Guide for establishing laboratory-based surveillance for antimicrobial resistance

Disease Surveillance and Response Programme Area
Disease Prevention and Control Cluster
Guide for establishing laboratory-based surveillance for antimicrobial resistance
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<td>Acquired Immune Deficiency Syndrome</td>
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<td>AMR</td>
<td>Antimicrobial resistance</td>
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<tr>
<td>AST</td>
<td>Antimicrobial Susceptibility Testing</td>
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<tr>
<td>ATCC</td>
<td>American Type Culture Collection</td>
</tr>
<tr>
<td>BSAC</td>
<td>British Society for Antimicrobial Agents and Chemotherapy</td>
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<tr>
<td>CA-SFM</td>
<td>Comité de l’Antibiogramme de la Société Française de Microbiologie</td>
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<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
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<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>DSR</td>
<td>Disease Surveillance and Response Programme Area</td>
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<td>DPC</td>
<td>Disease Prevention and Control Cluster</td>
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<td>IQC</td>
<td>Internal Quality Control</td>
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<td>IDSR</td>
<td>Integrated Disease Surveillance and Response</td>
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<td>EQC</td>
<td>External Quality Control</td>
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<td>EUCAST</td>
<td>European Committee on Antimicrobial Susceptibility Testing</td>
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<td>GERMS-SA</td>
<td>Group for Enteric, Respiratory and Meningeal Disease Surveillance- South Africa</td>
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<td>KEMRI</td>
<td>Kenya Medical Research Institute</td>
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<td>HIV</td>
<td>Human Immunodeficiency virus</td>
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<td>HIV-DR</td>
<td>HIV drug resistance</td>
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<td>IHR</td>
<td>International Health Regulations (2005)</td>
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<td>KIA</td>
<td>Kligler iron agar</td>
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<td>LIA</td>
<td>Lysine iron agar</td>
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<tr>
<td>LTC</td>
<td>Laboratory Technical Committee</td>
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<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant TB</td>
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<tr>
<td>MIC</td>
<td>minimum inhibitory concentration</td>
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<tr>
<td>NIC</td>
<td>National Influenza Center</td>
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<td>NHLS</td>
<td>National Health Laboratory Service</td>
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<td>NICD</td>
<td>National Institute for Communicable Diseases</td>
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<td>NTS</td>
<td>Non-typhoid Salmonella</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<td>PT</td>
<td>Proficiency testing</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
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<tr>
<td>RDT</td>
<td>Rapid diagnostic tests</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TCBS</td>
<td>Thiosulfate Citrate Bile Salts Sucrose agar</td>
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<tr>
<td>TSI</td>
<td>Triple sugar iron agar</td>
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<tr>
<td>XDR-TB</td>
<td>Extensively drug-resistant TB</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Antimicrobial agents play a critical role in reducing morbidity and mortality due to communicable diseases the world over. However, the emergence and spread of resistance to many of these agents are negating their efficacy. Antimicrobial resistance (AMR) threatens the effectiveness of successful treatments for infections and is a public health issue with local, national and global dimensions. In low-income countries, AMR frequently occurs in microorganisms that are likely to be transmitted in the community such as those that cause pneumonia, diarrheal diseases, typhoid fever, tuberculosis, sexually transmitted diseases and malaria. Resistance to antimicrobial agents renders drugs for these illnesses ineffective, resulting in the need for wide-scale use of broad-spectrum agents, in the process creating a major global threat. Almost all studies on the outcomes of patients with bloodstream infections demonstrate high mortality in hospitals due to inappropriate use of antimicrobial agents.

Resistant organisms or their resistance genetic materials can be spread widely by travellers or through contaminated goods traded internationally. Antimicrobial resistance thus is a global challenge requiring multidisciplinary and multisectorial efforts at national, regional and global levels. It is possible to minimize the spread of antimicrobial resistance through adopting approaches such as combination therapy, rational prescription of medication, patient adherence to prescription regimen, strong regulatory mechanisms, and educational activities, along with creating an efficient surveillance system. This is feasible through strong national monitoring programmes that aim to detect the emergence and spread of resistant strains. A number of initiatives have been launched by the WHO Regional Office for Africa and other agencies to combat the growing threat of AMR.

Members States in the WHO African Region endorsed the Integrated Disease Surveillance and Response (IDSR) strategy in 1998 and recommended the implementation of the International Health Regulations (IHR 2005) in the framework of IDSR. Effective implementation of IDSR will strengthen networks of public health laboratories and thus contribute to effective monitoring of antimicrobial resistance.

Accurate, reliable and timely laboratory testing is an essential component of effective disease prevention and management. High quality AMR testing is essential for clinicians to make accurate diagnoses, formulate treatment plans and subsequently monitor the effects of treatment. It is also important to guide national policies and treatment guidelines according to the national AMR patterns. Improving laboratory-based surveillance of AMR is a key component of health system strengthening and is critical to the enhancement of health care delivery and disease prevention and control. In addition, the WHO Global Strategy for Containment of Antimicrobial Resistance recognized laboratory-based surveillance of antibiotic resistance as a fundamental priority for the development of strategies to contain antibiotic resistance and for assessment of the impact of interventions.

To contribute to the improvement of surveillance of antimicrobial resistance at the country level, the WHO Regional Office for Africa has developed this guide to facilitate establishing of laboratory-based surveillance for priority bacterial diseases in the WHO African Region.
Situation analysis

Of the 451 isolates of the *Shigella* responsible for bloody diarrhoea identified in 18 countries in the WHO African Region between 2008 and 2009, 78% were resistant to the primary drug used to treat this condition (13). This led to the use of new but more expensive medicines. Antibiotic susceptibility of 137 isolates of *Neisseria meningitidis* recovered between 2000 and 2006 in 18 countries, mainly within the meningitis belt, was determined using E-test. All *N. meningitidis* isolates were susceptible to ceftriaxone and chloramphenicol. Only 2% of the isolates displayed reduced susceptibility to penicillin G (2).

