Ad hoc consultation on rapid methods for antimicrobial susceptibility testing at point-of-care in lower- and middle-income countries

8-9 April 2014
Geneva, Switzerland
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ACKNOWLEDGEMENTS

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The success of the consultation would not have been possible without the outstanding contributions of the participants.

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFRO</td>
<td>WHO Regional Office for Africa</td>
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<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
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<td>AST</td>
<td>Antimicrobial susceptibility testing</td>
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<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
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<td>CMPT</td>
<td>Clinical microbiology proficiency testing</td>
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<tr>
<td>DARPA</td>
<td>Defense Advanced Research Projects Agency</td>
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<tr>
<td>DOD</td>
<td>United States Department of Defense</td>
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<tr>
<td>EQAP</td>
<td>WHO External Quality Assessment Project (EQAP)</td>
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<td>EUCAST</td>
<td>European Committee on Antimicrobial Susceptibility Testing</td>
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<tr>
<td>ID</td>
<td>Infectious disease</td>
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<tr>
<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
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<td>GAP</td>
<td>Global Action Plan</td>
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<tr>
<td>HCAI</td>
<td>Healthcare-associated infection</td>
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<tr>
<td>LMIC(s)</td>
<td>Lower- and middle-income country/countries</td>
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<td>MRSA</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
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<tr>
<td>NAAT(s)</td>
<td>Nucleic acid amplification techniques</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>POC</td>
<td>Point of care</td>
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<tr>
<td>QA</td>
<td>Quality assurance</td>
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<tr>
<td>SLIPTA</td>
<td>Stepwise Laboratory Quality Improvement Process Towards Accreditation</td>
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<tr>
<td>SLMTA</td>
<td>Strengthening Laboratory Management Towards Accreditation</td>
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<tr>
<td>SOP(s)</td>
<td>Standard operating procedure(s)</td>
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<tr>
<td>STAG</td>
<td>Strategic and Technical Advisory Group</td>
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<tr>
<td>TPP</td>
<td>Target product profile</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHONET</td>
<td>Windows-based database software for management and analysis of microbiology laboratory data (with focus on analysis of antimicrobial susceptibility test results)</td>
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EXECUTIVE SUMMARY

As the United Nations (UN) agency for health, the World Health Organization (WHO) recognizes the importance of the growing problem of antimicrobial resistance, the particular problems this causes in lower- and middle-income country (LMIC) settings, and the need for stakeholder consensus to address these problems.

WHO convened an ad hoc consultation on rapid methods for antimicrobial susceptibility testing at point-of-care in LMICs in Geneva from 8 to 9 April 2014. The objective was to facilitate dialogue between stakeholders including subject matter experts, representatives from industry, academia, NGOs, WHO and others, with the goal of creating a roadmap to stimulate development of and access to suitable rapid diagnostic tools for antimicrobial susceptibility testing (AST) at all levels of healthcare in LMICs, with an emphasis on point of care, where need is greatest. Discussion also covered the need for diagnostics for bacterial versus viral differentiation, and for pathogen identification.

The principal outcome of the meeting was the framework for this roadmap, as follows:

- In addition to the target product profiles (TPPs) of the necessary diagnostic tools, the roadmap should cover related barriers and enablers, including regulatory issues; distribution issues; education and training; vendors; supply chains; tariffs; government support for hospitals; reimbursement; and market opportunities and risks for industry.

- The roadmap for diagnostics tools against AMR should be divided into three functional areas:
  1. Policy and awareness
  2. Building of human, laboratory and systems capacity, including implementable standard operating procedures (SOPs)
  3. Developing technology applicable in LMICs.

- The roadmap should be integrated within the WHO Global Action Plan on AMR currently under development.
As an immediate first step, participants suggested that working groups be organized to address the following tasks, which constitute part of the third functional area proposed above (i.e. developing technology applicable in LMICs):

- Coordinating the necessary mapping of existing diagnostic tools for AMR
- Assessing the needs and developing TPPs, with clear definitions of point of care and, if relevant, of any tiering of health systems
- Coordinating market analysis for diagnostics in response to the TPPs.

This meeting report summarizes the proceedings and outcomes of the forum.
Note to the reader

Because of the richness of the discussion and in an attempt to keep this report simple and readable, comments are not attributed unless their content renders attribution necessary.

This report attempts to condense the themes of each session – including the interventions from the floor – according to the themes addressed, rather than attempting to provide a chronological summary of the dialogue.
**BACKGROUND**

Antimicrobial drug resistance is a growing global threat to health security. Drugs that were previously efficacious to treat infectious diseases are rapidly losing their effectiveness due to a combination of overuse and misuse of antimicrobial drugs in both people and animals. Some of the most effective drugs to treat – for example – malaria, tuberculosis, gonorrhoea, and infections due to pathogens such as Acinetobacter spp., E. coli and Klebsiella spp. are now useless in some parts of the world. Common community-acquired bacterial infections, including those affecting urinary and respiratory tracts, are also becoming more difficult to treat.

Antimicrobial susceptibility testing is therefore becoming more essential in order to guide the treatment of many types of infectious diseases. The usual method for characterizing antibiotic resistance following pathogen identification is to detect phenotype resistance by measuring bacterial growth in the presence of the antibiotic being tested. This method is highly sensitive but is not suitable for local health care centres due to cost and complexity – obstacles for widespread use in many developing countries. In addition, its long incubation time does not allow prospective intervention with specific treatment, thus obliging physicians to initiate the use of broad spectrum antimicrobial agents, a leading contributor to AMR.

