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Impact of antibiotic use in the swine industry

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Antibiotic resistance in bacteria associated with pigs not only affects pig production but also has an impact on human health through the transfer of resistant organisms and associated genes via the food chain. This can compromise treatment of human infections. In the past most attention was paid to glycopeptide and streptogramin resistance in enterococci, fluoroquinolone resistance in campylobacter and multi-drug resistance in *Escherichia coli* and salmonella. While these are still important the focus has shifted to ESBL producing organisms selected by the use of ceftiofur and cefquinome in pigs. In addition Livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) suddenly emerged in 2007. We also need to consider multi-resistant strains of *Streptococcus suis*. Environmental contamination arising from piggery wastewater and spreading of manure slurry on pastures is also a growing problem.

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Introduction

Antimicrobial resistance in human pathogens has been described as a global health challenge by the World Health Organisation (WHO). It is generally accepted that it is use of antibiotics in human medicine that has been the major driver for the emergence of resistant bacteria and dissemination of resistance genes but use of antibiotics in animals also makes a significant contribution. Chantziaris and co-workers [1] have described a strong correlation between use of antimicrobials and the extent of antimicrobial resistance in *Escherichia coli* isolated from livestock in a number of European countries. Interestingly the same correlation with human use of antimicrobials is more difficult to confirm [2]. Increasingly animal health authorities such as the World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation (FAO) have sought to cooperate with the WHO and many countries have taken or are starting to take action to control and reduce antibiotic use in animals [3]. Antibiotics are used extensively in intensive livestock industries such as swine production. This paper will address how and why antibiotics are used and briefly summarise the well-established link between antibiotic use in pigs and resistance in enteric organisms such as salmonella, campylobacter, enterococci and *E. coli* before addressing some of the newer and emerging problems that include methicillin-resistant *Staphylococcus aureus* (MRSA), extended β-lactamase producers, fluoroquinolone, ceftiofur, carbapenem and colistin resistance in coliforms and resistance in *Streptococcus suis*. The threat of environmental contamination will also be mentioned.

Use of antibiotics in pigs

Antibiotics are used in pigs in three main ways — as growth promoters, as prophylactic or metaphylactic treatment to prevent disease and for therapeutic purposes to treat disease.

Traditionally growth promotant use has been the most controversial because this has involved addition to pig feeds of antibiotics that are in the same chemical family as antibiotics that are valuable or critical in the treatment of human infections. Unfortunately the antimicrobial growth promotant (AGP) treatment regime creates the ideal situation for selection of antibiotic resistant bacteria and spread of antibiotic resistance genes between enteric bacteria in the pig intestinal tract in that it involves medication of pig feeds that can be fed for the whole life of the pig using low (generally subtherapeutic) concentrations of the antibiotic. Feed companies can prepare AGP medicated feeds on farmers' instructions and there is often no veterinary oversight of their use. Use of AGPs was banned by the EU in 2006 (a number had been removed from the market before that) and many other countries have significantly restricted AGPs too [3].

Prophylactic (individual animal) and metaphylactic (whole pen or herd) preventive use of antibiotics again involves addition of antibiotics to animal feeds. The intention is that the medicated feed is only used when there is a threat of an outbreak of an infectious disease and is only used for a short period of time, perhaps 5–10 days. However there is clearly the opportunity to use these medicated feeds repeatedly during one cycle of production or to use them for extended periods of time. The concentration of antibiotic in the feed is usually much higher than AGP and often at therapeutic concentrations. In most countries medicated feeds for

prophylactic/metaphylactic use require a veterinary prescription. The fact that the purpose for use is disease control means that an even wider range of antibiotics important in human medicine can be used in animal feeds.

An extensive range of antibiotics is used therapeutically in pigs. Generally pigs are dosed individually either orally or by injection although in-feed medication is used. One can question the effectiveness of the latter as the farmer cannot ensure each pig receives the appropriate dose of antibiotic and of course sick animals often experience inappetence. Therapeutic use generally requires a veterinary prescription in countries where supply of antibiotics is regulated. Interestingly US data records that significant quantities of antibiotics are used in animal feeds for therapeutic purposes [4]. Callens and co-workers in Belgium where prudent use guidelines have not been implemented reported that almost half of oral antibiotics given were at inadequate doses and that antibiotics used included some important human antimicrobials such as colistin and amoxicillin [5]. A systematic review has concluded that oral use of antibiotics in animals increases the risk of antibiotic resistant *E. coli* in treated pigs and by extension the risk of transfer of this resistance to humans [6].

