Topic: The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Antimicrobial-resistant (AMR) bacterial strains killed 25 000 people in the EU in 2007 and cost the economy €1.5 billion a year. Many antibiotics that were once thought to put an end to infectious diseases are no longer working. Huge amounts of antibiotics are prescribed and consumed unnecessarily in almost all healthcare systems. The misuse of antibiotics has created a huge global health crisis. Prudent use of antibiotics is urgently required in order to protect the efficacy of our currently available antibiotics. We can reduce their unnecessary use in many ways; nevertheless diagnostics have the potential to provide more targeted, accurate use of antibiotics which is in the best interest of patients and the wider population. Diagnostics play a critical role in guiding treatment in infectious diseases. However, the value of diagnostics as a critical component of antimicrobial stewardship programmes is not fully established throughout Europe, with guidelines, funding and policy varying in each country. This hinders the adoption and use of currently available diagnostic tests by health professionals, as well as the development of advanced or innovative diagnostic tools. Therefore, a pan-European approach is required, to demonstrate the medical, economical and public health value of diagnostics for combating AMR: rapid and reliable characterisation of pathogens and their antibiotic resistance characteristics along with host susceptibility biomarkers. One way to determine the full value of diagnostics, and the optimal means of addressing the multitude of obstacles for their creation, valuation and deployment, is to analyse all these aspects in a standardised clinical trial network.

The overuse of antibiotics and the underuse of diagnostics occur within the entire breadth of healthcare: primary care, as well as hospitals with acute care, rehabilitation facilities and long-term care facilities, where most of the emerging antibiotic-resistant pathogens can be found. In Europe, 30-50% of antibiotics are prescribed unnecessarily, according to estimates from the European Centre for Disease Prevention and Control (ECDC). It is also well-described that the largest volume of antibiotics for human use is prescribed in the community setting (e.g. physician offices, clinics), most often for respiratory complaints and suspected

respiratory tract infections - and over half of the time unnecessarily. Better diagnostic capabilities and more aggressive antimicrobial stewardship are amongst the top five unmet medical needs in strategies to combat antibiotic-resistant infections.

One of the most convincing means of demonstrating the value of diagnostics is to conduct prospective clinical trials and data collection which evaluate their impact in real-life patient-care settings. Due to the need for large numbers of patients in such analyses, a network of well-defined patient-care settings is necessary to carry out the type and extent of studies needed to demonstrate the value of diagnostics. The goal for setting up a network of clinical sites is to assess the impact of "standardised care and management algorithms" using well-defined diagnostics in a proscribed manner in a well-defined and common infectious syndrome, compared to "usual care". The choice of the targeted infectious disease is expected to be Community-Acquired Acute Respiratory Tract Infection (CA-ARTI) since it best reflects an area of importance where the over-prescribing of antibiotics is most flagrant. Possible outcomes which could be measured include, among others: i) doses or days of antibiotics prescribed, ii) proportion of patients not receiving antibiotics, iii) development of antibiotic-resistant colonisation post antibiotic therapy, iv) pathogen mutation to a resistant phenotype during or post therapy, v) emergence of antibiotic resistance among "normal" intestinal flora during or after therapy.

There is currently a dearth of studies which can provide the evidence of the value of diagnostics in well-characterised situations, and this has been a hindrance for diagnostic innovation. Furthermore, the current financial framework (i.e. inadequate reimbursement of diagnostics, reimbursement based on technology rather than medical value) does not encourage innovation related to *in vitro* diagnostic tests. The current *in vitro* diagnostic business model - focused on technology used, lab activity measures, and complexity indicators – is antiquated, and should focus on patient outcomes and health-economic benefits to incentivise the creation and utilisation of high-medical-value diagnostics. Moreover, regulatory approval has historically been based on analytical performance, rather than on clinical effectiveness. Inserting patient-based benefits into the regulatory process would advantage diagnostics which confer the most benefit to individuals and the healthcare system.

More background information is available in the following list of publications:

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Need and opportunity for public-private collaborative research

The urgent action to address the escalating problem of antibiotic resistance requires cooperation amongst industry, academia, patients and patient groups, policy makers, public health experts and healthcare decision-makers in order to implement critical solutions, including impactful diagnostics, which will allow preserving the efficacy of the antibiotics currently available or in development. Multiple diagnostics already exist which can be used to accurately and efficiently guide and improve antibiotic prescribing, but they are under-utilised across Europe. A public-private project is required to address the barriers which prevent the uptake and development of diagnostics for antimicrobial stewardship, which include studies, policy development, funding and reimbursement formulae and schemes, physician education and patient awareness, psychosocial factors, appropriate and innovative assessment (e.g. modern HTA), and disparate regulatory requirements.

Scope

The main objective of this action is to understand, demonstrate, and quantify the value of diagnostics and the obstacles to their adoption and use in the framework of a Standardised Care Network in order to combat antimicrobial resistance (AMR) by optimising antibiotic use in Europe.

The overuse of antibiotics and the underuse of diagnostics occur within the entire breadth of healthcare. It is a major issue especially in the "community" setting (e.g. non-hospital clinics, private physician offices, para-medical clinics) where the majority of human antibiotics are used, most of which are inappropriately and unnecessarily prescribed. It is crucial to demonstrate both the economic and clinical value of diagnostics to health systems and purchasers. Governments and healthcare systems need to understand the wider value of diagnostics – including how their use can help them to achieve reductions in AMR and healthcare costs.

