An overview of the veterinary dimension to antimicrobial resistance

At a recent symposium on antimicrobial resistance hosted by Huvepharma in Bulgaria, Irish veterinarian, Declan O'Rourke, gave a practical overview of the veterinary dimension of this topical issue.

In many parts of the world there is a serious overuse of antimicrobials in animals and this results in public opinions such as:

- Banning antimicrobials is safer for human health.
- Antimicrobial resistance is endangering human health.
- Antimicrobials are over used so the veterinarian can make more money.
- Medicated feed is used as a growth promoter.
- Medicated feed drives antimicrobial consumption.

This begs key questions such as:

- How do we measure exposure?
- Does a lower use of antimicrobials in animals equate to less resistant infections in humans?
- Does responsible use mean less antimicrobials?
- Is antimicrobial consumption under control?

However, Dr O'Rourke stressed that:

- Antimicrobials have saved millions of human lives.
- Antimicrobials have contributed significantly to improving human health.
- Antimicrobials have contributed significantly to improving animal health.

Antibiotic-resistant bacteria[a]	No. cases of infection (four main types)[b] (% bloodstream infections)	No. extra deaths (% from bloodstream infections)	No. extra hospital days (% from bloodstream infections)
Antibiotic-resistant Gram-positive bacteria			
Methicillin-resistant Staphylococcus aureus (MRSA)	171,200 (12%)	5,400 (37%)	1,050,000 (16%)
Vancomycin-resistant Enterococcus faecium	18,100 (9%)	1,500 (28%)	111,000 (22%)
Penicillin-resistant Streptococcus pneumoniae[c]	3,500 (27%)	-[f]	-
Sub-total	192,800 (12%)	6,900 (35%)	1,161,000 (16%)
Antibiotic-resistant Gram-negative bacteria			
3rd-gen. cephalosporin-resistant Escherichia coli[d]	32,500 (27%)	5,100 (52%)	358,000 (27%)
3rd-gen. cephalosporin-resistant Klebsiella pneumoniae	18,900 (27%)	2,900 (52%)	208,000 (27%)
Carbapenem-resistant Pseudomonas aeruginosa[e]	141,900 (3%)	10,200 (7%)	809,000 (3%)
Sub-total	193,300 (9%)	18,200 (27%)	1,375,000 (13%)
Total	386,100 (11%)	25,100 (29%)	2,536,000 (14%)

[a] Data on antimicrobial resistant for Klebsiella sp. other than K. pneumoniae, Enterobacter spp. and Acinetobacter spp. were not available from EARSS. Although coagulase-negative staphylococci as well as beta-haemolytic and viridans streptococci are among the 10 most common bacteria isolated from blood cultures (20), they were excluded from the study because reliable resistance data are not available for these bacteria.
[b] Bloodstream infections, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections.
[c] Most fully penicillin-resistant Streptococcus pneumoniae isolates are resistant to both penicillin and macrolides.
[d] Resistant to cefotaxime or ceftriaxone or ceftazidime. [e] Resistant to imipenem or meropenem. [f] could not be calculated.

Table 1. Estimated yearly human burden of infections due to the selected antibiotic-resistant bacteria and percentage of this burden due to bloodstream infections, EU Member State, Iceland and Norway, 2007.

This has resulted in:

- Healthier, more productive animals.
- Lower disease incidence and reduced morbidity and mortality and good health contributes to animal welfare.
- Production of abundant quantities of nutritious, high quality, and low cost food for human consumption.
- A reduction in animal disease outbreaks that can have devastating consequences for animal health, the food supply and the economy.

He stressed that the prevention and control of animal diseases represents a top priority for the European Union and that we must not forget that animal health products contribute to the health and welfare of animals and provide a safe food supply for people.

In addition, there is a need to feed a growing population and by 2050 we will require 100% more food for mankind and some 70% of this must come by improving technologies to enhance efficiency.

When it comes to antimicrobial resistance in pathogenic bacteria the real issues are in man, so why is the concern targeted at animals where (in the EU) the issue is monitored and under control (see Fig. 1 for the Danish swine story).

