REPORT on the Joint EU-US Workshop

Challenges and Solutions in the Development of New Diagnostic Tests to Combat Antimicrobial Resistance

Co-organised by the US National Institutes of Health and the European Commission's Directorate for Health Research

28 - 29 September 2011
European Commission
Brussels, Belgium

This workshop on diagnostic tests for invasive bacterial infections was jointly organised by the European Union (EU) and US members of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR[1]) responsible for research, with support from the European Commission's Directorate-General for Research and Innovation and the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID). The rationale for this workshop was twofold: 1) the lack of rapid diagnostic tests is a major hindrance to the development of novel antimicrobial drugs to treat resistant infections and 2) rapid diagnostics have the potential to reduce inappropriate use of antimicrobial drugs. Rather than focusing on technology development alone, the goal of the workshop was to identify existing barriers and possible solutions in the following areas:

1. Factors limiting the development and use of contemporary diagnostic tools
2. Identification of key partners that need to join the effort to advance diagnostics into clinical practice
3. The role of improved diagnostic tests in enhancing clinical development of novel antimicrobials

The Workshop was opened by Director Ruxandra Draghia-Akli (European Commission, DG Research and Innovation), who welcomed the participants. She presented information about TATFAR and mentioned that only one week after the adoption of the TATFAR recommendations this workshop represented the first concrete outcome by bringing together relevant scientific communities to discuss scientific hurdles and regulatory standards in a key area such as diagnostics for invasive bacterial infections. In addition, both Dr. Draghia-Akli and Dr. Dennis M. Dixon from NIAID discussed various initiatives and resources for diagnostics R&D on both sides of the Atlantic.

The workshop then started with an introductory session with three keynote lectures. There were then four sessions, each of which was followed by an extended panel discussion:
Session 1: Technical and Scientific Challenges in the Development of Rapid Diagnostics
Session 2: Regulatory Challenges in the Development of Diagnostic Tests
Session 3: Economic Factors Impacting the Development of Novel Rapid Diagnostics
Session 4: Challenges in the Acceptance and Adoption of New Diagnostic Tests

[1] http://ecdc.europa.eu/en/activities/diseaseprogrammes/tatfar/pages/index.aspx

Introductory session

Three keynote lectures were delivered in the introductory session:

- **Donald Low (University of Toronto, Canada) - Setting the stage: significance and need for rapid diagnostic tests for invasive bacterial infections**

- **Rosanna Peeling (London School of Hygiene and Tropical Medicine, UK) - Review of candidate technologies for rapid diagnostic tests**

- **John Rex (AstraZeneca) - The importance of rapid diagnostics for advancing antibacterial development**

The emergence of antimicrobial resistance (AMR) is an enormous public health problem both in hospital and community settings. Inpatients in hospitals suffer from infections with resistant strains of Gram-positive (e.g. vancomycin-resistant *Enterococci* [VRE], hospital-associated methicillin resistant *Staphylococcus aureus* [MRSA]) and Gram-negative bacteria (e.g. multidrug-resistant Enterobacteriaceae*, Acinetobacter, Pseudomonas*). Outpatients are often infected with resistant strains of the Gram-positive bacteria *Streptococcus pneumoniae* and community-associated MRSA as well as resistant strains of the Gram-negative bacteria *Echerischia coli* and *Neisseria gonorrhoeae*. Many resistant strains can produce β-lactamases such as penicillinases, carbapenemases, cephalosporinases and extended-spectrum beta-lactamases (ESBLs). For some resistant strains, for example those carrying the New Delhi metallo-β-lactamase-1 (NDM1) and the Klebsiella Pneumonia Carbapenemase (KPC) resistance elements, there are few or no treatment options available. Alarmingly, resistant clones can rapidly spread worldwide due to widespread international travel, making AMR a truly global problem.

The consequences of infections with antimicrobial resistant pathogens include morbidity, mortality and spread of resistant strains. It is, thus, vital that AMR be combated by developing new classes of antimicrobials (virtually no new major classes of antibiotics were developed between 1962 and 2000) and also by restricting the use of existing antimicrobials to when effective and necessary. In medicine, prudent use of antibiotics could be promoted through the use of diagnostic tests, which could determine whether or not an infection is present, the identity of the pathogen, which antimicrobial to use and the resistance profile if any. This could lead to a reduction in inappropriate therapies, improve patient outcome and prevent the spread of infections.

