

EURL-AR, Work Plan for 2016 and 2017

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 for Genomic Epidemiology. The main activities of this research group relate to global real-time surveillance including antimicrobial resistance among bacteria from food animals. The research group conducts targeted research to predict and prevent infectious diseases pathogens and support the global detection and control with a particular focus on reducing the occurrence of antimicrobial resistance and antimicrobial resistant bacteria among food animals and food products. The scope of activities of the laboratory includes several international research activities, projects, and programmes, education and teaching, and research-based decision support - advisory service such as the EURL for Antimicrobial Resistance, and the WHO Collaborating Center for Antimicrobial Resistance and Genomics. The EURL-AR corresponds to circa 11 % of the total activities of the research group. 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 Member States, EU agencies and the Commission

In 2016 and 2017, 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 to the Member States on: the methodologies for detection of ESBL, AmpC and carbapenem resistant *E. coli* and *Salmonella* and quantitative enumeration of ESBL and AmpC resistant *E. coli* new ECOFF's for temocillin and possible other substances if needed. The EURL-AMR will also produce guidance documents i.e. "how to use next generation sequencing for monitoring of antimicrobial resistance genes", "What is needed for QA/QC", and "target list for reference testing using MIC and whole genome sequencing", and needed training in "Next generation sequencing for monitoring of antimicrobial resistance genes", "Detection of ESBL, AmpC and carbapenem resistant *E. coli* and *Salmonella*" and "Detection of other emerging relevant antimicrobial resistance pheno – and geno-types". The EURL-AR will participate in workshops and working groups on antimicrobial resistance initiated by EFSA, EMA, ECDC,

¹ OJ L 303, 14.11.2013, p.26

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

Codex, FAO/WHO/OIE or other relevant organisations. The EURL-AR will continue to actively support the WHO established Advisory Group in Surveillance of Antimicrobial Resistance (AGISAR), which has as the aim to develop global standards for monitoring of antimicrobial resistance. The positions taken by the EURL-AR during those workshops and working groups will be in line with the Commission's strategy on AMR as expressed in the Commission Action plan against the rising threats from Antimicrobial Resistance (COM (2011) 748). The EURL-AR has designated trained personnel available for emergency situations occurring within the European Union related to emergence of new or unusual resistant strains or spread of new resistance mechanisms by providing assistance to Member States for detection of antimicrobial resistance genes using whole genome sequencing in combination with bioinformatics.

For 2016 and 2017, 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 72000 DKK, for 5-6 short travels per year.

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

2.1. Meetings on standardization of monitoring of antimicrobial resistance

International collaboration and the development and harmonisation of global standards is high priority, as also indicated by the launch of the Commission Implementing Decision (2013/652/EU) on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria and the Commission's Action Plan against antimicrobial resistance. In 2016 and 2017, the EURL-AR will 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 the capacity building in some countries for antimicrobial resistance monitoring (phenotypic and genotypic) in particular in poor performing Member States, or applicant and candidate countries. Furthermore, the EURL-AR will in 2016 and 2017 conduct at least two surveys in Member States of which one will target MIC panel availabilities and observed deviations as suggested during the 2015 workshop whereas the other will focus on experiences related to the selective enrichment of ESBL protocols including suggestions for changes incl. MIC panels etc: The replies retrieved will be summarised in a report and improvement to the protocols will subsequently be evaluated.

2.2. Maintaining the network of NRL's

The EURL-AR will during 2016 and 2017 maintain and continuously update a full list of contact persons from all NRL's. In addition, the EURL-AR will attempt by the help of the Commission, to identify relevant contact persons from applicant and candidate countries to be included in the network. In 2016 and 2017, the EURL-AR will also undertake the preparation and organization of one annual workshop and aim at organizing the workshop in 2017 jointly with participation of the ECDC Food and Waterborne Disease network (FWD).

2.3. Dissemination and collection 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 e-mails messages or newsletters to the NRL's.

Specifically for 2016 and 2017, 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 in specific new protocols and updates to current protocols.

Quarterly, the EURL-AR will monitor any new release of ECOFF values or changes from EUCAST (www.eucast.org) in relation to the current list in the Commission Implementing Decision (2013/652/EU) on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria. Any observed discrepancies will be disseminated to the network. The EURL-AR will offer the assistance in determining new ECOFFs e.g. for colistin, temocillin etc.

The EURL-AR will continue to disseminate to Member States 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 2016 and 2017, the EURL-AR intends to continue the above mentioned activities (2.1; 2.2; 2.3; and 2.4) which represent circa 12,9% of the total salary expenses of the EURL-AR. To perform the administrative activities we will have the need to acquire two laptops/PCs during the period 2016-2017 which will cost around 10134 DKK and are included in the budget under the budget item for capital equipment.

