Chapter 1

Background to the inquiry

Terms of Reference

1.1 On 29 November 2012, the Senate referred the following matters to the Finance and Public Administration References Committee (the committee) for report by 21 March 2013:

> Progress in the implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR), including:
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> (a) examination of steps taken, their timeliness and effectiveness;
>
> (b) where and why failures have occurred;
>
> (c) implications of antimicrobial resistance on public health and the environment;
>
> (d) implications for ensuring transparency, accountability and effectiveness in future management of antimicrobial resistance; and
>
> (e) any other related matter.[1]

1.2 The reporting date was subsequently extended to 7 June 2013.

Conduct of the inquiry

1.3 The committee invited submissions from interested organisations and individuals, and government bodies. The inquiry was also advertised on the committee's website.

1.4 The committee received 38 submissions. A list of individuals and organisations which made public submissions to the inquiry is at Appendix 1. The committee held one public hearing in Melbourne on 7 March 2013. A list of the witnesses who gave evidence at the public hearing is available at Appendix 2. Submissions, additional information and the Hansard transcript of evidence may be accessed through the committee's website at www.aph.gov.au/senate_fpa.

1.5 The committee thanks those organisations and individuals who made submissions and gave evidence at the public hearing.

Antimicrobial resistance

1.6 The development of antibiotics in the 20th Century was a significant step in improving healthcare and decreasing mortality rates. Antibiotics are part of a broader group of agents called antimicrobials, which include antivirals, antifungals, and antiprotozoals. Microbes that are resistant to antimicrobials have developed over time. Microbes can become resistant to antimicrobials by mutating or changing their genes

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1 *Journals of the Senate*, No. 129, 29 November 2012, p. 3485.

or internal functions after being in contact with an antimicrobial agent. When microbes are exposed to an antimicrobial agent, occasionally a mutated microbe will survive, where its peers either die or are unable to reproduce. As the mutated microbe starts multiplying, a population of resistant microbes is produced. In some cases this resistance can be passed on to other microbes as indicated by National Prescribing Service (NPS) MedicineWise:

> [B]acteria can also develop antibiotic resistance through contact with other bacteria. Resistant bacteria can pass their genes to other bacteria, forming a new antibiotic resistant 'strain' of the bacteria.[2]

1.7 The way antimicrobials are used is thought to have a significant impact on the development of antimicrobial resistance (AMR). The more antibiotics are used, the more chances bacteria have to become resistant to them. Common causes of increasing AMR identified by NPS MedicineWise include using antibiotics when they are not needed and not taking antibiotics at the correct doses and times.[3]

1.8 AMR is a world-wide concern with the World Health Organisation (WHO) in the late 1990s identifying AMR as a significant health issue.[4] The WHO summarised the potential dangers of AMR as follows:

> Now, at the dawn of a new millennium, humanity is faced with another crisis. Formerly curable diseases such as gonorrhoea and typhoid are rapidly becoming difficult to treat, while old killers such as tuberculosis and malaria are now arrayed in the increasingly impenetrable armour of antimicrobial resistance.[5]

Antimicrobial resistance in Australia

1.9 In the early 2000s it was noted that there was an increasing prevalence of resistant bacteria and that 'antibiotic resistance remains one of the most important emerging public health issues facing Australia'. At the same time, Australia was one of the highest users of antibiotics in the Western world with about 24 million prescriptions being provided annually.[6]

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2 NPS MedicineWise, *Antibiotic resistance – what is it*, http://www.nps.org.au/medicines/infections-and-infestations/antibiotic-medicines/antibiotics-for-respiratory-tract-infections/for-individuals/what-is-antibiotic-resistance, (accessed 1 March 2013).

3 NPS MedicineWise, *Antibiotic resistance – what is it*, http://www.nps.org.au/medicines/infections-and-infestations/antibiotic-medicines/antibiotics-for-respiratory-tract-infections/for-individuals/what-is-antibiotic-resistance, (accessed 1 March 2013).

4 The Australia Institute, *Submission 13, Attachment 1*, p. 6.

5 World Health Organisation, World Health Report on Infectious Diseases 2000, *Overcoming Antimicrobial Resistance*, http://www.who.int/infectious-disease-report/2000/index.html, (accessed 26 February 2013).

