

Senate Finance and Public Administration References Committee

Inquiry into the progress in the implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antibiotic Resistance.

Submission from Emeritus Professor Mary Barton AO, BVSc, PhD, Dip Bact, MBA, FACVSc, FASM.

Transparency statement: I was a member of JETACAR and the subsequent Expert Advisory Group on Antimicrobial Resistance (EAGAR). I am a Science Fellow of the Australian Veterinary Medicines and Pesticides Authority (APVMA) and on occasions review applications and material for them. I am an active member of the Australian Veterinary Association but have not been involved in their Therapeutic Advisory Group. I am an active researcher in antimicrobial resistance but have never received any funding or benefits from pharmaceutical companies apart from the supply of some antimicrobials not available commercially. I was previously Professor of Microbiology at the University of South Australia and now hold an emeritus position there. This submission reflects my personal views and not those of any organisation with which I have been or am associated.

a. **Steps taken (since the JETACAR report), their timeliness and effectiveness.**

Below find comments on each of the recommendations accepted by the government in August 2000.

- i. Antimicrobials registered for growth promotant purposes should not be used unless of demonstrated efficacy and they are rarely or not used at therapeutic agents in human or animal medicine and are unlikely to impair therapeutic use of antimicrobials through development of resistance.

While no new growth promotant antimicrobials have been registered since JETACAR a number continue to be used. Most are in classes distinct from classes of antimicrobials used therapeutically but some macrolides such as kitasamycin and tylosin are still registered as growth promotants. Whilst most use of antimicrobial growth promotants has shifted from over the counter availability to prescription only, the use pattern is still that of growth promotant use ie used for extensive periods of time or even the whole life of the animal. Any use of macrolides will facilitate the spread of *erm* and other macrolide resistance genes and can lead to macrolide resistance in important human pathogens such as *Campylobacter jejuni*, *Mycoplasma pneumoniae* and *Streptococcus suis*. In addition, use of macrolides as growth promotants compromises their effectiveness in treatment of animal diseases caused by organisms such as *Lawsonia intracellularis*, *Clostridium perfringens* and *Mycoplasma* spp. Co-location of other resistance determinants macrolide resistance genes will allow for selection of resistance to other antibiotics when macrolides are used.

- ii. Reviews of the use the growth promotant classes – glycopeptides, streptogramins and macrolides.

Avoparcin (glycopeptide) was voluntarily withdrawn from the market by the manufacturer in mid-2000 before any proposed review could commence. Virginiamycin (streptogramin) was reviewed and it was recommended that growth promotant use cease and that its use be permitted by prescription for a limited number of conditions and that the period of therapy

be limited. The decision was appealed and it is not clear what the final outcome really was but in the end virginiamycin has become a prescription only antimicrobial but the duration of use is not really adequately controlled. The macrolide review was started by EAGAR but was stopped when there virginiamycin decision was appealed.

iii. A scheme for auditing and reporting on antimicrobial use in humans and animals

The APVMA has established a voluntary scheme with veterinary pharmaceutical companies but the results are not transparent and reports are much delayed. It is not clear if anything has been done with human antimicrobials.

iv. The then National Registration Authority (NRA) to evaluate new applications and extension of use of antimicrobials for use in animals by applying the Special Data Requirements for registration of veterinary antimicrobials.

In fact EAGAR carried out Part 10 (special data requirements) risk assessments on all new applications and extensions of use for all veterinary and human antimicrobials referred to it by APVMA and various health authorities. However, EAGAR only survived until 2007. This system worked very well as there was both medical and veterinary expertise on EAGAR and the reviews for all antimicrobials were carried out carefully and thoroughly. The risk assessment process was used to ensure that antimicrobials of critical importance in human medicine were controlled in veterinary medicine and that use of critical human antibiotics was also properly managed in human medicine. Unfortunately since EAGAR has been disbanded the APVMA has had to rely on individual assessors some of whom perhaps are not aware of some of the antimicrobial resistance issues in human medicine and the role of animal use in amplification of resistance genes that could be transferred to human pathogens. The demise of EAGAR also meant that new products with the same active antimicrobial component were registered without due consideration – so for example five companies (instead of one) now have ceftiofur (3RD generation cephalosporin) products registered for use in cattle (see comment about this later) and this no doubt extends the use of this critical (for human medicine) antimicrobial in animals. In addition, there is also a 3rd generation product (cefovecin) registered for use in cats and dogs. This product would not have been registered had EAGAR or an equivalent advisory group been in existence.

v. Determination of threshold or trigger rates of antimicrobial resistance for antimicrobials used in animals

EAGAR struggled with this and had not been successful in finding a solution before it was disbanded. One problem was the lack of data provided by the pharmaceutical companies in their applications to register products. There was (is) rarely any molecular data in applications and relevant information on phenotypic resistance is usually quite limited. Applications from veterinary pharmaceutical companies are particularly deficient in relevant antimicrobial resistance data.

vi. That all antimicrobials for use in humans and animals (including fish) be classified as S4 (prescription only).

