AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE

Antimicrobial Resistance

A Report of the Australian One Health Antimicrobial Resistance Colloquium

18 July 2013

Contents

Abbreviations

ACSQHC	Australian Commission on Safety and Quality in Health Care
AMR	Antimicrobial Resistance
AMRPC	Antimicrobial Resistance Prevention and Containment
AMRSC	Antimicrobial Resistance Standing Committee
APVMA	Australian Pesticides and Veterinary Medicines Authority
DAFF	Department of Agriculture, Fisheries and Forestry
DDD	defined daily dose
DoHA	Department of Health and Ageing
ESBL	extended spectrum beta-lactamase
FQR	fluoroquinolone-resistant
JETACAR	Joint Expert Technical Advisory Committee on Antibiotic Resistance
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSP	methicillin-resistant *Staphylococcus pseudintermedius*
OIE	World Organisation for Animal Health (Office International des Epizooties)
TGA	Therapeutic Goods Administration
VRE	vancomycin-resistant enterococci
WHO	World Health Organization

Summary

The World Health Organization has identified antimicrobial resistance (AMR) as one of the key health global issues facing our generation. Strong focus is needed on encouraging the appropriate use of antibiotics to achieve a reduction in AMR in clinical practice, veterinary practice and agriculture. This must be supported by good evidence and appropriate data to enable effective decision-making, and robust risk analysis.

The Australian One Health Antimicrobial Resistance Colloquium brought together medical, veterinary and agricultural professionals and policy makers for a collaborative exchange of views about the issue to inform the development and implementation of a National AMR Strategy for Australia.

The Colloquium was requested by the Australian Antimicrobial Resistance Prevention and Containment (AMRPC) Steering Group and convened by the Australian Commission on Safety and Quality in Health Care (ACSQHC) on their behalf. 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 AMR Strategy for Australia. The Steering Group has committed to consult with stakeholders in developing the Strategy, and called together the Colloquium to commence this process.

The forum was conducted under the framework of One Health, which is a worldwide strategy for expanding interdisciplinary collaborations and communications across all aspects of health care for humans, animals and the environment.[1] Participants discussed key issues to inform development of the National AMR Strategy.

The risk

The risk of treatment failure in animals and humans attributable to AMR arising from the use of antimicrobial agents in food-producing animals or companion animals is a serious concern. Internationally, it is estimated that the volumes of antimicrobials used in food animals exceeds the use in humans worldwide. However, further data on usage in the Australian context is required to inform local strategy development.

Infections in humans with organisms that exhibit AMR are found most commonly among people who have been in hospital. However, people in community settings, including overseas travellers and farmers, also present with antimicrobial resistant infections, and the relative contributions of AMR acquired from community settings, food animals and companion animals is not known.

AMR is a bidirectional zoonosis. It also has multidirectional links to other environmental compartments, including aquaculture, food plants and drinking water. The ease with which AMR genetic material can be transferred between organisms means we are all ‘swimming in the same gene pool’ and all sources of AMR organisms need to be taken seriously.

The prevalence of multi-resistant organisms in animals appears low in Australia relative to the rest of the world, and the organisms rarely cause untreatable infection in animals. However, even a low incidence of AMR infections in animals (as reported in Australia) is important to be aware of and assess potential impact. An individual case can be the index case for a new resistance mechanism; identification allows risk assessment and early action to be taken.

[1] http://www.onehealthinitiative.com/

The AMR risk to human health associated with human use of antibiotics is probably more significant than with animal use, but is also poorly quantified with no standardised approach to collecting data.

Overall, the more antibiotics that are used across all sectors, the greater the risk of development and amplification of AMR.

The evidence

The science of antibiotic selection of AMR organisms, amplification, and the spread and transfer of genes between organisms is well understood in humans. The same principles apply for antibiotic use in animals. This is supported by case studies published overseas and reported anecdotally in Australia.

There is considerable uncertainty in Australia and elsewhere about what and where the 'hot spots' are for AMR selection, amplification and dissemination. Collection of data is critical to fill this information gap, prioritise risks, target resources, inform policy and focus communications.

The knowledge gaps

Collection of data is critically important to identify how significant the spread of resistant organisms from animals to humans and transfer of resistance genes is in Australia. Appropriate data collection and monitoring would have the following benefits:

- detecting changes in AMR prevalence and distribution
- targeting of resources
- identifying if there is a problem and, if so, where
- empowering decision makers
- setting priorities and developing the most cost-effective actions
- developing risk communication messages
- allowing the impact of risk management measures to be assessed.

Ongoing and systematic surveillance and monitoring of antibiotic use and AMR resistance in animals is required to complement the proposed improved surveillance and monitoring of human use.

To assess the risks arising from antibiotic use in animals, data is needed on:

- antibiotics — animal species treated, quantity, type (class/mechanism of action), why used and route of administration
- AMR bacteria — species, number, type, location and potential for spread
- AMR resistance genes — properties of gene construct, ability and opportunity to transfer genetic material to other organisms.

To meet these requirements, a reliable baseline and ongoing data collection is essential to capture:

- antibiotic use in animals (prescriptions, sales), and pattern of usage (what, where, why, when, how)
- where and how frequently AMR bacteria are present in food animal and companion animal populations, food products and farm environments.

The following information is also needed on:

- imported AMR bacteria (such as in food, returning travellers, immigrants)

- non-animal sources of AMR (e.g. plant foods, wastewater).

Targeted research is required, to further understand AMR gene transfer, including the potential for genes to be transferred to and from microorganisms of humans, food animals and companion animals; and development of new diagnostic tools for AMR bacteria and genes in different laboratory settings and at the point of care.

The data collection

The requirements of effective data collection summarised above can be achieved through a broadly based, systematic surveillance program to complement the proposed improved surveillance and monitoring of human use. Ideally, such a program should cover all parts of the food chain: live animals, animal products, and other agricultural and environmental products. Interpretation would be aided by development of a universal measure for antibiotic use in animals (equivalent to a defined daily dose in humans).

To succeed, AMR surveillance and monitoring needs:

- clear purpose agreed upon by all parties (based on the One Health program as a framework)
- clear ownership of data (including the role of regulation to allow access to data)
- meaningful data sets
- robust industry partnership and engagement
- accurate and timely data collection, analysis, interpretation, and reporting of data
- cost-effective and sustainable methods of diagnosis, surveillance and monitoring
- flexible, agile programs that can adapt to emerging issues
- sustainable funding support.

In animals, the purpose of surveillance, and the interpretation of data, is different to that in humans, and more complex. In humans, surveillance is about diagnosing and monitoring disease-producing organisms. In animals, it is important to also look at commensals from healthy food animals. This would require active sampling and analysis of samples from abattoirs, farms and food of animal origin at the retail outlet. Environmental sampling is also required to complete the epidemiological approach.

The key priorities for action

The One Health approach to action provides an opportunity to find common ground across sectors and develop a unified management plan. The Strategy should be guided by the ‘5Rs’ (reduce use, refine use, replace antibiotics, regulate, research) and underpinned by risk assessment and outcome effectiveness measures.

The fundamental priority is to develop an integrated, risk-based surveillance system that covers human and animal use of antibiotics, and the incidence and spread of organisms with AMR. Building on that, it is vital to harmonise control of use regulation of veterinary medicines across Australian states and territories, and develop systems to identify and react to emerging threats, including triggers for review and powers that regulators have to investigate and take corrective action.

Critical points requiring further consideration, in terms of regulation, include: registration, prescription and use of antibiotics (through regulatory agencies, professional boards and state and territory health departments); import of food and medical products such as vaccines (through review and modification of current arrangements to better meet AMR needs); and, guidelines for infection control and prudent antibiotic use.

It will be important to review import regulations for vaccines used to combat bacterial and viral diseases of food animals, as the greater availability of vaccines could reduce the demand for antimicrobials in some circumstances. Access to vaccines from abroad is currently difficult because of restrictions in relation to potential for introduction of unwanted biological agents and vaccines based on genetically modified organisms.

Regulation should be supported by targeted education programs, which can also drive action by linking professional development with specific outcomes (e.g. linking prudent-use guidelines with auditing of prescribing and accreditation).

Robust, sustainable research programs are needed across the AMR development and dissemination chain, vaccines, antibiotic alternatives, and more rapid and reliable diagnostic methods.

The One Health approach to communication

AMR affects the whole community. Audiences include practitioners and professionals, food producers, pharmaceutical and food industries, government, researchers and educators, media and the public. One Health provides a golden opportunity for community and interdisciplinary dialogue to create communications with a consistent approach across all sectors (doctors, veterinarians, farmers, industry and community).

Messages need to stress judicious use of antibiotics, infection prevention, containment and control in animal and human sectors, as well as emphasising the benefits of vaccines and improved diagnostic methods.

The most effective messages are simple and action-oriented; focus on what can be done now (e.g. four top actions); reinforce positive achievements; raise awareness of risks while keeping risks in proportion; and acknowledge health science, social, environmental and economic dimensions of the issue, including uncertainties.

Introduction

The AMRPC Steering Group was established in February 2013 to provide high-level governance and leadership on antimicrobial resistance (AMR). 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 Australian Chief Medical Officer and Chief Veterinary Officer are also members. The group will also oversee the development of a comprehensive National AMR Strategy for Australia.

AMR extends across both animal and human health. 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. An effective response to the challenges of AMR will involve a combination of regulation, monitoring and surveillance, targeted activity on specific organisms, and research and education. To this end, the Steering Group recently endorsed the overarching framework for the development of the National AMR 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)
- Research.

To develop the Strategy, the Steering Group will consult widely with stakeholders. The Australian One Health AMR Colloquium was convened by the Australian Commission on Safety and Quality in Health Care to start this process. The colloquium brought together over 60 food animal, animal health and human 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 to identify gaps and set priorities for action, and to develop advice to the Steering Group on the next steps.

A list of participants is provided at Appendix 1 and a briefing paper that was circulated to all participants before the event is at Appendix 2.

Colloquium report

An expert writing group of health and non-health experts were supported by a professional medical writer to develop a consolidated report of the Colloquium discussion and outcomes. This report will be provided to officers of DoHA and DAFF to inform preparation of departmental advice to the AMRPC Steering Group. Appendix 1 includes a list of writing group members.

Program

The program for the Colloquium was as follows:

0830	**1. Official welcome** Speakers: Professor Jane Halton PSM, Secretary Department of Health and Ageing and Mr Andrew Metcalfe AO, Secretary Department of Agriculture Fisheries and Forestry
0900	**2. Overview and purpose of the Australian One Health Antimicrobial Resistance Colloquium** Speaker: Facilitator Dr Stephen Page
0915	**3. Antimicrobial resistance in animal and agriculture overview** Speaker: Dr Mark Schipp, Australian Chief Veterinary Officer
0945	***4.* Antimicrobial resistance in human health overview** Speaker: Professor Chris Baggoley, Australian Chief Medical Officer
1015	**5. National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health** Speaker: Dr Marilyn Cruickshank, Chair Antimicrobial Resistance Standing Committee (AMRSC)
	MORNING TEA 1030–1100
1100	**6. Group discussion morning session** Facilitator, Dr Stephen Page
	LUNCH 1300–1345
1345	**7. Group discussion afternoon session** Facilitator, Dr Stephen Page
	AFTERNOON TEA 1545–1600
1600	**8. Summation of the colloquium outcomes** Facilitator, Dr Stephen Page
1620	**Closing remarks** Dr Mark Schipp

Approach to One Health discussions

Participants at the Colloquium were pleased to be involved in the first major forum that has included representatives from the human health, animal health and food animal production sectors. The forum, based on One Health principles, was independent, cooperative and designed to benefit all parties. The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment.[1] Participants appreciated the collaborative nature of the forum.

The Colloquium understood that antibiotic use in the human health care sector is one of the major drivers of antimicrobial resistance (AMR) and the associated risks to human health. These risks are starting to be managed in humans through programs of antimicrobial stewardship, accreditation and standards.[2]

Meanwhile, the use of antibiotics in food animal production and treatment of companion animals, and the close association of people and animals in many settings, make the transmission of AMR from animals to humans a potentially serious concern. There is high-level support, both internationally and in Australia, for the principles of antimicrobial stewardship developed for human health care to be implemented for animals and agriculture. There is also high-level support for extending the same accreditation and standards across the human and animal health sectors. Implementation has started in Australia through a number of high-level interdisciplinary processes and committees. The focus of discussions at the Colloquium was therefore directed to identifying, characterising and managing the risks to humans of AMR originating in animals and conveyed by close contact with animals or via food.

After the morning plenary sessions, participants discussed four questions about AMR. The questions followed a risk analysis framework for the risk of AMR organisms from nonhuman sources, particularly animals, spreading to humans or sharing their AMR genes with human organisms. Table 5.1 shows the four topic areas and questions discussed. Four tables with experts from various fields discussed each of the first two questions for one hour in the morning followed by a one-hour plenary feedback session. The process was repeated in the afternoon for the last two questions. The discussions were led by AMRSC members.

The discussions for each question are summarised in Sections 6 and 7 of this report.

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1 www.onehealthinitiative.com

2 The Antimicrobial Resistance Subcommittee (AMRSC) has recently prepared a program for surveillance and monitoring of human AMR (see Section 5).

