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Antimicrobial resistance – on-going problems and new threats

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Outline

- Background in relation to antimicrobial resistance
- Areas that are currently topical
  - *Salmonella*
  - MRSA
  - Beta lactamase resistance in *Enterobacteriaceae*
- Other areas of concern
  - Erythromycin and Fluoroquinolone resistance in *Campylobacter* spp
  - Glycopeptide resistance in *Enterococci* spp

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Background

- Penicillin first became available for human use in 1944
- Antimicrobials introduced into veterinary medicine ~1950s
- From the 1940s to 1980s new antimicrobial agents were developed faster than bacteria developed resistance
- No longer the case over the last two decades – developments have been within classes
- Concern is that bacteria are evolving faster than AMs are being developed, which is limiting therapeutic options
- 1953 – use of specified antibiotics (penicillin, oxy- and chlortetracyline) was permitted for growth promoting purposes in UK

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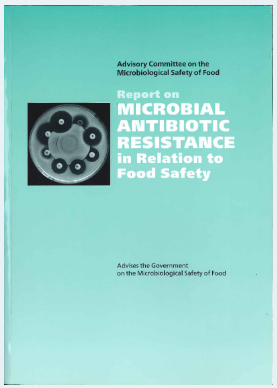
Concerns about antimicrobial resistance

- 1960s also saw the recognition of transferable drug resistance
- Swan Committee report in 1969
  - Use of AM's in animal feed should be restricted to those that had little or no therapeutic application in man or animals
  - Antibiotics for therapeutic purposes should only be available if prescribed by a vet
- Standing Medical Advisory Committed (1998) The Path of Least Resistance
- House of Lords Select Committee on Science and Technology (1998). Resistance to Antibiotics and Other Antimicrobial Agents
- ACMSF (1999) Report on Microbial Antibiotic Resistance in Relation to Food Safety



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What influences the occurrence of AMR?

- Emergence
  - Individual mutational events
  - Transfer of AMR from one species or genera to another
- Importation of AMR
  - Human travel
  - Food
  - Animals
  - Animal Feed
- Spread
  - Ability to colonise etc
  - Selective pressure due AM usage

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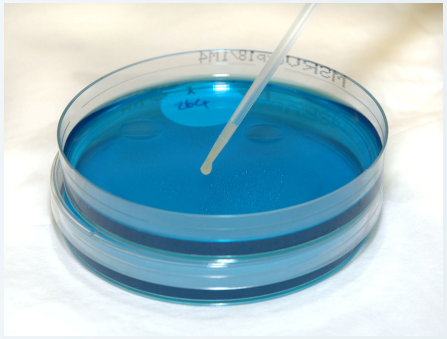
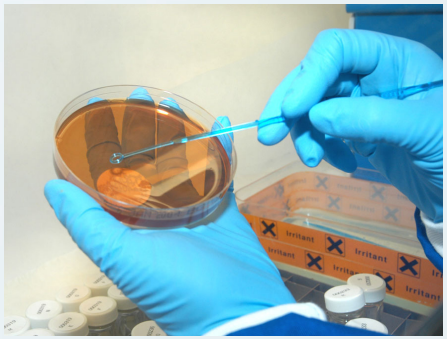
Salmonella

- Majority of concern surrounds *S.* Typhimurium
  - mid to late 60s – DT29
  - Mid 70s to mid 80s – DT 204c & related PTs 204 and 193.
    - DT204c R-types CSSuTTm - ACGKSSuTTM
  - Mid 1990s - DT104 R-type ACSSuT (ACSSuTTmNx)
  - Currently monophasic derivative
- *S.* Dublin and *S.* Enteritidis – level of resistance is low





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Salmonella Typhiumurium DT104