Diagnostic tests can be used for a variety of different purposes. When designing a test, it is necessary to answer the following questions: (1) What is the test for? (2) Who is the patient? (3) What is the setting? (4) Who will do the test? For example, it might be important to be able to differentiate between a bacterial or viral infection, or to be able to distinguish malaria from other febrile syndromes. Rapid diagnostic tests also have the potential to markedly reduce the costs of antibacterial clinical trials by enabling the selection of patients who likely have the disease that is being studied before lengthier culture results are returned. Furthermore, if the test is sufficiently sensitive and specific, it could offer greater diagnostic certainty, permit by-organism outcome analyses, and allow subsequent correlation of susceptibility with clinical response.

There are various diagnostic methods that can be used for tests, ranging from direct methods such as culture/microscopy, genome detection and antigen detection to indirect methods including serology (Fig. 1). These methods differ in their accuracy, ease of use and amount of time taken. Culture requires time scales on the order of days, while genome and antigen detection require hours and some serological methods only minutes. In terms of ease of use, parameters such as storage temperature of reagents, necessity for a source of electricity, type of sample (e.g. blood, oral exudate, vaginal swabs, and sputum) and need for user training for performing the tests as well as interpretation of its results must be considered. The time to results being available is crucial. In primary care, quick results are necessary so as to enable physicians to decide whether antibiotic prescription is necessary. In a seriously ill hospitalised patient with pneumonia, starting treatment immediately is critical for patient survival. This is a very different situation than treating HIV/AIDS or tuberculosis, for which there is time to start treatment.

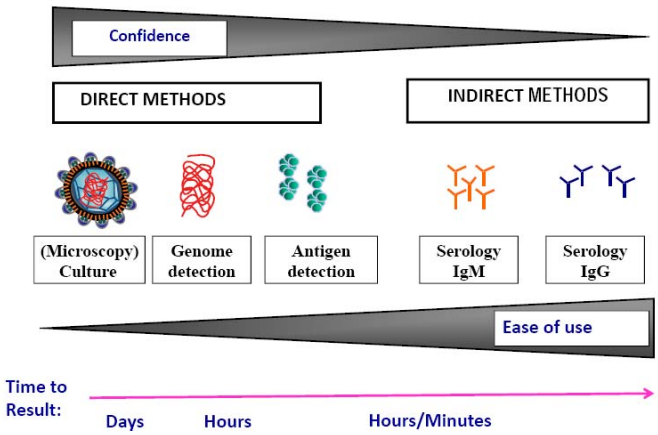

Figure 1: Diagnostic methods (from Slide 5 of R. Peeling's keynote lecture).

Rapid diagnostic tests that have been developed include those based on immunochromatographic tests (e.g. HIV, hepatitis C, syphilis) and target amplification techniques (e.g., PCR, transcription-mediated amplification, recombinase polymerase amplification, helicase-dependent amplification, isothermal amplification). The GeneXpert system (Cepheid) is a platform developed for testing for multiple diseases (tuberculosis and rifampicin resistance, HIV viral load, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*) based on real-time PCR, giving results in under 2 hours. A caveat of molecular-based tests that should be borne in mind is that the presence of DNA in a sample from a particular pathogen does not necessarily mean that the patient is suffering from an active infection due to the presence of that organism. Some pathogens are also present in the normal flora but do not cause the host any symptoms.

Some major challenges for the development of diagnostics include: inadequate specimen processing, lack of advocacy and investment, and differences in regulatory requirements in the US and across the EU.

One innovative approach to funding Diagnostics R&D is a joint initiative from Grand Challenges Canada and the Bill & Melinda Gates Foundation focused on developing diagnostic components into one or more interoperable 'plug-and-play' point-of-care platforms capable of running a variety of diagnostic tests from different developers.

Session 1: Technical and Scientific Challenges in the Development of Rapid Diagnostics

In session 1, talks by Patrick Murray (BD Diagnostics) and Herman Goossens (University of Antwerp, Belgium) focused on the technical and scientific hurdles in the development of diagnostics for bacterial bloodstream and respiratory tract infections, respectively.

