

TECHNICAL CONSULTATION ON IN VITRO DIAGNOSTICS FOR AMR

27–28 March 2019, WHO headquarters, Geneva

Meeting report



World Health
Organization

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Introduction

The Technical Consultation on In Vitro Diagnostics on AMR was held on 27–28 March 2019 at WHO headquarters in Geneva, Switzerland. The agenda and list of participants for the meeting are attached as Annex A and Annex B, respectively.

The meeting had the following objectives:

- review a draft landscape of in vitro diagnostics (IVDs) to combat antimicrobial resistance (AMR) (with a focus on antibacterial resistance [ABR]);
- identify gaps in such diagnostics suitable for use in patient management at primary and secondary healthcare facilities (Levels I and II) in low- and middle-income countries (LMICs);
- agree on a research and development (R&D) priority list of diagnostics for use in Levels I and II in those settings; and
- identify priorities for target product profiles (TPPs) for the highest-priority AMR diagnostics to be developed.

Dr Marc Sprenger, Director, Antimicrobial Resistance Secretariat, WHO, opened the meeting with a reminder that the burden of infectious diseases is highest in LMICs and the need for choosing the right treatment is greatest in those settings. Dr Sprenger reviewed the WHO Global Action Plan on Antimicrobial Resistance (GAP) objectives:¹ (i) improve awareness and understanding; (ii) strengthen knowledge through surveillance and research; (iii) reduce the incidence of infection; (iv) optimize the use of antimicrobial medicines; and (v) ensure sustainable investment. Dr Sprenger emphasized that the development and implementation of national action plans is key for countries to address these objectives; yet countries are challenged in these efforts by scarce financial and technical resources. With respect to diagnostics, it is also imperative for WHO and other stakeholders to promote R&D of new, affordable diagnostic tools to combat AMR, and to promote access to existing and new diagnostic tools of assured quality in order to reach the GAP goals.

Diagnostics landscape

The landscape analysis of in vitro ABR diagnostics was presented, including its methodology and scope. It was emphasized that the landscape primarily focuses on:

- Diagnostics to improve patient management and ensure access to appropriate treatment while reducing unnecessary antibiotic prescription (antibiotic stewardship). It should be noted that with respect to IVDs for national surveillance, the Global Antimicrobial Surveillance System (GLASS) has published a landscape titled *Molecular methods for antimicrobial resistance (AMR) diagnostics to enhance the Global Antimicrobial Resistance Surveillance System*, which is available at: <https://www.who.int/glass/resources/publications/molecular-methods-for-amr-diagnostics/en/>. It is a resource that is complementary to the ABR diagnostics landscape.
- The WHO priority bacterial pathogen list for R&D for drug development (PPL),² which pathogens are closely related to the diagnostics needed to guide the treatment of infection.
- Diagnostics for specific identification (ID) of bacterial pathogens as well as nonspecific tests to identify host response markers.
- Diagnostics appropriate for use at Level I and Level II of the laboratory system (i.e., primary and secondary healthcare facilities) in LMICs with a focus on community-acquired infections (CAIs).

Excluded from the landscape analysis are:

- diagnostics for *Mycobacterium tuberculosis* (MTB), for which WHO has already done extensive landscaping of diagnostics and drug-susceptibility testing (DST) and for which a number of TPPs have already been developed and published. However, due to the importance of MTB, the report highlights previously recognized gaps and priorities for TB diagnostics R&D;
- diagnostics for meningitis, which is not on the WHO PPL, but for which work is ongoing at WHO;
- health system weaknesses, which along with regulatory barriers are primary barriers to implementation and uptake of new diagnostics in LMICs;
- performance of diagnostics;
- cost of diagnostics; and
- clinical or other laboratory findings (e.g., complete blood count, basic metabolic panels, etc.)

¹ The WHO Global Action Plan on Antimicrobial Resistance is available at: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1.

² The PPL is available at: https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf.

that should accompany a diagnosis for a bacterial pathogen or syndromes associated with bacterial pathogens.

