Current and **future directions** for rapid AMR diagnostics

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“I call on the governments of the richest countries to mandate now that by 2020, all antibiotic prescriptions will need to be informed by up-to-date surveillance information and a rapid diagnostic test wherever one exists.”

AMR Review May 19, 2016 – Tackling Drug-Resistant Infections Globally: final report and recommendations

“... be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool by 2024.”

For Dx: UK AMR Diagnostics Collaborative
Contained and controlled

To incentivise R&D for new diagnostics, the UK will:

- Address R&D gaps, including in the identification of biomarkers
- Work with international partners to develop global plans for incentivising new diagnostics and for stimulating the behaviour change needed to realise the benefits for human and animal patients.
- Support the establishment of the Accelerated Access Collaborative and Pathway and ensure antimicrobials and diagnostics can be supported by its work.
- Work with NHS partners and industry to tackle the barriers to new innovations being adopted in the NHS, building on the Life Sciences Industrial Strategy and the response to the Accelerated Access Review
- Prepare a 2 to 5 year urgent diagnostics priority list and use Target Product Profiles to push research and development.
- Introduce incentives to develop and evaluate rapid diagnostics.
- Support existing and emerging PDPs for new diagnostics, including through the Foundation for Innovative New Diagnostics (FIND).

Tackling antimicrobial resistance 2019–2024

4.4. Development of, and access to, diagnostics

To support rapid uptake of diagnostics, the UK will:

- Make antimicrobials and diagnostics a priority area for the Accelerated Access Pathway.
- Use modelling and test-pilot data to develop alternative funding models for faster diagnostics that support targeted treatment. This includes commissioning work to develop a method for assessing the value of new technologies that considers not only cost-effectiveness but the value proposition at a system level.
- Maximise use of NICE guidance, including the Medical Technology Innovation briefs, to assess new diagnostic tests and offer prescribers advice on their use.
- Streamline the regulation process to help get new diagnostics through as quickly as possible, including developing evidence-based guidance for using tests.
Product Development **Valleys** of Death

**DEVELOPMENT => COMMERCIALIZATION**
- Insufficient evaluation in settings of intended use
- Weak end-user involvement in product research and development
- Mis-alignment in the product design and manufacturing process

**COMMERCIALIZATION => ROLL-OUT**
- Lack of focus on demand generation
- Weak engagement of country decision-makers and stakeholders, including civil society and community
- Lack of planning and resources for country adoption

UK GOVERNMENT COLLABORATES WITH FIND TO BOOST DIAGNOSTIC CONNECTIVITY TO HELP COMBAT GLOBAL THREAT OF AMR

- Memorandum of Understanding (MOU) establishes a 3-year project focusing on connecting vital data from patients’ diagnostic test results to national antimicrobial resistance surveillance programmes in low- and middle-income countries to help combat the growing threat of drug-resistant infections.
- Announcement to be made at a side event on 22 May 2018, during the 71st World Health Assembly, being held in Geneva, Switzerland.
- This MOU between FIND and the UK Department of Health and Social Care expands the ongoing relationship between FIND and the UK Government.

FIND AND UK GOVERNMENT SPEARHEAD NEW DIAGNOSTICS INITIATIVES TO FIGHT ANTIMICROBIAL RESISTANCE; FIND LAUNCHES DIAGNOSTICS USE ACCELERATOR

- Diagnostics Use Accelerator, supported by catalytic funding from the UK and Swiss governments, will speed up data generation to inform policy makers on the best real-world diagnostic solutions and drive positive behaviour change; Professor Piero Olliaro joins FIND to lead this initiative.
- Expanded FIND partnership with the UK government underscores UK commitment to tackling the global threat of AMR by supporting development of companion diagnostics for new gonorrhoea drugs, and evaluating technologies to protect the public from substandard and falsified antibiotics.
- Announcements made at the second AMR Call to Action meeting in Geneva.

https://www.finddx.org
Possible objectives of the IMI call (2)

- **Addressing the “Market access” issues of diagnostics for AMR**
  - Regulatory pathway for AMR diagnostics
    - Increasingly complex, costly, not favorable to innovative AMR diagnostics and region-specific (CE marking, FDA, CFDA); not harmonized
  - Capturing the “true value” of AMR diagnostics (HTAs)
    - HTA methodology for diagnostics not well established and implemented; country-specific; not standardized

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

- **Topic identifier:** IMI2-2017-13-03
- **Publication date:** 30 November 2017
- **Types of action:** IMI2-RIA Research and Innovation action
- **Deadline Model:** two-stage
- **Opening date:** 30 November 2017
- **Deadline:** 28 February 2018 17:00:00
- **2nd stage Deadline:** 06 September 2018 17:00:00
- **Time Zone:** (Brussels time)
1. To design a health-economic framework (HEF) 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.

2. To establish a sustainable European Standardised Care Network adequately trained and resourced to conduct clinical trials evaluating the value of diagnostics.

3. 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).