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 during 2016 and 2017 annually organize each of 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. Matrix EQAS, including qualitative detection of ESBL and AmpC producing *E. coli* from a matrix of caecal and food samples (cattle swine, and chicken/ beef pork, and chicken meat). The EQAS in 2016 will focus on chicken samples whereas 2017 will be on pig / pork and cattle / beef samples.

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.

The activities related to the organization of the ring trials, including shipments (temperature-monitored using thermologgers for the matrix EQAS), preparation and testing of online databases, 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, database design and testing, data collection, data analysis, report writing including presentation of results, follow up on deviations by email communication and /or missions) 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 55,6% 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. In specific, the EURL-AR have a stock of most relevant ATCC reference strains but intends, in 2016, to provide a set of new internal reference strains more resistant than the *E. coli* ATCC 25922 allowing for a better quality assessment of the EUVSEC and EUVSEC2 but also EUVENC and EUCAMP2 MIC plates being used by the NRLs.

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 2016 and 2017 the EURL-AR will initiate or continue the following projects:

- 4.2.1. Continue the work on the 2014 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.
- 4.2.2. Evaluate procedures and methodologies for quantification ESBL- or AmpC- or carbapenemase producing *E. coli* in pig and cattle caecal samples as well as from pork and beef according to the MS-adopted Decision on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria.
- 4.2.3. The EURL-AR will collaborate with EUCAST and EFSA to provide ECOFF data for antimicrobials where such for the moment do not exist or where a

change is necessary in Decision 2013/652/EU on the Monitoring and Reporting of Antimicrobial Resistance in Zoonotic and Commensal Bacteria. The work also includes collaboration in terms of interpretation of the data collected.

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 11,6% of the salary expenses for the EURL-AR in 2016 and 2017 6,7 % of the consumables and 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 - 4.2.3

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 and EFSA. Specifically, the EURL-AR will provide reference testing of putative *Salmonella* and *E. coli* isolates producing beta-lactamases with extended spectrum, and carbapenemases. This specific targeted 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 offer relevant legal Material Transfer Agreements (MTAs) between the EURL and MSs to ensure the legal aspects of strain and publication ownership. This confirmation will be used to assure the quality of results for MS, confirm the presumptive phenotypes observed, determine the respective corresponding genotypes and detect resistance mechanisms. The calculation for this activity includes the application of certain selection criteria to ensure diversity among strains and MSs and subsequently testing circa 100 isolates by MIC determination and next generation sequencing .

Additionally, the EURL-AR will 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 2016 and 2017 is therefore not predictable but believed to be the same as in 2015.

The expenses related to this activity would represent circa 3,4% 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 the Commission.

In 2016 and 2017, the EURL-AR plans to visit one selected NRL per year 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 3,2% of the EURL-AR salary expenses and travel expenses are calculated to 81900 DKK, for three 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 keep the focus on this point and continue to invest efforts in the creation of new e-learning lectures during the period 2016-2017. The focus will be on extending the currently available e-learning on basic AMR and susceptibility testing to also include 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 3,2% of the total EURL-AR salary expenses for 2016 and 2017.

8. Workshop

The EURL-AR will in 2016 and 2017 host annual workshops at DTU and aim to organizing a joint workshop with the ECDC/FWD network in 2017. Any expenses related to the FWD-network's participation in the joint workshop will be covered by the ECDC. The EURL funding will solely be used to host the EURL network.

The meeting agendas 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 2015 and 2016
- Monitoring aspects e.g.– protocols, data provision, data interpretation and challenges.
- Presentation of scientific projects and other activities at the NRL's

The workshops 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 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 one training course in 2016 and one in 2017

The curriculum for the training course in 2016 will target methodologies related to the Decision 2013/652/EU but will also aim towards detected difficulties in relation to antimicrobial susceptibility testing in general. This might include the relevant parts of identification by selective enrichment, phenotypical testing of ESBL, carbapenem, and AmpC using the EU plate formats, and interpretation of those result categorizing them according to the legislation, and if possible updates on genomic tools.

The 2016 training course will include up to eight participants in total - including representatives from the NRL network (reimbursement of one NRL per MS), representatives from 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 eight representatives).

Currently, a number of countries worldwide have started using next generation sequencing and detection of antimicrobial resistance genes for research and monitoring purposes. The EURL-AR has already held one-day introduction courses for the NRLs bringing their knowledge up to date with the current state of art within this area. In 2017, the EURL-AR plans to arrange a four days training course focusing at the use of next generation sequencing in monitoring of antimicrobial resistance as several NRLs now have the equipment installed.

The 2017 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 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 training course in 2016 is 84 600 DKK. This includes 20 000DKK in travel expenses for up to eight participants 32 200 DKK for lodging, and 32 400 DKK in daily allowance.

The total budget for the 4 days training course in 2017 is 505 000 DKK. This includes 100 000DKK in travel expenses for up to forty participants 207 000DKK for lodging, and 198000 DKK in daily allowance.