

EURL-AR, Work Plan for 2014

The main purpose of the European Union Reference Laboratory on Antimicrobial Resistance (EURL-AR) is to ensure the quality of antimicrobial susceptibility testing in the Member States, including the use of the most optimal detection methods for antimicrobial resistance and to harmonise the procedures and methodologies used. Thus, most of the activities aim at implementing, from an analytical point of view, the provisions of monitoring of antimicrobial resistance, improving communication, education and training, and ensuring harmonization set down in the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria (with reference to Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC, and in particular Article 7(3) and the fourth subparagraph of Article 9(1) of Directive 2003/99/EC and Annex II (B) and Annex IV) as well as the Communication from the Commission to the European Parliament and the Council, Action plan against the rising threats from Antimicrobial Resistance.

In addition, the EURL-AR will provide assistance to the Member States and the Commission on other relevant aspects of antimicrobial resistance. Furthermore, the EURL-AR will work in an international context and ensure that EU influences and follows global standards and guidelines.

The EURL-AR is located at the National Food Institute-DTU as part of one of the activities of Research Group of Bacterial Genomics and Antimicrobial Resistance, within the Division of Bacterial Genomics and Epidemiology. The main activities of this research group relate to surveillance including antimicrobial resistance among bacteria from food animals, and conducting targeted research with the aim of reducing the occurrence of antimicrobial resistant bacteria among food animals and food products and infectious disease pathogens. The scope of activities of the laboratory includes several international activities, education and research projects, such as the EURL-AR, the WHO Collaborating Center for antimicrobial resistance, advisory tasks, teaching, as well as several ongoing research projects. The EURL-AR corresponds to circa 30.5 % of the total activities of the Research group, and to circa 12,5 % of the total activities of the Division of Bacterial Genomics and Epidemiology (www.food.dtu.dk). DTU-Food is supporting (co-funding) the EURL-AR with basic housing and access to equipment, as well as administrative and IT-support.

1. Scientific advice and support to the Commission

During 2014, the EURL-AR will provide advice as stated under the general terms with an emphasis on the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria and the Communication from the Commission to the European Parliament and the Council, Action plan against the rising threats from Antimicrobial Resistance. This will include e.g. advice on table / MIC plate updates (ranges, antimicrobials, ECOFF's), guidance documents, and needed training etc. The EURL-AR will participate in workshops and working groups on antimicrobial resistance initiated by EFSA, EMA, ECDC, Codex, FAO/WHO/OIE or other relevant organisations. The WHO has established an Advisory Group in Surveillance of Antimicrobial Resistance (AGISAR), which has as the aim to develop global standards for monitoring of antimicrobial resistance. The EURL-AR is obliged to actively support this initiative.

For 2014, the EURL-AR plans to take part in several of the above mentioned activities and workshops in the auspice of WHO GFN / AGISAR, EMA, ECDC, and EFSA with a budgeted workload expected to represent around 9,5 % of the total EURL-AR salary expenses. Travel expenses for the EURL-AR staff related to this activity are calculated to circa 5,000 EUR, for 5-6 short travels.

2. Co-ordination of National Reference Laboratories and provision of technical support

2.1. Meetings on standardization of monitoring of antimicrobial resistance

An important problem in relation to ring trials and monitoring of resistance is the lack of common interpretive criteria. This is a global problem and not only related to EU. The EU is the world's largest exporter and importer of food products and European citizen travel with an increasing frequency outside the EU. Thus, international collaboration and the development and harmonisation of global standards is high priority, as also indicated in the Commission's strategy for antimicrobial resistance. The EURL-AR will in 2014 continue the work with WHO (AGISAR) and other important stakeholders such as ECDC, EUCAST, CLSI, OIE, FAO and Global Foodborne Infections Network (GFN) in order to promote a common international standard for harmonization of antimicrobial resistance monitoring and support of capacity building in member countries for antimicrobial resistance monitoring. Furthermore, the EURL-AR will in 2014 strive toward influencing producers of antimicrobials test panels making the future common EU MIC plates available for NRLS as standard EU plates facilitating a reduced price and small volume orders.