6 National Summit on Antibiotic Resistance, Commitment and Communication, *CIJIG Communique*, July 2001, p. 2.

1.10 AMR has continued to increase dramatically both overseas and in Australia.[7] Friends of the Earth Australia stated that:

> The problem of antimicrobial resistance is now worse than ever, with superbugs – bacteria resistant to most antibiotics – spread throughout hospitals and communities around the world. The numbers of deaths caused by bacterial resistance to antimicrobials and antibiotics in hospitals continues to rise, with experts warning of a possible return to the pre-antibiotic era.[8]

1.11 A number of trends in the prevalence of AMR have been identified over the last decade. One has been the emergence of community-acquired resistant infections in addition to hospital-acquired resistant infections. The Australian Society for Infectious Diseases (ASID) stated:

> Since the publication of the JETACAR report in 1999 rates of resistant bacterial infections [have] risen markedly and the dynamic had changed from being confined to hospital associated infections, to a real change in antibiotic resistance patterns in common community acquired infections. Today, it is a common event to see patients (including children) with resistant *Staphylococcus aureus* infections of the skin, bones and soft tissues, and resistant *Escherichia coli* infections of the urinary tract, gall bladder and bowel being sent to hospitals for intravenous therapy as there are now no effective oral antibiotics available.[9]

1.12 The Department of Health and Ageing (DoHA) also commented that data concerning resistance in community settings is limited and the problem is less than in hospitals. However, from the data that is available, resistant community-acquired infections have also increased.[10]

1.13 Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials (ASA), also pointed to the emergence of multiresistance[11] and stated while this was a concern when the JETACAR report was released, multiresistance is now a daily issue for many specialists:

> [W]hen the JETACAR was first formulated, we saw the future sceptre of multiresistance as something truly worrying that needed action, but it was mostly an abstract idea because we still had antibiotics for most situations…What I and a lot of our members have seen in the last decade is that the issue of untreatable infections is no longer an abstract notion; it is now a reality. It is a day-to-day issue for specialists in many medical

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7 Australasian Society for Infectious Diseases, *Submission 18,* p. 2.

8 Friends of the Earth, *Submission 3*, p. 3.

9 Australasian Society for Infectious Diseases, *Submission 18,* p. 2; see also Professor M Lindsay Grayson, *Submission 19,* p. 2; Dr David Looke, President, Australasian Society for Infectious Diseases, *Committee Hansard,* 7 March 2013, p. 14.

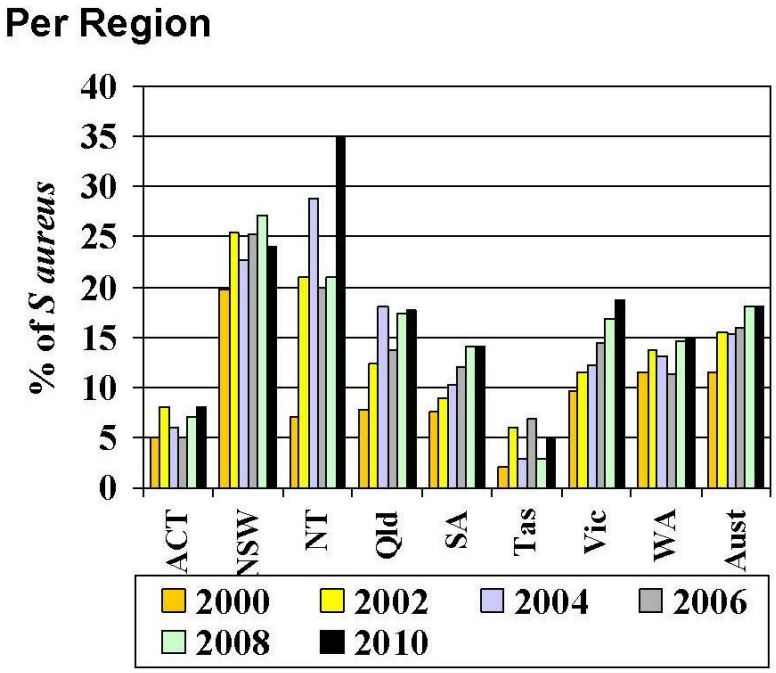
10 Department of Health and Ageing, *Answer to question on notice* , received 16 May 2013.