Newer approaches such as PCR (e.g. GeneXpert for TB) and other nucleic acid amplification techniques (NAATs) are now being introduced in developing countries, but still in a limited fashion. In addition to NAATs, novel approaches such as those based on microfluidics, microarrays, mass spectroscopy and whole genome sequencing also offer the potential for rapid detection of antimicrobial drug resistance. However, the applicability of these techniques in LMICs remains to be demonstrated.

In order to stimulate the development of and access to affordable and appropriate technologies for antimicrobial susceptibility testing (particularly at the point-of-care (PoC)), WHO convened a consultation of experts on rapid methods for antimicrobial susceptibility testing in LMICs.

The consultation had the following goals:

- Review the status of antimicrobial susceptibility testing (AST) in LMICs
- Review current AST methods
- Review new methods and their potential for use in LMICs
- Develop a road map to stimulate the development of and access to suitable rapid diagnostic tools for AST in LMICs (with a focus on PoC tools).
OPENING REMARKS

Dr Marie-Paule Kieny, Assistant Director-General, Health Systems and Innovation Cluster, World Health Organization

Dr Kieny welcomed the participants to the forum and to Geneva, noting participation from diagnostics users, NGOs, academia and the diagnostic industry. She pointed out that antimicrobial drug resistance is a growing global threat to health security, and that many of the most urgent concerns relate to bacteria and antibiotic resistance. In order to address this problem, she said, in September 2013 the WHO Director-General set up a Strategic and Technical Advisory Group (STAG) on Antimicrobial Resistance. The STAG recommended that WHO work with life-science industries and other sectors to facilitate the development, application and evaluation of (i) diagnostics and diagnostic tools; and (ii) new treatment and prevention options, including new business models to encourage investment in and preservation of new products.

Dr Kieny pointed out that antimicrobial susceptibility testing (AST) is increasingly essential to guide treatment of many types of infectious diseases, and that WHO wants to stimulate development of and access to affordable and appropriate technologies for AST at point-of-care in developing countries. She then outlined the goals of the consultation:

- To review the needs and status of antimicrobial susceptibility testing (AST) in LMICs as well as the current AST methods used
- To review new technologies and their potential for use in LMICs
- To develop a road map to stimulate development of and access to suitable tools for AST in LMICs (with a focus on point-of-care tools).

Dr Keiji Fukuda, Assistant Director-General, Health Security and Environment Cluster, World Health Organization

Dr Fukuda also welcomed participants and thanked the meeting organizers. He noted the unusual circumstance of having a meeting opened by two Assistant Directors-General as evidence of the importance WHO now lends to AMR. Attention to AMR, he said, is in midst of a major transition from public health concern to international priority. WHO is stepping up in response – with deep engagement at headquarters, regional and country levels – and elevating work in this area to a previously unseen degree. Dr Fukuda summarised the public health repercussions of AMR and its adverse impacts on health and society, pointing out that solutions will require engagement by broad mix of stakeholders.
Dr Fukuda informed the meeting that Member States would adopt a resolution reflecting this transition at the World Health Assembly in May 2014, calling on WHO to develop a Global Action Plan, or GAP, that will form the basis for ensuring that all countries, especially LMICs, have the capacity to counter antimicrobial resistance. Before the Assembly, he said, a meeting of the STAG was imminent, at which core elements of the GAP would be determined; one purpose of today’s meeting would be to feed into that process.

Enhanced diagnostic capacity, Dr Fukuda continued, will be an essential element of the GAP, lending particular importance to this consultation. While other important initiatives are underway worldwide to develop rapid diagnostic tests, this meeting would complement existing actions by WHO and other stakeholders by focussing on closing the equity gap between LMICs and developed countries in terms of access to technology.

Dr Fukuda concluded by wishing participants a fruitful discussion.
PRESENTATION OF OBJECTIVES OF THE CONSULTATION

Dr Francis Moussy, Scientist, World Health Organization (HIS/EMP/PHI) and meeting organiser

Dr Francis Moussy, organiser of the meeting, presented the context of the discussion to come, underlining the role of diagnostics in remedying mis- and over-use of antibiotics. He defined “diagnostics innovation” in the context of this meeting as:

To facilitate the development of and access to low cost, robust, quality assured and appropriate diagnostics with a particular focus on the point-of-care in low- and middle-income countries.

Dr Moussy then outlined WHO’s work in facilitating the development of diagnostics, emphasising the development of target product profiles (TPPs), standardization, and facilitation of interoperability. The goal of the meeting was then described:

The development of a road map to stimulate the development of and access to suitable tools for AST in LMICs

Dr Moussy concluded by summarising the meeting’s expected outputs as a better definition of needs and barriers; a summary of current technologies used and the potential for newer technologies in the pipeline; and the foundation of the road map.

STRATEGY FOR GLOBAL SURVEILLANCE OF AMR

Dr Sergey Eremin, Medical Officer, World Health Organization (HSE/PED)

Dr Sergey Eremin then took the floor to outline WHO’s global strategy for surveillance of AMR. He elaborated on current problems and pointed out that these are underpinned by major gaps in global information, then detailed WHO’s strategy and role in providing guidance and available tools and resources. A précis was given of WHO Member States’ action against AMR to date, highlighting their contribution at the World Health Assembly and the creation of the STAG; the achievements of WHO’s disease-specific programmes to counter AMR; and recent initiatives by governments.