Table 5.1 Antimicrobial resistance (AMR) One Health Colloquium discussion questions

Risk analysis topic	Question	Considerations
Risk assessment	What are the major AMR risks to human health from antibiotic use in food and animals?	• Are the risks perceived or real? • How strong is the evidence of risk to human health? • How can the evidence base of risk be strengthened? • What are the major information gaps and how can they be addressed?
Surveillance and monitoring	What are the most important components of a program for surveillance and monitoring of antibiotic use and AMR?	• What are the priorities for surveillance and monitoring of antibiotic (drug) use? • What are the priorities for surveillance and monitoring of AMR? • What is the most appropriate mechanism for collecting and quantifying data on antimicrobial use in animals? • What are the most appropriate mechanisms for surveillance and monitoring of AMR in food animals? • What is the most appropriate frequency for the collection of antimicrobial use and resistance data? • What is the most appropriate means of analysing and integrating AMR and antibiotic use information?
AMR risk management	What are the key priorities for action for human health protection against AMR?	• Regulation (importation, registration and antibiotic use controls; collection of data) • Education — what objectives and how to measure effectiveness • Data gaps and the need for specific research and development • How can effectiveness be measured?
AMR risk communication	What are the key messages and approaches for communicating the national approach to AMR prevention and containment?	• Who are the key audiences? • What is the most effective means of communication? • What are the key messages for communication? • Priority and timing of communication strategies for each of the groups (e.g. veterinarians and medical general practitioners first, consumer groups next)

Part 1
Overview of the issue

1 Official welcome

The facilitator, Dr Stephen Page introduced the colloquium, noting that it was a unique occasion that brought together medical, veterinary and agricultural professionals and policy makers for a common goal. He noted that 'colloquium' means an informal meeting for the exchange of views (from the Latin for conversation).

Dr Page said that the goal of the Colloquium is to inform the development and implementation of a comprehensive National Antimicrobial Resistance (AMR) Prevention and Containment Strategy for Australia (see Introduction). He said that such a strategy has not been developed before in Australia and it has the potential to have a major impact in the field.

Dr Page introduced the Secretaries of the Australian Government Department of Health and Ageing (DoHA) and the Department of Agriculture, Fisheries and Forestry (DAFF), who welcomed participants and described the heath and agriculture portfolio aims for the process.

Professor Jane Halton PSM, Secretary Department of Health and Ageing

Professor Halton stressed that AMR is an extremely important issue and that she was very pleased that the Colloquium had drawn together such a distinguished group of people across the veterinary and medical divide. She thanked Mr Andrew Metcalfe AO, Secretary of DAFF for his participation and for responding to her request for help with this major issue as soon as he took up the position of DAFF Secretary.

Professor Halton said that AMR is a global security issue and, in relation to the health portfolio, it is an issue that galvanises action. She said it is not always highly visible but it is crucial, because the responsibility to make sure Australian citizens are safe includes ensuring that life-saving treatments will be available for the community. She said there are very few people alive today who remember what the world was like before antibiotics, but that it doesn't take much to imagine what it would be like if we lost the use of these important agents.

Professor Halton is Chair of the Executive Board of the World Health Organization (WHO), and she said that WHO has identified AMR as one of the key global health issues facing our generation. However, she noted that although it is generally accepted at a macro level that AMR is a major issue, the answers lie in the micro issues. She said that it is about what happens day-to-day in clinical practice, veterinary practice and agriculture. She emphasised that we need to be clear on the science behind the practice, so that we know what we should advise and mandate in these day-to-day arenas. She also said that we need to be clear about what we don't know, and what we need to know, so that we know what to measure and monitor.

Professor Halton said that in this they are working from the health portfolio with colleagues across the world, including Dame Sally Davies — the Chief Medical Officer of the United Kingdom — who is very engaged with this issue. Professor Halton believes that Australia is an important player in the space, and that we need to think about how we prosecute the issue as good global citizens.

Professor Halton said that the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) was commissioned to review the issue in the late 1990s. She explained that the JETACAR report was published in 1999 with 22 recommendations across the human and animal sectors. She noted that many of the recommendations have been implemented, but we now need to revisit the outstanding issues. She also said that we need to think carefully about how we can work together as medical and veterinary practitioners and organisations, and as parliamentarians, clinicians and the community.

Mr Andrew Metcalfe AO, Secretary Department of Agriculture Fisheries and Forestry

Mr Metcalfe added his appreciation for the Colloquium and noted that he was particularly pleased that participants included medical and veterinary professionals, as well as food industry colleagues.

Mr Metcalfe said that AMR is recognised as a problem for companion animals and agriculture in general and is an important issue for animal health, welfare and productivity. He noted that the Australian Government has a long-standing commitment to regulate and register agricultural and veterinary chemicals through the Australian Pesticides and Veterinary Medicines Authority (APVMA). He explained that through the APVMA, Australia has one of the most thorough systems for regulating chemicals, including antibiotics, in the world. He said that we also have one of the lowest nonhuman uses of antibiotics in the world, and one of the lowest levels of AMR, but we cannot be complacent. He said that humans and animals share many of same bacteria and also environments, and AMR bacteria are able to move between species and environments across the world.

Mr Metcalfe said that AMR is one of the major issues facing humanity; it is also an acute problem, because of the low numbers of new antimicrobials entering the market. He said that we therefore need to preserve antimicrobial efficacy across the animal and human health systems, which points to a clear need for cooperation between human and animal health and production sectors. He said that in the global context, Australia needs to lead by example and be active in international forums to implement change.

Mr Metcalfe said that DAFF has already held a roundtable forum about AMR; the meeting identified the key priorities as the collection of data on antibiotic use and AMR in Australia, and research into activities that could potentially reduce the routine use of antibiotics. DAFF has released a brief communiqué summarising the discussion at the forum. However, Mr Metcalfe noted that we need to look at all aspects of antibiotic use, including clinical and veterinary practice, food production and research. He said the meeting showed the importance of the issue and the interest from the agricultural sector in tackling it. He finished by saying that this Colloquium will build on that commitment.

2 Overview and purpose of the Australian One Health Antimicrobial Resistance Colloquium

Dr Stephen Page

Dr Page said that participation in the Colloquium is representative of the expertise and organisations in human and animal health in Australia, and shows the high level of interest in the issue across sectors. He said that there is great enthusiasm in accepting the baton to develop advice around AMR issues.

He explained that the Colloquium has been structured around four key questions, which are intended to provide guidance to an AMR strategy and monitoring program. The four questions are:

- **Risks:** What are the major AMR risks to human health from antibiotic use in food and animals?
- **Surveillance and monitoring:** What are the most important components of a program of surveillance and monitoring of antibiotic use and AMR?
- **Priority actions for protecting human health:** What are the key priorities for action for human health protection against AMR?
- **Communication:** What are the key messages and approaches for communicating the national approach to AMR prevention and containment?

Collaboration

Dr Page said that a successful AMR strategy will depend on cross-sectoral collaboration. Key elements of effective cross-sectoral collaboration are:

- political will and high-level commitment
- common objectives and priorities
- shared benefits
- trust (transparency, communication and relationship building)
- adequate and equitably distributed resources
- identification and involvement of all relevant partners
- coordinated planning of activities
- capacity development.

He said that we clearly have the political will — this colloquium has already seen opening addresses from the most senior officials responsible for human and animal health in Australia. He said that the Australian Government is committed to addressing AMR.

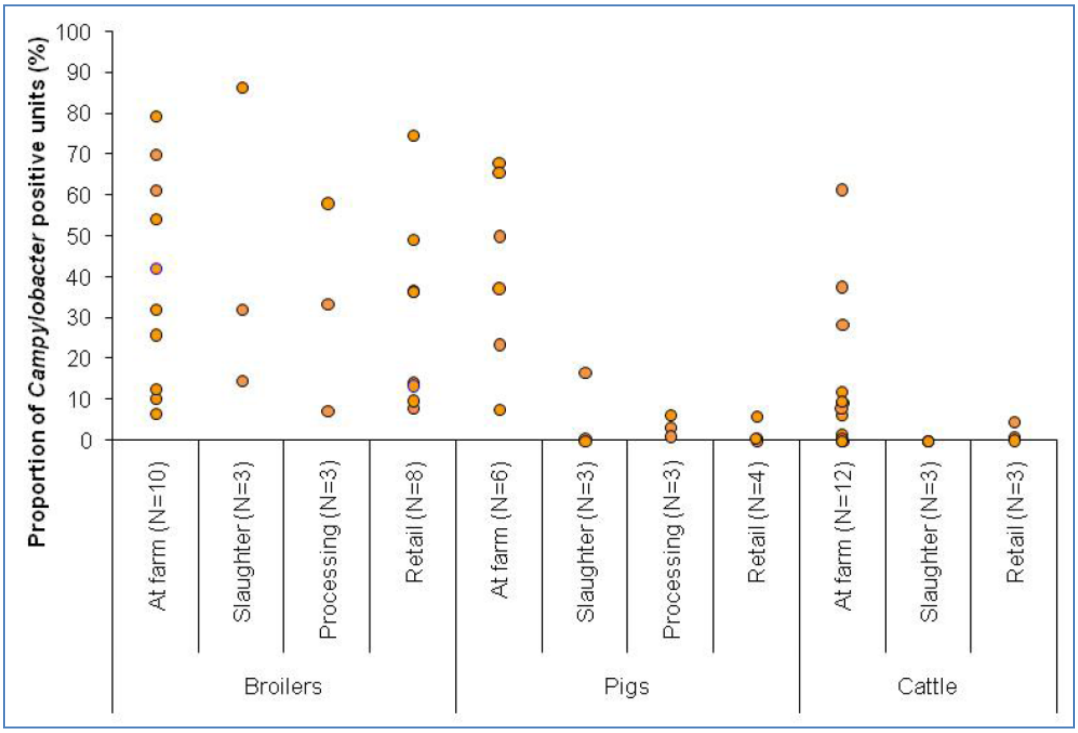
Dr Page said that we clearly all recognise AMR as an important issue and are keen to do something about it. He said that today is about people stating their position and gaining an understanding of others' opinions and views; it provides us with an opportunity to start to build the relationships we need. He also said that there may be other stakeholders that could and will be identified to join the collaboration.

The challenge

Dr Page said that AMR is a complex phenomenon, which is changing all the time. He said many countries have introduced measures to contain AMR, but not always with success. He said it is clear that unless something effective is done, the issue will expand and become more serious.

Dr Page said that it is also clear that any strategies we develop need to be based on facts and evidence; so, our first steps must be to increase our understanding. He said that, without the data, it is impossible to quantify and understand the issue.

Dr Page said that one example of the complexity of information we need to deal with and understand is provided in a recent report from the European Food Safety Authority, which shows differences in bacterial populations between species at different stages along the food chain (Figure 1): in this case differences in contamination rates of broilers, pigs and cattle by the foodborne pathogen *Campylobacter* from farm animals to food at the retail level.



Source: EFSA (2010). The community summary report on trends and sources of zoonoses, zoonotic agents and foodborne outbreaks in the European Union in 2008. *European Food Safety Authority Journal* 1496.

Figure 1 *Campylobacter* contamination of food animals from farm to fork

Dr Page said that another issue is the changing relationship between humans and animals. He said that in particular, the relationship between humans and companion animals has increased over the last decade, such that animals share many aspects of people's lives. He said that we know that AMR can travel in both directions between humans and animals, and these close relationships have significant potential to affect the progression and impact of AMR. For example, a recent report found that dog ownership significantly increased the shared skin microbiota in cohabiting adults, and dog-owning adults shared more skin microbiota with their own dogs than with other dogs.[3] Similarly,

3 Song SJ, Lauber C, Costello EK, Lozupone CA, Humphrey G, Berg-Lyons D, Caporaso JG, Knights D, Clemente JC, Nakielny S, Gordon JI, Fierer N, Knight R (2013). Cohabiting family members share microbiota with one another and with their dogs. *eLife* 2013;2:e00458.

Fitzgerald demonstrated the likely human origins of methicillin-resistant *Staphylococcus aureus* (MRSA) in livestock.[4]

The future

Dr Page said that the research we need is made a little easier by the fact that Australian regulation limits the availability and use of many antibiotics that are used in animals in this country, and information on annual sales of antibiotics is a requirement of registration.

Dr Page concluded that, although we still have a long way to go, the more than 1000 years of expertise amongst the Colloquium participants had the potential to solve any problem and plot a pathway of collaboration for a healthier future.

4 Fitzgerald JR (2012). Human origin for livestock-associated methicillin-resistant *Staphylococcus aureus*. *mBio* 3(2):doi:10.1128/mBio.00082-12.

3 Antimicrobial resistance in animals and agriculture overview

Dr Mark Schipp, Australian Chief Veterinary Officer

Dr Schipp began by saying that tince the first use of antibiotics in animals, there has been controversy about links to AMR in humans.

He said that the most comprehensive study of these links in Australia was the Joint Expert Technical Advisory Committee on Antibiotics (JETACAR) report published in 1999, which recognised that while antibiotic use in animal production can affect human health, it is the use and overuse of antibiotics in human medicine that has been the major factor contributing to the development of AMR.

JETACAR and its impact

Dr Schipp said that the JETACAR report made 22 recommendations for the appropriate future management of antibiotic use in Australia. He said the Australian Government published its response to the JETACAR report in August 2000, generally agreeing to implement the recommendations with a few variations. These recommendations overall have been, and continue to be, implemented (with some exceptions, which were recently spelled out in a Senate Inquiry report[5]).

Dr Schipp said that the detailed recommendations in JETACAR are consistent with more recent recommendations, such as those in the World Health Organization (WHO) Global Strategy for the Containment on Antibiotic Resistance. He said that despite the report of JETACAR now being around 14 years old, the fundamental thrust of its key objectives are still appropriate in the context of the more recent advances in scientific knowledge about AMR.

Dr Schipp said that the 22 recommendations can be categorised into five general elements for application in both human and animal medicine. These are:

- regulatory controls
- monitoring and surveillance
- infection prevention strategies
- education
- research.

Regulatory control

Dr Schipp said that in Australia, regulatory control has the following components.

- Control of importation:
  - The Therapeutic Goods Administration (TGA) maintains the Australian Register of Therapeutic Goods. All antibiotics to be imported into, manufactured in, supplied in or exported from Australia must be included on this register. The TGA is also responsible for the scheduling of antibiotics. Nearly all antibiotics used in animals are now S4 or prescription only.

5 *Inquiry into the progress in the implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antibiotic Resistance*, www.aph.gov.au/Parliamentary_Business/Committees/Senate_Committees?url=fapa_ctte/completed_inquiries/2010-13/jetacar/index.htm.