- *S*. Typhimurium DT104 was first isolated in the early 1980s in the UK and later became endemic in bovine animals, from where it spread to the whole food animal production.
- Multidrug-resistant (MDR) *Salmonella* Typhimurium definitive phage type (DT) 104 with chromosomally encoded resistance to ampicillin, chloramphenicol, streptomycin/spectinomycin, sulfonamides, and tetracyclines (ACSSpSuT) was first identified and characterized in the United Kingdom in the early 1990s.
- All isolates of MDR DT104 ACSSpSuT contain the same gene cassettes irrespective of source or country of origin
- Although MDR DT104 has declined during the last 5 years, the organism remains the most common MDR *Salmonella* in the United Kingdom and many other European countries
- One of the major areas of concerns was the acquisition of low level fluoroquinolone resistance

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The emergence of a *Salmonella enterica* monophasic serovar 4,[5],12:i:-

- Monophasic *S.* Typhimurium strains have rapidly increased in prevalence in cases of human illness in the EU in recent years
- Appear to be derived from the *S.* Typhimurium genetic lineages and are exactly like a pathogenic strain of *S.* Typhimurium in terms of their ability to infect and cause disease in both animals and the human population.
- On the basis of genetic similarity and ability to obtain a recognised *Salmonella* Typhimurium phage type, these emerging epidemic monophasic strains with formula 1,4,[5],12:i:- are recognised as variants derived from *S.* Typhimurium.
- During the last three years monophasic *S.* Typhimurium R-type ASSuT DT193/DT120 clonal group emerged (2007-2009) (VLA, 2010).

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Salmonella – emergence of ESBLs and other cephalosporin resistance

- Since 2000, increasing reports of ESBL and AmpC resistance has been reported from Salmonella from animals in a number of countries
  - Serotypes involved include Agona, Typhimurium DT104, Infantis, Virchow, Senftenbertg, Newport
  - Involved a variety of enzyme types including TEM, CTX-M and CMY-2
- First detected in humans in the UK in 2004 and since that time a number of different ESBLs and AmpC enzymes have been detected in *Salmonella* isolates from humans in the UK, including CTX-M enzymes and TEM enzymes.
- Small number of reports in animals in the UK (since 2008) including
  - CTX-M-1 monophasic ST (4,5,12:i) pigs
  - CTX-M-16 (+ fluoroquinolone R) Paratyphi B var Java from dog
  - AmpC CMY-2 in monophasic Salmonella from a dog
- Surveillance of all *Salmonella* isolates from animals in NI negative to date

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S. Newport – North America

- Multidrug-resistant (MDR) *S.* Newport isolates were first reported in the United States in 1998
- S. Newport causes significant clinical disease in livestock, particularly cattle, in humans, and in other animal species.
- All of these strains are resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline (ACSSuT). In addition, many of these strains show intermediate or full resistance to third-generation cephalosporins, kanamycin, potentiated sulphonamides and gentamicin.
- It has been hypothesized that use of ceftiofur, a third-generation cephalosporin licensed in the United States for use in cattle, could have selected for Newport MDR-AmpC

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MRSA -background

- *Staph. aureus* can cause a range of infections from mild skin infections, wound infections to life-threatening bacteraemias.
- Majority of strains of SA are penicillin resistant and meticillin was introduced in human medicine in the late 1950s to treat penicillin-resistant staphylococcal infection
- MRSA first emerged in hospitals in the 1970s, and by the 1990s increased dramatically worldwide, becoming a serious clinical problem in hospital environments (HA – hospital acquired)
- ~30-40% of human SA bacteraemias in UK are meticillin resistant
- In recent years a major change in epidemiology of MRSA has been observed affecting people having no epidemiological connection with hospitals (CA – community acquired)

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MRSA –companion animals

- Majority of companion animal Staphylococcal isolates are *Staph pseudointermedius*, with Staph. aureus accounting for ~10%.
- Since the 1990s, an increasing number of studies have reported MRSA infections in pet animal patients at veterinary clinics and hospitals.
- Typing studies indicate that MRSA from dogs and cats are indistinguishable from human hospital associated clones. [Suggests initial transfer from humans to pets, but both infected and healthy animal carriers can act as reservoirs from human infections].
- Clinical conditions are pre-dominantly skin and wound infections infections.
- Antimicrobial use is a risk factor for MRSA carriage in companion animals, which agrees with the evidence from MRSA epidemiology in human medicine
- Meticillin resistant *Staph pseudointermedius* (MRSP) also recognised

