EMPIR Call 2015 – Health, SI, Normative and Research Potential

Selected Research Topic number: **SRT-h01**
Version: 1.0

Title: Novel materials and methods for the detection, traceable monitoring and evaluation of antimicrobial resistance

Abstract

Infectious diseases are a major burden on national healthcare systems with wider implications in areas vital for public health such as chemothetapy and surgery. The impact of infections is being re-emphasised by the spread of antimicrobial resistance (AMR), now acknowledged globally as one of the most prominent potential threats to human health and envisaged to become the main cause of death in the next 30 years. Management of AMR is hindered by a lack of fast, accurate and reproducible methods to target existing therapies and for efficient identification of emerging antibiotics. Thus an underpinning metrology framework is needed to support the development of new accurate materials and methods for the detection, monitoring and evaluation of hospital acquired (primary) and treatment induced (secondary) AMR. Reference standards for the functional validation and screening of last-resort and emerging antibiotics should be developed as should novel higher order materials and methods to support next generation approaches for the early and rapid detection of antimicrobial resistance.

Keywords

Infectious diseases, antibiotics, antimicrobial resistance, diagnosis, detection, monitoring, hospital acquired infection, treatment induced infection, viruses, bacteria

Background to the Metrological Challenges

Antimicrobial resistance (AMR) currently affects over 400,000 Europeans per annum and it is predicted to account for 45 % of global deaths by 2050 [1]. Thus, it is one of the three greatest threats to human health (WHO, 2009), threatening effective prevention and treatment of an increasing range of infections, and it requires global action [2]. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and such patients frequently have worse outcomes and consume more healthcare resources. There are several European initiatives to improve the detection and treatment of AMR [3] which are being supported by major pharmaceutical and diagnostic companies. However, AMR testing in Europe is currently performed using a wide range of inadequate diagnosis tools. Therefore, more effective standard approaches need to be developed.

Current methods for the identification of infection in patients, and their AMR status, primarily involve microbial culture in the presence of a given antibiotic, but molecular methods and biochemical analyses are increasingly being used for the rapid identification of AMR. However, there are currently no reference materials or methods available to support proficiency testing in this area, with laboratories comparing clinical samples to meet accreditation. In both cases there is no traceable value assignment, which can result in a high degree of inter-laboratory error and an inability to accurately evaluate novel next generation methods. Therefore materials and methods need to be developed for independent validation. The above challenges all relate to detecting primary (acquired) AMR. Culture is also used to test the development of secondary resistance, however this is usually too late as it requires empirical suspicion that the patient has stopped responding to treatment (e.g. Mycobacterium tuberculosis); thus resistance has already developed. Molecular methods are also used for routine monitoring in viral infections (e.g. HIV) to guide treatment and to reduce the impact of AMR. For routine quantitative molecular testing, proficiency schemes are, in cases, supported by WHO standards, however these are not traceable to the SI nor do they contain comprehensive, robust estimations of uncertainty thus making intercomparison between technology platforms difficult to assess. The lack of higher order materials and methods leads to problems in understanding sources of variance and bias, meaning that laboratories are more concerned with agreeing with the group than in obtaining the correct results. Thus, traceable dynamic measurements are an essential need for the reproducible determination that AMR has occurred.

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The widespread use of antibiotics has resulted in some medically-important bacteria becoming antibiotic resistant. The expiry of background patents for traditional antibiotics in 2013, new regulations which limit their use, and antibiotic resistance itself, has all resulted in the repertoire of effective antibiotics being confined, in some cases, to "last-resort" (e.g. *vancomycins, gramicidins*) and emerging (e.g. *teixobactin*) antibiotics, which target the bacterial cell as a whole by destroying their cell walls and membranes. Although, once deemed unlikely, cell wall/membrane resistance is already developing at an alarming rate (e.g. vancomycin-resistant *Staphylococcus aureus* (VRSA)). Current methods for the development of novel therapies are limited to bioactivity tests against e.g. Methicillin-resistant *Staphylococcus aureus* (MRSA), which take no account of cell wall/membrane resistance development. Therefore, higher order reference methods for testing and validating antibiotic cell wall/membrane resistance need to be developed. Such methods will allow us to measure and relate membrane composition with resistance to commercial, "last-resort" and emerging antibiotics. Also, primary biophysical standards of resistant membranes need to be developed as screening platforms for new antibiotics.

New advanced approaches, like matrix-assisted laser desorption ionisation–time of flight (MALDI-TOF) and next generation sequencing (NGS), have been used in clinical research and are in routine use. They have provided new methods to both detect known AMR in an increasingly powerful manner and to discover new resistance mechanisms. These approaches are fundamental to tackling AMR, yet pre-clinical research does not pay sufficient attention to sources of error and reproducibility, as demonstrated through the publication of minimum information guidelines like MIQE and MINSEQE, a fact that will only be complicated by the increased dependence on bioinformatics approaches.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the JRP-Protocol.

The JRP shall focus on metrology research for the detection, traceable monitoring and evaluation of antimicrobial resistance.

The specific objectives are

1. To establish a metrology framework to support the highly accurate measurement of 'primary' antimicrobial resistance, which includes hospital acquired infections e.g. highly resistant bacteria. This will be achieved by:
    - developing higher order materials and methods for the validation and improved traceability of culture, biochemical and molecular approaches. This should enable the accurate stratification of patients with infection, to prevent unnecessary antibiotic use, and the subsequent detection of antimicrobial resistance in acute clinical management.
    - introducing a reference method for bioassays (e.g. the minimum inhibitory concentration (MIC)), which are used for performing comparable measurements of antimicrobial susceptibility and resistance to antibiotics. This should provide highly accurate reference methods for the validation of advanced applied methods.
2. To establish a metrology framework to support the use of higher order accurate materials and methods for the monitoring of 'secondary' antimicrobial resistance, which is induced during the treatment of chronic infectious agents e.g. HIV and *Mycobacterium tuberculosis*. This approach should lead to the validation and improved traceability of the molecular approaches which are used for the management of patients with chronic disease.
3. To develop reference standards for the functional validation and screening of last-resort and emerging antibiotics. Quantitative analysis measurements of microbial cell walls/membranes, intact, resistant, and microbes challenged by antibiotics, should be validated as should the kinetics of antimicrobial action against resistant bacteria.
4. To apply novel higher order materials and methods to support next generation (molecular, mass spectrometry) approaches for the early and rapid detection of antimicrobial resistance. This approach should lead to the methods being validated in a robust and reproducible manner i.e. test case evaluations should be compared to available orthogonal methods.
5. To facilitate the take up of the technology and measurement infrastructure developed by the project by healthcare professionals (hospitals and health centres) and industry (pharmaceutical companies). This should include the establishment of a European network,

including NMIs and stakeholders, to support the standardisation of comparable and traceable measurements related to antimicrobial action and resistance. Pilot studies could be supported by the BioAanalysis Working Group of the CCQM.

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution to the project. Any deviation from this must be justified.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the medical sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”.

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.

Additional information

The references were provided by PRT submitters; proposers should therefore establish the relevance of any references.

[1] Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. http://www.jpiamr.eu/wp-content/uploads/2014/12/AMR-Review-Paper-Tackling-a-crisis-for-the-health-and-wealth-of-nations_1-2.pdf

[2] World Health Organisation. http://www.who.int/mediacentre/factsheets/fs194/en/

[3] Combatting Bacterial Resistance in Europe http://www.combacte.com/