The O’Neill Review on Antimicrobial Resistance

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Background about the Review on AMR

• Established in 2014 as independent arms length group by the UK Prime Minister, co-sponsored by the Wellcome Trust.
• Chaired by Lord Jim O’Neill.
• Tasked to recommend solutions to tackle antimicrobial resistance globally – through the lens of economics and policy-making.
• Mandate to build international consensus for action.
• Published seven interim papers before final report in May 2016 – www.amr-review.org.
Recommended actions across ten areas

Special focus on how to increase the supply of drugs and diagnostics
Three strands for surveillance of AMR

1. data on consumption of antibiotics in both humans and animals, [...] which would help understand the link between antimicrobial use and the development of resistance.

2. data on resistance rates for various drug–bug combinations and their impact on patients’ health.

3. molecular biological data to explain the biological basis of resistance, through characterisation of the types of resistant bacteria and the genetic reasons for their resistance.

• This information should be gathered within a ‘one health’ perspective, covering animals and humans and the environment to provide a complete picture.
The apex of *current* resistance problems?

- only colistin is currently active against 90% of CRE (UK data)
- colistin resistance is a growing threat (chromosomal and *mcr* genes)
Which antimicrobials? What are the priorities?

• What our report said:

<table>
<thead>
<tr>
<th>Urgent need and current funding structures inadequate</th>
<th>Urgent need but current funding structures largely adequate</th>
<th>Need will arise and require future consideration</th>
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<tbody>
<tr>
<td>TB treatment regimen</td>
<td>New malaria treatments</td>
<td>HIV/AIDS drugs</td>
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<td>Antibiotics</td>
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<td>Antifungal medicines</td>
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• Future work needed to set national and global priorities, in particular for antibiotics: public funding should focus on highest needs only.
WHO Priority Pathogens list for R&D of new antibiotics

Priority 1: CRITICAL*

- Antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria.
- Antibiotics for the paediatric population and for oral formulations for community diseases with a high morbidity burden such as drug-resistant *Neisseria gonorrhoeae*, *Salmonella typhi* and ESBL-producing *Enterobacteriaiceae*.
- New classes of antibiotics without cross- and co-resistance to existing classes should be supported.
- Must also reduce the burden of infections e.g. increased vaccination coverage, improved sanitation or sustained implementation of infection control measures.

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter*, fluoroquinolone-resistant
- *Salmonella spp.*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella spp.*, fluoroquinolone-resistant

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* Mycobacteria (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), is subjected to review for inclusion in this prioritisation exercise as it is already a globally extra priority for which innovative new treatments are urgently needed.

* Enterobacteriaiceae include: Klebsiella pneumoniae, *Escherichia coli*, *Enterobacter spp.*, *Serratia* *Pseudo spp.*, and *Providencia spp.*, *Morganella spp.*
Assessing the potential of the antibiotic pipeline

We don’t have enough antibiotics in development to tackle the resistance issues we face now

…and the success of those in development is not guaranteed

Analysis in 2015 of data from www.pewtrusts.org
Securing new drugs

• More predictable market to make antibiotics R&D commercially sustainable
  – lump-sum payments for ‘successful’ drugs
  – ‘de-link’ profitability from sales
• jump-start a new innovation cycle in antibiotics
  – Global AMR Innovation Fund
  – boost early-stage R&D into drugs and diagnostics
• reduce barriers to drug development
  – lower costs
  – improve the efficiency of research
  – lower global regulatory barriers
“Push” incentives have been insufficient
Now there are new “Push” incentives

- History of under-investment in AMR but course correction has started, eg:
  - NIH, BARDA
  - CARB-X partnership with AMR Centre in Alderley Park and Wellcome Trust
  - EU IMI programme.
  - GARDP in Geneva, a new product development partnership focused on antibiotic R&D.
  - UK global AMR innovation fund
New ‘Push’ incentives: CARB-X (March ‘17)

- initial investment of $24 million in 11 projects, chosen from among 168 applications by an advisory board of antibiotic experts.
- CARB-X will also be awarding an additional $24 million in milestone-based payments to the companies to advance the projects beyond the early stages of development.
- The companies are matching the money with private funds to bring the total investment to $75 million
Our proposal for a global ‘pull’ incentive that co-exists with diverse national arrangements
Market entry rewards would have a powerful impact on antibiotic R&D given the size and shape of the current yearly global market

Patented antibiotics form a small percentage of the total $40 billion per year antibiotics market, so $1.6 billion a year would have a material impact.

$4.7 bn
Patented antibiotics market

$1.6 bn
Market entry reward

Data and analysis by IMS Health, in the countries they had patent data for only 12.3% ($3.8bn) of sales were on patent while $3.8bn were off patent. We then presumed that this ratio remained the same in the 80% of countries they did not have patent data for, even though these countries tend to buy less patented drugs, making the above figures a high estimate of the patented market.
New drug development …and antibiotic stewardship

• **Not mutually exclusive**

• In the future, new antibiotics must be viewed differently
  • not regarded as ‘cure more’ replacements by prescribers
  • not regarded as market blockbusters by manufacturers

• Changes in behaviour and expectation are essential
  • ***This must be underpinned by better and faster diagnostics***
    • old drugs should be used for ‘susceptible infections’
    • new drugs must be held in reserve for ‘resistant infections’
What might new tests do?

AMR diagnostics might tell the prescriber:

1. that there is / is not evidence of bacterial infection
2. that a pathogen is potentially resistant to particular drugs (molecular)
3. that an infecting organism is susceptible to particular drugs (rapid AST)
A PLAN TO OVERHAUL DIAGNOSTIC DEVELOPMENT

Barriers

- Difficult to show cost and clinical effectiveness
- Difficulty raising capital
- Diagnostics are more expensive than empirical prescribing

Solutions

- Fund and facilitate research
- Global innovation fund
- Diagnostic Market Stimulus

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally
New ‘Push’ incentives: CARB-X (March ‘17)

### CARB-X Antibacterial Devices and Diagnostic Product Portfolio

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Type</th>
<th>Technology</th>
<th>Development Stage</th>
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<tbody>
<tr>
<td></td>
<td>Rapid POC Dx</td>
<td>Optical bacterial imaging</td>
<td>Feasibility Demonstration</td>
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<td>Optimization and Preparation for Development</td>
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<td>Product Development</td>
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<td>System Integration and Testing</td>
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<tr>
<td>Proteus</td>
<td>POC Diagnostic</td>
<td>POC Diagnostic</td>
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The above projects are Powered by CARB-X utilizing non-dilutive funding from BARDA, Wellcome Trust & NIAID. The stage of development is approximate as of March 2017 (please refer to the companies’ website for updated information). Characterizations by CARB-X experts and external expert opinion. Dx = Diagnostics

- 1/11 funded projects is for a novel diagnostic
UK Response to O’Neill

Published the formal response in September 2016, setting out proposed action including:

- Halving the inappropriate prescription of antibiotics in human health by 2020;
- Halving the number of healthcare associated bloodstream infections that pose the biggest risk – such as *E. coli* - by 2020;
- Antibiotic use in livestock and fish farmed for food to 50mg/kg, by 2018.
- Working with the global finance and health community to develop a global system that rewards companies that develop new, successful antibiotics and make them available to all who need them.
Specific focus of the UK AMR Strategy

- **PREVENT** (people from being infected – infection prevention and control)
- **PRESERVE** (the antibiotics we have – good stewardship)
- **PROMOTE** (development of new antimicrobials, new approaches, better diagnostics – the independent review by Lord Jim O’Neill)

**Underpinned by:**
- Surveillance
- R&D
- One Health approach
- International collaboration