  - The Australian Customs and Border Protection service have the power to seize any shipment of antibiotics if the importer is unable to present a permit issued by the Australian Government Department of Health and Ageing (DoHA) Office of Chemical Safety.
  - Through its biosecurity programs, the Department of Agriculture, Fisheries and Forestry (DAFF) are responsible for quarantine risks associated with the importation of biological products.
- Registration:
  - The Australian Pesticides and Veterinary Medicines Authority (APVMA) is responsible for the registration of veterinary antibiotics under the Agricultural and Veterinary Chemicals Code. Prior to registration, the APVMA evaluates products to ensure they are safe, effective and of suitable quality. The evaluation of 'safety' includes safety to humans, including the need to manage risks associated with development of AMR in animals that may be transferred to humans. The APVMA also has the power to place label restraints on veterinary antibiotics should they find it necessary to prohibit or limit their use in specific circumstances.
- Control of use:
  - State and territory government agencies are responsible for the supply and use of antibiotics in their respective jurisdictions. These agencies include departments of primary industries and veterinary practitioner boards. Control of use includes the supply of products, veterinary prescribing, 'off-label use', and traceback of residue detections. Controls are generally consistent, but there is some variation between jurisdictions.
  - Off-label use is the use of a veterinary medicine to treat an animal in a way that is not described on the registered label, including a change in the species, dose rate, frequency or duration of use, or withholding period.

Monitoring and surveillance

Dr Schipp said that there are currently no nationally coordinated veterinary or agricultural AMR monitoring and surveillance programs in Australia; however, sales data are kept. He said this data cannot always show what species an antibiotic was used in and for what purpose, but it gives a good indication of the volumes used.

Dr Schipp said that The Australian Government's initial response after the release of the JETACAR report was to conduct a pilot survey of AMR in bacteria of animal origin. He said the results of the DAFF pilot survey were published in 2007 and were generally reassuring, with the exception of some highly resistant organisms being found, particularly in isolates from the more intensive animal industries. He said a similar pilot survey was conducted for food and published in 2008.

Dr Schipp said that the pilot survey has not been used to design an ongoing nationally coordinated monitoring and surveillance survey that can assess antibiotic usage and resistance trends in the long term, including between the animal and human sectors. He said a report was prepared for the National Health and Medical Research Council's Expert Advisory Group on AMR in 2006 by veterinarian Jonathan Webber on 'A Comprehensive Integrated Surveillance Program to Improve Australia's Response to AMR'. He said the report costed various surveillance programs, which have not been implemented.

Dr Schipp said that Australia is in the extremely fortunate position of not having the most significant foodborne bacteria with AMR found in Europe and North America, notably:

- *Salmonella* Enteritidis (resistant strains and clinical problems are rare or absent in Australia)
- *Salmonella* Typhimurium DT104 (multiresistant strain absent from Australia)
- van B vancomycin-resistant enterococci (VRE) (dominant in medical isolates in Australia but not in Europe or the United States where van A predominates, but never isolated from animals and reported in peer-reviewed literature)
- fluoroquinolone-resistant *Campylobacter* spp and *Escherichia coli* (not present in locally produced food, but can be imported)
- cephalosporin-resistant salmonellae (rarely reported)
- extended spectrum beta lactamase (ESBL)-producing bacteria (not isolated from food of animal origin).

Dr Schipp presented Table 2.1, which shows the resistances reported from animal or meat isolates in Australia and elsewhere. The table was prepared based on the recent literature, as well as overseas information from the *National Antimicrobial Resistance Monitoring System — Enteric bacteria (NARMS) 2010 Executive report*,[6] and Australian information from the *Pilot survey for antimicrobial resistant (AMR) bacteria in Australian food*[7] and the Australian Salmonella Reference Centre annual reports.

Dr Schipp said that dogs have been found to be the source of AMRs, indicating that the role of companion animals in the transmission of AMR to humans warrants further investigation.

He said that while the evidence base does not include a national systematic survey of AMR, it is important to note that an absence of evidence does not provide evidence of absence.

6 www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm312952.htm

7 www.health.gov.au/internet/main/publishing.nsf/Content/A8AAD3C3038C79BBCA2572E3000A8ACC/$File/Pilot%20survey%20for%20AMR.pdf

Table 2.1 Resistances reported from animal or meat isolates in recent publications, Australia vs overseas

Bacterial species	Resistance	Poultry	Pigs	Cattle	Dogs	Horses
Enterococcus faecium	Vancomycin (VREfm)	OS	OS	OS	OS	OS
Enterococcus faecium	Streptogramin (SREfm)	OS	OS	OS	OS	OS
Enterococcus faecalis	Vancomycin (VREfs)	OS	OS	OS	OS	OS
Salmonella Enteritidis	Fluoroquinolone	OS	OS	OS		
Salmonella Typhimurium *(et al)*	Extended spectrum β lactamase (ESBL)	OS	OS	OS		OS
Escherichia coli	Extended spectrum β lactamase (ESBL)	OS	OS	OS	AU OS	OS
Escherichia coli	Fluoroquinolone	OS	OS	OS	AU OS	OS
Campylobacter jejuni	Fluoroquinolone	OS	OS	OS	OS	
Campylobacter coli	Fluoroquinolone	OS	OS	OS		
Staphylococcus aureus	Methicillin (MRSA)	OS	OS	OS	AU OS	AU OS
Staphylococcus pseudintermedius	Methicillin (MRSP)				AU OS	OS

AU = resistance reported in Australia; OS = resistance reported overseas
Source: Page SW (2013). *Antimicrobial resistance: the facts. Part 1. The animal sector,* Presentation at the Australian Government Department of Agriculture, Fisheries and Forestry Antimicrobial Resistance Roundtable (as it relates to the agricultural sector), 4 July 2013, Rydges Lakeside Canberra.

Dr Schipp said that an example of the importance of the One Health approach is exemplified by the recent report of a survey of MRSA among Australian veterinarians[8] with accompanying editorial by the eminent MRSA expert Professor Ian Gosbell.[9]

Dr Schipp said that this survey confirmed previous overseas findings of an increased risk of MRSA carriage by particular groups of veterinarians. He said the survey found that small animal veterinarians have a 5-fold increased risk of MRSA carriage, and veterinarians who focus only on horses have a 23-fold increased risk.

Dr Schipp said that a large survey is being carried out at the University of Adelaide, of *E. coli* isolated from infections in food-producing and companion animals. Evidence of fluoroquinolone or third-generation cephalosporin resistance was not found in food-producing animals, but was found in companion animals. He said that these findings again highlight the need to include companion animals (which should include horses) in any national systemic surveys of AMR.

Dr Schipp said that the World Organisation for Animal Health (OIE — Office International des Epizooties) *OIE Terrestrial Animal Health Code* (2012)[10] includes standards and recommendations for

8 Jordan D, Simon J, Fury S, Moss S, Giffard P, Maiwald M, Southwell P, Barton MD, Axon JE, Morris SG, Trott DJ (2011). Carriage of methicillin-resistant *Staphylococcus aureus* by veterinarians in Australia. *Australian Veterinary Journal* 89(5).

9 Gosbell IB (2011). Methicillin-resistant *Staphylococcus aureus* in veterinary practice. *Australian Veterinary Journal* 89(5).

10 www.oie.int/international-standard-setting/terrestrial-code/access-online

AMR monitoring and surveillance in animals. He noted that Australia, like most other countries, does not meet these requirements.

Dr Schipp said that Article 6.7.3 in Chapter 6 of the Code[11] states that:

> Surveillance of antimicrobial resistance at targeted intervals or ongoing monitoring of the prevalence of resistance in bacteria from animals, food, environment and humans, constitutes a critical part of animal health and food safety strategies aimed at limiting the spread of antimicrobial resistance and optimising the choice of antimicrobial agents used in therapy.

Dr Schipp said that government in Australia at all levels has responsibility for animal health and food safety strategies. He said that the OIE Terrestrial Animal Health Code would suggest that we need to be doing more on AMR. He said that AMR is a global problem, and developed countries like Australia have an obligation to lead by example in addressing the AMR challenge internationally.

Dr Schipp said that meeting OIE requirements also has the potential to safeguard our food exports. He said that consumers around the world are becoming more aware of the AMR issue, and consequently want to know that their food is sourced from countries that have rigorous food safety strategies — including on AMR — in place.

Infection prevention strategies

Dr Schipp said that very good progress has been made by both industry and government in the animal and food sectors since the JETACAR report was published. He said this is particularly the case in the implementation of critical control points-based procedures as a means of reducing the contamination of food products with foodborne organisms. He said these procedures typically cover on-farm infection control all the way through to the finished product, and are often underpinned by quality assurance auditing programs.

Education and research

Dr Schipp said that, for education, the Australian Veterinary Association and other animal/agricultural industry groups have put in place various prudent-use initiatives. He said veterinary practitioner boards also have responsibility for this work.

Dr Schipp said that, for research, the government response after JETACAR was initially to generally acknowledge the independence of animal industries in determining their research priorities. He said animal industries are looking for ways to reduce disease burdens and improve growth rates without relying on antibiotics, which, apart from any AMR concerns, are expensive.

Current activities

Dr Schipp said that DAFF, together with DoHA, is engaged in a range of activities to address the AMR challenge. He said these include the engagement processes of the DAFF Roundtable and the AMR Colloquium. He said these processes are feeding into the work of the AMRPC Steering Group, which consists of the Secretaries of both DAFF and DoHA and the Chief Veterinary and Medical Officers. He said the Steering Group was established earlier this year to provide governance and leadership on AMR and oversee the development and implementation of a coherent national framework for current and future work related to AMR. DAFF and the APVMA are providing input into the AMR Standing Committee, which was established last year, to report to the Australian Health Protection Principal Committee to provide ongoing expert advice on AMR issues. Dr Schipp said that they have

[11] www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.6.7.htm

also been involved in the international standard setting and capacity-building work being carried out, particularly by the OIE and the Food and Agriculture Organization of the United Nations.

Dr Schipp presented Figure 6 (in Section 4), which shows an organisational chart of the various committees involved in AMR activities.

The future

Dr Schipp said that the report of the Senate Inquiry into the progress in JETACAR implementation was released in June and makes ten recommendations. He noted that the first four recommendations predominantly concern the JETACAR monitoring and surveillance strategy:

- Recommendation 1: The committee recommends that the Commonwealth establish an independent body or national centre, to develop a strategy, report publicly on resistance data and measures taken to combat antimicrobial resistance and to manage the response to antimicrobial resistance in Australia.
- Recommendation 2: The committee recommends that the independent body be resourced to implement a rigorous monitoring and reporting regime of antibiotic use in humans and animals and of multiple drug-resistant infections in humans and animals.
- Recommendation 3: The committee recommends that the voluntary reporting of the quantity of antimicrobials sold by volume be made mandatory for the registrants of antimicrobials.
- Recommendation 4: The committee recommends that the Australian Pesticides and Veterinary Medicines Authority publish, as a matter of priority, the antibiotic usage report for the period 2005–06 to 2009–10; and publish antibiotic usage reports on an annual basis and within 18 months of the end of the relevant financial year.

Recommendations 5 and 6 concern the human health sector.

Recommendation 7 recommends that consideration be given to banning all antibiotics listed as critically important in human medicine by WHO for use in animals in Australia. Australia already has a very conservative approach to antibiotics relative to most other countries. This includes the fluoroquinolones, and to an extent, the 3rd and 4th generation cephalosporins, which are listed as critically important in human medicine.

Recommendation 8 concerns the human health sector.

Recommendations 9 and 10 look to bolstering AMR research and development.

Dr Schipp said that the Australian Government is currently formulating its response to the Senate Inquiry report and its recommendations, and it is anticipated that this will be made publically available in the near future.

In concluding, Dr Schipp said that the challenges that the animal sector faces in the near future in relation to antibiotic use and AMR include:

- increased pressure to phase out antibiotics used for growth promoter or prophylactic purposes, particularly those antibiotics within antibiotic classes used both in animals and humans
- increased pressure to monitor antibiotic usage
- increased pressure for a coordinated, ongoing AMR surveillance program integrated with human AMR surveillance activities generating comparable surveillance data
- a need to renew our focus on education
- pressures to increase our influence in identifying research and development priorities for funding

- pressures to increase our input into international forums and international capacity-building projects.

He finished by saying that the difficulty, of course, is in the detail and who pays. We look forward to engaging with you on this important topic.

4 Antimicrobial resistance in human health overview

Professor Chris Baggoley AO, Australian Chief Medical Officer

Professor Baggoley said that AMR is a vital and very current issue. Just this month in the *British Medical Journal*, Wallinga and Burch pose the question: 'Does adding routine antibiotics to animal feed pose a serious risk to human health?'.[12]

He said that the answer to this question is still being debated. He said that on the one hand, AMR is one of human health's greatest risks, and physicians and policy makers ignore the critical role of overuse in animals, especially in feed, at our peril. He noted that in the United Kingdom, there is a campaign to end overuse of antibiotics in animals, and in the Netherlands their use in feed has been banned. Since meat production is international, measures must be implemented internationally.

He said that on the other hand, the full evidence is not yet in. Critical human drugs are not used in animals – instead, the major cause of AMR in these drugs is overuse in humans.

Professor Baggoley said that earlier this month, the Australian Chief Scientist published an occasional paper on *Meeting the threat of antibiotic resistance.* He said that this recognition by the Chief Scientist has made it clear that this is not just a sectoral issue, but a global, high-level science problem that has the potential to affect everyone. He said that the paper generated a lot of media attention on the issue.

Professor Baggoley said that the paper discusses the global unrestrained use of antibiotics, the increase in AMR within Australia and coming from overseas, the collapse in antibiotic research and development, and the need for new research avenues.

He said that the paper also contains quotes on the issue from a range of international spokespeople. The notable thing about these quotes is not their message — which is not new — but who is saying them.

He presented a number of recent quotes. The World Economic Forum, talking about global risks in 2013, said:[13]

> Many people take for granted that antibiotics will always be available, but soon this may no longer be the case.