Between 1998 and 2008 susceptibility testing of isolates from 37 cases of invasive meningococcal disease was performed in patients 15 years and younger in Mozambique. Antibiotic susceptibility and minimum inhibitory concentrations for chloramphenicol and penicillin G were determined by E-test following the manufacturer’s recommendations and the results were interpreted according to CLSI standards. *N. meningitidis* remained highly susceptible to all antibiotics used for its treatment in the countries, although the presence of isolates with intermediate susceptibility to penicillin highlights the need for continued surveillance (3). In addition, the Group for Enteric, Respiratory and Meningeal Disease Surveillance–South Africa (GERMS-SA) has documented emerging antimicrobial resistance in several pathogens: a single fluoroquinolone-resistant *S. Typhi* isolate; several fluoroquinolone-resistant NTS isolates; a single fluoroquinolone-resistant *Shigella* isolate; and significantly increased penicillin and ceftriaxone resistance among *S. pneumoniae* isolates predominantly from young children during 2008 and 2009.

In summary, evidence is emerging of AMR among several bacterial causes of enteric disease and meningitis in the Region. Emergence of antimicrobial resistance in these important bacterial pathogens will have impact on the choice of empiric treatments of common disease syndromes such as sepsis, pneumonia and meningitis (1).

Access to accurate laboratory results on antimicrobial susceptibility testing is an important challenge to overcome for public health laboratories in the African Region. There is scarcity of accurate and reliable data on AMR, especially for meningitis pathogens, whose appropriate AMR testing methods are complex and are not done well in many countries.

Furthermore, a recent study by WHO and the National Institute for Communicable Diseases (NICD) on external quality assessment of national public health laboratories in Africa revealed weakness in many countries in testing for antimicrobial susceptibility (6). Only a few laboratories perform minimum inhibitory concentration testing when disc diffusion testing is considered unreliable for penicillin G in *N. meningitidis* and *S. pneumoniae* (6).

Other major problems associated with laboratory capacity for monitoring AMR in the WHO African Region include lack of essential reagents such as ATCC (American Type Culture Collection) control strains for monitoring the quality of antimicrobial susceptibility testing, inadequate standard operating procedures, noncompliance with internationally recognized guidelines on antimicrobial susceptibility testing (AST), insufficient capacity for AST data analysis and dissemination, inadequate training of staff performing and interpreting AST, lack of
national guidelines on antimicrobial use, and weakness of national programmes for AMR. These challenges call for national commitment to build capacity for laboratory-based surveillance of AMR. The main goal of this guide is to support countries in the African Region in their efforts to improve laboratory-based surveillance of AMR.

**Justification for surveillance of antimicrobial resistance**

AMR surveillance data help monitor susceptibility patterns of microorganisms to antimicrobial agents. Regular dissemination of data can help policy-makers to revise the recommendations for case management in health facilities and contribute to systematic combating of AMR. In addition, such information can be used for sensitizing clinicians, regulators, pharmacists and the general public.

AMR surveillance is crucial to demonstrate treatment efficacy when treating communities during outbreaks. It is important for detecting the emergence of novel resistance patterns and for monitoring the impact of interventions aimed at minimizing the spread and burden of AMR. It is clear that an efficient surveillance system for AMR, which is part of IDSR implementation and health systems strengthening, is necessary to reduce mortality and morbidity due to infectious diseases.

This guide aims to provide background information and define the key steps for the countries to conduct AMR surveillance for meningitis, bacteraemia and common enteric epidemic-prone diseases in a national bacteriology reference laboratory. While this guide promotes the dissemination of laboratory data on AMR for high priority bacterial diseases such as meningitis, cholera, salmonellosis and shigellosis, its adaptation to the national context and its adoption would contribute to minimizing the spread of AMR among these microorganisms.

This document supports IDSR implementation and global health security as envisaged by IHR (2005) through strengthening laboratory services and sharing information on AMR. It also promotes discussion on a step-by-step approach for involving multidisciplinary teams from hospitals, laboratories, universities and national surveillance units in containment of AMR.

This guide does not describe laboratory methods for isolating and identifying bacterial agents from clinical specimens or standardized antimicrobial susceptibility testing techniques and criteria for their interpretation. These standardized methods are described in publications from organizations such as the Clinical and Laboratory Standards Institute (CLSI) and the Comité de l’Antibiogramme de la Société Française de Microbiologie (CA-SFM) and they that can be used as references in the implementation of this guide at the country level.

This document is designed to be used in conjunction with the IDSR strategy.
Application of this guide

This guide promotes the development of a plan for implementing and strengthening laboratory-based AMR surveillance and strengthening the capacity of laboratories responsible for isolation and identification of selected bacterial diseases.

The application of this guide will improve the standardization process used by bacteriology reference laboratories to confirm the bacterial causative agents of severe diseases such as bacteraemias, enteritis and meningitis; strengthen the capacity of bacteriology reference laboratories to monitor AMR; improve the quality of AMR data by harmonizing laboratory techniques; and enhance the regional database on AMR.

Elements of a laboratory-based surveillance system for AMR

Surveillance is the primary strategy for tracking emerging drug resistance in the population, allowing for early and appropriate action. Countries should therefore strengthen their capacity for early detection and identification of resistant organisms that cause diseases of public health importance.