If we look at antimicrobial consumption in swine across the EU on a like for like basis, and if we benchmark the Czech Republic at 100,

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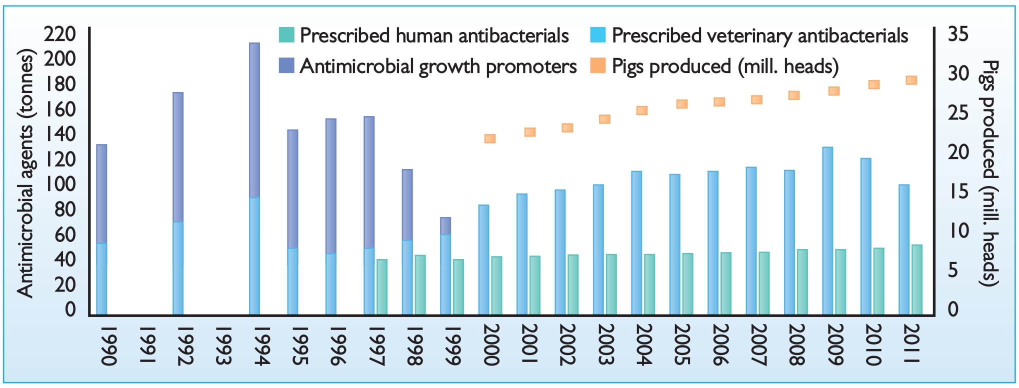
Fig. 1. Consumption of antimicrobial agents and growth promoters in animal production, number of pigs produced and prescribed antibacterials in humans, Denmark.



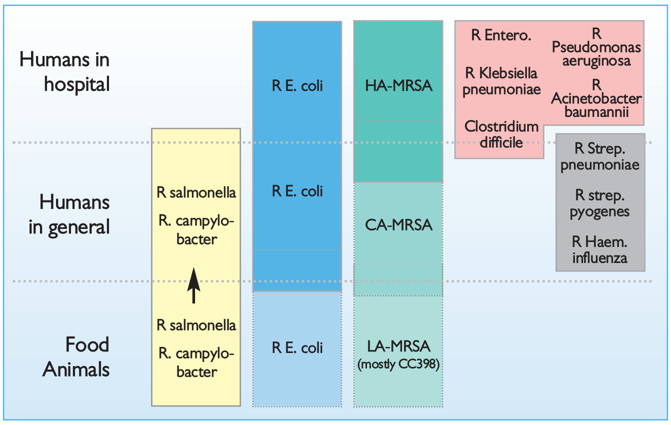


Fig. 2. Compartments of antimicrobial resistance.

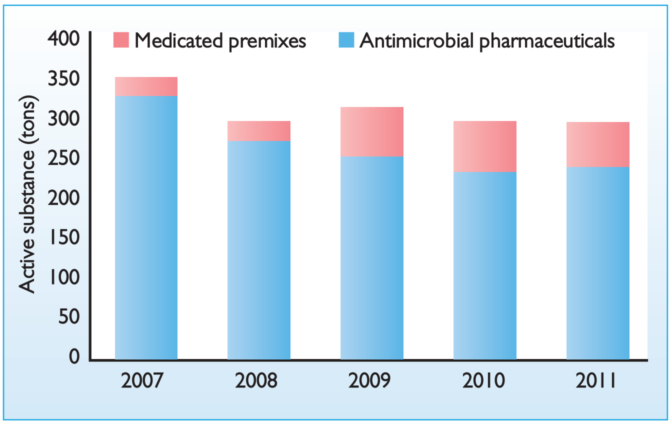


Fig. 3. Belgian consumption of antimicrobial compounds (Belvetsac).

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other countries, relatively speaking, are at 140 – the Netherlands, 120 – France, 60 – the UK, 40 – Denmark, 25 – Finland and 15 – Sweden.

If antimicrobial use in animals was banned totally there would be a substantial increase in animal disease which would mean more animal welfare issues and a severe impact on food supply.

