AMR in the Environment
- The Neglected Environmental Dimension of AMR

Dr Donald Morrison
Antibiotic resistance is increasing
On cusp of post-antibiotic era
Misuse of antibiotics is the main driver of antibiotic resistance
The AMR Crisis

One Health

Healthy Humans

Healthy Animals

Healthy Environment

http://www.jbsa.mil/News/Art/igphoto/2000087752/
Nosocomial infections with Vancomycin-Resistant Enterococci

Prof. Neil Woodford
Head of the Antimicrobial Resistance and Healthcare Associated Infections Reference Unit
Avoparcin
- a glycopeptidyl peptide used in agriculture as an additive to livestock feed to promote growth in chickens, pigs, and cattle
Scottish MRSA Reference Laboratory
“Community” MRSA (CA-MRSA)

“Hospital” MRSA (HA-MRSA)

“Livestock Associated” MRSA (LA-MRSA)

Companion Animals
One Health Perspective

- AMR transmission
- Supported by traditional, low-resolution typing methods
“challenges established tenets that DT104 in domestic animals and humans are from the same well-mixed microbial population”
A. E. Mather,¹ S. W. J. Reid,² D. J. Maskell,³ J. Parkhill,¹ M. C. Fookes,¹ S. R. Harris,¹ D. J. Brown,¹ J. E. Coia,⁴ M. R. Mulvey,³ M. W. Gilmour,⁴ L. Petrovska,⁵ E. de Pinna,⁷ M. Kuroda,⁸ M. Akiba,⁹ H. Izumiya,¹⁰ T. R. Connor,¹† M. A. Suchard,¹¹ P. Lemey,¹² D. J. Mellor,¹³ D. T. Haydon,¹¹ N. R. Thomson¹‡

The global epidemic of multidrug-resistant *Salmonella* Typhimurium DT104 provides an important example, both in terms of the agent and its resistance, of a widely disseminated zoonotic pathogen. Here, with an unprecedented national collection of isolates collected contemporaneously from humans and animals and including a sample of internationally derived isolates, we have used whole-genome sequencing to dissect the phylogenetic associations of the bacterium and its antimicrobial resistance genes through the course of an epidemic. Contrary to current tenets supporting a single homogeneous epidemic, we demonstrate that the bacterium and its resistance genes were largely maintained within animal and human populations separately and that there was limited transmission, in either direction. We also show considerable variation in the resistance profiles, in contrast to the largely stable bacterial core genome, which emphasizes the critical importance of integrated genotypic data sets in understanding the ecology of bacterial zoonoses and antimicrobial resistance.

27 SEPTEMBER 2013 VOL 341 SCIENCE

Whole Genome Sequencing

• **Contrary to current tenets** supporting a single homogeneous epidemic

• ...the bacterium and its resistance genes were largely maintained within animal and human populations separately

• ..there was limited transmission, in either direction
• the majority of \textit{E. faecium} strains infecting patients are largely distinct from those from livestock

• …with \textit{limited} sharing of strains and resistance genes”

• Uncommon for \textit{E. coli} strains to be shared between animals and humans
• Limited sharing of AMR genes between livestock and humans
• Different plasmid encoding CTX-M-15 present in livestock and humans
• failed to demonstrate evidence for recent clonal transmission of cephalosporin-resistant E. coli strains from poultry to humans

• cephalosporin resistance genes are mainly disseminated in animals and humans via distinct plasmids.
• ESBL-E coli strains from bacteraemia in the UK ...
  ..are largely distinct from those in food animals and retail food

• ..actions on the food chain, however desirable for animal husbandry, are unlikely to contribute to reductions in human infection
One Health Perspective

- Supported by traditional, low resolution typing methods
- Not supported by high resolution typing methods
Antibiotic consumption has fallen by 9%

Number of infections resistant to antibiotics rises by 9% in one year

Increasing burden of infection and antibiotic-resistant infection 2014-2018

BS infections

21% increase since 2014

AMR BS infections

32% increase since 2014

Total consumption of antibiotics continued to decline

Antibiotic consumption has fallen by 9%
One Health Perspective

Healthy Humans

Healthy Animals

Healthy Environment

One Health

(Singer et al (2016) Review of AMR in the Environment and its relevance to Environmental Regulators (Frontiers in Microbiology (7) 1728.)
Antimicrobial Resistance Action Plans