4. To explore, define and attempt to resolve the psychological, ethical and social barriers which prevent the more widespread adoption of diagnostics delivering healthcare to the population.
### Access to Community Care Networks

<table>
<thead>
<tr>
<th>Primary care</th>
<th>Hospital care + Labs</th>
<th>Pediatric care</th>
<th>Long Term Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;200 primary care practises in &gt;20 European countries</td>
<td>&gt;800 hospitals and &gt;600 labs in &gt;40 European countries</td>
<td>90 paediatric clinical sites in 18 countries</td>
<td>Nursing homes and rehabilitation centres in 11 countries in Europe and Israel with more than 14,000 LTCF beds</td>
</tr>
</tbody>
</table>

- **Primary care**
  - Recruited over 20,000 patients into clinical studies on ARTI
  - Randomised 3,268 participants in a response-adaptive platform trial of a drug for a CA-ARTI

- **Hospital care + Labs**
  - To date, this network is managing 17 trials, including phase I – III trials for 6 new compounds against multi-resistant bacteria, and recruited over 12,000 patients.

- **Pediatric care**
  - Active a.o. in ZIKACTION, PREPARE, C4C (IMI2)

- **Long Term Care**
  - Experience in clinical trials on antibiotic use, influenza epidemiology and vaccines, microbiome and more.

**unpublished**
UK-India Antimicrobial Resistance Sandpit Event: 'Addressing the challenge of antimicrobial resistance in India'
Call for Expressions of Interest

Date of sandpit: 6-10 November 2017
Location: Delhi, India
Diagnostic Trends
Emerging Commercial Diagnostics
Upcoming Technology Solutions: Expanding AST Throughput

Bacteromic makes extensive use of microfluidic technologies to provide massive amount of phenotypic information for every pathogen tested:

- Single panel hosting up to 80 antibiotics.
- Full compliance with EUCAST and CLSI guidelines.
- MIC values for every tested antibiotic.
- Determination of resistance mechanisms.
- Up to 20 checkerboards for antibiotic combination screening on a single panel.

Graphical interface offers real-time test status to provide MIC values as soon as possible.

Panel composition:
each antibiotic probed in 8 up to 16 dilutions.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
</tr>
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<tbody>
<tr>
<td>Amikacin</td>
<td>Fosfomycin</td>
</tr>
<tr>
<td>Amoxicillin + Clavulanic acid</td>
<td>Fucidic acid</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Ampicillin + sulbactam</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Levofloxacin</td>
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<tr>
<td>Aztreonam</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>Metillin</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Moxopenem</td>
</tr>
<tr>
<td>Cefepine</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>Mogersen</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Cefotaxime + avibactam</td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Ceftolozane + tazobactam</td>
<td>Piperacillin + tazobactam</td>
</tr>
<tr>
<td>Cefturoxime</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Cefalaxin</td>
<td>Teicoplanin</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Ticarcillin + clavulanic acid</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Tigecycline</td>
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<tr>
<td>Clindamycin</td>
<td>Tobramycin</td>
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<tr>
<td>Colistin</td>
<td>Tristethoptim</td>
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<tr>
<td>Daptomycin</td>
<td>Trimepethil- sulfmethoxazole</td>
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<tr>
<td>Dicyclomine</td>
<td>Vancymycin</td>
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<tr>
<td>Efrapezol</td>
<td>EEBL</td>
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<tr>
<td>Erythromycin</td>
<td>Inducible Clindamycin Resistance</td>
</tr>
</tbody>
</table>
Upcoming Technology Solutions: Single Cell AST

Sub-Cellular Fluctuations Imaging

Figure 1. The interaction between an E. coli bacterium and the evanescent field. (A) Diagram of an E. coli bacterium with its main components and illuminated using SCFI. Only the lower part of the bacterium is in the evanescent field generated by total internal reflection of a laser beam. (B) Finite-difference time-domain (FDTD) simulation of the electromagnetic field generated using SCFI at the glass-water interface with a bacterium. The model shows how part of the evanescent wave is frustrated by the bacterium and propagates in the water. The model confirms a small penetration of the laser in the cell. At 100 nm from the glass surface the value of the field is less than half its value at the surface. (C) Close-up model of the region of the bacterium illuminated by the most intense part of the field, including the tethering antibodies. Most of the scattering collected by the video camera is originated in this area.

