AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

1 Evidence for antimicrobial stewardship

# Antimicrobial Stewardship in Australian Health Care

2018

This chapter is part of *Antimicrobial Stewardship in Australian Health Care 2018*, Australian Commission on Safety and Quality in Health Care, 2018.

The publication summarises current evidence about AMS strategies and interventions, and their implementation. Chapters 1–7 provide strategies for implementing and sustaining AMS, and Chapters 8–12 examine the roles of the different clinicians in AMS.

The publication will continue to evolve with additional chapters over time that address AMS in specific settings, such as primary care.

As new resources become available, they will be added as hyperlinks to the resources section in each chapter or to the appendices.

# Chapter contents

# Acronyms and abbreviations

| Abbreviation | Definition |
|---|---|
| AMR | antimicrobial resistance |
| AMS | antimicrobial stewardship |
| AURA | Antimicrobial Use and Resistance in Australia |
| CI | confidence interval |
| Commission | Australian Commission on Safety and Quality in Health Care |
| ESBL | extended-spectrum β-lactamase |
| IRR | incidence rate ratio |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| NAPS | National Antimicrobial Prescribing Survey |
| NAUSP | National Antimicrobial Utilisation Surveillance Program |
| NHMRC | National Health and Medical Research Council |
| NSQHS Standards | National Safety and Quality Health Service Standards |
| RACGP | Royal Australian College of General Practitioners |

## Key points

- The growing problem of antimicrobial resistance (AMR) presents a threat to public health and patient safety.
- Antimicrobial-resistant infections can lead to prolonged or serious illness, escalation in therapy (and associated healthcare costs), hospitalisation or death.
- Other healthcare interventions, such as surgery and oncology treatments, are also threatened by AMR because antimicrobials are essential to those interventions.
- The decreasing pipeline of new antimicrobials limits options for treating infections.
- High levels of antimicrobial use and inappropriate use of antimicrobials are associated with increasing AMR.
- Reducing inappropriate antimicrobial use is an important strategy to preserve the effectiveness of antimicrobials.
- Antimicrobial stewardship (AMS) programs have been shown to improve the appropriateness of antimicrobial use, reduce patient morbidity and mortality, and reduce bacterial resistance rates and healthcare costs.
- Effective AMS is a suite of coordinated strategies that aims to ensure that antimicrobials are prescribed according to evidence-based guidelines, with antimicrobial choice, dose and duration selected to optimise clinical outcomes and minimise adverse consequences.
- In Australia, AMS programs are required by the National Safety and Quality Health Service Standards, which are mandated for all hospitals in Australia.
- AMS initiatives in human health settings are also supported by the Antimicrobial Stewardship Clinical Care Standard.
- The Australian Commission on Safety and Quality in Health Care has established other programs that support AMS initiatives, such as the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System.
- The work of many states and territories, non-government organisations, professional bodies and research organisations also supports AMS in human health.
- An objective of Australia's first National Antimicrobial Resistance Strategy is to implement effective AMS practices across human health settings to ensure appropriate and judicious prescribing, dispensing and administering of antimicrobials.
- The AURA Surveillance System provides support to the implementation of the National Antimicrobial Resistance Strategy.

## 1.1 Introduction

The ability of antimicrobial agents to control infection is critical, not only for the treatment of infectious diseases, but to support many of the advances and interventions of contemporary health care. Neonatal care, organ transplantation, chemotherapy, surgery and intensive care all rely on effective antimicrobials to prevent and manage infections. However, the increasing use of antimicrobials is contributing to growing rates of antimicrobial resistance (AMR). AMR is a threat to the ability to treat and prevent infections. It increases morbidity and mortality, and healthcare costs. Treatment options are also limited by the decreasing development pipeline for antimicrobials.

Around one-third to half of antimicrobial use in Australian aged care homes and hospitals surveyed in 2015 was considered to be unnecessary or inappropriately prescribed.[1,2] In 2014, NPS MedicineWise found that more than 50% of people in the community with colds and other non-specific upper respiratory tract infections were prescribed an antimicrobial when it was not recommended by national guidelines.[3] Inappropriate or suboptimal antimicrobial use contributes to the development of AMR and medication-related adverse events, and can lead to poorer outcomes for individual patients with infection.[4,5]

Antimicrobial stewardship (AMS) programs have developed as a response to these issues. As a systematic approach to optimising antimicrobial

use, AMS aims to minimise the unnecessary use of antimicrobials and promote the appropriateness of antimicrobial prescribing, resulting in improved patient outcomes, cost-effective therapy and reduced adverse consequences of antimicrobial use, including AMR.[6-9] AMS is a key strategy to conserve the effectiveness of antimicrobials, and is carried out by both the public and the private sectors in Australia. Implementing effective AMS practices across human health settings is also an objective of Australia's first National Antimicrobial Resistance Strategy.[10]

Successful management of infections in the future will require a multifaceted approach, including:

- The development of novel antimicrobial agents and therapies
- Coordinated efforts to limit the spread of resistant organisms
- Measures such as AMS to conserve the effectiveness of antimicrobials and contribute to preventing and containing AMR.

This chapter presents the evidence for AMS and outlines a national framework for AMS in Australia. It describes the problem of AMR in human health and the contribution of appropriate antimicrobial use to preventing and containing AMR, and reducing patient harm. The chapter presents the key elements of an effective AMS program, and the evidence for AMS as a means of reducing unnecessary antimicrobial use, improving clinical outcomes and patient safety, and containing healthcare-related costs.

## 1.2 Challenge and impact of antimicrobial resistance

AMR is a growing global problem. Infections caused by antimicrobial-resistant organisms are becoming increasingly prevalent and more difficult to treat. In some cases, they are untreatable. Antimicrobials that were previously active against infections are becoming less effective. Multi-drug resistance in organisms such as *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and *Neisseria gonorrhoeae* is becoming more common.[11] Resistance is associated with treatment failure, increased mortality, and higher costs for therapy and health care.[12]

To compound the problem, the number of new antimicrobials being developed has decreased, further diminishing the capacity to treat antimicrobial-resistant infections.[13] As a result, there is greater reliance on the effectiveness of currently available agents. One of the major roles of AMS is to preserve the effectiveness of currently available antimicrobial agents.

The causes of the rise in AMR are multi-factorial and include the:

- Selection or amplification of resistant clones through antimicrobial use
- Acquisition of resistance genes from other bacteria in humans, animals and agricultural food sources
- Spread of resistant bacteria and resistance genes through environmental and person-to-person mechanisms.

A key contributor to AMR is unnecessary or inappropriate use of antimicrobials.

### 1.2.1 Association between antimicrobial use and resistance

Evidence for the association between the use of antimicrobials and the rise in AMR is documented in laboratory, ecological and human studies, and can be seen at both population and individual levels.[14-16]

#### Association at the population level

In the community, increasing resistance to specific antimicrobials used to treat respiratory tract infections and other infections has been demonstrated.[17] Similar associations between antimicrobial use and AMR in the aged care sector have been seen, especially with extended-spectrum β-lactamase (ESBL)–producing gram-negative organisms and treatment with fluoroquinolones and third-generation cephalosporins.[18] Aged care homes often have high rates of antimicrobial use, and residents with comorbidities require frequent admissions to hospital, which may further contribute to the spread of AMR.