Health economic models for the use of diagnostics must be developed to:

- address the costs and benefits of the use of diagnostics and their impact on antibiotic prescribing;
- propose funding models (e.g. research incentives, reimbursement framework, adoption motivation) which would facilitate the development, introduction, deployment and use of diagnostics into routine medical care.

A global roadmap must be defined to promote the use of diagnostic tools that would have distinct and clearly defined objectives: (i) avoiding unnecessary antibiotic use, (ii) optimising patient treatment and antibiotic use (iii), identifying high-risk patients and/or pathogens for targeted and personalised antibiotic therapy, and (iv) using diagnostics in clinical trials for supporting the development of new anti-infective approaches (prophylactic or therapeutic).

This project aims at providing clinical evidence to demonstrate the medical value, health care benefit and economic viability of diagnostic tests for combatting antibiotic resistance and improving patient outcome in conditions such as Community-Acquired Acute Respiratory Tract Infection (CA-ARTI).

Four objectives need to be addressed in this project:

Objective 1

The first objective is to establish a health-economic framework to assess and demonstrate the value of diagnostics both for individual patients and for public health impact by reducing antibiotic use and subsequent antibiotic resistance among patients. The framework should build on the available evidences and utilise an extensive consultation with key stakeholders including, for example, traditional and innovative value-based evaluation methods, reimbursement schemes, research incentives, evaluation models, policies etc. Results should be disseminated in an adapted way to all stakeholders, including policy makers, clinicians and patients.

Objective 2

The second objective is to establish a Standardised Care Network (pre-existing or new) in order to conduct clinical trials evaluating the value of diagnostics. This network should include high-, medium- and low-antibiotic-use countries in Europe, including countries with and without an antibiotic stewardship programme in place. At a minimum, it should include five high-income EU countries representing a large population base, and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries. A business model must be constructed which will assure the sustainability of the Standardised Care Network after the IMI project completion. In addition, within this network, a bank of appropriate clinical specimens – properly annotated and curated – must be kept for the duration of the project and a model proposed to sustain the biobank *a posteriori* in cooperation with the diagnostics industry.

Objective 3

A third objective is to design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of Community-Acquired Acute Respiratory Tract Infections (CA-ARTIs), by using the outputs, measures and deliverables defined in the health-economic framework (Objective 1). The study must use combinations of "host-based" and "pathogen-based" diagnostic tests in order to determine the optimal testing algorithm for reducing inappropriate antibiotic use and the subsequent development of antibiotic-resistant bacteria (colonisation and/or infection).

Objective 4

The fourth objective is to explore, define and attempt to resolve the psychosocial aspects which prevent the more widespread adoption of diagnostics when delivering healthcare to the population. Focus on patient and healthcare provider education, psychological, ethical and social barriers, as well as pragmatic obstacles will be necessary in order to understand and address this complex issue.

Expected key deliverables

Main deliverables include (i) a defined framework to assess and demonstrate the value of diagnostics to optimise antibiotic therapy and reduce antibiotic resistance, taking into account all expected evidences from key stakeholders; (ii) a sustainable Standardised Care Network representing the different countries mentioned above and encompassing the entire range of healthcare establishment from community clinics to long-term care, able to collect and share thorough information on pathogen, patients status, treatment regimen and outcome; (iii) comprehensive clinical studies on the value of diagnostics in Community-Acquired Acute Respiratory Tract Infection (CA-ARTI) by using outcomes and measures specified in the framework; and (iv) a definition and better understanding of the psychosocial aspects preventing widespread adoption of diagnostics during healthcare delivery, focusing on education, psychological, ethical and social barriers, as well as pragmatic obstacles.

- A framework has to be set up for demonstrating how the use of diagnostics can help to achieve reductions in antibiotic use and the emergence of AMRs. It requires a precise and shared methodology agreed and defined with main stakeholders to:

    1. benchmark the standard of care and identify the most promising opportunities for improvement,

    2. specify the required clinical evidence for the adoption of the best practice and define measurable clinical outcome and success parameters,

    3. describe necessary standards and quality controls to allow the use of the generated evidence for IVD registration,

    4. review the current regulatory environment and recommend improvements for product approvals to accelerate their time to market,

    5. propose funding models facilitating the introduction and application of diagnostics into primary care,

    6. develop a health economic model acceptable to payers for establishing value-based reimbursement for innovative diagnostics.

    7. develop an education and dissemination programme to facilitate the implementation of the framework.

- **Standardised Care Network comprising high-, medium- and low-antibiotic use countries in Europe, including at least five high-income EU countries that represent a large population base and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries, should be established to:**

    1. perform extensive characterisation of clinical samples and pathogens isolated from patients;

    2. create and maintain a biobank of samples associated with a database and repository of information;

    3. propose an information flux architecture for data sharing and analysis;

    4. define a business concept to sustain the infrastructure for future rapid benchmarking and translation of innovative diagnostics and/or other process changes.

- **A multi-country and multi-centre clinical study must be designed and conducted on the value of diagnostics in Community-Acquired Acute Respiratory Tract Infection (CA-ARTI) in order to:**

    1. establish the optimal combination of pathogen-based and host-based diagnostics to achieve the outcomes being measured;

    2. define measurable clinical and other outcomes as well as success parameters to support quantification of the clinical impact and value of diagnostics.

- **A thorough exploration and analysis of the psychosocial obstacles preventing widespread adoption of diagnostics when delivering healthcare to the population should be conducted to:**

    1. define the psychosocial obstacles related to adoption of diagnostics by healthcare providers and patients, and;

    2. provide pragmatic solutions to each of the obstacles outlined, as well as evidence-based methods for their resolution within a European framework.

