AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

Australian One Health Antimicrobial Resistance Colloquium

Background Paper

July 2013

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Purpose of the Colloquium

The Australian Antimicrobial Resistance Prevention and Containment (AMRPC) Steering Group was established in February 2013. The Steering Group is jointly chaired by the Secretaries of the Department of Health and Ageing (DoHA) and the Department of Agriculture, Fisheries and Forestry (DAFF). The Commonwealth Chief Medical Officer and Chief Veterinary Officer are also members. The Steering Group is providing high level governance and leadership on this important issue, and will oversee the development of a comprehensive National Antimicrobial Resistance (AMR) Prevention and Containment Strategy for Australia.

AMR extends across both animal and human health and to achieve real progress, Australia's response must take a whole-of-system perspective and be joint, coordinated and workable across governments, industries, educators, health and veterinary professionals, and the community. The Australian Government also recognises that responding effectively to the challenges of AMR will involve a combination of regulation, monitoring and surveillance, targeted activity on specific organisms, research and education. To this end, the Steering Group recently endorsed the overarching framework for the development of the Australian National AMR Prevention and Containment Strategy. The key elements of the framework are:

- Governance;
- Surveillance;
- Infection prevention and control;
- Regulation;
- International engagement;
- Communication (which includes Education, Stakeholder engagement and Partnerships); and
- Research.

The Steering Group has committed to consult with stakeholders in developing the Strategy, and has convened the Australian One-Health AMR Colloquium to commence this process. The forum will bring together food/animal and health experts to discuss key 'one health' priorities and strategies to address AMR in Australia, with particular reference to surveillance strategies, regulatory measures and the most significant zoonotic AMR risks. The outcomes of the Colloquium will assist DoHA and DAFF in identifying gaps and priorities for action, and inform advice to the Steering Group on next steps.

Funding of $11.9 million over three years has been committed in the 2013-14 Health Budget to support the development of the Australian National AMR Prevention and Containment Strategy.

Introduction

AMR is a critical health issue, with urgent action being called for by the World Health Organization.[1,2] Some resistant bacterial pathogens that were originally primarily the concern of hospitals are now seen with increasing frequency in the community, and patients are arriving in hospitals carrying resistant bacteria acquired in the community setting, both in Australia and overseas. These bacteria produce infections that are difficult to treat and impact clinical care.

AMR contributes to increased patient illness and death, the complexity of treatments and the duration of hospital stay.[3,4] All of these factors result in substantial increases to health care system costs and financial burden to the community. It has been estimated that AMR adds more than $250 million per year to the Australian health-care budget and costs the community as much as $500 million per year.[5]

The evolving threat AMR presents to human health is demonstrated by international and Australian evidence showing that AMR, including multidrug resistance, is increasing among many pathogens responsible for infections in health-care facilities and in the community.[6,7] Moreover, the frequency of resistance to antibiotics used to treat human pathogens is rising at varying rates in different parts of the world; the highest rates outside of Europe are observed in Asia, Africa and South America.[3]

The situation is exacerbated by the ability of many bacteria to share genetic material and pass on resistance genes, and the inadvertent transportation of resistant bacteria through international travel and medical tourism.

Micro-organisms, antimicrobials and antibiotics

Micro-organisms include bacteria, fungi, parasites and viruses. While many exist in an innocuous relationship to human health, some are essential to normal human life while others cause significant illness and death. Some exist normally in the human body but can cause infections under certain circumstances, such as following a dental extraction, a penetrating injury, or when the normal immunity of a person is reduced due to illness or various forms of medical treatment such as cancer therapy. When the health of a person is threatened by an infection, antimicrobials play a key part in controlling that infection.

Antimicrobials may be used against bacteria (e.g *Staphylococcus aureus,* TB), viruses (e.g HIV), fungi (e.g. candida) parasites (e.g malaria) and as disinfectants. Antibiotics used against bacteria are by far the most commonly used antimicrobials and their use and resistance to their effect is the focus for this paper.

Antibiotics used for treatment and prophylaxis are essential for complex surgery, intensive care, organ transplants, survival of people with suppressed immune systems and the elderly.[2,8]

Antibiotic mechanisms of action

There are a large number of antibiotics available for the treatment of bacteria that cause infections. These can be grouped according to aspects of their molecular structure and/or according to their mechanisms of action against bacteria (Table 1).

