EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

EXECUTIVE AGENCY FOR HEALTH AND CONSUMERS
Health unit

INTERIM REPORT 02_2013

Contract number: **2010 21 02**

Acronym: **QUANDHI**P

Proposal title:

Quality Assurance Exercises and Networking on the Detection of Highly Infectious Pathogens

Starting date: **1st August 2011**
Duration of the project: **36 months**
Ending date: **31st July 2014**

Project website: **http://www.quandhip.info**

List of 5 key-words using Mesh terms (http://www.nlm.nih.gov/mesh/MBrowser.html)

Diagnostics; Quality assurance; Zoonoses; Communicable diseases; Biosafety And Biosecurity

Executive Summary

The Joint Action (JA) aims to link and consolidate the objectives of two existing networks dealing with highly infectious bacteria and viruses that emerged from the EU funded project EQADeBa, coordinated by the Robert Koch-Institut (RKI), Germany (EAHC n° 2007 204) and the ENP4-Lab project, coordinated by L.Spallanzani National Institute for Infectious Diseases (INMI), Italy (EAHC n° 2006 208). The primary objective of the project is to stabilise both network activities that link 37 highly specialised and advanced partner laboratories from 22 European countries. The common work is establishing a universal exchange of best diagnostic strategies able to support a European response strategy to outbreaks of highly pathogenic infectious agents plus generating a biodiverse repository of reference materials. The JA provides a supportive European infrastructure and strategy for external quality assurance exercises (EQAE, bacterial antibiotic susceptibility testing, training, and biosafety and biosecurity review of current practices).

During the first period of the Joint Action, successful activities undertaken in relation to the horizontal work packages were directed on actions undertaken to manage the project and to make sure that it is implemented as planned (WP1 coordination), actions undertaken to ensure that the results and deliverables of the project will be made available to the target groups (WP2 dissemination), and actions undertaken to verify if the project is being implemented as planned and reaches the objectives (WP3 evaluation). All planned deliverables and milestones for the management of the Joint Action have been achieved timely with a high quality.

Both networks, NIB (network on highly pathogenic bacteria) and NIV (network on highly pathogenic viruses), have performed two External Quality Assurance Exercises (EQAE) in accordance with the time line and planned aims (WP4 External Quality Assurance Exercises). For evaluation of the EQAEs markers for evaluating capabilities were included reviewing the sensitivity and specificity of the detection and identification systems used to detect highly infectious pathogen infections in accordance with the principles of having a biosafe and biosecure facility and using acceptable operational practices. For specific questions and methods working groups were set up in the NIB dealing with antibiotic susceptibility testing (AST-group), with mass spectroscopy as an upcoming tool for rapid identification of bacteria (MALDI-TOF-group), and testing of rapid hand-held test kits focusing on lateral flow assays (HHTK-group). All EQAEs were performed on a very high quality level and the results showed a well-established preparedness of the partners. However, continuous exercises are necessary to maintain and further improve the high quality level for the diagnoses of highly pathogenic bacteria and viruses.

Repositories of reference material for BSL 3 and BSL 4 pathogens have been extended and distributed to network participants for evaluation of established and innovative diagnostic tools (WP5 Repository). The Repository of reference material has been used for the so far performed EQAEs. Moreover, quantitative standards are under development in the NIB which will be held available for the next years. Several partners have already taken the opportunity to order material for evaluation purposes.

Partners of the network have offered practical laboratory based training to other partners covering laboratory diagnostic response strategies in terms of preparation and analysis of samples within BSL-3, and/or BSL-4 facilities with regard to best practices (WP6 Training). All Associated Partners have agreed on the course content, established learning objectives and outcomes. A number of practical training courses have been carried out.

The check lists developed in the framework of the previous projects EQADeBa and ENP4 were compared with guidelines and recommendations derived from documents produced by EC, WHO, CDC, CEN workshops and national authorities (WP7 Biosafety and Biosecurity). Based on the practical requirements of institutions running or developing high containment

laboratories BSL3 or BSL4 the check lists will be further developed and validated considering external input.