Expected impact

Expected impact will be the reduction of antibiotic use and AMR resulting in improved patient care through better routine use of diagnostics. It should be adapted according to national/regional requirements and maintained based on a sustainable business model beyond the proposed funding period. A decrease of antibiotic-prescribing rates should further happen in countries involved in the study. This would happen thanks to a raised awareness of health professionals and patients on the necessity to effectively replace empiric therapy by avoidance of antibiotics where unnecessary and definitive targeted therapy when required, particularly for acute respiratory tract infections (ARTIs) with short-term health benefits for patients, short-term economic benefits for the healthcare system, and mid-term / long-term benefits on reducing antibiotic resistance.

The main expected impacts should be : (i) optimum use of diagnostic tests in CA-ARTI for achieving improved patient outcomes, reduction in the inappropriate use of antibiotics, and decrease in the incidence of key antibiotic-resistant pathogens; (ii) wide dissemination of evidence-based conclusions that will sensitise the medical and patient communities, as well as decision makers, to the clinical and economic value of diagnostics; (iii) incorporation of guidance using diagnostic tests and testing algorithms in national and international guidelines; (iv) assistance to regulatory bodies to facilitate adoption of diagnostic tests into wider routine practice; (v) assistance to Health Technology Assessment (HTA) bodies to enable appropriate, fit-for-purpose assessment of the clinical value of diagnostics; (vi) reform of pricing policies (including reimbursement) related to diagnostic tests, according to the demonstrated or anticipated medical value and health outcomes.

New health economic models demonstrated through the project will lead to new pan-European guidelines and algorithms to facilitate the widespread introduction, deployment, adoption and reimbursement of existing and new diagnostics to guide appropriate antibiotic use and reduce unnecessary antibiotic prescribing. Economic models will illustrate to governments, third-party payers and healthcare providers the economic feasibility and benefits of utilising diagnostics to guide appropriate antibiotic prescribing in various healthcare settings.

This evidence should then be published, disseminated, and adopted in order to sensitise the medical, political, regulatory and patient communities to the value of diagnostics in the targeted condition, and promote adoption of the diagnostic tests and testing algorithms into national and international guidelines. Additionally, it is expected that interactions will occur with European (and other) regulatory bodies to assist in the timely approval of diagnostic tests for quick introduction into routine clinical practice.

Health Technology Assessment (HTA) bodies will be also consulted separately in order (i) to facilitate future, fit-for purpose assessments of the clinical value of diagnostics and (ii) to enhance, improve and reformulate information on the financial decision of diagnostic tests according to their medical value and the health outcomes which they confer.

Applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable Small- and Medium-sized Enterprises (SMEs).

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

For example, the initiatives listed below might be relevant in that respect:

▪ **COMBACTE-Net** and **New Drugs for Bad Bugs (ND4BB) programme** (www.combacte.com): This IMI project has established large clinical investigator site and laboratory networks comprising more than 800 clinical sites and more than 600 laboratories across more than 40 European countries. Where possible, this project could build upon the established ND4BB networks and explore synergies. Applicants should

note however that there is no requirement to include partners currently engaged in ND4BB in their proposal, but partners should be chosen to best match network needs and the objectives of this call topic.

- **DRIVE-AB**: The IMI project DRIVE-AB (Driving re-investment in R&D and responsible use of antibiotics) (http://drive-ab.eu/) is assessing the present and future burden of antibiotic resistance, defining the value of new antibiotics, and proposing new economic models for antibiotic development, bearing in mind innovation, stewardship, and access.

- **ND4ID** (http://www.nd4id.eu/): the H2020 project ND4ID (New Diagnostics for Infectious Diseases) is addressing the current shortcomings in the training of IVD researchers through an inter-sectorial, multidisciplinary and translational approach by transversal researchers to close the apparent gap between the clinical perspective and the technological perspective on IVDs.

- **ECRIN** (The European Clinical Research Infrastructure Network - http://www.ecrin.org/) is facilitating clinical research in Europe.

- **Enpr-EMA** (European Network of Paediatric Research at the European Medicines Agency - http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp).

- **PREPARE** (Platform for European Preparedness Against (Re-)emerging Epidemics - www.prepare-europe.eu) and its associated GRACE network.

- Upcoming **pan-European Paediatric Clinical Trials Network** (part of the 10th Call for proposals of IMI2)

- The UK Department of Health project Innovate UK AMR is focused on creating an infrastructure that will fast-track the research, development, evaluation and commercialisation of new drugs, diagnostics and vaccines, also, establishing a global multi-centre clinical trials network for drugs, diagnostics and vaccines, with a focus on antibiotic resistance.

- **CARB-X** (http://www.carb-x.org/) mostly devoted to drug development, but new diagnostic technologies are in scope.

- **JPIAMR** http://www.jpiamr.eu/: The scientific research agenda and recommendations of JPIAMR are aligned with the objectives of this project.

- **Joint action Antimicrobial Resistance and Health Care Associated Infections** (European Commission, 3rd Health Programme - http://ec.europa.eu/chafea/health/actions-2016.html).