It is acknowledged that the development of any new diagnostic to combat antibacterial resistance, even one that has been designed specifically for use in primary healthcare settings, will not be taken up and implemented successfully without efforts on many fronts, including, but not limited to, health system strengthening in LMICs. Many barriers to adoption of tests for AMR were presented and discussed. As examples of tests that are available but not used, it was mentioned that rapid Strep A and C-reactive protein (CRP) tests are available in France and the United Kingdom, respectively; however, their uptake is less than 30% in both cases. It is further acknowledged that new diagnostics are not the only way to improve access to diagnostics to combat ABR in LMICs. Better use of existing diagnostics, including manual phenotypic methods, through improved algorithms for use, can also be a solution. These are not mutually exclusive.

In summary, the diagnostic landscape seeks to answer the following question: What are the gaps in diagnostics to combat ABR for bacterial pathogens on the PPL, with an emphasis on CAIs, at Levels I and II of the healthcare system in LMICs?

After an extensive review of existing (and pipeline) test methods, the landscape concludes that there are many commercially available test systems for ID of bacterial pathogens and antimicrobial susceptibility testing (AST), both phenotypic and nonphenotypic, to identify and/or perform AST/resistance testing with respect to virtually all priority bacterial pathogens, but most systems are predicated on:

- well equipped laboratories/solid infrastructure; and
- well trained laboratory staff able to perform sophisticated techniques.

Therefore, most tests/platforms/systems available today are not suitable for use at Levels I and II, and simpler and faster methods of bacterial pathogen ID and AST/resistance testing are needed at all levels of the healthcare system.

Diagnostic gaps

In order to arrive at the most pressing needs for diagnostics R&D, meeting participants agreed that certain clinical syndromes should be prioritized for diagnostic testing at Levels I and II. These are:

- fever without a known source
- sepsis
- sore throat/cough, upper respiratory infection (URTI)

- TB
- pneumonia/lower respiratory tract infection (LRTI)
- diarrhoea
- visible skin/soft tissue infection
- wounds (traumatic and chronic)
- urethral and vaginal discharge suggestive of a sexually transmitted infection
- urinary tract infection (UTI).

Diagnostics for these syndromes at each of Level I and Level II should be considered and selected depending on the objective: (a) guidance for appropriate treatment of drug-resistant infections (i.e., optimizing patient management), (b) reducing unnecessary antibiotic prescriptions and (c) surveillance. Further, the assessment of availability and suitability of existing test systems at each of Level I and Level II should be based on the following categories: (i) bacterial versus nonbacterial infection, (ii) bacterial ID (culture, rapid diagnostic test [RDT], molecular), (iii) phenotypic AST and (iv) resistance testing. For each clinical syndrome and for each test category at each level of the laboratory system, testing should be identified as available, not fully available/not ideal or not applicable (NA).

The results of this approach to identifying diagnostic gaps are shown in Table 1, which sets out the participants' informal consensus. Where tests were considered to be appropriate (i.e., applicable) for use at Level I or Level II, the table illustrates significant gaps in testing availability, especially at Level II. Indeed, only tests for UTIs were considered sufficiently available at both Level I and Level II. It is these gaps that should drive diagnostic R&D priorities against ABR.

Considering both the existing diagnostics and those in the pipeline to combat ABR, the landscape identifies the following specific gaps:

- inadequate near-patient testing for (i) biomarker-based, non-sputum-based detection of TB, (ii) patient triage evaluation for TB, (iii) sputum-based replacement for acid-fast bacilli smear microscopy and (iv) TB DST;
- little or no ability to perform simplified phenotypic bacterial ID (i.e., culture) and AST to enable definitive therapeutic decision-making at Level III, and potentially at Level II, in LMICs, particularly in the context of bloodstream infections (BSIs), especially sepsis;
- inadequate near-patient testing options for ID and AST for multidrug-resistant *Neisseria gonorrhoeae* (NG);

