Standing Committee on Finance and Public Administration

ANSWERS TO QUESTIONS ON NOTICE

Inquiry into the Progress in the implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antibiotic Resistance March 2013

Agriculture, Fisheries and Forestry

1. **The Department's and APVMA's submissions note that a significant range of actions were taken following JETACAR and outputs from some of those actions.**
    - **Is possible to have some information linking the actions to evaluated outcomes? For example, what has been achieved in terms of outcomes, such as where antimicrobial resistance has been slowed down or reduced, or where infection rates have been reduced?**

The APVMA regulatory processes acknowledge Australia's conservative approach to the registration and use of veterinary antimicrobials. To manage the risk of antimicrobial resistance posed by the veterinary use of antimicrobials, the APVMA undertakes rigorous and comprehensive risk assessment on all new antimicrobials for use in animals, major extensions of use of existing antimicrobials and reviews of currently registered antimicrobials, in accordance with Part 10 Special Data Requirements as per JETACAR Recommendation 4, which were updated in 2000 and 2006.

The second JETACAR recommendation (under the broad theme of Regulatory Controls) asked the APVMA to review three categories of antibiotics, based on those antibiotics not appearing to fulfill the Recommendation 1 criteria to adopt a conservative approach to antibiotic registration.

1. glycopeptides (avoparcin)
2. streptogramins (virginiamycin)
3. macrolides (tylosin, kitasamycin, oleandomycin)

Avoparcin

This review was discontinued, as the registrants of avoparcin products did not renew their registrations after 30 June 2000 and the products were voluntarily withdrawn from the market. Avoparcin was considered, through selecting for the Van A gene resistance factor, to be contributing to the overall level of resistance of vancomycin. Surveys of vancomycin resistance in *Enterococcus faecalis* isolated from Australian health care institutions showed an increase from approximately 5% of isolates in 2003 to over 35% of isolates in 2010.[1] However, interpretation of this data is complex as much of the observed resistance increase may be due to the Van B gene or other resistance mechanisms.

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[1] J Pearson, K Christiansen, J Turnidge, J Bell, T Gottlieb and N George on behalf of the Australian Group for Antimicrobial Resistance (AGAR) *Vancomycin resistant enterococci in Australia: results of the AGAR surveys 1995 to 2010* < http://www.agargroup.org/publications > at 17 April 2013.

Virginiamycin

The APVMA released a final virginiamycin review report in 2004. An outcome of the review was to limit use of this antimicrobial to therapeutic and short-term treatment only. This decision was successfully challenged in the Administrative Appeals Tribunal by the registrant. The end result of this legal challenge was an agreement to amend the labels to allow ongoing use of virginiamycin under tighter prescribing arrangements, by reference to the Australian Veterinary Association's Prescribing Code of Practice. Once the Code of Practice changes were made, the APVMA was in a position to finalise the labels as agreed with the registrant. These changes were gazetted in March 2012.

Macrolides

One of the consequences of the virginiamycin AAT proceedings has been that the macrolides review has been effectively 'stalled' since a similar outcome would be expected. Currently, there are no plans to reactivate the review.

Collection of data on antibiotic usage

In regards to the use of antibiotics in animals, Australia has no mandatory mechanism or legal framework to collect detailed information on the usage in different animal species. The collection of such data would be complicated as the label restraints for use of many registered antibiotics include more than one species. The APVMA has however instituted a program which collects information from registrants of antimicrobials on the quantity of antimicrobials sold by volume. It is reasonable to assume that there is a close relationship between the quantities of antimicrobials sold and amounts used in animals. Although submission of data to APVMA is voluntary, compliance with the request has been high. In 2003, the APVMA published its first report on the quantity of antibacterial products sold for veterinary use in Australia, for the period July 1999 to July 2002.

Due to resource constraints there was a gap in the collection of data. The next report, to be published this year, will cover the period July 2005 to June 2010.