The then National Registration Authority moved very quickly to review the scheduling of antimicrobials then not scheduled as S4. Most antimicrobials were rescheduled but it is disappointing that some human as well as animal products remain non-S4.

- vii. That the then ARMCANZ implement harmonised approach to control of use antibiotics

To some extent this has been done but the result is very disappointing in that the lowest common denominator approach was finally used to get all of the States and Territories on board. In some jurisdictions veterinarians can prescribe and dispense whatever antimicrobials they like provided the use is not specifically prohibited. They can use antimicrobials “off-label” with no constraints at all in cats, dogs and horses and can manipulate off-label use in livestock. Provided an antimicrobial is registered for use in one livestock species in most situations vets can use that antimicrobial in all livestock species, even if it is not registered for use in that species. One particular problem is the extension of use of the critically important antimicrobial ceftiofur to a wide range of animal species including pigs and poultry when it is only registered very specifically for treatment of respiratory disease and foot infections in cattle. Clearly it is used for a wider range of conditions in cattle too. The emergence of compounding pharmacies since JETACAR further complicates the problem as APVMA has no control over them and they can formulate anything and everything – so for example they can prepare formulations of enrofloxacin (a fluoroquinolones, a key human antimicrobial class that is not registered for use in any livestock species in Australia) quite legally for use in horses – but that formulation is eminently suitable for use in other livestock species and in aquaculture. It is clear that from time to time vets illegally dispense some antimicrobials and the “free” availability from compounding pharmacies makes illicit use much easier.

- viii. Amend State and Territory legislation to make it an offence to prescribe and or use a veterinary chemical product (antimicrobial) contrary to a label restraint.

As indicated above implementation of this seems to be imperfect.

- ix. TGA to implement requirement for resistance data to be included in applications for registration of human antimicrobials, implement threshold/trigger points of resistance, include resistance prevalence data in product information

This was discussed by EAGAR but I do not know what has happened since 2007.

- x. Comprehensive surveillance program for antimicrobial resistance

You could sum this up as – no action because no-one was/is prepared to pay for it. There are some limited human programs largely run on a volunteer basis with very little funding. DAFF conducted a very limited pilot study of antimicrobial resistance in carcass isolates of *E coli* and enterococci – 150 isolates each from cattle, pigs and chickens; 150 isolates of campylobacter from chickens were also tested. This was completed in 2004 and there has been nothing since. FSANZ conducted an even smaller pilot study of antimicrobial resistance

in some isolates from foods. The situation is a total disgrace and Australian Health and Agriculture authorities should hang their heads in shame.

xi. Comprehensive monitoring and audit system for antibiotic usage.

Thanks to the hard work and dedication of one hospital pharmacist in SA there is now a small voluntary system for monitoring antimicrobial use in hospitals. Funding for this seems tenuous. No doubt the Pharmacy Guild would have the data for community pharmacies but this was not made available to EAGAR and I don't know if the situation has changed. The APVMA has established a voluntary scheme with veterinary pharmaceutical companies but the data is crude, not transparent and much delayed. Clearly as veterinary surgeons in Australia have the privilege of both prescribing and dispensing antimicrobials used in animals they should be required to keep records and resources provided by government to collect and collate the information.

xii. Implementation of HACCP based food safety programs

There has been a roll-out of HACCP based programs to improve food safety and clearly this will assist in reducing transmission of antimicrobial resistant enteric organisms. In addition there is now much greater emphasis on on-farm QA programs and these also contribute to improved food safety and reduced transfer of antimicrobial resistant organisms. Some of these programs require farmers to record all chemicals used on the farm but I am not sure that this awareness would lead to reduced antimicrobial use.

xiii. Intensive animal industries to invest in non-antibiotic strategies to replace use of antimicrobial growth promotants