Dr Eremin then outlined WHO’s roadmap for global surveillance to define AMR worldwide, which he said was sorely needed and which he described as follows: standard surveillance methodologies with focus on antibiotic resistance (target: 2014-2015); a collaborative platform for global surveillance (2014-2015); and pilot surveillance studies (target: 2015-2016). He also highlighted the forthcoming publication on April 30 2014 of WHO’s Global AMR Report, which will focus on antibacterial resistance and will contain national or published data in nine defined “bug-drug” combinations; systematic reviews of health and economic burdens; information on the availability of data and existing surveillance; and summaries of surveillance and AMR in disease-
specific programmes (TB, Malaria, HIV and Influenza) and related areas (food chain, antifungal resistance etc.).

Existing surveillance gaps were then described: a lack of common targets and methods; a lack of basic data on the AMR burden; a lack of integrated surveillance across humans and animals; and variable use of data to inform policies and guidelines. Counter to this, Dr Eremin then described the rationale for surveillance, which he summarised as “data for action”: to inform public health actions; to identify priority areas for interventions; to inform on the magnitude and economic impact of the problem; and to support monitoring and evaluation of actions against AMR. Its objectives are to provide an up-to-date picture of the magnitude of antibiotic resistance, to monitor trends, to assess impact and to improve early detection of new resistance patterns.

Dr Moussy concluded the session by handing the Chair to Dr Olga Perovic of the University of Witwatersrand in South Africa for the remainder of the meeting.

Dr Perovic greeted the meeting and noted the impressively wide attendance; her hope for the consultation, she said, was to engage diagnostics companies in realising the dream of achieving WHO targets for prevention of AMR.
SESSION 1: **NEEDS FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING AS PERCEIVED BY END USERS IN LOWER- AND MIDDLE-INCOME COUNTRIES**

**Moderator:** Dr Olga Perovic, University of Witwatersrand, South Africa

**Presenters:** Dr Celia Carlos, Philippines; Dr Olga Perovic, South Africa (presenting for the African region); Dr George Araj, Lebanon

The first session was composed of three presentations outlining the picture of AMR in the Philippines, the Africa region and Lebanon respectively. These provided a spectrum of different types of country and regional experience, from the middle-income context of the Philippines, where much of the difficulty in implementing AST is in convincing government of the importance of diagnostics; to the extremely resource-limited settings of parts of Africa lacking basic equipment and infrastructure; to Lebanon, where the health system has frequently been disrupted by war, and the country – with a basic population of just over 4m – must currently also cater for 1.5 million refugees from Iraq and Syria.

The meeting learnt about demographic and health systems contexts in all of these areas, with particular focus on lab capacity and surveillance. The speakers gave a rapid global tour of the need for AST as perceived by end users; the demand and decision-making processes for testing in different resource-limited contexts; and the various methods currently in use. They also highlighted the challenges and barriers to AST in LMICs settings, many of which were associated with a lack of capacity – human and technical – and the costs associated with building it. While the range of contexts under discussion was very wide, the general picture was one of high need, with widespread difficulties and some isolated successes, and of a shared desire for a greater range of clinically relevant, rapid and cost-effective diagnostic solutions.

There was some discussion of the nature of cost-effectiveness in the wider health economics context but a consensus was reached that for the purposes of this meeting “cost” referred to the price of technologies, consumables and direct running costs.

In addition to brief Q&A sessions after each presentation, an hour of open discussion followed on issues surrounding antimicrobial susceptibility testing in lower- and middle-income country contexts. In summary, with some regional variations, perceived barriers to AST in LMICs are organised around a few major themes:

- A lack of harmonisation and standardization of diagnostic methods/techniques
- Lack of supplies and equipment
- Insufficient or outdated training (lack of experts)
- Difficulties in quality control/assurance stemming from paucity of training, logistical and capacity issues, and cost barriers
Lack of buy-in from national, regional and hospital authorities

Poorly functioning infrastructure (with wide variations in infrastructure between different contexts)

Poorly functioning accreditation and/or certification

Reimbursement and cost issues: lack of government/reimbursement structures, guidelines and control (often with the patient paying for diagnostics)

Overheads that increase the price per test (for example, extra distribution costs imposed by intermediate parties)

Overload of laboratories

Lack of awareness of AMR

Lack of coordination/interaction between treating physicians and laboratory staff.

There are also common themes with regard to perceived needs:

Capacity building through training

Essential diagnostics

Further research to build evidence for new ID and rapid AST testing

Improved surveillance for AST, with high quality data

Better coordination at national and subnational level, especially between labs

Specific diagnostic needs at community level include: rapid time to results; viral versus bacterial differentiation; and antimicrobial susceptibility testing.
**SESSION 2: REVIEW OF CURRENT STATUS OF ANTIMICROBIAL SUSCEPTIBILITY TESTING IN LMICs AND THE AST METHODS USED**

**Moderator:** Dr Olga Perovic, University of Witwatersrand, South Africa

**Speakers:** Dr Jan Jacobs, Institute of Tropical Medicine, Antwerp; Mr Jean-Baptiste Ronat, Laboratory advisor, Médecins Sans Frontières (MSF)

The afternoon began with two presentations designed to give the audience a better understanding of life on the ground in low-income settings. Dr Jan Jacobs of the Institute of Tropical Medicine in Antwerp gave the first talk, providing a rapid overview of current AST methods both in hospitals and at point-of-care in resource-limited settings. His presentation covered national approaches and commitments, the rational use of antibiotics in hospitals and in communities, the state of education and changing norms, infection control, the role of diagnostics, and antibiotic use in animal health. He identified a number of key issues: human capacity and lack of training was emphasised again, as it had been earlier in the day, but Dr Jacobs also pointed out that the context for discussion of AMR was weakened by important research gaps and by substandard regulation and control in LMICs, leading to an incomplete picture of the problem. On the technical side, he argued that sample preparation and handling is the real bottleneck at point-of-care, and that any new or updated diagnostic solutions needed to be usable in resource-limited settings, which in real terms could mean by staff without training as health professionals and working with no infrastructure (e.g. without electrical power). Pointing out that rapid diagnostics for malaria are currently being used at a rate of 150m per year, he also emphasised that scale of production should keep up with need.