The United Kingdom's Chief Medical Officer, Dame Sally Davies, has said that untreable infection caused by antibiotic-resistant bacteria 'poses a catastropic threat' to humans and has urged immediate global action.[14]

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12 Wallinga D and Burch D (2013), Does adding routine antibiotics to animal feed pose a serious risk to human health? *British Medical Journal* 347:f4214 doi:10.1136/bmj4214, 9 July 2013.

13 World Economic Forum, Global Risks (2013). http://reports.weforum.org/global-risks-2013.

14 Davies SC, Fowler T, Watson J, Livermore DM and Walker D (2013). Annual report of the Chief Medical Officer: infection and the rise of antimicrobial resistance. *Lancet* 381:1606–09.

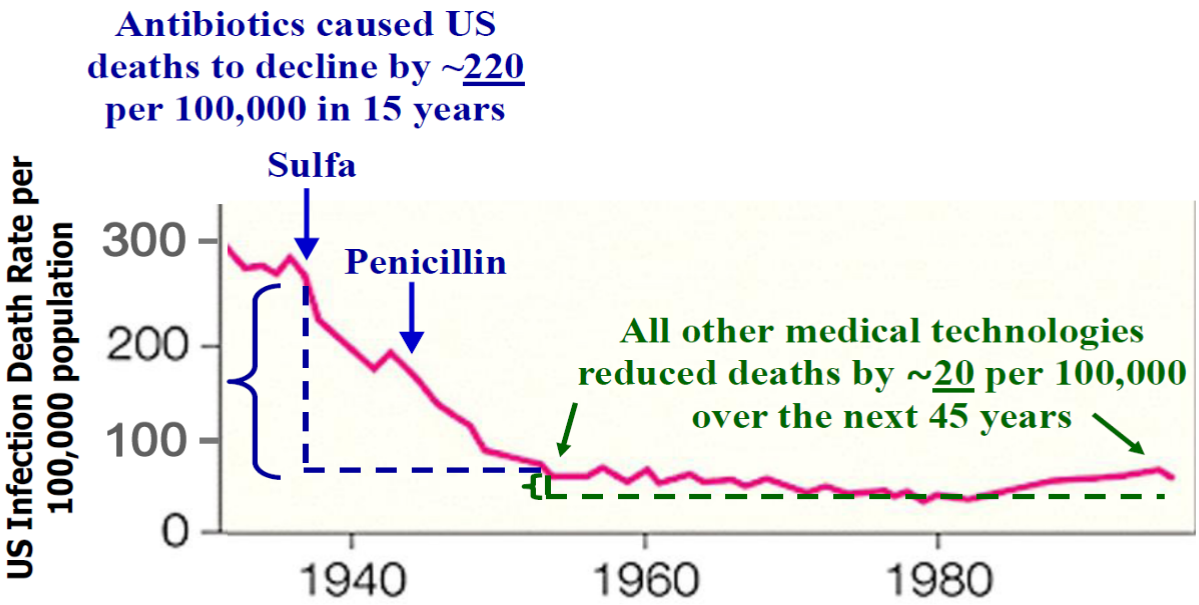
The Director-General of the World Health Organization (WHO), Dr Margaret Chan, has said:[15]

> A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill.

Professor Baggoley said that Dr Chan's message is very bleak. We would hope that this view is overly pessimistic and that science will prevail, but it is clear that we will need political will and cooperation, and significant financial support.

He asked what the consequences of antibiotic resistance might be? He said that, most importantly, some infections may become difficult or impossible to treat: this is happening now. He also said that many of modern medicine's achievements are only possible with effective antimicrobials, such as routine and complex surgery, intensive care medicine, neonatal care, modern obstetrics, organ transplantation and cancer treatment.

He presented Figure 2, which shows what effect antibiotics have had on our death rates.

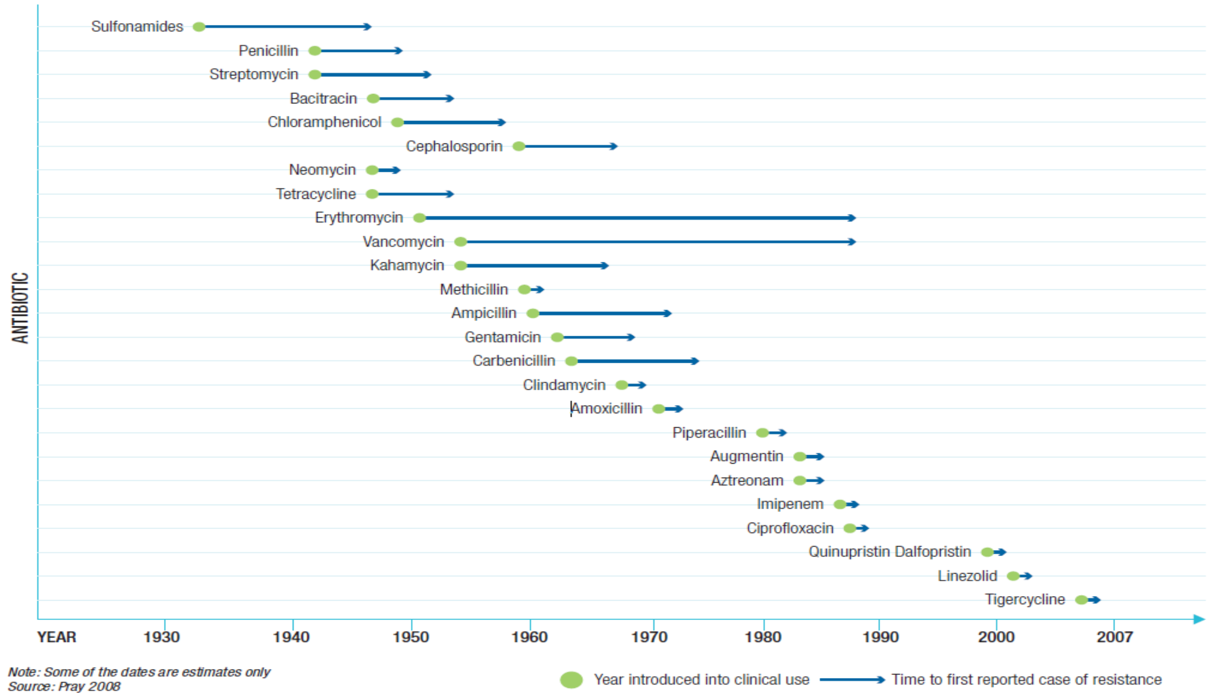


Source: Armstrong GL, Conn LA and Pinner RW 1999. Trends in infectious disease mortality in the United States during the 20th century. *JAMA* 281:61–66.

Figure 2 Decline in infection death rates in the United States, 1930–90

He said that unfortunately, we have discovered that AMR is inevitable; the lifespan of antibiotics is growing shorter and shorter (Figure 3).

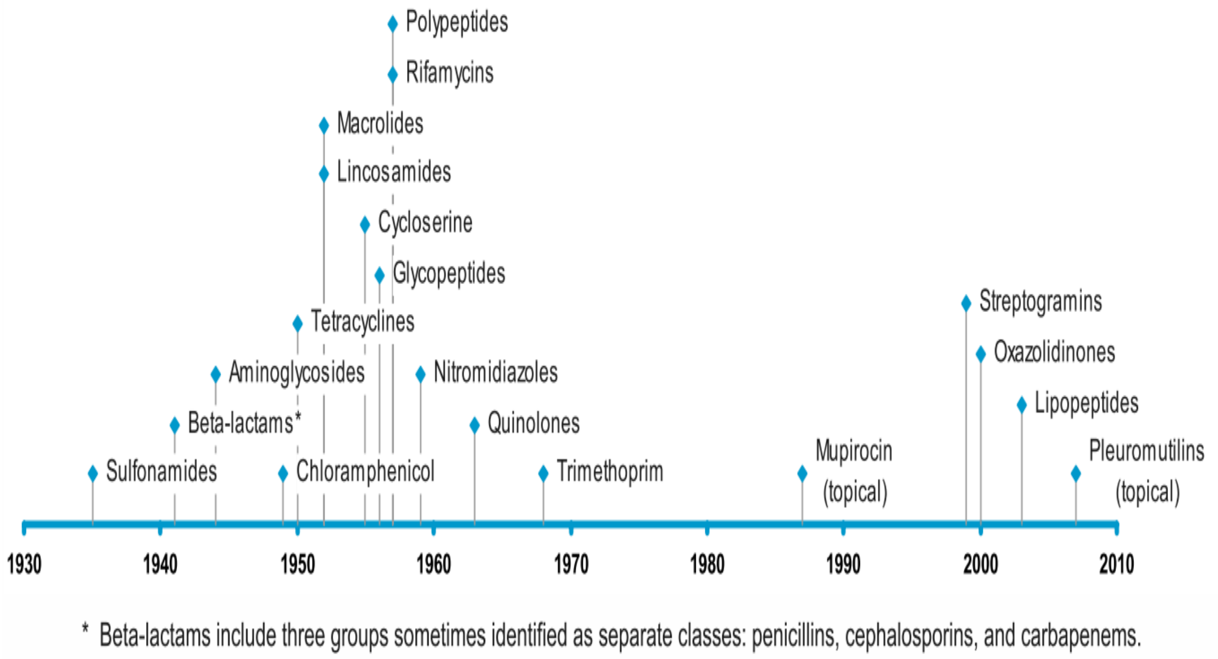
15 *Antimicrobial resistance in the European Union and the world,* www.who.int/dg/speeches/2012/amr_20120314/en/index.html.



Source: Pray LA (2008). Antibiotic research and development: Resolving the paradox between unmet medical need and commercial incentive. *Insight Pharma Reports*. Needham, MA, Cambridge Healthcare Institute.

Figure 3 Time to resistance for antibiotics

He also said that at the same time, we are not developing new antibiotics (Figure 4). He said there are major impediments to antibiotic development, the most important of which is that antibiotics represent a very low rate of return for drug companies, and thus they have little incentive to invest.



Source: Colson A (2008). *Policy responses to the growing threat of antibiotic resistance*. Center for Disease Dynamics, Economics and Policy, Washington DC.

Figure 4 Introduction of antibiotics, 1930–2010

He presented another quote by Dr Chan, who in addressing the World Health Assembly in May, said that: [16]

> Efforts to stimulate the development of new medical products (to fight infection) are critically important for every country in the world.

Professor Baggoley said that around the world, a wide range of groups is looking at AMR.

He noted that in June 2013, the G8 Scientist Ministers declared AMR as a major health security challenge of the 21st century, and discussed the need to:

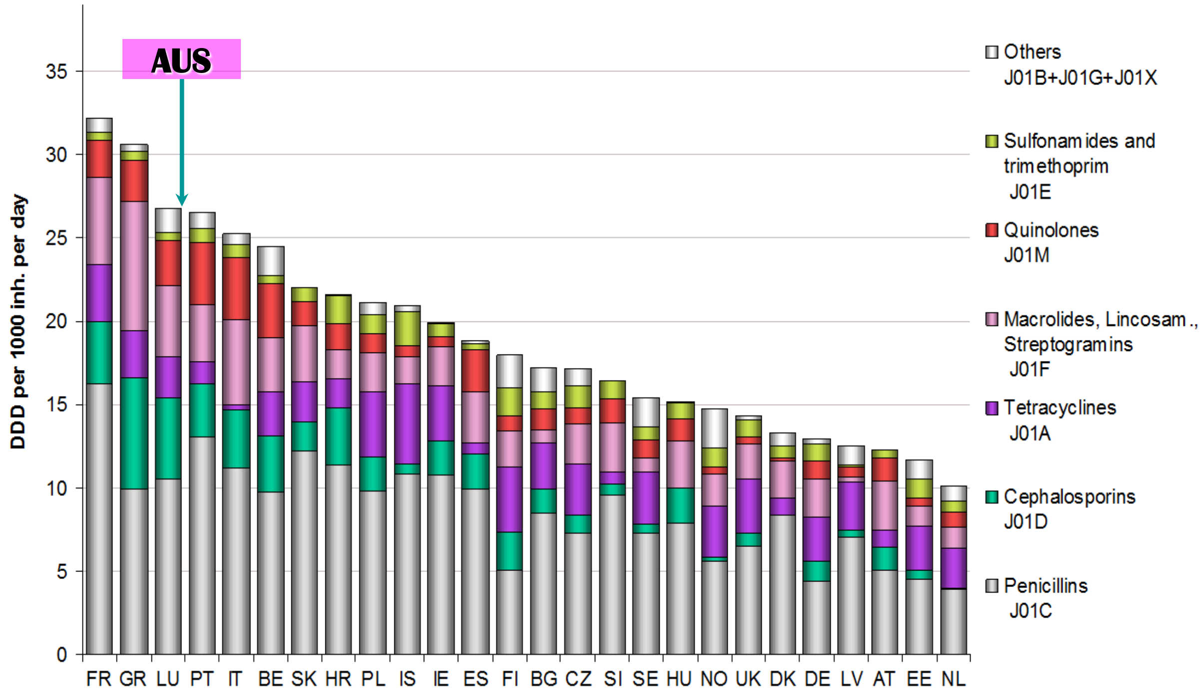
- preserve efficacy of existing antimicrobial agents
- develop rapid diagnostics to inform antimicrobial drug use
- support development of new antimicrobial agents and diagnostics to provide early diagnosis of AMR infections
- share surveillance data internationally
- support theoretical and applied research.

He also said that at the World Innovation Summit in Health in December 2013, a number of similar AMR themes are being examined, including the need for:

- surveillance
  - organisms
  - antibiotics
- conservation
  - infection prevention and control
  - antimicrobial stewardship
  - education (provider, public)
  - regulation (Therapeutic Goods Administration (TGA), Pharmaceutical Benefits Scheme, Standing Committee on Health — national standards, accreditation)
- innovation
  - diagnostic tools (viral versus bacterial, resistant bacteria)
  - novel agents.

Professor Baggoley said that as doctors, we can't walk away from the fact that we prescribe too many antibiotics in Australia (Figure 5). He said many of these are prescribed for viral respiratory infections. If we had an office test to identify infections as viral or bacterial, it would make a huge difference to these prescribing rates.

