

PROJECT FINAL REPORT

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Glossary

AMR	Antimicrobial Resistance
CAP	Community acquired pneumonia
CE	Cell equivalent
eICID	electronic Clinical Infection Database
ESBL	Extended Spectrum Beta-lactamase
GW	Genewave
HAP	Hospital acquireud pnemonia
LOD	Limit of detection
LRTI	Lower Respiratory Tract Infection
MD	Mobidiag
NUIG	National University of Ireland, Galway
ORTI	Opportunistic Respiratory Tract Infection
PCR	Polymerase Chain Reaction
RFH	Royal Free Hospital
RTI	Respiratory Tract Infection
SME	Small to Medium Enterprise
UCL	University College London
UCLH	University College London Hospital
UI	User Interface
VAP	Ventilator associated pneumonia

EXECUTIVE SUMMARY

Respiratory tract infections (RTIs) are caused by a variety of bacterial, viral, and fungal pathogens. RTIs are amongst the top 4 major causes of morbidity and mortality in adults and children worldwide. Current laboratory diagnosis of such infections takes 2-3 days and in the meantime the patient receives empirical antibiotics, which may be ineffective compromising outcomes for the patient, or unnecessary prescribing contributing to the burden of AMR. The principal objective of the RiD-RTI project has been to develop a “sample-in, answer-out” diagnostic platform for the rapid diagnosis of different types of pneumonia in less than 2h. This objective has been achieved via successful collaboration of SME and academic partners.

The first task of the project was to consult the available literature and a panel of experts in order to arrive at the RiD-RTI product format and a list of targets. The end result was three panels, CAP, HAP&VAP and ORTI consisting of bacteria and viruses, bacteria and resistance genes and opportunistic pathogens including fungi, bacteria and viruses respectively. Following product definition the consortium set to work on product development.

For sample preparation we developed a method that was easy to use, fast, able to extract and purify both DNA and RNA, able to cope with respiratory specimens and could be integrated into the product cartridge. Process control organisms and assays were developed to monitor our progress and extensive testing was carried out with real respiratory samples. The characteristics of respiratory samples were extensively evaluated in order to aid downstream development.

Meanwhile, development of the GeneSpress platform proceeded as planned. The platform incorporates a single use closed cartridge with embedded reagents where all the processes occur. The instrument automates all the operations in the cartridge, which is driven by a user friendly software which analyse the results. The integrated platform operates sample preparation, nucleic acids amplification and detection using microarray hybridization and imaging.

For assay development sensitive and specific multiplex real-time PCR assays were designed and tested for each of the 3 panels, comprising 2 multiplexes each to be housed in separate cartridge chambers. Microarray capture probes were designed and microarrays were printed in 96 well format and tested using PCR amplicons. The end result was sensitive and specific combined multiplex PCR and microarray assays able to detect the target pathogens on the three RiD-RTI panels.

In parallel with platform and assay development we developed bespoke instrument control, analysis and user interface software. First the software requirements were mapped out, following an extensive development and testing period. The final software has been integrated into the platform and controls the instrument via the linked desktop computer.

Once all components were complete the next task was to integrate them to form the complete RiD-RTI product line, followed by analytical testing of the integrated cartridge and platform. Integration is now complete for the HAP/VAP cartridge which has undergone analytical testing.

The final phase of the project has been clinical evaluation of the tests. Nearly 500 specimens have been collected from individuals suffering from LRTIS at two hospital sites, UCLH and RFH. Routine microbiology culture and genotypic ESBL and carbapenemase results have been collected for all specimens. Clinical specimens have been tested with the integrated HAP/VAP cartridge and combined PCR & microarray assays for CAP and ORTI, with encouraging initial evaluation results.

PROJECT CONTEXT AND OBJECTIVES

Respiratory tract infections (RTIs), particularly those of the lung parenchyma (pneumonia), are caused by a variety of bacterial, viral, and fungal pathogens. RTIs are amongst the top 4 major causes of morbidity and mortality in adults and children worldwide. RTIs are usually classified into three main categories, displaying a contextual variety of clinical presentations: RTIs acquired in the community are called Community Acquired Pneumonia (CAP) and those acquired in hospitals are called Hospital Acquired Pneumonia (HAP), which include Ventilator Associated Pneumonia (VAP). In hospitals, opportunistic RTIs are also major causes of pneumonia in immunosuppressed or immunocompromised patients and these Opportunistic Respiratory Tract Infections (ORTIs) commonly cause serious morbidity and mortality in several inpatient wards. Each of these categories of RTIs is caused by different types of microorganisms.

Currently all ill patients presenting with any form of RTIs (CAP, HAP, VAP or ORTIs) are treated empirically without an accurate diagnosis of the causative microorganism and their antibiotic sensitivity patterns. Correctly identifying the exact microorganism causing RTIs and treating RTIs with appropriate antibiotics they are susceptible to is essential, since morbidity and mortality rates are high. RTIs remain difficult to diagnose accurately since a broad range of pathogens and opportunistic microorganism are involved in their aetiology. Patient management mainly relies on clinical evaluation and in many cases management outcome is dependent on initial empiric antimicrobial therapy. Inappropriate antibiotic therapy contributes greatly to increased morbidity and mortality rates, and inappropriate antibiotic overuse generates antibiotic resistance, which is a major public health concern. Guidelines for diagnosis and management of CAP and HAP state that microbiological studies may support the diagnosis of pneumonia due to an infectious agent, but routine tests are frequently falsely negative and often nonspecific. They also state that there is a clear need for improved diagnostic testing, most likely using molecular methodology rather than culture. Microbiological culture remains the gold standard for the diagnosis of RTIs, the limitations of which include long analysis times and labour intensiveness. Using current methods, it takes 2-3 days minimum to identify the pathogen and its antibiotic susceptibility profile (Figure 1). Delays in accurate pathogen-specific diagnoses may result in the prescription of inappropriate antibiotic therapy and poor treatment outcomes. Thus, there is a great need for rapid, accurate molecular diagnostics tests for the detection of RTIs, capable of identifying a large panel of causative microorganism/s to enable appropriate microorganism-specific therapy to be rapidly initiated for improved management outcomes.

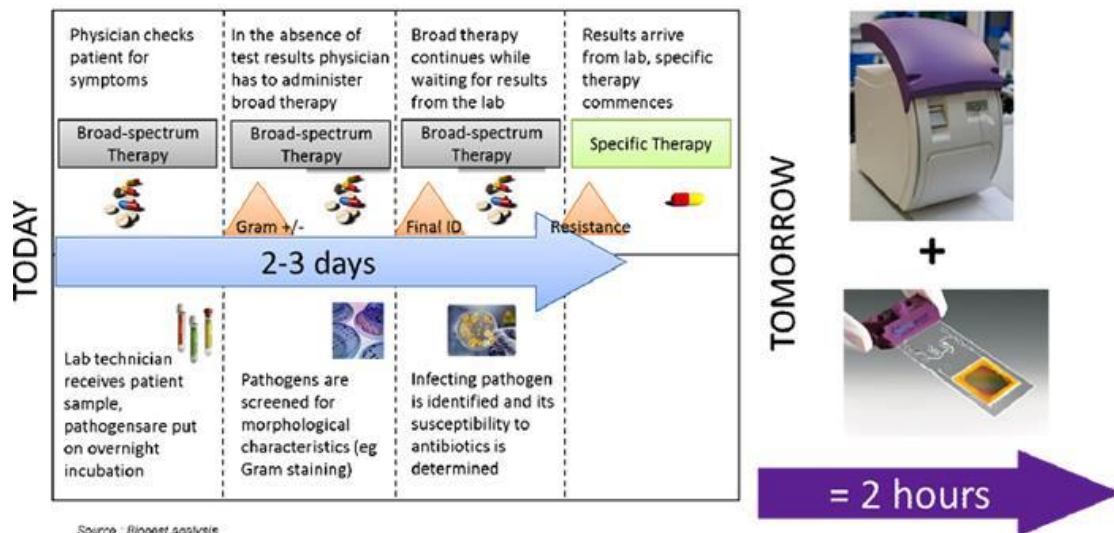


Figure 1. Flowchart showing current practice for pathogen identification and treatment of patients in RTIs.

The principle objective of RiD-RTI is to:

To develop and to validate a multiplex diagnostic system, based on a novel “sample-in, answer-out” diagnostic platform, for the rapid detection (< 2 hrs) of the specific microbial aetiology of RTIs in adults and children acquired in the community and in hospitals.

This will be achieved through automated sample extraction, sensitive and specific, multiplex PCR and microarray detection of amplicons, with processed by onboard analysis software. The concept is summarized visually in figure 2.

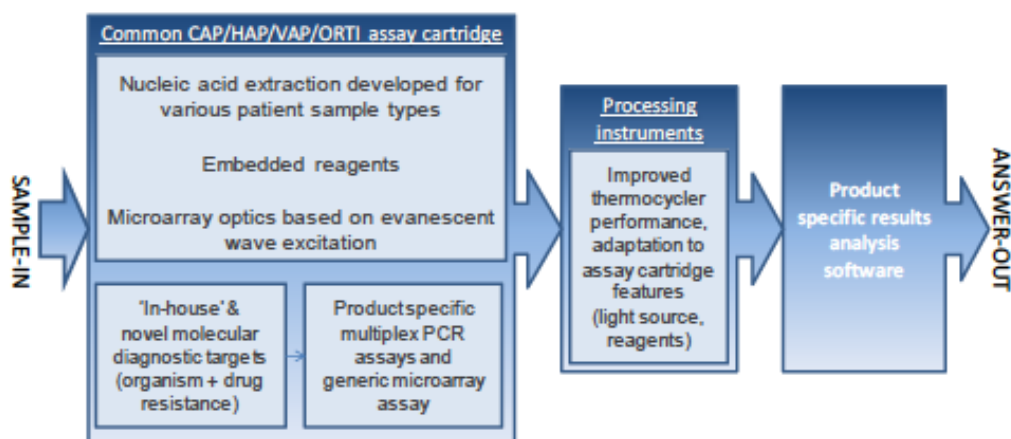


Figure 2. RiD-RTI, “sample-in, answer-out” instrument concept

To achieve this a number of subsidiary objectives, need to be achieved. These are listed below.

- To validate the target panel and product format
- To identify novel molecular diagnostics markers/targets for target organisms and resistances for which existing targets are not suitable.
- To deliver a sample preparation method that enables an easy, fast and integrated DNA extraction method.
- To develop the processing instrument
- To design and validate multiplex PCR assays for target microorganisms, drug resistance markers and controls
- To design and validate a microarray with capture probes specific for target microorganisms, drug resistance markers and controls
- To develop and validate novel end-user analysis software together with flexible and dynamic assay design tools
- To integrate the pre-tested assay protocols provided by early stages of the project into a diagnostics platform
- To perform a prospective observational clinical evaluation study to determine the performance characteristics of the three RiD-RTI diagnostics products compared to culture based reference method
- To develop and facilitate efficient communication between beneficiaries and thus optimization of indirect benefits of the project
- To promote the dissemination and exploitation of project results

DESCRIPTION OF MAIN S&T RESULTS

WP1 Panel Validation And Molecular Targets Identification

Objectives:

- To validate the target panel and product format.
- To evaluate the suitability of the molecular diagnostics targets currently held by the consortium for the specific detection of target organisms and drug resistances.
- To identify novel and existing molecular diagnostics markers for organisms and resistances for which existing molecular targets are not suitable.