2.2. Maintaining the network of NRL's

The EURL-AR will during 2014 maintain and continuously update a full list of contact persons from all NRL's. In addition, the EURL-AR will attempt to identify expected members from applicant countries to include in the network. This list will also be maintained during the following years. In 2014, the EURL-AR will also undertake the preparation and organization of one workshop and one training course.

2.3. Dissemination of knowledge and information

The EURL-AR will maintain the official EURL-AR website where relevant information is posted. In addition, the EURL-AR will distribute updates, highlights or other relevant information through newsletters to the NRL's.

Specifically for 2014, the EURL-AR will ensure dissemination of all relevant information and development related to the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria.

The EURL-AR will provide updated lists of cut-off values in relation to interpretation of MIC-values obtained for monitoring purposes based on the work done by EUCAST (www.eucast.org) and other international standardization committees. In addition, when relevant, the latest guidelines on which antibiotics to test for and ranges to use as well as other problems encountered will be disseminated between the NRL's.

The EURL-AR will continue to disseminate latest state of the art information as regards scientific findings. This will include emerging resistance issues related to for example resistance mechanisms or genes in relevant microorganisms.

2.4. Collection of data of methodology and plate designs used for the performance of AST testing, using commercial microtiterplates in the network.

The golden standard method for antimicrobial susceptibility testing (AST) is the minimum inhibitory concentration (MIC) testing methodology which has been adopted in most MS for harmonization purposes and to improve the quality of susceptibility testing in general. However, there are different brands and plate designs available, different methodologies and equipment which can be used in the performance of such tests. We intend to utilize the information collected in 2012 (questionnaire-based survey) for trouble shooting in connection with the results obtained in proficiency tests in order for AST results to comply with current guidelines.

2.5. Improve and extend databases of primers, reference material and antimicrobial resistance genes.

For detection and characterization of resistance mechanisms it is necessary to identify an extremely large number of resistance genes and mutations responsible for the phenotypes observed. At the EURL-AR, databases containing primers and reference strains are currently available to our network for setting up molecular methods for detection. These databases will continuously be improved and extended.

In 2014, the EURL-AR intends to continue the above mentioned activities (2.1; 2.2; 2.3; 2.4; and 2.5) which represent circa 15.6% of the total salary expenses of the EURL-AR.

3. Ring trials, comparative testing and quality assurance

External quality control is the one of the main and important part of ensuring and maintaining the analytic quality of laboratory tests performed. The EURL-AR will in the spring and autumn 2014 organize the following ring trials on antimicrobial susceptibility testing for participation of one designated NRL per MS.

3.1. *Salmonella*

3.2. *Campylobacter*

3.3. *Escherichia coli*

3.4. Enterococci

3.5. Staphylococci

3.6. Genotypic characterization also including detection of ESBL, carbapenem, and ampC genes

The organization and evaluation of the results are given under the general terms.

The ECDC-network of Food and Waterborne Diseases will be offered the participation in the *Salmonella* and *Campylobacter* proficiency test. The funding for including ECDC FWD network will be external to the EURL-AR.

The EURL-AR will adjust the ring trials according to the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria to meet the needs of the decision and to fulfil the objectives.

The activities related to the organization of the ring trials, shipments, evaluation of results, production of reports and the maintenance of a quality assurance system with accredited proficiency testing encompasses the largest part of the EURL-AR staff workload, involving

both academic personnel (quality assurance, organization, communication with NRL's, planning, data collection, data analysis and report writing and presentation of results, follow up on deviations and /or missions related to follow up on ring trial results) and technicians (testing of isolates, preparation of samples, quality control activities, shipping of samples) representing circa 54.2% of the total salary expenses. Furthermore, the organization of ring trials represents circa 89,4 % of the consumables and 83,3 % of the shipping expenses.

4. Evaluation and development of analytic methods

4.1. Reference strains

Reference strains for use in quality control or other analyses are an important part of the internal quality control and validation of on-going analyses. The EURL-AR will continuously extend its already available strain collection and make the strains available for NRL's on request.