2. **The Australian Chicken Meat Federation in its submission provided some useful tables, which appear to indicate that resistance levels are very low in the Australian poultry industry, relative to a range of other countries.**

   a. **What information on antimicrobial resistance rates and infection rates does the government collect and publish across a broad range of animal food products in Australia?**

Australian Government responsibility for food safety is shared at different levels across FSANZ, DoHA, and DAFF. DAFF in the past has published antibiotic resistance rates in animals from projects it has funded/coordinated. The most recent example is the 2007 DAFF Pilot Surveillance Program 'Antimicrobial Resistance in Bacteria of Animal Origin'. The results of that survey compared favourably with like studies conducted overseas. DAFF currently is not directly funding/coordinating any projects into antibiotic resistance rates in animals or in food products. Rather it is working in partnerships with others, especially through the SAFEMEAT partnership, to monitor AMR developments. A current project on antimicrobial resistance rates across food products co-funded by an Australian Government agency is the CSIRO and Meat and Livestock Australia project 'Antimicrobial Resistant Bacteria in Red Meat Production in Australia'. A report of this project is expected to be published in 2014.

3. If antimicrobials were no longer used for prevention and growth promotion in animals:

a. Would antimicrobial resistance decrease?

JETACAR acknowledged that the use and overuse of antibiotics in human medicine 'is the major factor contributing to the development of antibiotic resistance', while noting that the use of antibiotics in food animals contributed to the overall AMR burden.

A 2002 WHO Report on the 'Impacts of Antimicrobial Growth Promoter Termination in Denmark'[2] found strong evidence that the termination of antimicrobial growth promoters reduced the food animal reservoir of enterococci resistance to these growth promoters. Clinical problems in humans related to resistance to antimicrobial growth promoters were however rare in Denmark before and after termination. Termination of antimicrobial growth promoters was not found to change the incidence of food borne diseases thought to be associated with the consumption of pork and poultry. These findings provide some reassurances considering the practice of using antimicrobials as growth promoters has been in existence for many decades. In this study the termination of antimicrobial growth promoters also coincided with the increased use of antibiotics for therapeutic purposes.

In Australia, a large proportion of antibiotic growth promoters used in animals are of the polyether/ionophore class. These antibiotics are not used in humans to combat bacterial infection and their mechanism of action and high degree of specificity means they are unlikely to contribute to the development of antibiotic resistance to important human drugs.

Data available in Australia is insufficient to indicate whether the discontinuation of sales from 2000 of avoparcin had any impact on the incidence of the vancomycin resistant *Enterococci* (VRE) type A (Van A) (Van A is the VRE type that has been associated with avoparcin use) or other bacteria of human clinical importance.

Studies on antibiotics used at therapeutic levels to treat or prevent disease in humans generally show a proportional relationship between usage and resistance. A similar relationship would be expected in animals. It is for these reasons that Australia has adopted a highly restrictive approach to the use of antibiotics in animals that are regarded to be of critical importance to human health.

b. What studies have been done to determine the impact of food prices?

DAFF is not aware of studies done to determine the impact of antimicrobial resistance on food prices. Owing to the number of variables that impact the price of any given food commodity, the confidence that could be placed on such studies would be expected to be

[2] <http://www.who.int/gfn/en/Expertsreportgrowthpromoterdenmark.pdf> viewed at 8 April 2013.

low. What is known is that the use of growth promoters can result in an improvement in daily growth rates up ten per cent, and meat with less fat and increased protein content.[3] The cost to farmers of using antibiotic growth promoters is typically outweighed by the increased financial returns from increased production. There are also environmental benefits through reduced greenhouse emissions from animals.[4]

A consideration for impacting food prices is that if AMR surveillance testing was to become a requirement such as through the Food Standards Code, the cost of testing would likely be passed on in food prices. AMR testing of imported food would also likely require the testing of domestic food to conform to Australia's obligations under the World Trade Organization agreements.

4. Please provide the committee with trends in infection rates of common resistant microbes in animals in Australia and overseas?

There are significant amounts of data on resistance levels in animal pathogens. Comparing data to look for trends in resistance in animal pathogens has however overall proven to be problematic for reasons including differing sampling points along the animal-food supply chain, differing laboratory testing/interpretation methods, and the intermittent nature of studies into particular bacteria. These issues are acknowledged by the World Organisation for Animal Health (OIE) which is working to provide solutions to these problems. This is also one of the reasons why standardised and integrated ongoing surveillance and monitoring systems are advocated. These issues also mean that comparisons against resistance trends in the same bacteria in humans are difficult.