Task 1.1 Validation of target panel and product format

Following a review of the literature and on consultation with a panel of clinicians with expertise in the area of RTIs a list of target pathogens and resistances was defined. In addition the proposed format of the diagnostics products that would give the most market penetration and have the biggest impact on patient management and outcomes has been validated. The product format has been validated and will constitute three separate products i.e. CAP, HAP/VAP and ORTI's

Task 1.2 To evaluate the suitability of the molecular diagnostics targets currently held by the consortium for the specific detection of target organisms and drug resistances

Each partner holding background IP on molecular diagnostics targets performed *in silico* evaluation on the usefulness of these targets for the detection of target organisms and resistances. In order to determine the most suitable target for each of the organisms and resistance, publicly available diagnostics target sequence information was analysed for each of the target organisms. In addition, a number of microorganisms (where little or no nucleotide sequence was available) were sourced commercially to evaluate target sequence. After substantial *in silico* analysis of all targets with background IP, the most suitable target to the RiD-RTI project was chosen for further development in WP4.

Task 1.3 Identification of novel and existing molecular diagnostics targets for target organisms and resistances

It was not possible to design assays for some microorganisms and/or resistances using background IP from consortium members. In these cases novel or existing targets described in the literature were used for assay development and freedom to operate (FTO) was performed to ensure the assays can be used in commercial products.

Significant results

The intended format of the three diagnostic products for HAP/VAP, CAP and ORTI has been developed and validated in consultation with independent international experts. A final panel of microorganisms and associated resistance determinants was decided upon for each of the three products. Based on *in silico* analysis, suitable diagnostics targets were identified for each microorganism and resistance marker of interest. Clinical, technical and scientific considerations were taken into account during this process.

Work Package 2 Sample Preparation

Objectives

The main aim of WP2 was to develop a simple and effective sample preparation protocol that can be integrated into the final product format. Respiratory samples can be very challenging to work with due to their variability in nature, often difficult to manipulate consistency and proneness to contamination by colonizing organisms.

Task 2.2 Sample characterization

As part of progress on this work package, the consortium has conducted a thorough literature and experimental survey on the physical characteristics and pathogen distribution in respiratory specimens resulting in a peer-reviewed abstract for presentation at the ECCMID 2014 conference.

The characteristics of three typical samples (Sputum for community-acquired pneumonia, Bronchoalveolar lavage (BAL), Endotracheal tube aspirates (ETT) for hospital acquired pneumonia including ventilator acquired and opportunistic infections analyzed were the:

- Volume
- Viscosity
- Pre-treatment in case of sputum with mucolytic agents
- Inhibitor presence
- Bacteria/ virus targeted concentrations
- Type of samples (sputums, BAL, ETT)

The conclusion was that these samples contain a large number and diversity of organisms, with a large proportion of samples containing multiple pathogenic organisms, many of which are present at high concentration.

Molecular diagnostics is believed to offer more sensitive detection than traditional culture, and is likely to reveal multiple organisms as demonstrated here. This could cause issues when results are interpreted. The prevalence of individual bacteria found is largely in line with results reported in the literature, with some exceptions. For example, in our study *P. aeruginosa* is more common and *S. aureus* is rarer than normally reported, however such discrepancies are minor and could be due to the patient population sampled.

A more worrying concern is that the frequencies of respiratory viruses detected is reported to be very low. These samples were specifically sent for diagnosis of bacterial infection, which could account for some for the difference. Another possible reason is that the sample type used was sputum, which may be detrimental to the preservation of virus. Traditionally viruses are detected from upper respiratory tract swabs, containing special viral transport media.

Task 2.1: Sample collection for a sample bank available to partners.

The consortium has also collected samples for a sample bank available to all partners and developed a framework for acquiring fresh clinical samples for testing.

UCL has made use of the overarching ethical framework and developed an arrangement with the local diagnostic laboratory for sample collection. This allows UCL to access all surplus respiratory samples in real

time, on average 5-30 different samples will be available for use on any given day. UCL has utilized this facility for all experiments conducted thus far and also sent some samples to GW.

Task 2.3 Extraction methods selection

Here, the consortium:

- a) Developed an effective lysis protocol for pre-cartridge processing.
- b) Developed an experimental protocol capable of extracting both DNA and RNA.
- c) Developed models and assays to be used as development tools and process controls.
- d) Adapted the extraction protocol to make it suitable for integration into the test cartridge and commenced development of the integration process.

Task 2.4 Off-line extraction method optimization

Here the consortium developed and optimized automated extraction protocol in mockup dedicated for sample prep with pure bacteria.

Task 2.5 Integration in the instrument

For this task, the consortium developed and optimized automated extraction protocol in prototype which includes all final features: sample prep, amplification and hybridization.

Task 2.6 Validation and performances evaluation

In the final task the consortium assessed the performances of the automated extraction protocol with pure bacteria and spiked sputums.

Significant results

The work has resulted to the ability to perform automated extraction within 25 minutes and down to 10^4 cfu/ml demonstrated with spiked bacteria in sputum at this stage.

Work Package 3 – Development of Disposable Chip and Processing Instrument

Objectives

The main objective of this work package was to develop a platform on which the RID-RTI tests can be performed which is an improved version of the existing technology of the two SME partners in this project: Mobidiag and Genewave. To achieve this ambitious goal, MD and GW developed:

An embedded-reagents disposable chip (Task 3.1)

A single use closed cartridge where all processes happen and incorporating the reagents needed for each test prototype.

Part of the **Subtask 3.1.1**: GW enhanced the lab-on-chip to enable the sample preparation protocols of respiratory tract multi-type (virus, bacteria, fungi, spores) samples and specificities of MD's molecular biology protocol: incremental re-design for the sample purification, PCR and microarray functions, new molds has been fabricated, tested and optimized.

Part of the **Subtask 3.1.2**: GW modified the Optical design

The microarray optical design used a novel evanescent wave excitation which was patented for better sensitivity and dynamic range.

Part of the **Subtask 3.1.3**: GW embedded reagents

GW added a superstructure to the processing chip with:

- Tanks for all the biological reagents:
 - Sample Prep buffers
 - PCR and RT-PCR mix reagents
 - Hybridization buffers
- Network of fluidic channels and valves to distribute the reagents from the tanks to the processing chip.
- A sample injection port.
- An on-board waste compartment.

During the RID-RTI project:

- 3 molds versions have been tested.
- 6000 prototype cartridges have been produced and used for development, analytical and clinical tests.

A processing instrument: GeneSpress (Task 3.2)

An instrument automating all the operations in the cartridge, and a software driving the instrument and analyzing the results (developed within WP5). The platform operates sample preparation, nucleic acids amplification and detection using microarray hybridization and imaging.

Part of the **Subtask 3.2.1**: GW fabricated a new dock:

GW re-designed the docking station which interfaces the cartridge and the instrument for thermal, mechanical, and optical functions.

The major modifications were:

- The accurate fluidic control of buffers inside the cartridge without any liquid contact to the instrument.
- 2 independent PCR chambers and 2 hybridization chambers.

The following features were implemented within the constraints of performances and usability:

- Compactness: benchtop, small-sized instrument
- Through-put: stack up to four instruments with 4 slots
- Flexibility: random access operation for on-demand testing
- User friendly, intuitive touch-screen software

As part of the **Subtask 3.2.3** GW improved microarray detection:

A new light source for evanescent wave excitation has been included in the dock. LED-based sources has been designed and fabricated, including excitation filters and cheap collimation optics. GW achieved the integration of the SMART and Touch array features (patented GW technologies) for microarray detection.

Significant Results

As part of progress on this work package the consortium has:

- a) Tested the compatibility of existing Mobidiag and Genewave technology.
- b) Designed a cartridge suitable for test needs and manufactured a prototype. Redesigned the existing thermal cycling system to reduce operating time.
- c) Assembled of all functional modules for sample preparation, nucleic acids amplification and microarray detection into a single cartridge operating prototype instrument.

Objectives

- To design and validate multiplex PCR assays for target microorganisms, drug resistance markers and controls
- To design and validate a microarray with capture probes specific for target microorganisms, drug resistance markers and controls
- To develop a microarray assay protocol for quantitative bacterial detection for selected targets

Task 4.1 PCR assay development

Multiplex PCR assays were developed to detect organisms and resistances in each panel of the three RiD-RTI products, HAP/VAP, CAP and ORTI. Each panel was divided into two multiplex PCR reactions. Where appropriate, slight modifications were made to the initial panels designed during WP1, either for reasons of clinical utility or due to technical considerations. In addition, assays were developed for process controls representing DNA and RNA: targeting *Bacillus subtilis* and MS2 phage respectively. Primers and Taqman probes were designed *in silico* and singleplex assays then tested stringently for inclusivity and exclusivity using panels of assembled micro-organisms. The sensitivities of the assays were then established by determining the LOD. The recommended LOD for singleplex assays was 10 CE. If assays did not perform satisfactorily as a singleplex they were redesigned. Once singleplex assays were complete, the assays were multiplexed and inclusivity, exclusivity and sensitivity testing was repeated. Process control assays were included in each multiplex. The target LODs for multiplexes was 100 CE. If necessary, assays were redesigned until the desired performance was reached.

Task 4.2: Microarray assay development

Bioinformatic software tools were used to generate candidate probe sequences for each target. Microarray probes were then printed onto 96-well microarray plates using the sciFLEXARRAYER S11 (Sciencion) printer at Genewave. Printing parameters were tested and optimized before the start. Printed arrays were then sent to Mobidiag where they underwent hybridization testing. Microarrays were scanned with the SensoSpot® Fluorescence (Sensovation) microarray scanner and spot intensities were reported with SensoSpot analysis software. The results were then further analyzed with Microsoft Excel.

The probes for all three RiD-RTI panels underwent initial screening in order to identify the best performing probe sequences. Optimally performing probes were then printed onto new arrays and underwent more detailed sensitivity and specificity testing. Most probes are now specific and have LODs of 400 CE or less. A small number of probes still need further optimization.

Significant results for WP4

Highly sensitive and specific multiplex PCR reactions have been designed and tested for each of the three RiD-RTI products, HAP/VAP consisting of bacteria and resistance genes, CAP consisting of bacteria and viruses and ORTI consisting of viruses, fungi and bacteria. Each panel is made up of 2 separate multiplexes which will be housed in separate chambers in the cartridge. The performance of all PCR reactions is good and meets the requirements for a commercial product. Microarray capture probes corresponding to each target have been designed, tested and optimized. The majority of capture probes are now highly sensitive and specific, some still need further optimization.