- Results and learnings of the following past EC-funded projects (now completed) might potentially be useful:

  o **C4L** (http://cordis.europa.eu/project/rcn/102035_en.html) developed rapid diagnostic tests to link antibiotic prescription with evidence-based diagnosis. Combining the Multiplex Ligation-dependent Probe Amplification (MLPA) and microfluidic technologies allows determination of viral or bacterial origin, as well as bacterial resistance mechanisms.

  o **PARCIVAL** (https://www.up2europe.eu/european/projects/partner-network-for-a-clinically-validated-multi-analyte-lab-on-a-chip-platform_15872.html) developed an integrated and automated multi-analyte lab-on-a-disk platform for the fast and reliable sample-in / answer-out diagnosis of highly infectious respiratory pathogens, resistance patterns and biomarkers for individual severity of the infection.

  o **ROUTINE** (http://cordis.europa.eu/project/rcn/104172_en.html) developed a test that integrates sample preparation, DNA amplification and a fluorescent-based read-out on one platform to allow direct detection of bacteria causing Upper Respiratory Tract Infection and the associated antibiotic resistances within 30 min.

  o **RiD-RTI** (http://cordis.europa.eu/project/rcn/104050_en.html) developed and evaluated diagnostic tools for the rapid (< 2 hrs) diagnosis of pneumonia. The diagnostics products are 'near patient', reliable, cost-effective and user friendly allowing for detection, identification, and quantification (for selected targets) and molecular drug susceptibility testing of RTIs.

Industry consortium

The industry consortium will contribute cash and/or in-kind contributions (expertise, training, diagnostic tests and instruments, data analysis support).

Indicative duration of the action

The indicative duration of the action is 36 months.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require that the applicant consortium satisfies the following conditions and mobilises, as appropriate, the following expertise or capabilities:

- health economists experienced in diagnostic studies;
- experience and know-how in conducting clinical trials including clinical operations and clinical programme management;
- access to a large population suffering from CA-ARTI across all age groups and differing healthcare environments (i.e. community, acute-care, rehabilitation, long-term care, home care);
- physicians and other health care providers experienced in working with the use of standardised procedures and processes in all clinical trials, uniform training of all research personnel, assistance in the design of clinical trials, inclusion of the patient/parent perspective in clinical trials, and the sharing information related to clinical trials;
- payers / prescribers / regulatory organisations able to actively contribute to the development and standardisation of study procedures and processes (e.g. creation of study documents, patient/parent information);
- psychologists, social workers, educators and other social science experts skilled in the analysis of psychosocial barriers to health intervention implementation;
- expertise in advocacy;
- expertise in information technology/data management;
- expertise in legal and clinical compliance/ICH GCP (International Council for Harmonisation – Good Clinical Practice) aspects;
- strong project management and communication expertise, office administration and website management.

Applicant consortia will be expected to include experts and sites in a "community" setting such as non-hospital clinics, private physician offices, para-medical clinics, etc. (where the majority of human antibiotics are used), as well as hospitals, rehabilitation facilities and long-term care facilities (where most of the emerging antibiotic-resistant pathogens can be found).

SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and

expertise. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The consortium is expected to have a strategy on the translation of the relevant project outputs into policy, regulatory, clinical and healthcare practice. A plan for interactions with decision makers, regulatory agencies/health technology assessment bodies with relevant milestones and allocated resources should be proposed to ensure this.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

It is anticipated that industry contribution would include:

- project management support (project design and continuous follow-up);
- legal expertise, health economics expertise;
- clinical operations, data management, and clinical expertise to support regular review of deliverables;
- training and support of professionals to use/run new diagnostic assays;
- co-leadership to contribute to consortium governance structure and meetings.

Work package 1 – Implementation of diagnostics

It aims at designing and testing a framework for establishing a sustainable infrastructure for the evidence based translation of innovative diagnostics into standard-of-care. The framework should assess and demonstrate the value of diagnostics both for individual patients and for public health. The framework should build on the available evidence and utilise an extensive consultation with key stakeholders.

Key tasks:

1. Establish a consulting network including physicians, European in vitro diagnostics (IVD) regulators, HTA and other assessment programmes, reimbursement experts, third-party payers, health economists, medical educators and psychosocial experts;

2. Undertake a systematic review of the existing (peer-reviewed) literature and ongoing European AMR-related activities;

3. Analyse the implementation process for innovative diagnostics into standard of care in CA-ARTI, describe key hurdles and propose actions to systematically drive their evidence based implementation, especially;

4. Provide a description of the framework for a rapid evidence based implementation of innovative diagnostics into routine based on a Standardised Care Network;

5. Facilitate the decisions regarding the implementation of the best practice process into routine with the key stakeholders;

6. Establish and define the measurable clinical and other outcomes and success parameters with which to measure the clinical impact and value of diagnostics.

Work package 2 – Establishment of a Standardised Care Network

The purpose is to establish a Standardised Care Network (pre-existing or new) in order to conduct clinical trials evaluating the value of diagnostics. This Network should include high-, medium- and low-antibiotic-use countries in Europe, including countries with and without an antibiotic stewardship programme in place. The network should include at least five high income EU countries that represent a large population base and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries. A business model must be constructed which will assure the sustainability of this network after the IMI project completion.

In addition, within this network, a bank of appropriate clinical specimens – properly annotated and curated – must be kept for the duration of the clinical trial, and a sustainability proposition should be proposed.