In hospitals, the incidence of resistant organisms has been correlated with the use of broad-spectrum antimicrobials. Examples include increasing fluoroquinolone resistance in *Pseudomonas aeruginosa* in association with increasing use of this antimicrobial class[19,20]; the prevalence of methicillin-resistant *S. aureus* (MRSA) associated with broad-spectrum antimicrobial use[21,22]; and the use of third-generation cephalosporins and the prevalence of ESBL-producing organisms.[23,24] Although use of fluoroquinolones in Australia is low, fluoroquinolone resistance in *E. coli* is slowly increasing, driven by high use of other antimicrobials.[25]

### Association at the individual level

Antimicrobial therapy can cause longstanding changes to an individual's resident microorganisms (their microbiome), significantly reducing microbial diversity and promoting overgrowth of antimicrobial-resistant organisms.[17] Longer duration and multiple courses of antimicrobial therapy are associated with higher rates of resistance.[17] For example, in people with recurrent urinary tract infections, causative organisms that are initially susceptible to first-line antimicrobials gradually accumulate resistance to multiple antimicrobials.[26] Therapy with a second- or third-line antimicrobial (if available) is often more expensive, is less well tolerated and, if all oral options have been exhausted, may require intravenous administration, even for less severe infections.[27] In some circumstances, nonresistant populations do not recover, allowing antimicrobial-resistant organisms to amplify.[28]

### Persistence of antimicrobial resistance

Once resistant organisms have been introduced into a particular setting, they may persist even if the selective pressure of inappropriate antimicrobial use is removed.[29] This can make it difficult to prove that a reduction in the use of antimicrobials will result in a concomitant decrease in AMR[30], and reflects the complexity of resistance emergence, transmission and persistence.[6]

Resistance may not always reduce the fitness of the microorganism, so the resistance can persist even without antimicrobial selection pressure. Additionally, even if antimicrobial use at one institution is effectively managed, frequent movement of patients between institutions, and lapses in infection prevention and control practices, can reintroduce resistant organisms. The prevalence of observed antimicrobial-resistant organisms in a particular setting will therefore not only reflect antimicrobial use in that setting, but will also be influenced by the types of organisms present, the rate of introduction of new resistant bacterial clones and how readily those clones spread.

This highlights the importance of a multifaceted approach to minimising AMR, including robust infection control management and AMS activities.

## 1.2.2 Consequences of antimicrobial resistance

Health service organisations and aged care homes are especially vulnerable to problems relating to AMR. These facilities bring together, in close proximity, people who are vulnerable to infections because of their medical comorbidities. The spread of antimicrobial-resistant organisms from person to person is a major contributing factor to AMR in these settings. Antimicrobial use selects for resistant organisms. This increases the prevalence of antimicrobial-resistant clones, which, when they cause infection, require empirical antimicrobial treatment to be broadened. In turn, the use of broad-spectrum antimicrobials selects for more resistant organisms, and promotes the colonisation of patients and their environment with multidrug-resistant organisms and opportunistic pathogens such as *Clostridium difficile*.[24] This creates a cycle of increasing AMR that requires broader-spectrum antimicrobial therapy, until, in some situations, no effective antimicrobial therapy remains.

When multidrug-resistant pathogens are prevalent, clinicians need to use broader-spectrum and (usually) more expensive agents for empirical therapy for seriously ill patients. Patients infected with antimicrobial-resistant organisms spend more time in hospital, and the total cost of their care is higher.[31] Roberts et al. estimated that medical costs attributable to antimicrobial-resistant infections in a United States public teaching hospital were US$18,500 to US$29,000 per patient, and were associated with an excess length of hospital stay of 6.4–12.7 days.[32] The authors also projected substantial medical and societal cost savings by reducing antimicrobial-resistant infection rates.

Because antimicrobials are used to support other areas of health care, AMR also affects those areas. One example is the use of implantable devices. There has been an almost 200% increase in the number of prosthetic hips and knees implanted in Australia over the past 20 years[33], and the number of pacemaker devices implanted increased by 250% between 2000 and 2013.[34] The success of these medical interventions would be significantly reduced if the availability of effective antimicrobials to support these procedures were to become limited.

## 1.3 Australian framework for antimicrobial stewardship

Responding to the challenge of AMR and preserving the effectiveness of antimicrobials requires a One Health approach, in which all sectors that use antimicrobials – human health, animal health and agriculture – work together to improve appropriate antimicrobial use and reduce AMR. One Health is a coordinated, collaborative, multidisciplinary and cross-sectoral approach to the development and implementation of health strategies for people, animals and the environment.[10] *Responding to the Threat of Antimicrobial Resistance: Australia's first National Antimicrobial Resistance Strategy 2015–2019* outlines the One Health approach to reducing AMR in Australia.[10] This includes implementing AMS practices across all human health and animal care settings. The focus of this chapter, and this publication, is AMS in human health.

A number of arrangements, activities and partnerships in Australia support AMS in human health at the national, state, territory and organisational level, including non-government organisations, professional bodies and research organisations. At the national level, the National Safety and Quality Health Service (NSQHS) Standards have provided the foundation for universal requirements for implementation of AMS in Australia. Effective AMS involves the coordination of a combination of strategies, including regulation, monitoring and surveillance, education and awareness raising, and research.

### 1.3.1 National standards and guidelines

AMS in Australia is supported by national standards and guidelines, including the:

- National Safety and Quality Health Service Standards
- Antimicrobial Stewardship Clinical Care Standard
- *Australian Guidelines for the Prevention and Control of Infection in Healthcare*.

#### National Safety and Quality Health Service Standards

The NSQHS Standards (first edition) were released in 2011, and assessment commenced in acute health service organisations from January 2013. The NSQHS Standards (second edition) and supporting resources were released in November 2017.[35] Assessment to the NSQHS Standards (2nd ed.) will commence from 1 January 2019. All public and private acute health service organisations are required to implement the NSQHS Standards and be assessed by an approved accrediting agency to verify their compliance with the NSQHS Standards.

The NSQHS Standards were developed by the Australian Commission on Safety and Quality in Health Care (the Commission) in collaboration with states and territories, clinical experts, patients and carers. The primary aims of the NSQHS Standards are to protect the public from harm and to improve the quality of health service provision. They provide a quality assurance mechanism that tests whether relevant systems are in place to ensure that expected standards of safety and quality are met. The NSQHS Standards describe evidence-based actions to improve health care.[35] They cover key areas relating to governance, partnering with consumers, preventing and controlling healthcare-associated infection, medication safety, comprehensive care, communicating for safety, blood management, and recognising and responding to acute deterioration.

The Preventing and Controlling Healthcare-Associated Infection Standard states:

> *Leaders of a health service organisation describe, implement and monitor systems to prevent, manage or control healthcare-associated infections and antimicrobial resistance, to reduce harm and achieve good health outcomes for patients. The workforce uses these systems.*[35]

The intention of this standard is:

> *To reduce the risk of patients acquiring preventable healthcare-associated infections, effectively manage infections if they occur, and limit the development of antimicrobial resistance through prudent use of antimicrobials as part of antimicrobial stewardship.*[35]

All private and public hospitals, day procedure services, public dental practices, and community health services attached to health service organisations are required to have an AMS program in place (Box 1.1).

The Preventing and Controlling Healthcare-Associated Infection Standard aligns with the criteria and actions of the Clinical Governance Standard, the Partnering with Consumers Standard and the Medication Safety Standard.

The Clinical Governance Standard defines clinical governance as the set of relationships and responsibilities established by a health service organisation between its governing body, executive,

## **Box 1.1:** Preventing and Controlling Healthcare-Associated Infection Standard – criterion and actions for antimicrobial stewardship

### Criterion: Antimicrobial stewardship

The health service organisation implements systems for the safe and appropriate prescribing and use of antimicrobials as part of an antimicrobial stewardship program.

