

## Pre-read IMI workshop 'Diagnostics in antimicrobial resistance' 19th June 2017

### Current situation and problem statement

In the past century, interventions and treatment with antibiotics have revolutionised our ability to combat infectious diseases. As a result, death rates from most infectious diseases have decreased considerably. However, because of their low unit cost for individuals (albeit high societal cost) and improved clinical outcome, antibiotics were overused which resulted in the pandemic spread of highly resistant bacterial clones. Because of the rising health threat associated with bacterial resistance, we need a paradigm shift in the way we deliver healthcare regarding infectious diseases: novel ways to prevent infections, innovative diagnostics and appropriate stewardship. Personalised medicine in infectious diseases, based on novel, rapid and reliable diagnostic strategies should help achieve this paradigm shift by identifying those patients who really need antibiotics, and by helping to select the narrow-spectrum antibiotic of choice.

There are five key ways in which diagnostics can help control the development and spread of global antimicrobial resistance:

1. **Guide antibiotic treatment:** Identifying the patients who are likely to benefit from antibiotics and prescribing them only when necessary. Diagnostic tests which e.g. can differentiate between bacterial and viral infections can play a substantial role in preventing over-prescription of antibiotics.
2. **Identifying pathogen and resistance patterns:** Rapid identification of the pathogen and its characteristics is key to beginning effective antibiotic therapy as early as possible and plays a decisive role in patient outcome.
3. **Monitoring resistance patterns:** Surveillance of antimicrobial resistance patterns at all levels - national, local, hospital and ward level - is essential to set up antimicrobial policies.
4. **Surveillance:** Tracking the spread of resistant pathogens by screening at-risk patients and healthcare workers for multidrug-resistant organisms (MDRO) is a key measure to contain the spread of resistance.
5. **Clinical trial optimisation:** Supporting and facilitating clinical trials of new antibiotics by using diagnostics to enrich the trial population, e.g. by recruiting only patients with the pathogen(s) of interest, significantly reducing the overall cost and the time to completion of such trials, and increasing the probability of success. As well, immune-related diagnostics may help determine which individuals are most likely to respond positively in vaccine effectiveness trials.

Importantly, novel technologies have been or will be developed,

- to rapidly and reliably determine the etiology of infection (bacterial/viral/fungal/parasitic),
- to rapidly determine the antimicrobial resistance traits of the implicated pathogen(s),
- to delineate and follow the human host immune response in order to target at-risk individuals for preventive strategies against infectious pathogens,
- to characterise the human host immune system (for predicting vaccine effectiveness),

- to provide real-time and reliable surveillance data on existing, emerging and potential pathogens along with their antimicrobial resistance profiles via diagnostic-based “big data” (e.g. real-time AMR surveillance information, microbiome analysis, WGS).

If put to effective use, most of these technologies can decrease, the time required for detection of biomolecules like proteins and nucleic acids from a few hours to a few minutes and can greatly improve medical diagnostics in the next decades. The present state of diagnostic R&D is lagging behind the medical needs, in large part due to the misalignment of economic incentives and rewards. Novel diagnostic tests (including tests based on nucleic acid amplification or whole-genome sequencing) are expensive to develop while reimbursement is low or not available and cost-benefit studies are usually lacking. At the same time, antibiotics are often cheaper and easier to prescribe. This is particularly true in primary practice, where 90% of human antibiotics are prescribed. This problem can only be addressed in partnership.