4.2. Interpretative criteria

In relation to the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria it will be necessary that the EURL-AR performs studies on the susceptibility of food borne pathogens to various antimicrobial agents in order to provide data for the establishment of interpretative criteria for categorizing isolates as susceptible or resistant.

On the annual workshop between all NRL's, the most urgent needs and problems were discussed. Thus, especially for 2014 the EURL-AR will initiate the following projects:

- 4.2.1. As follow-up on the survey on MIC methods and plate design there might be a need to perform comparisons of the performance of different plates under the same conditions.
- 4.2.2. The EURL-AR will facilitate the collection and dissemination of antimicrobial susceptibility data of relevant veterinary and food microorganisms for EUCAST.
- 4.2.3. Continue the work on determine the phenotypic MIC value based on single gene cloning focusing on carbapenemase-genes.
- 4.2.4. Evaluate procedures and methodologies for development of selective enrichment protocol to detect ESBL- or AmpC- or carbapenemase producing *Salmonella* spp. and *E. coli* according to the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria.
- 4.2.5. The EURL-AR will collaborate with EUCAST to provide ECOFF data for antimicrobials where such for the moment do not exist according to the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria

The activities related to evaluation and development of analytical methods will involve close collaboration between elements of the EURL-AR and of the NRLs, representing therefore excellent networking opportunities. The workload related to these projects is expected to represent circa 8.4% of the salary expenses for the EURL-AR in 2014, 7,4 % of the consumables and a 16,7% of the shipping costs due to the need of exchange of materials, isolates or reference strains between the involved laboratories. Furthermore, the EURL-AR will collaborate with other relevant scientists in relation to point 4.2.4 on the development of selective enrichment procedures and therefore point 6 includes one mission for 2 EURL-AR representatives.

5. Confirmatory testing

The EURL-AR will provide confirmatory testing for NRL's on bacterial isolates of particular relevance or on request by the European Commission. Specifically, the EURL-AR will provide reference testing of putative *Salmonella* and *E. coli* isolates producing beta-lactamases with extended spectrum, and carbapenemases. Additionally, the EURL-AR will also provide reference testing to the NRLs for characterization of isolates resistant to fluoroquinolone or harbouring transferable fluoroquinolone resistance mechanisms, and confirmation of MRSA.

Confirmatory testing requests are sent on ad-hoc basis and their volume for 2014 is therefore not predictable, depending on the needs of the Commission, and the NRLs, we have therefore calculated that these represent circa 2.2% of the salary expenses and 3% of the consumables used in the laboratory.

6. Missions for specific assistance to individual laboratories (site visits) or activities related to the implementation of the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria

Some NRL's might have a need for special assistance. The EURL-AR will to the extent possible within the financial limits provide specific assistance to individual laboratories based on individual needs in the follow-up of ring trial results or need to implement methodology.

In 2014, the EURL-AR plans to visit one selected NRL that requires special training or advice. Such site visits also provide the EURL-AR with a better understanding and knowledge in terms of used methodologies, routines etc. in the NRL. This information is crucial to provide the optimal assistance and help. The organization of the one site visit will include hands-on practical training and theoretical lectures (related to the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria). In addition, one consultation abroad will be conducted related to the development of the carbapenemase-testing scheme to be adopted from 2015 according to MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria (as referred under point 4.2.5). The overall expenses related to item 6 are expected to represent circa 4.8% of the EURL-AR salary expenses and travel expenses are calculated to 4900 EUR, for two 4 to 5-day travels including 2 members of EURL-AR staff.

7. E-learning

The continuous changing of staff at the different NRLs makes it difficult to ensure sufficient training through individual and larger training courses. The EURL-AR will increase the focus on this point and invest more efforts in the creation of e-learning tools during the next years. Therefore, more activities will be set up in 2014, for the implementation of e-learning in an online and interactive interface. The focus will be on making the material created in 2013 available online (on basic principles and methods of susceptibility testing, and detection of emerging resistance problems).

As referred before, this activity is budgeted separately from the other activities related to the support of NRL's as it will increase in focus and is expected to represent circa 5,1% of the total EURL-AR salary expenses for 2014.