### Action required

3.15 The health service organisation has an antimicrobial stewardship program that:

a. Includes an antimicrobial stewardship policy

b. Provides access to, and promotes the use of, current evidence-based Australian therapeutic guidelines and resources on antimicrobial prescribing

c. Has an antimicrobial formulary that includes restriction rules and approval processes

d. Incorporates core elements, recommendations and principles from the current Antimicrobial Stewardship Clinical Care Standard

3.16 The antimicrobial stewardship program will:

a. Review antimicrobial prescribing and use

b. Use surveillance data on antimicrobial resistance and use to support appropriate prescribing

c. Evaluate performance of the program, identify areas for improvement, and take action to improve the appropriateness of antimicrobial prescribing and use

d. Report to clinicians and the governing body regarding

- compliance with the antimicrobial stewardship policy
- antimicrobial use and resistance
- appropriateness of prescribing and compliance with current evidence-based Australian therapeutic guidelines or resources on antimicrobial prescribing

clinicians, patients and consumers to deliver safe and high-quality health care. It ensures that the community and health service organisations can be confident that systems are in place to deliver safe and high-quality health care and continuously improve services.

Clinical governance is an integrated component of corporate governance for health service organisations. In relation to AMS, it ensures that everyone – from frontline clinicians to managers and members of governing bodies, such as boards – is accountable to patients and the community for assuring effective AMS.

The NSQHS Standards guide this publication and support implementation of effective AMS through the provision of information and resources for clinicians and health service managers.

AMS is also included as a component of hospital accreditation in other countries. In Canada, AMS was introduced as a Required Organizational Practice for accreditation in 2013. In the United States, health service organisations and aged care homes seeking accreditation through the Joint Commission are required to collect, analyse and report on AMS data.[36] This is done using the measures in *Core Elements of Hospital Antibiotic Stewardship Programs* and *Core Elements of Antibiotic Stewardship for Nursing Homes* produced by the Centers for Disease Control and Prevention.[37,38]

### Antimicrobial Stewardship Clinical Care Standard

The clinical care standards developed by the Commission are nationally agreed statements about the care that a patient should be offered by clinicians and organisations for a specific clinical condition, in line with current best evidence. The standards support clinicians' decision-making about appropriate care, and require health services

to review the performance of their organisation and make improvements in the care they provide. Clinical care standards aim to improve the appropriateness of health care provided to patients by reducing unwarranted variation in care – that is, variation in care that is not explained by the clinical circumstances or personal choices of the patient. The clinical care standards also help consumers to know what they should expect from their healthcare system and to make informed treatment decisions in partnership with their clinicians.

The Antimicrobial Stewardship Clinical Care Standard contains nine quality statements that describe the key aspects of care that a patient should be offered when antimicrobials are being considered for treatment of a bacterial infection or for prophylaxis.[39] The quality statements relate to high-priority areas for improvement regarding antimicrobial prescribing, based on available evidence (Figure 1.1). The Antimicrobial Stewardship Clinical Care Standard complements the NSQHS Standards and other national efforts that support AMS. It has been developed for use in all healthcare settings, including hospitals, general practice and aged care homes.

### *Australian Guidelines for the Prevention and Control of Infection in Healthcare*

The *Australian Guidelines for the Prevention and Control of Infection in Healthcare*, published in 2010, established the national approach to infection prevention and control. The guidelines provide a basis for healthcare facilities and members of the workforce to develop detailed protocols and processes for infection prevention and control specific to local settings. They incorporate AMS, and outline key requirements of an AMS program and the role of AMS in preventing and managing

**Figure 1.1:** Antimicrobial Stewardship Clinical Care Standard quality statements

**1** A patient with a life-threatening condition due to a suspected bacterial infection receives prompt antibiotic treatment without waiting for the results of investigations.

**2** A patient with a suspected bacterial infection has samples taken for microbiology testing as clinically indicated, preferably before starting antibiotic treatment.

**3** A patient with a suspected infection, and/or their carer, receives information on their health condition and treatment options in a format and language that they can understand.

**4** When a patient is prescribed antibiotics, whether empirical or directed, this is done in accordance with the current version of the Therapeutic Guidelines[42] (or local antibiotic formulary). This is also guided by the patient's clinical condition and/or the results of microbiology testing.

**5** When a patient is prescribed antibiotics, information about when, how and for how long to take them, as well as potential side effects and a review plan, is discussed with the patient and/or their carer.

**6** When a patient is prescribed antibiotics, the reason, drug name, dose, route of administration, intended duration and review plan is documented in the patient's health record.

**7** A patient who is treated with broad-spectrum antibiotics has the treatment reviewed and, if indicated, switched to treatment with a narrow-spectrum antibiotic. This is guided by the patient's clinical condition and the results of microbiology tests.

**8** If investigations are conducted for a suspected bacterial infection, the responsible clinician reviews these results in a timely manner (within 24 hours of results being available) and antibiotic therapy is adjusted taking into account the patient's clinical condition and investigation results.

**9** If a patient having surgery requires prophylactic antibiotics, the prescription is made in accordance with the current Therapeutic Guidelines[42] (or local antibiotic formulary), and takes into consideration the patient's clinical condition.

Source: Australian Commission on Safety and Quality in Health Care[39]

healthcare-associated infections.[40] The Commission has worked with the National Health and Medical Research Council (NHMRC) to review these guidelines, and publication is expected in 2018.

Infection prevention and control standards written specifically for general practices and clinicians in other office-based and community-based settings have been published by the Royal Australian College of General Practitioners (RACGP). The Dental Board of Australia has issued infection control guidelines for dental practitioners.

### 1.3.2 National Antimicrobial Resistance Strategy

In 2015, Australia's first National Antimicrobial Resistance Strategy was jointly produced by the Australian Government Department of Health and Department of Agriculture.[10] The vision of the National Antimicrobial Resistance Strategy is:

> *a society in which antimicrobials are recognised and managed as a valuable shared resource, maintaining their efficacy so that infections in humans and animals remain treatable and communities continue to benefit from the advances that antimicrobials enable.*[10]

The goal of the National Antimicrobial Resistance Strategy is to minimise the development and spread of AMR in Australia and ensure the continued availability of effective antimicrobials. It aligns with the World Health Organization's Global Action Plan on Antimicrobial Resistance.[41] To achieve this goal, the Australian Government, state and territory governments, non-government organisations, professional bodies and research organisations need to work together on priority areas to achieve the strategy's seven objectives:

1. Increase awareness and understanding of antimicrobial resistance through **communication**, **education** and **training**
2. Implement effective **antimicrobial stewardship** across human and animal care settings
3. Develop nationally coordinated **surveillance** of antimicrobial usage and resistance
4. Improve **infection prevention and control** measures across human and animal care settings
5. Agree a **national research agenda** and promote investment in innovative approaches to containing antimicrobial resistance
6. Strengthen **international partnerships**
7. Establish clear **governance** arrangements.

The Australian Government Department of Health and Department of Agriculture and Water Resources are responsible for the National Antimicrobial Resistance Strategy.[10] The Australian Antimicrobial Resistance Prevention and Containment Steering Group, led by the secretaries of both departments, reports publicly on AMR for the Australian Government.

An implementation plan outlining key areas of focus and specific actions to support the strategy was released in 2016. This outlines the areas of activity that the Australian Government identifies as important to achieving the seven objectives identified in the strategy.[43]

### 1.3.3 Antimicrobial stewardship in the states and territories

State and territory governments are responsible for planning and implementing AMS and infection prevention and control guidelines in public health service organisations. States and territories have undertaken significant work to support AMS policy and practice, and many have expert advisory processes to provide technical and strategic advice. Several states and territories have also developed jurisdictional antimicrobial formularies, and some conduct training and have produced resources to assist health service organisations to implement AMS programs.