Table 1: Mechanism of action of different groups of antibiotics

Mechanism of action	Antibiotic group
Inhibits cell wall synthesis	*B-lactams (penicillins, cephalosporins, carbapenems, monobactams), bacitracin, glycopeptides*
Inhibits protein synthesis	*Aminoglycosides, aminocycitols, amphenicols, macrolides, lincosamides, streptogramins, tetracyclines*
Interferes with cell membrane function	*Polypeptides*
Interferes with DNA/RNA synthesis	*Quinolones, rifamcyins*
Inhibits metabolism	*Sulfonamides, sulfones, trimethoprim, nitrofurans, nitroimidazoles*
Unknown	*Polyethers*

Antibiotics that are very specific and target particular organisms or groups of organisms are referred to as narrow spectrum antibiotics. Antibiotics that are active against a wider range of organisms are referred to as moderate or broad spectrum.
Examples of antibiotics that differ in their spectrum of activity include:

- narrow spectrum e.g. benzylpenicillin which is mainly active against gram positive organisms;
- moderate spectrum agents e.g. amoxicillin, first and second generation cephalosporins that are effective against a wider range of organisms; through to
- broad spectrum agents e.g. piperacillin combined with a beta lactamase inhibitor, carbapenems and 3rd and 4th generation cephalosporins that are active against a wide range of organisms.

Best practice is to prescribe the antibiotic with the narrowest spectrum of action to cover the known or likely pathogens.

Since the innovation of antibiotics, there have been discoveries of new classes of antibiotics and modifications of existing antibiotics to improve the clinical effectiveness of existing antibiotics [2]. These are sometime referred to as *second-*, *third-* or *fourth-generation* antibiotics. Many of these modifications have been driven by increasing emergence of resistance to the earlier antibiotic.

AMR and antimicrobial uses in humans, animals and their environments

The emergence and epidemiology of AMR is determined by a complex (and largely uncertain) interaction of environmental, epidemiological, clinical and behavioural factors in humans, animals and agriculture.[6]

Humans

The term 'antimicrobial resistance' or AMR is used to describe microorganisms that have developed the ability to resist the effect of antibiotics that have been in use.

Within several years of the introduction of antibiotics in the 1930s and 40s, some bacteria developed mechanisms to combat the antibiotics in use.

AMR occurs when antibiotic levels that would normally prevent growth or kill a particular bacterium become ineffective because of a change in the bacterium. An antibiotic is no longer clinically effective when this occurs at a therapeutic dose for treatment of infection.

All antibiotics in common use for human health have been impacted by this phenomenon. While some antibiotics were able to be used for several decades before resistance was seen, for others the time difference for the development of resistance has been much shorter. Those antibiotics where the development of resistance has been slower, notably vancomycin, were highly valued because of their continued ability to treat infections that had become impervious to other commonly used antibiotics. The increasing level of vancomycin resistance is now an example of significant concern as some types of bacteria, such as Vancomycin Resistant Enterococci (VRE), have changed their profile from being of little concern in human health, to a cause of significant morbidity and mortality, particularly in hospital settings.

Figure 1 shows for a range of antibiotics the time lag between their introduction and the first appearance of resistance.[9] It is of note that the duration between release of an antibiotic and development of resistance since 1970 has been significantly shorter.