A Working Group under the lead of INMI was established to develop proposals for the support in coordination of laboratory activities in case of outbreak response (WP 8 Support to coordination of laboratory response to cross-border events with highly infectious pathogens). The topic of the WP was further defined, leading to the task to develop standard operational procedures (SOPs) for the coordination of laboratory activities during outbreaks; moreover, this should include the "validation" of these SOPs during real outbreaks or specific exercises. A first draft on detailed description of capabilities of QUANDHIP laboratories was collected. An agreement with the ECDC supported project ENIVD was achieved to cooperate and complement activities in outbreak situations. Practical activities occurred already when the network responded to provide technical support for the shipment and testing for the diagnosis of the Hantavirus infection, when QUANDHIP partners were involved in the collection of information regarding diagnostic capabilities for the novel coronavirus (hCoV-EMC) in different countries, and when QUANDHIP partners were directly or indirectly involved in the laboratory investigation of anthrax cases among heroin users (Grunow R et al. Anthrax among heroin users in Europe possibly caused by same Bacillus anthracis strain since 2000. Euro Surveill. 2013 Mar 28;18(13)).

Both, the EQADeBa and ENP4-Lab projects revealed a need for sustainability in European capacity and capability building for the detection and identification of highly infectious bacteria and viruses based on national and international cooperation. The consolidation of the existing networks will ensure European laboratory preparedness to manage natural and deliberate outbreaks of high consequence pathogens. This structure will provide the necessary early response capabilities to support and inform public health control measures, clinical patient management, epidemiological and forensic investigations. The laboratory preparedness for risk group 3 and 4 for the diagnostic of highly pathogenic agents will be evaluated and further improved and intervention activities to support the coordination of response to highly infectious cross-border pathogens will be developed and documented.

Description of the work performed since the beginning of the project and the main results achieved so far

Work package number 1 "coordination"

The RKI and INMI have established and shared technical and managerial coordination of the project. The JA has included common and separate actions for the bacterial and viral network, the Network on Highly Infectious Bacteria (NIB), coordinated by the RKI, and the Network on Highly Infectious Viruses/P4-Laboratories (NIV), coordinated by INMI. A common management structure was developed. The Steering committee started to work in addition to the Advisory board. A Consortium agreement was developed and agreed between the associated partners and a Collaboration agreement for the collaborating partners. Terms of reference were developed and agreed for the activities of the Advisory board. The network websites and electronic mail transfer has ensured the regular communication between participants (official website: http://www.quandhip.info; internal workspace: https://paracelsus.bfarm.de/share).

Furthermore, the communication and coordination with the ECDC funded project European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) was established and agreed in a Letter of Intent to improve collaboration and to avoid duplications in any international activities.

The main partner is overviewing all finances using the experienced financial management at the Robert Koch-Institut.

The JA consists of 5 Core Work Packages led by designated Associated Partners or the Main Partner. The two Technical Coordinators have organised the exchange of information on all

activities between partners. Each network has performed 3 of the 6 planned meetings. Two meetings were joint meetings to bring together all participants of both, NIB and NIV.
The coordinators have developed a communication and laboratory diagnostic management infrastructure. Beyond face-to-face-meetings the applied communication tools are extensive e-mail exchange and the internal QUANDHIP website. The performed two EQAEs were intensively planned to ensure, in some cases, the exchange of living agents of risk group 3. The established communication and transportation strategy and regulatory framework have been the basis of these exercises. A list of European laboratories with diagnostic capabilities and expertise is under development of WP 8 and will be posted on the restricted area of the website.