**Worldwide**
- 1998 - first World Health Assembly (WHA) AMR resolution
- 2001 - WHO Global Strategy for Containment of AMR
- 2011 - EU AMR Strategic Action Plan
- 2015 - WHO global action plan on antimicrobial resistance
- 2016 – UN High-Level Meeting on AMR

“a lack of environmental focus in AMR Action Plans & the O’Neill Review”
Six key emerging issues:

• **Environmental dimension of antimicrobial resistance**
• Nanomaterials
• Marine Protected Areas & sustainable development
• Sand and dust storms
• Off-grid solar solutions
• Environmental displacement
Antimicrobial Resistance Action Plans

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UK
- 1998 - ‘Path of Least Resistance’ report
- 2000 - first ‘UK AMR Strategy
- 2011 - Annual Report of the Chief Medical Officer
- 2013 - UK 5 Year Antimicrobial Resistance Strategy
Antimicrobial Resistance Action Plans

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- 2018 - Antimicrobial resistance Report
  - House of Commons Health and Social Care Committee
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One Health Perspective

• Pollution - AMR regarded as a pollutant
  • ARB – antibiotic resistant bacteria
  • ARG – antibiotic resistant genes

(Singer et al (2016) Review of AMR in the Environment and its relevance to Environmental Regulators (Frontiers in Microbiology (7) 1728.)
Environment as reservoir of clinically relevant antibiotic resistance genes

**Resistance gene**
- Methicillin (mecA)
- Vancomycin (vanA)
- Cefotaxime (bla\textsubscript{CTX-M})
- Ciprofloxacin (qnrA/qnrS)
- Carbapenem (bla\textsubscript{NDM})

**Environmental species**
- *Staphylococcus fleurettii* (*S. sciuri* gp)
- *Paenibacillus spp* / *Rhodococcus spp*
- *Kluyvera* spp
- *Shewanella* spp and *Aeromonas* spp
- *Erythrobacter litoralis*
AMR in the Environment
Role of the Environment in the Transmission of Antimicrobial Resistance to Humans: A Review

Patricia M. C. Huijbers, †,* Hetty Blaak,*‡ Mart C. M. de Jong, † Elisabeth A. M. Graat, † Christina M. J. E. Vandenbroucke-Grauls, ‡ and Ana Maria de Roda Husman †,∥

†Quantitative Veterinary Epidemiology Group, Wageningen Institute of Animal Sciences (WIAS), Wageningen University, P.O. Box 338, 6700 AH Wageningen, The Netherlands

✔ ESBL E.coli
✔ VRE
✔ MRSA
Model of AMR in Environment

2 Sources

4 Compartments

4 Exposure Relevant Sites

ESBL Resistant *E. coli* in Environment

<table>
<thead>
<tr>
<th>Source</th>
<th>Compartment</th>
<th>Exposure site</th>
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<tbody>
<tr>
<td>Wastewater</td>
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<tr>
<td>Domestic Animals (manure)</td>
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<td>Soil</td>
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<td>Air</td>
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<tr>
<td>Fresh Produce</td>
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109 papers - 2006-2014

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<td>100% (5/5)</td>
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<tr>
<td>(manure)</td>
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<td></td>
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<tr>
<td>Water</td>
<td>92% (24/25)</td>
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<tr>
<td>Soil</td>
<td>80% (4/5)</td>
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<tr>
<td>Air/dust</td>
<td>100% (2/2)</td>
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<tr>
<td>Wildlife</td>
<td>85% (29/34)</td>
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<tr>
<td>Recreational Area</td>
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<tr>
<td>Drinking Water</td>
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<tr>
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<td>Fresh Produce</td>
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<td>Wastewater</td>
<td>100% (23/23)</td>
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<tr>
<td>Domestic Animals (manure)</td>
<td>100% (5/5)</td>
<td></td>
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<tr>
<td>Water</td>
<td>92% (24/25)</td>
<td></td>
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<tr>
<td>Soil</td>
<td>80% (4/5)</td>
<td></td>
</tr>
<tr>
<td>Air/dust</td>
<td>100% (2/2)</td>
<td></td>
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<tr>
<td>Wildlife</td>
<td>85% (29/34)</td>
<td></td>
</tr>
<tr>
<td>Recreational Area</td>
<td>100% (3/3)</td>
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</tr>
<tr>
<td>Drinking Water</td>
<td>100% (3/3)</td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>100% (2/2)</td>
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<tr>
<td>Fresh Produce</td>
<td>57% (4/7)</td>
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Joakim Larsson
Johan Bengtsson-Palme
Topp Ed
William Gaze
Elizabeth Wellington
David Verner-Jeffreys
Ramanan Laxminarayan
Celia Manaia
Kornelia Smalla
Role of Environment in AMR Development & Dissemination

