Tackling antimicrobial resistance

Professor Neil Woodford (@Prof_Neil)

NIS Laboratories, National Infection Service

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Global commitment to combat AMR

- WHA 2014 resolution
- Global Health Security Agenda: AMR action package - mechanism and collaboration to accelerate implementation
- Many other national action plans
- UNGA, 2016
- UN Inter-Agency Coordination Group, 2017
The UK's long record of high-level leadership

AMR has a cyclical history
- hard now to be genuinely original
- much done, thought or written before
- recurring losses of momentum, necessitating new waves of activity

Jim O’Neill’s Review on AMR

Commissioned by the UK Prime Minister, July 2014 to revitalize antibiotic discovery – focused on economics.

“Drug-resistant infections already kill hundreds of thousands a year globally, and by 2050 that figure could be more than 10 million. The economic cost will also be significant, with the world economy being hit by up to $100 trillion by 2050 if we do not take action.”

www.amr-review.org, 2015
Defining our defences against AMR

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:
1. Surveillance
2. R&D
3. One Health approach
4. International collaboration
The complexities of AMR

Antimicrobial Usage
All sectors

Patients, non-human reservoirs
Hospital / community setting; risk factors; outcomes

Host species
Strains, clones

Genes
etc.

Monitoring antibiotic usage in England (ESPAUR)

- Established by PHE in 2013 in response to the strategy
- Focuses on bringing together NHS, PHE, Private sector across all prescribers and clinicians to improve
  - Surveillance data on antibiotic resistance and prescribing
  - Antimicrobial stewardship activities
  - Education and training for healthcare professionals
  - Education and awareness to public
Open access to surveillance data

- Fingertips: [http://fingertips.phe.org.uk/](http://fingertips.phe.org.uk/)
- AMR local indicators hosted on PHE fingertips site contain a selection of data across 5 domains:
  - Antimicrobial Resistance
  - Antibiotic Prescribing
  - Healthcare Associated Infection
  - Infection Prevention and Control
  - Antimicrobial Stewardship
- Indicators are intended as information for action and may enable healthcare organisations to benchmark the data for their organisation

Simple messages …for targeting action

**WHO IS PRESCRIBING?**

- Hospital inpatient: 11%
- Hospital outpatient: 5%
- General practice: 74%
- Dental practice: 5%
- Other community settings: 5%

1 in 3 patients in hospitals in England are on antibiotics at any one time

1 in 3 individuals in England takes at least one course of antibiotics each year
…and more questions to challenge us

- Regional variations in E. coli BSI rates
- Why?
- Socio-economic deprivation scores and other indices?
- Intervention measures

We need to build global capacity

Available National Data* on Resistance for Nine Selected Bacteria/Antibacterial Drug Combinations, 2013
National & international capacity building

- Without lab testing we’re blind to (the extent of) AMR problems
- Improve lab access; aim for a reference lab in every country / region
  - Each serving as the hub of a national network
  - Each acting as a spoke in an international network
  - Performing essential techniques, proficient to international standards
  - Sharing data / experience
MDR & PDR Gram-negatives

- MDR increasingly seen in BSI across Europe
- PDR also a reality, but low numbers in most countries
- MBL + ESBL (all beta-lactams) + 16S RMTase (aminoglycosides)
- + resistance to colistin + upregulated efflux

Fighting ‘AMR’ outbreaks is hugely expensive

Superbug outbreak costs an NHS hospital one million pounds, says new study

Manchester trust struggling to contain hospital bug
Countering AMR - then and now

Fig. 1. Past and present cycle of antibiotic discovery and resistance. For approximately 70 years (1940s–1970s) pathogens’ bacteria and the diseases they cause were controlled with the discovery of many new antibiotics. Following the resistance challenge, the discovery of new antibiotics, along with the rise of multi-drug resistant pathogens, has been a global public health challenge.

Antibiotic access: ‘AWARE’

<table>
<thead>
<tr>
<th>Treatment line and stewardship advice</th>
<th>Access: always on the shelf</th>
<th>Watch a balancing act</th>
<th>Reserve: the last resort</th>
</tr>
</thead>
<tbody>
<tr>
<td>First- and second-line treatments that should be widely available: e.g. amoxicillin,</td>
<td>Second-line treatments that should be prescribed only for specific indications, since they are at higher risk of bacterial resistance, e.g. quinolones and fluoroquinolones.</td>
<td>Last resort or third-line treatments e.g., aztreonam, colistin, that should be used to treat only the most severe cases, in order to limit the risk of resistance.</td>
<td></td>
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<table>
<thead>
<tr>
<th>Market at a glance</th>
<th>Governance approach needed</th>
<th>Company strategy needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercially attractive</td>
<td>Local governance: requires collaboration between pharmaceutical companies, governments and local organisations.</td>
<td>Broad strategies are needed to improve access to these antibiotics in countries where health systems are weak. Key elements include plans for easily registering antibiotics, affordability, strengthening supply chain and stewardship practices. An agile approach is necessary for responding to shortages and stockouts.</td>
</tr>
<tr>
<td>Commercially viable</td>
<td>Local governance: requires collaboration between pharmaceutical companies, governments and local organisations.</td>
<td>To manage antibiotics in this group, companies must take a nuanced and weighted approach, developing suitable access plans that are integrated with stewardship practices that limit excessive use and predict emerging resistance trends.</td>
</tr>
<tr>
<td>Small global market</td>
<td>Global governance: requires the expertise and efforts of governments, multilateral organisations such as WHO, regulators and pharmaceutical companies.</td>
<td>Antibiotics in the Reserve group are essential treatments against the most resistant pathogens. It is vital that companies engage in stewardship activities that facilitate the appropriate use of these antibiotics, while rigorously monitoring demand and growing threat of their resistance. Global strategies must include mechanisms to reserve stock, and facilitate an agile and rapid response to need.</td>
</tr>
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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
WHO Priority Pathogens list

