

EURL-AR, Work Plan for 2015

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 Commission Implementing Decision (2013/652/EU) on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria¹ as well as the Communication from the Commission to the European Parliament and the Council, Action plan against the rising threats from Antimicrobial Resistance (COM (2011) 748)².

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 and genomics, advisory tasks, teaching, as well as several ongoing research projects. The EURL-AR corresponds to circa 16.5 % of the total activities of the Research group, and to circa 8.7 % 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

In 2015, the EURL-AR will provide advice as stated under the general terms with an emphasis on the Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria and the Commission's Action plan against the rising threats from Antimicrobial Resistance. This will include e.g. specific advice on the methodologies for detection of ESBL and carbapenem resistant *E. coli* and *Salmonella*, new 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. The EURL-AR has designated trained personnel available for emergency situations occurring within the European Union related to antimicrobial resistance including whole genome sequencing.

¹ OJ L 303, 14.11.2013, p.26

² http://ec.europa.eu/food/food/biosafety/antimicrobial_resistance/index_en.htm

For 2015, 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 9.9 % of the total EURL-AR salary expenses. Travel expenses for the EURL-AR staff related to this activity are calculated to circa 39259 DKK, 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 Action Plan against antimicrobial resistance. The EURL-AR will in 2015 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 (phenotypic and genotypic). Furthermore, the EURL-AR will in 2015 summarise in a report the replies retrieved from the survey conducted in 2014 on the organization and responsibilities of the NRLs and a number of details related to the conduct of the Decision 2013/652/EU on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria.

2.2. Maintaining the network of NRL's

The EURL-AR will during 2015 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 by the help of WHO to be included in the network. In 2015, the EURL-AR will also undertake the preparation and organization of one workshop.

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 2015, the EURL-AR will ensure dissemination of all relevant information and development related to Decision 2013/652/EU on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria.

The EURL-AR will provide updated lists of ECOFF 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. Depending on the release of reported MIC from MSs to EFSA, the EURL-AR will offer the assistance in determining new ECOFFs eg. for colistin, temocillin etc..

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. 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 2015, the EURL-AR intends to continue the above mentioned activities (2.1; 2.2; 2.3; and 2.4) which represent circa 13,0% 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 2015 organize the following ring trials on antimicrobial susceptibility testing for participation of the by the MS designated NRLs.

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

3.7. Qualitative detection of ESBL and AmpC producing *E. coli* from a matrix of caecal and food samples (cattle and swine / beef and pork)

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

The EURL-AR will adjust the ring trials according to Decision 2013/652/EU 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. In the WP 2014 the ring trials for MRSA was put on hold due to the priority on the test included in the Decision and has not been reintroduced the program for 2015 due to budget limitations, in spite of the increased focus of the on transmission of MRSA from farm animals to man.

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) database developer (enhancing the structure of and update data in the databases) and technicians (testing of isolates, preparation of samples, quality control activities, shipping of samples) representing circa 53.2% of the total salary expenses. Furthermore, the organization of ring trials represents circa 80.0 % of the consumables and 83.5 % 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 Decision 2013/652/EU 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 detection and susceptibility of food borne pathogens to various antimicrobial agents in order to provide the necessary advice and guidance.

Especially for 2015 the EURL-AR will initiate or continue the following projects:

- 4.2.1. Continue the work on determine the phenotypic MIC value based on single gene cloning focusing on carbapenemase-genes.
- 4.2.2. Continue the work on validation, optimization and application of the protocols for detection ESBL- or AmpC- or carbapenemase producing *E. coli* to meet the MS level including the needs for updates in the protocols and QC schemes.
- 4.2.3. Evaluation of the protocols for detection of ESBL- AmpC or carbapenemase-producing *E. coli* focusing on poultry samples (cecal samples and meat).
- 4.2.4. Evaluate procedures and methodologies for quantification ESBL- or AmpC- or carbapenemase producing *E. coli* in chicken meat /cecal samples 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 and EFSA to provide ECOFF data for antimicrobials where such for the moment do not exist according to Decision 2013/652/EU 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 13.2% of the salary expenses for the EURL-AR in 2015, 6.7 % of the consumables and a 6.2% 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 experts in relation to points 4.2.1-4.

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. Furthermore, the EURL-AR will support the implementation of the new monitoring introduced in 2015 on ESBL/AmpC and carbapenemases producing bacteria by MS, especially in countries with expected high prevalence. 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 2015 is therefore not predictable but believed to be more than previous years.

As agreed with the EC (at the expert meeting on the 27th August 2014), additional confirmatory testing will be offered by the EURL-AR to support the activities related with the implementation of the new monitoring and selective enrichment methods. The EURL-AR will prepare general material transfer agreements (MTAs) between the EURL and MSs to ensure the legal aspects of strain and publication ownership of the MSs in terms of confirmatory testing of strains and performance the necessary confirmations, including re-testing for confirmation of the phenotype and additional characterization using appropriate methods including whole genome sequencing. This confirmation will be used to assure the quality of results for MS and confirm the presumptive phenotypes observed and respective corresponding genotypes and resistance mechanisms. We have therefore calculated that in this activity we would test circa 100 isolates following a certain selection criteria to ensure diversity among strains and MSs. The expenses related to this activity would represent circa 3.3% of the salary expenses, 13.2% of the consumables used in the laboratory and 10.3% of the shipping costs due to costs related to the shipment of the isolates from the NRLs to the EURL-AR.

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 and 3rd countries such as candidate countries might have a need for special assistance in the implementation of the EC action plan on AMR, especially on Action 10 on monitoring and surveillance. 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 (training). The third countries to be visited will be selected in coordination with international organizations (WHO Europe)

In 2015, the EURL-AR plans to visit one selected NRL and one 3rd country 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 and beyond. This information is crucial to provide the optimal assistance and help. The organization of the site visit will include hands-on practical training and theoretical lectures (related to Decision 2013/652/EU on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria). The overall expenses related to item 6 are expected to represent circa 4.3% of the EURL-AR salary expenses and travel expenses are calculated to 43000 DKK, 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 2015, for the implementation of e-learning in an online and interactive interface. The focus will be on extending the currently available e-learning on basic AMR and susceptibility testing to also include smaller elements targeting ESBL testing, carbapenemases, MRSA, etc.

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 3.0% of the total EURL-AR salary expenses for 2014.

8. Workshop

The EURL-AR will in 2015 host the annual workshop at DTU. 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 2014
- Integrated monitoring aspects – the new legislation
- Presentation of scientific projects and other activities at the NRL's

The 2015 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 Europe network and FAO in relation to Action 8 of 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. We reserve the possibility of collaboration with ECDC and their network in the workshop organization, depending on the possibilities and aims from both networks.

The total budget for the two-day workshop is 335,000 DKK. This includes 100,000 DKK in travel expenses for up to 40 participants, 125,000 DKK for lodging, and 110,000 DKK 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 to the new legislation (Decision 2013/652/EU). This will include the relevant parts of 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 2015 training course will include up to 40 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 Europe network in relation to action 8 of the EC action plan on AMR (reimbursement for up to 10 representatives).

The total budget for the 3 days workshop is 443,000 DKK. This includes 100,000 DKK in travel expenses for up to 40 participants, 178,000 DKK for lodging, and 165,000 DKK 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-EURL 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 2015, 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 2015.
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. 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.