Introduction to antimicrobial resistance

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HCAI and AMR Project Lead

4th March 2015
What is antimicrobial resistance?

- Antibacterials either kill or stop bacteria replicating
- Bacteria try to avoid being killed in 4 ways (see fig)
- Can mutate (<1 day) or inherit resistance.
- Can spread their resistance mechanisms to other species (on plasmids), and then onto other people.
- Resistant bacteria multiply more slowly then susceptible
- Gram –ve resistance is usually irreversible, unlike Gram +ve
Why we need new antibiotics

• Bacteria will always become resistant to antibiotics sooner or later
Antibacterials are used for short courses = poor return on investment. Registration requires trials in infections where unlikely to use. We reserve or don’t use new ones. Eg ceftaroline: “it’s a cephalosporin!”
New antibiotics coming in 2015-7

- **Oritavancin** IV weekly (Q2 ‘15) - cSSTI
- **Telavancin** IV daily G+ve HAP (Q3 ‘14) = teicoplanin / vancomycin
- **Dalbavancin** IV weekly – cSSTI (Q1 ’15), CAP 2017
- **Tedizolid** –po/IV daily - Q2’15: like linezolid but without the interactions or haematological side-effects
- **Ceftolozane-tazobactam** IV – Q4’15: cUTI, cIAI (abdo), (VAP later) – covers ESBL E.coli and MDR PsA, but not Kleb pneum
- **Ceftibiprole** – licensed but launch 2015 for CAP/HAP (= linezolid + ceftazidime)
- **Ceftazidime – avibactam** IV Q1/2’16 – where no other options for cUTI/cIAI – broad activity vs ESBL E.coli & Kleb, PsA and carbapenemases. Some Acin baum activity.
- **Eravacycline** IV/po 2017 – cIAI by ESBLs = ertapenem

http://antibiotics-theperfectstorm.blogspot.co.uk/2014/12/antibiotics-in-2014-banner-year.html
http://www.ukmi.nhs.uk/applications/ndo/dbSearch.asp
Global AMR picture is poor

Bacteria commonly causing infections in hospitals and in the community

<table>
<thead>
<tr>
<th>Name of bacterium/resistance</th>
<th>Examples of typical diseases</th>
<th>No. of WHO regions with national reports of 50% resistance or more</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>Urinary tract infections, blood stream infections</td>
<td>5/6</td>
</tr>
<tr>
<td>- vs 3rd gen. cephalosporins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- vs fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>Pneumonia, blood stream infections, urinary tract infections</td>
<td>6/6</td>
</tr>
<tr>
<td>- vs 3rd gen. cephalosporins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- vs 3rd carbapenems</td>
<td></td>
<td>2/6</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Wound infections, blood stream infections</td>
<td>5/6</td>
</tr>
<tr>
<td>- vs methicillin ”MRSA”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Poor sanitation, OTC antibiotics and worldwide travel spreads AMR

www.england.nhs.uk
Antimicrobial resistance in Europe, 2012: percentage of invasive isolates showing resistance

*Staphylococcus aureus*, meticillin resistance (MRSA)  
*Klebsiella pneumoniae*, combined resistance*

*Combined resistance: resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides*

Source: EARS-Net, 2013

The symbols † and ‡ indicate a significant increasing or decreasing trend for the period 2009-2012, respectively. These trends were calculated on laboratories that consistently reported during 2009-2012
No (clean-contaminated/dirty) surgery, no chemotherapy (neutropenic sepsis) Cost will be $100 trillion per year ($100,000,000,000,000)
Superbugs to kill 'more than cancer' by 2050

Deaths attributable to antimicrobial resistance every year compared to other major causes of death

- Tetanus: 60,000
- Cholera: 100,000 - 120,000
- Measles: 130,000
- AMR: 700,000
- AMR in 2050: 10,000,000
- Road traffic accidents: 1,200,000
- Diarrhoeal disease: 1,400,000
- Diabetes: 1,500,000
- Cancer: 8,200,000

Source: Review on Antimicrobial Resistance 2014

www.england.nhs.uk
UK 5yr AMRS: 7 key areas for action

DH – High Level Steering Group

PHE
Human health

- Optimising prescribing practice
- Improving infection prevention and control
- Improving professional education, training and public engagement
- Better access to and use of surveillance data

Defra
Animal health

- Improving the evidence base through research
- Developing new drugs, vaccines and other diagnostics and treatments
- Strengthening UK and international collaboration