A summary of the few Australian studies on resistance levels in Australia to common animal microbes can be found in Professor Mary Barton's paper to the APVMA Science Fellows Symposium, April 2010.[5]

Food animal species seldom experience infection and disease problems identifiable to multi-drug resistant bacteria like that seen in the human population – that is disease from bacteria resistant to last line of defence antibiotics. Infection and disease associated with bacteria such as vancomycin-resistant *S. aureus* (VRSA), or extended spectrum beta-lactamase (ESBL) *Enterobacteriaceae* are very rarely seen in animals compared with the human population. Animals may however be carriers of such bacteria in the absence of disease symptoms[6].

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[3] Eg. see Hughes P and Heritage J, *Antibiotic Growth-Promoters in Food Animals*, FAO <http://www.fao.org/docrep/007/y5159e/y5159e08.htm> viewed at 8 April 2013; Thomke S and Elwinger K, *Growth Promotants in Feeding Pigs and Poultry II; Mode of Action of Antibiotic Growth Promotants*, Annales de Zootechnie, 1998, No 47, pp 153-167; Prescott JF and Baggot JD, *Antimicrobial Therapy in Veterinary Medicine* (2nd Ed, 1993) pp 564-565.

[4] Eg. see Mathison, GW et al., *Reducing methane emissions from ruminant animals*, Journal of Applied Animal Research, 1998, Vol 14, Issue 1, pp 1-28.

[5] <http://www.apvma.gov.au/news_media/docs/symposium_2010/4_mary_barton_summary.pdf> viewed at 4 April 2013.

[6] Eg. see Axon JE et al., *Methicillin-resistant Staphylococcus aureus in a population of horses in Australia*, Australian Veterinary Journal, 2011, Vol 89, No 6, pp 221-5.

5. **Please provide the committee with trends in resistance rates or percentages for common resistant microbes in animals in Australia and overseas?**

   See answer to question 4.

6. **Would you be able to provide the committee with trends on where infections by common resistant microbes are acquired by animals? Where possible, please provide information differentiated by:**

   a. **geographic location; and**

   b. **each part of the supply chain from farm to prepared food.**

The development of antibiotic resistant strains generally occurs as a result of a genetic mutation in a bacteria's chromosome, or from the transfer of an antibiotic resistance gene from another resistant bacterium. Once the genetic mutation or gene acquisition has occurred, the bacterium is able to grow in the presence of antibiotic. Naturally resistant organisms are also favoured. It is generally accepted that the use of antibiotics for whatever reason will result in an increase in antibiotic resistance.[7] Thus where greater levels of antibiotics are used, the expectation is that the chances of the development of antibiotic resistant strains will be higher.

Resistance in animal bacteria usually emerges in the part of the supply chain where the antibiotics are used – in the live animal. It is also recognized that the potential exists for resistance to develop in the environment where antibiotic residues exist from animal/human waste or antibiotic disposal. Once resistance develops, it can spread, particularly where selection pressure continues through the use of antibiotics. Most resistant bacteria in animals are acquired from other animals or their waste through usual routes of bacterial transmission. Where antibiotics are no longer used, wild-type non-resistant strains usually regain their domination of the bacterial population of the animal owing to the 'biological fitness cost' of maintaining resistance, which makes resistant bacteria less competitive in bacterial populations where selection pressure from antibiotic use no longer applies.

As meat is further processed after slaughter, its bacterial flora will increasingly include organisms transferred from people handling the food and from contaminated surfaces. HACCP-based quality assurance programs in the various food sectors seek to limit contamination along the supply chain. It is also significant that most food of animal origin is consumed after cooking or preserving. Through these activities the risks of food-borne transmission of resistant bacteria of animal or human origin is accordingly reduced.

There are very few examples of where an antibiotic resistant microbe has developed in a geographic sense. Also where resistance to a particular antibiotic by a particular species of bacteria exists in different countries, it is possible resistance in the two countries has evolved separately and/or that different resistance mechanisms may exist. A further complication in making conclusions about the geographic emergence of AMR in bacteria of

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[7] Woolridge M, *Evidence for the Circulation of Antimicrobial-Resistant Strains and Genes in Nature and especially between Humans and Animals*, OIE Antimicrobial Resistance in Animal and Public Health, 2012, Vol 31, No 1, pp 231-241.

animal origin is that the limited surveillance data often precludes comparisons between different areas over time.