Figure 5. (A) The distribution of the fluctuation levels for untreated and kanamycin treated susceptible bacteria (n=52 and 51 respectively). The treated bacteria have been affected by the antibiotic and are statistically different to the untreated control (p-value < 0.001). (B) The fluctuation distributions for untreated (n=51) and kanamycin treated (n=52) kanamycin resistant bacteria. The distributions differ slightly, but the difference is far lower than for the susceptible strain (p-value = 0.15). The resistant strain shows very little effect from the antibiotic treatment after 30 minutes incubation. (C) The fluctuation distributions for untreated (n=50) and trimethoprim treated (n=50) susceptible bacteria, showing a slight decrease on average in the fluctuation levels for the treated sample. The difference in the distributions is, however, statistically significant (p-value < 0.001). (D) The individual measurements of the fluctuation levels of the different bacteria in the samples shown in plotted at the time the measurement was taken along with the mean fluctuation level (dashed line). The fluctuation levels of the trimethoprim treated bacteria decrease on average due to the continued action of the antibiotic, as shown by the linear fit (solid line). The data in this figure show the effectiveness of our technique as a susceptibility test for distinguishing between susceptible and resistant bacterial samples for both bacteriostatic and bactericidal antibiotics.

C. Bermingham et al., Imaging of sub-cellular fluctuations provides a rapid way to observe bacterial viability and response to antibiotics, bioRxiv 460139; https://doi.org/10.1101/460139
Monitor bacterial activity in real-time

- Directly see response to antibiotics

C. Bermingham et al., Imaging of sub-cellular fluctuations provides a rapid way to observe bacterial viability and response to antibiotics, bioRxiv 460139; doi: https://doi.org/10.1101/460139

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Upcoming Technology Solutions: Rapid AST with high resolution

QuickMIC™ AST system
Follows Gram-staining or bacteria identification

Blood sample workflow (simplified)

<table>
<thead>
<tr>
<th>BLOOD CULTURE</th>
<th>ID</th>
<th>AST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive blood culture</td>
<td>Gram staining</td>
<td>MALDI-TOF MS</td>
</tr>
<tr>
<td>QuickMIC™</td>
<td>2h</td>
<td>Saves &gt; 22h</td>
</tr>
<tr>
<td>Disk diffusion</td>
<td>Standard methods</td>
<td>20 - 48h</td>
</tr>
</tbody>
</table>

Automated growth rate analysis

QuickMIC has high speed and repeatability
E. coli + amikacin

Full growth (resistant/control) | MIC 25% of max | No growth (sensitive)
Upcoming Technology Solutions: AST Through Nanotechnology

Diagnostic Workflow - Resistell

- **BLOOD CULTURES**
- **STRAIN ID**
- **AST — ANTIBIOTIC SUSCEPTIBILITY TEST**

- Positive Blood Culture
- Pellet
- MALDI-TOF

**Time to Result:** 6-12 hours

Nanomotion of fast growing bacteria

Sensitive *E. coli* and ampicillin

5 minutes!
Upcoming Technology Solutions: Expanding Biomarker Space

Bacterial vs Viral

http://levels.bio/
Training the Next Generation
Clinical Case Challenge on Diagnostics and AMR

- Original cases
- Adapted cases
- Focus on diagnostics and AMR (cases that deal only with AMR are not eligible)
- Relevance to medical teaching, especially for medical students
- Capacity to enhance appropriate antibiotic use

- Solicit diagnostic and AMR clinical cases through a global call for participation
- Encourage medical students, trainees, physicians, and others to collect or write clinical cases that could be used in medical education and shared online
- Deadline 1 May 2018
- New Round 2019/20

http://www.seshglobal.org/Clinical-Case-Challenge
ANTIMICROBIAL RESISTANCE DIAGNOSTICS CHALLENGE

Schools | Competitions | Network

Inspire and Connect the Next Generation of Innovators
Build Capacity and Seed Innovation
Turn AMR into an Opportunity for Sustainable Development

info@amrdxc.org | www.amrdxc.org | @AMR_DxC

Edinburgh 2015
Mexico 2018
Bangalore 2017
Edinburgh 2017

AMR DxC was supported by

C-CAMP
BBSRC
Innovate for the Future

Initiative for Infection & Pathway Medicine
LONGITUDE PRIZE
SULSA
MRC
MarkieD
Newton Fund
4. Training & Capacity Building

Strategic Action Plan on Training

AMR Dx Global

Input from our existing Training Initiatives & Network and Stakeholder Base

JPIAMR AMR-RDT, COMBACTE LAB-Net, IMI-2 Value-Dx, AMR DxC, ND4ID, ACDx, ESCMID (TAE, ESGMD, EUCIC, ECCMID) Longitude Prize, DOSA, VetDx, EuroLife, FIND, WHO, ICAN, LSHTM IDC, AMR Centre, iSense, One Health Platform/Congress, AMR Dx MOOC, AMR Dx Case Challenge, Online distance learning programmes, Fleming Fund Fellowship Scheme, C-CAMP/ CARB-X, Tiba Partnership, etc.
Where are we **today** and what is **next**?

- **Empiric treatment is the norm**
  - By 2024 we know % Dx guided therapy (UK)

- **Lack of adoption of new diagnostics**
  - Pull incentives for Dx
  - Enhanced Dx training

- **Diagnostic stewardship**

- **Challenge Prizes**
- **Public funding**
- **Start-ups**
  - Diagnostic success stories
  - Someone won $20m and £8m
  - **Innovation**
Many Thanks for Your Attention

Questions?