[16] The Telegraph (2013). *Antibiotic-resistant superbugs pose 'catastrophic' risk,* The Telegraph, www.telegraph.co.uk/health/healthnews/10069620/Antibiotic-resistant-superbugs-pose-catastrophic-risk.html, 20 May 2013



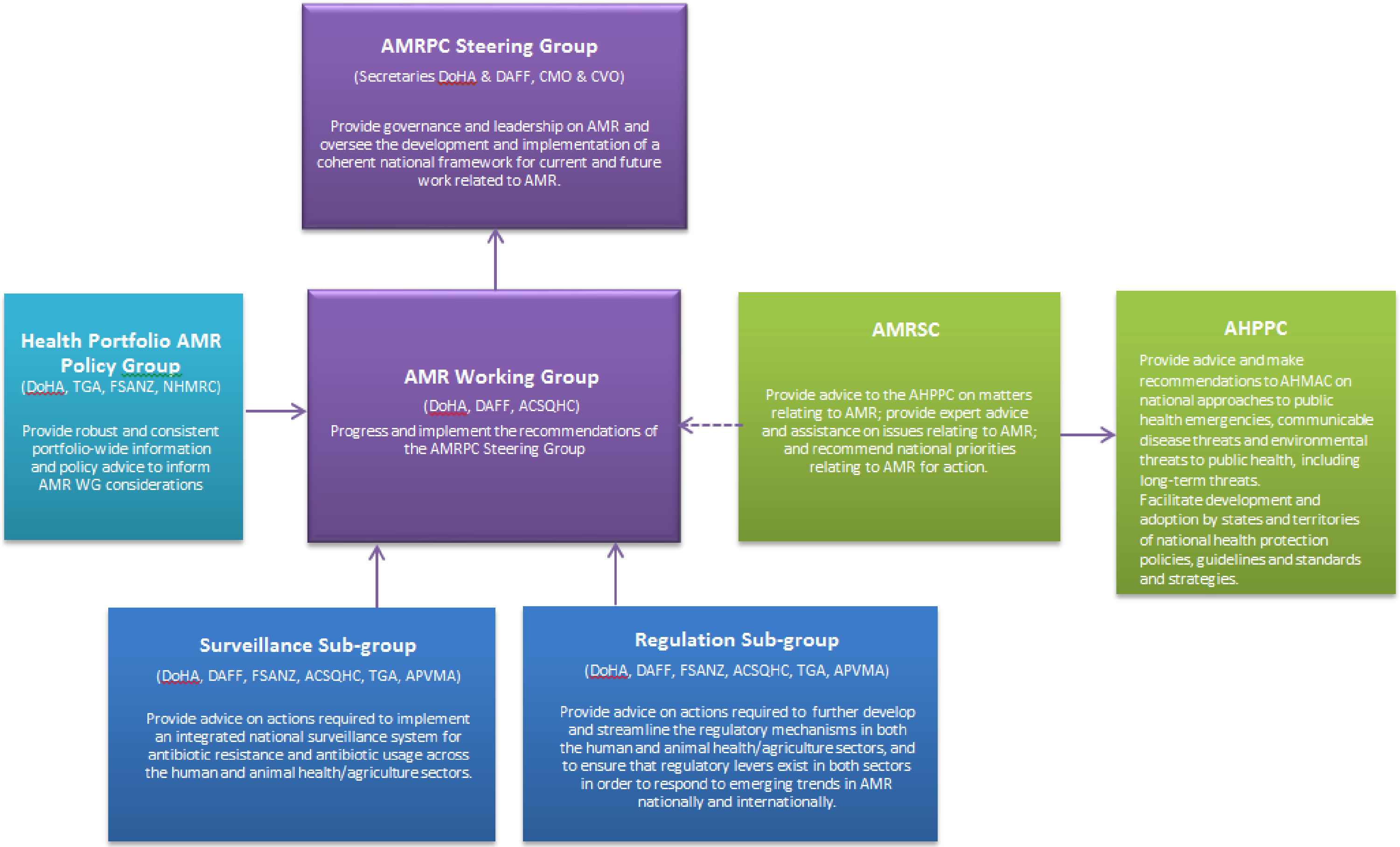
AUS = Australia; DDD = defined daily dose (per 1000 inhabitants per day)
Source: European Surveillance of Antimicrobial Consumption. Australian data from Australian Statistics on Medicines, www.pbs.gov.au/statistics/asm/2010/australian-statistics-on-medicine-2010.pdf.

Figure 5 European rankings of antibiotic use

Professor Baggoley said that we have had a range of AMR initiatives in Australia (Figure 6); these include those developed and implemented by the Australian Commission on Safety and Quality in Health Care (Hospital-Associated Infections Program, 2007 onwards; National Standards for Safety and Quality, 2013; AMR Colloquia, 2011; Antimicrobial Stewardship, 2011; Accreditation, 2013), DoHA (Pharmaceutical Benefits Division, TGA, Office of Health Protection), Antimicrobial Resistance Standing Committee (established in 2012, reports to the Australian Health Protection Principal Committee), Antimicrobial Resistance Prevention and Containment Steering Group (set up in February 2013), and the Senate Inquiry into the Joint Expert Technical Advisory Committee on Antibiotics (JETACAR) in 2013.

He said that current AMR activities in the health and ageing portfolio include monitoring and surveillance activities, infection prevention strategies and hygiene measures, education, research and communication.

He said that most importantly, we are working towards a national comprehensive AMR management plan for Australia.



ACSQHC = Australian Commission on Safety and Quality in Health Care; AHMAC = Australian Health Ministers Advisory Council; AHPCC = Australian Health Protection Principal Committee; AMR = antimicrobial resistance; AMRPC = AMR Prevention and Containment; AMRSC = AMR Standing Committee; APVMA = Australian Pesticides and Veterinary Medicines Authority; CMO = Chief Medical Officer; CVO = Chief Veterinary Officer; DAFF = Department of Agriculture, Fisheries and Forestry; DOHA = Department of Health and Ageing; FSANZ = Food Standards Australia New Zealand; NHMRC = National Health and Medical Research Council; TGA = Therapeutic Goods Administration; WG = Working Group

Figure 6 Governance arrangement for the development of the comprehensive Australian antimicrobial resistance management plan

Professor Baggoley said that any national plan needs to be comprehensive. He said there are many people involved, and many issues to cover. He said we need to understand what people are doing and bring it together in a way that is comprehensive and interactive, working at different levels and across jurisdictions.

He concluded by listing his take-home messages:

- The aetiology of the increase in AMR is complex.
- Improved antimicrobial use through antimicrobial stewardship can contribute to decreasing established AMR, but is not enough for resistance control.
- Infection control at the hospital and community level must be part of the response for maximum impact.
- When it comes to an AMR response, ‘there is no such thing as too much’.

5 National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health

Dr Marilyn Cruickshank, Chair, Antimicrobial Resistance Standing Committee (AMRSC)

In 2011 the Antimcrobial Resistance Summit was held, bringing together experts from a wide range of fields. There was a sense of purpose and willingness to work together, but at same time, there was a general feeling that nothing much was happening on a national scope. Despite the range of efforts in Australia, existing programs had a patchwork approach.

The summit identified that an Australian antimicrobial resistance (AMR) plan would require:

- implementing a comprehensive national resistance monitoring and audit system
- coordinating education and stewardship programs
- implementing infection prevention and control guidelines
- expanding funding to support research into all aspects of antibiotic resistance
- reviewing and upgrading the current regulatory system applying to antibiotics
- undertaking community and consumer campaigns.

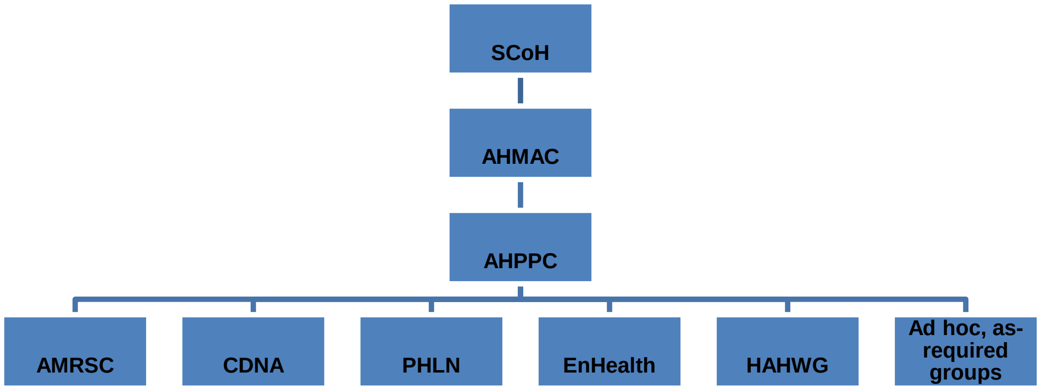
In 2012, the Australian, state and territory governments agreed to establish the AMR Standing Committee (AMRSC). Its role was to include identifying national priorities for action to address AMR across the health system.

AMRSC membership includes:

- Dr Marilyn Cruickshank (Chair), Australian Commission on Safety and Quality in Health Care
- Prof Chris Baggoley, Australian Chief Medical Officer
- Dr Mark Schipp, Australian Chief Veterinary Officer
- Dr Lynn Weekes, Chief Executive Officer, NPS MedicineWise
- Dr Allen Bryce, Australian Pesticides and Veterinary Medicines Authority
- Ms Claire Boardman, President, Australasian College of Infection Prevention & Control
- A/Prof Jim Buttery, Pharmaceutical Benefits Advisory Committee
- A/Prof John Ferguson, Australian Commission on Safety and Quality in Health Care
- Dr Jenny Firman, Medical Advisor, Australian Government Department of Health and Ageing
- A/Prof Tom Gottlieb, President, Australian Society for Antimicrobials
- Dr Rosemary Lester, Chair, Communicable Diseases Network Australia
- A/Prof David Looke, President, Australasian Society for Infectious Diseases
- Prof John McCallum, National Health and Medical Research Council
- Dr John Skerritt, National Manager, Therapeutic Goods Administration
- Dr David Smith, Chair, Public Health Laboratory Network

- Prof John Turnidge, National Health and Medical Research Council
- Mrs Margaret Duguid, Australian Commission on Safety and Quality in Health Care
- Prof Graeme Nimmo, expert.

The AMRSC is placed in the national structure, and so can bring attention to the issues at a high level (Figure 7).



AHMAC = Australian Health Ministers Advisory Council; AHPPC = Australian Health Protection Principal Committee; AMRSC = AMR Standing Committee; CDNA = Communicable Diseases Network Australia; EnHealth = Environmental Health Committee; HAHWG = Health All Hazards Working Group; PHLN = Public Health Laboratory Network; SCoH = Standing Committee on Health

Figure 7 Australian health committees and organisations

The AMRSC's first project has been the development of a report to examine the current situation of AMR in Australia. The report, *National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health in Australia,*[18] is based around the following questions:

- What reporting and surveillance of antibiotic usage and AMR currently occur in Australia?
- What options for a nationally coordinated approach are most applicable to the Australian context?
- What are the enablers and barriers to the establishment of a nationally coordinated approach to AMR in Australia?

The scope of the report is limited to bacteria in the context of human health, and is broadly consistent with elements of the proposed Communicable Disease Control Framework for Australia. The report proposes options applicable to the Australian context for short, medium and longer-term actions. It expresses strong support for national coordination using a One Health framework, linking data on resistance and antibiotic use from humans, animals and agriculture.

The AMRSC identified 28 key AMR and antimicrobial use in health stakeholders across Australia, and invited them to participate in a survey regarding proposed model(s) for a nationally coordinated approach. The stakeholders supported the need for national coordination and integration, and favoured the Danish and Swedish models detailed in the report.

The report recommendations are being considered by the AHPPC.

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18 AMRSC (2013). *National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health in Australia,* Antimicrobial Resistance Standing Committee, Sydney.

Part 2 Time to talk

6 Group discussion morning session

Risk assessment

Question

In Australia, what are the major antimicrobial resistance (AMR) risks to human health associated with antimicrobial use in food animals and companion animals?

The risk

The participants noted that AMR is a risk for infectious disease management in all sectors: hospitals, community, food animals and companion animals. Hospitals are often cited as the most significant problem, but the relative contribution from other sectors is not known.

Anecdotally, participants reported that major groups of people associated with AMR infection in clinical practice include returning travellers and people who have been in hospital. Increasingly, people from community settings, including farmers, are also presenting with AMR infections. There is concern that AMR from nonhuman sources may be contributing to this disease burden in humans.

The risk to human health associated with antibiotic use in animals (now or in the future) that was the focus of discussions at the Colloquium was the risk of treatment failure attributable to AMR arising from the use of antimicrobial agents in food-producing animals or companion animals.

The complex epidemiology of AMR (see the briefing paper in Appendix 2) highlights the challenges involved in identifying and prioritising AMR risks. Participants noted that AMR can be considered to be a bidirectional zoonosis. It also has multidirectional links to other environmental compartments, including aquaculture, food plants and drinking water.

Are the risks perceived or real, and how strong is the evidence of a risk to human health?

We have an extensive scientific understanding of the physiology of animals, spread of bacteria and transfer of AMR genes. AMR bacteria and their genes can become very widely distributed in the environment and move between animal species. Although there is little direct evidence within Australia, the spread of AMR organisms from animals to humans and transfer of AMR genes from animal to human strains of bacteria, has been documented overseas. For example, the Canadian Integrated Program for Antimicrobial Resistance has described a strong correlation between a ceftiofur-resistant *Salmonella enterica* serovar isolated from retail chicken and infections with the same Salmonella serovar in humans across Canada.[1] In Australia, rifampicin-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated from equine practitioners and horses, and enrofloxacin-resistant MRSA has been isolated from companion animal vets and dogs.[2]

In the same way that scientific understanding of the influenza virus confirms the potential for emergence of new strains of influenza and a possible influenza pandemic, the risk of overuse of antibiotics in humans is underpinned by very clear scientific understanding of the selection, amplification and dissemination of AMR in humans treated with antibiotics.
These same scientific principles also underpin the potential AMR risk to human health associated with antibiotic use in animals.