- 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 Enterobacteriaceae.

- 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 1: CRITICAL

- Antibiotics (beta-lactam, carbapenem-resistant)
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

- Enterococcus faecalis, vancomycin-resistant
- Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
- Helicobacter pylori, clarithromycin-resistant
- Campylobacter, fluoroquinolone-resistant
- Enterococci spp., linezolid-resistant
- Neisseria gonorrhoeae, 1st generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- Enterococcus faecalis, penicillin-resistant non-enterococcal
- Neutrophilic influenza, amoxicillin-resistant
- Shigella spp., fluoroquinolone-resistant


CPE in the UK, 2000-2017


AMRHAI Unpublished data
New anti-Gram-negatives

<table>
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<tr>
<th>Name</th>
<th>Phase</th>
<th>Company</th>
<th>Class</th>
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<tbody>
<tr>
<td>Ceftolozane+ tazobactam</td>
<td>FDA approved Dec 19, 2014</td>
<td>Merck</td>
<td>Novel cephalosporin + beta-lactamase inhibitor</td>
</tr>
<tr>
<td>Ceftazidime+ avibactam</td>
<td>FDA approved Feb 25, 2015</td>
<td>Pfizer / Allergan</td>
<td>Cephalosporin + novel beta-lactamase inhibitor</td>
</tr>
<tr>
<td>Meropenem+ vaborbactam</td>
<td>FDA approved Aug 29 2017</td>
<td>The Medicines Company</td>
<td>Meropenem + novel beta-lactamase inhibitor</td>
</tr>
</tbody>
</table>

Resistance to new agents: never say ‘never’!

"Now, here, you see, it takes all the running you can do, to keep in the same place."
Bacteria can be made resistant...

- In the lab:
  - In-vitro selection of CAZ-AVI mutants of *E. cloacae* and *K. pneumoniae*, all with the KPC-3 enzyme.
  - CAZ-AVI mutants at up to 16 x MIC, with frequencies of ca. $10^{-9}$
  - CAZ MICs rose; MICs of carbapenems, other cephalosporins and PTZ reduced
  - The most frequent change was Asp179Tyr, increasing CAZ specificity
  - Clinical relevance uncertain

...or can become resistant in the clinic

- Clinical failure of CAZ-AVI in 10/37 CPE patients
- CAZ-AVI-R *K. pneumoniae* from three patients after CAZ-AVI for 10-19 d.
- D179Y/T243M, D179Y or V240G mutations in *bla*KPC-3, which were not present in baseline isolates
- MEM-S phenotype restored in *K. pneumoniae* from two patients; clinical successful Rx in one case
- clinical impact of CAZ-AVI-R may be ameliorated if carbapenem-S is restored
New drugs, but the companies still pass the baton

• 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
New drug development vs. focus on 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’

Why new AMR diagnostics?

- Prescribers must know earlier and more often that the infecting bacteria are susceptible to the drug they intend to use
  - Reduce empirical, broad-spectrum prescribing
- We need instruments and tests that can be deployed widely throughout the developed and developing world
- These new generations of diagnostics for AMR will facilitate
  - improved antibiotic stewardship
  - improved individual patient management
  - reduced onwards transmission of resistant bacteria
AMR is a **societal** issue: many stakeholders

- Prescribers – primary and secondary / tertiary care
- Prescribers – veterinarians
- Other healthcare professionals
- Social scientists
- Agriculturalists
- Public Health – local, regional, national
- Patients / public
- Academia + educators
- Industry (pharma and diagnostics)
- Politicians
- Funding agencies
- International agencies and organisations
Summary

The fight against AMR needs action on multiple fronts:

- Advocacy at highest level, and engagement downwards
- Better education (prescriber, user and wider public)
- Reducing infections and onwards transmission
- Better diagnostics and wider adoption of them
- Laboratory capacity building
- Better surveillance data to inform (local, national and global) action
- Reducing inappropriate prescribing (multi-sectoral)
- Reducing duration of broad-spectrum antibiotic treatment
- Assessment of any unintended consequences