**Today, a roadmap is lacking for the successful development and implementation of these emergent diagnostic technologies to meet these goals.** Many of the new diagnostic technologies have been developed based on current clinical practice, traditional “primary care” and hospital-based healthcare infrastructure, older forms of care delivery and existing incentive systems. Not many diagnostic projects have been sufficiently guided by the medical and public health needs. Therefore, many of these technologies and diagnostic advances have not yet found applications in clinical medicine and have not been rigorously evaluated for their health impact and economic benefits. Moreover, they are often not accessible to emerging countries or low- and middle-income countries (LMIC) which can be a source of multi-drug resistant organisms and should also be the beneficiaries of improved diagnostics. The “personalised medicine” approach has not been as aggressively promoted nor appreciated in infectious diseases, as it has been in oncology, leading to less emphasis on creative and innovative diagnostic tools which can increase the benefits of a particular therapy or antibiotic treatment. The problem is that these “supportive” or “facilitating” diagnostics for antibiotic development and registration trials are often not developed by diagnostic companies because there may be no market for them after the drug trials. In order to ensure a successful implementation of these new technologies in future care delivery, it will be crucial to move away from the business-as-usual approach and to develop new and smarter care-maps and patient pathways combining diagnostics and therapeutics/vaccines, and then to demonstrate that they are making a positive difference for individual patients, public health and the overall healthcare system.

The existing environment is clearly unfavourable for the development of new diagnostic tests, mainly due to the fact that the **value of diagnostics is under-appreciated and under-estimated**, leading to reduced recognition and under-utilization of this important aspect of healthcare. There are still knowledge gaps in understanding the clinical and public health utility and demonstrating the cost-effectiveness of diagnostics. The next challenge will be to make sure that the entrenched habits of over-prescribing antibiotics are dislodged by a more appropriate use of these valuable drugs, based on the utility and value of diagnostics for benefiting patient outcomes, the healthcare system and for preserving the utility of these antibiotics for as long as possible.

Diagnostic companies are facing serious challenges such as extensive R&D costs and long time to market due to differences in legislation. E.g. the requirements in China (CFDA), US (FDA) and EU (CE marking) are often very different, which impacts on late-stage development, validation and globalisation of new diagnostic tests.

**The regulatory framework for diagnostics is getting more complex, costlier and more difficult to manage.** As a result, many innovative diagnostic technologies arrive very late and some of them never make it into the marketplace. Although some of the new generation diagnostics have the required specifications to deliver a clinically actionable result, they are technologically complex and hence significantly more expensive compared to the culture-based diagnostics that reigned throughout the last century.

**In consequence, uptake of these tests in hospitals and especially primary care centers has been limited**, reducing their favourable impact on antibiotic stewardship. To create a viable situation, it is not only necessary to address the scientific and regulatory challenges, but also the commercial challenge of generating financial returns. This challenge is exacerbated by the current low cost of antimicrobials versus the much higher cost of the new rapid molecular diagnostics. Unfortunately, the societal value attributed to these rapid diagnostic tests to support the development and responsible use of (new) antibiotics is not considered in setting the reimbursement price.

**Currently, reimbursement of diagnostic assays is not aligned with medical value.** It is mainly technology-based. There is no “price premium” for a diagnostic assay which spares antibiotic use or assists in appropriate antibiotic use. Health technology assessments (HTA) on diagnostics are rare, heterogeneous, their evaluations are often not adapted to the specificities of diagnostics, and the influence of HTA results on reimbursement decisions is limited. Innovative diagnostics require additional clinical proof to ensure market access and adoption, adding to complexity, cost and timelines. For optimal integration of these tests into healthcare practice, it is mandatory that methods for well-designed pre-clinical and clinical trials for the proper evaluation of rapid diagnostic tests, as well as for the evaluation of the effectiveness of interventions in real-life routine practice, are available and implemented.

To address these challenges and to generate an attractive return on investment, new viable and sustainable business models, methods and capacities for technology evaluations and reimbursement systems need to be developed.

Moreover, the lack of evidence-based training programs and advocacy initiatives in diagnostics for professionals, patients and healthcare decision makers, as well as social, ethical, economic and psychological factors do affect the perception and adoption of diagnostics.