There was some discussion of how exactly to define of point of care – while a number of definitions exist, Dr Jacobs suggested a focus on very low income countries, remote settings, with tests carried out by people who are not health professionals, in communities without lab infrastructure and possibly even in homes.

In conclusion, Dr Jacobs said that while “traditional” laboratories are slow, they are robust. New approaches needed to be designed for speed, and for use at an extremely basic point of care that might lack even the most basic infrastructure. In addition, they must also be robust, and suitable for an end-user who is not a health professional.

Mr Jean-Baptiste Ronat of Médecins Sans Frontières (MSF) gave the next presentation, providing an overview of existing solutions in LMICs that reinforced many of the themes discussed earlier in the day. His presentation provided a summary of contextual issues and a breakdown of current access to technology in low-income countries. Among the limitations he listed were a lack of standardized diagnostic methods; shortages of funds, consumables, and basic equipment; a lack of skilled personnel, training programmes, and logistical support; and a lack of national standards or quality assessment programmes.
with which to remedy the above.

Mr Ronat also identified key issues in terms of actions at point-of-care that contribute to the growth of AMR in these settings, including: the prevailing trend of a syndromic approach to treatment; the fact that in many low-income settings it costs less to treat than to test, with AST a time- and money-consuming option that is often not possible or not considered practical; and issues of public awareness leading to widespread pressure from patients to be treated with antibiotics. The talk also emphasised the issue of logistics surrounding diagnostics, which was to become a major theme of discussions.

Providing a quick comparative summary of the limitations of different diagnostic methods, Mr Ronat concluded by identifying a few trends in low resource settings. Existing strong financial support for epidemics or particular pathogens (avian flu, STDs, hepatitis, etc.) he considered to be working well, in contexts where clinical bacteriology departments otherwise tend to survive by treating very rare specimens and using scarce revenue to buy two or three essential media whenever possible. Using the example of AIDS programmes, he argued that results in countering infection are dramatically better in situations where a combination of easy rapid tests allows patients to get their results within a day. To fight AMR, he said, increased awareness of the problem was essential on the part of the public, prescribers and investors. When this was achieved, he predicted the creation of a market opportunity in LMICs for point-of-care diagnosis of bacterial versus viral infection; the development of more robust and easy-to-use AST methods; and the reinforcement of existing AST methods.
**Discussion**

A lively discussion took up the rest of the afternoon as the meeting considered the suitability of current tools available for AST in LMICs, and the barriers to access. The following themes emerged.

**General themes**

- Distinction between the broader LMIC category and real resource-limited settings is significant. In some LICs there can be no lab infrastructure at all, and 75% of health posts in Africa have no electricity. This understanding is crucial to framing diagnostic approaches.
- The limits of such settings are often exacerbated by poor or absent quality control and quality assurance mechanisms.
- “Point-of-care” must be clearly defined.
- Industry desires a tighter definition of target product profiles.
- Addressing barriers to access requires systematic approaches at country level.
- Increasing awareness and market opportunities is a priority.

**Diagnostic needs**

Various needs for multiple diagnostic approaches were indicated in the discussion, but some consensus was achieved:

- There are parallel needs for laboratory and point-of-care; while different products are needed for different settings there was some consensus within the meeting that point-of-care is where highest impact can be made.
- Simple tests are needed for use in the field or lower-level labs.
- The priority need is for rapid tests to distinguish between bacterial and viral infection. The next need is tests for pathogen identification; and then tests for susceptibility patterns.
- Consumables for use in LMICs have to be cheap.
- Diagnostics must be designed to fit into the patient care management system; whatever the target, the results should be unequivocal. If non-clinical healthcare workers were provided with simple diagnostics that allowed them to refer immediately then lives would be saved.
- Issues outside the capabilities of the core technology need to be part of the roadmap, including manufacturing barriers, updating schedules, servicing, distribution, cold chain etc.
- Antibiotic stewardship is critical; this must be backed up by medical staff who resist public pressure to provide antibiotics. Some LMIC experience suggests that 40-60pc of patients at point of referral are already on antibiotics, either supplied to them or self-administered.

- WHO should convene a working group to develop targeted product profiles. A number of existing consortia are already examining different aetiologies in different settings that could feed into the work of this group.

**Engaging industry**

A number of incentives and incitements are possible to encourage industry to engage with this task, including:

- Providing clarity about requirements and TPPs in terms of sensitivities and specificities, specimen types and expected usage environments - bearing in mind the trade-offs between different capabilities.

- Recognition that industry is not a closed environment, and many products start with academics, start-ups and publicly-funded research efforts.

- Minimising the risk to industry - examples were cited of the approach of the Gates Foundation and others in identifying companies with the technology to fulfil clearly-established requirements targeting specific diseases and backing several such companies, thereby reducing the odds of failure both for the companies and for the project.

**Human capacity in LMICs**

- Major gaps are as much to do with people as they are to do with tools and technology: diagnostic tests of any kind must influence clinical practice through medical staff who can interpret and act correctly on test results.

- Gaps in training, and in SOPs that are implementable and sustainable, are critically important.

**Accreditation**

- Accreditation professionals and bodies should be included in discussions to shape strategy.