National laboratories responsible for monitoring drug resistance must have trained technologists, scientists and pathologists. They should be adequately equipped with instruments and consumables in order to produce reliable data to support surveillance of drug resistance. The information generated should be regularly shared with stakeholders and national authorities for informed decision-making. In addition, for a laboratory to successfully undertake isolation, identification and antimicrobial susceptibility testing responsibilities, it must make ongoing investments in acquiring supplies, media and reagents, and ensuring quality control, along with providing periodic training for personnel and conducting external quality assessment or proficiency testing.

It is advantageous for the AMR surveillance report to include a summary of the main findings from national surveillance and clinical data from sentinel sites (17). A country with limited resources may first perform laboratory-based surveillance involving collection of susceptibility data for common or epidemic-prone bacterial pathogens without seeking additional reports from hospitals. If sufficient resources are available and the laboratory has experience in monitoring drug resistance, additional data may be collected prospectively, which should help in improving documentation on AMR.

Laboratory-based surveillance has several requirements:

- Prioritization of organisms that should be monitored, taking into account the burden of the disease in the country;
- Selection of antibiotics to be tested for each isolate, taking into account the list of essential medicines and treatment guidelines;
• Development or updating of standard operating procedures (SOPs) for the isolation, identification and antimicrobial susceptibility testing of the selected pathogens using standardized methods;
• Establishing or strengthening of laboratory quality systems;
• Setting up a database for collecting and sharing information with stakeholders through existing mechanisms such as IDSR.

The following sections describe the requirements for laboratory based-surveillance of AMR.

1. National laboratory surveillance system for AMR

Several components are essential to strengthen surveillance by national bacteriology reference laboratories for monitoring drug resistance:

(a) National commitment

The ministry of health should make a commitment to support the improvement of laboratory capacity for undertaking proper antimicrobial susceptibility testing and surveillance for resistance mechanisms. This should be part of the national agenda for monitoring AMR as required by the Integrated Disease Surveillance Strategy and for implementation of resolution AFR/RC58/R2 on strengthening public health laboratories in the WHO African Region. In this regard it is recommended that each country designate a national bacteriology reference laboratory for AMR.

(b) Designation of a national bacteriology reference laboratory for AMR

Testing of antimicrobial susceptibility is resource intensive. Each government should select and officially designate one national bacteriology reference laboratory that will contribute to surveillance of AMR for bacterial pathogens. The laboratory should have the mandate to coordinate nationwide activities on AMR monitoring. This reference role should be given to the national public health laboratory, where one exists, as it is important in detection of severe bacterial diseases. The terms of reference should be endorsed by the selected laboratory and the national health authorities and should clearly describe the role of this laboratory in the laboratory system. The national reference laboratory should perform antibiotic susceptibility testing on specimens or isolates received from other laboratories or health care facilities where AST capacity is not adequate. If other hospital, university or private laboratories have the capacity to perform AST, the selected national AMR laboratory should offer confirmatory and specialized testing, such as MIC (minimum inhibitory concentration) determination and molecular testing on isolates received from these laboratories, using the laboratory networking mechanisms in the country.

A template of the terms of reference for the national reference laboratory for AMR is provided in Annex 1.
A focal point should be officially designated for coordinating AMR surveillance activities in the reference laboratory. The person in that role will be responsible for maintaining contacts with stakeholders such as clinicians, epidemiologists and pharmacists. He or she may be an active member of the national IDSR or the antimicrobial and therapeutic committees in countries where they or their equivalent exist.

A country that cannot yet properly monitor AMR should consult WHO for guidance, technical support and advice on where to send isolates for investigation. However, the designation of a national reference laboratory for AMR is crucial for all Member States for contributing to the regional and global initiatives to combat the threat of AMR.

(c) Training of laboratory personnel

To deliver quality service, the reference laboratory requires an appropriate workforce equipped with necessary technical skills in bacteriology and AST. Training is indispensable in improving the quality of the laboratory services.

Bacteriology laboratories have benefited from several advancements such as the recent WHO guidelines on bacterial meningitis and enteric diseases (8, 9, 12), regular updates on standard international guidelines for AST (CLSI, CA-SFM, etc.), regular training on meningitis and enteric diseases organized by WHO and WHO/NICD Microbiology Reference Laboratories, and enrolment in WHO/NICD External Quality Assessment Programme (EQA). Each WHO/NICD EQA survey report includes commentary and recommendations on the most appropriate laboratory methods for improvement of antimicrobial treatment (6).

Senior scientists or other experienced laboratory personnel should conduct short-term courses once needs are assessed and gaps identified. In addition it would be advisable to organize regular AST workshops at the country level. Training should be standardized across the countries, and the WHO African Regional Office should develop outlines of the workshop content using the reference materials available and improve existing SOPs if necessary.

The training programmes could be organized by the office that coordinates the laboratories within the ministry of health or the national laboratory network using its own contacts or through WHO or other partner agency.

(d) Procurement of essential reagents, supplies and equipment

The bacteriology laboratory should develop a list for equipment, reagents and supplies based on the scope of its activities and AST protocols, which follow recognized international guidelines.

The laboratory should follow ISO guidelines for total quality system implementation
to monitor the consumption of reagents and supplies and to restock these in sufficient time so that regular activities are not interrupted. Also, a system for timely repairs and preventive maintenance of equipment should be put in place along with a mechanism for replacement of laboratory equipment that becomes redundant.

(e) Resource mobilization

The countries are encouraged to mobilize resources though national and international partners to adequately support the laboratory’s capacity for isolation, identification and testing of antimicrobial susceptibility of priority infectious diseases. However, funds for this service should mainly be derived from government budgetary allocation and income-generating activities.