Key tasks:

1. Define and set-up a network of well-defined patient-care settings, in order to demonstrate and quantify the value of diagnostics for CA-ARTI management:

   - Covering countries mentioned above;

   - Encompassing the entire range and spectrum of healthcare establishments from community clinics to long-term care, including physician offices;

   - Being coordinated and led through a single entity or group and providing a one-stop point of access;

   - Establishing and sharing standardised care procedures and algorithms both for usual care and prospective clinical trial to generate data that feed criteria and evidences specified in work package 1;

   - Leveraging or synergising with existing European networks or clinical research infrastructures (IMI, others) in a collaborative effort to shorten set-up time and expand access to patients and samples;

2. Conduct multi-center prospective/randomised clinical trials in order to demonstrate and quantify the value of diagnostic for CA-ARTI and their impact in real-life patient-care settings:

   - Respecting the frame of clinical studies defined in Work package 4;

   - Comparing use of novel diagnostics and procedure with usual care in a standardised manner;

   - Ensuring relevant patient and sample data collection and storage in agreement with work package 3 requirements.

3. Perform extensive characterisation of clinical samples and pathogens isolated from patients:

   - Including both isolated pathogens, commensal flora and patient (host) sample analysis;

   - Using reference (phenotypic) and state-of-the-art deep characterisation methods (Whole genome Sequencing, Mass Spectrometry, epidemiological tools) for pathogen analysis (identification, antibiotic resistance);

   - Evaluating host status and response (immune profile, biochemical and genetic markers);

   - Covering all antibiotic resistance traits encountered and allowing the identification of new markers or mechanism of resistance.

4. Create and maintain a Biobank of samples, clinical specimen and pathogens isolated from patients:

   - Constituting a comprehensive collection of micro-organisms and primary clinical samples with high quality standards (redundancy, traceability, storage);

- Constantly curated and updated based on latest results (new samples, patient follow-up) to allow reliable analyses (statistical performance, regulatory evaluation).

5. Propose and validate a scheme and business model to allow the created Standardised Care Network to be sustainable and permanently accessible in Europe for further studies with an emphasis on diagnostics for infectious diseases in order to reduce global antibiotic use and AMR, and so:

- Broadening diagnostic evaluation to other clinical situation;

- Allowing long-term analysis of diagnostic value (patient outcome, infection and resistance recurrence).

Work package 3 – Data Analysis

The purpose is to provide tools and organisation suitable for the analysis of the data from the clinical study undertaken in the Standardised Care Network, including surveillance data, "best practices" which are based on optimal patient outcomes, and all of the outcomes, measures and deliverables outlined in work package 1.

Key tasks:

1. Establish a Database and Repository of information:

- Gathering results and information obtained in Clinical Studies (work package 4) performed in the Standardised Care Network (work package2);

- Containing all detailed information on isolated pathogens (identification, resistance traits, epidemiology, prevalence);

- Interfaced with Laboratory / Hospital information System;

- Connected with Patient Electronic Record / Retrieving key (anonymised) information relevant for the Project;

- Collecting treatment information related to patient care (drug prescribed, treatment regimen, posology, antibiotic stewardship);

- Consolidating health-care associated expenses by category (hospital stay duration, cost of antibiotic treatment, complementary care, cost of testing…);

- Providing inter-operability features to allow connections between laboratory information systems and partners, and favoring information exchange across laboratories of the consortium);

- With a user interface suitable for clinicians and health care professionals of the network to load, consult or extract information.

2. Allow (Meta) Data analysis including :

- Data mining relevant to evidences and criteria expected from work package 1;

- Extraction of information of Clinical Studies managed in work package 4.

3. Propose a data flux information architecture suitable for:

- Future decision-support tools to implement optimal treatment and management of patient for health care professionals;

- Clinical context use to implement / optimise use of diagnostic solutions.

Work package 4 – Clinical study on the value of diagnostics in Community-Acquired Acute Respiratory Tract Infection (CA-ARTI)

The objective is to design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of community acquired – acute respiratory tract infections (CA-ARTIs), by using the outcomes, measures and deliverables outlined in work package 1 within the Standardised Care Network of

Work package 2. The studies must use combinations of "host-based" and "pathogen-based" diagnostic tests in order to determine the optimal testing algorithm for reducing inappropriate antibiotic use and the development of antibiotic-resistant bacterial strains.

Key tasks:

1. Design a multi-country and multi-centre clinical study within the Standardised Care Network as set out in Work package 2, to demonstrate the value of diagnostics in the optimal treatment of community acquired – acute respiratory tract infections (CA-ARTIs);

2. Implement the clinical study with the following objectives:

   o Evaluate the impact of the use of diagnostics in relation to their impact on antibiotic prescribing rates;

   o Assess the defined measurable clinical outcome and success parameters (clinical utility) which will be derived from the results of work package 1;

   o Include combinations of "host-based" and "pathogen-based" diagnostic tests;

   o Evaluate and test the implementation process for new devices (change management and sustainability) as derived from work package 1;

   o Include parameters to evaluate the health economic models as derived from work package 1;

3. Implement a system for collecting, monitoring and validating measurable / data as set out above;

4. Periodically report the status, results to date and progress;

5. Analyse, interpret and publish the results of the study in a peer-reviewed journal.

Work package 5 – Education & Advocacy

Key stakeholders who can influence practice, policy and prescribing culture must be made aware of the available research, evidence, clinical utility and societal value (i.e. reduction in antibiotic resistance) of diagnostics. A thorough exploration and analysis of the psychosocial obstacles preventing widespread adoption of diagnostics when delivering healthcare to the population should be conducted. The social, ethical, environmental, economic, and psychological factors, that influence the perception and adoption of new diagnostic technologies and their delivery into health systems, should be identified. With the input and help from behavioural sciences and social marketing, this work package should address barriers for acceptance of rapid diagnostic tests and help understanding motivational factors which may help overcoming hurdles to effectively use these tests in patient management. This work package should also study how patients and populations can be empowered to become value-conscious beneficiaries of rapid diagnostic tests. Coordinated education and awareness raising will facilitate this.

