Antibiotic resistance – intensive vs. extensive industries

Professor Mary Barton
University of South Australia

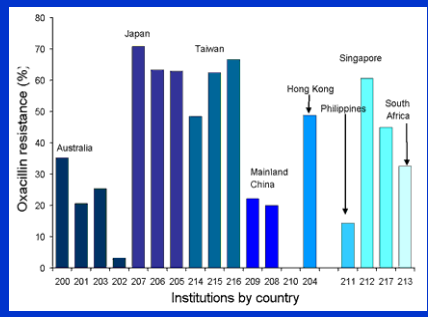
Outline

- Human health concerns
- Link between animals and humans
- Patterns of use & emergence of resistance
- Intensive industries
- Extensive industries
- Dairy industry
  - Adult cattle
  - Calf rearing units
- Future directions & conclusions

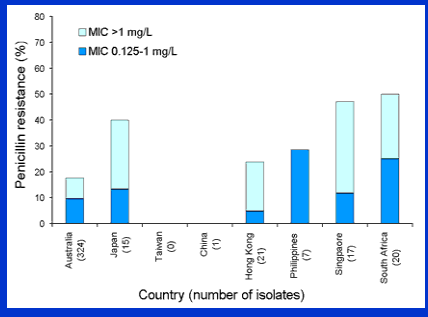
Human health concerns

- Major issues – multi-resistant *S aureus* (MRSA), vancomycin resistant *E faecium* & *E faecalis* (VRE), multi-resistant Gram-negative infections, resistance in pneumococci & gonococci, multi-resistant tuberculosis
- Lesser issues – resistant enteric bacteria - multi-resistant salmonella & *E coli*, fluoroquinolone resistant campylobacter

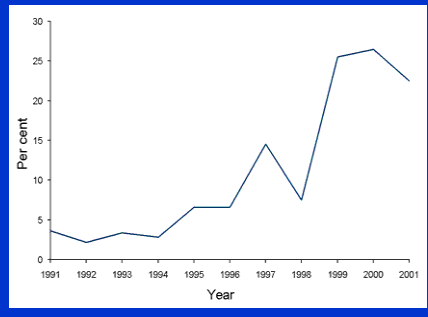
Oxacillin resistance *S aureus*– blood stream infections
(Bell & Turnidge CDI May 2003)



Pen resistant blood stream isolates *S pneumoniae*
(Bell & Turnidge CDI May 2003)



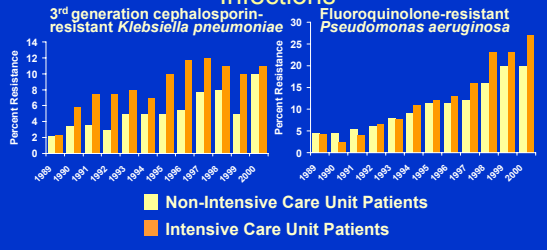
Quinolone resistance – gonococci
(Tapsell CDI May 2003)



WHO Press release – 16 March 2004

- WHO's leading infectious disease experts estimate there are 300,000 new cases per year of MDR-TB worldwide. There is also new evidence proving drug resistant strains are becoming more resistant, and unresponsive to current treatments. 79% of MDR-TB cases are now "super strains", resistant to at least three of the four main drugs used to cure TB.

Antimicrobial Resistance among Pathogens Causing Hospital-Onset Infections

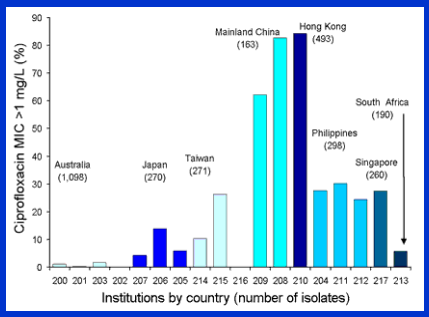


Source: National Nosocomial Infections Surveillance (NNIS) System

➢ *Link to: NNIS Online at CDC*

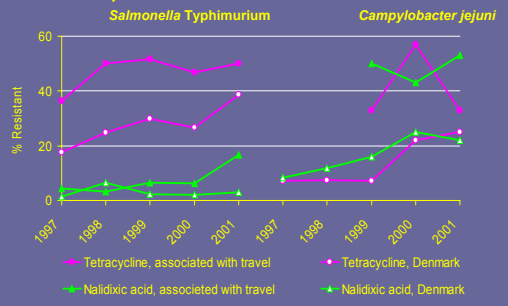
Ciprofloxacin resistant *E coli*

(Bell & Turnidge, CDI May 2003)



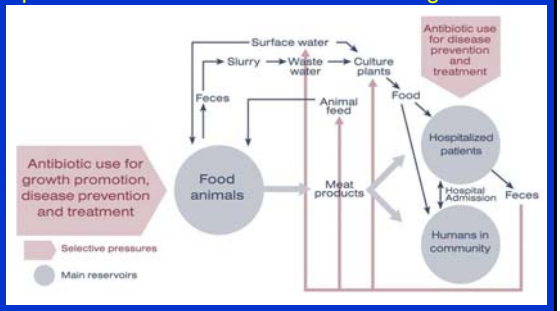
http://www.srga.org/Workshop/gbg2003/17

Tetracycline and Nalidixic Acid Resistance in Imported and Domestic *Salmonella* Typhimurium and *Campylobacter jejuni*, Denmark, 1997-2001



Source: Dept. of Gastrointestinal Infections, Statens Serum Institut, 2002.