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1 Dutil L, Irwin R, Finley R, Ng LK, Avery B et al (2010). Ceftiofur resistance in *Salmonella enterica* Serovar Heidelberg from chicken meat and humans, Canada. *Emerging Infectious Diseases* 16:48–54.

2 Emeritus Professor Mary Barton, veterinary pathologist, University of South Australia (unpublished data).

As noted above, AMR can be considered as a bidirectional zoonotic and multidirectional environmental disease. Farmers, abattoir workers and veterinarians are at particular risk of AMR associated with antibiotic use in animals, because of occupational exposure to AMR bascteria in animals. Consumers of animal products have a lower risk of exposure to those bacteria. Companion animals can be reservoirs for human infectious agents, including AMR organisms, and can reinfect their owners after the initial infection has cleared and initiate the need for further antibiotic treatment. For example, recurrence of MRSA infection and nasal colonisation in a couple was prevented only after successful eradication of MRSA from the family dog's nares; and cross movement of MRSA occurs between pets and children).[3,4]

The prevalence of multi-resistant organisms in animals appears low in Australia relative to the rest of the world, and the organisms rarely cause untreatable infection in animals. However, the significance of even a low incidence of AMR infections in animals becomes clear when we consider that an individual case can be the index case for a new resistance mechanism. Identification of such an individual case allows early action to prevent spread of the infection and transfer of the genes to other organisms.

The AMR risk to human health associated with human use of antibiotics is more significant than with animal use, but is also poorly quantified, with no standardised approach to collecting data. Overall, the more antibiotics that are used across all sectors, the greater the risk of development and amplification of AMR.

Traditionally, microbiological risk assessment has been mainly concerned with the spread of organisms, including AMR bacteria (such as from animals to humans via food). However, the 'promiscuous' nature of AMR genes means that the risk of gene transfer also needs to be assessed. Ideally, we also need to look at use of antibiotics in plant food production and imports, contaminated agricultural products, aquaculture, water, etc. Professor Turnidge noted that we are all 'swimming in the same gene pool', which makes quantitative risk assessment difficult!

How can the evidence base of risk be strengthened?

Risk assessment requires understanding how and why antibiotics are used in different situations (e.g. humans, food-producing animals, companion animals, other agricultural uses). The data required for assessing the risks arising from resistance caused by antibiotic use in animals involves three components:

- antibiotics — quantity, type (class/mechanism of action), why used and route of administration
- AMR bacteria — species, number, type, location and potential for spread
- AMR resistance genes — properties of gene context, ability and opportunity to transfer genetic material to other organisms.

For existing uses of antibiotics, data need to be collected through surveillance and monitoring programs that target these components. International data is also useful in this regard. For new antibiotics, or new uses of existing antibiotics, assessments can be based on the properties of the

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3 Manian FA (2003). Asymptomatic nasal carriage of mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) in a pet dog associated with MRSA infection in household contacts. *Clinical Infectious Diseases* 36(2):e26-e28.

4 Bender JB, Waters KC, Nerby J, Olsen KE and Jawahir S (2012). Methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from pets living in households with MRSA-infected children. *Clinical Infectious Diseases*, 54(3):449–50.

proposed antibiotic, proposed use patterns, resistance selection in target pathogens and non-target commensals, likely AMR mechanisms, and properties of the expected AMR genes.

Further research is needed in Australia to collect reliable data that takes account of Australian livestock and companion animal practices and regulation. This information can be used to build a risk profile to help identify and prioritise risks, and guide decisions on risk management actions, as discussed above.

See below for a more detailed discussion of surveillance and monitoring requirements for animals and food.

What are the major information gaps, and how can they be addressed?

Participants identified the following knowledge gaps:

- Baseline and ongoing data are needed for antibiotic use in animals (at a gross level, which is currently available from sales), as well as the pattern of usage (what, where, why, when, how?).
- Baseline and ongoing data are needed on where and how many AMR bacteria there are in food animal and companion animal populations, food products and farm environments.
- Little is known about imported AMR bacteria (e.g. in food, returning international travellers, immigrants).
- Very little is known about non-animal (including human) sources of AMR (e.g. plant foods, wastewater).

These information gaps can be addressed by a broadly based surveillance program involving live animals, animal products, and other agricultural and environmental products.

Some participants noted that if all antibiotic use in animals was stopped, it could have a major negative impact on food production (and thus food security), animal welfare, trade (import/export) and human health. There may be some circumstances where antimicrobial use can be curtailed without a loss of production, thus providing savings on antibiotic use. There are currently no baseline data to measure these, or any other, effects that may result from reducing antibiotic use. To help resolve these issues, surveillance is needed at multiple points along the food production chain.

Other information gaps identified by participants included:

- understanding of AMR gene transfer, including the potential for genes to be transferred to and from companion animal organisms
- the potential of new diagnostic tools for AMR organisms and genes in different laboratory settings, and at the point of care to reduce antibiotic use
- from the methods currently described, how to develop a universal measure for antibiotic use in animals (equivalent to a defined daily dose in humans).

Some participants also mentioned the need to monitor antibiotic residues in food products. However, others noted that (i) residues are already measured as part of the National Residue Survey, and must comply with maximum residue limits set by Food Standards Australia New Zealand; and (ii) antibiotic residues in food are unlikely to contribute significantly to development of AMR in humans.

Surveillance and monitoring

Question

What are the most important components of a program of surveillance and monitoring of antibiotic use and antimicrobial resistance (AMR)?

Surveillance principles

There was agreement among participants that risk-based, ongoing and systematic surveillance and monitoring of antibiotic use and AMR resistance in animals is required to complement the proposed improved surveillance and monitoring of human antibiotic use.[5]

Collection of data is critically important to identify the significance of the spread of resistant organisms from animals to humans and the transfer of resistance genes in Australia. Collecting data would have the following benefits:

- detecting changes in AMR prevalence and distribution
- targeting of resources
- identifying if there is a problem, and if so, where
- empowering decision makers
- setting priorities and developing the most cost-effective actions
- developing risk communication messages
- allowing the impact of risk management measures to be assessed.

Participants identified a number of principles to underpin an AMR surveillance and monitoring program:

- clear purpose agreed upon by all parties (based on One Health principles as an 'umbrella')
- clear ownership of data (including the role of regulation to allow access to data)
- meaningful data sets
- robust industry partnership and engagement
- appropriate analysis and interpretation
- timely collection, analysis and reporting of data
- cost-effective and sustainable methods
- flexible, agile programs that can adapt to emerging issues.

These principles reflect those set out the *CDC Guidelines for Evaluating Public Health Surveillanc*e *Systems*, which also provide further useful guidance.[6]

The sustainability of the program is very important, including secure and ongoing funding, personnel and a mechanism to bring together human and animal data.

5 AMRSC (2013). *National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health in Australia,* Antimicrobial Resistance Standing Committee, Sydney.

6 www.cdc.gov/mmwr/preview/mmwrhtml/rr5013a1.htm

What are the priorities for surveillance and monitoring of antibiotic use?

Surveillance and monitoring of antibiotic use has two components:

- the type and amount of antibiotics used
- why, how and when the antibiotics are used (species, indication, dosage regimen).

To capture these two components, surveillance needs to provide clarity and rigour for antibiotic data in terms of:

- imports and manufacturing of each active constituent
- point-of-sale quantities
- levels of use
- indications for use (e.g. prophylaxis vs metaphylaxis vs treatment vs growth promotion)
- defined daily dose (DDD) or animal equivalent, and use of specific agents.

Participants stressed that surveillance needs to include all antibiotics used in animals and humans, including antibiotic use in aquarium fish and aviary birds (subject to risk assessment). However, it should not be too intensive or burdensome, and should, where possible, use existing systems or processes.

What are the priorities for surveillance and monitoring of antibiotic resistance?

Surveillance and monitoring of antibiotic resistance also has two components:

- AMR bacteria — species, prevalence and setting
- AMR genes — characterisation (genomic analysis) and tracking.

To capture data on these components, surveillance programs need to consider the following issues:

- sampling that provides a robust basis for inferences about the location of AMR bacteria in relation to animals in Australia
- development of minimum data sets (with standard data definitions)
- passive and active data collection methods, with the ability to modify as needed
- laboratory requirements
- timing and frequency.

Specimens for surveillance

- Animal species
  - livestock
  - aquatic animals
  - companion animals
- Animal specimens
  - infected animals
  - well animals
  - food products (distinguishing imported from domestic, and addressing cross-contamination issues)
- Settings
  - farms
  - veterinary clinics

  - food-processing environments
  - environment and water

- Standard organisms (consistent with international programs)
  - Salmonella spp.
  - *Escherichia coli*
  - Campylobacter spp.
  - *Staphylococcus aureus,* including methicillin-resistant strains (MRSA)
  - Enterococcus spp.
  - *Clostridium difficile*
  - Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP)

- Specific organisms
  - pathogens in animal production systems that attract the greatest use of antimicrobials, and that have a known propensity to develop AMR (e.g. enterotoxigenic *E. coli*)

- AMR genes: examples of special interest include
  - MRSA ST398 (which has been found in Australian pigs, but its origin is unknown)
  - extended spectrum beta lactamase (ESBL) producing Enterobacteriaceae and resistance to carbapenems
  - fluoroquinolone resistances

- Other specimens
  - food plants
  - water
  - environment.

The issues identified above would form a basis for a surveillance technical group to formulate a program that would meet microbiological, epidemiological, economic and practical requirements. For example, surveillance is not required for all organisms, but needs to include a range of indicator organisms consistent with international programs (including *C. difficile*, MRSP and MRSA) and be guided by the outcomes of risk profiling.

Testing and surveillance of food-producing animals should consider multiple points throughout the food chain (from carcase to prepared food).

Participants stressed that data need to be meaningful, cost-effectively collected, reported to people who can do something with it, and purposeful. We need to engage industry, decide who is going to take action, and conduct appropriate analysis and interpretation.

Data collection methods

There are three methods of AMR data collection:

- Passive data collection — disease-producing organism reports from pathology laboratories

- Active data collection — prospective screening for commensal and pathogen organism AMR reports from well people or animals

- Targeted data collection — for additional resistance testing of isolates from the other programs to antimicrobial agents not tested routinely, and to conduct genetic analyses for clonal spread and resistance gene types.

In animals, the purpose of surveillance, and the interpretation of data, are different from that in humans, and are more complex. In humans, surveillance is about diagnosing and monitoring disease-producing organisms (e.g. using passive reporting of pathology laboratory disease diagnosis results). In animals, it is also important to look at commensals from well food animals. This requires active sampling and analysis of samples from abattoirs, farms and food of animal origin at the retail outlet. The design of the sampling program is critical in this instance. Environmental sampling is also required to complete the epidemiological approach.

Standardising AMR surveillance is challenging. Although there is considerably more experience in human AMR surveillance than for animals, passive AMR reporting for human laboratory isolates is not standardised. AMR and antibiotic use in community medicine also requires more surveillance.

Laboratory requirements

A number of issues relating to veterinary laboratory requirements were raised (including access to technology and funding) to overcome differences in laboratory methods and systems in the animal and human sectors. Veterinary laboratories also need resources to allow them to follow similar international standards and quality assurance systems as those used by their human counterparts.

What is the most appropriate mechanism for collecting and quantifying data on antibiotic use in animals?

Antibiotic use data can be collected from prescribers (to enable collection of information on therapeutic uses) and from other parts of the distribution chain, for example feed mills (for prescribed and non-prescribed uses in feed).

Under current professional standards for veterinarians, it is mandatory to record antibiotic prescription information, but there is no requirement to report prescription details. Veterinarians currently record the information in many formats, making collection and collation possible, but very difficult. However, veterinarians among the participants at the colloquium noted that most veterinary practices use one of a small number of common software programs to manage their prescribing, and that in theory, at least, it would be relatively straightforward from a technology perspective to collect data using these programs. It was also suggested that this approach would lend itself to development of an app for use with mobile computing devices.

There was considerable discussion about whether reporting of prescription data could be made mandatory. However, the mechanisms for this need to be explored more fully with the state health authorities and veterinary practitioner/surgeon boards in each state (who administer legislation).

A technical and practical consideration to be addressed is the most appropriate level of aggregation for antimicrobial use data. Ideally, data would be recorded on a per-animal basis to generate something like the equivalent of 'defined daily dose' that is used in humans. However, in some cases, data may not be available at the level of individual animals – it might only be procurable when aggregated at the herd or industry level. Nevertheless, the latter is still considered valuable information. In the European Union, the current parameter of antibiotic use that enables inter-country comparisons is the population correction unit – the denominator of which is based on the total live mass of animal production per year.[7]

Interpretation of the data collected on antimicrobial use in animals is not as straightforward as in humans, owing to the extreme variation within and between animal species. Thus, the European Union has developed a summary measure of antibiotic use in livestock that countries can use to report their level of prescribing of veterinary antimicrobials. This statistic provides a basis for comparison of countries, but does have some disadvantages arising from its very generalised nature.

7 Grave K, Greko C, Kvaale MK, Torren-Edo J, Mackay D, Muller A, et al (2012). Sales of veterinary antibacterial agents in nine European countries during 2005–09: trends and patterns. *Journal of Antimicrobial Chemotherapy*, 67(12):3001–08.

An Australian effort on surveillance for antimicrobial use in animals will need to consider this and other approaches to reporting and appropriate interpretation.

What are the most appropriate mechanisms for surveillance and monitoring of antimicrobial resistance in food and animals, including frequency?

In addition to what has been summarised above, the most appropriate methods, including frequency, need to be determined based on risk assessment, cost-effectiveness and other pertinent considerations. Flexibility is also important to allow for changes in priorities (such as the emergence of a new AMR strain). Passive systems, especially for monitoring antibiotic use, have the advantage that they can be continuous.