AMS resources available in some states and territories include:

- AMS policies
- AMS committee terms of reference
- Education and training modules
- Information about formulary management and guidelines
- Statewide surveillance data
- Resources for patients
- AMS self-evaluation toolkits.

Examples of state and territory AMS activities and resources are listed in Appendix A.

### 1.3.4 Therapeutic Guidelines

Evidence-based prescribing guidelines for antimicrobials are a fundamental component of AMS programs because they guide appropriate antimicrobial use. They can also be used to educate prescribers and students on accepted practice

for antimicrobial prescribing in the organisation. The NSQHS Standards require that health service organisations provide access to, and promote the use of, current evidence-based Australian therapeutic guidelines.

In Australia, prescribers have access to *Therapeutic Guidelines: Antibiotic*, which provides guidance on optimising the selection, dose, route of administration, duration and timing of initial antimicrobial treatment.[40] These guidelines represent the best available evidence and opinion about treatment and prophylaxis for infections in community and hospital settings in Australia. They are listed in the RACGP *Standards for General Practices* as a resource that supports evidence-based practice, and are available in hard copy and electronically.

*Therapeutic Guidelines: Antibiotic* are supplemented by *Therapeutic Guidelines: Oral and dental* for dental practitioners, *Therapeutic Guidelines: Dermatology*, *Therapeutic Guidelines: Gastrointestinal* and *Therapeutic Guidelines: Respiratory*, all of which are now incorporated into the *eTG complete* electronic bundle.

### 1.3.5 Surveillance of antimicrobial use and resistance in Australia

Effective surveillance provides the basis for informed efforts to improve antimicrobial use, and prevent and control AMR, in combination with prescribing guidelines. At the local level, data can be used to provide feedback to clinicians, inform policy and program development, guide formulary listings, and develop other activities to promote appropriate antimicrobial use. At the national level, data can also be used to inform policy and program development – for example, the revision of the list of subsidised medicines, and identification of priorities for public health action to reduce the spread and impact of AMR, such as education campaigns or regulatory measures.[44]

In 2016, the Commission completed the establishment phase of the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System, with funding from the Australian Government. The system enables collection, analysis and reporting of antimicrobial use and AMR surveillance data. The AURA National Coordination Unit at the Commission oversees the strategy for surveillance activities, and implements activities to enhance national surveillance of antimicrobial use and resistance in the acute care and community sectors.

AURA uses a partnership model that has both strengthened support for existing surveillance programs and developed new systems to fill identified gaps (Box 1.2). AURA continues to be enhanced, and broaden its scope of surveillance activities and reporting to inform appropriate prescribing.

AURA program partners include:

- Australian Group on Antimicrobial Resistance
- National Antimicrobial Prescribing Survey (NAPS)
- National Antimicrobial Utilisation Surveillance Program (NAUSP)
- Queensland Health, which enables the use of the OrgTRx System as the IT platform base for the Australian Passive AMR Surveillance System.

#### **Box 1.2:** Antimicrobial Use and Resistance in Australia (AURA) Surveillance System

The AURA Surveillance System and the AURA National Coordination Unit:

- Provide the framework for effective planning and coordination of surveillance and reporting of antimicrobial use and antimicrobial resistance (AMR)
- Improve quality, coverage and utility of existing high-quality data collections on antimicrobial use and AMR through improved integration and coordination
- Provide detailed analyses across data collections, including opportunities for analysing relationships between antimicrobial use and AMR, at a system level
- Provide systematic, coordinated and centralised national reporting on antimicrobial use and AMR
- Establish new data collections, if needed, such as for the systematic and timely identification of critical antimicrobial resistances
- Provide a means for rapidly consulting and communicating with stakeholders to further improve the system and its reporting, and to better inform AMR prevention and control strategies.

Source: Australian Commission on Safety and Quality in Health Care[25]

The Commission has also established a national surveillance system for critical antimicrobial resistances, called CARAlert. This has enabled a more timely and effective mechanism to monitor and report on these resistances, which are of vital importance in the development of strategies to prevent and contain AMR and respond appropriately to outbreaks.

To further supplement surveillance and strengthen the value of reporting, the AURA National Coordination Unit works with other important surveillance data programs and organisations to ensure comprehensive reporting on antimicrobial use and AMR, including the:

- Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme
- NPS MedicineWise MedicineInsight program
- National Neisseria Network, on *N. gonorrhoeae* and *N. meningitidis*
- National Notifiable Diseases Surveillance System, on *M. tuberculosis*
- Sullivan Nicolaides Pathology, on AMR rates from the community and private hospital settings.

*AURA 2017: Second Australian report on antimicrobial use and resistance in human health* provided a comprehensive picture of antimicrobial use, AMR and the appropriateness of antimicrobial prescribing in Australia.[25] Several reports from AURA are now available, including those developed in conjunction with partner programs such as NAPS and NAUSP, and locally developed surveillance reports such as CARAlert. These reports provide extensive data for those responsible for AMS programs to review and consider, alongside local data, to help target AMS efforts. See Chapter 6: 'Measuring performance and evaluating antimicrobial stewardship programs'.

### 1.3.6 Education and awareness raising

Australians are increasingly recognising that AMR is a problem, but their understanding of how individual behaviours can contribute to the development and spread of AMR is limited. Increasing clinician and consumer awareness and understanding of AMR and the importance of using antimicrobials appropriately is seen as a critical component of AMS. It constitutes the first objective of the National Antimicrobial Resistance Strategy.[10] Priority areas identified for action include:

- Strengthening consumer awareness initiatives
- Supporting clinicians to reinforce messages relating to appropriate antimicrobial use and reducing the spread of infections with patients and consumers
- Strengthening communication and education initiatives for clinicians on AMR, AMS, and infection prevention and control
- Increasing access to reliable sources of information about antimicrobials and AMR.

The implementation plan for the National Antimicrobial Resistance Strategy outlines the activities being undertaken by organisations and health sectors to consider these action items.[43]

#### Consumer engagement

Consumers, patients and carers can be engaged in AMS through formal and informal education, improved health literacy and shared decision making. Several government and non-government organisations in Australia are involved in developing resources and delivering programs to increase consumer awareness about AMR and change consumer attitudes towards antimicrobial use. Some resources are directed at consumers, and others are directed at clinicians to equip them with the tools and skills to communicate effectively with consumers. These resources are discussed further in Chapter 7: 'Involving consumers in antimicrobial stewardship' and Chapter 10: 'Role of prescribers in antimicrobial stewardship'.

#### Clinicians

Strengthening communication and education for clinicians on AMR, AMS, and infection prevention and control is another priority area for action. This should start during the clinician's formal training and be regularly reinforced by workplace education and training. A multidisciplinary approach is recommended.[10] A number of online educational resources developed in Australia are available to educators and clinicians. Further information, including information on AMS competency standards, is available in Chapter 5: 'Antimicrobial stewardship education for clinicians' and Chapter 10: 'Role of prescribers in antimicrobial stewardship'.

#### Antibiotic Awareness Week

Australia has been participating in Antibiotic Awareness Week every November since 2012. The week is jointly organised by the Commission and NPS MedicineWise, and supported by several Australian Government departments and professional societies. The Australian campaign is

aligned with international efforts to promote greater understanding of AMR and the responsible use of antibiotics. It takes a One Health approach, and targets consumers and clinicians in human health, as well as prescribers and users in animal health and agriculture.