WP5 Software Development

Objectives

The overall objective of WP5 was to develop and validate novel end-user software for the instrumentation.

Requirements, architecture and design

The work started by specifying software requirements. Software architecture and design were specified based on the detailed software requirements. This included identifying and designing needed software modules and interfaces between them. Suitable software technologies were chosen and software development process was defined. Based on the defined process and chosen technologies software development environments were set up, including frameworks for automated software testing and quality assurance.

Milestone M9 was reached once software requirements and design specification were completed.

Prototype Analysis Software

In the next phase work was done towards deliverable D5.1, Prototype end-user control and analysis software for reporting assay results, and related milestone M10, Delivery of prototype software for results interpretation.

The main activity was to implement a prototype desktop application that is able to analyze a list of images by processing them through 4 distinct steps: image cleaning, gridding, segmentation and finally results building. The main focus at this phase was on the analysis module. Although this software was a prototype, it was not developed to be abandoned, but to be used as the foundation of the final analysis software. The software designed and implemented robust as well as easily maintainable and extendable from the very beginning.

The analysis module takes as input a parameter file as well as a series of images to perform the analysis on. For better accuracy several images can be used. They are taken with different exposure times and combined to increase the dynamic range.

After several steps of image enhancements such as filtering and background subtraction, the segmentation is performed in two phase, a detection phase and a clustering phase to obtain the spot boundaries.

Finally software gives as results a detailed list of detected probes and their corresponding statistics.

Each step of the analysis were designed and implemented in such a way that they could be tuned by changing various parameters. Quite a significant effort was put tuning analysis parameters of each step. Analyzing experiments with known expected results were used to search for optimal parameters that lead to consistent and correct results.

Data Management

A shared database was implemented and set up so that analysis results are automatically added to the database. Results are accessible from multiple locations. Tools were also implemented that allows re-analyzing data in the database with varying parameters.

Final Validated End User Software

The final phase was to implement deliverable D5.2, Validated end-user analysis software with advanced functionality including ability to control multiple instruments.

User Interface

A sophisticated and simple user interface has been designed and implemented. The goal was to create a user experience that is self-explanatory and as straightforward to use as possible. The interface has been designed so that status of each connected instrument and each of their cartridge operating units (COUs) is easy to determine from the main status screen even from distance and that it can guide the user through the workflow.

Instrument Control

For controlling the instruments connected to the computer that runs the desktop software (DSW), the instrument communication and instrument state machine modules were designed and implemented. The fact that up-to 16 units running assays need to be controlled in parallel was an important factor all the way from the beginning of design of these components.

Verification

The verification of the software has been built into the architecture so that it supports automated testing of each module and unit in the software. In the architecture, each module has then been split into small units that have as few interdependencies as possible. An integral part of each task to implement a unit has been to implement automated unit tests for it. For the analysis module, a separate test application has been implemented that allows re-analysing data efficiently and thus training parameters and verifying correct analysis without executing the whole workflow. Other verification activities contain peer reviews of all the implemented tests in the framework, but also peer reviews of all the software codes in the codebase.

Validation

The software is not standalone but a part of the platform. This means that the software is really operational with one or more instruments containing cartridges. Therefore in addition to verifying that the software works in the manner specified as described previously, it has also been validated in its intended use as part of the platform. This has been done on two levels. Firstly, it has been tested with real hardware without cartridge with test assays to verify that software and instrument behave well together and perform correct steps as specified in the test protocols. Secondly, it has been tested as a part of the whole platform using real assays and real samples by biologists

Work Package 6 – Integration, productisation and product validation

Objectives

The purpose of WP6 is to take the individual components of the product developed in the preceding WPs and integrate them together to produce the new RiD-RTI platform and test cartridges:

Design, implementation and selection of an appropriate production technology for the reagents (Task 6.2)

Reagents and components were selected and embedded into the GW cartridge and their functionality verified:

- Cartridge material and film
- Filter
- Cover film
- Biological buffers for SP, Amplification and hybridization
- Microarray
- Syringe

Thus far candidate production technology has been selected, tested and chosen for the final product format and a prototype cartridges have been manufactured and tested.

Appropriate production technologies for the reagents have been selected with respect to quality and costs. Preliminary stability and shelf-life studies have been conducted for the selected reagents. The required packing and labelling of the reagents and consumables have been designed and implemented.

Integration of the pre-tested sample preparation, amplification and hybridization protocols into a single, disposable GW cartridge with embedded reagents (Task 6.1)

To assess the functionality of the product specific multiplex PCR assays (WP4) and microarray capture oligos (WP4) integrated into a single GW cartridge with embedded reagents (WP3), standard operating procedures have been defined. Therefore, in this WP, the separately established and pre-tested sample preparation, product specific amplification, hybridization and detection protocols have been integrated into a single GW cartridge with embedded-reagents and validated in terms of analytical specificity and sensitivity, limit-of-detection, and reproducibility using DNA samples from target organism pure cultures.

The result interpretation and rule-sets for the products integrated into the GW platform (Task 6.3)

Test result is reported based on the identification of the positively hybridized targets and an evaluation of the control capture oligos. Result interpretation and reporting is done automatically with the analysis software using pre-determined, built-in rule-sets and parameters. The rule-sets can be determined and the parameters fine-tuned specifically for each diagnostics product (CAP, HAP/VAP and ORTIs), using the MD's bioinformatics tools linked to the analysis software. Dataset containing microarray images can be retrospectively analyzed numerous times with different rule-sets when determining the most optimal rule-set and parameters. Furthermore, when fine-tuning rule-sets and parameters, the specificity panel (DNA samples

isolated from non-target organisms) will be analyzed with the integrated GW cartridge in order to avoid false positive results due to the cross-hybridization. The final rule-set and parameters will be implemented in the analysis software.

Significant Results

The main result of the WP6 is the ability to perform:

- A fully automated protocol (including sample prep, amplification, hybridization and detection).
- Integration of the HAP/VAP assay developed within WP4 with 2 different multiplex assays.
- 3 min of manual preparation.
- 2h30 min of automated protocol.
- Detection down to of 10^4 CFU/ml of bacteria spiked in negative sputum (tested on *Acinetobacter baumannii*).
- All biological buffers embedded in a seal cartridge.

The final integrated instrument and cartridge are depicted in figure 3



Figure 3. Prototype platform (instrument and cartridge and UI from the software)

Objectives

- To perform a prospective observational clinical evaluation study to determine the performance characteristics of the three RiD-RTI diagnostics products compared to culture based reference methods.
- To determine the clinical applicability of the 3 RiD-RTI products for the identification of RTI-causing microorganisms and molecular DST from sputum, BAL or similar, tracheal aspirates and endotracheal tube exudates
- To evaluate the operational performance of the modified GW Genespress® System

Task 7.1 Ethics Approval and Data Protection

Ethical approval was sought and granted for the collection of surplus clinical respiratory specimens and associated patient data in November 2012. This overarching ethical approval termed the “DNA Infection Bank” covers access to specimens across a number clinical sites associated with UCL, including UCLH and RFH from where clinical samples have been collected for RiD-RTI.

A customized database, elCID, was designed and built for the storage of patient and test data for the RiD-RTI specimens. This database, housed behind the secure firewalls at UCLH, has facilities for anonymising patient identifiable details and blinding different arms of the study from operators, in order to avoid bias.

Task 7.2 Study design, patient recruitment and data collection

The study design was pragmatic and aimed to collect the maximum number of specimens and mirror the real-world conditions in which the GeneSpres may be used once introduced. A research practitioner conducted a daily screen of incoming respiratory specimens at the diagnostic microbiology laboratories of the participating hospitals. Non-duplicate specimens from patients with clinically confirmed pneumonia with sufficient surplus volume for research were collected. Basic clinical details, as well as the routine microbiology diagnosis and antimicrobial susceptibility test results were recoded in the elCID database. For bacteria with suspected ESBLs or carbapenemases, routine phenotypic results were supplemented with a Checkpoints CT103XL genotypic test.

In total 494 specimens were collected and stored, 412 of which were from the RFH and 82 from UCLH. Of these, 210 were from patients with HAP, 192 from patients with CAP, 50 from patients with VAP and 42 in which the type of pneumonia was unknown. Of these 207 specimens had one or more significant organisms reported by routine microbiology, while 278 had normal respiratory flora and 9 produced no growth. The most common organisms found were *P. aeruginosa*, *H. influenzae*, *S. aureus* and *E. coli* (Figure 4)

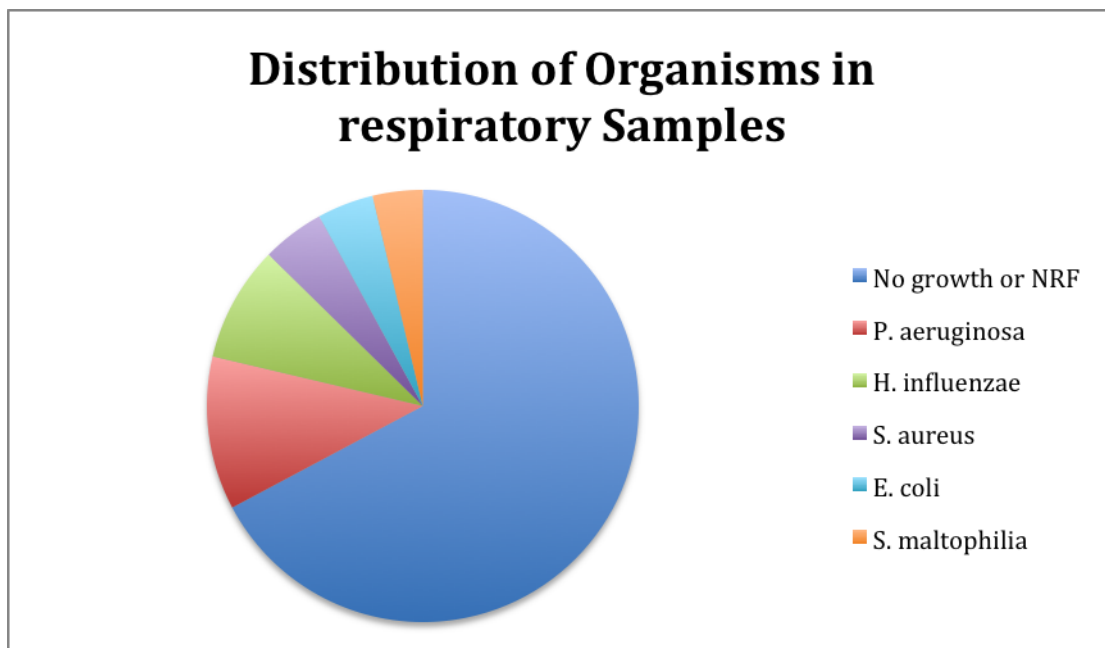


Figure 4. Distributions of organisms isolated by routine microbiology from respiratory samples

Among the bacteria isolated, 133 were resistant to at least one antimicrobial, while 73 were multi-drug resistant. 37 isolates had putative carbapenemases, ESBLs or AmpCs, of which 13 were genotypically confirmed.