11 Multiresistant bacteria include: MRSA and Vancomycin-resistant enterococci (VRE). See Australia Society for Antimicrobials, *Submission 5*, pp 4–5.

> practices…We are seeing them now in individual patients, many of whom will die of their infections, not through inadequate medical care but through unavailability of antibiotics. That is a poor scenario.[12]

1.14 The growth in AMR in Australia can be seen in currently available data on marker species such as Methicillin-Resistant Staphlococcus Aureus (MRSA) which shows increasing levels of resistance. As Figure 1.1 below shows, for Staphlococcus Aureus there have been high rates of resistance in NSW and the Northern Territory for a decade. In addition, the rates of resistance in Queensland, South Australia and Victoria have grown rapidly and doubled in a decade.

Figure 1.1: Percentage of Staphylococcus Aureus bacteria that are resistant



Source: Geoffrey Coombs, Julie Pearson, Graeme Nimmo, Keryn Christiansen, AGAR SAP10: Molecular Epidemiology of MRSA in the Australian Community, Australian Group on Antimicrobial Resistance, Antimicrobials, Brisbane, 2012, p. 1.

1.15 Professor Lindsay Grayson, infectious diseases physician, also pointed to resistance rates for urinary tract infections which have risen from five to 20 per cent in a five year period.[13]

1.16 The ASA added that for many bacterial pathogens, resistance to last-line antibiotics, such as carbapenems, fluoroquinolones, glycopeptides and third-generation cephalosporins, is now commonly found in Australian hospitals and, to an increasing extent, in the community.[14] More concerning was Professor Grayson's

12 Associate Professor Thomas Gottlieb, President, Australian Society for Antimicrobials, *Committee Hansard,* 7 March 2013, p. 38; see also Professor M Lindsay Grayson, *Submission 19,* p. 2.

13 Professor M Lindsay Grayson, *Committee Hansard,* 7 March 2013, p. 8.

14 Australia Society for Antimicrobials, *Submission 5,* pp 4–5.

evidence that there are now occasional cases of totally resistant pathogens. These cases are expected to become more prevalent:

> Current occasional cases of totally-resistant pathogens, which are impossible to cure with presently-available antibiotics, are almost certain to increase and are likely to become the norm in some sections of healthcare – especially areas with patients who are highly immunocompromised (e.g. transplantation medicine, hematology, neonatal medicine and intensive care medicine), since without effective antibiotics there are currently no other treatment options.[15]

Implications of antimicrobial resistance

1.17 The prevalence of AMR is increasing and the difficulties in managing it are growing. NPS MedicineWise stated that 'this potentially leads us to world wide crisis where antibiotics are no longer effective'.[16] If this were to occur, the implications for public health would be profound. Gottlieb and Nimmo note that it 'would render many routine infections untreatable and would seriously affect current practice in surgery, intensive care, organ transplantation, neonatology and cancer services through major increases in morbidity and mortality'.[17]

1.18 The ASA also pointed to a potentially grim future where removing a burst appendix will become a dangerous operation and peri-partum infections and incurable tuberculosis will again become a reality. In addition, simple community-onset infections will be difficult to manage, and more likely to require hospitalisation, due to lack of available oral antibiotics.[18] Empiric antibiotic choices in sepsis and for other infections will become complex and precarious.[19]

1.19 Not only will increasing AMR lead to increased morbidity and mortality, the health care sector will face increasing costs for treating patients and for implementing changes to patient management systems.[20]

1.20 NPS MedicineWise pointed to a range of factors contributing to increased costs: illnesses caused by AMR bacteria are more difficult to treat and often result in complications and even death; patients stay infectious for longer; and antibiotics act on normal bacterial flora, which enables colonisation with resistant bacteria that can be carried and cause infection later. In addition, treatment may require second or

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15 Professor M Lindsay Grayson, *Submission 19*, p. 2.

16 NPS MedicineWise, *Submission 30*, p. 1; see also Professor M Lindsay Grayson, *Committee Hansard*, 7 March 2013, p. 9.