Diagnosis of bloodstream infections

Historically, diagnosis of bloodstream infections has relied on growth-based technologies (e.g. broth cultures, impedance monitoring, lysis-filtration, lysis-centrifugation), which include drawbacks such as time taken to obtain results (currently 1-5 days) and culture bias towards organisms that are culturable. The challenges in diagnosis of bloodstream infections include having to detect small numbers of organisms in a large blood volume, the recovery of intracellular and adherent organisms, and the presence of contaminating microbial nucleic acid. Although there have been incremental steps in improving broth culture methods, the next generation of solutions for diagnosis of bloodstream infections requires a paradigm shift with growth-independent methods replacing culture-based ones. An ideal test should be able to process a small volume of blood, be rapid, technically simple or automated, inexpensive, and not require batch processing. It should eliminate all negative specimens and detect all positive specimens by a growth-independent, non-destructive method. Microbial identification can be performed by gene sequencing, MALDI-TOF or other methods such as Raman or PCR-ESI-TOF. Regarding antimicrobial susceptibility tests, gene sequencing can identify known resistance markers but cannot predict susceptibility. Furthermore, gene sequencing cannot detect expression of resistance markers; thus sequencing of RNA targets may be a better predictor of known resistance expression. Metabolic-based systems would theoretically not require cell division and could, thus, be very rapid. They could also potentially detect known and previously unrecognised antibiotic resistance. New approaches will be required for rapid diagnostic tests for test validation and clinical decision making, and will pose challenges to lab directors, regulatory agencies, and physicians.

Diagnosis of respiratory tract infections

Rapid diagnostic tests are necessary for respiratory tract infections (RTIs) as there is an unmet clinical need to be able to distinguish between bacterial and viral infections and also to be able to rapidly detect drug resistance profiles. Acute cough is the most common reason for antibiotics being prescribed in the community (in the EU). However, only about 20% of acute cough cases are bacterial, thus resulting in antibiotics overuse. Studies show that empirical broad-spectrum antibiotic treatment is associated with increased mortality. In patients with ventilator-associated pneumonia, delayed or inappropriate therapy (due to resistance) results in increased mortality.

There are numerous challenges in developing rapid diagnostics for RTIs, including (1) consideration of which clinical specimen to collect and how to collect it; (2) choice of pathogen(s) to be detected; (3) distinguishing colonisation from infection; (4) sample preparation; (5) diagnostic algorithms.

It is necessary to be able to distinguish bacterial colonisation from infection. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* can cause community-acquired lower respiratory tract infections but can also be present in the flora of asymptomatic carriers. Cut-offs between colonisation and infection need to be experimentally delineated. The GRACE project, funded under the 6th EU Framework Program for Research and technological development, undertook such a study in which the number of *S. pneumoniae* DNA copies detected by PCR was

compared between patients with community-acquired lower respiratory tract infections and healthy controls.

Sample preparation represents a major bottleneck in developing point of care tests. Macro-scale lab tests are laborious and can take a few hours, reagents are often refrigerated or frozen, large sample volumes are required and specialized equipment such as centrifuges and bead beaters are used. Rapid point of care diagnostic tests, on the other hand, should use reagents stable at room temperature, microlitre volumes and the results should be ready in minutes. The TheraEdge project, funded under the 7th EU Framework Program for Research and technological development, is developing a bacterial lysis and DNA purification protocol on a prototypal microfluidic chip to use in an assay for community-acquired lower respiratory tract infections. A movie was shown of on-chip bacterial lysis and DNA purification developed by the TheraEdge project.

Session 1 panel discussion

Patrick Murray (BD)
Herman Goossens (University of Antwerp)
Ellen Jo Baron (Cepheid)
Gorm Lisby (Quantibact)
Rosanna Peeling (London School of Hygiene and Tropical Medicine)

1. Rapid tests for AMR are required and DNA sequence-based techniques hold promise for this. Nevertheless, such techniques also have limitations. DNA sequencing can predict known resistance, but there is scepticism about it predicting susceptibility. Culture-based methods are slower but have the advantage of being able to detect new resistance and to recognise susceptibility.
2. In a hospital setting, a diagnostic that allows antibiotic de-escalation quickly is necessary to reduce unnecessary antimicrobial exposure. Physicians may not de-escalate based on culture results if the patient is already showing signs of improvement by the time the result is available.
3. Microbiology labs might oppose point of care tests as they would lose revenue with current reimbursement rules.
4. There was concern that there has been a loss of expertise in microbiological microscopy techniques such as Gram-staining.