The ideal surveillance system would address a precise set of objectives derived from the risk assessment, while accounting for cost and logistical constraints that might be encountered. The objectives should be prioritised, such that high-priority issues will be evaluated more often and with more accuracy than low-priority issues. A technical group could be charged with defining the details of this approach with ratification by the Steering Group.

What is the most appropriate means of integrating antimicrobial resistance and antibiotic use surveillance information?

Epidemiology networks need to be established to ensure that data can be communicated effectively across sectors. A One Health national coordinating centre, based on capture of the full continuum from animals to food to humans, would allow the best integration of surveillance information. Human and veterinary research in this area (e.g. research on gene markers) also needs to be linked.

A wide variety of avenues exist for extending the results from surveillance to decision makers in clinical practice and policy settings. Surveillance reports or extracts could be targeted to specific decision-making needs. There is also a need to coordinate the findings from different sources, including animals and humans. Because of this large variation in stakeholder needs, a One Health national centre will need to coordinate the role of communication and extension (see Section 7 for further discussion of risk communication).

7 Group discussion afternoon session

Risk management — priority actions for protecting human health

What are the key priorities for action for human health protection against AMR?

As noted in Section 6, 'we are all swimming in the same gene pool', which makes the management of AMR risks to human health challenging. The One Health approach to action provides an opportunity to find common ground across sectors and develop a unified management plan.

Risk management priorities should be guided by the outcomes of risk assessment, and interventions should be measured to ensure they are effective and cost-efficient. Risk management can be guided by the '5Rs' (reduce use, refine use, replace antibiotics, regulate, research alternatives). In addition, systems to identify and react to emerging AMR threats should be developed, including triggers for review and powers that regulators have to investigate and take corrective action.

Legislation and regulation of antibiotic use should be harmonised across Australian states and territories, especially control of antibiotic use in veterinary and agricultural practice.

Regulation (importation, antimicrobial registration, antibiotic use controls, collection/audit of data)

Participants discussed many options for regulation of antibiotic use, import of food and vaccine and other issues. Risk assessment was seen as important to underpin all regulation processes.

Availability of vaccines in Australia is dependent on strict quarantine regulations. Participants from the veterinary medicines industry noted that some vaccines available overseas cannot be imported, producing a greater need for antibiotics.

Antimicrobial registration and use: discussion points

Participants suggested a number of important actions to be taken in antimicrobial registration and use:

- Regulate the availability and use of critically important human antibiotics at state, territory and federal level.
- Assess the risks associated with the use of critically important human antibiotics by small animal veterinarians (allow use only if no other treatment is available and it is an animal welfare issue).
- Further enforce existing regulations (e.g. via veterinary surgeon boards, state health departments).
- Review AMR risks posed by existing and approved antibiotic products.
- Tighten veterinary prescribing authority (e.g. for use by farmers) and introduce a requirement to report use.
- Consider separating prescription and dispensing rights to remove motivation for over-prescription.
- Increase existing regulatory activities and functions to explicitly include AMR risk assessment for all new antibiotic products and indications, and for human products and Pharmaceutical Benefits Scheme applications.

- Review off-label antibiotic use controls and clarify restraints indications and restrictions of administration and use (e.g. mass medication).
- Review and strengthen regulation of compounding pharmacies.

Import of food and medical products

Participants suggested actions around the import of food and medical products:

- Evaluate the potential for improving the surveillance of imported food for resistant organisms. Where opportunities exist to generate meaningful data on important risks in imported food, then surveillance should be initiated.
- Explore ways of creating a level playing field for local and overseas producers of food items with respect to risk of resistance. Currently, because there is no surveillance of AMR in Australian food-producing animals, under World Trade Organization arrangements there is no ability to use the results of tests of imported foods for AMR bacteria to restrict importation. Also, as we have no food standards related to the acceptable level of AMR bacteria in domestic food, we cannot impose such a requirement on imported food.
- Review import regulations for vaccines used to combat bacterial and viral diseases of food animals. Greater availability of vaccines could reduce the demand for antimicrobials in some circumstances. Access to vaccines from abroad is currently difficult, because of Biosecurity Australia and Office of the Gene Technology Regulator restrictions in relation to potential for introduction of unwanted biological agents (e.g. the agents of transmissible spongiform encephalopathies) and vaccines based on genetically modified organisms.

Guidelines

Participants thought that central to managing AMR is universal adoption and implementation of high standards of hygiene and infection control, including:

- standardised infection control guidelines in medical and veterinary practice, and
- guidelines for prudent antibiotic use.

Education — objectives and how to measure effectiveness

Options discussed included the need to:

- develop best-practice guidelines, including nutrition, hygiene, infection control and biosecurity
- increase practitioner awareness about responsible use
- provide education for medical, veterinary, other health professions and consumers on antibiotic stewardship
- increase public awareness about the risks of close contact with animals
- educate the medical profession about non-human use of antibiotics, and the veterinary profession on human use; encourage interdisciplinary learning
- reinforce undergraduate education about antimicrobials, including pharmacology (pharmacokinetics, pharmacodynamics), resistance issues and responsible prescribing
- link education with auditing and accreditation (including right to prescribe), including self-audit of prescribing as a mechanism to improve prescribing practice.

The effectiveness of education initiatives must be measured to ensure appropriate changes in infection control behaviour and reductions in antibiotic use and AMR importance.

Data gaps and need for specific research

Data gaps and research needs include:

- better understanding of the contribution that animals make to AMR
- AMR genetics
- AMR prevalence in imported foods
- vaccines
- antibiotic alternatives
- more rapid diagnostic methods.

In terms of research into alternatives to antibiotics, there is currently no incentive to biotechnology companies to sell to Australia because of the small market. Import restrictions for vaccines are a disincentive to importation, and the small market is a disincentive to domestic vaccine development and use.

Other alternatives include probiotics, prebiotics, synbiotics, eubiotics and modification of systems to improve animal health outcomes and reduce requirement for antibiotics (e.g. measures to reduce stress in cattle being moved to feedlots). Some research is occurring (e.g. the use of bacteriophages to control enterotoxigenic *Escherichia coli* in pigs), but this type of research requires further support. It is important that alternative veterinary medicines are subject to the standard regulatory assessment of efficacy, safety and quality.

There need to be funding incentives for AMR-related research: particularly targeted research to answer specific questions about risk assessment and to help make risk management decisions. This could be addressed through commissioned research to address specific problems.

How can effectiveness of risk management be measured?

Trends can be established through longitudinal studies to measure prevalence of AMR in humans and indicator organisms in animals.

Risk communication — getting the message out there

What are the key messages and approaches for communicating the national approach to antimicrobial resistance (AMR) prevention and containment?

One Health approach to communication

One Health is an umbrella for community and interdisciplinary dialogue to allow health science, social, environmental and economic issues to be addressed, including areas of ongoing uncertainty.

AMR risk management requires a whole-of-government approach. Department secretaries can issue joint communiqués.

Under One Health, communications can have a consistent approach across all sectors (doctors, veterinarians, farmers, industry and community). There can be parallel editorials in the *Australian Veterinary Journal* and the *Medical Journal of Australia*.

Key audiences

AMR affects the whole community. Therefore, the audience includes all citizens. More specifically, participants identified the following audiences:

- Practitioners — clinicians, veterinarians (individuals, organisations)
- Professionals, experts (individuals, organisations)
- Animal producers (individuals, industry groups)
- Public (individuals, community groups)
- Governments (national, state)
- Politicians
- Policy makers
- Pharmaceutical industry
- Processors of food
- Antibiotic manufacturers and sellers
- Pet owners
- Research funders (government, nongovernment)
- Media.

Audiences may be local, national or international. The most important audiences are the prescribers (human and animal use), and the farmers (nonhuman use). We also need to change the culture of the general community. The professional groups are educated and health aware, but a large proportion of people are not well informed and do not understand the issues of AMR.

Key messages of a communication strategy

Messages need to stress judicious use of antibiotics, infection prevention, containment and control in animal and human sectors (e.g. ‘every prescription matters’, ‘save our antibiotics’, ‘we are running out of weapons to fight infections’). More technical issues include the need for vaccines and improved diagnostic methods (especially in veterinary laboratories). Collaboration between human and veterinary laboratories may promote rapid diagnosis and better prescribing in animals.

Messages need to be action-oriented, with a focus on what can be done now (e.g. four top actions). Messages that value and reinforce positive achievements are also important. Messages also need to raise awareness of risks while keeping risks in proportion (this is particularly important for stories to the media, to avoid ‘scare stories’). Above all, messages need to be simple; see the Chief Scientist’s brief (Appendix 3) for key messages, which carry the authority of the Chief Scientist and have generated immediate media interest.

Participants noted that even where prescribers and consumers appreciate the need for conservative use, they may not know what to do about it. To reinforce this, under the One Health umbrella, messages can be developed that are tailored to the needs for different groups, have emotional appeal, and are designed to promote action (e.g. for consumers: ‘Don’t pay for antibiotics that you don’t need’). Professional groups respond better to messages that are tailored to the reality of their practice. Commercial sectors (particularly farmers and veterinarians) require supporting data and communication to justify action with financial implications (such as sale of antibiotics by veterinarians).

As with science communication about other emerging biotechnology and science issues, it is important to recognise that AMR is not just a science and health issue, but also a social, environmental and economic issue. Understanding these interactions is important, because the enablers and barriers for appropriate prescribing differ between animal and human sectors. It is easy for the discussion to become blocked and polarised in the absence of opportunities to listen to all perspectives.

Most effective processes for communication to each of the groups

AMR communication needs a sustained campaign, with saturated media and a public education program: not just public relations program. It takes a long time to find a tipping point in public awareness and culture, and communication strategies have to be consistent and sustainable in the long term. NPS MedicineWise has already been working in this area, and can provide advice on what communication messages and approaches are effective. This program could also adopt a One Health approach by the inclusion of animal health prescribing messages.

Champions (trusted experts) can promote messages in clinical, veterinary and other professional arenas to make best practice more visible and to raise the profile of AMR issues. Personal contact is important. In the community, celebrities can exert great influence and promote messages widely.

A 'One Health' website would provide a central resource that is easy to access, with key information for different audiences (e.g. 'everything you need to know about AMR'). Existing guidelines and evidence provided can be showcased on this site (and in other communication messages). Social media and email will also be important.

Community dialogue and interdisciplinary engagement are important to allow expression of all the aspects of AMR (i.e. science, health, social, economic, environmental) in relation to harms and benefits. This is needed to build trust and commitment to action. Such dialogue would also allow discussion of ongoing uncertainty, so that issues can be creatively explored instead of becoming adversarial. Such dialogue can occur at all levels (i.e. between colloquium participants and their industry, or between health and agriculture professionals).

Community perceptions are complex. Some argue the impact of overseas use of antibiotics is much larger than use in Australia; and – like climate change – our ability to have a global impact is limited because China, for example, has a bigger effect. However, we are part of a global effort to do what we can and to contribute to international advances and improvements.

The timing of vertical communication strategies for each target group is also important, so that the chain reaction is a positive and reinforcing experience, with no one feeling as if they are on the back foot (e.g. don't approach consumer groups before general practitioners). It is not useful to 'point the finger' at doctors, because consumer demand is also a problem. Strategies that allow bottom-up communication may also be important to encourage community engagement. Thorough understanding of the target audiences, including personality profiling, would strengthen these approaches and communication in general.

Public communications campaigns are expensive and need a sustainable source of funding (e.g. in the area of road safety, speeding advertisements were paid for from car registration fees). A surcharge on antibiotics could provide an equivalent funding mechanism for AMR communications; this might also reduce usage in some contexts through increased cost.

Professional organisations (e.g. Australian Veterinary Association, Australian Medical Association) can conduct education within their groups as part of their charter, and like champions, have impact when they take a public stand. However, participants reported that less than 50% of doctors and veterinarians are members of these organisations.

8 Summation of the colloquium outcomes

Stephen Page summed up the main themes that had emerged during the day:

Risk assessment

- Risk assessment is an important driver – if you don’t know the risks, you cannot target and measure them.
- The risks of human use of antibiotics are real and significant.
- The contribution of animal use of antibiotics to human health risks is less clear and needs further research in the Australian context.
- We need local data to underpin the development of a risk matrix/risk profile to assess and identify key priorities for action.
- Key ‘bug–drug’ combinations overseas include foodborne fluoroquinolone-resistant (FQR) *Campylobacter* and *Escherichia coli*, and FQR and extended spectrum beta lactamase (ESBL) *Salmonella*, with emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* as potential foodborne agents of the future.

Risk measurement: Surveillance and monitoring

- Surveillance to date is limited and not collected systematically. We need better data on the use of antibiotics in veterinary practice and food production, and improved surveillance of AMR organisms.
- Principles for a surveillance and monitoring program include clarity of purpose and ownership of data; meaningful datasets; robust industry partnerships and engagement; appropriate and timely analysis and interpretation; cost-effective and sustainable methods; and ability to adapt to emerging issues (flexibility).
- There needs to be a sustainable funding strategy (which may, for example, include any single source or combination of government and industry).
- There need to be clear benefits to gain and maintain active participation of key stakeholders.
- There are a huge number of possible combinations of ‘drugs, bugs and hosts’, so programs need a clear focus.
- Surveillance needs to be a continuum across all of One Health to build the complete story.

Risk management

- Recognition that ‘we are all swimming in the same gene pool’ is a fundamental consideration when designing risk management plans.
- The One Health approach provides opportunities for education and stewardship across sectors.
- Regulation is important, but further research is needed to better understand the development of AMR and the direct actions needed to intervene in chain of development.
- Research is also needed to reduce the need for antibiotics through the development of other methods of infectious disease treatment and prevention.

- In addition to regulation and research, risk management can also use the other 3Rs of: refinement of current use, reduction of antibiotic use and replacement of antibiotics.

Risk communication

- Messages need to raise awareness of risks, while keeping risks in proportion.
- Key messages include judicious use of antibiotics, infection prevention, and containment and control in animal and human sectors.
- There are many audiences for AMR communication (e.g. practitioners, professionals, livestock producers, general public, policy makers); messages need to be targeted to meet the needs of these different audiences.
- Champions (trusted experts) and celebrities will help to reach different audiences.
- Messages need to be simple, action-oriented and reinforce positive achievements.
- Online and social media are increasingly important.
- AMR is not just a science and health issue, but also a social, environmental and economic issue.