17 Gottlieb, T & Nimmo, GR, 'Antibiotic resistance is an emerging threat to public health: an urgent call for action at the Antimicrobial Resistance Summit 2011', *Medical Journal of Australia*, Vol. 194, no. 6, 21 March 2011, pp 281–83.

18 Australia Society for Antimicrobials, *Submission 5*, p. 5.

19 Australia Society for Antimicrobials, *Submission 5*, p. 5; see also Professor M Lindsay Grayson, *Committee Hansard*, 7 March 2013, p. 10.

20 Professor M Lindsay Grayson, *Committee Hansard*, 7 March 2013, p. 9.

third-line antibiotics, which are more expensive and may be more toxic, causing serious adverse effects.[21]

1.21 Professor Grayson provided an illustration of changes to the way patients are managed:

> For instance, when patients come in for prostate biopsies we now have to give them an infusion of antibiotics because the tablets we would have given them three years ago now do not work, and on numerous occasions we have had men come back the next day with bloodstream infections from a super-bug that was no longer sensitive to the tablets that we would have given them as part of the routine for that procedure.[22]

1.22 The ASID noted that MRSA is now a growing problem in the community, especially in indigenous Australians, resulting in a significant increase in the burden of disease. This is seen in both general practice and hospital emergency departments and results in increased admissions and surgical procedures. Some strains possess a toxin that can cause serious disease and even death.[23]

1.23 A further area of concern is the spread of AMR from returning travellers. Professor Grayson commented that:

> In my own hospital now, anyone who has returned from one of a number of key countries—including Greece, India and China—and has a fever goes into isolation until we prove that they are not carrying a superbug. Five years ago or even two years ago we did not have to do that. Currently, about one third of return travellers from India are perfectly healthy in India but they are carrying a superbug in their faeces that if we found in Australia we would put them into strict isolation. So we are now having to install these strict measures.[24]

1.24 Evaluation of the costs to economies of AMR has been undertaken overseas. In the European Union, about 25,000 patients die each year from infections caused by selected multidrug-resistant bacteria and the associated costs are estimated at about 1.5 billion euros per year. In the United States, infections with pathogens resistant to antimicrobials cost the healthcare system in excess of $US20 billion per year and generate more than eight million additional hospital days. The annual societal costs exceed $US35 billion.[25] While no evaluation of healthcare costs attributable to AMR has been undertaken in Australia, Professor Matthew Cooper estimated that the cost in

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21 NPS MedicineWise, *Submission 30*, p. 1.

22 Professor M Lindsay Grayson, *Committee Hansard,* 7 March 2013, p. 8.

23 Australia Society for Antimicrobials, *Submission 5*, pp 4–5.

24 Professor M Lindsay Grayson, *Committee Hansard,* 7 March 2013, p. 9.

25 World Health Organisation World Health Day Antimicrobial Resistance Technical Working Group, 'The WHO policy package to combat antimicrobial resistance', *Bulletin of the World Health Organisation,* 2011, 89, pp 390–392.

Australia may be around $1 billion annually based on cost studies in the United States.[26]

1.25 The committee also received evidence from practitioners with first-hand knowledge of the implications of AMR for patients. For example, Dr David Locke, President, ASID, pointed to the example of staph aureus (golden staph). This is the commonest cause of infections of the skin and the bones but it has progressively become more resistant to antibiotics. Now 25 to 30 per cent of severe staph aureus infections are resistant to all penicillins and the alternative drug has its own toxic side effects.[27]

1.26 Professor Grayson also cited the recent case of a patient who had undergone a minor surgical procedure on their wrist. Following the development a super-bug diarrhoeal infection, the patient's colon was removed, 'so they went home with a colostomy bag after a minor surgical procedure, simply because they picked up a super-bug because of misuse of antibiotics'.[28] Professor Grayson added that physicians are 'returning to a pre-antibiotic approach to controlling infections such as removing the colon of someone who has got a bowel infection that could have been previously treated with antibiotics. We are returning to a pre-antibiotic era as we speak.'[29]

Development of antimicrobial drugs

1.27 In addition to the increasing prevalence of AMR, a further matter of concern is the dwindling number of new antimicrobials that are being developed. The ASA commented that:

> There are too few new antibiotics coming onto the market to deal with these bacteria and a dwindling pipeline of new antimicrobial agents. Hence we cannot rely on newer antibiotics filling the void.[30]

1.28 The Public Health Association of Australia (PHAA) commented that since 1970 there have been only three new chemical classes of antibiotics developed for use for serious infections in humans – linezolid (2000) and daptomycin (2003) for systemic infections, and fidaxomicin (2012) for the treatment of gut infections caused by Clostridium difficile.[31] NPS MedicineWise added that there is only one new antibiotic in the US Federal Drug Administration approval pipeline.[32]

1.29 The decline in the development of new antibiotics has been attributed to a range of factors including government funding arrangements, profitability of drug

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26 Professor Matthew Cooper, *Committee Hansard*, 7 March 2013, p. 30.

27 Dr David Locke, President, Australasian Society for Infectious Diseases, *Committee Hansard,* 7 March 2013, p. 14.

28 Professor M Lindsay Grayson, *Committee Hansard,* 7 March 2013, p. 8.

29 Professor M Lindsay Grayson, *Committee Hansard,* 7 March 2013, p. 9.

30 Australian Society for Antimicrobials, *Submission 5*, p. 5.

31 Public Health Association of Australia, *Submission 14*, p. 8.

32 NPS MedicineWise, *Submission 30*, p. 2.

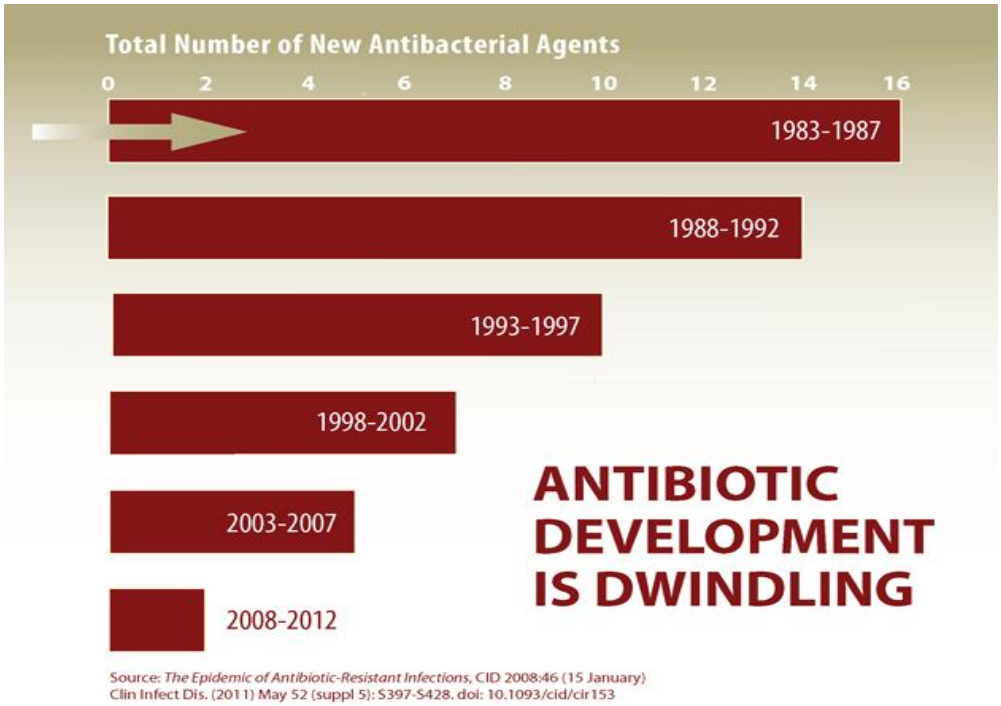
companies and diminishing research and development pipelines.[33] The PHAA indicated that there are no financial incentives for pharmaceutical companies to develop new antibiotics as companies work on a risk assessment of investment against profit and antimicrobial agents now have a low return. Any new drugs may only have a useful life of a few years due to the development of resistance. Furthermore, new antibiotics will be more expensive as companies build these factors into their costs.[34]

1.30 The Consumers Health Forum of Australia (CHF) also noted the low levels of funding allocated by pharmaceutical companies for new antibiotic development:

> It was recently estimated that major pharmaceutical companies allocate less than two per cent of their overall investments into antibiotics research, and it has been decades since a new class of antibiotics has been developed.[35]

1.31 Figure 1.2 indicates the number of new antibacterial agents made available over recent periods.

Figure 1.2: Dwindling development of new antibacterial agents



Source: Centers for Disease Control and Prevention, Mission Critical: Preventing Antibiotic Resistance, http://www.cdc.gov/features/antibioticresistance/charts.html#chartA, (accessed 1 March 2013). Research into new antibiotics

1.32 The lack of new antibiotics is a major concern worldwide with scientists from the Infectious Diseases Society of America (IDSA) calling for the Congress and relevant US federal agencies to give clear guidance on design and implementation of

33 Australia Society for Antimicrobials, *Submission 5*, p. 5.

34 Public Health Association of Australia, *Submission 14*, p. 8.

35 Consumers Health Forum of Australia, *Submission 10*, p. 2.

necessary research on antibiotics.[36] In addition, the IDSA has proposed a new global research and development enterprise focussed on developing ten new antibiotics by 2020.[37]

1.33 Research for the development of new antibiotics is discussed further in chapter 5.

Tackling antimicrobial resistance

1.34 As noted above, the WHO has identified AMR as a significant health issue. The WHO Global Strategy for the Containment of Antimicrobial Resistance provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial resistant microorganisms through:

- reducing the disease burden and the spread of infection;
- improving access to appropriate antimicrobials;
- improving use of antimicrobials;
- strengthening health systems and their surveillance capabilities;
- enforcing regulations and legislation; and
- encouraging the development of appropriate new drugs and vaccines.[38]

Overseas response

1.35 A number of countries, including the United States, Canada, France, Denmark and Japan, have established programs to address antibiotic resistance, covering issues including monitoring, regulation, education, and research and development.

1.36 Canada for example, has a well-integrated system that includes quality surveillance.[39] Denmark is also considered by some to be making significant steps, establishing an integrated monitoring and research program in 1995. However, despite the implementation of this system, the number of cases of AMR in Denmark has grown over the past decade. A significant proportion of these cases can be attributed to community-acquired infections. Figure 1.3 shows the number of MSRA cases in Denmark between 1994 and 2011.

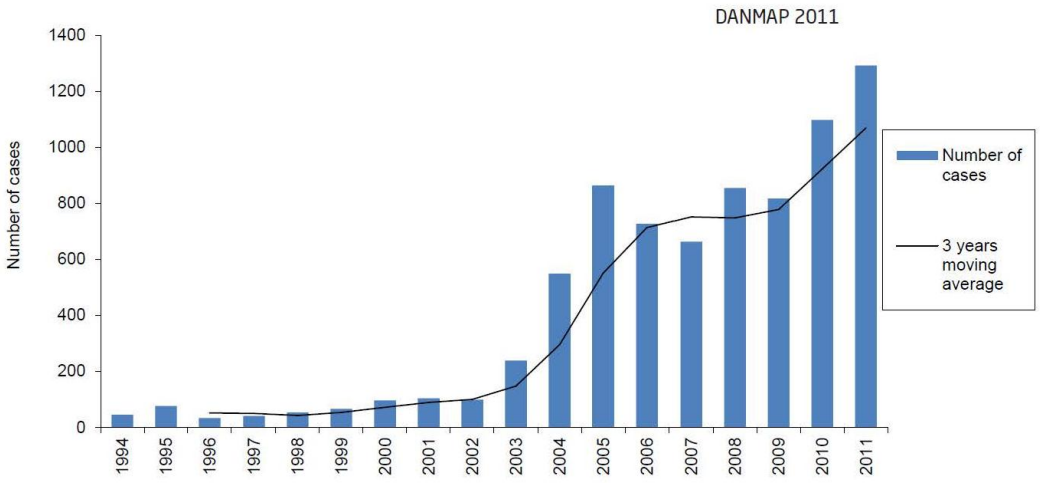
36 The Australia Institute, *Submission 13, attachment 1,* p. 27.