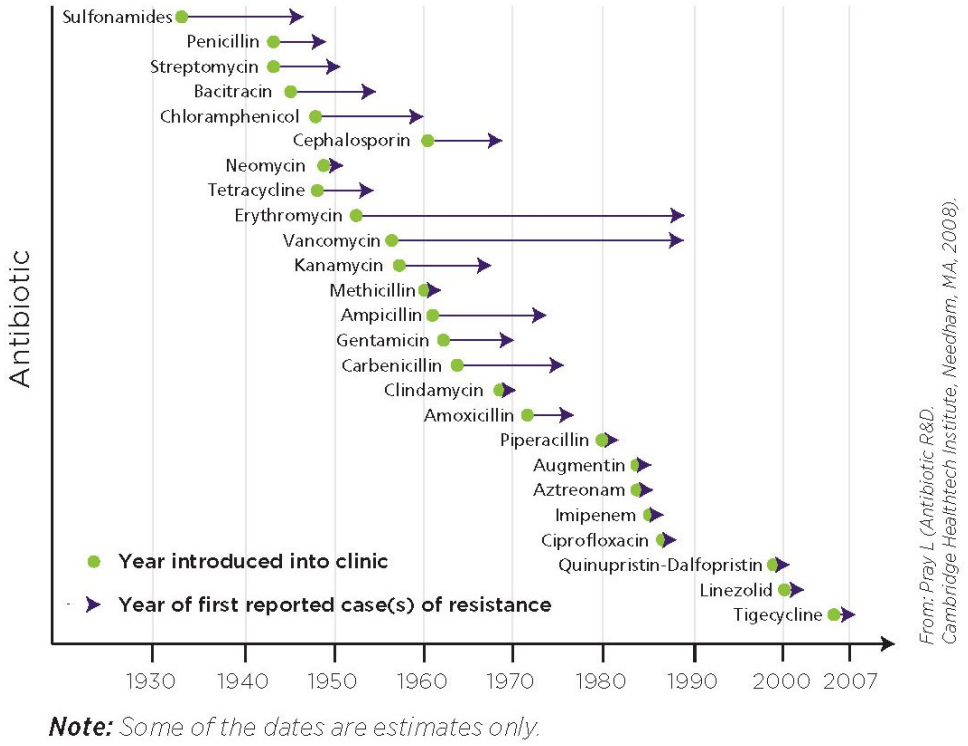

Figure 1: Time lag between an antibiotic being introduced to clinical use and the first appearance of resistance

One of the current challenges in addressing AMR is the lack of development of new antibiotics. Two key factors that are thought to contribute to this lack of new products. First, in the current world of complex treatments and interventions, pharmaceutical companies pursue more profitable causes than the development of new types of antibiotics.

Second, it is difficult to justify the expenditure required for research and development in a commercial environment when it has been demonstrated that resistance to a new antimicrobial is likely to emerge within a foreseeable timeframe, rendering the new product less marketable.

Therefore, while one strategy that must be considered in addressing AMR is finding ways to promote research into new antimicrobial agents, we cannot rely on this alone to solve the problems.

There are two stages in the emergence of antibiotic-resistant bacterial strains:

- *Genetic mutation or gene acquisition* – resistance arises due to a *mutation(s)* in the relevant gene(s) in the bacterial chromosome, or because the existing antibiotic resistance gene is transferred into the bacterium from another resistant bacterium (*gene acquisition*).
  Many mutations confer resistance to more than one antibiotic. Exposure to one antibiotic can enable resistance to other antibiotics of the same class *(cross-resistance)* and because the genes for resistance are often close to each other, when this genomic material transfers between bacteria, all the resistance genes are transferred together *(co-transfer*).[2] Exposure to one class of antibiotic may then select for resistance to an unrelated class.
- *Selective advantage* - once a resistance gene or mutation is present (and is expressed), the cells containing it are able to grow in the presence of the antibiotic and therefore increase in numbers at the expense of susceptible cells. Naturally resistant organisms are also favoured. The total amount of antibiotic used is a general indicator of the selection pressure and continuous exposure to an antibiotic provides the strongest selection pressure.

The use of antibiotics in humans is the primary cause of antimicrobial resistance in humans. Moreover, there is overwhelming evidence that the use and overuse of antibiotics has been a powerful selector of resistance.[11]

What is understood less well is the relative contributions of transmission routes, resistance determinants and antimicrobial selective pressures in animals, humans, and the broader environment on the amplification of AMR.

In addition to the increased transmission of antibiotic resistance between bacteria as a result of antibiotic use, the other contributor to the spread of AMR is the physical spread of resistant bacteria to Australians from one environment to another (e.g. animal to human or vice versa) and the geographical spread of resistant bacteria. Such spread can occur through direct contact (e.g. between animal and human, human and human) or indirectly (e.g. in food or water). The spread of resistant organisms globally is well documented and presumably due to movement of hosts or contaminated products between locations (including continents).[12] Although there are examples of resistant bacteria spreading from one geographical region to others, it is unclear to what extent this movement contributes to the problem of AMR in humans.

What can be said is that there are multi-resistant bacteria identified outside of Australia for which there is no effective antimicrobial therapy. Appearance of these organisms in Australia will almost certainly be as the result of geographical spread of the particular bacteria by human or other vectors.

Animals

Antimicrobials have a variety of uses in animals. These include use in companion animals (notably dogs, cats and horses), aquaculture, bees and livestock (principally poultry, pigs and ruminants such as cattle, sheep and goats). They are used for therapeutic, prophylactic, and growth promoting purposes and are regarded as important for animal health, welfare, and production.

A major indication for antibiotic use is for the prevention of disease, and this use pattern has become an integral part of modern industrialized food-animal production, to the extent that the feed for growing animals maintained intensively commonly includes antimicrobials to prevent or treat infectious diseases. This use, together with improvements in biosecurity, infection control, genetics, nutrition and management has facilitated earlier weaning, higher animal densities, and lower morbidity and mortality with the intent of improved health and welfare and increased outputs and lower prices of meat.