MRSA - production animals

- A new specific clone of MRSA (ST or CC 398) associated with farm animals was first reported in The Netherlands 2005
- The primary reservoir of ST398 in affected countries are pigs, veal calves and broilers but has also been found in companion animals and horses on farms with colonised livestock.
- In humans, colonisation with MRSA ST398 originating from pigs has been identified as an occupational risk for farmers and veterinarians and their families (EFSA, 2009).
- While overall ST398 represents only a small proportion of total MRSA in EU, in countries with low prevalence of human MRSA ST398 is a major contributor
- MRSA ST398 can be introduced into hospitals via colonised farmers and other persons in a region

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MRSA - production animals

- In particular, pigs have been acknowledged as an important source of colonisation of this MRSA strain for pig farmers, veterinarians and their families, through direct or indirect contact with pigs.

- The reason for the colonization by MRSA CC398 of pigs and other production animals, and the epidemiology of this clone are currently not known.

- As with human medicine, antimicrobial consumption is considered a driving force in the emergence and spread of CC398.

- Animals in food production and their products are therefore a potential source of community-acquired MRSA

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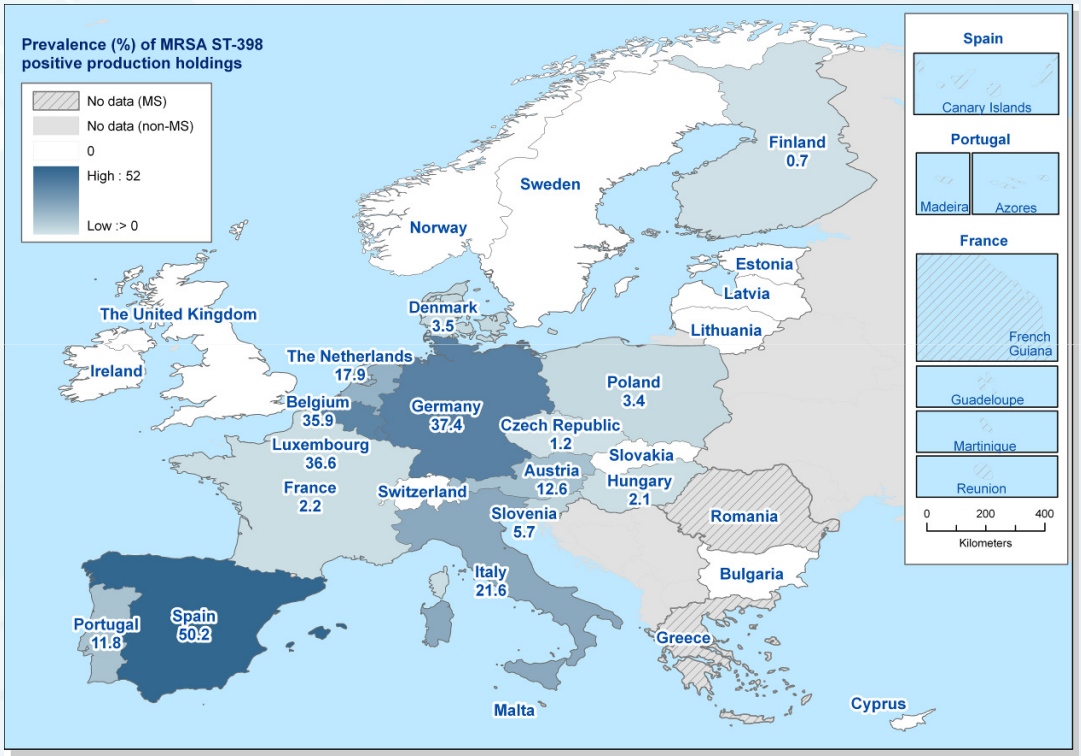
MRSA – pigs