Session 2: Regulatory Challenges in the Development of Diagnostic Tests

In session 2, talks by Steve Gitterman (Food and Drug Administration, USA), Rosalind Polley (Medicines and Healthcare Products Regulatory Agency, UK) and Brad Spring (BD Diagnostics) focused on the regulatory challenges in the development of diagnostic tests.

The US approach to the regulation of diagnostic tests for bacterial bloodstream and respiratory tract infections

In the USA, there are three device classes under which a diagnostic test could fall:

Class I:	General controls	510(k) submission	90 day review

		(or FDA exempt)	
Class II:	General and special controls	510(k) submission	90 day review
Class III:	Premarket approval	PMA submission	180 day review

Classes I and II are for devices that pose a low/moderate risk to patients. Class I would apply for culture media and staining and Class II for automated systems and drug susceptibility from culture; most Class I devices are FDA exempt, i.e., FDA submission is not required, although manufacturers must still adhere to FDA regulations and register their product. Class III devices are defined as being those "of importance in preventing impairment of human health or if the device presents a potential unreasonable risk of illness or injury". There are several microbiology devices that are classified as Class III. Examples are devices for detecting CMV viral load or direct detection of ***M. tuberculosis***, for the diagnosis of HIV, Hepatitis B, C & D and HPV. The standards of evidence necessary for devices are: analytical detection, clinical detection, clinical validation (current standard) and clinical utility (not a regulatory mandate for FDA). There are challenges for clinical validation for both respiratory and bloodstream infections. Clinical utility includes aspects such as how common a pathogen is as well as individual and potential population benefit from earlier treatment. For example, pertussis is caused by an uncommon pathogen of the upper respiratory tract but early diagnosis is of benefit to the patient. In sepsis, there are challenges associated with biomarker validation. Prospectively archived panels of well characterized specimens could potentially be very beneficial for diagnostic developers and regulators.

The future of European regulation: proposed changes to the *In Vitro* Medical Devices (IVD) Directive

In Europe, diagnostic tests are regulated by Directive 98/79/EC on *in vitro* Medical Devices (IVDs), which came into force in 2003. IVDs are classified into four groups according to risk to the user, patient or a third party:

1. Low individual risk and low Public Health Risk
2. Moderate individual risk and/or low Public Health Risk
3. High individual risk and/or moderate Public Health Risk
4. High individual risk and high Public Health Risk

As there have been technological advances since the Directive was written, the Directive is being reviewed and a new version will most likely come into effect as early as 2013. A wider range of devices will require Notified Body intervention. The major changes concern "in house" tests, point of care tests, clinical evidence and companion diagnostics. In house tests will most likely be exempt from the Directive. The specific requirements for point of care tests are: (1) demonstrated clinical validity in the same conditions as use; (2) equivalent sensitivity and specificity to laboratory based tests; (3) tests and users to be subject to a quality management system including education quality assurance. Clinical evidence, including clinical validity and a justification of the comparator test used will be necessary. Companion diagnostics will remain under the IVD Directive. There will be closer cooperation between the IVD sector and the European Medicines Agency. There must be demonstration of clinical utility.