Internationally, it is estimated that the volumes of antimicrobials used in food animals exceeds the use in humans worldwide, recognising that the total number and mass of animals produced each year may exceed that of humans. Many of the classes of antimicrobials that are used for humans are also used in food animals, including the critically important classes of drugs such as third- and fourth-generation cephalosporins and fluoroquinolones.[11]

Antimicrobials are important therapeutic substances across a wide range of animal health sectors. Of the agents prescribed by veterinarians, there are a number of classes that are considered of critical importance in human health. Foremost amongst these classes are the third-generation cephalosporins and the quinolones, including the fluoroquinolones and the carbapenems.

Small animals

A wide range of antibiotics is registered for use in companion animals. Of those agents from classes considered of critical importance in human health, cefovecin (Convenia®) is a third generation cephalosporin administered as an injection that is claimed to provide therapeutic concentrations for 14 days. It is one of the more commonly used antibiotics in cats due to its efficacy and increased compliance as it avoids the difficult task of giving tablets to cats.[12] Fluoroquinolones are used in dogs

and cats, [13] although in Australia they are typically reserved for severe infections or as a second-line antibiotic.

Horses
Ceftiofur, a third generation cephalosporin is registered for use in horses. No fluoroquinolones are registered for use in horses. Commonly used antibiotics include penicillin, gentamicin, oxytetracycline, and trimethoprim-sulphonamide.

Poultry
Antimicrobial use in Australian poultry is very limited. This is mostly attributed to the high standards of disease prevention as well as the very short life of meat chickens and residue concerns in eggs (Barton 2012).[14] No cephalosporins or fluoroquinolones are registered for use in poultry. Antibiotics which are used more commonly include tetracyclines and sulphonamides. There is, however, widespread usage of anticoccidial agents to prevent coccidiosis, almost none of which have human equivalents.

Pigs
There is widespread use of antibiotics in the pig industry to deal with the respiratory and gastrointestinal disease problems. Multi-drug resistant isolates have been found in Australian pigs. The Pork CRC is very aware of these issues and currently is embarking on a 5 year goal to significantly decrease their use in the industry.[14] Commonly used antibiotics include oxytetracycline, erythromycin, lincomycin, olaquindox and amoxicillin.

Cattle/Sheep
There is significant antimicrobial use particularly in the more intensive practices of feed-lotting (e.g. to control respiratory diseases and problems with feeding grain/high energy feeds) and dairy farming (particularly for mastitis control). Only limited AMR data for these species are currently available. As part of filling this information gap, Meat and Livestock Australia are currently in the process of funding a project *Antimicrobial Resistant Bacteria in Red Meat Production in Australia.* This project is scheduled for completion in May 2014.

Ceftiofur, a third generation cephalosporin is registered for use in cattle for respiratory infections. It is also commonly used to treat foot infections in dairy cattle as it has no milk withholding period.

There is use of in-feed antibiotics in both cattle and sheep. Products include ionophores, macrolides (e.g. tylosin) and virginiamycin. The latter is used to reduce the risk of lactic acidosis where high levels of grain are fed.

Aquaculture
There are no antibiotics registered by the APVMA specifically for use in aquaculture. The small market for antibiotics in Australian aquaculture is a disincentive for pharmaceutical manufacturers to invest in product registration for this sector.

Australian aquaculture producers may use antibiotics for treatment of aquatic animal diseases under the minor use permit (MUP) system. MUPs have specific conditions to ensure efficacy and safety. The conditions include requirements for authorisation by a veterinarian, reporting of use to state regulators, adherence to specified uses, directions for use, environmental monitoring, and withholding periods. MUP conditions require that all fish released for human consumption have residue levels below the Australian maximum residue limits. In some jurisdictions, requirements may exceed MUP conditions; for example, regulatory approval may be required for each instance of antibiotic use. MUPs currently exist for oxytetracycline and florfenicol (an amphenicol) use in Atlantic salmon and trout.

Imported aquarium fish can be exposed to antibiotics in their country of origin and there have been reports of antimicrobial resistance in bacteria associated with these fish. Currently, all aquarium fish imported into Australia are quarantined post arrival and all water used in transport is sterilised before disposal. Imported ornamental fish do not enter the human food chain. The aquaculture industry has developed a number of vaccines to assist in the control of bacterial diseases.

Bees

Oxytetracycline is APVMA registered for use in bees. It is typically used in the treatment of European Foul Brood, a bacterial disease. Supplying or prescribing treatments for diseases of bees requires the same responsibility from veterinary surgeons as all other treatments, particularly because any treatment of bees which are producing honey has the potential to produce residues in the honey.

Zoonotic Transmission

Transmission of resistance from animals to humans can take place through a variety of routes, where the food-borne route is thought to be the most important. Most infections with enteric bacterial pathogens, such as *Salmonella enterica and Campylobacter coli/jejuni* probably occur through this route in industrialized countries, although in Australia, limited evidence suggests that only a small proportion of these two pathogens harbour important resistances. For other pathogens, direct contact between animal and humans may be the major route of transmission (e.g., MRSA).