2. Selection of pathogens

A number of microorganisms colonize and infect humans but only a few of these cause severe disease. Not all disease-causing microorganisms need to be included in the surveillance programme. Selection criteria should be applied based on local and regional prevalence of diseases. During the initial phase of the existence of the surveillance network in the WHO African Region it may be important to include pathogens of at least the following diseases:

Bacterial causes of meningitis:
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

Bacterial causes of enteric diseases:
- *Salmonella* serotype Typhi
- *Shigella* spp.
- *Vibrio cholerae*

Bacteraemia causes:
- *Staphylococcus aureus*
- *Enterobacteriaceae*
- *Pseudomonas aeruginosa*

3. Selection of antibiotics

The selection of antimicrobial agents is a dynamic process and hence the list of selected antibiotics may need frequent revision based on introduction of new medicines, changes in common antibiotics in the list of essential medicines used by clinicians, nature of data requested by the national surveillance system, and recommendations from international guidelines. Each laboratory must determine its own level of susceptibility testing that will be adequate to provide
essential data for public health decision-making and relevant to that laboratory’s situation. In
resource-limited settings it may be useful to use the guidelines provided in tables 1 and 2.

Table 1: Suggested antimicrobial agents for AMR surveillance for bacterial meningitis

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Clinical guidelines</th>
<th>Basic set (disk and gradient strips) for antibiotics</th>
<th>Additional set (disk and gradient strips) for antibiotics¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td>CLSI</td>
<td>Ampicillin 10 µg (B-lactamase test) Chloramphenicol 30 µg (disk)</td>
<td>Ampicillin 10 µg (strip) Chloramphenicol 30 µg (strip) Ceftriaxone 30 µg (disk and strip)</td>
</tr>
<tr>
<td></td>
<td>CA-SFM</td>
<td>Ampicillin 2 µg (B-lactamase test) Chloramphenicol 30 µg (disk)</td>
<td>Ampicillin 2 µg (strip) Chloramphenicol 30 µg (strip) Ceftriaxone 30 µg (strip)</td>
</tr>
<tr>
<td><strong>Neisseria meningitidis</strong></td>
<td>CLSI</td>
<td>Penicillin (MIC) Chloramphenicol 30 µg (disk)</td>
<td>Chloramphenicol 30 µg (strip) Ceftriaxone 30 µg (disk and strip)</td>
</tr>
<tr>
<td></td>
<td>CA-SFM</td>
<td>Oxacillin 5 µg (disc screening test) Penicillin G (strip) Chloramphenicol 30 µg (disk)</td>
<td>Chloramphenicol 30 µg (strip) Ceftriaxone 30 µg (strip)</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>CLSI</td>
<td>Penicillin (as determined by oxacillin disk 1 µg testing) Penicillin (strip)</td>
<td>Ceftriaxone 30 µg (strip)</td>
</tr>
<tr>
<td></td>
<td>CA-SFM</td>
<td>Penicillin (as determined by oxacillin disc 5 µg testing) Penicillin G (strip)</td>
<td>Ceftriaxone 30 µg (strip)</td>
</tr>
</tbody>
</table>

It is important to remember that disk diffusion testing is the least expensive method for AST, but the results from AST testing must be interpreted strictly according the latest published version of the relevant guideline.

¹ See the 2nd edition of the WHO Manual “Laboratory methods for diagnosis of meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae” for detailed information on AST and/or request of additional selection of antibiotics such as erythromycin, trimethoprim-sulfamethoxazole, tetracycline, rifampicin, ciprofloxacin, etc.
Table 2: Suggested antimicrobial agents for AMR surveillance for bacterial enteric diseases

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Basic set (disk) for antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em> serotype Typhi</td>
<td>Ampicillin, chloramphenicol, ciprofloxacin, nalidixic acid, trimethoprim-sulphamethoxazole</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>Ampicillin, ciprofloxacin, nalidixic acid, trimethoprim-sulphamethoxazole</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Ampicillin, ciprofloxacin, nalidixic acid, tetracycline, trimethoprim-sulphamethoxazole</td>
</tr>
</tbody>
</table>

This list is in line with the WHO/NICD EQAP on microbiology.

4. Standard operating procedures

Standard operating procedures (SOPs) contain written step-by-step instructions that laboratory staff need to meticulously follow for every procedure. A laboratory should have an SOP for each procedure it performs (refer to Annexes 2 and 3).

To ensure consistency in performing laboratory activities for AMR on selected pathogens or any other procedure, it is essential to develop SOPs that describe all the steps to be followed for the tests. The SOPs should be drawn up by laboratory personnel working in the bacteriology fields, revised by their immediate supervisor and approved and validated by the head of the units. Their use by all laboratory staff should be mandatory for every activity they perform.

SOPs describe in detail the activities performed in the laboratory to (i) provide uniformity, consistency, repeatability and reliability for each of the activities performed in the laboratory; (ii) reduce systematic errors; and (iii) introduce the total quality system in the laboratory.

It is necessary to standardize the format of SOPs so that staff can easily recognize the flow of the information for the procedure to be undertaken (Annex 4). In addition, it is mandatory to assess the scientific validity of the procedure. It is important to keep in mind that the manufacturer’s instructions do not replace SOPs but can serve as additional reference material. The instructions that manufacturers provide in their product inserts show how to perform the test but do not include other important information that is specific to laboratory policy, such as algorithms, safety practices and how to record results. Laboratories must not rely solely on manufacturers’ product inserts for SOPs; they must use information from these inserts in conjunction with SOPs specific to each laboratory (11).