An interesting study by Smith et al in 2007 was then cited in which 140,000 birds were reared under four different conditions:

- Commercial flocks that were given antibiotics.
- Commercial flocks that had not been given antibiotics.
- Flocks raised in a laboratory that were given antibiotics.
- Flocks raised in a laboratory that were not given antibiotics.

There were two very interesting findings. Birds raised in laboratory conditions had levels of antibiotic resistance levels comparable to what is seen on farms that use antibiotics.

This suggests that poultry come to the farm harbouring resistant bacteria, possibly acquired as they were developing in their eggs.

When it comes to human health we need to appreciate that antimicrobial resistance is a complex issue that has been occurring for millennia and that resistance genes have evolved as part of the natural competition between bacteria, leading to a vast reservoir of possible genes (including genes coding resistance to never used antimicrobials).

Antimicrobial resistance occurs in three 'compartments' – humans in hospitals, humans in the world at large and food producing animals (see Fig. 2).

In the EU, a reported 25,000 human deaths (see Table 1) are put down to antibiotic resistance and the passing of bacteria such as E. coli from farm to fork.

How many, if any, of these 25,000 deaths were related to the fact an antibiotic used in an animal led to resistant bacteria being transferred to a human? Probably none or very few!

If we look at the level of risk or odds on a human dying from various causes of death (Table 2) this helps to put death due to antibiotic resistance into context.

A recently reported study on the data relating to Salmonella typhimurium DT104 between 1990 and 2004 in Scotland (2,439 animal isolates, 2,761 human isolates) were used to investigate the patterns and diversity of resistance.

Risk of death	
Moderate – 1/100 to 1/1,000	
Smoking 10 cigarettes per day	1/200
Natural causes at age 40	1/850
Low – 1/1,00 to 1/10,000	
Influenza	1/5,000
Road accident	1/8,000
Leukaemia	1/12,000
Very low – 1/10,000 to 1/100,000	
Antibiotic resistant bacteria	1/20,100
Playing soccer	1/25,000
Accident at home	1/26,000
Antibiotic resistant bacteria of animal origin	<1/75,000

Table 2. The level of risk.

It was concluded that the sympatric animal population is unlikely to be the major source of resistance diversity in humans and that this suggests that current emphasis on restricting antimicrobial use in domestic animals may be overly simplistic!

In other words, putting antibiotics into animals does not regularly result in resistant pathogens arising in the human population via the food chain. Other routes, such as via workers or through the environment, need to be considered.

A good example to illustrate this is the occurrence of ESBL producing bacteria. These were found at levels ranging from 10 to almost 65% in samples from live animals yet none were found in milk or meat.

'Is medicated feed used as a growth promoter?' The use of antimicrobial growth promoters was banned in the EU in 2006 because of concerns about antimicrobial resistance.

The use of antimicrobials is restricted to the treatment of disease in individual animals and the treatment of 'in contact' clinically normal animals when disease present in flock or group of animals. That is in an outbreak situation.

In the EU, medicated feed is an oral administration route for antimicrobials that can only be used under the prescription of a veterinarian if it is the most appropriate route of administration.

Recent Belgian data shows the relative importance of feed and water for the administration of antimicrobials (Fig 3). However, this data should be interpreted with care as the feed route is often used for older antimicrobials that require a higher dosage in mg per kg for a longer duration of treatment (see Fig. 4).

There is a lot of evidence to suggest that a lower use of antibiotics in animals does not impact on the level in man.

A good example of this is vancomycin resistance in Enterococcus faecium and E. faecalis following the EU ban of antibiotic growth enhancers in 1999 (see Fig. 5).

In closing Declan O'Rourke returned to the responsible use of antimicrobials and stressed 'as little as possible, but as much is needed, and for the right length of time and in the right way'. Withdrawal times for meat, eggs and/or milk should be respected and he emphasised the need to ensure correct dosage is used because under dosage can lead to a lack of efficacy which could lead to resistance. ■

Fig. 5. Resistance to vancomycin in Enterococcus faecium and E. faecalis from bacteraemia, England, Wales and Northern Ireland, 1994-2007.