Bacteria as well as antibiotic residues from food-animal production and from human hospitals are spread widely in the environment, mainly with waste. Thus, the environment and its fauna and flora have the potential to become reservoirs of resistance and a source of reintroduction of resistant bacteria into the food-animal and human reservoirs[11].

The public health consequences of zoonotic antibiotic resistance are invariably difficult to assess for a number of reasons: the epidemiology is highly complex because it involves complex production and distribution systems of animals and food, it involves the spread of bacterial clones as well as resistance genes, and, finally, the impact on public health includes several end points that are difficult to determine[15].

Livestock Production

Regulatory Environment

Overall, Australia can be regarded as having one of the most conservative approaches to antibiotic approval and use in livestock production in the world. Australia has a highly restrictive approach to the use in production animals of antibiotics regarded to be of 'critical importance' to human medicine. These include quinolones and fluoroquinolones. Fluoroquinolones are currently not used in food animals in Australia unlike in most other countries.

In Australia, the Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian government statutory authority responsible for assessing and registering veterinary antibiotics into the Australian marketplace. This includes the conducting of independent resistance risk assessments as recommended by JETACAR. The APVMA also monitors the quantities of antibiotics used in food producing animals. In 2010, 359 tonnes of antibiotics were used in food producing animals in Australia. The APVMA can issue permits (e.g. Minor Use Permits) if necessary for unregistered treatments.

Nearly all veterinary antibiotics are classified as Schedule 4 under the *Poisons* Standard, meaning that they can only be sold/dispensed on prescription by a registered veterinarian. The control of use of antibiotics is regulated at the state/territory level. Differences exist between jurisdictions in their control of use laws, particularly in the area of 'off-label' prescribing rights. 'Off-label' prescribing is writing a prescription or authorisation to a client to allow them to use a registered drug or veterinary chemical in a manner outside the range of uses permitted by the APVMA approved label directions - including species of animal, dosage, treatment interval etc, but not contrary to a specific label restraint. Work continues through the COAG review process to harmonize state/territory control of use laws in the veterinary and agricultural sectors.

Overseas practices in crop production

Antibiotics have had successful application in plant disease control overseas where the more traditional plant protection methods have been inadequate, however they are not currently used by the agronomy and horticulture sectors in Australia. Use of pesticides and veterinary medicines in Australia, including antibiotics are regulated by the APVMA. Currently no antibiotics are approved for use on food producing plants in Australia, and as such, no maximum residue limits for any antibiotics on plant products have been established by the APVMA or Food Standards Australian New Zealand (FSANZ).

In 2011, the Australian Government permitted the importation of apples from New Zealand subject to meeting specified conditions. In response to concerns regarding the possible introduction of the bacterial disease fire blight into Australia, industry has been in discussion with the APVMA regarding requirements for obtaining an emergency use permit and/or registration should there be detections of fire blight within Australia to allow the use of streptomycin by Australian producers. No formal application for such a permit has been made. In addition, FSANZ has completed a risk assessment on the use of antimicrobials in some New Zealand apple orchards in response to concerns about possible health and safety risks on imported apples from New Zealand. The antimicrobial, streptomycin is used in a small proportion of New Zealand apple orchards (about five per cent) to control the plant disease fire blight. Following its risk assessment FSANZ has concluded there is a negligible food safety concern. This view has been confirmed by internationally recognised experts in the field of antimicrobial resistance, who have peer-reviewed the FSANZ assessment.

Research and Development (R&D)

Australia invests significant resources in research and development (R&D) activities to improve the health and welfare of livestock including R&D focused on genetics of disease resistance, vaccine

development, infection prevention, and alternatives to antibacterial agents to improve animal productivity. These activities all serve to reduce the reliance on antibiotics. Research and development priorities are independently determined by individual industry bodies, but AMR has been a focus before and since the JETACAR Report.

Current monitoring of antibiotic use in animals

The Department of Agriculture, Fisheries and Forestry (DAFF) monitors the scientific literature and is aware of the increasingly complex One Health dimensions of AMR emergence involving incompletely understood interactions between the environment, animal and human populations.

At the industry level, the Australian Veterinary Association has developed *Guidelines for Prescribing, Authorizing and Dispensing Veterinary Medicines*. Various regulatory bodies and agricultural sectors have also produced standards/codes of practice to manage antibiotic use and their consequences. There is also a high level of reliance placed on Hazard Analysis Critical Control Point (HACCP) based safety standards in minimizing bacterial carriage in foods and subsequent potential food-borne transmission of antibiotic resistant bacteria. Imported food is expected to be produced to the same level of hygiene as domestically produced food. Antibiotic residues are monitored under the National Residue Survey (NRS), with current testing results showing a very high level of compliance with labelled directions for use conditions. The NRS does not test for AMR patterns in bacteria isolated from livestock/products.