This is complicated because many of the antimicrobial growth promotants contribute to mitigation of subclinical disease caused by enteric organisms such as *Serpulina hyodysenteriae* and *Lawsonia intracellularis* in pigs and *Clostridium perfringens* in meat chickens; ruminal upsets such as bloat can be a problem in cattle and sheep fed grain-based rations. The pig industry has clearly taken antimicrobial resistance very seriously and the Pork CRC has a strategy to reduce antimicrobial use by 50% in 5 years. Unfortunately the other industries do not recognise a problem and so antimicrobial resistance is a low priority or seen as a public health issue that is not their responsibility.

xiv. Department of Health – surveillance of hospital-acquired infections

I do not know what has been done since 2007 but there was no action prior to that.

xv. Codes of practice for prudent use be developed and regularly updated

I can only comment on veterinary codes. The current codes are deficient and do not adequately address antimicrobial resistance. The Codes developed by the Australian

Veterinary Association have been developed by livestock industry and pharmaceutical industry vets from a perspective that ignores mechanisms of antimicrobial resistance, spread of resistance genes between bacteria and transfer of antimicrobial resistance from animals via the food chain or direct contact between animals and humans.

xvi. Antibiotic use guidelines

There is human Therapeutic Guidelines and many overseas countries have veterinary guidelines – but there are none in Australia.

xvii. Continuing education programs on antibiotic resistance

In the last two years there have been two programs organised by medical colleagues on antimicrobial resistance. There was little veterinary involvement in developing the program for the first session. Interestingly a medical specialist discussed antimicrobial use in animals which many of the attending veterinarians found unacceptable. However the second session was jointly organised and resulted in a much better shared understanding of medical and veterinary issues. Hopefully this cooperation can continue. It has been very difficult to get the Australian Veterinary Association to take antimicrobial resistance seriously –with the notable exception of the current past-President who facilitated the holding of a forum on antimicrobial resistance. Many vets would prefer to ignore antimicrobial resistance as it is just seen as getting in the way of their service to their clients. In veterinary schools although the microbiologists will educate students about responsible antimicrobial use and the risks to animal and human health from antimicrobial resistance, once the students get into the clinical years this is dismissed as irrelevant by many of the clinician veterinarians and the vets with whom they do work experience.

xviii. Funding agency support for research into antimicrobial resistance

The NHMRC does not fund much work around the topic of antimicrobial resistance. It wants sexy cutting edge research publishable in high ranked academic journals and so does fund some esoteric molecular research but not practical research that might provide some tools for addressing the antimicrobial resistance problem. I was the beneficiary of funding from RIRDC Chicken Meat, the then Pig Research and Development Corporation and then Australian Pork Limited to carry out some baseline studies and the Meat and Livestock Australia have funded some work in the beef feed lot industries. Other industry funding bodies appear to have no interest – some respond that antimicrobial resistance is a public health issue and so research should be funded by the NHMRC.

xix. Community education

NDPSC has run some programs but there seems to be no government interest in this area.

xx. DAFF and Health cooperate to develop a communications strategy etc

No action at all to the best of my knowledge.

xxi and xxii coordination of the resistance program

EAGAR was established in 2001 to take over from the WGA but was disbanded by NHMRC after 6 years. Between 2008 and 2009 NHMRC had a small medically focussed group, the Expert Panel on Health Advice. More recently Health has established another medically-focussed advisory group. Health was totally unresponsive and disinterested for all the time EAGAR was active. Health and Agriculture did establish a Commonwealth Interdepartmental JETACAR Implementation Group (CIJIG) as a joint committee to implement the JETACAR recommendations but they rarely met and did nothing. Any actions arising from JETACAR were carried largely by EAGAR with cooperation from APVMA , the then NDPSC and TGA.