All health service organisations and clinicians are encouraged to participate in Antibiotic Awareness Week each year. Resources to support Antibiotic Awareness Week are available from the Commission, NPS MedicineWise and professional societies.

### 1.3.7 Antimicrobial stewardship research

Objective 5 of the National Antimicrobial Resistance Strategy is to agree to a national research agenda, and promote investment in the discovery and development of new products and approaches to prevent, detect and contain AMR.[10] Priority areas for action are to:

- Identify current gaps, and agree to national research and development priorities
- Coordinate national research activities and information sharing
- Explore opportunities to increase support for research and development, including incentives for greater private sector investment
- Explore opportunities to support the translation of promising research findings into new products, policies and approaches.

The NHMRC currently provides funding for four Centres of Research Excellence to research aspects of AMR (Table 1.1). Their focus is on accelerating knowledge translation into changes in policy and practice.

The Australian Medical Research Future Fund has listed AMR as a priority for medical research and innovation for 2016–2018. The research must be consistent with the National Antimicrobial Resistance Strategy. The fund focuses on research that brings point-of-care solutions to market.

### 1.3.8 Professional societies and organisations

Professional organisations can play an important role in setting professional standards, providing guidelines and educating their members. Several professional organisations in Australia are active in promoting AMS, developing resources, and assisting their members develop the knowledge and skills required to actively participate in AMS activities. Key professional organisations and societies that have provided leadership in AMS in human health are the:

- Australasian Society for Infectious Diseases
- Australian Society of Antimicrobials

**Table 1.1:** Centres of Research Excellence in antimicrobial resistance

| University | Centre of Research Excellence name | Research themes |
|---|---|---|
| Bond University | Minimising Antibiotic Resistance for Acute Respiratory Infections (CREMARA) | • Delayed prescribing<br>• Shared decision making and patient decision aids<br>• Diagnostic tests and biomarkers |
| Queensland University of Technology | Reducing Healthcare Associated Infections (CRE-RHAI) | • Effective infection prevention and control interventions and policy<br>• Modelling transmission dynamics<br>• Cost-effectiveness studies |
| University of Melbourne | National Centre for Antimicrobial Stewardship (NCAS) | • One Health antimicrobial stewardship<br>• Antimicrobial prescribing studies |
| University of Queensland | Redefining Antimicrobial Use to Reduce Resistance (CRE REDUCE) | • Development of guidelines<br>• Clinical pharmacokinetics studies<br>• Modelling of novel antimicrobial doses |

- Australasian College for Infection Prevention and Control
- Society of Hospital Pharmacists of Australia.

## 1.4 Antimicrobial use

Antimicrobials that are used inappropriately or unnecessarily not only contribute to AMR but can also lead to patient harm.

### 1.4.1 Factors contributing to unnecessary and inappropriate antimicrobial use

Antimicrobials continue to be used unnecessarily and inappropriately, despite the availability of well-established evidence-based treatment guidelines.[45] The reasons for this vary. Prescribers may be unaware that guidelines are available or are too busy to consult them. They may be confident that they know the best antimicrobial choice, or unconvinced of the risks of inappropriate use, including the risk of AMR.[45] Many clinicians are unwilling to withhold antimicrobial therapy if the diagnosis is uncertain or to risk treatment failure by using a narrow-spectrum agent. Some prescribers and consumers believe that antimicrobials have few adverse effects, potentially leading to prescribing 'just in case' or for longer than necessary because no negative consequences are perceived. However, it is clear that antimicrobials can cause lasting and detrimental disruptions to the normal flora of individual patients, reducing microbial diversity and promoting overgrowth of antimicrobial-resistant organisms.[46,47]

The knowledge of both consumers and prescribers is a major factor influencing antimicrobial prescribing. In the community, consumer knowledge about antimicrobials and AMR is limited, and preconceptions about the efficacy of antimicrobials and the conditions for which they are of benefit are frequently inaccurate.[48] Prescribers may overestimate consumer expectations for antimicrobials[49], or think that consumers will go to another practitioner if they are not prescribed an antimicrobial[49-51] (see Chapter 7: 'Involving consumers in antimicrobial stewardship').

### 1.4.2 Antimicrobial use in Australia

Antimicrobial use is high in Australia compared with many other high-income countries, in both hospitals and the community.

#### Community use

In the community, Australia has the eighth highest rate of antimicrobial prescribing among member countries of the Organisation for Economic Co-operation and Development, and a prescribing rate more than double that of some other countries.[25]

In Australia in 2015, more than 30 million prescriptions were dispensed in the community. Each year, almost half (around 45%) of the Australian population is prescribed at least one course of an antimicrobial. It is estimated that a considerable proportion of those prescriptions are unnecessary[25], especially for respiratory tract infections. In 2015, 60% of people presenting to a general practitioner with colds and other undifferentiated upper respiratory tract infections – conditions for which antimicrobials are generally not recommended – were prescribed an antimicrobial.[25]

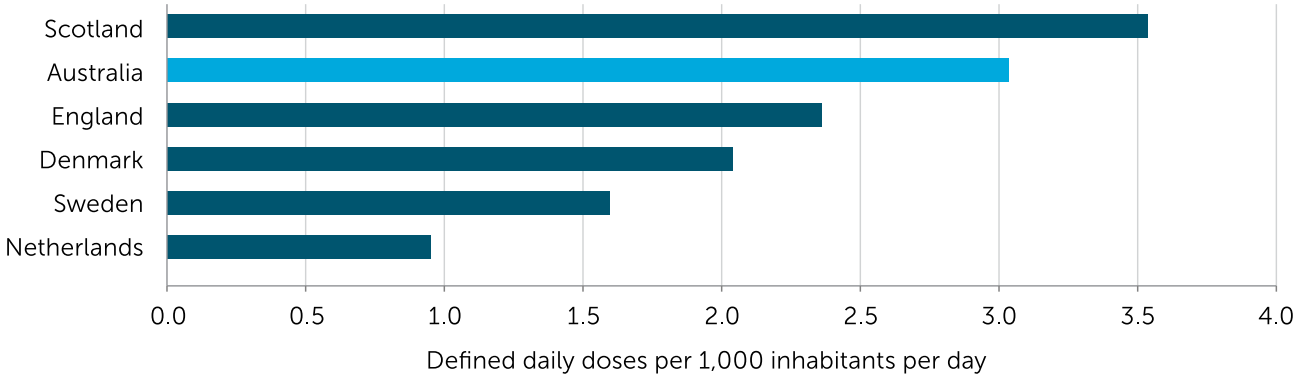
#### Hospital use

In Australian hospitals, on any given day in 2015, nearly 40% of inpatients were prescribed antimicrobials. Of those prescriptions, almost one-quarter were considered inappropriate, and almost one-quarter were noncompliant with guidelines. The volume of antimicrobial use in Australia is higher than in most comparator countries[25] (Figure 1.2).

### 1.4.3 Harmful effects of antimicrobial use

In addition to contributing to the development of AMR, antimicrobial use is associated with other risks that may lead to patient harm. Inappropriate antimicrobial use can lead to poor outcomes for individual patients, whether these agents are underused (such as in delayed, omitted or ineffective treatment) or overused (such as starting treatment unnecessarily or continuing treatment for longer than required). Inadequate antimicrobial therapy – such as poor antimicrobial choice, and suboptimal dose, route or duration – is unlikely to be effective against the causative pathogen, and is associated with increased patient morbidity and mortality.[4,5] It is an independent risk factor for death among critically ill patients with severe infection.[5] Other

**Figure 1.2:** Comparison of hospital antimicrobial use in Australia and similar countries, 2015




Source: Australian Commission on Safety and Quality in Health Care[25]

risks associated with antimicrobial use include increased risk of infection, allergies and other adverse drug reactions, drug interactions, and drug toxicity. These risks can be decreased by reducing unnecessary and inappropriate use.