Figure 2 illustrates the epidemiology of AMR in terms of human, animal, agricultural factors.

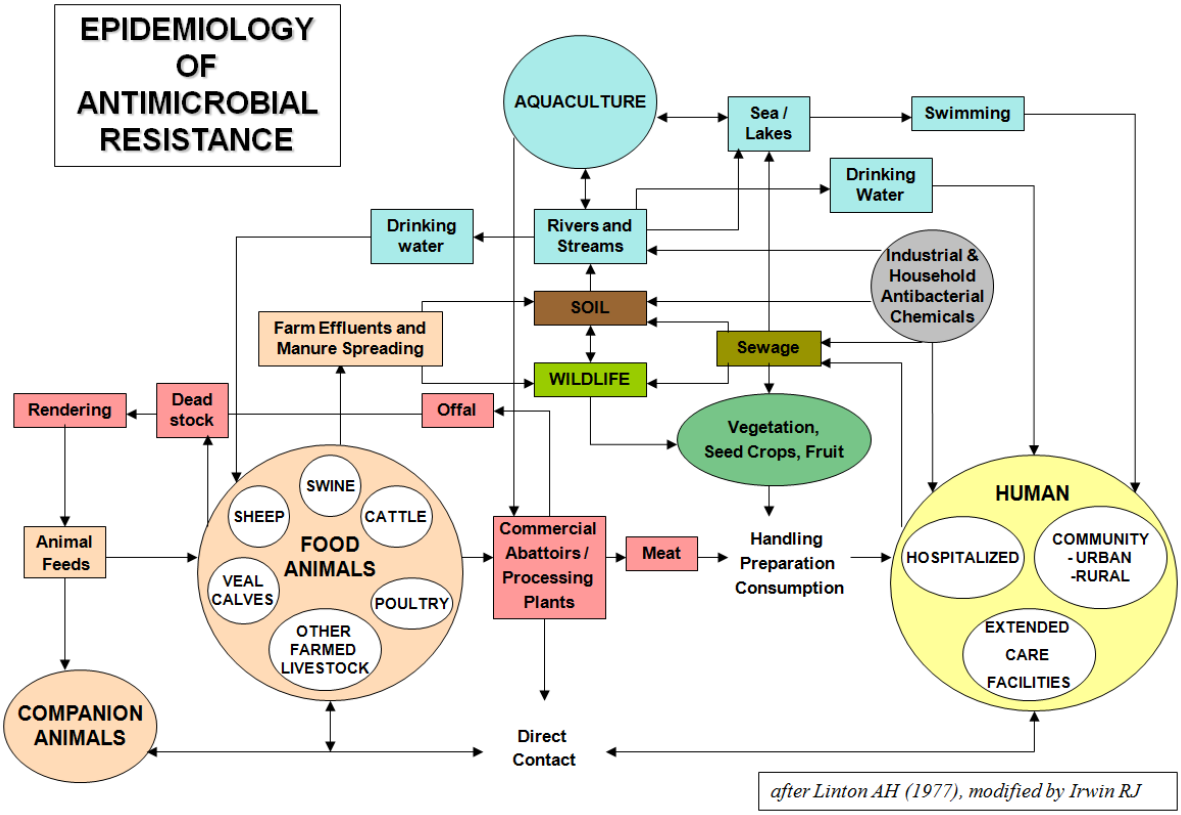

Figure 2: Factors in AMR epidemiology

Key aspects for consideration in formulating a national response

Reducing antimicrobial usage will be one element of a comprehensive national approach to preventing and containing the spread of AMR in Australia. Reducing inappropriate antimicrobial usage requires collaboration between experts, regulatory authorities, and producers, and integrated monitoring of the effects of interventions is essential. Therefore a One Health approach, which encourages the collaboration between medical and health professions, veterinarians, farmers, food safety specialists, and other experts is critical in the monitoring and control of activities when addressing transmission of zoonotic and commensal AMR bacteria[15].

National AMR surveillance programs

Information on the prevalence and trends of antimicrobial resistance is needed at the local, national, and international levels to guide policy and detect changes that require intervention strategies. Such monitoring programs should be continuous and standardized, enabling comparison between countries as well as over time. The main aspects to be considered in establishing a monitoring system include animal or food groups to be sampled, the number of samples to take and the strategy for collection, bacterial species to be included, methods for susceptibility testing, antimicrobials to test, breakpoints to use, quality control, data to be reported, analysis and interpretation of data, and reporting[16].