Task 7.3 Product and system evaluation

40 specimens in which HAP or VAP was confirmed underwent testing with the GeneSpress instrument & HAP/VAP cartridge. Results were concordant in 24 specimens and overall sensitivity and specificity were calculated as 54% and 96% respectively. This is an encouraging result at stage of development, although further work is needed on PCR and hybridisation conditions in the integrated interment.

The instrument also underwent user feedback and evaluation which was generally positive. Users felt the test was easy and quick to use, with the software being user friendly and intuitive (Figure 5). Some aspects, such as cap insertion in the sample holder and difficulties with the gentle push need improvement

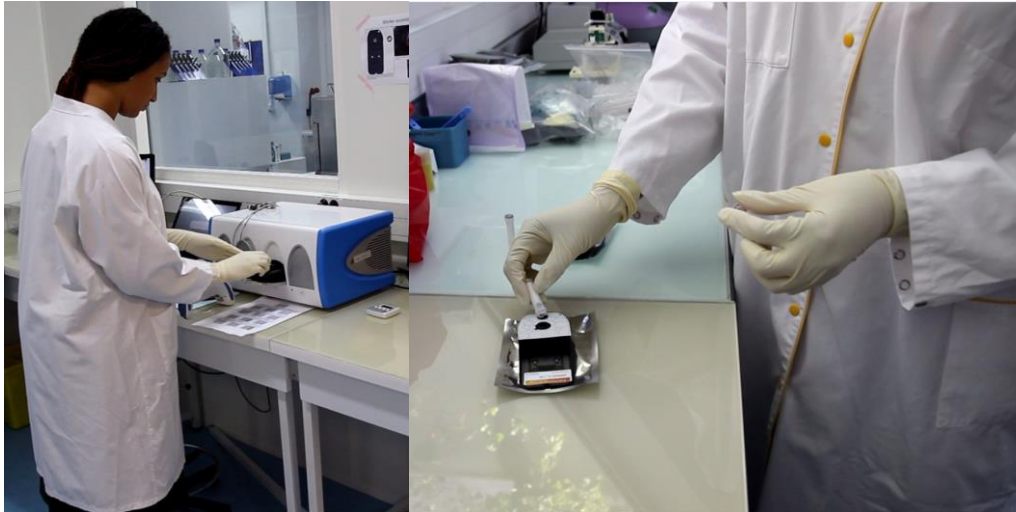


Figure 5. The GeneSpress instrument undergoing user testing. Cartridge insertion into the instrument is shown on the left hand side, the right hand side shows pouring of sample into the cartridge.

Significant results for WP7

Infrastructure and permissions for collection of respiratory specimens from pneumonia patients at the UCLH and RFH hospitals has been put in place. The study has received ethical approval and has a customized database for secure storage of patient information.

In total just under 500 respiratory specimens from pneumonia patients have been collected, with HAP the most commonly represented pneumonia type. Of these, just under half of the specimens contain significant micro-organisms (as determined by routine microbiology). Initial performance of the GeneSpress platform and HAP/VAP test is encouraging, with positive user feedback.

Objectives

The main objectives of WP8 period were the:

- Development and facilitation of efficient communication between beneficiaries and thus optimization of indirect benefits of the project.
- Promotion of the dissemination of project results.
- Development of a Commercialisation Strategy that is consistent with the commercial aspirations of the beneficiaries.
- Management of IPR to (i) ensure freedom to operate for existing diagnostics targets for which the consortium do not hold IP and to (ii) appropriately protect any novel diagnostics targets identified.

As part of progress on this work package the consortium has done:

Task 8.1 External communication

- Deliver the external website, <http://www.rid-rti.eu> and a project brochure

The project website includes public information on the project, including its goals, workplan and management structure, description of project partners and key people involved in the project, and news and events regarding the project. The website also includes a Partners' Area, which requires a login and is intended for the project members only. The Partners' Area is an efficient tool for sharing internal material among project members and is used in e.g. sharing material that has been presented during partners' meetings.

UCL has maintained and regularly updated the project website like project partners, updates on the news and events section including publications and other dissemination activities, more detailed personal profiles for individuals involved in the project and updating the repository of project documents and presentations in the secure Partners' area.

A project information brochure was designed in the first months of the project by UCL with the collaboration of all partners in order to promote the project's scientific and industrial results to the conferences attended by the consortium. The brochure (submitted as attachment on SESAM) include 4 main sections: The Goal, The Project, The Impact and The Partners.

Task 8.2 RiD-RTI dissemination of project results

RiD-RTI researchers attended the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) conference, Barcelona May 2014 and in Copenhagen, April 2015.

The project was invited to participate in the European Network Corner at both ECCMIDs. NUIG and UCL attended the conference and were involved in the presentation of a general project poster in the Network Corner as well as distributing brochures. MD also attended ECCMID contributed to preparation of the project poster. MD also promoted the project at their exhibition booth, handing out project brochures and discussing the project with interested individuals. They exhibited a prototype of the GeneSpress platform at ECCMID 2015.

The consortium produced 8 peer-reviewed publications and made several presentations – for details, see Template A1 and A2

Task 8.3 Management of knowledge and exploitation

- Existing diagnostics targets identified in the literature for the specific detection of target organisms and resistances have been investigated to ensure there is sufficient freedom to operate (FTO), using these targets, for the development of the RiD-RTI diagnostics products.
 - UCL commissioned an FTO search for influenza A&B, RSV A & B and coronaviruses as well as MS2 phage.
 - Mobidiag has designed novel antibiotic resistance genetic markers for beta-lactam resistance groups. Mobidiag commissioned an FTO study on the novel sequences.
- The exploitation plan strategy focused on reviewing the market and competitive situation has been defined by Mobidiag, The document covers:
 - Identification of threats and competitors (including regulatory constraints): Possible exploitation barriers (standards, ethical and regulatory aspects) have been identified and their impact assessed to optimize the market entry strategy. The emergence of other competing technologies have been analyzed.

Market overview: Mobidiag examined the main areas of business, the market structure in the main sectors of application including its customers, end users and competitors. This gave precise information on market size and accessibility. Details are included in the section below.

IMPACT, DISSEMINATION & EXPLOITATION

Impact

Expected impacts

The novel diagnostic platform called Genespress allows the rapid detection (< 2 hrs) of the microbial etiology and drug resistance profile of RTIs in adults and children. This will result in improved patient management (see Figure 6), reduced patient morbidity and mortality, and reduced RTI associated healthcare costs.

The Genespress platform is an automated sample-in, result-out diagnostics system. It is simple to use, with minimal hands-on time. The main benefit of the Genespress platform is the simplicity of the process to results. Once the sample is added to the cartridge, and the cartridge inserted into the Genespress machine, the work of user is done.

The cartridge itself (see picture below) is fully sealed and disposable. This means the process of adding the sample to the cartridge is easy without extra manual steps. There is no danger of contamination or added requirements to clean after the test, or establish specific lab protocol, as there is no contact with the sample and the reagents. Once the process is finished, the whole cartridge is disposed of, including all reagents and samples, which are sealed. This removes any complicated disposal processes.



The full process only requires five steps. Firstly, the protective film is peeled off from the cartridge. Secondly, the sample is added to the test cartridge. Thirdly the sample is sealed with a cap on the cartridge. The fourth stage is using a vortex to combine the reagents with the sample, then the cartridge is finally inserted into the Genespress instrument and the assay begins.

Genespress allows random access testing, with up to four cartridges in each individual machine. The main benefits of random access are time and efficiency. There is no need to wait for all the slots to be filled before



beginning a test and the ability to use different cartridges at the same time makes it a very flexible testing instrument. This function adds to the use of Genespress, as each cartridge is a multiplex assay, and multiple tests can be run simultaneously, without need for co-ordination with other patients or departments.

The Genespress comes with software for the qualitative analysis of results, and the software is presented in a user-friendly, intuitive touchscreen. The format of the touchscreen, prompting the tester to scan the barcodes

of the sample and the tests, with walk through instructions, means no specific training is required to be able to use Genespress. This makes it efficient and easy to use, as well as accessible to a wide range of staff.

Patient management impacts

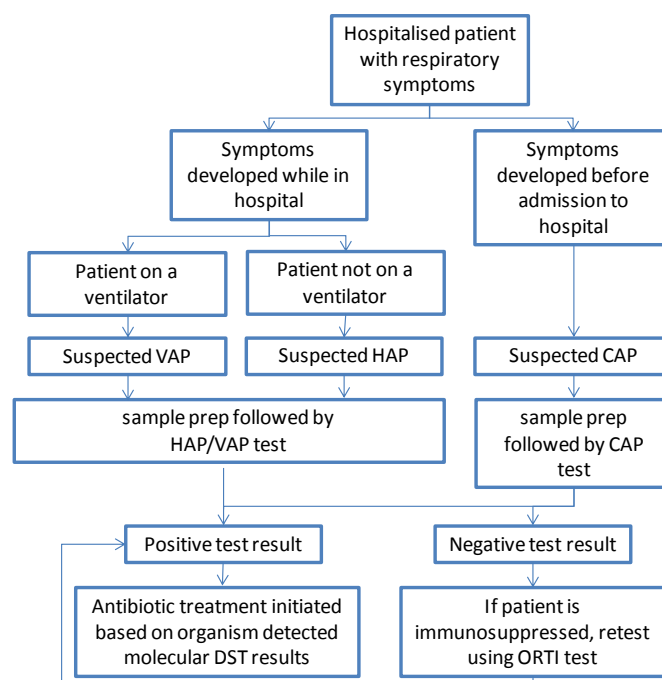


Figure 6. Patient management flow chart

This approach allows microorganism-specific antibiotic therapy to be initiated promptly and appropriately. There is an association between treatment success and the adequacy of therapy⁷, therefore the RiD-RTI diagnostics tests have the potential to improve management outcomes and increase survival rates in RTI patients in hospitals worldwide.

Health system impacts

Considering the high patient and economic burden RTIs represent worldwide, rapid identification of the RTI aetiological agent and drug resistance profile using the new RiD-RTI platform will reduce healthcare costs.

In 2002, pneumonia resulted in 6.9% of all deaths worldwide.¹ Within Europe, pneumonia accounts for 3.5% of all deaths.² In a study of VAP taken globally, at 56 sites in 11 countries, the prevalence of VAP was:³

Globally – 15.6%

United States – 13.5%

Europe – 19.4%

Latin America – 13.8%

Asia Pacific – 16.0%.