### Increased risk of infection

Broad-spectrum antimicrobials can disrupt an individual's microbiome, leaving the individual susceptible to infection by opportunistic bacterial pathogens such as *C. difficile* and fungal infections such as *Candida*. Patients taking antibiotics are 7–10 times more likely than patients not taking antibiotics to be infected with *C. difficile* while the patient is taking the antibiotic and for one month after discontinuation.[52]

### Allergies and other adverse drug reactions, drug interactions, and drug toxicity

All antimicrobials can cause adverse effects. Although many of these are minor or self-limiting, some can be serious, such as anaphylaxis or liver failure. In the United States, antimicrobials have been implicated in around 20% of emergency department visits for drug-related adverse events reported to the National Electronic Injury Surveillance System.[53] Allergic reactions were the most common events in this system. Around 10–15% of hospitalised patients are labelled penicillin allergic. If penicillin is administered to a patient with a true severe allergy, they may experience a fatal anaphylactic reaction. Many patients are labelled as being penicillin allergic based on a vague history and may not have a true allergy. However, because they are labelled 'allergic', they are often prescribed suboptimal reserve agents with less favourable safety profiles, which increases their risk of treatment failure or adverse events.[54-56]

Patients with altered pharmacokinetic profiles (such as older patients, and patients with kidney or liver impairment) are more likely to have an adverse event and are at risk of drug toxicity if the dose or dose frequency is not adjusted.[40] Patients receiving antimicrobials that require therapeutic drug monitoring (such as aminoglycosides and vancomycin) are at risk of poorer clinical outcomes, adverse events and extended length of stay if appropriate systems for monitoring are not in place.[57]

Some antimicrobials interact with other medicines, which can cause adverse events. For example, giving macrolides (erythromycin and clarithromycin) with medicines that prolong the QT interval can increase the risk of cardiac arrhythmias.

## 1.5 Antimicrobial stewardship

AMS is described as a systematic and coordinated approach to optimising antimicrobial use with the goals of improving patient outcomes, ensuring cost-effective therapy and reducing adverse consequences of antimicrobial use, including AMR.[6-9] It is an integral component of patient safety.

### 1.5.1 Effective antimicrobial stewardship

Effective AMS requires a suite of coordinated strategies to promote the use of antimicrobials in a way that maximises their benefit, while causing the least harm. The aim is to reduce unnecessary use and improve the appropriate use of antimicrobials by

prescribing according to evidence-based guidelines, with medicine choice, dose and duration selected to optimise clinical outcomes and minimise adverse consequences such as drug toxicities, *C. difficile* infection or the selection of resistance.[58] In short, AMS promotes the use of the right antimicrobial, at the right dose, for the right duration, at the right time and by the right route.

AMS requires a systems-based approach that operates with support of the health service organisation executive, within the governance framework of the organisation, using the expertise and resources of a multidisciplinary team to coordinate activities (see 'Structure and governance' in Box 1.3). AMS programs need sustained effort to remain effective; otherwise, antimicrobial consumption patterns can rapidly revert to pre-AMS levels.[59]

AMS programs aim to change antimicrobial prescribing behaviour through different strategies. These include restrictive approaches (such as requiring approval to prescribe a specific antimicrobial) and enabling approaches (such as post-prescription review and feedback).

Strategies considered essential to establishing an effective AMS program are summarised in Box 1.3. Evidence for each of the strategies, and resources and

## **Box 1.3:** Essential elements and strategies for antimicrobial stewardship programs

### Structure and governance

Overall accountability for antimicrobial stewardship (AMS) is defined by an organisation's corporate and clinical governance. Managers and senior clinicians are responsible for the AMS program, including:

- Ensuring that AMS resides within the organisation's quality improvement and patient safety governance structure
- Establishing a multidisciplinary AMS team that includes, at least, a lead doctor and pharmacist
- Providing the necessary human, financial and information technology* resources for AMS activities
- Ensuring ongoing education and training for prescribers, pharmacists, nurses, midwives and consumers about AMS, antimicrobial resistance and optimal antimicrobial use.

### Essential strategies

The essential strategies that sit within the AMS governance structure are:

- Implementing clinical guidelines† consistent with *Therapeutic Guidelines: Antibiotic* that take into account local microbiology and antimicrobial susceptibility patterns
- Implementing formulary§ restriction and approval systems that include restricting broad-spectrum and later-generation antimicrobials to patients in whom their use is clinically justified
- Reviewing antimicrobial prescribing, with intervention and direct feedback to the prescriber
- Implementing point-of-care interventions (including directed therapy, intravenous-to-oral switching and dose optimisation)
- Ensuring that the clinical microbiology service
  - provides guidance and support for optimal specimen collection
  - targets reporting of clinically meaningful pathogens and their susceptibilities
  - uses selective reporting of susceptibility testing results
  - generates location-specific antimicrobial susceptibility reports (antibiograms) annually
- Monitoring antimicrobial use and outcomes, and reporting to clinicians and management.

* Information technology examples include electronic prescribing with clinical decision support, online approval systems for restricted agents, post-prescription alert systems and antimicrobial use surveillance systems.
† Guidelines include clinical pathways and care bundles.
§ Refers to institutional formularies; in the community, the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme act as the formulary.

tools to support their implementation in different health settings are described in subsequent chapters.

Most evidence about the effectiveness of AMS initiatives has been generated from public hospitals, including those in Australia, and AMS is maturing in the hospital sector. AMS programs in other settings, such as the community and aged care homes, are in their infancy; however, evidence to support implementation in those settings is growing. Although the principles of AMS are common to all settings, it is recognised that different approaches will be required and interventions will need to be adapted for use in those settings.[60]

### 1.5.2 Evidence to support the benefits of antimicrobial stewardship

It is sometimes difficult to draw a direct relationship between system interventions and their effects. In the hospital sector, many of the studies of the efficacy of AMS have reported on structural and process measures (such as the presence of guidelines and reduction in antimicrobial use). However, the studies have been limited in their ability to evaluate outcomes, particularly patient outcomes, whether the development of AMR is prevented or minimised, and unintended consequences of AMS.[61] Evidence of positive outcomes associated with AMS is increasing, including reductions in unnecessary antimicrobial use and institutional resistance rates, improved clinical outcomes, improved patient safety, and cost savings.[61-64]

#### Reduction in unnecessary antimicrobial use

At the community level, there is evidence that media campaigns and specific education programs, in combination with a dedicated workforce to conduct coordinated AMS activities, can lead to broadscale changes in prescribing behaviour and a decrease in antimicrobial use. This has been demonstrated in public campaigns in France and Belgium to improve the use of antimicrobials in outpatients[65,66], which resulted in a 26.5% decrease in antimicrobial prescriptions in France over five years and a 36% decrease in packets of antimicrobials supplied in Belgium over seven years.

In the hospital setting, a 2017 Cochrane review on interventions to improve antibiotic prescribing practices for inpatients showed that AMS interventions can safely reduce unnecessary antimicrobial use in hospitals by improving adherence to guidelines and decreasing the treatment duration.[64]

#### Reduction in antimicrobial resistance

There is growing evidence that a reduction in antimicrobial use can result in a decrease in AMR in specific settings.

AMS interventions in the community have been associated with a decrease in AMR (Table 1.2).