AMR surveillance systems that demonstrate high levels of uptake and produce information that is useful at both local and national levels for driving developments in policy and practice across broad networks and geographies typically exhibit most, or all, of the following features:[9]

- centralised coordination and direction setting, involving clinical experts and policy makers;
- standardised datasets derived from pathology laboratory systems;
- quality assured laboratory services providing the data;
- structured data submission and management protocols;
- a defined set of organisms, antibiotics and specimen sites for which data are gathered (which may be narrow or broad);
- a high level of participation from pathology laboratories in all sectors;
- a centralised database that receives laboratory data, preferably online;
- a centralised data-processing location that is resourced to undertake analysis and facilitate reporting;
- publicly available online access to reports and information that addresses a range of priorities and purposes;
- defined funding support, usually from government;
- the ability to link with data from other systems, such as those monitoring antimicrobial use, and AMR in animal and food sources;
- the ability to demonstrate trends across time, between geographic locations and between population groups, such as inpatients and outpatients;
- the ability to promptly detect and support investigation of emerging threats;
- outputs that support policy development at a national level, and guideline development and modification at a local level; and
- regular reports that measure and report on the impact of interventions.

Consideration of mechanisms to reduce inappropriate antibiotic use

Antimicrobial stewardship is the key approach being used by health clinicians, health service providers and national organisations including the Australian Commission on Safety and Quality in Health Care and NPS MedicineWise to reduce the inappropriate use of antibiotics in humans.

Improvement in antimicrobial stewardship in health services in Australia is strongly reinforced by the explicit requirement for demonstration of antimicrobial stewardship as part of the National Safety and Quality Health Service (NSQHS) Standards. Accreditation against these NSQHS Standards is a Ministerially-mandated requirement for all Australian hospitals and day procedure centres from January 2013.

Studies have demonstrated that changing the way antibiotics are used in humans does result in a decrease in the level of resistance seen in bacteria of interest to human health. A study published in the United States in 2012, showed the association between a seasonal increase in antibiotic use in winter each year over a nine year period, with a corresponding increase in antibiotic resistance in a range of bacteria, lagging the antibiotic consumption trend by a month.[17]

Some European countries have banned the use of certain types of antibiotics in food animals, and other changes in practice have been achieved through widespread but voluntary changes in farming practice. This seems to have resulted in a significant reduction in the level of AMR in important bacteria.[18]An encouraging feature of these studies is the demonstration that decreasing antibiotic use leads to a decrease in the level of resistance seen.

The Codex Alimentarius Commission (CAC), under the United Nations' World Health Organisation and the Food and Agriculture Organisation (FAO), provides recommendations for the responsibilities of regulatory authorities, the veterinary pharmaceutical industry, veterinarians, and wholesale and retail distributors and producers.[15] In Australia the AVA and the International Dairy Federation (IDA) has provided guidelines for the appropriate selection and use of antibiotics.

In response to risks posed by offshore AMR, DAFF actively participates in the World Organisation for Animal Health (OIE), Codex and FAO initiatives on AMR. These include raising the awareness of AMR, development of standards and expertise/capacity building roles. There is significant scope to increase work in these areas.

Preliminary List of Potential Approaches for Limiting Antibiotic Use in Animals

a) **Drug Approval.** All drugs intended for human or animal use undergo an approval process before licensing. The traditional risks that are considered in the approval process include proof of efficacy against the target pathogen, target animal safety, environmental safety, and human health safety with a focus on toxicological effects (residues). For example, in Australia, fluoroquinolones have never been approved for use in food animals. Fluoroquinolone-resistant strains are either at very low levels or nonexistent in food animals.

b) Fluoroquinolone use in humans has also been restricted by a variety of measures, mainly through the instrument of the Pharmaceutical Benefits Scheme. The rates of fluoroquinolone resistance are also very low in human isolates in comparison to other countries (e.g., community onset bloodstream infection resistance rate in *E. coli* of 2 percent).[19] Many fluoroquinolone resistant isolates from humans have been associated with travel overseas.