¹ http://www.worldmapper.org/display_extra.php?selected=404 (Accessed 5th August 2015)

² <http://www.erswhitebook.org/chapters/the-burden-of-lung-disease/> (figure 3) (Accessed 5th August 2015)

³ <http://www.ncbi.nlm.nih.gov/pubmed/25054674> (Accessed 5th August 2015)

HAP is the nosocomial infection with the highest mortality. The incidence ranges from 5-20 cases per 1,000 hospital admissions. Non-ventilator HAP increases both the length of hospital stay and the cost of each patient. The overall mortality from HAP is around 27-51%, with the mortality rates being highest amongst the elderly population. Both HAP and VAP are costly and time-consuming infections. VAP accounts for 90% of all HAP cases. According to the American Thoracic Society, the development of HAP increases hospital stay by an average of 7 to 9 days per patient with an associated additional cost of more than \$40,000 per patient⁶. In a recent study, the ability to identify the causative agent of RTIs, resulted in significant decreases in the length of patient hospitalisation, patient mortality and antibiotic dispensation. The average length of a hospital stay was halved, dropping from 10.6 days the previous year to 5.3 in the following year, representing an average savings of almost \$6,000 per patient.

Socio-Economic Impact of Project Outcomes

Pneumonia can be a deadly disease, affecting over 3.4 million people in Europe annually.⁴ It is classified by the source of the infection, commonly either community acquired (CAP), hospital acquired (HAP), or ventilator acquired (VAP). There have been extensions to these classifications, including healthcare acquired (HCAP) amongst others. There is no set clinical definition for pneumonia, but looking at the guidelines and reviews of guidelines passed worldwide, there is a common consensus, for what counts as CAP, HAP or VAP as well as how to diagnose pneumonia.

CAP is pneumonia in someone who has not been in hospital. Some definitions allow elderly people in nursing homes under this category, whilst others introduced HCAP to deal with that specific incidence. CAP is pneumonia that has appeared within 48 hours of being in hospital, to distinguish between incubating HAP that had no symptoms on admission. A subset of HAP is VAP, again defined by the 48 hours after admission.⁵ It is very difficult to gather accurate statistics on the prevalence of pneumonia, as HAP and VAP are not reportable diseases, and there have only been five studies on CAP, all these countries within Europe. There are studies by the UN focusing on pneumonia in children aged under five, but a comprehensive study, looking at people of all ages and backgrounds, does not exist. For example, most pneumonia statistics from Ukraine are suspiciously low, the lowest in Europe, which does not fit the trend with lifestyle and climate. It is important to remember this whilst discussing pneumonia and its prevalence.

Firstly, looking at the criteria that allow clinicians to diagnose pneumonia, it is clear that there are still relative difficulties in diagnosis. Pneumonia can present in a variety of ways, and a range of other lower respiratory tract infections can present in the same manner as pneumonia. Distinguishing between pneumonia and other lung diseases is important for deciding the correct treatment path, as well as being aware of people who may be at risk, and require admission into hospital. In cases of CAP, there are a few factors which must be present to gain a pneumonia diagnosis. As taken from the British Thoracic Society's guidelines, a diagnosis of CAP is given with an acute cough, and one of the following; new focal chest signs, dyspnea, tachypnea, fever lasting over four days and a diagnosis confirmed by chest radiograph. The criteria for HAP and VAP requires a new

⁴ <http://www.erswhitebook.org/chapters/acute-lower-respiratory-infections/> (Accessed 14th August)

⁵ <http://emedicine.medscape.com/article/234753-overview> (Accessed 14th August 2015)

infiltrate and two of the following; fever, raised white blood cell count or purulence (the British guidelines also have increase in oxygen requirements) for a diagnosis to be reached.

Looking at pneumonia in general, it is an infection with a global reach. There are a number of risk factors which have been identified, and how these factors are likely to impact on mortality. In most cases it is the very young and very old who are likely to suffer from deadly pneumonia. This is where the socioeconomic impact of Genespress is very important. Both infants and elderly have weaker immune systems, and are more likely to both suffer from and die from pneumonia. In an argument made by Genome Web about arrays, they claim that one of the main benefits from accurate diagnosis for small children is the speed of the diagnosis and the peace of mind of the parents after being diagnosed.⁶ Another point that can be taken away from this is the fact that doctors will be treating people who cannot speak for themselves, or describe their symptoms, at both ends of the age spectrum. In cases like these, with vulnerable people, being able to come to a diagnosis quickly and easily is very important. As infants and the elderly, presenting with potential pneumonia, are likely to have compromised immune systems, another benefit is the singular test required for diagnosis. Sometimes people will stop following up doctor's appointments, potentially because the journey is too far or they do not see the point, which can be difficult with time-expensive diagnosis such as blood cultures. With Genespress, the diagnostic test can be done whilst the patients wait, and antibiotics can be offered after the results, reducing the amount of time required for trips to a surgery or clinic.

Discussing this from the perspective of the developed world, the **benefits** to using Genespress are considerable. The main tangible gain would be in healthcare costs. In a few cases, people will be admitted to hospital to be on the safe side, so that they can be monitored. With a specific diagnosis such as this from Genespress, there is no need for cautious monitoring, as the root cause will be found. Alongside this, HAP often lengthens the hospital stay for the original illness, and with specific antibiotic treatment, this can be shortened drastically, saving costs. In Europe, pneumonia costs around €10.1 billion each year⁷. The high cost of CAP has encouraged hospitals to search for methods to lower costs, which is an area that Genespress could be useful in. The results of Genespress tests could reduce the hospital length of stay, use of less expensive antibiotics, and identify who could best be cared for as an outpatient rather than an inpatient.

Whilst this is an important development in healthcare in economically developed countries, the **real benefit could be felt in developing countries**. In developing countries the outlined risk factors for pneumonia are often present, influencing the high numbers of reported pneumonia. Factors such as smoking, poor air flow at home (for example from internal fires in buildings with poor ventilation) and malnourishment all contribute to levels of pneumonia. The main socioeconomic impact of Genespress could be felt in newly industrialized or developing countries. Genespress is cost-effective, with a small laboratory footprint, all the reagents are included in the cartridge, and the only other things needed are samples and a vortex. It is not complicated to use, and is also not difficult to dispose of the samples after testing. It could be used in smaller clinics without the need for a fully equipped laboratory, which is the main strength. In places such as India, one of the key problems for people who fall ill is access to healthcare. In remote and rural locations, there may be a local clinic, but this is likely to be poorly equipped. However, comprehensive testing using something such as Genespress would change this.

⁶ <https://www.genomeweb.com/pcr/economic-model-describes-cost-effectiveness-filmarray-respiratory-panel-kids>

⁷ <http://thorax.bmj.com/content/67/1/71.full>

The adoption of Genespress in remote areas would allow doctors to provide more specific and effective treatment to those members of the population who present with pneumonia. The current focus is reducing the pneumonia deaths of under 5s worldwide. One of the main problems with the healthcare provisions is the diagnosis. Only 14% of children were clinically diagnosed with pneumonia using a chest radiograph in ambulatory settings.⁸ By introducing efficient and effective testing, this can be raised, leading to a greater awareness of the efficiency of the antibiotics treatments, reducing treatment times and costs. It will also reduce the number of respiratory infections unnecessarily treated with antibiotics. The case for shortening antibiotic courses as well as reducing the number of clinic visits is crucial, because of a series of factors: people may be less likely to attend follow-up appointments, or visit enough to get accurate treatment. The main concern about the current approach, with potential over-diagnosis of pneumonia, is the efficacy of the antibiotics. It is a legitimate problem, as the efficiency of these prescribed antibiotics will fall if they are overprescribed, leading to bacteria developing resistance to them.

As outlined, the socioeconomic impact of Genespress has potential to be very considerable, worldwide. Both developed and developing countries stand to benefit from this. The narrowing of antibiotic treatment and making it more targeted is the main improvement, as this will lower healthcare costs for patients and hospitals, as well as reducing unnecessary antibiotic use. This will allow the diagnostic process to speed up, making it less time- and labor-intensive. It will also reduce the exposure to hospital pathogens, especially important for the very young and old, who are already at highest risk for pneumonia anyway. The benefit of Genespress is the removal of diagnostic measures which may make it difficult to diagnose someone who cannot speak, for example an infant or someone who potentially has VAP. Pneumonia is a costly disease with a considerable level of associated mortality. The introduction of Genespress to the marketplace has the opportunity to affect this, but this would require a widespread uptake of new technologies.

Looking at the current market trends and estimated cost of supply, once a market has been established in developed countries, and there is a specific level of production, then expansion into developing countries would be possible. It would make economic sense as then the company would be able to make use of economies of scale, and although the profit margin from selling to developing countries would be lower, the exposure and brand awareness is highly beneficial.

Benefits for scientific and technological knowledge

The products developed in the RiD-RTI project will enable epidemiological studies to be performed on the causative agents of pneumonia where the tests are used. Such epidemiological information could be useful for determining the most common causes of pneumonia in different settings and will also be useful for monitoring contact and source tracing. In addition, the novel nucleic acid diagnostics targets identified during the study may be useful for the specific detection of other microorganisms causing human infections and also in other diagnostics market sectors such as the environmental, veterinary and food sectors. Finally the fully integrated, multiparametric device developed will be state-of-the art with a high multiplexing capability. Such a technological advancement will allow for a range of diagnostics products other than RTIs to be targeted in the future.

⁸ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2083673/>

The assays developed in the RiD-RTI project will further extend the current portfolio of MD, and will answer to the specific customer needs communicated to MD for these types of products. With the prospect of implementing different assays into the Genespress platform in the future, market opportunities will grow as the applicability broadens. The sample preparation and detection techniques developed in RiD-RTI shall provide novel solutions which can be combined with MD's current diagnostic products, enabling their versatile use in various laboratory scales and reducing the number of separate instruments required.

Market application and technological advantages

The main market that will be initially targeted is European IVD market where the product roll-out will commence. This will be used as a reference market to inform decisions on expanding the geographical coverage and further developing the products. The customer marketing of the products with CE-marking can be initiated immediately after the successful performance evaluation study at the end of the project. For products diagnosing CAP, HAP/VAP, and ORTIs the estimated maximum market potential in the US and Europe combined is 22.6 million tests. The current lower RTI diagnostics market has been estimated to be worth €1.6 billion. It should be noted that the developed diagnostics assays have alternative potential applications and can be used with alternative patient sample types. Thus the true maximum market potential of the project products is larger than these estimates.

Two of the most important dimensions of successful market entry are i) credible demonstration of the potential cost savings associated with the introduction of the products (via e.g. a cost-benefit study in European laboratories or clinics) and ii) providing evidence for the treatment improvements that can be attained. Sample-in answer-out products are a new form of diagnostics which makes it possible to conduct testing anywhere in the hospital or even outside the hospital. Sample-in answer-out products will bring dramatic changes to diagnostics test turn-around time. Moreover, because of their ease of use, the tests could be applied at point of care, used by technicians with no or minimal microbiology training. Ongoing collaborations possess complementary multi-parametric detection technologies (multiplex PCR amplification followed by detection on low density microarrays) ideal for the diagnosis of complex microbial infectious diseases such as RTIs. Market penetration will be facilitated by MD.