Regulatory challenges in the development of diagnostic tests: **Industry perspective**

The regulatory requirements for the EU (IVD-Non Annex II) and the FDA (IVD Class I & II) were compared in terms of safety & effectiveness (S&E) evidence versus time to market. The most time-consuming aspect of the EU regulations is clinical evaluation and that of the FDA,

prospective clinical studies and regulatory submission. There is a difference in the balance between safety and effectiveness evidence versus time to market in the EU and the US. The prospective clinical studies required by the FDA were compared to the clinical evaluations required in the EU. Both have pros and cons. Prospective clinical studies require multi-centre studies in human subjects to assess safety and performance. Advantages include real-time product performance in its intended setting and good control of specimen collection and handling. However, the process is time-consuming and costly, and informed consent can reduce patient enrolment. Clinical evaluations require an assessment and analysis of clinical data to verify safety and performance. These evaluations are quicker than the prospective studies required by the FDA, and many sources of clinical evidence can be used (e.g. data from pre- and post-market clinical studies, data from scientific literature). However, they are retrospective studies, and specimen integrity and lack of patient information can be a problem. Suggestions were put forward to improve clinical evaluations. These included: (1) using different approaches to choosing a reference method in studies; (2) improving access to specimens with low prevalence organisms; (3) relying on prospective data from a limited geographic location for 'seasonal' diseases or localised outbreaks (e.g. for a flu study, test in Hong Kong first then with post-market studies in Latin America, Canada, U.S. and Europe once the disease migrates to these regions).

Current and future challenges of the European and US regulatory systems were outlined. In the US, submission review times are increasing and the regulatory burden for some assays are barriers to market. In the EU, changes to the IVD Directive will lead to increasing requirements for clinical evidence. Ideas about easing regulatory barriers included allowing tests on the market based on analytical testing and limited clinical evidence with a requirement for post-market studies and structured pre-submission meetings between government and industry as is currently done with the pre-investigational device exemption (pre-submission) model of the FDA. Harmonisation of EU and FDA requirements would also be desirable.

Session 2 panel discussion

Steve Gitterman (FDA)
Rosalind Polley (MHRA)
Brad Spring (BD)
Edward Cox (FDA)
Anne DeBock (AstraZeneca)
Philippe Jacon (European Diagnostics Manufacturers' Association)
Guus Simons (PathoFinder)

1. There was much support for prospectively archived sample repositories. It was also acknowledged that such repositories are very expensive, it can be difficult to anticipate exactly what types of samples will be needed for yet to be developed tests, and informed consent is necessary for use/storage of discarded medical samples. However, several workshop participants noted that we can learn from existing examples of specialized resources of clinical samples that could be used by diagnostics developers, including NIAID’s Clinical Laboratory Diagnostics for Invasive Aspergillosis contract, the NIAID-supported Tuberculosis Research Unit, and various academic/clinical laboratories.

2. A novel platform-based regulation/approval for diagnostics, similar to the annual approval of the influenza vaccine, was suggested.

3. Care must be taken when using point of care tests, as a diagnostic test is not equivalent to a diagnosis. A point of care test can be lethal if its result leads to the wrong treatment. Clinical decision support systems may help to improve the use of diagnostic tests.

4. In some circumstances in the US, Research Use Only tests have been used during drug trials to aid patient selection. Developers considering taking this approach should consult with FDA.

5. The pros and cons of the US and EU regulatory approaches were reiterated. Some panelists felt that FDA requirements were too burdensome, while others felt that the EU system was not thorough enough.

Session 3: Economic Factors Impacting the Development of Novel Rapid Diagnostics

In session 3, talks by Ellen Jo Baron (Cepheid, USA), Gorm Lisby (Quantibact, Denmark) and Matthew Stevenson (University of Sheffield, UK) focused on economic factors impacting the development of novel rapid diagnostics.

Gauging the market for new diagnostic tests for bloodstream and respiratory tract infections

A diagnostics laboratory within a university or hospital will introduce a new test based on medical need, enhanced clinical value, volume of test orders, ease of performance versus lab personnel skills, ability to test more sample types, physical requirements (drains, electricity, space), validation requirements and cost/return on investment. In contrast, corporate decision factors for developing a new test include market opportunity, competitive offering, strategic corporate alignment, legal and net margin (e.g. intellectual property/patents), feasibility of successful product development, reimbursement issues, corporate responsibility and external incentives. The global market for molecular diagnostics is growing ($4765 million in 2010, predicted to increase to $8085 million in 2015), with infectious diseases accounting for around 50% of the market. Cepheid has developed a modular rapid molecular diagnostics system called GeneXpert that enables a variety of tests to be performed on the same workstation. Each Xpert test uses a specially designed cartridge that is inserted into the work station. Eleven GeneXpert tests are currently on the US market, including tests for healthcare-associated infections such as MRSA, *Clostridium difficile* and vancomycin-resistant Enterococcus. By 2016, Cepheid plans to have 39 rapid tests for a wide range of areas including healthcare-associated infections, critical infectious diseases, women's health, oncology & genetics, Clinical Laboratory Improvement Amendments (CLIA)-waived testing and virology. Several examples described how Cepheid decides to develop a test, including the likely volume of use of the test. In addition, a few examples were given about interactions that can encourage a company to develop a test, including a request from FDA to develop a rapid H1N1 test during the 2009 pandemic, a collaboration with FIND to support development of the GeneXpert rapid TB test, and a collaboration with Dr. Lance Peterson on an NIH grant for rapid detection of multi-drug resistant organisms from rectal swabs.