5. Quality control

Quality control is the backbone of quality performance by the laboratory. Establishing or strengthening a quality assurance system will ensure the improvement of the reliability and reproducibility of the laboratory’s results.
Assessments conducted in recent years in some national bacteriology reference laboratories in the WHO African Region reveal the lack of appropriate SOPs for isolation, identification and AST of bacterial meningitis and enteric diseases despite the provision of materials and training by WHO on these subjects. This may generate inconsistencies in performance of the WHO/NICD EQAP in some laboratories. The Laboratory Technical Committee on AMR will play a critical role in ensuring compliance with the requirement to provide SOPs for each procedure. The African Regional Office will continue to provide technical support to Member States to improve the services of their national bacteriology reference laboratories in the effort towards achieving international standards and accreditation. This will be implemented through the Stepwise Laboratory Improvement Process Towards Accreditation (SLIPTA) initiatives.

Internal quality control

Internal quality control (IQC) is a routine procedure undertaken by laboratories to ensure quality of tests. IQC procedures can be set up by laboratory management on regular periodic basis for tests they perform, and the results should be recorded and discussed with all staff members.

Quality control procedures must be practised for each testing method used by the laboratory. Ordinarily, each test kit has a set of positive and negative controls that are to be included in each test run. Quality control data sheets and summaries of corrective action should be retained for documentation.

IQC should cover all steps of each diagnostic test from the collection of specimen to the transmission of the results, as well as media production and maintenance of equipment. IQC testing should be performed regularly with each laboratory determining the frequency depending on the load of specimens it receives for antimicrobial susceptibility testing. Ideally, each batch of AST should be accompanied by an IQC. Laboratory equipment should be assessed on a regular basis to ensure maintenance and quality.

The main objectives of quality control in antimicrobial susceptibility testing are to control for the quality of reagents, precision and accuracy of the test method, accuracy of results disseminated, and performance of the laboratory staff carrying out the tests and the equipment in use.

The use of reference bacterial strains as recommended by standard guidelines on AST such as CLSI and CA-SFM will contribute to the monitoring of the accuracy of the results.

If the results for the control strain are accurate, i.e. all antimicrobial agents are in the control range, the procedure is assumed to be accurate and so AST may be performed on significant isolates. If the zones produced by the QC strains are out of the expected ranges, the technical personnel should try to determine the possible sources of the error and should troubleshoot the causes. IQC must be performed prior to initiating AST on the isolates.

The sources of quality control strains may vary among the laboratories, but many laboratories purchase QC strains from official collections such as the American Type Culture Collection (ATCC) and the National Collection of Type Cultures (NCTC). Examples of antimicrobial susceptibility testing QC organisms are *H. influenzae* ATCC 49247, *S. pneumoniae* ATCC
49619 and E. coli ATCC 25922. The laboratory should select the appropriate QC strains to be used for each organism based on the international guidelines adopted in the national SOPs, e.g. E. coli ATCC 25922 for Shigella spp. and S. pneumoniae ATCC 49619 for S. pneumoniae.

**Participation in the international external quality assessment programmes**

Any national bacteriology reference laboratory that contributes to the surveillance network of AMR in the WHO African Region must participate regularly and successfully in EQA programmes such as WHO/NICD external quality assessment surveys. The reference laboratory should score 70% or better on the proficiency test (PT) panels each time. PT results must be reported according instructions and submitted within required deadlines. Each laboratory manager or head of laboratory must deal with unacceptable PT results, and corrective action must be taken and documented. The microbiology WHO/NICD EQA programme includes challenges for bacterial meningitis, diarrheal diseases and other significant bacterial infections.

**Table 3: Clinical conditions and diagnostic tests for WHO/NICD EQAP**

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<thead>
<tr>
<th>Clinical conditions (causative agents)</th>
<th>Diagnostic tests included in the EQA programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial meningitis (<em>Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae</em>)</td>
<td>Microscopy</td>
</tr>
<tr>
<td></td>
<td>Serological identification</td>
</tr>
<tr>
<td></td>
<td>Culture and identification</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial susceptibility testing</td>
</tr>
<tr>
<td>Bacterial diarrhoeal diseases (<em>Salmonella</em> spp., <em>Shigella dysenteriae</em>, <em>Vibrio cholerae</em>)</td>
<td>Serological identification</td>
</tr>
<tr>
<td></td>
<td>Culture and identification</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial susceptibility testing</td>
</tr>
<tr>
<td>Significant bacterial diseases such as bacteraemias, urinary tract infections, skin and soft tissue infections (<em>S. aureus, Enterobacteriaceae, Pseudomonas aeruginosa, Enterococcus spp., Acinetobacter baumannii</em>)</td>
<td>Microscopy</td>
</tr>
<tr>
<td></td>
<td>Serological identification</td>
</tr>
<tr>
<td></td>
<td>Culture and identification</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial susceptibility testing</td>
</tr>
</tbody>
</table>

The WHO/NICD EQA programme benefits participating laboratories through:

- Allowing identification and evaluation of the capability of laboratories through an external assessment;
- Guiding laboratories in corrective action and continuous improvement;
- Developing or updating SOPs using requirements of recognized standards;
- Providing continuous education for laboratory staff on standard diagnostic methods;
- Raising awareness on the successes and challenges in laboratory practice;
- Providing information for advocacy.

In addition, EQAP can help to overcome the potential difficulties arising from the use of different methods by members of the AMR network in the Region.
6. Data management and information sharing

The national bacteriology reference laboratory will collect, collate and analyse antimicrobial susceptibility data and disseminate them to stakeholders on a regular basis using existing systems such as IDsR.