Exploitation plan of project results

The project has resulted in 3 categories of exploitable results: 1) Intellectual property; 2) Methodologies; 3) Diagnostics platform and products. An exploitation plan developed as part of WP8 will enable the exploitation of the project results in terms of commercial products.

	Results	Exploitation
Intellectual property	Novel molecular diagnostics	<ul style="list-style-type: none"> • Limiting competitors' freedom to operate by patenting • Freedom to commercialize our tests • Out-licensing of patents to other molecular diagnostics companies
	New biomarkers	<ul style="list-style-type: none"> • Limiting competitors' freedom to operate by patenting • Freedom to commercialize our tests • Out-licensing of patents to other molecular diagnostics companies

	Diagnostics methods	<ul style="list-style-type: none"> Combination of PCR and microarray Limiting competitors' freedom to operate by patenting Out-licensing of patents
	Multiplex PCR Mix	<ul style="list-style-type: none"> Freedom to commercialize our tests Out-licensing of patents to other molecular diagnostics companies
	Novel multi type sample preparation cartridge	<ul style="list-style-type: none"> Freedom to commercialize our tests Out-licensing of patents to other molecular diagnostics companies
Methodologies/ know how	Sample preparation method for respiratory samples	<ul style="list-style-type: none"> Adaptation of the developed solutions to other diagnostic applications Future development and refinement of the products
	Complex multi type extraction methods	<ul style="list-style-type: none"> Possibility of novel test beyond the RiD-RTI tests
	Novel multi type sample preparation cartridge	<ul style="list-style-type: none"> Novel products beyond the RiD-RTI tests
Products	Integrated Genespress diagnostics system	<ul style="list-style-type: none"> Commercialization after the product development and validation R&D for adaptation of the developed solutions to other diagnostic applications
	RiD-RTI CAP, HAP/VAP and ORTI diagnostics cartridges	<ul style="list-style-type: none"> Commercialization after the product development and validation R&D for adaptation of the developed solutions to other diagnostic applications

Market

To bring the product to market additional technical developments will be required. The diagnostics products for CAP, HAP/VAP, and ORTIs will be launched after an optimization phase after the project. These IVD products sold in the EU member countries are required to comply with the European IVD Directive (98/79/EC) requirements and to have a CE-IVD marking.

Positioning of RiD-RTI Outcome Products

There are a few instances in which the Genespress product would be beneficial and useful in pneumonia diagnostics.

- Influencing treatment options. Unless there is sufficient reason for a clinician to suspect the pneumonia is caused by a specific virus or bacteria, then usually broad spectrum antibiotics will be offered. By using a test which is fast and can look for antibiotic resistant markers, then the treatment can be narrower, and more precise. This is important because it will hopefully reduce the number of antibiotic-resistant types of pneumonia. This does not currently happen, as the testing is too delayed to effectively influence the treatment.
- Many of the important bacterial pathogens are present in normal flora in low quantity. Nested PCR based competitive broad tests are not able to distinguish infection from colonization. They panels are incomplete focusing strongly on viruses and a few rare absolute bacterial pathogens, such *Mycobacterium tuberculosis* or *Clamydophila pneumoniae* when qualitative result is sufficient. These

tests are not able to replace traditional diagnostics as they must be fully covered by culture methods for most common bacterial pathogens.

- The other benefit from influencing treatment options is looking at how effective the treatments are. If antibiotics work well, then shorter courses can be offered, which is beneficial for the patients, as they are taking fewer medicines, the healthcare service, as it won't cost as much as well as future patients, to slow down potential antibiotic resistance developing.⁹
- A strength of Genespress is relative price to other treatments, and ease of treatment. An article written about PCR with sepsis argued that although real-time PCR is very beneficial in diagnostics, the problem currently is getting the levels of automation without the costs involved in increasing lab size.¹⁰ This is where Genespress comes in, as there is no need for automated robots to handle nucleic acids, as it is all done inside the Genespress.

Summary of Competition

Through research, around 26 alternative respiratory tests were found, which are either developed and on the market already, or coming out within the next few years. The tests included in this research were ones where there was a wide range of information available. There are alternatives on the market, dependent where you are buying from, but they have not been included as there is insufficient information for comparative purposes.

The competition is also very varied, from single tests made for open systems, to assays which test for over 30 pathogens on a proprietary system. Looking at the direct competitor, that is multiplex PCR, automated and proprietary systems, the majority have an established presence. They have a range of tests which work on their proprietary system, occasionally with announcements of new systems overall. There is a clear division between the general panels and those which are specific to pathogen type, for example respiratory virus panels. Each type has its benefits and drawbacks, but the main drawback with real-time PCR is choosing what to test for. This is where the multiplex PCR tests with bacteria and virus identifiers come in, as being able to choose from 30 different potential pathogens by doing one test does assist in diagnosis.

The competitors have varying levels of specificity and sensitivity, but the directly competitive ones have very high percentages for both factors. A lot of competitors have specific sample requirements, the most common being nasopharyngeal swabs, with others requiring the extracted RNA to be able to complete the test.

Business plan

MD, the lead for commercializing the RiD-RTI products, will commercialise diagnostics products for CAP, HAP/VAP, and ORTIs all over the world through their own, already-built sales channels as well as through distributors. Several customer engagements and pilot installations will be needed to generate sales through routine use. Thus, the sales numbers may stay rather modest in the months following the market launch, but after sufficient investments into marketing and sales activities, the sales figures are projected to rise significantly. The long-term goal should be to attain a 5 % market share of all HAP/VAP/CAP/ORTI

⁹ <http://www.ncbi.nlm.nih.gov/pubmed/17496574> (Accessed 12th August 2015)

¹⁰ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2806664/> (Accessed 12th August 2015)

diagnostics. This would mean sales around one million test annually. Attaining this kind of a market share will require several years. As an estimate 10,000-30,000 tests would be sold annually in first two years after market penetration. During the third year from launch, sales of approximately 100,000 tests would be estimated, with double- or triple-digit annual growth projected each year after the product launch.

Use and dissemination of foreground

Section A (public)

TEMPLATE A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE MOST IMPORTANT ONES

NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers (if available)	Is/Will open access provided to this publication?
1	<i>Advances in multiparametric molecular diagnostics technologies for respiratory tract infections.</i>	Reddington K, Tuite N, Barry T, O'Grady J, Zumla A.	<i>Curr Opin Pulm Med.</i> 2013	May 2013 (3)	<i>Current Opinion in Pulmonary Medicine</i>	London United Kingdom	Epub May 2013	298-304	11	No
2	<i>Aetiology of hospital-acquired pneumonia and trends in antimicrobial resistance</i>	Enne VI, Personne Y, Grgic L, Gant V, Zumla A	<i>Current Opinion in Pulmonary Medicine</i>	Vol 20, May 2014	Lippincott Williams & Wilkins	Philadelphia USA	May 2014	252-258	12	No
3	<i>Rapid nucleic acid diagnostics for the detection of antimicrobial resistance in Gram-negative bacteria: is it time for a paradigm shift?</i>	Tuite N, Reddington K, Barry T, Zumla A, Enne VI	<i>Journal of Antimicrobial Chemotherapy</i>	Vol 69, July 2014	Oxford University Press	Oxford, UK	July 14	1729-1733	13	No
4	<i>Emerging infectious diseases and pandemic potential: status quo and reducing risk of global spread</i>	McCloskey B, Osman D, Zumla A, Heymann DL	<i>Lancet Infectious Diseases</i>	Vol 14, Oct 2014	Elsevier Science	Oxford, UK	October 14	1001-1010	14	No
5	<i>Rapid point of care diagnostic</i>	Zumla A, Al-Tawfig JA, Enne	<i>Lancet</i>	Vol 14, Nov	Elsevier	Oxford, UK	November 14	1123-1135	15	No

¹¹ http://journals.lww.com/co-pulmonarymedicine/Abstract/2013/05000/Advances_in_multiparametric_molecular_diagnostics.16.aspx

¹² http://ovidsp.tx.ovid.com/sp-3.18.0b/ovidweb.cgi?&S=IJHPFPNFJBDDKCJONCJJKCJCIDECAA00&Link+Set=S.sh.22.24.32|8|sl_10

¹³ <http://jac.oxfordjournals.org/content/69/7/1729>

¹⁴ <http://www.sciencedirect.com.libproxy.ucl.ac.uk/science/article/pii/S1473309914708461>

¹⁵ <http://www.sciencedirect.com/science/article/pii/S1473309914708278>

	<i>tests for viral and bacterial respiratory infections - needs, advances and future prospects</i>	VI, Kidd M, Drosten C, Breuer J, Muller Ma, Hui D, Maeurer M, Bates M, Mwaba P, Al-Hakeem R, Gray G, Gautret P, Al-Rabeeah AA, Memish ZA, Gant VA	<i>Infectious Diseases</i>	2014	Science					
6	<i>Emerging novel and antimicrobial-resistant respiratory tract infections: new drug development and therapeutic options</i>	Zumla A, Memish ZA, Maeurer M, Bates M, Mwaba P, Al-Tawfig JA, Denning DW, Hayden FG, Hui DS	<i>Lancet Infectious Diseases</i>	Vol 14, Nov 2014	Elsevier Science	Oxford, UK	November 14	1136-1149	¹⁶	No
7	<i>Totally drug-resistant tuberculosis and adjunct therapies</i>	Parida SK, Axelsson-Robertson R, Rao MV, Singh N, Master I, Lutckii A, Keshavjee S, Andersson J, Zula A, Maeurer M	<i>Journal of Internal Medicine</i>	Vol 277, April 2015	Wiley-Blackwell	Hoeboken, USA	April 2015	388-405	¹⁷	No
8	<i>Comparison of Established Diagnostic Methodologies and a Novel Bacterial smpB Real-Time PCR Assay for Specific Detection of Haemophilus influenzae Isolates Associated with Respiratory Tract Infections</i>	Kate Reddington, Stefan Schwenk, Nina Tuite, Gareth Platt, Danesh Davar, Helena Coughlan, Yoann Personne, Vanya Gant, Virve I Enne, Alimuddin Zumla, Thomas Barry	<i>Journal of Clinical Microbiology</i>	Vol 53, Sep 2015	<i>Journal of Clinical Microbiology- American Society for Microbiology</i>	Washington, USA	September 2015	2854-2860	¹⁸	yes

¹⁶ <http://www.sciencedirect.com.libproxy.ucl.ac.uk/science/article/pii/S147330991470828X>

¹⁷ <http://onlinelibrary.wiley.com.libproxy.ucl.ac.uk/doi/10.1111/joim.12264/abstract>

¹⁸ <http://jcm.asm.org/content/53/9/2854>

TEMPLATE A2: LIST OF DISSEMINATION ACTIVITIES

NO.	Type of activities ¹⁹	Main leader	Title	Date/Period	Place	Type of audience ²⁰	Size of audience	Countries addressed
1	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON	Rapid Identification of Respiratory Tract Infections	27/10/2013	Workshop on PoC at microTAS Conference in Freiburg	Scientific community (higher education, Research) - Industry - Civil society - Policy makers - Medias	100	Europe
2	Exhibitions	MOBIDIAG OY	Mobidiag booth	10/05/2014	ECCMID 2014, Barcelona	Scientific community (higher education, Research) - Industry - Civil society - Policy	10000	World-wide

¹⁹ A drop down list allows choosing the dissemination activity: publications, conferences, workshops, web, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters, Other.