## A potential topic for a call for proposals under IMI2?

The Innovative Medicines Initiative (IMI) initiated in 2012 a major programme called New Drugs for Bad Bugs (ND4BB) aiming at addressing the antimicrobial resistance challenge. Several projects address the resistance mechanisms, specialised clinical trials infrastructures, acceleration of development of new antibiotics and their combinations, and identifying new classes of products. A specific project, DRIVE-AB, aims at identifying new business models that balance conservation of antibiotics (rational use) and business conditions for continued investment into antibiotics.

With opening of IMI to the non-pharmaceutical sectors, the initiative and its ND4BB programme would be an ideal framework for joining forces between diagnostic companies, other private entities, public organisations and stakeholders to develop a vision on how diagnostics could help to ensure future generations are not faced with untreatable infections due to resistant bacteria.

A potential call topic under IMI could provide answers to the following questions:

- How can new diagnostics be developed responding to clinical and public health needs?
- How can diagnostics be used to select optimal patients in antibiotic trials?
- How can diagnostics help choose the narrowest-spectrum antibiotics?
- How can diagnostic innovation be incentivised & rewarded?
- How can the perception of “medical value” in diagnostics be improved?
- How can the evaluation of diagnostics be standardised?
- How can regulatory requirements be harmonised?
- How can reimbursement of diagnostics be correlated with the medical value produced?
- How can social, ethical, economic and psychological factors affect use of diagnostics?

The expected impact will be to develop meaningful, long-term public health policies which encourage the sustainable development of diagnostics which in turn impact on the development and stewardship of antibiotics. The project represents an attempt to develop new forms of collaboration between the public and private sector supporting the need to address the use of diagnostics in a responsible and sustainable way.

## Workstreams currently considered for a potential IMI project

The following four work streams are currently envisaged to be covered by a potential topic under a future IMI2 call for proposals, and will be presented at the workshop. The objective of the workshop is to consult with the relevant stakeholders on the current plans, to hear from different stakeholder's perspectives what the challenges and hurdles are for diagnostic innovators, and to get a better understanding of what evidence is needed from regulators, health technology assessment and payers for implementation and adoption by healthcare systems. It is expected that the conclusions from the discussion at the workshop will feed into topic development and help drive the finalisation of a call topic for a future IMI call for proposals.

### 1. Implementation of diagnostics

#### OBJECTIVE

Design and test a framework for establishing a sustainable infrastructure for the evidence based translation of innovative diagnostics into standard-of-care. The network should assess and demonstrate the value of diagnostics both for individual patients and for public health impact, which could be achieved by optimising the antimicrobial therapy and, by extension, reduce a driver of antimicrobial resistance in patients. The framework should build on the available evidence and utilise an extensive consultation with key stakeholders.

#### KEY TASKS

- Establish a consulting network including physicians, European IVD regulators, HTA programs, reimbursement experts, third-party payers, health economists, medical educators and psychosocial experts
- Undertake a systematic review of the existing (peer-reviewed) literature and ongoing European AMR-related activities
- Analyse the implementation process for innovative diagnostics into standard of care in LRTI, describe key hurdles and propose actions to systematically drive their evidence based implementation, especially:
- Provide a description of the framework for a rapid evidence based implementation of innovative diagnostics into routine based on a Standardised Care Network
- Facilitate the decisions regarding the implementation of the best practice process into routine with the key stakeholders

#### KEY DELIVERABLES

- Describe the standard of care, identify opportunities for improvement and select the most promising best-practices (benchmarking)
- Specify the required evidence for the adoption of the best practice and define measurable clinical outcome and success parameters (clinical utility)
- Describe necessary standards and quality controls to allow the use of the generated evidence for IVD registration (quality requirements)
- Review the current regulatory environment and recommend improvements for product approvals to accelerate their time to market (regulatory)
- Propose funding models facilitating the introduction and application of rapid diagnostics into primary care considering their impact in reducing antimicrobial prescribing and AMR (HE-model)