- Unless engagement and support is offered from accrediting bodies, accreditation processes can place a great burden on labs; this may prevent voluntary accreditation schemes from working in resource-limited settings. The alternative of mandatory accreditation can only be borne by strong systems that may be absent in most LMICs.

- Even in high-income countries accreditation is difficult to achieve due to high costs.
Discussion of accreditation must be pragmatic in resource-limited settings, where the priority may be to achieve basic laboratory capacity, then apply step-by-step, internal and external quality assessment and then accreditation only to the more capable facilities.

**Standardization, market shifts and regulatory issues**

- Standardization exists but problems lie with implementation in labs.
- Efforts are underway worldwide to create greater harmonization of standards but further effort and funds are needed; this is a long term process.
- There is need to balance the conflict between the use of closed systems, exclusively confined to one vender and methodology, with the widespread call for open systems that broaden access to diagnostic testing; clear definition will be needed of any proposed “open system.”
- There is a need to develop solutions for less profitable markets in remote settings.
- Proliferation of regulations in different markets is a problem for manufacturers. A number of initiatives exist to counter this but it remains a significant barrier
- Regulatory systems must adapt accordingly: there is a need for faster approval mechanisms to engage with the needs of LMICs and provide faster evaluation and assessment by recognised entities.
- Diagnostic tests should be evaluated in target populations and settings, including consideration of environmental conditions for transport/storage and disposal of consumables.

**Role of WHO**

- WHO, particularly through WHO country offices, has a key role to play in raising awareness of AMR, targeting the public, health workers, and investors.
- WHO should also raise awareness of the fact that discussion around diagnostic priorities relates to many of WHO’s other accepted strategic priorities (for example, the right diagnostics are fundamental to the discussion around essential medicines).
- WHO should take the initiative in quality control and quality assurance, devising a system to implement with governments.
**SESSION 3:** REVIEW OF NEW METHODS AND THEIR POTENTIAL FOR RAPID ANTIMICROBIAL SUSCEPTIBILITY TESTING IN LMICs

**Moderator:** Dr Olga Perovic, University of Witwatersrand, South Africa

**Speakers:** Dr Michael J. McConnell, Instituto de Biomedicina, Seville; Dr Pierre Bogaerts, NRC for AR in Enterobacteriaceae and non-fermenters, Belgium; Dr Andrea Endimiani, Institute for infectious Diseases, University of Bern, Switzerland; Dr Paul J.A. Kenis, University of Illinois at Urbana-Champaign

The second and final day of the meeting began with four presentations. The first provided an overview of existing methods of rapid antimicrobial susceptibility testing; subsequent talks provided more detailed respective explorations of PCR-based techniques, microarrays and microfluidics.

Dr Michael McConnell gave the overview, reminding the meeting of the context of discussions so far, then briefly summarising each of the major alternative AST methods, and the strengths and limitations of each approach. The presentation covered established methods – detection of genetic determinants of resistance, flow cytometry, real-time microscopy, metabolomics and RNA sequencing – and a précis of associated challenges. These challenges were identified as achieving high correlation with phenotypic resistance testing; detection of uncharacterised resistance mechanisms; direct use with clinical samples, without need for purity culture; and provision of MIC data (or approximations). Specific barriers to their use in LMICs settings included the expense of associated infrastructure (real-time PCR, mass spectrometry); the need for operation by highly trained personnel (PCR, whole genome sequencing); the robustness of reagents and devices; and an inability to provide results at point of care. Dr McConnell concluded with the observation that while progress has been made in the development of rapid AST methods, there is still much work to do before an ideal method is achieved; and that significant – but not insurmountable – obstacles remain to applying existing methods in resource-limited settings.

Dr Pierre Bogaerts then addressed NAATs at point-of-care, defining POC as outside a central lab with a dedicated room for molecular diagnostics. His presentation outlined a number of key issues to be held in mind when considering the decision-making for such methods (method of amplification and choice of targets, interpretation of results, controls, transmission of results, waste management, etc.). It then provided an overview of detection technologies currently in use, including PCR-based methods and a LAMP-based system, and a list of those POC platforms potentially in use in the near future.
A list was also provided of commercial real-time kits designed for use away from point of care. One conclusion was that there is still a significant gap between point of care PCR-based technologies and detection kits. The presentation reminded the audience that real-world usefulness of technology is defined by asking the right questions about targets and having the capacity to interpret results correctly. He also discussed the safe disposal of biomedical waste in the LMIC context. Dr Bogaerts’ conclusions were that there is a need to develop new kits with technologies adapted to point of use, with targets identified according to the epidemiology. The context of use and complexity of the interpretation of results need to be considered in their design, as detection of resistance genes does not always correlate with phenotypic resistance.

The next presentation was given by Dr Andrea Endimiani of the University of Berne, who provided an overview of the basic concepts of microarrays and their potential applications in clinical biology. Dr Endimiani focussed on DNA microarrays to detect genetic resistance, explaining the working methods and the systems used for detecting target DNA and outlining typical workflows and their impacts on patient outcomes and the costs of the health care system. In order to improve capacity to work, he argued, rapid, standardized and easy-to-use commercial platforms are needed, though there are drawbacks in terms of the resources necessary to run these methods. Dr Endimiani summarised the advantages of microarrays as strength in the simultaneous detection of multiple drug-resistance genes; ease of use; flexibility and updateability; and the ability to accommodate large collections and clinical samples. The downsides he summarised as only moderate speed; an inability to detect novel mechanisms; potential for cross-hybridisation; expense and a need for apparatus.

