Agricultural and Environmental Challenges

Mark Holmes (mah1@cam.ac.uk)

Department of Veterinary Medicine
Where are we coming from?

• Agriculture is a heavy user of antibiotics
• Exposure to antibiotics provides a selection pressure for AMR
• Increasing AMR is an undisputed problem in public health

• Universal agreement to use less antibiotics in animals
  • Better antibiotic stewardship
Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lu, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen
The Environment!

- Where does the antibiotic end up
- Animal waste spread on arable fields
- Complex microbiomes
- Sub-inhibitory concentrations
Industrial pollution (Lubbert et al, Infection April 2017)

- BNF dose of fluconazole is 150-800mg (depending on the condition)
- One of these environmental samples contains 237mg/L

<table>
<thead>
<tr>
<th>Antimicrobial agent (µg/L)</th>
<th>Number of samples tested positive for (%)</th>
<th>Proposed environmental regulation limit (µg/L)</th>
<th>Sample ID (corresponding location with GPS coordinates: see Table 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>S1*  S2*  S3*  S4*  S5*  S6*  S8*  S9*  S11*  S12*  S21*  S22*  S23*  S24*  S26*  S27*</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>13 (81.3)</td>
<td>0.25</td>
<td>N/D  N/D  24.007 48.311 1753 236,950 261.5 37.1 199.8 13.1 37.1 18.5 N/D 1331 243.8 147.3</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>12 (75.0)</td>
<td>N/A</td>
<td>N/D  N/D  306.4 324.9 4.3 5.0 1.5 2500 4.0 1.7 24.5 45.4 N/D N/D 6.2 8.0</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>9 (56.3)</td>
<td>0.125</td>
<td>BDL  N/D  31.7 7.1 8.3 29.5 N/D N/D 279.4 BDL N/D N/D N/D 694.1 BDL</td>
</tr>
<tr>
<td>Linezolid</td>
<td>8 (50.0)</td>
<td>8</td>
<td>BDL  N/D 37.0 13.6 BDL N/D N/D N/D N/D 6.7 8.5 5.4 N/D N/D N/D</td>
</tr>
<tr>
<td>Levofoxacin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (37.5)</td>
<td>0.25</td>
<td>N/D  N/D N/D N/D N/D N/D N/D 2.1 12.8 10.0 4.6 N/D N/D 2.2 N/D</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>6 (37.5)</td>
<td>0.25</td>
<td>N/D  N/D N/D N/D N/D N/D 13.5 N/D N/D N/D BDL 27.7 13.3 N/D BDL N/D N/D</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5 (31.3)</td>
<td>0.064</td>
<td>BDL  N/D N/D N/D NN 19.4 N/D N/D N/D 40.1 44.7 BDL N/D N/D N/D</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>5 (31.3)</td>
<td>0.5</td>
<td>N/D  N/D N/D N/D N/D N/D N/D N/D BDL BDL N/D N/D N/D N/D</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>4 (25.0)</td>
<td>16</td>
<td>N/D  N/D N/D N/D N/D BDL N/D N/D N/D BDL 10.6 BDL N/D N/D N/D N/D</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3 (18.8)</td>
<td>0.25</td>
<td>N/D  N/D N/D N/D N/D BDL N/D N/D N/D BDL N/D N/D N/D 29.1 N/D</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>1 (6.3)</td>
<td>2</td>
<td>N/D  N/D N/D N/D N/D N/D N/D N/D N/D N/D N/D N/D N/D N/D N/D</td>
</tr>
</tbody>
</table>

No. of proven antimicrobials in the same sample: 3 0 4 4 4 7 2 3 5 9 8 8 0 2 5 3
Farm animal medicine in contrast to human medicine

- Farm animals with severe injury or disease will be killed (rather than treated)
- Farm animals are nearly all juveniles or young adults
- The vast majority of antibiotic use is for the control of endemic disease
  - Often enteric or respiratory disease syndromes (often opportunist pathogens)
- Diagnosis on clinical signs
  - Diagnostic microbiology is rarely performed
- When one member of a group presents with disease, the group receives treatment
- Antibiotic resistance is not generally a problem
We reap what we sow!

• Our farmers are among the best in the world and have responded to the inexorable market pressures to produce cheap food

• Historically infectious disease research (human or animal) has been relatively poorly funded

• Veterinary research is even more poorly funded

• State support for animal health has been slashed over the last 30 years
  • AMR surveillance is relatively crude (very granular)
Figure 2.10 Number of isolates referred from UK hospital microbiology laboratories confirmed as carbapenemase-producing Enterobacteriaceae by AMRHAI, 2003–2014
Not all gloom and doom

- Poultry industry have responded well
- Pig industry are also responding
  - Colistin use down 70%
  - Monitoring ab use
What are the challenges?

• To what extent do animal and environmental reservoirs really contribute to AMR problems in man (now, and potentially in the future)?
  • What are the population (and gene) dynamics?
  • Where do they come from, and where do they go?
• Can we measure/quantify/estimate the risk (objectively)?
  • Is there a quantity of known resistance (genes/species) that breaches a threshold?
  • How likely is a catastrophic event to emerge from livestock/environment?
• Can we be confident that we are making truly “informed” decisions?
Any questions