Seafield WWTP

• Built in 2000
• 0.85 million population served
• 300 million litres waste water treated per day

http://wwtonline.co.uk/news/thp-gets-the-go-ahead-at-seafield#.Whl/pkpl82w
Seafield WWTP

MV Gardyloo - used to dispose of solid waste from Seafield WWTP in the Forth (1978-1996)

Site opened in 1978.
Seafield WWTP Catchment Area (Edinburgh)
Seafield WWTP Catchment Area (Edinburgh)

Discharge - How many ESBL resistant E.coli per minute?

6 billion / minute
Wild Bird as a Reservoir of Antibiotic Resistant Bacteria in the Environment

MRes - Bimo Andrianus Djuwanto
## ESBL resistance - gulls

<table>
<thead>
<tr>
<th>Populations (n=97)</th>
<th>Resistant <em>E. coli</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seafield WWTP</td>
<td>57%</td>
</tr>
<tr>
<td>St Abbs</td>
<td>2%</td>
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</table>
THE PREVALENCE OF ESBLs IN SCOTTISH BATHING WATERS (JUNE TO SEPT 2017-18)
ESBL resistant E.coli in bathing water

- **8% sample positive** (115/1456)

- Detected in 50/86 Bathing Waters at least once

- Detected at 26 Bathing Water more than once
Indicators of antibiotic resistance level in treated wastewater

Water Quality Regulation

• Maximum admissible values of “universal” indicators
  • Escherichia coli
  • Enterococcus spp.

• Maximum admissible values of antibiotic resistance prevalence ??
Participants

- 57 WWTPs in 22 countries across five continents
- Samples - December 2016, January 2017, February 2017

- Canada
- USA
- Portugal
- Spain
- UK/Scotland
- France
- Germany
- Italy
- Switzerland
- Austria
- Slovenia
- Croatia
- Estonia
- Poland
- Norway
- Cyprus
- Israel
- India
- China
- Australia
- South Africa
- South Korea
Data for samples with <5% ESBL-R, some samples up to 12% ESBL-R
Environmental limits – Antibiotic residue

- MSC - minimal selective concentrations
- PNEC - Predicted No Effect Concentrations

- PNECs - 8 ng/L to 64 μg/L

Environmental limits – maximum values of ESBL-R *E. coli*?

<table>
<thead>
<tr>
<th>Country or organism (year)</th>
<th>Irrigation categories</th>
<th>Total coliform (CFU/100 mL)</th>
<th>Faecal coliform (CFU/100 mL)</th>
<th><em>Escherichia coli</em> (CFU/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>California (1978) [1]</td>
<td>ND R</td>
<td>2.2 × 10²</td>
<td>10²</td>
<td></td>
</tr>
<tr>
<td>Israel (1999) [8]</td>
<td>ND R</td>
<td>10</td>
<td></td>
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</tr>
<tr>
<td>Kuwait (2001) [9]</td>
<td>ND R</td>
<td>4 × 10²*</td>
<td>20*</td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia (2000) [9]</td>
<td>UR R</td>
<td>2.2*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China (2007) [10]</td>
<td>UR R</td>
<td>2 × 10⁴</td>
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</tr>
</tbody>
</table>

< 10%
Interventions

• WWTPs as critical control points
  • Advanced treatment technologies (e.g., membrane separation)
  • Disinfection of WW - ultraviolet radiation, chlorination, ozonation
  • Thermophilic anaerobic sludge digestion

• Environmental AMR surveillance scheme
  • Monitor levels in different compartments
  • Evaluate interventions

“Unless society is prepared to assume the non-trivial costs associated with a precautionary approach, e.g., increased water bills to pay for substantial upgrades in WWTPs, there will be a need to prioritize the research that addresses the ‘Knowledge Gaps,’”