European Partnership on Metrology
Call 2022 – Digital Transformation, Health, Integrated European Metrology, Normative and Research Potential

Selected Research Topic number: **SRT-h07**
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Title: Metrology to enable accurate surveillance and diagnosis of pathogens with pandemic potential

Abstract

COVID-19 is one of the most devastating recent societal challenges with unprecedented socioeconomic impact and >5 million global deaths. Early in the pandemic it was clear that tests for surveillance and diagnosis were essential to its control. Yet after rapid development of bioanalytical tools for SARS-CoV-2 detection, routes to assure their accuracy or traceability were not central to wider deployment; this may have hindered the COVID-19 global response. Even today as diagnostics are marketed as part of the pandemic recovery solution, they are often poorly standardised. Therefore, there is a need for the development of a metrological framework to ensure reliable and efficient application of the test procedures used by those tasked with assuring pandemic preparedness.

Keywords

Pandemic, Diagnosis, Epidemiology, Pathogen, Surveillance, Accuracy

Background to the Metrological Challenges

In June 2021 the G7 published its 100 days mission to reduce the impact of future pandemics by making diagnostic, therapeutics and vaccine available within 100 days with accelerated delivery of these key areas a priority for World Health Organisation (WHO). Yet of the three, diagnostics, which represents the first line of defence in responding to and preventing a potential pandemic, is by far the least supported in terms of routes to ensure traceable, accurate and reliable results. The United Nations Industrial Development Organisation (UNIDO) has also emphasised the impact of quality infrastructure improvement on for example the SDG9 *Industry, innovation, and infrastructure* to mitigate the negative effects of pandemics and ensure the provision of essential services. These initiatives place the need for a surveillance network and responsive diagnostic sector as the first factors that would have allowed us to better respond to COVID-19.

Surveillance of pathogens exists with notifiable diseases reported at a national level and monitored regionally by the European Centre for Disease Control (ECDC). Diagnostic surveillance relies primarily on two analytical strategies: either detecting and quantifying the genetics/genome of the pathogen or the serological (antibody) responses produced in response to infection.

SARS-CoV-2 has demonstrated the clear role for genetic/genomic techniques in epidemiology through detection of variants of concern and has illustrated a need for standardisation and quality assurance globally to improve the accuracy of reporting and error definition to avoid mistaken conclusions. SARS-CoV-2 has also highlighted a role for surveillance using wastewater which is currently unstandardised.

The pandemic has illustrated how a handful of analytical tools are essential to deliver the required surveillance and diagnosis. These methods are all in the realm of bioanalysis where metrology is in its infancy with stakeholders broadly unaware of the value of considering factors like uncertainty and traceability. This is reflected in agreement with the need for ‘standards’ without clarity as to what exactly constitutes a material, methodological or documentary standard in this context or how this can be applied to support test performance in a changing pandemic.

A lack of certified reference materials early during the COVID-19 pandemic meant *In vitro* diagnostic (IVD) manufacturers were forced to turn to control materials which were not accurately value assigned and varied from batch to batch. Poor metrological support must in part explain the huge (10,000-fold) variation in limit of detection reported by laboratories submitting tests for emergency use authorisation a fact that was likely exacerbated by arbitrary use of units (leading to >1000-fold difference between laboratories). This is

confounded by the absence of measurement uncertainty from international guidelines describing diagnostic targets like limit of detection.

It is likely that the absence of metrology to assure diagnostic accuracy hindered the global response to COVID-19 given that decisions were made using data derived from highly variable diagnostic measurements. This problem will remain and hinder public health and clinical management decisions in future outbreaks unless metrological principles are built into national guidelines and EU and other regional regulations for IVD solutions. For this reason, metrological traceability is a central requirement of the *In vitro* diagnostic Regulation (IVDR) which must include diagnostic tools deployed in response to pandemics and epidemics.

The "CCQM workshop on a roadmap for future pandemic response" highlighted that reference laboratories tasked with initial diagnosis of COVID-19, struggled when trying to support its wider deployment. Throughout 2020 and 2021 high demand and emergency use authorisation meant numerous formats were deployed with few routes corroborating performance claims. Today across Europe, COVID-19 diagnosis is delivered in two formats; molecular methods, like PCR, or point of care lateral flow devices (LFDs). While NMIs have provided early reference measurement procedures to support molecular methods on a small scale, support for LFDs is limited to initial evaluation using patient samples. This means the billion LFDs conducted in Europe are completely dependent on manufacturer self-certification. Given the absence of a reference measurement system for LFDs it is unclear how they might vary by manufacturer or from batch to batch.

Assumptions on how disease dynamics in COVID-19 can lead to oversimplification of diagnostic performance evaluation have already been demonstrated. Conformity assessment criteria, as specified in EU documentation, currently focus on conventional sensitivity/specificity which are inaccurate: this is confounded by the lack of metrology described above, but also due to the fact harmonised/quality-assured evaluation methods for pandemic response do not exist or are inadequate. This is partly due to incomplete measurement system analysis, together with not exploiting the unique properties of item response theory (IRT) models to enable a measurand restitution.

COVID-19 has resulted in myriad national, regional, and international initiatives for better pandemic preparedness. Many of these discuss the need for advanced measurements as part of the solution. Yet the current situation is that metrology is generally absent from these initiatives. This is confounded by limited bioanalysis capabilities across (Regional Metrology Organisations) RMOs including EURAMET.

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 protocol.

The JRP shall focus on the development of metrology capability in rapid response to outbreaks to ensure complex measurements are made accurately to underpin public health and clinical management decisions.

The specific objectives are:

1. To develop and characterise reference materials to support pandemic surveillance and improve traceability of serological (antibody) testing for COVID-19 and other infectious diseases. In addition to develop reference measurement procedures for pathogen genetic/(meta)genomic surveillance.
2. To establish a reference measurement infrastructure to ensure accurate pandemic diagnostics by describing the comparability of different analytes, including traceability, and use of uncertainty to report IVD performance criteria. To implement strategies for reference measurement procedures and materials to support quality assurance needs of test procedures and kits during a pandemic by using outputs from objective 1. To evaluate innovative technology independent solutions for a potential new standard.
3. To develop analytical methods and statistical models using clinical reference data sets to provide alternative routes for diagnostic evaluation (e.g. by using analyte characteristics to guide tests evaluation and thresholds setting and by using compartmental models to investigate clinical sensitivity shifts on diagnostic performance). To use test evaluation measurement systems to determine the performance of different diagnostic pipelines and outline conformity assessment criteria in accordance with current European directives.
4. To establish a European metrology Network of Excellence between NMIs, stakeholders and wider pandemic initiatives established because of COVID-19, building on the examples of metrological success during the pandemic and with the above objectives contributing to the broader lessons

learned exercises to implement metrology into future policy for improved preparedness and response of the diagnostics and public health community for the future pandemics.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (CCQM Working groups on Nucleic Acid, Protein and Cell Analysis), standards developing organisations (ISO/TC212/TC276), and end users (e.g. international organisations focussed on clinical diagnosis (ESCMID, SoGAT, IFCC; JCTLM)).

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 1.9 M€ and has defined an upper limit of 2.6 M€ for this project.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated 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 and health 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 the Partnership 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.