When analysing results it is important to review the sources of the organisms that are tested and consider how representative they are of the country as a whole. Isolates from patients in a restricted setting may give a biased picture of the national situation. Also, it is important to ensure a sufficient number of isolates are included in the database to increase the chances of detecting changes in sensitivity profiles.

Clinical isolates that give inconsistent or uncommon results are important for recognizing the emergence of a new resistance profile such as penicillin- or chloramphenicol-resistant Neisseria meningitidis or fluoroquinolone-resistant Salmonella. Such isolates should be sent for confirmation to a reference laboratory and for determination of minimum inhibitory concentration. A clinical bacteriologist should coordinate the validation of AMR test results and review atypical or unusual results to maintain the quality of the results and performance of the laboratory, which are requirements of IDsR.

All national bacteriology reference laboratories and members of the AFR laboratory network on AMR\(^2\) should maintain standard records of AMR data.

Any pathogen found to have unusual susceptibility profiles in the course of AST surveillance should be referred to the reference laboratory for confirmation of the uniqueness of the profiles and further investigation.

The African Regional Office is supporting countries to collect, collate and analyse data on susceptibility test results from the members of the regional laboratory network using the DPC Real-time Strategic Information System web-based software. This information can be obtained through all the existing channels such as the ministries of health, which can provide the WHO/AFRO IDR software. It will allow biannual or annual reporting on regional profiles of AMR of bacterial enteric, bacteraemic and meningitis diseases. The members of the regional network are also encouraged to develop an annual report on AMR (refer to Annex 5).

Experiences and lessons learned from the WHO laboratory networks show that sharing data with WHO African Regional Office is crucial not only to provide data on resistance patterns but also to allow WHO to improve the total laboratory quality assurance system, promote exchange of information and seek additional funds from outside the countries’ ministry of health budgets.

Data on overall levels of resistance can be shared regularly with stakeholders using formats such as those shown in tables 4 and 5.

\(^2\) AFR laboratory network on AMR is described in Section VII (Regional antimicrobial resistance network).
Table 4: Example of an AMR rates report for a microorganism (name of the microorganism) during January to June 2012

<table>
<thead>
<tr>
<th>Name of the microorganism and total number tested</th>
<th>Ampicillin</th>
<th>Tetracycline</th>
<th>Trimethoprim-sulfamethoxazole</th>
<th>Nalidixic acid</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td># S</td>
<td># I</td>
<td># R</td>
<td># S</td>
<td># I</td>
<td># R</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>3</td>
<td>19</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

#= number  
S = susceptible  
I = intermediate  
R = resistant

It is important to mention the reporting method, e.g. "reported susceptibility results using breakpoint interpretive criteria obtained from CLSI, CA-SFM or other guidelines, which are subject to change on annual basis”.

Table 5: Example of AMR surveillance data from one country that has submitted data to the African Regional Office.

Antimicrobial susceptibility test results for *Shigella* isolates, name of the country, year of data collection, number of isolates (n= 1612)

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Susceptible (%)</th>
<th>Intermediate (%)</th>
<th>Resistant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>866</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>679</td>
<td>42</td>
<td>24</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>259</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>1594</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1611</td>
<td>99.9</td>
<td>0</td>
</tr>
</tbody>
</table>

3 Which are subject of change according latest guideline recommendations.
7. Expansion of the national surveillance for AMR

The introduction of laboratory-based surveillance could use a phased approach beginning with a few pathogens such as bacterial meningitis and enteric diseases. With experience and adequate resources, the bacterial agents could be expanded to include other pathogens such as *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Escherichia coli*, *Klebsiella*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. This will permit monitoring of methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum *B*-lactamase (ESBL) and metallo-*B*-lactamase (MBL) producing gram-negative bacteria.

8. Monitoring and evaluation

The WHO Global Strategy for Containment of Antimicrobial Resistance (19) emphasizes that diagnostic laboratories ensure:

- Access to microbiology laboratory services according the level of the hospital;
- Implementation of a quality assurance system in each laboratory that will guarantee quality of diagnostic tests, including microbial identification, antimicrobial susceptibility tests of clinically significant pathogens, and timely and relevant reporting of results;
- That laboratory results are recorded, preferably in an electronic database, and are used to produce clinically and epidemiologically useful surveillance reports on resistance patterns of common pathogens in a timely manner with feedback to relevant stakeholders such as prescribers, policy-makers and the infection control programme.

Establishment and strengthening of monitoring and evaluation systems with targets and measurable indicators\(^4\) will allow the countries to improve the delivery and quality of laboratory services.

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\(^4\) Number of Member States whose national laboratory system is engaged successfully in at least one international external quality assessment programme on bacteriology.
Laboratory performance and activities for enhancement of AMR surveillance will be regularly monitored through the results of proficiency panel testing, adherence to standard operating procedures and safety guidelines, dissemination of AMR data to WHO, and introduction of standard performance indicators in line with the WHO Global Strategy.

**Steps for establishing laboratory-based surveillance for AMR**

Table 6 outlines the key steps in establishing laboratory-based surveillance of AMR. The table serves only as a guide since many factors such as the capacity of the bacteriology reference laboratory, achievements of national AMR programmes and other elements may influence the laboratory schedule.