DH
English Surveillance Programme for Antimicrobial Usage and Resistance

- Key element of the 5 year AMR strategy was to introduce surveillance systems for antimicrobial resistance and usage
- 1st English data for antimicrobial usage data for hospitals AND community in 2014 report
  - Data from 2010 to 2013
  - Data down to Area Team level
  - Update on AMS activity in hospitals since 2011/2
Antimicrobial resistance

- European data has shown that infection with a resistant organism will double mortality rate
- 12% increase in the number of *E. coli* bloodstream infections between 2010-3
  - Resistance has remained stable across all antibiotic groups
  - Wide regional variation in resistance rates with London 2-3x higher resistance rates
- 10% increase in number of *Klebsiella pneum* infection
  - Resistance generally stable with widespread variation
- 9%↓ in *Pseudomonas* and 25%↓ in *Strep pneum* BSI (13-valent vaccine introduced in 2010)
Table ES.1. Summary of key antibiotic resistance in bacteraemia in England

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Rate per 100,000, 2013 (compared to 2010)</th>
<th>Antibiotic or antibiotic class</th>
<th>% resistant 2013 (compared to 2010)</th>
<th>Change in number of resistant bacteria 2010 to 2013</th>
<th>% resistant Europe 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>52.6 (↑)</td>
<td>Ciprofloxacin 18.2 (↔)</td>
<td>↑</td>
<td>22.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third-generation cephalosporins 10.9 (↔)</td>
<td>↑</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentamicin 9.7 (↔)</td>
<td>↑</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem/meropenem 0.1 (↔)</td>
<td>↑</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>8.8 (↑)</td>
<td>Ciprofloxacin 11.1 (↔)</td>
<td>↑</td>
<td>25.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third-generation cephalosporins 11.4 (↔)</td>
<td>↑</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentamicin 8.5 (↑)</td>
<td>↑</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem/meropenem 1.0 (↑)</td>
<td>↑</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas spp.</em></td>
<td>6.3 (↓)</td>
<td>Ciprofloxacin 10.4 (↔)</td>
<td>↑</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime 6.7 (↔)</td>
<td>↓</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentamicin 3.6 (↓)</td>
<td>↓</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem/meropenem 9.5 (↔)</td>
<td>↓</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>6.1 (↓)</td>
<td>Penicillin 3.1 (↔)</td>
<td>↓</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrolides 8.1 (↑)</td>
<td>↑</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetracycline 6.1 (↑)</td>
<td>↑</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Check for true penicillin allergy

England still has less AMR than Europe
Table 1. Antibiotic susceptibilities of carbapenemase-producing Enterobacteriaceae isolates from the UK, submitted to the AMRRAI Reference Unit in 2014

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Proportion of susceptibility, % [a]</th>
<th>Metallo-enzyme producers (NDM, VIM, IMP) (n=c. 400)</th>
<th>Non-metallo-enzyme producers (KPC, OXA-48, GES, IMI) (n=c. 1250)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
<td>Klebsiella</td>
<td>Enterobacter / Citrobacter</td>
</tr>
<tr>
<td>Imipenem (IPM)</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>IPM-EDTA [b]</td>
<td>100</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Meropenem</td>
<td>6</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Piperacillin (PIP)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PIP-tazobactam</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>13</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>17</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>31</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>22</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Amikacin</td>
<td>49</td>
<td>33</td>
<td>62</td>
</tr>
<tr>
<td>Colistin</td>
<td>100</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>99</td>
<td>52</td>
<td>73</td>
</tr>
</tbody>
</table>

a. Susceptibility defined using BSAC v. 13 (June 2014) breakpoints
b. Diagnostic test to distinguish metallo- from non-metallo- enzymes; not for therapeutic use

Active in vitro against <50% isolates
Active in vitro against 50-90% isolates
Active in vitro against >90% isolates
Travellers carry CPE resistant bugs for up to 3 months
Has 31%↑ in carbapenems driven AMR?

Manchester ↓ by 7% over 4 years
6%↑ in consumption between 2010-13

GPs: 78% of total with 4.1% growth in 2010-3 but 3.5%↓ in last year

Hospitals: 9.1% IP and 6.2% OP, but 11.9%↑ over 3 years for IP
ESPAUR 2014: 1\textsuperscript{st} total sector data. We’re not as good as we thought!