Links between animals & humans – spread of antibiotic resistant bacteria & genes

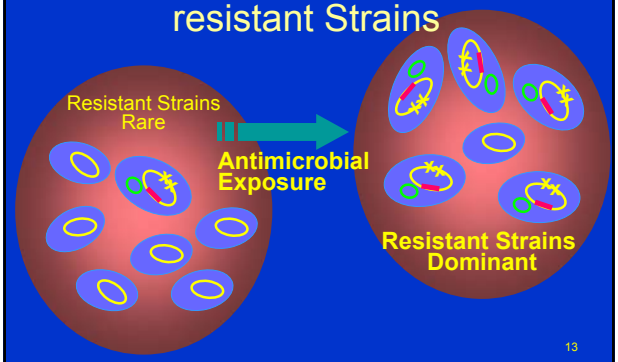


http://www.oznet.ksu.edu/

Links between animals & humans

- Inappropriate use of antimicrobials in human medicine is the major driver of human resistance problems
- Animal use is generally of less importance
  - *van*A type VRE – use of avoparcin
  - Streptogramin (Synercid®) resistant VRE – use of virginiamycin
  - Fluoroquinolone resistant campylobacter, *E coli* & salmonella
  - Multi-resistant salmonella & *E coli* – eg Salmonella Typhimurium DT 104
  - Macrolide resistance in enterococci, campylobacter – tylosin & other macrolide use in animals
  - 3rd generation cephalosporin AmpC resistance in salmonella – use of ceftiofur

Selection for antimicrobial-resistant Strains



Patterns of use

- Long term low concentration → selects for antibiotic resistant strains
- Higher concentrations tend to kill sensitive bacteria ≡ less selection for resistance
- In agriculture growth promotant use patterns tend to select for resistance:
  - Avoparcin → vancomycin resistance
  - Virginiamycin → Synercid^{R} resistance
  - Tylosin → macrolide resistance???
- Inappropriate prophylactic use patterns can also be a problem

Patterns of use

- Emergence of a problem with resistant strains in humans is a 2-step event:

Eg vancomycin

- Avoparcin use in animals → avoparcin/vancomycin resistant *E faecium* (VRE) in gut of animal → carcass contamination → VRE in gut of human. No problem – but…
- If human goes to hospital & treated with vancomycin – VRE in the gut selected & patient ends up with a VRE infection
- Note that this only applies to *van*A VRE and not *van*B VRE which is the major problem in Australian hospitals

Transfer of resistance

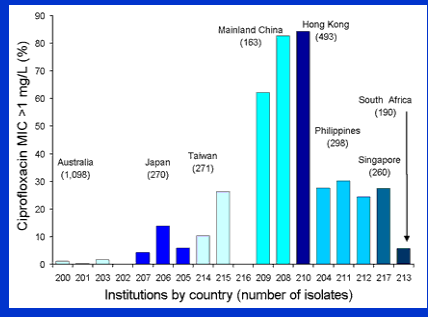
- Bacteria have the capacity to pass resistance genes from one to another
- Occurs frequently
- Often involves plasmids or other genetic elements which can carry multiple resistance genes
- Co-selection of resistant strains occurs where resistance genes are co-located on the some piece of DNA
  - Use of one antibiotic will select for strains resistant to all the antibiotics on that same piece of DNA
- The gut is an ideal environment for gene transfer - eg
  - Enterococci ↔ enterococci
  - *E coli* ↔ *E coli* ↔ salmonella
  - Non-cultivable bacteria as reservoirs of resistance genes ↔ gut commensals & pathogens

Intensive industries

- Use more antibiotics
- Use more growth promotants – low dose regimens to prevent/control chronic diseases
- Opportunities for close contact between animals increases chance of spread of bacteria between animals
- Associated most frequently with problem organisms (VRE, fluoroquinolone resistant campylobacters & *E coli*)

Ciprofloxacin resistant *E coli*

(Bell & Turnidge, CDI May 2003)



Extensive industries

- Previously not under such close scrutiny
- Less antibiotics used (generally)
- Growth promoter/production enhancers not used as much
- Some changes
  - Fluoroquinolone use (overseas)
  - Ceftiofur use

Dairy industry – adult cattle

- *S aureus* associated with mastitis - no evidence of transfer of resistance to humans
- Virginiamycin use to control lactic acidosis
- Ceftiofur – originally registered for respiratory disease; clearly also used off-label for foot rot & other conditions
- Little resistance in cattle respiratory pathogens, but ….

Ceftiofur

- 3rd generation cephalosporin – key class of antimicrobials in human medicine
- Found to be associated with emergence of multi-drug resistant salmonella in USA – resistant to ceftriaxone & up to 5 other antibiotics
  - Specific gene (AmpC CMY-2 β-lactamase)
  - Transfers from one organism to another (plasmid)
  - found in human, cattle, pig isolates
  - Increase in resistance from 0.1% to 2% in human isolates in USA over 5 years 1996 - 2001
  - Same strain in sick child & cattle
  - Now reported in Canada, Eastern Europe, Thailand, UK – in *E coli* as well as salmonella
  - Australia??

Calf rearing units

- Stressed calves
- Little or no colostrum
- Poor hygiene
- Scours & pneumonia
- Wide range of antimicrobials used – multiple resistant *E coli*, salmonella common
  - Sometimes resistant to all available antibiotics

Future directions and conclusions

- The goal must be to reduce antibiotic resistance
  - Human health
  - Animal health
  - Cost of production

Strategic approach – the “5 Rs”

- Reduce the quantities of antibiotics used
- Refine the way in which antibiotics are used
- Replace antibiotics with alternative disease treatment/control strategies
- Reverse resistance – cause a decline in the resistance of resistant bacteria
- Research “resistant proof” antibiotics

Conclusions

- Antimicrobial resistance is an issue for both extensive & intensive animal industries
- AMR is also an issue for the dairy industry
- There are strategies available to address the issue
- Medical, consumer, veterinary/agriculture & farmer groups must cooperate to attack the problem