- few RDTs or easy-to-use, robust diagnostic platforms for use at Level I and/or Level II that can reliably distinguish between bacterial/nonbacterial infections from accessible, minimally invasive clinical specimens (e.g., whole blood, urine, stool and nasal swabs);
- no multiplex platform suitable for Level I and/or Level II settings to detect bacterial pathogens, including those causing BSIs, from multiple specimen types (without culture), including whole blood, with AST/resistance testing done on a separate platform or combined with AST/resistance testing done on the same platform; and
- no simple, easy-to-use test/platform suitable for use at Level I and Level II facilities for AST/resistance testing from multiple specimen types (without culture), including whole blood or other sample matrices (urine, stool, respiratory specimens), that could be used for reflex testing following positive bacterial ID results on another platform.

R&D priorities and TPPs

Based on the diagnostic gaps identified above, the following R&D priorities and suggested TPPs were identified:

- Improved near-patient testing for TB: to enable point-of-care assays capable of (i) detecting all forms of TB by identifying characteristic biomarkers or biosignatures in specimen(s) other than sputum; (ii) low-cost patient triage by first-contact healthcare providers to identify those patients who need further testing; (iii) replacing AFB smear microscopy for detecting pulmonary TB; and (iv) determining first-line regimen-based therapy via DST that can be used at the microscopy-centre level of the healthcare system.

Suggested action: These proposed TPPs have been developed. WHO will continue to support the development of the proposed diagnostics. For detail, see: https://www.who.int/tb/publications/tpp_report/en/.

- Simplified phenotypic ID and AST: to enable the performance of blood culture and AST in key resistance categories, in particular in BSIs (e.g., sepsis), at Level II and higher facilities. Proposed TPP has been published and is available at: <https://www.mdpi.com/2075-4418/9/1/10>.

Suggested action: Review published TPP and build on it as needed.

- Improved diagnostics for AST for NG: to provide a (i) rapid test to detect and distinguish

NG and *Chlamydia trachomatis* for use in primary care settings, and (ii) a comprehensive test to both confirm NG infection and enable genotypic resistance testing of NG infection in primary/secondary care settings. WHO, FIND, and the Global Antibiotic Research and Development Partnership are already developing TPPs for each of these tests, which are not yet publicly available.

Suggested action: Assuming alignment, support this work.

- Host response test(s): to provide additional tests to help distinguish between bacterial and nonbacterial infections at primary healthcare facilities. A consensus TPP for such tests has already been developed, but should be revisited to consider whether it should be refined/revised. The TPP is available at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0161721>.

Suggested action: Review/revise TPP and bring renewed attention to it.

- Multiplex platform to identify bacterial pathogens and perform AST/resistance testing without culture: to provide a platform suitable for Level II and higher facilities to identify a broad range of bacterial pathogens from whole blood, as well as from urine, stool, swabs, etc. (no culture required), and that optimally could perform AST/resistance testing on the same platform.

Suggested action: Develop consensus TPP.

- Simple stand-alone test for AST or resistance testing: minimally to perform testing at Level I and Level II settings without culture from various sample matrices, optimally including whole blood.

Suggested action: Develop consensus TPP.

Other considerations

In addition to the diagnostic R&D priorities and potential TPPs suggested by the diagnostics landscape, participants at the meeting also discussed what else should be done to enable dissemination and adoption of new diagnostics against AMR. There are numerous considerations that will have to be taken into account and addressed by stakeholders, including the private sector, to successfully implement such diagnostics. These include:

- staging strategies for market entry of diagnostic platforms;
- role of dual markets in enabling or hindering market entry of new, disruptive diagnostic technologies;

- strategies for targeting gaps in Levels I and II;
- strategies for prioritizing and adopting new technology platforms in-country; and
- reimbursement strategies for diagnostics to ensure uptake.