Regulation and policy can largely influence the development and use of IVD tests regarding AMR. Currently, a coordinated advocacy effort is missing in that regard. IVD industries and non-industry actors have a common interest in providing evidence to policy makers by sharing best practice and suggesting policies, regulations and guidelines that help in the fight against AMR.

The European Commission has published a new AMR Action Plan and all countries are defining or have defined their national AMR plans. A coordinated public-private action through an advocacy platform is needed to analyse existing policies, identify examples of good practice and evidence regarding diagnostics and surveillance of AMR, discuss with stakeholders and establish concrete recommendations. Advocacy actions should not only target the European level, and collaboration with international associations and initiatives should be envisaged. A public-private partnership will efficiently address the barriers which prevent the uptake of diagnostics and their use in antimicrobial stewardship, which include policy, funding, awareness and disparate regulatory requirements. Economists, public health bodies, healthcare groups and other public bodies are all required to demonstrate independently from industry the value and benefits of rapid diagnostics in antimicrobial stewardship, in order to guide policy, awareness campaigns and funding models.

From an international advocacy stand point, the consortium could build on the work started at Davos, by the G20 and other initiatives suggesting increased use of diagnostics. The advocacy effort performed for low-resource settings from the European continent could be extended to low and middle-income countries (LMICs).

Key tasks:

1. Mapping of stakeholders and policies;

2. Establishment of an advocacy platform;

3. Analysis of existing policies and good practice;

4. Definition of priorities for future policies and actions;

5. Writing of position papers and sharing of evidence provided in other work packages;

6. Organisation of events and meetings with stakeholders and decision makers;

7. Analysis of the psychosocial obstacles preventing widespread adoption of diagnostics.

Work package 6 – Unmet needs in diagnostics to combat AMR

Beyond the project and to further extend to other target diseases, further needs in diagnostic tests to impact on antibiotic use and the development of AMR should be anticipated.

A diagnostic test needs to provide the clinician with sufficient information to decide on the most appropriate antibiotic strategy or to deviate from prescribing antibiotics altogether. This need differs between various infectious diseases, between different clinical settings and between geographies within Europe and beyond.

The Project team and public/private partnership should elaborate further on a roadmap including:

- **User Requirement Specifications** outlining the minimal and optimal requirements of a diagnostic test from an end-user perspective. A separate document could be generated per disease and per clinical setting specifying regional differences with clear indication on how the specifications drive clinical utility. Such a document requires an extensive outreach to the various stakeholders, integrating their viewpoints. A number of case studies can be used to anchor these concepts in concrete examples.

- **Proposals of clinical algorithms** for use of diagnostics within various clinical settings. Such use should be based on what is considered "responsible use" of antibiotics and should integrate in a first instance the result of one or more diagnostic tests with the results of the clinical evaluation of the patient. To this end, the different viewpoints held by different stakeholders should be mapped and linked to current and future (ideal) diagnostic concepts.

This study should reveal shortcomings in the currently available diagnostic tests – even if currently underused, which should feed a technological roadmap addressing both bioassay content (host and pathogen biomarkers, probes, antibodies, metabolic substrates, etc.) and device/instrument gaps. Indeed, investments into novel technologies that might result in new returns could be considered to incentivise new technology development.

Work package 7 – New models of sustainability

This work package should identify criteria which result in long-term investments, incentivised innovation that reflect the unique public health and medical needs for diagnostics in support of responsible use of antibiotics. As some diagnostic tests are technologically complex, their costs by far exceed the price of antibiotics.

Key tasks:

1. Define value from different perspectives: patient, clinician, payer, health-care system,
2. Propose ways to have value reflected in alternative valuation paradigms,
3. Evaluate reimbursement based on the benefits and the outcome for patients.

Work package 8 – Project Management

The objective is to establish a framework to optimise resources and ensure delivery of results in due time and/or mitigate the risks associates to the project, maximizing interaction and cross-fertilisation across the various work packages.

Project management should furthermore ensure the strategic alignment of efforts to key deliverables, oversee, coordinate, manage and facilitate the project and its work packages among the consortia members and with IMI.

Key tasks:

1. Set-up a joint governance structure for the project,
2. Define charters and clear accountabilities,
3. Provide coordination and support to work package leaders,
4. Define work plan, time lines, deliverables, dates, adherence to budget and review progress,
5. Identify project interdependencies, stakeholders, risks and mitigation plan,
6. Verify that partners are committed and engaged,
7. Ensure meetings and interactions between work packages, sub-groups, and consortium governance,
8. Ensure internal and external communication.

References

[1] Cals, J.W., Butler, C.C., Hopstaken, R.M., Hood, K. and Dinant, G.J. (2009) Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ. 2009;338(51):1374. [Online] doi:10.1136/bmj.b1374.

[2] Stanton, N., Francis, N.A. and Butler, C.C. (2010) Reducing uncertainty in managing respiratory tract infections in primary care. British Journal of General Practice.

[3] Gjelstad, S. et al. (2011) Do general practitioners' consultation rates influence their prescribing patterns of antibiotics for acute respiratory tract infections? Journal of Antimicrobial Chemotherapy. 2011, 66: 2425-2433.