There is limited information on the quantities of antimicrobials used in pigs. A Danish study reported an increase in use of tetracyclines between 2002 and 2008 but a decline in use of macrolides, sulphonamides–trimethoprim, cephalosporins and fluoroquinolones [7]. Estimates from the USA indicate that annual usage is highest for chlortetracycline (533 973 kg) and tylosin (165 803 kg) [4] whereas Canadian data suggest the penicillin (35%), tetracyclines (11%) and ceftiofur (8%) were the most frequently used antibiotics, based on reports by veterinary practitioners [8]. Jordan and co-workers reported that in Australia few of the antibiotics used for control of *E. coli* were of significance in human medicine although ceftiofur was used in almost 25% of herds sampled [9]. It is noteworthy that Denmark imposes restrictions on pig producers who use more than twice the average quantities of antimicrobials [10].

Antimicrobial resistance in bacteria associated with pigs

Enterococci

It was the detection of glycopeptide resistance in pigs in 1997 [11•] that stimulated the resurgence of concerns about antibiotic use in livestock and the resulting antimicrobial resistance. The problem was the use of avoparcin as an AGP in pigs and other livestock which had led to the emergence of *van*A vancomycin resistant enterococci (VRE) in humans consuming pork from treated pigs. These findings led to a focus on the antimicrobial resistance profiles of enterococci isolated from animals even though these organisms cause no disease in animals and are simply intestinal tract commensals. *van*B enterococci which cause human infections in many countries are not associated with avoparcin use in animals. Enterococci are intrinsically resistant to many antibiotics but antibiotics of concern include the older antibiotics such as amoxicillin and high-level gentamicin resistance. Resistance in *Enterococcus faecium* to virginiamycin, a streptogramin antibiotic as is quinupristin–dalfopristin is also an issue. This early material has been reviewed by Hammerum and co-workers [12•]. MLST was carried out on pig VRE isolates from 1986 to 2009 from the USA and Europe and it was found that clones of VRE are shared by humans and pigs (*E. faecium* CC5 and CC17 and *E. faecalis* CC2) and that these strains carry identical antibiotic resistance encoding plasmids [13]. Interestingly *E. faecium* belonging to CC5 was reported in the USA in 2010 — the first report of *van*A enterococci in the USA [14]. Avoparcin has not been used as an AGP in the USA. It has also been noted that strains of *E. faecalis* from pigs and humans in Denmark that are highly resistant to gentamicin belong to an identical clonal group [15]. A recent European study of pig *E. faecium* and *E. faecalis* reported that there was some resistance to vancomycin, substantial resistance to quinupristin/dalfopristin, little or no resistance to ampicillin or gentamicin, and no resistance to linozelid (an important human antimicrobial not used in pigs) [16]. In countries where glycopeptide resistance is still an issue in pig isolates resistant organisms can be found in the piggery environment [17,18] or the vancomycin resistance genes may be co-located with other resistance genes such as the *erm*B macrolide resistance gene where the use of macrolides in pigs is selecting for *van*A VRE [19]. Copper and zinc are frequently added to pig feeds so co-location of heavy metal resistance determinants could play a role as well [20,21].

Campylobacter

The pig intestinal tract is a reservoir for both *Campylobacter coli* and *Campylobacter jejuni* although carriage of the former is more common. Resistance rates are generally higher in *C. coli*. Resistance to macrolides is well-established and is associated particularly with decades of use of tylosin as an AGP, prophylactic and therapeutic antibiotic in pigs [22]. Tetracycline and ampicillin resistance are common and in countries where fluoroquinolones are used in livestock significant levels of fluoroquinolone resistance are recorded too [23–25]. Multi-drug resistance is common in campylobacter from pigs and pig farm environments [23]. Fluoroquinolone resistance in campylobacter is still a major issue [25–28] as this restricts options for treating serious human infections. Fluoroquinolones have never been registered for use in livestock in Australia. As a result there is negligible resistance in campylobacter, *E. coli* and salmonella from livestock and much reduced resistance rates in human isolates [29•].