In the final presentation of the meeting Dr Paul Kenis ran through a non-exhaustive list of examples of microfluidic applications – some simple, some very advanced and some in between. The advantages of the technology he listed as the ability to work with small sample volumes, allowing greater number and speed of tests and simplifying shipping of samples; exquisite control over transport phenomena; and a cheapness, safety and efficiency that permit a wide range of applications. While complex microfluidic systems can be very expensive and are not portable, small, self-loading chips can produce reliable diagnostic results. His conclusions were that microfluidics can do many different things, some sophisticated, some simple, with the latter displaying great potential for use in low-income settings. Simpler systems offer a wide range of possibilities and can be changed quickly to get simple answers; but to adapt advanced systems it is necessary work with developers, and developing more complicated chips takes time and is very expensive. Dr Kenis characterised the biggest hurdles for the technology in resource-limited settings as defining the necessary tools and providing microfluidics scientists/engineers with guidance on specific targets; integrating and simplifying sample preparation; and simplifying the readout of results.
**CLOSING SESSION: DEVELOPING THE ROAD MAP**

*Moderator: Dr Olga Perovic, University of Witwatersrand, South Africa*

Dr Perovic introduced a rich and wide-ranging final discussion by laying out targets for participants. In the final session, she said, the meeting would try to clarify the nature of the desired technology; differentiate between short- and long-term options; decide on the level of labs that should be covered; define point-of-care; and discuss whether a syndromic approach is preferable to one that is directed and specific.

Broadly speaking, the main threads of the discussion turned out to be a need for improved mapping of the current global situation in terms of AMR, technology, and lab and health system capacity; the need for improved market analysis to help industry; and the need for clearer identification of needs to feed into the TPPs.

The following specific points emerged.

**General themes**

- **Awareness of AMR is not high**, partly because there has been no endorsement of its importance from most governments. LMICs typically face numerous and diverse challenges that compete for attention and funds, and raising awareness of AMR is a major priority.

- A **review of current methods** may be necessary to counter AMR in the short term: several alternatives exist today that can provide short-term solutions to resistance and mortality. As no product will fit all cases, and given varying conditions at different levels of healthcare settings in LMICs, it is likely that there is room for several technologies of different complexities to be employed.

- The **level of professional education in LMICs** must define all other efforts; the user of the technology is of critical importance in planning. Whatever technology is introduced must fit the ability of the end user to understand and deploy it.

- **Planning must combine decisions about technologies with a focus on building up and improving diagnostic workflow**; initial diagnoses at point of care can later be referred to settings with greater infrastructure in order to define emerging resistance markers and AST in combination with molecular diagnostic tools.

- **Production, distribution and quality control of what is in the field** are key limiting factors. Getting technology diffused into the field and into the mind of the end user is a challenge fundamental to the use of any technology.

- **Regulatory issues** must be addressed.
Defining LMIC needs

- The consultation revealed a struggle between different sets of needs: there is consensus that a better definition of needs is required, geographically specific based on the classification of different healthcare settings.
- It was suggested that follow-up meetings should include direct representation from medical professionals working in low-resource settings, and the pharmaceutical industry.
- At the point of creating target product profiles (TPPs), emphasis should not be on technology but on performance – clarity about what exactly the product should do.
- Needs will include tools for use at point-of-care in isolated, rural and community settings.
- It is important for companies to validate needs and goals before committing to the development of products.
- While TPPs for suitable AST devices have yet to be formed, in the shorter term a simple test to differentiate between bacterial and viral infection could contribute significantly to a reduction in the unsuitable use of antibiotics.

Resources, research and surveying

- WHO’s global report on AMR surveillance will be launched on 30 April 2014 and attempts to provide a map of the global AMR situation, covering all regions and countries.
- WHO provides an essential medicines list and a survey of pricing of medical devices.
- WHO Member States could benefit from a thorough taxonomy of available devices, relevant approvals and means of purchase as a template of prequalified products. A number of publications exist that review available AST options, and market reviews have also been done, but not all of this information is in the public domain, some is covered by non-disclosure agreements, and many of the relevant articles are in journals that have to be purchased.
- Attention should be given to up-to-date surveys and classifications of LMIC health care settings according to their capabilities; this is crucial in terms of knowing where to place the appropriate technology.
- Surveillance is crucial and must be kept in mind as the STAG does its job: what pathogens are surveyed and where?
- Sample databases and strain collections are very useful. Many of these already exist; they should be enhanced and shared as widely as possible.
- To engage larger manufacturers, more information is required on the nature of the global market – for example, prevalence of resistance markers for different areas of the world.
One possible way forward would be an in-depth landscape analysis, mapping existing technology and feasibility of use in target settings.

**Industry**

- The key to success in LMIC contexts is specificity and tight focus: addressing TB, for example, allows clear definition of the market and the opportunity.
- Smart partnerships unlock opportunities – examples were cited of industry’s work with WHO, the Gates Foundation, FIND, the DOD and DARPA.
- New staff are not generally hired to meet LMIC diagnostic demands; companies work with what they already have. Assessing the best use of people at a given time therefore requires examination of both opportunity and opportunity cost. This trade-off has to be part of the discussion of how to motivate corporate sector.
- To incentivise companies, stakeholders should follow industry’s development model: companies tend to hold regular meetings to rank opportunities for developing new products against one another, focussing on the ROI for new products. In terms of LMIC requirements, “win-win” situations where new products can work in developing and developed countries will push products up the ranking. In addition, as companies launch new products (related to HIV, for example), their worldwide footprint is expanded in favour of the LMIC marketplace.
- To create interest, it is necessary to create a “buzz” around AMR, as has been the case with – for example – tuberculosis.
- Allied with a precise understanding of needs, market research is an effective way to pull companies into the field: the example was cited of WHO’s thorough study, publicly available, of the market for TB diagnostics.
- There are lessons to be learnt from what’s been done in other areas, and particularly in TB and HIV; for example, FIND has published work on what’s available worldwide in terms of technology, skills, power, infrastructure etc.
- Industry could do more to clarify pricing logic.