Work package number 2 "dissemination"

The primary target groups to be considered in the dissemination strategy will be laboratory workers of the beneficiaries and collaborating partners dealing with the diagnostics of high threat pathogens, biosafety experts, first responders, clinical staff and security forces. In the framework of this project, various documents including recommendations for diagnostics, biosafety and biosecurity, management of biological events and risk assessment from the laboratory perspective etc. will be developed. In the framework of WP 8, a Working Group has been set up to collect these documents and to produce recommendations in form of a downloadable and printable PDF file to be posted on the website, targeting at first responders related with laboratory analyses in case of an event. In addition, the visibility of the specific QUANDHIP website and the utility of the access to the website have been promoted. A leaflet has been developed describing the network and its activities. So far, 8 scientific publications and reports were used for dissemination of information on the JA.

The developed appropriate BSL 3 and BSL 4 biosafety and biosecurity checklist, covering infrastructure requirements, containment, training requirements and practices, is under development and will be offered as a guidance system to evaluate and monitor new and established laboratories not yet joining our project.

A dissemination plan has been developed.

Work package number 3 "evaluation"

A Steering committee has been set up consisting of the Technical Coordinators and experienced Associated Partners and is preparing and making decisions together with the Associated partners. The Advisory board was also set up and has been constituted; terms of reference were developed and agreed. The Advisory board will support the implementation of action and will be asked to contribute to the dissemination, evaluation and sustainability of the JA. The documents produced by the Working Group (WP 8) will need extensive evaluation taking into consideration different experts' opinions which primarily will come from the Advisory board. In addition, a very experienced expert, who is also member of the Steering committee, was included by subcontracting. A continuous evaluation process was agreed between the Advisory board, coordinators and WP leaders to ensure that the project meets its defined targets, deliverables, and milestones using indicators for the process, output and outcomes. The results of evaluation will be presented at each project meeting twice a year. The evaluation strategy for coordination, dissemination and performance of core work packages was agreed at a joint network meeting.

Work package number 4 "external quality assurance exercises"

The aim is to ensure that the quality of laboratory diagnostic methodology and strategy at the participants' laboratories is adequate and conforms to 'best practice'. Both networks, NIB and NIV, have performed two External Quality Assurance Exercises (EQAE) in accordance with the time line. For evaluation of the EQAEs markers for evaluating capabilities were included reviewing the sensitivity and specificity of the detection and identification systems used to

detect highly infectious pathogen infections in accordance with the principles of having a biosafe and biosecure facility and using acceptable operational practices. The EQAEs on bacteria were focused on B. anthracis, Y. pestis, F. tularensis, C. burnetii, B. pseudomallei, B. mallei, B. melitensis-group. Twenty samples containing inactivated bacteria in a variety of complex matrices and living bacteria, partially mixed with typical "contaminating" bacteria were provided by the RKI. For specific questions and methods working groups were set up dealing with antibiotic susceptibility testing (AST-group), with mass spectroscopy as an upcoming tool for rapid identification of bacteria (MALDI-TOF-group), and testing of rapid hand-held test kits focusing on lateral flow assays (HHTK-group). Data on antibiotic susceptibility of high threat bacteria are under development. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has been interested in our activities which will be presented to the committee at a special meeting in 2013.
The NIV performed an EQAE focusing on Lassa, Marburg and Ebola viruses prepared in serum samples.
All EQAEs were performed on a very high quality level and the results showed a well-established preparedness of the partners. However, continuous exercises are necessary to maintain and further improve the high quality level for the diagnoses of highly pathogenic bacteria and viruses. For better data exploitation of the exercises, a professional subcontractor has been engaged to support planning and analysis of the next EQAEs.
At face-to-face meetings the results and best practices obtained in the EQAEs were exchanged and discussed. For the next exercises, more efforts will be put on the development of a more simplified process for the development of reference materials. Furthermore, as a consensus output by all participating laboratories, quantitative standards are under development.