In the hospital setting, there are many examples of changes in antimicrobial prescribing practices having a significant effect on outbreaks of resistant pathogens. Those changes have often been implemented in times of crisis, such as in response to the emergence of resistance in a unit or across a hospital. However, evidence is growing for the effectiveness of AMS programs in institutions, which show reduced prevalence of resistant organisms over time.[63,72] In a meta-analysis, Beryl et al. found that, overall, AMS activities in hospitalised patients[72]:

- Reduced AMR rates by 34% (incidence rate ratio [IRR] 0.66; 95% confidence interval [CI] 0.47, 0.93; $P = 0.02$)
- Reduced *C. difficile* colonisation by 62% (IRR 0.38; 95% CI 0.23, 0.65; $P < 0.001$)
- Were more effective in reducing AMR among gram-positive bacteria (43% reduction) than gram-negative bacteria (28% reduction); AMS activities were most effective in reducing
  - MRSA (49% reduction; IRR 0.51; 95% CI 0.33, 0.80)
  - carbapenem-resistant gram-negative bacteria (48% reduction; IRR 0.52; 95% CI 0.32, 0.84)
- Did not appear to be effective in reducing vancomycin-resistant enterococci rates.

Another meta-analysis of the clinical outcomes associated with implementating AMS programs showed a reduction in infections due to MRSA, imipenem-resistant *P. aeruginosa* and ESBL-producing *Klebsiella* species.[63] A survey of 448 hospitals in the United States showed that implementing guideline-recommended practices and optimising the duration of empirical therapy were associated with a lower prevalence of resistant organisms.[73] However, the 2017 Cochrane review of interventions to improve antimicrobial prescribing in hospitalised patients reported an inconsistent effect on resistant gram-negative and gram-positive bacteria, citing too few studies and too much variance in microbial outcomes to reliably assess any relationship between microbial outcomes and change in antimicrobial use.[64]

**Table 1.2:** Community interventions for antimicrobial stewardship

| Country | Intervention | Result |
|---|---|---|
| Belgium[66,67] | National campaign to reduce unnecessary prescriptions in the community | Reduced penicillin resistance in *Streptococcus pneumoniae* from 17.7% to 10.0% between 2000 and 2007 |
| Iceland[68] | Public media campaign aimed at reducing consumption of antimicrobials | Reduced frequency of penicillin-nonsusceptible *S. pneumoniae* from 20% to 12% between 1993 and 1997 |
| Finland[69] | Community education campaign to reduce macrolide prescribing | Reduced macrolide resistance in *Streptococcus pyogenes* (Group A streptococci) over five years, to 48% of 1991 levels |
| Scotland[70] | Restriction of the '4C' antimicrobials (cephalosporins, clavulanate, clindamycin and ciprofloxacin) in National Health Service trusts | Around 50% decline in the incidence of *Clostridium difficile* |
| Australia[11,25,71] | Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme subsidies for fluoroquinolones restricted to a limited number of indications and durations | Low rate of fluoroquinolone resistance among gram-negative bacteria compared with other countries with otherwise similar overall antimicrobial use |

Some of the most successful AMS programs reported are those aimed at reducing *C. difficile* infection rates. Restricting use of antibiotics deemed high risk for *C. difficile* infection has been associated with significant reductions in targeted antibiotics and *C. difficile* infection rates.[64,74] The 2017 Cochrane review of interventions to improve antimicrobial prescribing in hospitalised patients reported an association of planned AMS interventions with a consistent reduction in *C. difficile* infection (median −48.6%; interquartile range −80.7% to −19.2%).[64] Other studies have demonstrated that reducing the overall use of antimicrobials, combined with improved infection control precautions, reduces the incidence of nosocomial *C. difficile* infection.[75-78] Figure 1.3 is an example of the outcome of a program of improved infection control and targeted antimicrobial consumption on the incidence of *C. difficile* infection in a Canadian hospital.[77]

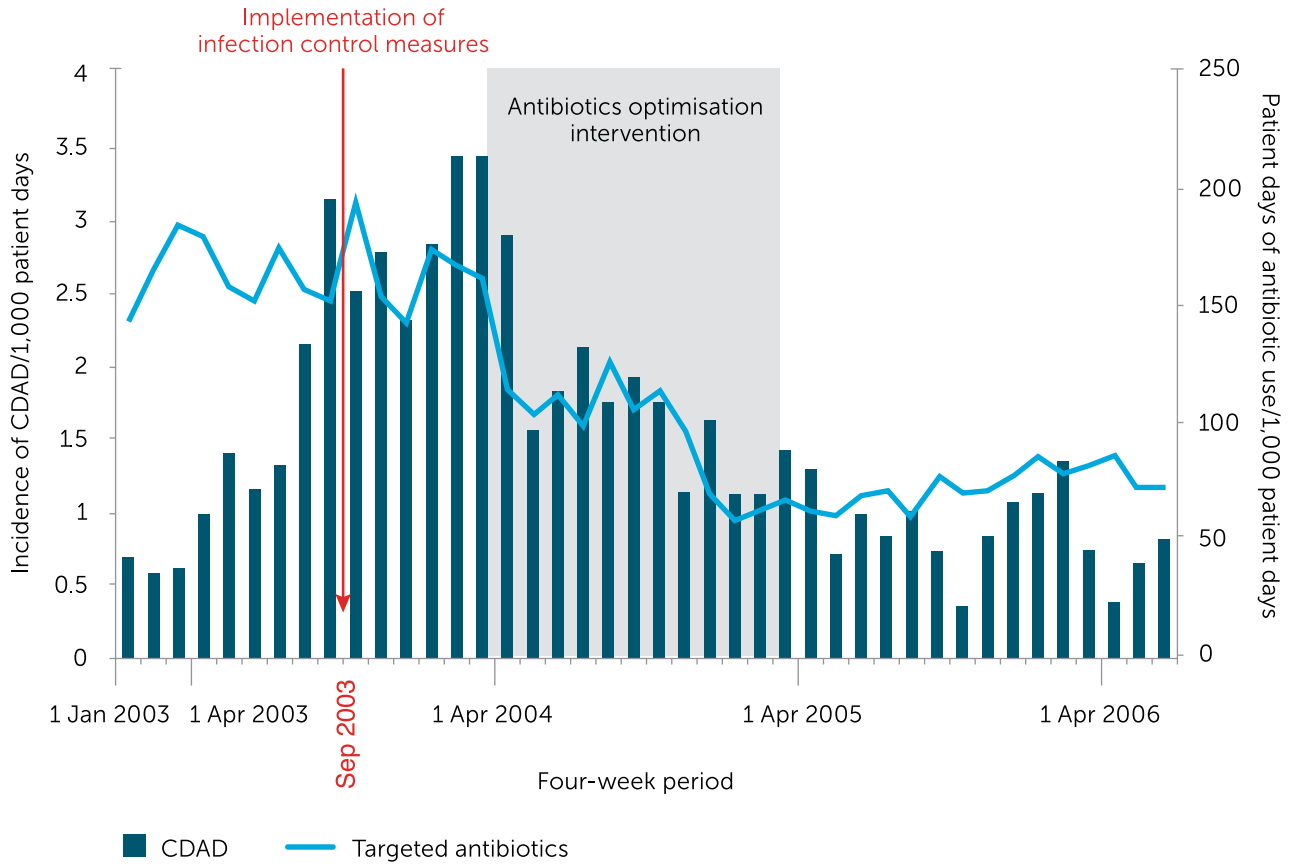
### Improved clinical outcomes

Inadequate antimicrobial therapy is associated with increased patient morbidity and mortality due to infection[4,5], and is an independent risk factor for death among critically ill patients with severe infection.[5] Programs that improve antimicrobial prescribing have been shown to increase cure rates, decrease treatment failures[79] and decrease mortality from infection.[61,80] The 2017 Cochrane review concluded that interventions to improve antimicrobial prescribing for hospital inpatients are effective at increasing compliance with antibiotic policies and reducing the duration of antibiotic treatment safely, without increasing mortality.[64] In addition, interventions were associated with reduced length of stay.