**Role of WHO**

- WHO should ensure the prominence of diagnostics in the work of the STAG, considering rewording the phrase “antimicrobial stewardship” to reflect the importance of diagnostics in effective stewardship.
- WHO should ensure that the STAG’s work on the global action plan considers means of incentivising companies to address specific solutions for LMIC settings.
- WHO could work with countries to reduce tariff barriers for product areas it identifies as important, in order to help industry deliver products as cheaply as possible to the maximum number of patients. WHO has a comparative diplomatic advantage in this area.
WHO could consider expanding its prequalification scheme to diagnostics for AMR as well as including them in its bulk procurement scheme.

WHO can act as a provider of information to help industry evaluate market potential.

WHO should consider organising a movement for standardized protocols for fast testing and evaluation of diagnostics, for situations where rapid response is required to emergent resistance genes.

WHO should consider recruiting someone with an industry background to filter this work according to an informed understanding of the technical landscape and a grasp of what is feasible for manufacture and deliverable to POC. Alternatively, WHO could consider subcontracting relevant work to an NGO with experience in this area (including any landscaping efforts that included naming and analysis of commercial entities).

The next stage of discussion should also involve representatives from pharmaceutical associations.

The roadmap

A roadmap is needed to facilitate the development, access to and use of suitable diagnostic tools to combat AMR at all levels of the health care systems in LMICs. The road map must take a systematic approach to analysing what is needed for this to happen, considering current diagnostic tools as well as new technologies.

In addition to the diagnostic tools themselves, it should also cover related barriers and enablers, including the regulatory situation; distribution issues; education and training; vendors; supply chains; tariffs; government support for hospitals; reimbursement; and the market opportunity and risks for industry.

The roadmap for diagnostics tools against AMR could be divided into three functional areas:

1. Policy and awareness
2. Building of human, laboratory and systems capacity, including implementable SOPs
3. Developing technology applicable in LMICs.

The roadmap should be integrated within the WHO Global Action Plan on AMR currently under development.
**Closing and Next Steps**

The Chair, Dr Perovic and Dr Moussy brought the discussion to a close and defined the next steps. Dr Moussy obtained consensus from the floor that developing working groups would be the next stage. He then told the meeting that a report of the consultation would be circulated for comment the following week, containing the themes of the discussion and allowing the generation of a list of potential topics for discussion therein. WHO would then organise small working groups and issue invitations. As a first step, these groups would address the following tasks, which constitute part of the third functional area of the proposed roadmap for diagnostic tools against AMR (i.e. developing technology applicable in LMICs):

- Coordinating the necessary mapping of existing diagnostic tools for AMR
- Assessing the needs and developing TPPs, with very clear definitions of point of care and, if relevant, of any tiering of health systems
- Coordinating market analysis for diagnostics in response to the TPPs.

It was then suggested that given the breadth and depth of the discussion, it was possible that some of the output of this joint workforce could help a number of other technical areas. Participants were encouraged to continue their mutual engagement beyond the consultation, and the suggestion was made that WHO host an electronic working group forum for subsequent discussion.

Participants were also encouraged to share discussions and related materials widely on return to their host institutions and countries.

The meeting was then closed.
### Agenda

**Geneva, Switzerland, 8-9 April 2014**

Kofi Annan Meeting Room, UNAIDS building, (directly opposite WHO HQ)

<table>
<thead>
<tr>
<th>TIME</th>
<th>Meeting Item</th>
<th>NAME</th>
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<tbody>
<tr>
<td>09:00 - 09:10</td>
<td>Welcome and Introduction of participants</td>
<td>Dr Marie-Paule Kieny, ADG HIS</td>
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<td>Dr Keiji Fukuda, ADG HSE</td>
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<td>09:10 - 09:20</td>
<td>Presentation of objectives of the consultation</td>
<td>Dr Francis Moussy, HIS</td>
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<td>09:20 - 09:30</td>
<td>Strategy for AMR Global Surveillance</td>
<td>Dr Sergey Eremin, HSE</td>
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<td>09:30 - 10:30</td>
<td>Need for AST in the Philippines (20 min.)</td>
<td>Dr Celia Carlos, Philippines</td>
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<td>Need for AST in Africa (20 min.)</td>
<td>Dr Olga Perovic, South Africa</td>
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<td></td>
<td>Need for AST in Lebanon (20 min.)</td>
<td>Dr George Araj, Lebanon</td>
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<td>10:30 - 11:00</td>
<td>COFFEE/TEA BREAK</td>
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<tr>
<td>11:00 - 12:00</td>
<td>Discussion focused on the need for AST in LMICs (60 min.)</td>
<td>All</td>
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<tr>
<td>Time</td>
<td>Session II: Review current status of AST in LMICs and the AST methods used. (review what is being done for AST in LMICs and description of the methods used as well as their suitability for LMICs) in hospitals and local health care centres</td>
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<td>13:30 - 15:30</td>
<td>Rapid overview of current AST methods both in hospitals and PoC (30 min.)</td>
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<td>Use of these methods in LMICs (30 min.) (how are these methods used in LMICs and what are the limitations?)</td>
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<td>Discussion focused on the suitability of the current tools available for AST in LMICs (60 min.)</td>
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<th>Time</th>
<th>COFFEE/TEA BREAK</th>
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<tr>
<td>15:30 - 16:00</td>
<td>Discussions focussed on the barriers to access for the current tools for AST in LMICs</td>
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<td>Summary of the day (definition of needs and barriers, and their impact on development of needed tests)</td>
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<td>Time</td>
<td>Session III: Review new methods and their potential for rapid antimicrobial susceptibility testing in LMICs (a general overview and 3 specific examples)</td>
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<td>08:30 - 10:30</td>
<td>General overview of new methods (20 min.)</td>
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<td>Example 1: PCR/NA- based techniques (20 min.)</td>
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<td>Example 2: Microarrays (20 min.)</td>
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<td>Example 3: Microfluidics (20 min.)</td>
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<td>Discussion (will also address other methods) (40 min.)</td>
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<td>10:30 - 11:00</td>
<td><strong>COFFEE/TEA BREAK</strong></td>
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<tr>
<td>11:00 - 13:00</td>
<td>Develop road map (with milestones and deliverables) to stimulate the development of and access to suitable tools for AST in LMICs</td>
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<td>13:00</td>
<td>Summary and next steps</td>
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<td>End of the consultation</td>
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ANNEX B — LIST OF PARTICIPANTS