- Develop a health economic model acceptable to payers for establishing value-based reimbursement for innovative diagnostics. (reimbursement)
- Describe psychological barriers and outline a (stepwise) implementation process for new devices (change management and sustainability)
- Document and publish the implementation framework in a peer-reviewed journal and draft guidelines recommendations for the optimal use of antimicrobials (dissemination)
- Develop an education and dissemination program to facilitate the implementation of the framework (education)
- Outline a business concept to sustain the infrastructure for future rapid benchmarking and translation of innovative diagnostics and/or other process changes (exploration)

## **EXPECTED OUTCOMES**

- Description of systematic methods for building evidence base that can: establish clinical utility, optimize use of antimicrobial therapeutics, demonstrate value in health economics
- Proposal of a pathway to accelerate the approval and use of innovative diagnostics, particularly those tools that support optimal antimicrobial usage

## **2. Establishment of a Standardised Care Network**

### **OBJECTIVE**

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-using countries in Europe, as well as including appropriate representation, at a minimum, the top 5 European countries by population. A business model must be constructed which will assure the sustainability of the 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 in cooperation with the industry.

### **KEY TASKS**

- Define and set-up a network of well-defined patient-care settings, in order to demonstrate and quantify the value of diagnostic for LRTI management :
- Covering top 5 countries by population and representing low, medium and high consuming/prescribing countries.
- 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 algorithm both for usual care and prospective clinical trial to generate data that feed criteria and evidences specified in WP1.
- Leverage or synergise on potential existing European networks or Clinical research infrastructure (IMI, other) in a collaborative effort to shorten set-up time and expand access to patients and samples.

- Conduct multi-center prospective/randomised clinical trials in order to demonstrate and quantify the value of diagnostic for LRTI and their impact in real-life patient-care settings :
- Respecting the frame of clinical studies defined in WP4.
- 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 WP3 requirements.
- 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, « metagenomics analyses » Mass Spectrometry, epidemiological tools) for pathogen analysis (identification, antimicrobial resistance).
- Evaluating host status and response (immune profile, biochemical and genetic markers).
- Covering all antimicrobial resistance traits encountered and allowing the identification of new markers or mechanism of resistance.
- 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).
- Propose and validate a scheme and business model to allow the created “standardised care network” including the biorepository to be sustainable and permanently available in Europe for further studies :
- Broadening diagnostic evaluation to other clinical situation.
- Allowing long-term analysis of diagnostic value (patient outcome, infection and resistance recurrence).

### 3. Data Analytics

#### OBJECTIVE

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 WP1.

#### KEY TASKS

- Establish a database and repository of information:
- Gathering results and information obtained in clinical studies (WP4) performed in the Standardized Care Network (WP2)
- 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 user interface suitable for clinicians and health care professionals of the network to load /consult or extract information.
- Allow (meta) data analysis including
- Data mining relevant to evidences and criteria expected from WP1
- Extraction of information of clinical studies managed in WP4
- 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

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

### OBJECTIVE

To design and implement a clinical study 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 WP1 within the Standardised Care Network in WP2. 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 development of antibiotic-resistant bacteria.

### KEY TASKS

- Design and implement a multi-country and multi-centre clinical study within the standardised care network as set out in WP2
- Design and implement a clinical study to demonstrate the value of diagnostics in the optimal treatment of community acquired – acute respiratory tract infections (CA-ARTIs).
- The clinical study must
- Primarily evaluate the impact of the use of rapid diagnostics in relation to their impact on antimicrobial prescribing rates
- Evaluate the defined measurable clinical outcome and success parameters (clinical utility) which will be derived from the results of WP1
- Include combinations of “host-based” and “pathogen-based” diagnostic tests
- Evaluate and test the implementation process for new devices (change management and sustainability) as derived from WP1
- Include parameters to evaluate the health economic model(s) as derived from WP1
- Implement a system for collecting, monitoring and validating measurables/data as set out above.
- Periodically report the status, results to date and progress to the consortium.
- Analyse, interpret and publish the results of the study in a peer-reviewed journal.