²⁰ A drop down list allows choosing the type of public: Scientific Community (higher education, Research), Industry, Civil Society, Policy makers, Medias, Other ('multiple choices' is possible).

						makers - Medias		
3	Posters	UNIVERSITY COLLEGE LONDON	Rapid Identification of Respiratory Tract Infections	10/05/2014	European Network Corner at ECCMID 2014, Barcelona	Scientific community (higher education, Research) - Industry - Civil society - Policy makers - Medias	10000	World-wide
4	Flyers	UNIVERSITY COLLEGE LONDON	Rapid Identification of Respiratory Tract Infections	10/05/2014	ECCMID 2014, Barcelona	Scientific community (higher education, Research) - Industry - Civil society - Policy makers - Medias	10000	World-wide
5	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON	Qualitative and quantitative analysis of the microbiota in lower respiratory tract infections reveals a high proportion of polymicrobial	11/05/2014	ECCMID 2014, Barcelona	Scientific community (higher education, Research) - Industry - Civil society - Policy	500	World wide participation

			infections			makers - Medias		
6	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON	Rapid Identification of Respiratory Tract Infections	26/05/2014	Medical School at Osijek University in Croatia	Scientific community (higher education, Research)	50	Croatia
7	Oral presentation to a scientific event	NATIONAL UNIVERSITY OF IRELAND, GALWAY	Infectious Disease Nucleic Acid Diagnostics – working with industry - an Academics perspective	10/06/2014	Singapore	Scientific community (higher education, Research) - Industry - Policy makers - Medias		Singapore, Malaysia (Southeast Asia)
8	Press releases	NATIONAL UNIVERSITY OF IRELAND, GALWAY	Possible Outcome	28/08/2012	Singapore	Scientific community (higher education, Research) - Industry		Global
9	Interviews	NATIONAL UNIVERSITY OF IRELAND, GALWAY	EU Galway Science Grant	05/09/2012	Press Release in relation to the grant giving a description of the project and the	Scientific community (higher education, Research) - Industry		Global

					partners involved			
10	Interviews	NATIONAL UNIVERSITY OF IRELAND, GALWAY	New EU project for Pneumonia	29/08/2012	European Commission	Scientific community (higher education, Research) - Industry		Global
11	Oral presentation to a scientific event	NATIONAL UNIVERSITY OF IRELAND, GALWAY	Infectious Disease Nucleic Acid Diagnostics – working with industry from an Academics perspective	10/06/2014	Singapore	Scientific community (higher education, Research) - Industry		Global
12	Oral presentation to a scientific event	NATIONAL UNIVERSITY OF IRELAND, GALWAY	Rapid Identification of Respiratory Tract Infections	12/12/2014	Galway, Ireland	Scientific community (higher education, Research) - Civil society		Ireland
13	Oral presentation to a scientific event	NATIONAL UNIVERSITY OF IRELAND, GALWAY	Real-time PCR diagnostics assay to quantitatively detect and identify human pathogenic microorganisms from water, water distribution and premise plumbing systems. Water	07/09/2015	Winchester, UK	Scientific community (higher education, Research) - Industry - Policy makers		Global

			Microbiology – Current and Emerging Issues in Healthcare Facilities					
14	Oral presentation to a scientific event	NATIONAL UNIVERSITY OF IRELAND, GALWAY	qPCR Diagnostics Assay Development for Infectious Disease – Working with Industry - an Academics Perspective	20/10/2015	London, UK	Scientific community (higher education, Research) - Industry		Global
15	Oral presentation to a scientific event	NATIONAL UNIVERSITY OF IRELAND, GALWAY	Current and emerging technologies for NAD development	18/12/2015	Galway, Ireland	Scientific community (higher education, Research) - Industry		Ireland
16	Posters	UNIVERSITY COLLEGE LONDON	RiD-RTI- Rapid Identification of Respiratory Tract infections	25/04/2015	Copenhagen, Denmark	Scientific community (higher education, Research) - Industry		Global
17	Posters	UNIVERSITY COLLEGE LONDON	RiD-RTI- Rapid Identification of Respiratory Tract infections	10/05/2014	Barcelona, Spain	Scientific community (higher education, Research) - Industry		Global

18	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON	Rapid Molecular Diagnostics of Antimicrobial Resistance and Respiratory Tract Infections	25/11/2014	Birmingham, UK	Scientific community (higher education, Research)		UK
19	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON	Rapid molecular diagnostics for antimicrobial resistance	19/02/2016	London, UK	Scientific community (higher education, Research)		UK
20	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON	The future of susceptibility testing	02/04/2015	Cardiff, Wales	Scientific community (higher education, Research)		UK
21	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON	The future of susceptibility testing	27/08/2015	Cardiff, Wales	Scientific community (higher education, Research)		UK
22	Organisation of Workshops	UNIVERSITY COLLEGE LONDON	Rapid diagnosis of Pneumonia	23/06/2015	London, UK	Scientific community (higher education, Research) - Civil society		UK

23	Posters	NATIONAL UNIVERSITY OF IRELAND, GALWAY	Sample in, answer out? Clinical evaluation of the P50 pneumonia assay	27/11/2015	Birmingham, UK	Scientific community (higher education, Research)		UK
24	Posters	UNIVERSITY COLLEGE LONDON	Checking up on resistance: aphenotypic and genotypic analysis of extended spectrum beta-lactamase and carbapenemase-producing Enterobacteriaceae	27/11/2015	Birmingham, UK	Scientific community (higher education, Research)		UK
25	Posters	UNIVERSITY COLLEGE LONDON	A clinical evaluation of the Curetis Unyvero P55 pneumonia application for doagnosis of hospital acquired and ventilator associated pneumonia	27/11/2015	Birmingham, UK	Scientific community (higher education, Research)		UK
26	Exhibitions	MOBIDIAG OY	Novodiag platform presentation and RiD-RTI brochures	25/04/2015	Copenhagen, Denmark	Scientific community (higher education, Research) - Industry		Global

27	Exhibitions	GENEWAVE SAS	Novodiag platform presentation and RiD-RTI brochures	25/04/2015	Copenhagen, Denmark	Scientific community (higher education, Research) - Industry		Global
28	Exhibitions	MOBIDIAG OY	RiD-RTI brochures	10/05/2014	Barcelona, Spain	Scientific community (higher education, Research) - Industry		Global
29	Exhibitions	GENEWAVE SAS	RiD-RTI brochures	10/05/2014	Barcelona, Spain	Scientific community (higher education, Research) - Industry		Global
30	Exhibitions	MOBIDIAG OY	RiD-RTI brochures	25/08/2014	Bergen, Norway	Scientific community (higher education, Research) - Industry		North Europe
31	Oral presentation to a scientific event	UNIVERSITY COLLEGE LONDON HOSPITALSNHS FOUNDATION	Gram-negative aerobe bacteria (Pseudomonas, Stenotrophomonas, Burkholderia, Alcanigenes, and	04/02/2015	Leuven, Belgium	Scientific community (higher education, Research)		Global

		TRUST	Acinetobacter spp.): importance for the immunocompromised patient and novel treatment strategies					
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Section B (Confidential or public: confidential information to be marked clearly)

TEMPLATE B1: LIST OF APPLICATIONS FOR PATENTS, TRADEMARKS, REGISTERED DESIGNS, ETC.					
Type of IP Rights:	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Application reference(s) (e.g. EP123456)	Subject or title of application	Applicant (s) (as on the application)
Patent	Yes	not to be disclosed	British Patent Application 1508860.2	Diagnostic Method	Kate Reddington, Elizabeth Minogue, Nina Tuite, Thomas Barry
Patent	Yes	not to be disclosed	PCT/IB2011/001719	Diagnostic Method	Kate Mary Reddington, Thomas Gerard Barry, Justin Joseph O'grady, Terence James Smith
Patent	Yes	not to be disclosed	PCT/EP2009/057338	P2/p2a/p2b gene sequences as diagnostic targets for the identification of fungal and yeast species	Thomas Gerard Barry, Terry James Smith, Marcin Jankiewicz, Louise O'connor, Nina Tuite, Sinead Lahiff, Majella Maher

Part B2

Please complete the table hereafter:

Type of Exploitable Foreground ²¹	Description of exploitable foreground	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Exploitable product(s) or measure(s)	Sector(s) of application ²²	Timetable, commercial or any other use	Patents or other IPR exploitation (licences)	Owner & Other Beneficiary(s) involved
	<i>Ex: New superconductive Nb-Ti alloy</i>			<i>MRI equipment</i>	<i>1. Medical 2. Industrial inspection</i>	<i>2008 2010</i>	<i>A materials patent is planned for 2006</i>	<i>Beneficiary X (owner) Beneficiary Y, Beneficiary Z, Poss. licensing to equipment manuf. ABC</i>
COMMERCIAL EXPLOITATION OF R&D RESULTS		YES		PCR ASSAY FOR DETECTION OF RSVB VIRUSES	DIAGNOSTIC INDUSTRY	2009 2010	LICENSING BEING CONSIDERD	UCL
COMMERCIAL EXPLOITATION OF R&D RESULTS		YES		PCR ASSAY FOR DETECTION FOR VARIOUS MICROBIAL PATHOGENS	DIAGNOSTIC INDUSTRY	2009 2010	LICENSING BEING CONSIDERD	NUIG

¹⁹ A drop down list allows choosing the type of foreground: General advancement of knowledge, Commercial exploitation of R&D results, Exploitation of R&D results via standards, exploitation of results through EU policies, exploitation of results through (social) innovation.

²² A drop down list allows choosing the type sector (NACE nomenclature) : http://ec.europa.eu/competition/mergers/cases/index/nace_all.html

Report on societal implications

Replies to the following questions will assist the Commission to obtain statistics and indicators on societal and socio-economic issues addressed by projects. The questions are arranged in a number of key themes. As well as producing certain statistics, the replies will also help identify those projects that have shown a real engagement with wider societal issues, and thereby identify interesting approaches to these issues and best practices. The replies for individual projects will not be made public.