Ad-hoc consultation on rapid methods for antimicrobial susceptibility testing at point-of-care in lower- and middle-income countries
Geneva, Switzerland
April 8-9, 2014

List of Participants

Dr George Araj, American University of Beirut, Lebanon
Dr Pierre Bogaerts, CHU UCL Dinant-Godinne, Yvoir, Belgium
Dr Rafael Cantón (also representing EUCAST), Hospital Universitario Ramón y Cajal Madrid, Spain
Dr Celia Carlos, Research Institute for Tropical Medicine, Department of Health, FILINVEST Corporate City, Alabang, Muntinlupa City, Philippines
Dr Arlene C Chua, Médecins Sans Frontières, Access Campaign, Geneva, Switzerland
Dr Jonathan M. Cooper, University of Glasgow, UK
Dr Andrea Endimiani, University of Bern, Switzerland
Dr Claudia Denkinger, Foundation for Innovative New Diagnostics, Geneva, Switzerland
Dr Ashley Grant, Department of Defense (DoD), Nuclear, Chemical, and Biological Defense Programs, Washington, DC, USA
Dr Jan Jacobs, Institute of Tropical Medicine, Antwerp, Belgium
Mr Jean-François de Lavison, Ahimsa Partners SAS, Lyon, France
Dr Paul J.A. Kenis, University of Illinois at Urbana-Champaign, Urbana, IL, USA
Dr Michael J. McConnell, Instituto de Biomedicina de Sevilla, Sevilla, Spain.
Dr Konstantinos Mitsakakis, University of Freiburg, Germany
Dr Carl Newman, Defense Threat Reduction Agency and USSTRATCOM Center for Combating WMD, Fort Belvoir, VA, USA
Dr Olga Perovic, University of Witwatersrand, Johannesburg, South Africa
Mr Jean-Baptiste Ronat, Médecins Sans Frontières – OCP, Paris, France
LTC Richard Schoske, Ph.D., Defense Threat Reduction Agency, Fort Belvoir, VA, USA
Dr Arjon Van Hengel, European Commission, Brussels, Belgium.

Dr Zhang Wenbao, National Health and Family Planning Commission, P.R. China

**Diagnostic Industry**

Dr Mike Brasch, BD (Becton, Dickinson and Company), Franklin Lakes, NJ, USA

Dr Martin Colla, Cepheid, USA

Mrs Manel Djiar, BioMérieux, Lyon, France

Dr Carlos Gouvea, Câmara Brasileira de Diagnostico Laboratorial, Sao Paulo, Brazil

Dr Merle Hanke, QIAGEN Lake Constance GmbH, Stockach Germany

Mr Manette Juvin (also representing EDMA), Bio-Rad, Marnes-la-Coquette, France.

Dr Oliver Liesenfeld, Roche Molecular Systems, Pleasanton, CA, USA

Mrs Tharini Sathiamoorthy, AdvaMedDx, Washington, DC, USA

Mrs Karen Schlein, Zyomyx, Inc., Fremont, CA, USA.

Dr Veronique Semjonow, Philips Healthcare Incubator, Eindhoven, The Netherlands

**WHO**

Dr Marie-Paule Kieny, ADG, Health Systems and Innovation Cluster

Dr Keiji Fukuda, ADG, Health Security and Environment Cluster

Dr Francis Moussy, Scientist, HIS/EMP PHI

Dr Carmen Pessoa Da Silva, Team Leader, HSE/PED

Dr Zafar Mirza, Coordinator, HIS/EMP PHI

Dr Sergey Eremin, Medical Officer, HSE/PED

Dr Christopher Oxenford, Technical Officer, HSE/GCR

Mr Jorge Matheu, AMRO/CHA/IR

Mrs Adriana Velazquez Berumen, Focal Point for Medical Devices, HIS/EMP/PQT

Dr Christopher Gilpin, Scientist, HTM/GTB/LDR

Dr Teodora Elvira C, Wi, Medical Officer, HQ/FWC/RHR/HRX

Ms José Schutter, Intern, HIS/EMP PHI

**Rapporteur**

Mr Mark Nunn, Chief Editor, Highbury Editorial, London, UK
Ad hoc consultation on rapid methods for antimicrobial susceptibility testing at point-of-care in lower- and middle-income countries

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