Molecular sepsis diagnostics: Great technology – Now what?

Until the advent of molecular diagnostic tests, blood culture was the gold standard for routine detection of non-viral pathogens in the blood. However, blood culture has limitations for sepsis due to the time delay in obtaining results and suboptimal sensitivity in clinical sepsis. Sepsis is generally treated empirically using a broad spectrum antibiotic without a prior diagnosis. However, a broad spectrum antibiotic is not always sufficient for treatment, and antimicrobial resistance (e.g. extended-spectrum β-lactamases [ESBLs], MRSA and VRE) is increasing. Appropriate and rapid treatment in sepsis patients is critical to their outcomes. Studies have shown that every hour effective treatment is delayed in sepsis patients leads to an increased mortality of 8%. The commercially available molecular Septi*Fast* test, which utilises real-time PCR to identify DNA from around 20 bacterial and fungal species directly from blood, was used to detect bloodstream pathogens from patients with suspected sepsis and the results compared to the results from conventional blood culture. The outcome was that blood culture and Septi*Fast* results agreed in some but not all cases. Septi*Fast* was more sensitive and produced quicker results than blood culture. Although bacterial DNA is not detectable in samples from normal individuals it is not clear that the presence of pathogenic DNA really reflects a true infection. This is an important consideration for cases in which Septi*Fast*-positive results cannot be confirmed by blood culture. It was judged that Septi*Fast* could be a valuable add-on to conventional blood culture but prospective clinical outcome analysis is necessary. Nevertheless, blood culture remains the cornerstone for sepsis diagnosis as it is a prerequisite for antimicrobial susceptibility testing. The molecular test is around 10 times the price of blood culture. However, it was suggested that a better price comparison would rather be the difference in price between the molecular test and a much more expensive stay in an intensive care unit. In the future, decision support systems could help to define targeted populations for a more expensive test that would ultimately save healthcare systems money and reduce deaths.

Modelling the impact of rapid diagnostic tests on healthcare costs

Countries, such as the United Kingdom, with a national health care system have finite health budgets and use cost-effectiveness calculations to decide whether to introduce a new treatment/diagnostic. This has been deemed necessary due to an ageing population and the emergence of expensive interventions. While most cost-effectiveness evaluations to date have been undertaken for pharmaceuticals, a few have also been performed for diagnostic tests. The UK's National Institute for Health and Clinical Excellence (NICE) has set up a Diagnostic Assessment Programme. Diagnostic assessments are more difficult than pharmaceutical evaluations. The sensitivity and specificity of a diagnostic test must be estimated. These values are combined with the estimated prevalence of the condition being tested for, to form an expectation of the number of true positives, true negatives, false positives and false negatives generated by the diagnostic test. For each of these four groups, an estimation is made of events that occur for the patient, such as risks of mortality, risk of morbidity, length of stay within hospital, costs for initial and subsequent care, treatment-related adverse-events and the quality of life for patients in each potential health state. The end result is the attribution of a measure called a quality-adjusted life year (QALY)[2] and a cost for the diagnostic test. In the UK, an intervention that costs more than £20 000-£30 000/QALY is unlikely to be recommended. An example of a cost-effectiveness calculation for the diagnostic test Septi*Fast* was given.

[2] The QALY is no. of life years x patient utility. A person living for 10 years at a utility of 0.5 would gain 5 QALYs.

