Transfer of antimicrobial resistant bacteria in food

Kari Gobius

Food Science Australia
Cnr Wynnum and Creek Rds
Cannon Hill QLD 4170
Tel: (07) 3214 2036
Fax: (07) 3214 2062
E-mail: Kari.Gobius@csiro.au

Antimicrobial therapy is essential for the treatment of infectious disease in humans and animals. However, the development, spread and persistence of bacteria resistant to antimicrobials threatens the effectiveness of antimicrobial therapy. Since food is a vehicle by which people can acquire antimicrobial resistant bacteria, there are growing risks to human health posed by the selection of antimicrobial resistant bacteria in the food chain.

Why are antimicrobial resistant bacteria present in food?

Antimicrobial resistant bacteria may be present in food as a consequence of their selection and amplification due to antimicrobial use in specific food production systems. The greatest use of antimicrobials is in meat production in food animals (including poultry, pigs and cattle) and aquaculture [1]. However, horticulture production also makes use of antimicrobials [2].

While antimicrobials are used therapeutically to treat infectious disease, the greatest use in food animals is for prophylactic disease control and growth promotion. Antimicrobial growth promoters are used at relatively low concentrations, with the intent of improving the efficiency of animal feed conversion through modification of microbial populations in the animal gastrointestinal tract. The use of low or 'sub-therapeutic' concentrations of antimicrobials over extended time periods has the effect of selecting resistant bacteria and their genes.

Transfer of antimicrobial resistant bacteria to humans

During the slaughter and processing of food animals, bacteria of animal origin (predominantly from the gastrointestinal tract and hide) spread to meat products. This has been extensively documented for conventional food-borne pathogens such as *Salmonella enterica* serovar Typhimurium and *E. coli*. Similarly, when antimicrobial resistant bacteria are selected in food animals, they are also found associated with meat products.

Multidrug resistant *Salmonella enterica* serovar Typhimurium was first recognised in the United Kingdom in the 1960s when an outbreak of *S.* Typhimurium DT29 occurred in humans and cattle [3]. Intensive animal production methods, including prophylactic antimicrobial treatment of cattle, were introduced in Britain in the early 1960s.

Subsequent to the use of therapeutic and prophylactic antibiotics for the control of *S.* Typhimurium DT29 infections in cattle, isolates of *S.* Typhimurium DT29 carrying R plasmids with multiple antibiotic resistance genes were recovered from both cattle and humans. As human DT29 isolates were frequently resistant to furazolidone, an antibiotic which was not used for treatment of human salmonellosis, this strongly indicated that the multidrug resistant *Salmonella* originated in cattle and were passed to humans through food [4].

More recently, links between the use of antimicrobial growth promotants in food animals and the presence of antimicrobial resistant *Enterococcus* in humans have been established. Vancomycin and quinupristin-dalfopristin are medically important antibiotics of last-resort used for treating infections in humans. When the antimicrobials avoparcin (related to vancomycin) and virginiamycin (related to quinupristin-dalfopristin) have been extensively used for growth promotion, reservoirs of enterococci expressing resistance to these antimicrobials (as well as related vancomycin and quinupristin-dalfopristin) have built up in the treated animal populations [5]. Evidence that resistant enterococci are transmitted to healthy humans in the community by direct animal contact and through food is apparent from the isolation of identical and closely related molecular subtypes from animals, food and humans [6, 7]. Conversely, in the United States where avoparcin has not been used as a growth promotant, high levels of community vancomycin resistant enterococci are not present [8].

Resistance gene transfer in food bacteria

In most cases, antimicrobial resistance in food-borne bacteria is associated with mobile genetic elements. A notable exception is resistance to fluoroquinolone antibiotics such as ciprofloxacin or enrofloxacin where resistance is conferred by mutation in the DNA gyrase genes of *Salmonella, Campylobacter* and *E. coli*. Resistance genes are found associated with plasmids, transposons and integrons, indicating that antimicrobial resistance can be transferred between bacteria. This potential for transfer may account for the original acquisition of resistance genes by particular bacterial genera and also their ability to then further transfer such genes to other genera and species.

An illustration of resistance gene transfer is provided by the internationally significant food-borne and multidrug resistant pathogen *S.* Typhimurium DT104 which expresses resistance to five different antibiotics. Two separate integron elements within the *Salmonella* chromosome carry all five resistance genes, supporting the notion that the antimicrobial resistance determinants have been acquired by gene transfer [9].

In addition, two of the DT104 resistance genes, *floR* and *tet(G)*, are also found in the fish pathogens *Photobacterium damselae* and *Vibrio anguillarum*, indicating that these resistance determinants may have first accumulated among bacteria in aquaculture and might then have been transferred to DT104[10].

Origins

While it is clear that reservoirs of antimicrobial resistant bacteria and associated genes can accumulate in food animals and their environments after prolonged antimicrobial use, the origins of resistance genes are less certain. It is difficult to know the specific origins of resistance genes prior to their selection, amplification and dissemination; however, they may be derived from the resistance genes naturally present in antimicrobial-producing microorganisms[11].