Where to from here?

Dr Mark Schipp (Chief Veterinary Officer) and Professor Chris Baggoley (Chief Medical Officer) closed the Colloquium.

Mark Schipp commented again on the unique bringing together of experts and the importance of communication among experts from different areas of antibiotic use and regulation. He said that the AMRSC report is world class and has already gained international interest. He said that extension of this work to include the animal sector is the next important step.

Chris Baggoley also stressed the significance of this first Australian One Health AMR gathering, and that the conversations started must continue. He thanked the organisers and attendees and said that this issue now has a momentum that it didn't before. He said we need to do something about it, and will be held accountable if we don't.

Appendix 1 Participants – AMR Colloquium

Facilitator: Dr Stephen Page

- Prof Chris Baggoley AO, Chief Medical Officer , Department of Health and Ageing (Antimicrobial Resistance Standing Committee [AMRSC] Member)
- Ms Marcia Balzer, National Public Affairs Manager, Australian Veterinary Association
- Ms Christina Bareja, Assistant Director, Vaccine Preventable Disease Surveillance Section
- Prof Mary Barton, Emeritus Professor, University of South Australia
- Dr Paul Brent, Chief Scientist, Food Standards Australia New Zealand
- Dr Allen Bryce, Australian Pesticides and Veterinary Medicines Authority (AMRSC Member)
- Ms Claire Boardman, Former National President, Australasian College for Infection Prevention and Control (AMRSC Member)
- A/Prof Jim Buttery, Chair of Pharmaceutical Benefits Advisory Committee (AMRSC Member)
- Dr Keryn Christiansen, Lead Clinician, *National surveillance and reporting of AMR and antibiotic usage in Australia*
- Mr David Chudleigh, Zoetis
- Dr Adrian Coghill, Senior Veterinarian Officer, Australian Government Department of Agriculture Fisheries and Forestry
- Dr Robin Condron, Dairy Australia
- Prof Matthew Cooper, University of Queensland
- Dr Marilyn Cruickshank, Director, National Healthcare Associated Infection Program, Australian Commission on Safety and Quality in Health Care (AMRSC Chair)
- Dr Peter Dagg, Animal Health Australia
- Dr George Downing, Department of Environment and Primary Industries, Victoria
- Mrs Margaret Duguid, Pharmaceutical Advisor, Australian Commission on Safety and Quality in Health Care (AMRSC member)
- Ms Kylie Evans, Principal Communications Writer and Editor, Biotext Pty Ltd
- A/Prof John Ferguson, Chair of the Healthcare Associated Infection Advisory Committee, Australian Commission on Safety and Quality in Health Care (AMRSC Member)
- Dr Jenny Firman, Medical Advisor, Office of Health Protection (AMRSC member)
- Mr Gerard Fitzsimmon, Epidemiologist, Australian Government Department of Health and Ageing
- Dr Ben Gardiner, Australian Veterinary Association
- A/Prof Thomas Gottlieb, President of the Australian Society for Antimicrobials (AMRSC Member)
- Prof Lindsay Grayson, Infectious Diseases, Austin Health
- Prof Jane Halton AM, Secretary, Australian Government Department of Health and Ageing
- Dr Marion Healy, Executive General Manager, Risk Assessment Branch, Food Standards Australia New Zealand
- Dr Peter Holdsworth, Food Ingredients and Additives Australia

- Ms Jacinta Holdway, Director, Health Protection Policy Section, Australian Government Department of Health and Ageing
- Ms Leonor Nacua, Assistant Director, Health Protection Policy Section, Australian Government Department of Health and Ageing
- Ms Cristal Jones, Assistant Director, Health Protection Policy Section, Australian Government Department of Health and Ageing
- Ms Peng Cheah, Departmental Officer, Australian Government Department of Health and Ageing
- Ms Cristel Leemhius, Director, Food Policy Section, Australian Government Department of Health and Ageing
- Ms Sara Mazzer, International Division, Australian Government Department of Health and Ageing
- Mr Ian Jensen, Meat and Livestock Australia
- Dr Vivien Kite, Australian Chicken Meat Federation
- Ms Andriana Koukari, Assistant Secretary, Health Protection Policy Branch
- Dr John Langbridge, Veterinary Counsel, Australian Meat Industry Council
- A/Prof David Looke, President of the Australasian Society for Infectious Disease (AMRSC Member)
- Mr Andrew Metcalfe AO, Secretary, Australian Government Department of Agriculture Fisheries and Forestry
- Dr Pat Mitchell, R&I Manager Production Stewardship, Australian Pork Ltd
- Ms Megan Morris, First Assistant Secretary, Office of Health Protection, Australian Government Department of Health and Ageing
- Dr John Owusu, Australian Pesticides and Veterinary Medicines Authority
- Mr Tom Parnell, Acting Assistant Secretary, Australian Government Department of Agriculture Fisheries and Forestry
- Prof Debora Picone, Chief Executive Officer, Australian Commission on Safety and Quality in Health Care
- Mr Mark Phythian, Director Import Food, Australian Government Department of Agriculture Fisheries and Forestry
- Dr Janet Salisbury, Director, Principal Science Writer and Editor, Biotext Pty Ltd
- Ms Karen Schneider, First Assistant Secretary, Australian Government Department of Agriculture Fisheries and Forestry
- Prof Ramon Shaban, Lead Author, *National surveillance and reporting of AMR and antibiotic usage in Australia;* Chair, Infection Control and Infectious Diseases, Griffith Health Institute, Griffith University
- Dr Mark Schipp, Australian Chief Veterinary Officer, Australian Government Department of Agriculture Fisheries and Forestry (AMRSC Member)
- Prof John Skerritt, National Manager, Therapeutic Goods Association (AMRSC Member)
- Dr David Smith, Chair of the Public Health Laboratory Network (AMRSC Member)
- Dr Michael C Smith, Clinical Director, Australian Commission on Safety and Quality in Health Care
- Mr Andrew Spencer, Australian Pork Ltd

- Mr Justin Toohey, Cattle Council
- Dr Darren Trott, Senior Lecturer Veterinary Microbiology, University of South Australia
- Prof John Turnidge, Chair, Antimicrobial Research Advisory Committee (AMRSC Member)
- Dr Lyn Waring, Royal College of Pathologists (AMRSC Member)
- Dr Lynn Weekes, Chief Executive Officer, NPS MedicineWise (AMRSC Member)
- Dr Stephanie Williams, Medical Advisor, Office of Health Protection, Australian Government Department of Health and Ageing
- Dr Kurt Zuelke, Australian Animal Health Laboratory, Victoria
- Mr Linden Moffatt, Senior Evaluator, Veterinary Medicines Program, Australian Pesticides and Veterinary Medicines Authority

Colloquium support staff, Australian Commission on Safety and Quality in Health Care

- Ms Fiona Gotterson
- Ms Sue Greig
- Dr Rebecca Hoile
- Ms Emma Stapley
- Ms Cate Quoyle
- Ms Amy Winter

Writing group

- Prof Mary Barton, Emeritus Professor, University of South Australia
- Dr Darren Trott, Senior Lecturer Veterinary Microbiology, University of South Australia
- Dr Keryn Christiansen, Lead Clinician, National surveillance and reporting of AMR and antibiotic usage in Australia
- Dr Adrian Coghill, Senior Veterinary Officer, Australian Government Department of Agriculture Fisheries and Forestry
- Dr David Jordan, Principle Research Scientist, Department of Primary Industries, New South Wales
- Dr Marilyn Cruickshank, Director, National Healthcare Associated Infection Program, Australian Commission on Safety and Quality in Health Care (AMRSC Chair)
- Dr Stephen Page, Advanced Veterinary Therapeutics
- Dr Stephanie Williams, Medical Advisor, Office of Health Protection, Australian Government Department of Health and Ageing
- Prof Ramon Shaban, Lead Author, *National surveillance and reporting of AMR and antibiotic usage in Australia;* Chair, Infection Control and Infectious Diseases, Griffith Health Institute, Griffith University
- Prof John Turnidge, Chair, Antimicrobial Research Advisory Committee (AMRSC Member)

Appendix 2 Australian One Health Antimicrobial Resistance Colloquium - Background Paper

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*

Mechanism of action	Antibiotic group
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.

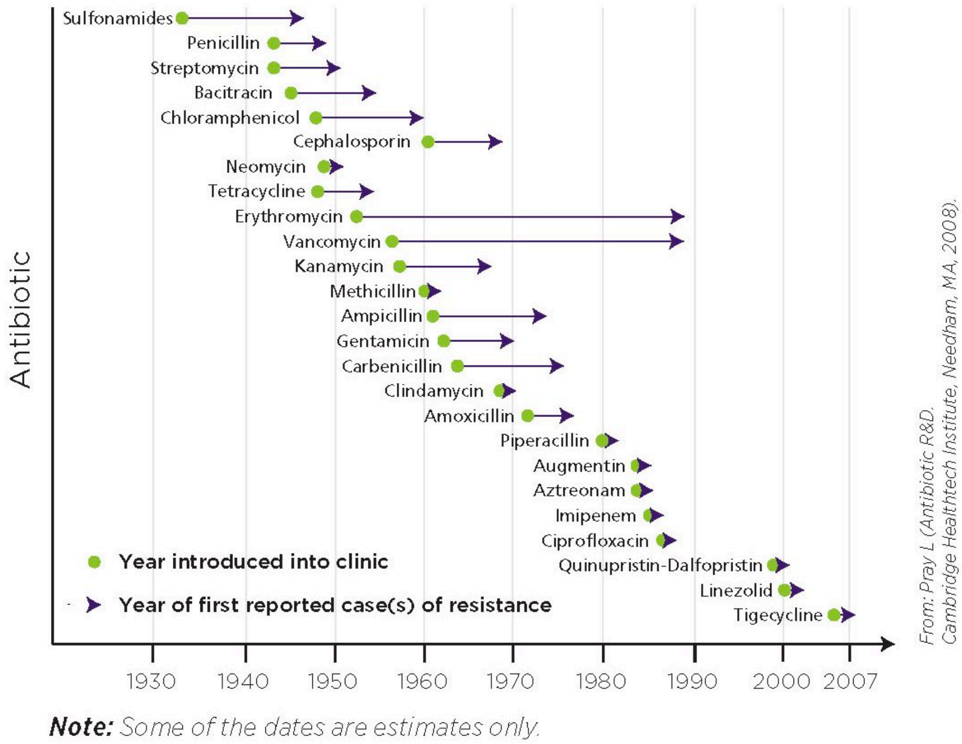

Figure 1: Time lag between an antibiotic being introduced to clinical use and the first appearance of resistance

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.

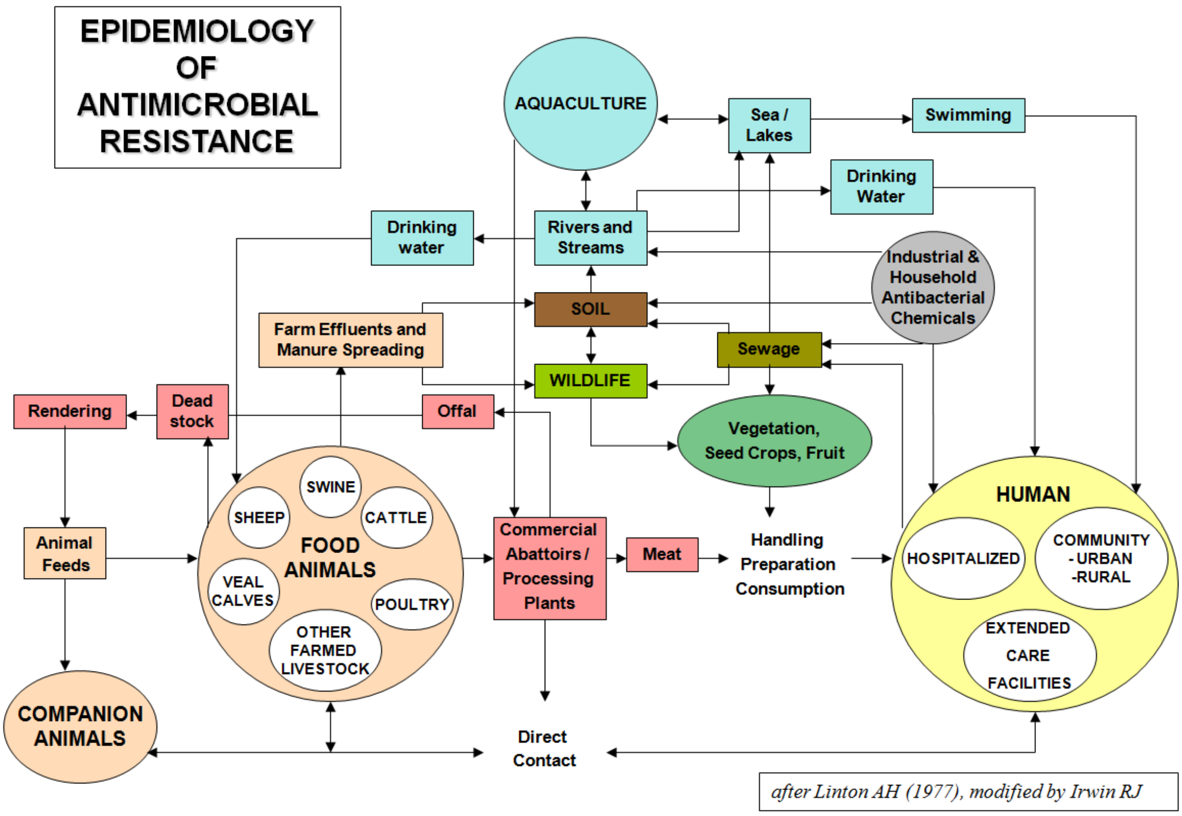

Figure 2: Factors in AMR epidemiology

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.[8]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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