Table ES.2. Summary of total antibiotic use in England and comparisons with Europe

<table>
<thead>
<tr>
<th>Antibiotic group</th>
<th>England 2013 (DDD per 1000 inhabitants per day)</th>
<th>England 2013 compared to England 2010</th>
<th>Europe 2011 (Median DDD per 1000 inhabitants per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>13.7</td>
<td>↑</td>
<td>10.4</td>
</tr>
<tr>
<td>Other β-lactam antibacterials</td>
<td>0.6</td>
<td>↓</td>
<td>2</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>4.9</td>
<td>↑</td>
<td>2.2</td>
</tr>
<tr>
<td>Sulfonamides and trimethoprim</td>
<td>1.9</td>
<td>↑</td>
<td>0.5</td>
</tr>
<tr>
<td>Macrolides &amp; similar</td>
<td>4.1</td>
<td>↑</td>
<td>3</td>
</tr>
<tr>
<td>Quinolones</td>
<td>0.6</td>
<td>↓</td>
<td>1.5</td>
</tr>
<tr>
<td>Other</td>
<td>1.7</td>
<td>↑</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27.4</strong></td>
<td>↑</td>
<td><strong>21.3</strong></td>
</tr>
</tbody>
</table>
How will AMR affect GPs?

**Short term**
- UTIs resistant to usual treatment (ESBLs)
- Options: unlicensed oral options (fosfomycin sachets) or IV ertapenem or others

**Longer term**
- More carbapenem resistant organisms
  - India 10% E.coli, 30% Kleb pneumonia
  - Travellers carry resistant bugs for up to 3 months
  - Limited treatment options
Undergraduate AMS teaching

(n= 88)

Imperial HPRU 2015
AMS & AMR E&T for registrants

1. Infection prevention and control
2. Antimicrobial resistance & antimicrobials
3. Prescribing antimicrobials
4. Antimicrobial stewardship
5. Monitoring and learning

Antimicrobial prescribing and stewardship competencies

HEE AMR competencies groups looking at post-graduate AMR E&T framework for prescribers and non-prescribers
In April 2015 these Regulations will be replaced by The Health and Social Care Act 2008 (Regulated Activities) Regulations 2014 which will introduce new registration requirements.

The main registration requirement for infection prevention and control (IPC) will be:

- Regulation 12 on Safe Treatment and Care, but
- Regulation 15 on Premises and Equipment is also relevant under which there are a number of criteria to follow.

Support implementation of the UK AMR Strategy by giving greater prominence to antimicrobial resistance

Reflect the NHS Structures introduced in 2013.

Update the bibliography
## Code of Practice: 10 criteria for CQC

<table>
<thead>
<tr>
<th>Compliance criterion</th>
<th>Registered providers will need to demonstrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Systems to manage and monitoring IPC</td>
</tr>
<tr>
<td>2</td>
<td>Provide &amp; maintain a clean and appropriate environment</td>
</tr>
<tr>
<td>3</td>
<td>Ensure appropriate AB use to improve outcomes &amp; ↓AMR</td>
</tr>
<tr>
<td>4</td>
<td>Provide suitable accurate information on infections</td>
</tr>
<tr>
<td>5</td>
<td>Prompt identification of infection (or risk). Timely treatment.</td>
</tr>
<tr>
<td>6</td>
<td>IPC followed by all care workers (incl volunteers &amp; contractors)</td>
</tr>
<tr>
<td>7</td>
<td>Adequate isolation facilities</td>
</tr>
<tr>
<td>8</td>
<td>Adequate access to lab support</td>
</tr>
<tr>
<td>9</td>
<td>Policies for IPC</td>
</tr>
<tr>
<td>10</td>
<td>Occupational health needs for staff (in relation to infection)</td>
</tr>
</tbody>
</table>

www.england.nhs.uk
Key questions – by 13th March

Q1 Does the revised Code explain the changes in the new registration requirements? Yes/No
   Any comments?

Q2 Does the revised Code explain the need to ensure infection prevention and control systems take a holistic approach by including antimicrobial stewardship and cleanliness? Yes/No
   Any comments?

Q3 Which phrase is most suitable for use in the Code? a) infection prevention or b) infection prevention and cleanliness? Why?

Q4 Are the definitions of AMR and stewardship clear on page 7? Yes or No and if not please suggest alternative wording and the basis for your suggestion.

New version of compliance criterion. Please explain the reasons for any concerns that you have in relation to this revised criterion.