Session 3 panel discussion

Ellen Jo Baron (Cepheid)
Gorm Lisby (QuantiBact)
Matthew Stevenson (University of Sheffield)
Isabelle Caniaux (bioMerieux)
John Hays (Erasmus Medical College)

1. In general, the price of a diagnostic test needs to be low in order to be recommended by NICE.

2. There is not currently a way to factor the value of preventing either infections or the development of resistance into a QALY. It might be possible to do so, but a model would have to be developed; this would be very complex and not easy to do.

3. In the US, the decision of whether to use a particular diagnostic test is made by individual hospitals or healthcare consortia. QALYs are not generally used and recommended treatment guidelines can be influential.

Summary of Day 1

The main points of Day 1 were summarised by Dennis M. Dixon (NIAID, USA) and Anna Lönnroth (European Commission):

1. Terminology. It is important to define terminology, such as biomarkers, point of care and speed. Is the biomarker a microbial marker, a pathological marker for establishing diagnosis, or used to track therapeutic intervention? Does the presence of DNA in a sample reflect infection? Where is the point of care? (1) the physician's office; (2) the central lab in a hospital; (3) in the field. How rapid is rapid: 24h? 4h? 2h? 2 minutes? This depends on the goal, such as enrolment in a clinical trial or for results in a hospital/physician's office.

2. Uniqueness of the Microbiology Infectious Diseases public health arena. Infectious diseases/infections are unique as anti-infective drugs have consequences beyond the infected individual that extend to the effectiveness of the drug for public health, which must be factored into the economic equation of cost-effectiveness. Related to this, how can one factor in prevention of disease in the future into the QALY? Health technology assessors should be involved in assessing diagnostic tests for combating antimicrobial resistance

3. Context. It is important to distinguish the differences in utility of detecting a pathogen in invasive disease from a sterile site such as blood, from that in a site such as epithelial lining material like lung, urethral swabs, or from sputum. It is also important to recognize that requirements may be different for a diagnostic to enable clinical trial enrolment and drug development versus that for rapid diagnosis in practice. For additional information on companion diagnostic devices, please see FDA guidance document on companion diagnostics.[3]

[3] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm

Session 4: Challenges in the Acceptance and Adoption of New Diagnostic Tests

In session 4, Don Lichti (Barnes Jewish Hospital, USA), Stephan Harbarth (University of Geneva, Switzerland), Chris Butler (Cardiff University, UK), Christine Ginocchio (North Shore – LIJ Health System Laboratories, USA) and Mark Finch (Blue Shield of California, USA) briefly presented the perspectives of a hospital administrator, a hospital physician, a primary care physician, a clinical microbiology lab and a payer, respectively. These presentations were followed by a panel session.

Don Lichti presented the perspective of a hospital administrator. Hospitals face challenges, such as reduction in reimbursement, which means that costs have to be reduced. For a new diagnostic test to be adopted by a hospital, FDA approval is important, but so is the ability to be reimbursed for the test by insurance companies. Other important factors are whether the test is a replacement or additive, as well the impact on length of stay and/or clinical outcome. Financial considerations are critical. An ideal test would replace another one at an equivalent or lower cost and have a low investment cost. The supply cost, labour cost and space are also taken into account. Tests that can be performed on outpatients rather than inpatients are preferred in the US due to additional reimbursement for outpatients.

Stephan Harbarth posed questions that must be asked about diagnostic tests: (1) Do they reduce diagnostic uncertainty? (2) Do they really influence treatment options? (3) Do they really have an impact on the outcome for patients and society? In the management of severe infections, there is an initial empiric treatment phase, followed by an adjustment phase and a final duration phase. In a situation such as sepsis, no test is necessary for the initial phase as treatment must be started immediately. Knowledge of conventional Gram-staining is being lost; the added value of more expensive molecular tests over cheaper traditional ones is often unclear. Clinical decision support systems could also improve prescribing. Biomarkers have a lot of potential to influence appropriate antimicrobial use, though much discovery and development still needs to be conducted. When moving from culture-based to molecular diagnostics, comparative effectiveness research is required for tests. For the future: (1) Do test results in infected patients differ from those in non-infected individuals? (2) Do test results distinguish patients with and without infection among those with clinically suspected infection and improve diagnostic accuracy? (3) High-quality clinical studies: Do patients undergoing the diagnostic test have better outcomes than similar untested patients? (4) Real-life effectiveness studies: In my hospital/ward, is this test clinically useful and cost-beneficial?