**Table 6: Key steps and activities**

<table>
<thead>
<tr>
<th>Step</th>
<th>Key points to consider</th>
<th>Role of WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adoption of the generic laboratory-based surveillance guide on AMR</td>
<td>- Technical meeting for adoption of the key elements of the guide. This will allow staff involved in AMR surveillance to learn and comply with its objectives and content even though CLSI or CA-SFM guidelines are subject to change annually&lt;br&gt;- Dissemination of the guide as appropriate</td>
<td>Technical support in adaptation or adoption of the guide</td>
</tr>
<tr>
<td>Designation of the national reference laboratory for AMR</td>
<td>- Selection of one national reference bacteriology laboratory with capacity for AST for meningitis and enteric and other pathogens&lt;br&gt;- Define or update the terms of reference of the national reference laboratory related to AMR surveillance (see Section VII)</td>
<td>Advocacy through WCO</td>
</tr>
<tr>
<td>Designation of technical committee</td>
<td>- Composition and development of terms of reference&lt;br&gt;- Contact details of the focal point shared with stakeholders</td>
<td>Advocacy through WCO</td>
</tr>
<tr>
<td>Assessment of the capacity for AMR surveillance, identification of the gaps and development on a national plan</td>
<td>- Self-assessment of laboratory capacity using existing WHO standardized tools and proposed key activities need to be supported based on findings of the assessment and the requirements of the national guidelines on AMR</td>
<td>Technical support to help develop an appropriate plan</td>
</tr>
<tr>
<td>Implementation of laboratory-based surveillance of AMR</td>
<td>- Key actions may include but are not limited to:&lt;br&gt;- Updating or creating new SOPs&lt;br&gt;- Procuring essential reagents and supplies for the national reference laboratory&lt;br&gt;- Ensuring the laboratory has adequate personnel and ongoing training of staff&lt;br&gt;- Active participation in WHO/NICD EQAP&lt;br&gt;- Collection and sharing of data on AMR for MoH and WHO&lt;br&gt;- Providing regular annual reports on AMR&lt;br&gt;- Monitoring, evaluating and improving the implementation process</td>
<td>Technical support to Member States through the AMR laboratory network activities</td>
</tr>
</tbody>
</table>
The WHO African Regional Office will continue to:

- Facilitate exchange of information and consistent communication on the initiatives on infectious diseases with respect to AMR such as tuberculosis, HIV, malaria and other bacterial pathogens;
- Monitor and evaluate the achievements of AMR initiatives for action;
- Develop overall advocacy and resource mobilization strategies;
- Provide technical support and guidance on AMR efforts as required by Member States;
- Harmonize and standardize practices;
- Coordinate and strengthen the regional antimicrobial laboratory network.

**Regional antimicrobial resistance network**

The national bacteriology reference laboratory on AMR is an institution designated by the ministry of health in its respective country and recognized by the WHO African Regional Office as a member of the WHO Regional Antimicrobial Laboratory Network. This network monitors susceptibility patterns of microorganisms to antimicrobial agents in the WHO African Region. It also functions as part of the regional alert system for emergence of new or extreme drug-resistant organisms.

The goals of the Regional Antimicrobial Resistance Laboratory Network are to:

- Build national laboratory capacity in African countries to conduct AST;
- Provide access to standardized practices for conducting laboratory-based surveillance of AMR;
- Promote advanced and specialized testing on selected pathogens by regional reference laboratories or collaborating centres;
- Build the foundation for future studies on the containment of AMR.
References

5. Establishment of national laboratory-based surveillance of antimicrobial resistance, World Health Organization Regional Office for SEA, New Dehli, 2011
9. Laboratory Methods for diagnosis of epidemic dysentery and cholera, WHO/CDS/CSR/EDC/99.8
10. Laboratory-based surveillance of antimicrobial resistance, Report of a bi-regional workshop, Chennai, India, 21-25 March 2011, World Health Organization Regional Office for SEA
12. Manual for the laboratory identification and antimicrobial susceptibility testing of bacterial pathogens of public health importance in the developing world, WHO/CDS/CSR/RMD/2003.6
16. Strengthening public health laboratories in the WHO African Region: a critical need for disease control (Resolution AFR/RC58/R2)
Annex 1

Terms of reference for the national bacteriology reference laboratories on surveillance of antimicrobial resistance

The proposed terms of reference for the national bacteriology reference laboratories on surveillance of antimicrobial resistance should include the following responsibilities:

- Perform laboratory confirmation and AST of bacterial meningitis, enteric diseases or other bacterial diseases using recognized AST standards;
- Provide to the ministry of health, the WHO country office and the WHO Regional Office for Africa regular and timely laboratory-based surveillance data on antimicrobial resistance profiles;
- Promote best practices including establishing and strengthening laboratories’ quality management systems;
- Participate regularly and successfully in WHO/NICD EQAP testing, scoring ≥70%;
- Support the scaling up of IDSR including the sustainability of the national public health laboratory network;
- Conduct or support research studies on AMR in collaboration with the ministry of health, and share findings with members of the network, the WHO country office and the WHO African Regional Office.
Annex 2

List of SOPs for isolation and identification of bacterial isolates for meningitis and enteric diseases of public health importance

Meningitis caused by Neisseria meningitidis, Streptococcus pneumonia, Haemophilus influenza, Group B streptococci (GBS) and enterobacteriaceae

SOPs developed may include but not be limited to the following processes:

- Collection, packaging, storage and transportation of CSF, including inoculating and transporting T-I medium or other transport media
- Cytological examination of the CSF
- Gram stain
- Inoculation (primary culture) blood agar and/or chocolate agar plates and macroscopic examination of colonies
- Kovac’s oxidase test
- Catalase test
- Optochin susceptibility test
- Bile solubility test
- Growth factor test for identification of Haemophilus influenzae
- Slide agglutination test for serotyping/serogrouping and quality control of antisera
- Quelling reaction
- Rapid diagnostic tests (RDTs)
- Biochemical identification of Neisseria meningitidis (carbohydrate utilization by N. meningitidis)
- Biochemical identification of Haemophilus influenzae
- Storage of isolates
- Preparation and quality control of media and reagents (e.g. for chocolate agar plate)
- PCR for detection and characterization of bacterial meningitis pathogens
Enteric diseases caused by *Salmonella Typhi, Shigella* and *Vibrio cholerae*