Q5 Do you agree that merging compliance criteria 3 and 4 reduces the scope for confusion on provision of information? Yes/No

Q5a Do you have any comments on the guidance for compliance for the new criterion 3? Yes/No

Q5b Do you have any comments on the guidance for compliance for the new criterion 4? Yes/No

Q5c Do you have any specific comments on the interpretation of criteria 3 and 4 is specific settings outlined in appendices Yes/No

Q6 Do you have any comments on the re-wording of criterion 10 on occupational health? Yes/No If yes, please explain the reasons for your concern

Q7 Do you have any comments on the inclusion of reference to a water safety lead on page 12? Yes/No If yes, please explain the reasons for your concern

Q8 Do you have any specific comments on the appendices? Yes/No If yes, please explain the reasons for your concern

Q9 Any other comments? Yes/No
   We would be interested to hear of any general concerns about the revised Code, including topics not covered by the guidance, areas where clarification is required and amendments to the bibliography

RESPONSE FORM FOR THE CONSULTATION ON THE REVISED VERSION HEALTH AND SOCIAL CARE ACT 2008 CODE OF PRACTICE ON PREVENT CONTROL OF INFECTIONS AND RELATED GUIDANCE (THE CODE)

Please send this completed form to AMR@dh.gsi.gov.uk by 13 March 2015

Name

Job role

Organisation

Telephone number e-mail
Aims to provide good practice recommendations on systems and processes for the effective use of antimicrobials

- All age groups
- Hospitals and all community areas

**Recommendations:**

- AMS programmes, teams & interventions
- Communication, guidelines & lab testing
- Prescribing antimicrobials
- New antimicrobial review & introductions

The guideline does NOT cover:

- Specific clinical conditions
- Named medicines
- Public health awareness of AMR
- Research into new antimicrobials
- Immunisation and vaccination
- Antimicrobial household cleaning products
- Antimicrobial use in animals
- Hand hygiene, decolonisation and IPC measures
- Medicines adherence
- Access to medicines
- Medicines shortages
- Prescription charges or waste

Become an Antibiotic Guardian

Champion

- **European Antibiotic Awareness Day (EAAD)** takes place annually on **18 November**
- **As an Antibiotic Guardian**, choose a simple action based pledge and encourage others to join you in protecting antibiotics against the growing threat of antibiotic resistance at: [www.antibioticguardian.com](http://www.antibioticguardian.com)
- The Antibiotic Guardian campaign was established by PHE to improve public and professional knowledge and stimulate engagement on tackling antibiotic resistance
- Public Health England is leading the co-ordination of EAAD activities in England in collaboration with VMD, Department of Health, devolved administrations, and other professional
Become an Antibiotic Guardian Champion –
Pledge system: http://antibioticguardian.com/ 
Behaviour change – ‘if-then’ approach

CURRENT PLEDGES: 12693

Antibiotic resistance is one of the biggest threats facing us today.

Why it is relevant to you: Without effective antibiotics many routine treatments will become increasingly dangerous. Setting broken bones, basic operations, even chemotherapy all rely on access to antibiotics that work.

What we want you to do: To slow resistance we need to cut the use of unnecessary antibiotics. November 18th is European Antibiotic Awareness Day. As part of that we're asking everyone in the UK, the public and the medical community to become Antibiotic Guardians.

Call to action: Choose one simple pledge about how you'll make better use of antibiotics and help save this vital medicine from becoming obsolete.
BECOME AN ANTIBIOTIC GUARDIAN
CHOOSE YOUR PLEDGE NOW!

I AM A

Human & animal health professionals

HEALTHCARE PROFESSIONAL OR LEADER
Select from the list below

- Antimicrobial/Infection Prevention
- Primary Care Prescribers
- Secondary Care Prescribers
- Antimicrobial/Infection Prevention and Control Specialists
- Nurses
- Pharmacy Teams
- Dentists
- Non-Medical Prescribers
- Other Healthcare Workers (eg. Psychiatrists, chiropractors, radiographers, therapists, social workers)
- Veterinary Practitioners
- Executive/Management/Government/Commissioners/Public Health

MEMBER OF THE PUBLIC
Select from the list below
One Health approach
Adults, families, pet owners, farmers

For illness that our bodies are good at fighting off on their own, like coughs, colds, sore throats and flu, I pledge to talk to my pharmacist about how to treat my child's symptoms first rather than going to the GP.

Washing your hands properly is the single best way to prevent the spread of infections. My family pledges to help cut the need for antibiotics by always washing our hands with soap and water for about 30 seconds (about the same time it takes to sing A, B, C, D song).

I will visit the ebug website (www.e-bug.eu) with my child(ren) and take one of the antibiotic awareness quizzes together.
As of 30th November 2014, the week after to European Antibiotic Awareness Day; 11,833 pledges had been made. The above is the distribution of pledges by target audiences.

Drs Anna Cichowska & Diane Ashiru-Oredope (PHE)
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Philip Howard
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4th March 2015