A General Information *(completed automatically when Grant Agreement number is entered.*

Grant Agreement Number:

304865

Title of Project:

Rapid Diagnosis of Respiratory tract Infections

Name and Title of Coordinator:

Dr. Virve Enne

B Ethics

1. Did your project undergo an Ethics Review (and/or Screening)?

- If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports?

0Yes

Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 'Work Progress and Achievements'

2. Please indicate whether your project involved any of the following issues (tick box) :

YES

RESEARCH ON HUMANS

• Did the project involve children?	NO
• Did the project involve patients?	NO
• Did the project involve persons not able to give consent?	NA
• Did the project involve adult healthy volunteers?	NO
• Did the project involve Human genetic material?	NO
• Did the project involve Human biological samples?	YES
• Did the project involve Human data collection?	YES

RESEARCH ON HUMAN EMBRYO/FOETUS

• Did the project involve Human Embryos?	NO
• Did the project involve Human Foetal Tissue / Cells?	NO
• Did the project involve Human Embryonic Stem Cells (hESCs)?	NO
• Did the project on human Embryonic Stem Cells involve cells in culture?	NO
• Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	NO

PRIVACY

• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	YES
• Did the project involve tracking the location or observation of people?	NO

RESEARCH ON ANIMALS

• Did the project involve research on animals?	NO
• Were those animals transgenic small laboratory animals?	NO
• Were those animals transgenic farm animals?	NO

• Were those animals cloned farm animals?	NO
• Were those animals non-human primates?	NO
RESEARCH INVOLVING DEVELOPING COUNTRIES	
• Did the project involve the use of local resources (genetic, animal, plant etc)?	NO
• Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	NO
DUAL USE	
• Research having direct military use	NO
• Research having the potential for terrorist abuse	NO

C Workforce Statistics

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator	1	1
Work package leaders	3	8
Experienced researchers (i.e. PhD holders)	4	9
PhD Students	0	0
Other	5	8

4. How many additional researchers (in companies and universities) were recruited specifically for this project? **10**

Of which, indicate the number of men: **5**

D Gender Aspects

5. Did you carry out specific Gender Equality Actions under the project?	x	Yes No																		
6. Which of the following actions did you carry out and how effective were they? <table style="width: 100%; margin-top: 10px;"> <thead> <tr> <th style="width: 60%;"></th> <th style="width: 20%; text-align: center;">Not at all effective</th> <th style="width: 20%; text-align: center;">Very effective</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/> Design and implement an equal opportunity policy</td> <td style="text-align: center;">○ ○ ○ ○ ○</td> <td></td> </tr> <tr> <td><input type="checkbox"/> Set targets to achieve a gender balance in the workforce</td> <td style="text-align: center;">○ ○ x ○ ○</td> <td></td> </tr> <tr> <td><input type="checkbox"/> Organise conferences and workshops on gender</td> <td style="text-align: center;">○ ○ ○ ○ ○</td> <td></td> </tr> <tr> <td><input type="checkbox"/> Actions to improve work-life balance</td> <td style="text-align: center;">○ ○ ○ x ○</td> <td></td> </tr> <tr> <td><input type="radio"/> Other: </td> <td colspan="2"></td> </tr> </tbody> </table>				Not at all effective	Very effective	<input type="checkbox"/> Design and implement an equal opportunity policy	○ ○ ○ ○ ○		<input type="checkbox"/> Set targets to achieve a gender balance in the workforce	○ ○ x ○ ○		<input type="checkbox"/> Organise conferences and workshops on gender	○ ○ ○ ○ ○		<input type="checkbox"/> Actions to improve work-life balance	○ ○ ○ x ○		<input type="radio"/> Other: 		
	Not at all effective	Very effective																		
<input type="checkbox"/> Design and implement an equal opportunity policy	○ ○ ○ ○ ○																			
<input type="checkbox"/> Set targets to achieve a gender balance in the workforce	○ ○ x ○ ○																			
<input type="checkbox"/> Organise conferences and workshops on gender	○ ○ ○ ○ ○																			
<input type="checkbox"/> Actions to improve work-life balance	○ ○ ○ x ○																			
<input type="radio"/> Other: 																				
7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed? <input type="radio"/> Yes- please specify <input checked="" type="radio"/> No																				

E Synergies with Science Education

8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?	
<input type="radio"/> Yes- please specify 	
<input checked="" type="radio"/> No	
9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?	
<input type="radio"/> Yes- please specify 	
<input checked="" type="radio"/> No	

F Interdisciplinarity

10. Which disciplines (see list below) are involved in your project?		
<input type="radio"/> Main discipline ²³ : Basic medicine		
<input type="radio"/> Associated discipline ²³ : Electrical engineering, Mathematics & computer sciences, biological sciences	<input type="radio"/> Associated discipline ²³ :	

G Engaging with Civil society and policy makers

11a Did your project engage with societal actors beyond the research community? (if 'No', go to Question 14)	○ X	Yes No
11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?		
<input type="radio"/> No		
<input type="radio"/> Yes- in determining what research should be performed		
<input type="radio"/> Yes - in implementing the research		

²³ Insert number from list below (Frascati Manual).

<input type="radio"/> Yes, in communicating /disseminating / using the results of the project					
11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?				<input type="radio"/> <input type="radio"/>	Yes No
12. Did you engage with government / public bodies or policy makers (including international organisations)					
<input type="radio"/> No					
<input type="radio"/> Yes- in framing the research agenda					
<input type="radio"/> Yes - in implementing the research agenda					
<input type="radio"/> Yes, in communicating /disseminating / using the results of the project					
13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?					
<input type="radio"/> Yes – as a primary objective (please indicate areas below- multiple answers possible)					
<input type="radio"/> Yes – as a secondary objective (please indicate areas below - multiple answer possible)					
<input type="radio"/> No					
13b If Yes, in which fields?					
Agriculture Audiovisual and Media Budget Competition Consumers Culture Customs Development Economic and Monetary Affairs Education, Training, Youth Employment and Social Affairs		Energy Enlargement Enterprise Environment External Relations External Trade Fisheries and Maritime Affairs Food Safety Foreign and Security Policy Fraud Humanitarian aid		Human rights Information Society Institutional affairs Internal Market Justice, freedom and security Public Health Regional Policy Research and Innovation Space Taxation Transport	

13c If Yes, at which level? <input type="radio"/> Local / regional levels <input type="radio"/> National level <input type="radio"/> European level <input type="radio"/> International level					
H Use and dissemination					
14. How many Articles were published/accepted for publication in peer-reviewed journals?	10				
To how many of these is open access²⁴ provided?	1				
How many of these are published in open access journals?	1				
How many of these are published in open repositories?	0				
To how many of these is open access not provided?	9				
Please check all applicable reasons for not providing open access:					
<input type="checkbox"/> publisher's licensing agreement would not permit publishing in a repository <input type="checkbox"/> no suitable repository available <input checked="" type="checkbox"/> no suitable open access journal available <input type="checkbox"/> no funds available to publish in an open access journal <input type="checkbox"/> lack of time and resources <input type="checkbox"/> lack of information on open access <input type="checkbox"/> other ²⁵ :					
15. How many new patent applications ('priority filings') have been made? <i>("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).</i>	3				
16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark				
	Registered design				
	Other				
17. How many spin-off companies were created / are planned as a direct result of the project?	0				
<i>Indicate the approximate number of additional jobs in these companies:</i>					
18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project: <table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <input checked="" type="checkbox"/> Increase in employment, or <input checked="" type="checkbox"/> Safeguard employment, or <input type="checkbox"/> Decrease in employment, <input type="checkbox"/> Difficult to estimate / not possible to quantify </td> <td style="width: 10%; vertical-align: top; text-align: center;"> <input checked="" type="checkbox"/> </td> <td style="width: 40%; vertical-align: top;"> In small & medium-sized enterprises In large companies None of the above / not relevant to the project </td> </tr> </table>			<input checked="" type="checkbox"/> Increase in employment, or <input checked="" type="checkbox"/> Safeguard employment, or <input type="checkbox"/> Decrease in employment, <input type="checkbox"/> Difficult to estimate / not possible to quantify	<input checked="" type="checkbox"/> 	In small & medium-sized enterprises In large companies None of the above / not relevant to the project
<input checked="" type="checkbox"/> Increase in employment, or <input checked="" type="checkbox"/> Safeguard employment, or <input type="checkbox"/> Decrease in employment, <input type="checkbox"/> Difficult to estimate / not possible to quantify	<input checked="" type="checkbox"/> 	In small & medium-sized enterprises In large companies None of the above / not relevant to the project			
19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (FTE = one person working fulltime for a year) jobs:	<i>Indicate figure:</i> 15				

²⁴ Open Access is defined as free of charge access for anyone via Internet.

²⁵ For instance: classification for security project.

Difficult to estimate / not possible to quantify	<input type="checkbox"/>
I Media and Communication to the general public	
20. As part of the project, were any of the beneficiaries professionals in communication or media relations?	
<input type="radio"/> Yes	<input checked="" type="radio"/> No
21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?	
<input type="radio"/> Yes	<input checked="" type="radio"/> No
22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?	
<input type="checkbox"/> Press Release	<input type="checkbox"/> Coverage in specialist press
<input type="checkbox"/> Media briefing	<input type="checkbox"/> Coverage in general (non-specialist) press
<input type="checkbox"/> TV coverage / report	<input type="checkbox"/> Coverage in national press
<input checked="" type="checkbox"/> Radio coverage / report	<input type="checkbox"/> Coverage in international press
<input checked="" type="checkbox"/> Brochures /posters / flyers	<input checked="" type="checkbox"/> Website for the general public / internet
<input type="checkbox"/> DVD /Film /Multimedia	<input checked="" type="checkbox"/> Event targeting general public (festival, conference, exhibition, science café)
23 In which languages are the information products for the general public produced?	
<input type="checkbox"/> Language of the coordinator	<input checked="" type="checkbox"/> English
<input type="checkbox"/> Other language(s)	

Question F-10: Classification of Scientific Disciplines according to the Frascati Manual 2002 (Proposed Standard Practice for Surveys on Research and Experimental Development, OECD 2002):

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES

- 1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]
- 1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)
- 1.3 Chemical sciences (chemistry, other allied subjects)
- 1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)
- 1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2. ENGINEERING AND TECHNOLOGY

- 2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)
- 2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]
- 2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as

geodesy, industrial chemistry, etc.; the science and technology of food production; specialised technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES

- 3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)
- 3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)
- 3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES

- 4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)
- 4.2 Veterinary medicine

5. SOCIAL SCIENCES

- 5.1 Psychology
- 5.2 Economics
- 5.3 Educational sciences (education and training and other allied subjects)
- 5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary, methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES

- 6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as archaeology, numismatics, palaeography, genealogy, etc.)
- 6.2 Languages and literature (ancient and modern)
- 6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group]