37 NPS MedicineWise, *Submission 30,* p. 3.

38 World Health Organisation, *WHO Global Strategy for the Containment of Antimicrobial Resistance*, 2001, pp 1–2.

39 Department of Primary Industries (NSW), *Submission 28,* p. 2.

Figure 1.3: Number of MSRA cases in Denmark



Source: DANMAP, *Selected graphs and figures*, 2011.

Response to AMR in Australia

1.37 The transfer of resistant bacteria from animals through the food chain gained attention in Australia in 1969, as a result of the United Kingdom's Swann report:[40]

> The Swan[n] Committee (1969) (which recommended separation between antibiotics used in humans from those used in animals) was established in response to the emergence of multidrug resistant salmonella in humans identical to strains causing problems in calves and the report from Japan (Watanabe, 1963) that resistance genes were carried on plasmids that could transfer from bacteria to bacteria.[41]

1.38 Following the Swann report, several countries, including Australia, took steps to limit or remove antibiotics such as penicillin from animal feeds.[42] In the 1980s, the Working Party on Antibiotics (WPA) was established under the National Health and Medical Research Council (NHMRC). The WPA made recommendations on surveillance and provided advice on human implications of antibiotic use in animals to regulatory bodies responsible for regulating agricultural and veterinary chemicals. Responsibility for the WPA moved from the NHMRC to the Therapeutic Goods Administration (TGA) in 1997.[43]

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40 UK Joint Committee of the Houses of Parliament (1969), *Report on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine*, Her Majesty's Stationary Office, London, November (reprinted 1971).

41 Professor Mary Barton, APVMA Science Fellows Symposium, *Antibiotic resistance in Australian animals in 2010 – what lies ahead?*, 19 April 2010, p. 1.

42 Professor Mary Barton, APVMA Science Fellows Symposium, *Antibiotic resistance in Australian animals in 2010 – what lies ahead?*, 19 April 2010, p. 1.

43 Professor John Turnidge, *Australian Government attempts at regulatory and other control of antimicrobial resistance*, Microbiology Australia, November 2007, p. 198; Professor Mary Barton, APVMA Science Fellows Symposium, *Antibiotic resistance in Australian animals in 2010 – what lies ahead?*, 19 April 2010, p. 1.

Joint Expert Technical Advisory Committee on Antibiotic Resistance

1.39 An association between a stockfeed antimicrobial (avoparcin) and resistant bacteria (Vancomycin-resistant enterococci) present in humans, gained attention in Europe in 1997. The association also became an important issue in Australia, as avoparcin was widely used in food-animal production in Australia.[44]

1.40 To address the above concerns, the then Minister for Health and Family Services and the then Minister for Primary Industries and Energy established the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) in December 1997.[45] Five specific terms of reference for JETACAR were agreed:

1. Examine the status of antibiotic resistance patterns in Australia in human and veterinary practice and in food producing animals.
2. Examine the full range of antibiotic usage patterns and control policies in Australia in all sectors, including health, veterinary and agricultural applications.
3. Identify priority medical problems arising from the use of antibiotics in livestock production.
4. Recommend a minimum set of criteria for assessing the potential human health impact prior to licensing of antibiotics for use in animals and agriculture, taking into account the likely benefits and potential adverse outcomes (informed by models in published scientific literature and relevant measures adopted in other countries).
5. Recommend antibiotic resistance management strategy/strategies.[46]

1.41 JETACAR reported in 1999 and made 22 recommendations. The Government responded to the recommendations in 2000.

Structure of this report

1.42 The committee's review of the JETACAR recommendations and the Government response and implementation are canvassed in chapters 2 to 6 as follows:

- Chapter 2 – overview and main conclusions;
- Chapter 3 – AMR surveillance and monitoring;
- Chapter 4 – regulatory controls of antibiotics;
- Chapter 5 – infection prevention and hygiene; and
- Chapter 6 – education and research.

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44 Professor John Turnidge, *Australian Government attempts at regulatory and other control of antimicrobial resistance,* Microbiology Australia, November 2007, p. 198.

45 Department of Health and Ageing and portfolio bodies joint submission, *Submission 32, Attachment 1,* The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR), August 2000, p. 3.

46 Joint Expert Advisory Committee on Antibiotic Resistance: *The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans,* p. 3.