[4] Brookes-Howell, L, Hood, K, Cooper, L, Little, P, Theo Verheij T, Coenen, S., Maciek Godycki-Cwirko, M., Melbye, H. Borras-Santos, A., Worby, P., Jakobsen, K., Goossens, H., Butler

[5] Rohr U-P, Binder C, Dieterle T, Giusti F, Messina CGM, Toerien E, et al. (2016) The Value of In Vitro Diagnostic Testing in Medical Practice: A Status Report. PLoS ONE 11(3): e0149856

[6] Albrich WC, Dusemund F, Bucher B, et al. Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life": an international, multicenter post-study survey (ProREAL) Arch Intern Med. 2012;172:715–722

[7] Altiner A, Berner R, Diener A, Feldmeier G, Köchling A, Löffler C, Schröder H, Siegel A, Wollny A, Kern WV. Converting habits of antibiotic prescribing for respiratory tract infections in German primary care--the cluster-randomized controlled CHANGE-2 trial. BMC Fam Pract. 2012 Dec 20;13:124.

[8] Alves Galvão MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. Cochrane Database Syst Rev. 2014 Feb 18;2:CD007880.

[9] Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003539.

[10] Charani E, Kyratsis Y, Lawson W, Wickens H, Brannigan ET, Moore LS, Holmes AH. An analysis of the development and implementation of a smartphone application for the delivery of antimicrobial prescribing policy: lessons learnt. J Antimicrob Chemother. 2013 Apr;68(4):960-7.

[11] Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013 Apr 30;4:CD003543.

[12] Davies, S.C. "Annual Report of the Chief Medical Officer, Volume Two, 2011, Infections and the rise of antimicrobial resistance" London: Department of Health (2013) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138331/CMO_Annual_Report_Volume_2_2011.pdf (accessed 15th October 2014).

[13] Department of Health and Department of Environment Food and Rural Affairs.UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf

[14] Department of Health. Innovation Health and Wealth: Accelerating Adoption and Diffusion in the NHS. Available at: http://www.dh.gov.uk/health/2011/12/nhs-adopting-innovation/ (accessed 7th October 2014).

[15] Deloitte Centre for Health Solutions. Working differently to provide early diagnosis. Improving access to diagnostics.

[16] Driskell OJ, Holland D, Hanna FW, Jones PW, Pemberton RJ, Tran M, Fryer AA. Inappropriate requesting of glycated hemoglobin (HbA1c) is widespread: assessment of prevalence, impact of national guidance, and practice-to-practice variability. Clin Chem. 2012;58:906-15.

[17] Fleming A, Browne J, Byrne S. The effect of interventions to reduce potentially inappropriate antibiotic prescribing in long-term care facilities: a systematic review of randomised controlled trials. Drugs Aging. 2013 Jun;30(6):401-8.

[18] Francis NA, Butler CC, Hood K, Simpson S, Wood F, Nuttall J. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. BMJ. 2009 Jul 29;339:b2885.

[19] Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, Wasserman RC, Keren R, Zaoutis TE. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. JAMA. 2013 Jun 12;309(22):2345-52.

[20] Gjelstad S, Høye S, Straand J, Brekke M, Dalen I, Lindbæk M. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study).BMJ. 2013 Jul 26;347:f4403.

[21] Ham C, Dixon A, Brooke B. The Kings Fund. Transforming the delivery of health and social care. the case for fundamental change. Available at: http://www.kingsfund.org.uk/publications/transforming-delivery-health-and-social-care (accessed 7th October 2014).

[22] Health Foundation Report. Evidence: Are clinicians engaged in quality improvement? Health Foundation, 90 Long Acre, London, UK.

[23] Howick J, Cals JW, Jones C, Price CP, Plüddemann A, Heneghan C, Berger MY, Buntinx F, Hickner J, Pace W, Badrick T, Van den Bruel A, Laurence C, van Weert HC, van Severen E, Parrella A, Thompson M. Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA. BMJ Open. 2014 Aug 8;4(8):e005611.

[24] Huang Y, Chen R, Wu T, Wei X, Guo A Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. Br J Gen Pract. 2013 Nov;63(616):e787-94.

[25] Jones CH, Howick J, Roberts NW, Price CP, Heneghan C, Plüddemann A, Thompson M. Primary care clinicians' attitudes towards point-of-care blood testing: a systematic review of qualitative studies. BMC FamPract. 2013;14:117.

[26] Leydon GM, McDermott L, Moore M, Williamson I, Hobbs FD, Lambton T, Cooper R, Henderson H, Little P; PRISM Investigators. A qualitative study of GP, NP and patient views about the use of rapid streptococcal antigen detection tests (RADTs) in primary care: 'swamped with sore throats? BMJ Open. 2013 Apr 3;3(4).

[27] Liddell A, Adshead S, Burgess E. Technology in the NHS. Transforming the patient's experience of care. The Kings Fund. Available at: http://www.kingsfund.org.uk/sites/files/kf/Technology-in-the-NHS-Transforming-patients-experience-of-care-Liddell-Adshead-and-Burgess-Kings-Fund-October-2008_0.pdf (accessed 7th October 2014).

[28] Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S, Cals JW, Melbye H, Santer M, Moore M, Coenen S, Butler C, Hood K, Kelly M, Godycki-Cwirko M, Mierzecki A, Torres A, Llor C, Davies M, Mullee M, O'Reilly G, van der Velden A, Geraghty AW, Goossens H, Verheij T, Yardley L; GRACE consortium. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. Lancet. 2013 Oct 5;382(9899):1175-82.