c) **Drug restrictions.** Approval for animal use of drugs for a limited number of indications, with label constraints (i.e. 'DO NOT' statements) prohibiting extra label or off-label usage or for some indications or use in non-labeled species (e.g. extra label use of cephalosporin antimicrobial drugs in food-producing animals).[20]

d) **Treatment formularies and prescriber guidelines.** A formulary of antimicrobials for every disease and associated pathogen(s) are listed and scored (1-3) within the following four categories: efficacy, resistance among the pathogen causing infection in animals, national criteria for human importance.[21]

e) **Restrictions on the use of certain antibiotic classes.** In Australia fluoroquinolones have not been registered for use in food animals. While there is no legal impediment to the registration of fluoroquinolones in livestock, there is a general understanding in the animal health industry that applications for such uses will not be made. Contrary to popular belief, the registration of fluoroquinolones in livestock has never been formally banned nationally, though a number of States have legislation that does not permit the use of fluoroquinolones in livestock. In Denmark fluoroquinolones were approved for use in production animals in 1993, and in the following years the emergence of resistance was observed. In the year 1999 Danish farmers voluntarily stopped the use of fluoroquinolones in livestock, and in 2002 the use and prescription of fluoroquinolones by veterinarians to food- producing animals were further restricted by the authorities. This reduced the total usage of fluoroquinolones in animals in Denmark from 183 kg in 2001 to 49 kg in 2006.[15]

f) **Limiting the prescribers' profit on the sale of antimicrobial agents**. In many countries a considerable part of the veterinarians' income comes from the direct sale of antibiotics to the farmers. An example from Denmark demonstrates that limiting the possibility of profit to veterinarians from the sale of drugs led to a reduction in total usage. Antimicrobial agents have to be bought at a pharmacy. This has resulted in a reduction of 40 percent in total use of therapeutic agents and a reduction in tetracycline use from almost 37 tonnes in 1994 to 9 tonnes in 1995.[22]

g) **Price and taxation.** In human medicine several studies have shown an association between expenses and the prescription of a specific drug. It is a reasonable assumption that the cost of the drug is a considerable factor for the farmer's decision on when and how to use antimicrobials over other disease control and prevention options. In Denmark, a tax was imposed on antimicrobial growth promoters in 1998.

h) **Voluntary withdrawals or banning of drugs.** The examples below show that reduction in the use of antimicrobial agents can have a positive effect on the occurrence of antimicrobial resistance. The disadvantage of relying on voluntary withdrawals is that there are no controls that prevent the same groups from later reintroducing these antibiotics and the consequential rise in resistance rates.

- In the United Kingdom (as well as Australia) the use of the tetracyclines and penicillins as growth promoters was banned following the recommendations of the Swann report.
- In 1995 the Danish Ministry of Agriculture, Fisheries and Food decided to ban the use of the growth promoter avoparcin because of its cross-resistance to vancomycin, a critically important antimicrobial for human use.
- In 1997, the European Union (EU) banned the use of avoparcin. In 1998 Denmark banned the use of virginiamycin because of cross-resistance to the critically important quinupristin-dalfopristin used in humans.
- In 1998, the Danish animal production industry voluntarily stopped the use of growth promoters; only pigs up to 35 kg bodyweight were still treated with growth promoters until January 2000.
- In 1999 the EU banned tylosin, spiramycin, virginiamycin, and bacitracin, and the remaining growth promoters were banned in the EU from January 2006. The gradual banning of growth promoters in Denmark resulted in a 50 percent reduction of the usage of antimicrobial agents in animal production from 1997 to 1998, and consequential reductions in the levels of antimicrobial resistance in a range of different bacterial species in food animals.[11]

- In 2005 there was a voluntary withdrawal in Québec chicken hatcheries of the extra-label use of the 3rd generation cephalosporin ceftiofur. After the withdrawal, a significant decrease in ceftiofur resistance was seen in *Salmonella* Heidelberg isolates from retail chicken and humans, as well as in *E. coli* from retail chickens.[23]

i) Preventive veterinary medicinal strategies. Disease prevention is an integrated part of food-animal production, and Specific Pathogen Free (SPF) pig and poultry production systems use this option actively. Preventing disease is considered an essential factor in reducing antimicrobial usage.

- In Norway the effect of introducing vaccines for prevention of disease in farmed salmon was investigated. The introduction of vaccines led to a substantial reduction in the use of antimicrobials in Norwegian aquaculture.[24]
- The introduction and widespread use of vaccines against *Mycoplasma hyopneumoniae* (the cause of enzootic pneumonia) in pigs and against the principal bacterial and viral agents of bovine respiratory disease (BRD) have also been associated with reductions in the use of antibacterial agents.

It is important to note that whenever antibiotics have been removed as routine feed additives for growth promotion and disease prevention purposes, there has been no or little evidence that this has resulted in any positive effect on public health.

j) Controlling Spread of Resistant Bacteria. Improved hygiene and infection control is a well-established and essential part of controlling infectious diseases. Improving the general hygiene in all stages of production and thereby reducing the microbial load on food products will also reduce the antimicrobial resistance load.

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