Chris Butler reported about a study looking at the perceived pros and cons of point of care tests in an outpatient physician's office from the point of view of clinicians and the public. 80% of antibiotics are prescribed in the community, mostly for respiratory tract infections, and perhaps 50% of these prescriptions are unnecessary. A physician needs to know whether antibiotic prescription can be ruled out. A study using a questionnaire was used to identify the pros and cons of a point of care test from the perspective of clinicians and the public:

Pros: Clinicians

- Confirmatory diagnostic value – provides a rationale for not prescribing that can be shared with the patient to help manage their expectations
- Helps clinician to be more confident of diagnosis

- Can improve patient outcomes.

Cons: Clinicians

- Concern about false negatives and the potential consequences of not treating
- Concern that the test will undermine clinical decision-making – fear of treating the result rather than the patient
- How to interpret a range if the test gives a range
- Patients might demand the test
- Patients might refuse the test

Pros: Public

- Would help clinician choose correct treatment
- It is thought that it could reduce consultations

Cons: Public

- Fear that clinician will treat test result rather than the patient
- Worry about having to wait for result
- Needle-phobia

Christine Ginocchio explained that for a clinical microbiology laboratory serving a hospital, for a new diagnostic test to be adopted, it has to be accepted by both the laboratory and the medical staff. The criteria for acceptance vary between these two groups. For the laboratory, important aspects include the FDA status, performance characteristics, strong clinical benefit but importantly also the cost-benefit ratio. For example, can the test generate revenue for the lab, save money, replace a costly send out test, save technical time, and decrease reagent costs? Medical staff are concerned about whether the test meets clinical needs and whether it will improve clinical outcome and be appropriate for diagnostic indications. Medical staff must receive advance notification and education about any impending changes to diagnostic tests.

Mark Finch gave the perspective of Blue Shield of California, which has about 3.5 Million members. He outlined differences in reimbursement practices for outpatient and inpatient settings. Insurers are ultimately interested in technologies that can save hospital days, as this can lead to a significant reduction in costs. Tests that can impact MRSA and *C. difficile* infection rates in hospitals are of particular interest. The Affordable Care Act in the US could have an impact on how diagnostics are reimbursed.

Closing panel discussion

Ruxandra Draghia-Akli (European Commission)
Anna Lönnroth (European Commission)
Dennis M. Dixon (NIAID, USA)
Representatives from all sessions

During the panel discussion several interesting points were raised as well as questions that should be addressed

- It is essential for stakeholders including researchers, regulators and the industry to continue to have interactions on how to advance diagnostics for invasive bacterial infections. Various stakeholders must be willing to share resources and risks in order to share rewards and must advocate for new technologies.

- It is important to continue public funding of diagnostics development, but also additional approaches to funding should be explored.

- Striking the right balance between regulation and innovation is difficult but essential. Harmonisation of regulatory procedures is desirable – both sides of the Atlantic can learn from one another.

- Cost/benefit analyses of using diagnostic tests before prescribing antibiotics must take into account the substantial benefit of the prevention of new infections and the emergence of resistance.

- What should our goals be to enable prudent use? (1) Prescription-only antibiotics worldwide; and /or (2) Prescriptions being based on state of the art diagnostic tests?

Information technology has to be further developed and implemented in particular in primary care to transfer diagnostic test results to physicians faster. The challenges of specimen processing must be overcome and methods to distinguish colonization from infections must be explored (e.g., detection of gene expression). Information technology to aid clinical decision making and to transfer the results of diagnostic tests to physicians more quickly have the potential to improve diagnosis and antimicrobial use.

Country-wide mapping of infectious diseases is also necessary.

Simply put, establishing a prompt and accurate diagnosis is the key first step in successful management. Moving forward with contemporary diagnostics for invasive bacterial infections is therefore essential in the preservation of existing anti-bacterials which risk being lost to antimicrobial resistance, and in facilitating the development of new antimicrobials.