8. Workshop

In 2013, the workshop organized by the EURL-AR was an integrated approach including a joint day between the ECDC-FWD-network and the EURL-AR network. The EURL-AR will in 2014 explore with ECDC if the same approach would be feasible. The meeting venue will

most likely be DTU, Denmark but if integrated with ECDC it cannot be ruled out that another alternative venue will be selected. All expenses and administration related to hosting the ECDC-FWD network will either be covered by ECDC or as in kind by DTU. EU funding will solely be used to host the EURL-AR network. The agenda will include the following key components:

- Update from EURL-AR, EFSA, ECDC, the European Commission and other parties
- Results of the proficiency tests performed in 2013
- Integrated monitoring aspects
- Presentation of scientific projects and other activities at the NRL's

The 2014 workshop will include up to 35 participants in total - including representatives from the NRL network (reimbursement of one NRL per MS), invited speakers from relevant organisations (reimbursement for up to three experts), representatives from 3rd countries including EU candidate countries and representatives from the WHO EURO network in relation to action 4 according to the EC action plan on AMR. This will hopefully give opportunity to expand the network and exert more influence on the quality of susceptibility testing performed in non-EU countries.

The total budget for the two days workshop is 40,600 EUR. This includes 12,250 EUR in travel expenses for up to 35 participants, 15,750 EUR for lodging, and 12,600 in daily allowance.

9. Training course

The EURL-AR plan to arrange a training course focused on harmonization, assuring that all MS are able to perform the harmonized monitoring according the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria that will apply from 2014/2015. This includes identification by selective enrichment, phenotypical testing of ESBL, carbapenem, and ampC using the new EU plate formats, and interpretation of those result categorizing them according to the legislation, and if possible updates on genomic tools.

The 2014 training course will include up to 35 participants in total - including representatives from the NRL network (reimbursement of one NRL per MS), invited speakers from relevant organisations (reimbursement for up to three experts), representatives from 3rd countries including EU candidate countries and representatives from the WHO EURO network in relation to action 4 according to the EC action plan on AMR.

The total budget for the two days workshop is 59,500 EUR. This includes 12,250 EUR in travel expenses for up to 35 participants, 26,250 EUR for lodging, and 21,000 in daily allowance.

ANNEX

The DTU-Food (antimicrobial resistance group) has additional activities relevant to the activities of the EURL-AR but not funded by the European Commission. These activities encompass research activities, participation in antimicrobial resistances related meeting activities, facilitation of training courses (as part of the obligations as a WHO collaborating centre in the area of antimicrobial resistance), and hosting a number of non-NRL associated researchers working within the area of antimicrobial resistance:

1. The EURL-ARs related web sites hosting additional tools such as the genomic ResFinder tool. Specifically for 2014, the EURL-AR will provide updates on new tool developments such as the inclusion of chromosomal point mutations in *Campylobacter* and *Salmonella* for implementation in the Resfinder tool. In addition, a database/tool for identification of most known genes and variants based on sequence data (including reads and assembled whole genomes) is available (ResFinder). All EU agencies will have free access to and can obtain a copy of the database. In 2012 we have started to collect information on available sequences, and this will be continued in 2014.
2. The technological developments in whole genome sequencing will soon allow this to be used in routine diagnostic, either as a supplement or a replacement to currently used phenotypic techniques. The EURL-AR will continuously keep the network closely informed about developments in this area and the progress of the Global Microbial Identifier (GMI) initiative.
3. As regards the annually organized proficiency tests, the ECDC-network of Food and Waterborne Diseases will be offered the participation in the *Salmonella* and *Campylobacter* proficiency test. The funding for including ECDC FWD network will be external to the EURL-AR.
4. The EURL-AR will as WHO Collaborating Center on AMR continue activities funded by DTU-Food but supporting the EURL-AR network – such as a global EQAS on eg. antimicrobial susceptibility of *Salmonella* and *Shigella* and MIC determination of *Campylobacter*. Furthermore, laboratory support by reference testing and hosting researchers, setting up research projects with the area of AMR, and collection AMR data through the WHONET.