[29] Little P, Hobbs FD, Moore M, Mant D, Williamson I, Mc Nulty C, Cheng YE, Leydon G, McManus R, Kelly J, Barnett J, Glasziou P, Mullee M; PRISM investigators. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). BMJ. 2013 Oct 10;347:f5806.

[30] Little P, Stuart B, Hobbs FD, Butler CC, Hay AD, Delaney B, Campbell J, Broomfield S, Barratt P, Hood K, Everitt H, Mullee M, Williamson I, Mant D, Moore M; DESCARTE investigators. Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study. Lancet Infect Dis. 2014 Mar;14(3):213-9

[31] Micek ST, Heard KM, Gowan M, Kollef MH. Identifying critically ill patients at risk for inappropriate antibiotic therapy: a pilot study of a point-of-care decision support alert. Crit Care Med. 2014 Aug;42(8):1832-8.

[32] Monitoring and Diagnosis in Oxford. Horizon scanning reports. Available at: http://madox.org/horizon-scanning-report (accessed 7th October 2014).

[33] https://longitudeprize.org/challenge

[34] Nesta Longitude survey. "Benefit of the doubt' is the basis for prescribing antibiotics, finds Longitude survey" http://www.nesta.org.uk/news/%E2%80%98benefit-doubt%E2%80%99-basis-prescribing-antibiotics-finds-longitude-survey

[35] NICE: How to change practice. Understand, identify and overcome barriers to change. https://www.nice.org.uk/Media/Default/About/what-we-do/Into-practice/Support-for-service-improvement-and-audit/How-to-change-practice-barriers-to-change.pdf

[36] Price CP, St John A. Innovation in healthcare. The challenge for laboratory medicine. ClinicaChimica Acta 2014;427:71-78.

[37] Ranji SR, Steinman MA, Shojania KG, Sundaram V, Lewis R, Arnold S, Gonzales R. Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies (Vol. 4: Antibiotic Prescribing Behavior). Rockville (MD): Agency for Healthcare Research and Quality (US); 2006 Jan.

[38] Ranji SR, Steinman MA, Shojania KG, Gonzales R. Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. Med Care. 2008 Aug;46(8):847-62.

[39] Right Care. The NHS Atlas of Variation in Diagnostic Services. Available at: https://www.england.nhs.uk/rightcare/

[40] Roberts R, Hota B, Ahmad I, Scott RD, Foster SD, Abbasi F, Schabowski S, Kampe LM, Ciavarella GG, Supino M, Naples J, Cordell R, Levy SB, Weinstein RA: Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin Infect Dis. 2009 Oct 15;49(8):1175-84.

[41] Sherrard-Smith E, White PJ, Dangerfield C, Choi Y-H, Green N, Jit M, Marshall RD, Bason J, Mercer C, Harding-Esch E, Lowndes CM. Point-of-care vs. Standard Practice for chlamydia: A new approach to assessing the public health effect of rapid testing and treatment at local level. The Lancet. Accepted for publication.

[42] Silvester KM, Mohammed MA, Harriman P, Girolami A, Downes TW. Timely care for frail older people referred to hospital improves efficiency and reduces mortality without the need for extra resources. Age Ageing. 2014 Jul;43(4):472-7.

[43] Siontis KC, Siontis GC, Contopoulos-Ioannidis DG, Ioannidis JP. Diagnostic tests often fail to lead to changes in patient outcomes. J Clin Epidemiol. 2014 Jun;67(6):612-21. doi: 10.1016/j.jclinepi.2013.12.008. Epub 2014 Mar 27.

[44] Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotics for respiratory infections. Cochrane Database Syst Rev. 2013 Apr 30;4:CD004417

[45] Stewart FM, Antia R, Levin BR, Lipsitch M, Mittler JE. The Population Genetics of Antibiotic Resistance II: Analytic Theory for Sustained Populations of Bacteria in a Community of Hosts. Theoretical Poplulation Biology 1998;53:152-65.

[46] Tonkin-Crine S, Yardley L, Coenen S, Fernandez-Vandellos P, Krawczyk J, Touboul P, Verheij T, Little P. GPs' views in five European countries of interventions to promote prudent antibiotic use. Br J GenPract. 2011 May;61(586):e252-61.

[47] van der Velden AW, Pijpers EJ, Kuyvenhoven MM, Tonkin-Crine SK, Little P, Verheij TJ. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. Br J GenPract. 2012 Dec;62(605):e801-7.

[48] Vodicka TA, Thompson M, Lucas P, Heneghan C, Blair PS, Buckley DI, Redmond N, Hay AD; TARGET Programme team. Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. Br J GenPract. 2013 Jul;63(612):e445-54.

[49] Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13:426–435.

[50] World Health Organisation. Antimicrobial resistance. Fact Sheet No 194. Available at: http://www.who.int/mediacentre/factsheets/fs194/en/ (accessed 15th October 2014).

[51] World Health Organization: Department of Communicable Disease Surveillance and Response: WHO Global Strategy for Containment of Antimicrobial Resistance. Available at: http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf [WHO/CDS/DRS/2001 1.2]

[52] York Health Economics Consortium. Organisational and behavioural barriers to medical technology adoption. In: NHS, editor. Coventry, UK: NHS Institute for Innovation and Improvement; 2009. Available at http://www.institute.nhs.uk/images/ResearchAndEvaluationReports/OBB_MTA.pdf (accessed 7th October 2014)