b. Where and why failures occurred

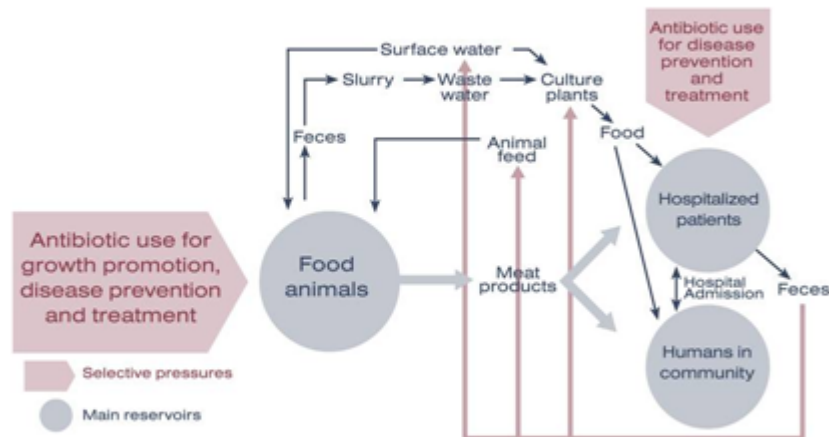
1. The complete failure of CIJIG – it seemed that DAFF did try to get CIJIG to meet regularly and to take on its responsibilities – but Health had no interest. It was almost as though Health felt that it had established JETACAR so the job was done.
2. The failure to implement comprehensive antimicrobial resistance surveillance and antimicrobial use monitoring schemes – it seems government was/is unwilling to fund
3. The disbandment of EAGAR as this meant APVMA no longer had access to advice on human health implications of registration/changes in use of veterinary antimicrobials. It also meant that there was no champion of antimicrobial resistance.
4. Location of EAGAR in NHMRC - EAGAR should have been in the communicable diseases area of health. NHMRC operates on 3 year cycles and sees working groups as temporary and used for task-and time-bound activities. EAGAR did not fit into this category. It is interesting that NHMRC refused to provide advice to APVMA in the later stages of EAGAR and after its demise.
5. The failure of medical and veterinary organisations to take up antimicrobial resistance as an issue (EAGAR tried to get their interest) and promote continuing education in responsible antimicrobial use – why did this happen? Hard to fathom except that they obviously saw other medical/veterinary issues as more important.
6. Failure of the States and Territories to implement strong uniform control of use legislation – probably the same problem as trying to get the States to agree on anything.

c. Implications of antimicrobial resistance on public health and the environment

This is a huge topic but there is a very body peer-reviewed literature setting out the serious implications of antimicrobial resistance to human health – directly from use of use of antimicrobials in human medicine and indirectly from animals or from environmental exposure.

It has taken humans a while to learn but any use of antimicrobials will select for resistant strains in the bacterial population. Bacteria have been dealing with inimical chemicals in their environment for billions of years and the antimicrobials we have exposed them to over the last 60-odd years are just another challenge. The short generation times means that mutational changes are almost sure to yield strains with a mutation that renders them resistant to whatever is causing them problems before the whole population is killed.

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



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

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<http://www.ksre.ksu.edu/bookstore/pubs/mf2593.pdf>

Antimicrobial resistance cannot be considered in isolation within human or veterinary medicine as microorganisms spread between humans, animals and the environment and antimicrobial resistance genes spread between bacteria.

- d. Implications for ensuring transparency, accountability and effectiveness in future management of antimicrobial resistance.

Antimicrobial resistance needs to be given a high priority by Health and Agriculture Departments at both Commonwealth and State government levels and Health needs to take responsibility for coordinating strategies to:

- Reduce antimicrobial use in human and veterinary medicine by ensuring antimicrobials are only used when needed
- Facilitate continuing education for medical and veterinary practitioners – including veterinary school clinicians – in responsible use of antimicrobials
- Establish programs for of antimicrobial resistance surveillance and monitoring of antimicrobial use
- Ensure control of use legislation at State level really does ensure use of antimicrobials is controlled appropriately

- Establish an open and transparent process by which Health provides appropriate advice to APVMA on the medical implications of registration or changes in use of antimicrobials
 - Ensure all antimicrobials are prescription only S4 drugs
 - Establish dedicated funding for research into practical aspects of antimicrobial resistance
- e. Any other related matter
- i. Antibiotics are just as important in veterinary medicine as they are in human medicine. Bacterial infections livestock must be controlled to ensure a healthy food supply and also to protect the welfare of animals. Similarly bacterial infections must be controlled in pet and companion animals. Many of the antimicrobial resistance problems in human health relate to use (sometimes inappropriate) in humans. Animal Health and Medical authorities must work together to resolve the problem. Attempts by some in the medical area to ascribe the whole problem to animal use of antimicrobials should cease and veterinarians who deny any link between use of antimicrobials in animals and human health problems must be re-educated.
 - ii. Antimicrobial use in aquaculture is a not well controlled and should be investigated
 - iii. The emphasis on testing imported and domestically produced foods for antimicrobial residues should be expanded to include antimicrobial resistant bacteria
 - iv. The need to control compounding pharmacies and their capacity to provide antimicrobials in any formulation should be investigated.