- 2008 EU Baseline survey found MRSA ST398
  - On breeding units in 12/24 MS (0%-46%)
  - On production units in 16/24 MS (0%-50%)



Source: Analysis of the baseline survey on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs, in the EU, 2008, Part A: MRSA prevalence estimates; EFSA Journal 2009; 7(11):1376. [82 pp.]. doi:10.2903/j.efsa.2009.1376. Available online: www.efsa.europa.eu

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MRSA – cattle in UK

- First report June 2011 of novel MRSA in cattle in UK (Garcia-Alvarez et al 2011Lancet Infectious Disease)
- The isolates contained a novel *mecA* gene which is not detectable by previous PCR *mecA* tests
- Found in small percentage of humans isolates in England, Scotland and Denmark

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ESBL resistance in *Enterobacteriaceae*

- ESBL – Extended Spectrum Beta Lactamase
  - Enzymes which confer resistance to a wide range of β-lactam antibiotics
  - Significantly bacteria carrying these enzymes are resistant to 3rd and 4th generation cepahalosporins
- ESBLs are defined as plasmid-encoded enzymes found in the *Enterobacteriaceae*, frequently in *Escherichia coli* and *Klebsiella pneumoniae*
- There are a range of different ESBL groups with the predominant types being
  - CTX-M, SHV and TEM
- Bacteria carrying ESBL resistance are also frequently co-resistant to other significant antimicrobial such as the fluoroquinolones

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ESBL- human problem

- 2nd, 3rd and 4th generation Cephalosporins are frequently used in human medicine
- Since the early 2000s, *E. coli* producing CTX-M enzymes (specifically CTX-M-15) have increasingly been found in Europe in uncomplicated and complicated (including bacteraemias) urinary tract infections as well as in serious intra-abdominal and skin and soft-tissue infections
- EFSA – “the broad resistance profile…is significant in human infections and poses an on-going and worrisome public health treat”
- While person to person spread is the predominant route of infection there is concern about exposure to humans *via* food or *via* direct contact with infected animals and contaminated food or indirectly through the environment
- UK a recent dramatic increase in ESBL-producing organisms is being observed both in hospitals and in the community, mainly caused by the CTX-M-15 enzyme

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ESBL- animals

- ESBL's have also been increasingly recognised in animals
- 2004 - first report of a CTX-M E. coli from animals in the UK – calves in Wales (CTX-M-14)
- Since reported from a range of species including cattle, pigs and poultry
- IN GB (Randall et al, 2011) CTX-M-carrying E. coli were isolated from
  - 54.5% of the broiler abattoirs and from 3.6% of individual broiler caecal samples (CTX-M types 1 (mainly), 3 and 15)
  - CTX-M-carrying E. coli were isolated from 5.2% of turkey meat production farms and 6.9% of turkey breeder farms and were CTX-M sequence types 1, 14 (mainly), 15 and 55 with mainly replicon types F, FIA, K and I1-γ, respectively.
  - None of the CTX-M isolates was serogroup O25.
- First report in NI was in 2008 (CTX-M-1) from diarrhoeic calves. Since then there have been small numbers of further CTX-M isolates
- 13% of non-mastitis *E. coli* isolates from cattle were Cefpodoxime R and 40% Enrofloxacin R (VSD, 2007)

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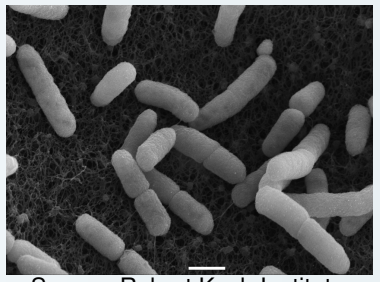
ESBL *E. coli* 104 in Germany