Similarly, for particular ecosystems, it may be useful to define what are the pools of antimicrobial resistant bacteria/genes prior to antimicrobial selection pressures. For example, we have recently found that bacteria such as *E. coli, Aeromonas* spp., *Proteus* spp., *Morganella morganii*, *Shewanella* spp., and urea-positive *Providencia stuartii* isolated from grazing cattle can carry integrons encoding streptomycin and trimethoprim resistance even though the cattle were not treated with these specific antimicrobials[12]. Related bacteria and integrons were also isolated from grazing pasture and urban soils, indicating that soil is a likely source of resistant bacteria in cattle, even in the absence of antimicrobial use and selection [Barlow and Gobius, unpublished].

Conclusions

Antimicrobial resistant bacteria in food pose a risk to antimicrobial therapy which remains a vital component of human and animal health care. Reservoirs of resistant bacteria can be distributed across national boundaries through global food production and distribution networks. In turn, antimicrobial resistance genes can be distributed to food-borne pathogens, human and animal pathogens, and commensal bacteria through horizontal gene transfer. Informed and prudent antimicrobial use in food systems is a necessary part in the overall limitation of bacterial resistance to important therapeutic antimicrobial agents.

References

1. Background document for the joint WHO/FAO/OIE expert workshop on non-human antimicrobial usage and antimicrobial resistance: Scientific assessment. 2003; http://www.who.int/foodsafety/publications/micro/en/background.pdf
2. Vidaver AK. Uses of antimicrobials in plant agriculture. *Clin Infect Dis* 2002; 34 Suppl 3: S107-110.
3. Anderson ES. Drug resistance in *Salmonella typhimurium* and its implications. *Br Med J* 1968; 3:333-339.
4. Rabsch W, Tschape H & Baumler AJ. Non-typhoidal salmonellosis: emerging problems. *Microbes Infect* 2001; 3:237-247.
5. Wegener HC. Antibiotics in animal feed and their role in resistance development. *Curr Opin Microbiol* 2003; 6:439-445.
6. Bruinsma N *et al.* Different levels of genetic homogeneity in vancomycin-resistant and susceptible *Enterococcus faecium* isolates from different human and animal sources analyzed by amplified-fragment length polymorphism. *Antimicrob Agents Chemother* 2002; 46:2779-2783.
7. van den Bogaard AE, Mertens P, London NH & Stobberingh EE. High prevalence of colonization with vancomycin- and pristinamycin-resistant enterococci in healthy humans and pigs in The Netherlands: is the addition of antibiotics to animal feeds to blame? *J Antimicrob Chemother* 1997; 40:454-456.
8. Bonten MJ, Willems R & Weinstein RA. Vancomycin-resistant enterococci: why are they here, and where do they come from? *Lancet Infect Dis* 2001; 1:314-325.
9. Boyd D *et al.* Complete nucleotide sequence of a 43-kilobase genomic island associated with the multidrug resistance region of *Salmonella enterica* serovar Typhimurium DT104 and its identification in phage type DT120 and serovar Agona. *J Bacteriol* 2001; 183:5725-5732.
10. Angulo FJ & Griffin PM. Changes in antimicrobial resistance in *Salmonella enterica* serovar Typhimurium. *Emerg Infect Dis* 2000; 6:436-438.
11. Schwarz S & Chaslus-Dancla E. Use of antimicrobials in veterinary medicine and mechanisms of resistance. *Vet Res* 2001; 32:201-225.
12. Barlow RS, Pemberton JM, Desmarchelier PM & Gobius KS. Isolation and characterization of integron-containing bacteria without antibiotic selection. *Antimicrob Agents Chemother* 2004; 48:838-842.

Food Microbiology websites of interest

General

Combase
www.combase.cc

Pathogen modelling
www.arserrc.gov/mfs/pathogen.htm

Growth predictor
www.ifr.ac.uk/Safety/GrowthPredictor/

OzFoodNet
www.ozfoodnet.org.au

Websites related to food biosecurity in the US

DHS
www.whitehouse.gov/homeland/

CDC
http://www.cdc.gov/

CDC's Bioterrorism Preparedness and Response Program
http://www.bt.cdc.gov/

CDC's Health Alert Network
http://www.phppo.cdc.gov/han/

FDA
http://www.fda.gov/

FDA CFSAN
http://www.cfsan.fda.gov

USDA
http://www.usda.gov/index.html

USDA FSIS
http://www.fsis.usda.gov

PrepNet
www.fsis.usda.gov/OA/background/biosecurity.htm

National Disaster Medical System
http://www.oep-ndms.dhhs.gov/

FEMA
http://www.fema.gov/

Incident Command System
http://www.uscg.mil/hq/g-m/mor/Articles/ICS.htm