Role of WHO

Participants also considered what WHO's role should be in this endeavour. Possibilities for WHO involvement include:

- accelerating processes;
- conducting situational analysis – e.g., end-user survey evaluation benefits and harm, acceptability, values/preferences and risks/benefits of a new diagnostic;
- providing guidance on the use of existing tests as part of diagnostic stewardship;
- developing relevant diagnostic algorithms for existing or future tests;

- promoting and supporting procurement mechanisms on a global level;
- harmonizing regulatory policies;
- estimating needs for testing; and
- creating a Global Drug Facility-like model for AMR diagnostics.

WHO next steps

- Circulate meeting report within WHO and to meeting participants.
- Finalize the diagnostics landscape to combat ABR.
- As appropriate, refine or develop suggested TPPs in small groups and, where required, commence Delphi process to arrive at consensus TPPs.
- Consider expanding the landscape to include other pathogens (e.g., fungi, viruses).

Table 1. Gaps in syndromic testing at Level I and Level II healthcare facilities*

Purpose Syndromes	Fever without a known source	Sepsis	Sore throat, cough, URTI	TB ¹	Pneumonia, LRTI	Diarrhea	Visible skin/soft tissue infection	Wounds (traumatic and chronic)	Urethral and vaginal discharge	UTI
Level I										
Bacteria vs other	A	NA	A	A	A	A	NA	NA	NA	A ³
Bacterial ID (culture, RDT, ..)	NA	NA	A, B	NA	A, B	NA	NA	NA	A, B	NA
Antibiotic Susceptibility	NA	NA	NA	NA	NA	NA	NA	NA	A, B	NA
Resistance Testing	NA	NA	NA	NA	NA	NA	NA	NA	A, B	NA
Level II										
Bacteria vs other	A	NA	A	A	A	A	A	A	NA	A ³
Bacterial ID	B, C	B, C	A, B, C	A, B, C	A, B, C	B ² , C	A, B, C	A, B, C	A, B	A, B, C
Antibiotic Susceptibility	B, C	B, C	C	A, B, C	B, C	B ² , C	B, C	B, C	B, C	A, B, C
Resistance Testing	B, C	B, C	C	A, B, C	B, C	B ² , C	B, C	B, C	B, C	C
If test desired	Available					Not fully available or ideal		Not available		

A Reduce unnecessary antibiotic prescriptions, B Guidance for appropriate treatment of drug-resistant infections, C Surveillance

*Based on informal consensus of participants attending the Technical Consultation on In Vitro Diagnostics for AMR.

Notes:

¹ MTB, the cause of human tuberculosis, was not subjected to review for inclusion in this prioritization exercise as it is already a globally established priority. And although priority TPPs to stimulate product development have been developed, more innovative new TB diagnostics are urgently needed. The section on TB was provided by the WHO Global TB Programme.

² In case it is needed in special populations.

³ Infection marker.

Annex A – Technical Consultation on In Vitro Diagnostics for AMR

27–28 March 2019, WHO headquarters, Geneva, Switzerland

Final agenda

Meeting objectives:

- Review landscape of in vitro diagnostics for AMR.
- Identify gaps.
- Agree on an R&D priority list for AMR diagnostics.
- Identify priorities for TPPs for highest-priority AMR diagnostics to be developed.

Day 1: 27 March 2019		
Time	Session	Presenter
09:30	Registration and welcome coffee	
10:00	Opening remarks and round of introductions	Marc Sprenger
10:30	Review of objectives, agenda and expected outputs of meeting	Francis Moussy
10:45	Conflict of interest management	Francis Moussy
11:00	Presentation and discussion of landscape analysis of AMR diagnostics <ul style="list-style-type: none">• Scope and methodology• Brief discussion on TB and GLASS• Context: laboratory systems in LMICs	Maurine Murtagh & all
12:30	Lunch	
13:30	Presentation and discussion of landscape analysis of AMR diagnostics <ul style="list-style-type: none">• Bacterial pathogen ID	Maurine Murtagh & all

预览已结束，完整报告链接和二维码如下：

https://www.yunbaogao.cn/report/index/report?reportId=5_25094