The list of SOPs may include, is but is not limited to:

- Collection, packaging, storage and transportation of stool
- Inoculation and macroscopic examination of growth on culture media
- Gram stain of isolates
- Biochemical screening tests (KIA, TSI, motility, urea, indole, LIA, string test, oxidase test, API test strips, etc.)
- Serologic identification
- Rapid diagnostic tests (RDTs) for cholera storage of isolates
- Preparation and quality control of media and reagents (specify e.g. TCBS)

Some of these proposed SOPs can be merged, if necessary, taking into account the existing quality manual and experience of the laboratory staff.
Annex 3

List of SOPs for antimicrobial susceptibility testing for meningitis and enteric diseases

Several laboratory techniques are available to determine susceptibility of microorganisms to antimicrobial agents. Some of these are the Kirby-Bauer disc diffusion method and minimum inhibitory concentration (MIC) determination through antimicrobial gradient strips or dilution methods.

Most national bacteriology reference laboratories in the WHO African Region use CLSI and CA-SFM standards. These standards provide clear information for determination and interpretation of antimicrobial susceptibility of most of the pathogens. These standards are updated regularly. The national reference laboratories engaged in the surveillance of antimicrobial resistance need to follow the requirements of the updated version of one of these standards to develop their standard operating procedures.

Antimicrobial susceptibility testing of bacterial meningitis

The list of SOPs may include but is not limited to:

- Testing *Haemophilus influenzae* for β-lactamase production
- Susceptibility testing of *Neisseria meningitidis* using disk diffusion or minimum inhibitory concentration testing
- Susceptibility testing of *Streptococcus pneumoniae* using disk diffusion and minimum inhibitory concentration testing
- Susceptibility testing of *Haemophilus influenzae* using disk diffusion and minimum inhibitory concentration testing

Antimicrobial susceptibility testing of bacterial enteric diseases

The list of SOPs may include but is not limited to:

- Antimicrobial susceptibility testing by disk diffusion of *Salmonella* serotype Typhi;
- Antimicrobial susceptibility testing by disk diffusion of *Shigella*;
- Antimicrobial susceptibility testing by disk diffusion of *Vibrio cholerae*.

If needed, one document may be developed to cover all topics on AST.

Antimicrobial susceptibility testing of bacteraemic isolates in the next phase

Antimicrobial susceptibility testing by disk diffusion of *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterococcus* spp. and Enterobacteriaceae
Annex 4

Content of standard operating procedures (SOPs)

Standard operating procedures may include the following items:

- Logo and name of the laboratory
- Facility: i.e. the department or unit issuing the SOP, e.g. bacteriology
- Title: e.g. Biochemical identification of *Neisseria meningitidis*
- SOP number: e.g. 2012-BAC-01
- Effective date: e.g. February 2012
- Writers: name, date and signature of the author
- Approver: name, date and signature
- Authorizer and releasing persons: name, date and signature
- Purpose: The aim of the procedure being described should be expressed clearly and concisely; e.g. standardized process for the biochemical identification of *Neisseria meningitides*.
- Test principles:
  - This section describes in detail the principles of the test: introduction to the pathogens, definitions, methods, key steps, summary on the interpretation of the results, background on the test, reference to international methods, etc.
  - Information from peer-reviewed literature may be used to develop segments of this section, but each laboratory may have its unique differences.
- Responsibilities
  - Staff responsibilities: This section presents the responsibilities specific to the execution of the SOP such as technical personnel to ensure that processing of pathogens and all the steps of the test methods are conducted correctly. The role of the laboratory supervisor and the quality officer may also be defined in this section.
  - Specific safety requirements and responsibility of the safety officers should be explained in the safety SOPs.
  - Bibliographic references and internet links also may be included in this section.
- Equipment, supplies and reagents: This section includes lists of all materials, supplies and equipment used for these procedures.
- Quality assurance programmes and quality control: This section should follow the recommendations from internationally recognized references.
- Procedure: Refers to all the steps involved in performing the test described. The contents should be developed so that all the staff in the unit will be able to understand and perform the procedures written in the SOP. Photos may be included to facilitate comprehension of the methods.
• Interpretation of results: This section clearly defines the different categories of the results from the test, e.g. gram positive/negative cocci, bacilli and others. It is also advisable to include some photos to help the interpretation of the results. It is possible to include references for interpretation.
  ● Limitation of procedures: This section details all the likely errors that could occur during the test.

• Recording and reporting
  - The process of recording in the department is defined.
  - The tool for reporting as well as the process for transmission of the results is determined in this section.

• References: The references used to draw up the SOP.
• Attachments: This section may include pictures, testing algorithm, table for comparison, etc.
Annex 5

Template for AMR annual report

Member States should regularly prepare a national annual report on AMR to guide them on the prevention and containment of the emergence of multi-resistance pathogens.

The suggested content of the annual report on AMR may include the following:

- Executive summary
- Introduction
- Methods
- Results
  - Operational reports that may include activities undertaken to coordinate and strengthen AMR
  - Surveillance reports that may cover antimicrobial susceptibility test results for all selected pathogens by antimicrobial agents, and robust data on trends of AMR by year for selected antibiotics
- Discussion
- References

Key sections of the report on AMR should include:

- Epidemiology and surveillance, including data management of selected diseases
- List of designated coordination committees with their terms of reference
- List of laboratories, hospitals, and other facilities or departments involved directly in AMR