Source: Robert Koch Institute

- On the 21st of May 2011, Germany reported an ongoing outbreak of Shiga-toxin (vero-toxin) producing *E coli* bacteria serotype O104:H4
- 13 countries affected in Europe
- At the stage the outbreak was declared over (27 July) **782** probable and confirmed Haemolytic Uremic Syndrome (HUS) STEC cases and **3128** non-HUS STEC cases reported, of which **46** people died (Robert Koch Institute, 2011).
- Associated with fenugreek seeds imported from Egypt.
- Isolate was unusual in a number of respects
  - that at the molecular level it more closely resembled an enteroaggregative *E. coli* (EAEC)
  - HUS cases were predominantly adults
- ESBL resistant – CTX-M-15 and TEM-1 β-lactamases (resistant to β lactam antibiotics & 3rd generation Cephalosporins); reduced susceptibility to the fluoroquinolones

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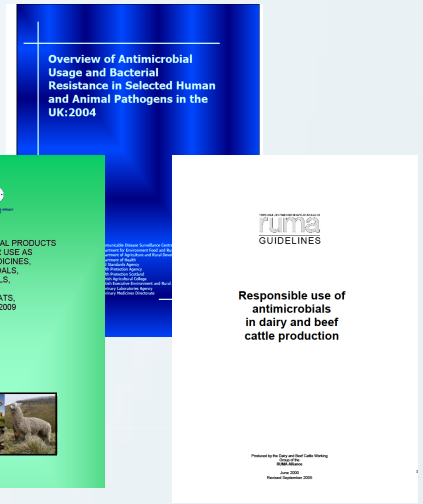
Actions to address the problem

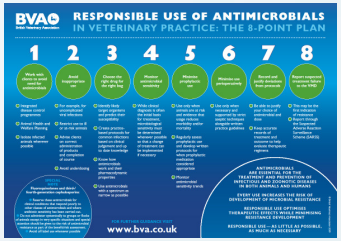
- Surveillance
  - specified requirements under EC Zoonoses Dir
  - Typically involves
    - Clinical Isolates
    - Food-borne organisms (*Salmonella* spp, *Campylobacter* spp)
    - Indicator organisms (*E. coli*, *Enterococcus* spp)

- Data on antimicobial usage
  - VMD annual publication on sales of antimicrobial products

- Promoting responsible use
  - RUMA
  - BVA
  - Defra

- Disease control
  - Biosecurity
  - Disease diagnosis
  - Promotion of health / flock health





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Calls for restriction on AM use in Animals

- CMO (Sir Liam Donaldson) Report of 2008 referred to
  - "Irresponsible antibiotic use in the agricultural sector".
  - Very large quantities of antibiotics are used in the agricultural industries, particularly in animal husbandry.
  - Some active ingredients authorised for animals are used to treat people too. Large volumes of quinolones and cephalosporins are prescribed by vets, even though they are important for treating human infections.
  - Resistant bacteria developing in animals could pose a threat to people. Antibiotics must be used in moderation in agricultural settings and only when necessary for animal welfare.

- EFSA Scientific Opinion on the public health risks of bacterial strains producing extended-spectrum β-lactamases and/or AmpC β-lactamases in food and food-producing animals (EFSA Journal 2011;9(8):2322)
  - Prioritisation is complex, but it is considered that a highly effective control option would be to stop all uses of cephalosporins/systemically active 3rd/4th generation cephalosporins, or to restrict their use (use only allowed under specific circumstances).

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Conclusions

- Use of antimicrobials exerts a selection pressure which can act as a driver for the emergence and spread of AMR clones
- Public health concerns
  - AMR in recognised zoonotic organisms
  - Circulating pool of AMR gene
- Most concerns centre on the use of fluorquinolones and 3rd / 4th generation Cephalosporins
- Steps to limit emergence and spread include
  - Surveillance of Am usage and AMR
  - Prudent use of currently available antimicrobials
  - Disease control, biosecurity

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Acknowledgements

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