin at the time of diagnosis. Collectively, this should make treatment more effective across populations, and help reduce the transmission of drug-resistant strains of TB. Other similar products designed for use at Level 1 are in the product development pipeline (e.g., Molbio).
    - *Funding is necessary to support implementation of molecular assays at Level 1, which will require capacity building in-country through training, technical assistance, building of quality assurance/control systems, and awareness campaigns targeting clinicians*

Figure 2: GeneXpert® Omni, an example of a next-generation molecular diagnostics system which, when used in front-line health care settings, may lead to faster, more targeted treatment, helping to find the missing 3.6 million people living with undiagnosed or untreated TB.

- *Innovative funding mechanisms are needed to support healthcare systems and patients to make an initial investment into the large scale rollout of molecular tests at Level 1, because returns on investment in these new tests (through reduction of transmission) will come only once they reach a reasonable scale*

- **Development needs**
  - Next Generation Sequencing (NGS) technology can identify up to 200 mutations in the TB bacterium in ~48 hours, allowing for rapid identification of any antibiotic-resistant strain, compared to the 120 days of culture-based methods. This tool would benefit public health efforts to control TB, and TB patients. Used for surveillance in reference laboratories in the highest burden countries, NGS could give the global health community an accurate picture of which drug-resistant strains exist and where they are spreading. Used as a clinical test to guide therapy, NGS could help clinicians select the appropriate TB treatments.
    - *Funding necessary to translate expanded drug resistance detection solutions such as NGS into solutions for patient care in resource limited settings and build evidence of the impact on TB care that can help support policy recommendations.*
  - A new kit to process stool samples collected from children and adults will help to detect TB in patients with minimal sputum production, based on ultrasensitive molecular tests like the Xpert Ultra test.
  - Research on new biomarkers, as the basis for a new test to triage or rule out TB quickly, will allow clinicians to separate suspect TB patients from those with similar symptoms, but without TB. This will allow the identification of patients at high-risk of TB early, reduce inadvertent transmission within health facilities, and enable providers to target molecular tests more efficiently to symptomatic patients at highest risk of having TB, to guide further treatment.
    - *Funding is necessary for biomarker research and development of products designed for triage of patients with respiratory symptoms, especially create to simple kits that can be used by providers with limited training at Level 1, and build evidence of the impact on TB care that can help support policy recommendations.*