Work package number 5 "repository"

The existing repositories in NIB and NIV have been further extended and characterised. Internal data bases have been set up for the repositories providing all available characteristics of the samples. Most of the bacterial and viral strains have been prepared as ready-to-use samples mainly in an inactivated format for the evaluation of new methods and approaches on request of the partners. The repositories were used to generate qualitative and quantitative samples for the EQAEs. Moreover, quantitative standards are under development in the NIB which will be hold available for the next years. Several partners have already taken the opportunity to order material for evaluation purposes.
An appropriate 'material transfer agreement (MTA)' has been arranged between the Main Partner and the Associated Partners in the framework of the Consortium Agreement. This MTA allows the transfer of material between all partners. It is intended to be used also for rapid exchange of material in outbreak situations.

Work package number 6 "training"

Partners of the network have offered practical laboratory based training to other partners covering laboratory diagnostic response strategies in terms of preparation and analysis of samples within BSL-3, and/or BSL-4 facilities with regard to best practices. Six training courses have been provided by selected partners at their institutions. The training programmes are also available for Collaborating Partners on their own account. All Associated Partners have agreed on the course content, established learning objectives and outcomes. The evaluation of the training courses provided so far have shown the high benefit for the participants which has been implemented for the optimisation of laboratory practices for both diagnostic and biosafety/biosecurity procedures.
The WP leader is serving as "training coordinator" who will support and monitor the development of training activities and prepare a final report on these activities.
Additionally, it has been considered to link the training activities with the documents outlined in WP 8.

Work package number 7 "biosafety/biosecurity"

The work is designed to identify, agree and disseminate key elements of construction and operating primary and secondary containment, building design and infrastructure, integrated special equipment, disinfection strategies, and biosecurity issues etc. The previously developed check lists were compared with guidelines and recommendations derived from documents produced by EC, WHO, CDC, CEN workshops and national authorities. Based on the practical requirements of institutions running or developing high containment laboratories BSL3 or BSL4 the check lists will be further developed and validated considering external input. Currently, this is under further development.

The Working Group as outlined under WP 8 will also use the developed and improved checklists for biosafety and biosecurity to produce documents which can be shared within the network and with other interested partners like ECDC.

Work package number 8 "support to laboratory outbreak response coordination"

A Working Group (WG) under the lead of INMI was established to develop proposals for the intervention activities to support the coordination of response to cross-border highly infectious pathogens. This WG was constituted by project partners and members of the Advisory board. Based on a first draft, one special coordination meeting together with the EAHC/DG SANCO was performed and further steps and modifications agreed. Questionnaires to evaluate the capacities, capabilities, and collaboration procedures of participating laboratories have been developed. An improved draft guideline is under development.

The network already came into action in the outbreak situations due to *Bacillus anthracis* in heroin users, hantavirus, influenza virus H7N9, and the novel coronavirus (MERS-CoV).

Expected final results and their potential impact and use (including the socio-economic impact, the wider societal implications of the project and contribution to the policy development at national and EU level)

The project is in the planned time line and all deliverables are visible. According to the main objective of the Joint Action the network activities that link 37 highly specialised and advanced partner laboratories from 22 European countries will be stabilised. This will ensure the universal exchange of best diagnostic strategies able to support a European response strategy to outbreaks of highly pathogenic infectious agents plus generating a biodiverse repository of reference materials. The JA will provide a supportive European infrastructure and strategy for external quality assurance exercises (EQAE, bacterial antibiotic susceptibility testing, training, and biosafety and biosecurity review of current practices). The consolidation of the existing networks will ensure European laboratory preparedness to manage natural and deliberate outbreaks of high consequence pathogens. This structure will provide the necessary early response capabilities to support and inform public health control measures, clinical patient management, epidemiological and forensic investigations. The laboratory preparedness for risk group 3 and 4 for the diagnostic of highly pathogenic agents will be evaluated and further improved and intervention activities to support the coordination of response to highly infectious cross-border pathogens will be developed and documented.

Project website: www.quandhip.info