A meta-analysis by Schuts et al. examined whether AMS programs in hospitals and long-term care facilities had effects in four predefined patient outcomes: clinical outcomes, adverse events, costs and bacterial resistance.[61] The overall evidence for benefits was assessed against one or more of the four patient outcomes for six AMS objectives:

- Empirical therapy according to guidelines
- De-escalation of therapy
- Intravenous-to-oral treatment switching
- Therapeutic drug monitoring
- Use of a list of restricted antimicrobials
- Bedside consultation.

**Figure 1.3:** Targeted antibiotic consumption and nosocomial *Clostridium difficile*–associated disease (CDAD) incidence per 1,000 patient days of hospitalisation




Source: Valiquette et al.[77]

The benefits included:

- 35% relative risk (RR) reduction for mortality (RR 0.65; 95% CI 0.54, 0.80; $P < 0.0001$) associated with guideline-adherent therapy
- 56% decrease in mortality (RR 0.44; 95% CI 0.3, 0.66; $P < 0.0001$) associated with de-escalation of therapy
- Improved patient outcomes with infectious diseases physician bedside management of *S. aureus* bacteraemia.

Although many studies in this meta-analysis showed benefit, many were of low quality, and further research is needed in this area. Additionally, no studies regarding predefined outcomes in long-term care facilities were able to be identified; this is also an area for future research.

### Improved patient safety

AMS is synonymous with antimicrobial safety and is an integral component of patient safety.[81] In addition to reducing the risk of individual patient harm from AMR and *C. difficile* infection, AMS intervention outcomes include the reduction of medication-related adverse events:

- Over four years (2009–2012), Cao et al. analysed AMS interventions in a hospital in Texas[82]
  - interventions primarily related to inappropriate dosing (39.0% of the AMS interventions), antimicrobial selection (20.5%) and drug allergy (13.0%)
  - serious adverse drug events were potentially avoided in 20.7% of all interventions
- Individualised pharmacokinetic monitoring and adjustment of aminoglycoside dosing have been shown to reduce nephrotoxicity, hospital length of stay and mortality.[57]

### Cost savings and cost benefit

Implementation of any new program usually requires some financial investment, through either further resources or reallocation of resources. Published studies indicate that AMS programs produce overall cost savings for organisations and

can be financially self-supporting over time.[7,62,83] However, calculation of the health–economic impact of AMS programs is complex because of uncertainties in long-term cost–benefit ratios, attributable costs and effects of avoided infection.

Examples of interventions that have direct cost savings include:

- Ceasing antimicrobial therapy when it is no longer indicated or when the infection has resolved
- Intravenous-to-oral therapy switching
- De-escalating from broad-spectrum or combination therapy to directed therapy
- Implementing evidence-based guidelines that direct the duration of therapy in surgical prophylaxis.

Reports of AMS cost savings in hospitals include a recent review summarising 26 published studies, which indicated that hospital AMS programs reduced antimicrobial costs by an average of 33.9% (95% CI –42%, –25.9%) and length of stay by 8.9% (95% CI –12.8%, –5%).[63] In a 2007 study from the United States, annual savings of between US$200,000 and US$900,000 were reported in large teaching hospitals and small community hospitals with multidisciplinary antimicrobial management programs.[62] Although reports describing the clinical and economic impacts of multidisciplinary antimicrobial management programs were limited to single-centre longitudinal studies, they consistently demonstrated a decrease in antimicrobial use (of between 22% and 36%).[62]

Hospital AMS programs with a narrower focus have also demonstrated cost savings and cost-effectiveness in different settings, and with different targets and strategies (Table 1.3).

Many of the cost savings will be most evident in the first year of introducing AMS, particularly pharmaceutical costs. Measures such as streamlining antimicrobial formularies to optimise purchase price are generally a one-off saving. Presuming that adherence is high, implementing guidelines for surgical prophylaxis will initially bring about antimicrobial cost savings through a decrease in duration of antimicrobial therapy, but is unlikely to provide further reductions. However, cost–benefit is only one consideration in determining economic benefit to support the maintenance of an AMS program. Improved quality of care and patient outcomes are important factors that should also be estimated.

### 1.5.3 Unintended consequences of antimicrobial stewardship programs

Several meta-analyses have identified no adverse clinical outcomes from AMS in hospitals.[61,63,89,90] To complement the studies showing a benefit in clinical outcomes of AMS, many other studies show that a significant reduction in antimicrobial use, although not showing a change in clinical outcomes, reassuringly does not show adverse clinical effects.[91-95] For example, reducing the duration of intravenous antimicrobial therapy for community-acquired or ventilator-associated pneumonia did not increase mortality or length of hospital stay.[96,97] Studies evaluating shorter duration of surgical prophylaxis also showed no increases in postoperative surgical site infections.[98,99]

**Table 1.3:** Cost savings from antimicrobial stewardship in hospital settings

| Country | Target of program | Outcome |
|---|---|---|
| Italy[84] | Perioperative prophylaxis | 22.9% reduction in direct drug costs |
| Singapore[85] | Broad-spectrum antimicrobial use in renal patients | Direct cost savings of S$90,045 |
| United States[86] | Broad-spectrum antibiotics in paediatric critical care | 62% reduction in purchase costs of broad-spectrum antibiotics |
| United States[87] | Optimising treatment of bacteraemia as a single infective syndrome | Maintaining an antimicrobial stewardship team was cost-effective |
| Germany[88] | Broad-spectrum antibiotic use in an orthopaedic unit | Overall cost savings (including drug cost, infectious diseases consultant time and laboratory costs) over 15 months |

However, this does not mean that unintended consequences may not occur in individual programs or strategies. In Scotland, when the national orthopaedic surgical prophylaxis guidelines were changed from cefuroxime to flucloxacillin and gentamicin, there was an associated significant increase in acute kidney injury.[100] Thus, when introducing AMS measures, it is necessary to monitor actual and potential adverse outcomes, as well as positive outcomes such as reduced AMR or *C. difficile* infection. Certain interventions, such as removing broad-spectrum antimicrobials from clinical areas to limit their inappropriate use, may delay antimicrobial delivery if appropriate pathways for antimicrobial supply do not accompany the restrictions. For example, a study in the United Kingdom found that first doses of restricted, non-ward stock antimicrobials were more likely to be delayed than first doses of unrestricted stock antimicrobials. Although the study was not powered to measure whether an adverse clinical outcome was associated with this delay, in the setting of sepsis, delaying antimicrobial prescription has been shown to have adverse consequences.[101,102] More research is needed to understand any unintended consequences of the use of restrictive interventions.[64]

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# Appendix A: Examples of antimicrobial stewardship (AMS) activities and resources in Australian states and territories

| State | Activities and resources |
|---|---|
| Australian Capital Territory (ACT) | Healthcare Associated Infections Standards Group based at Canberra Hospital and Health Services, and AMS working group<br>ACT Health Formulary<br>Comprehensive restrictions policies |
| Northern Territory (NT) | Policies and guidelines available for all hospitals via the policy portal on the intranet homepage<br>Electronic approval systems for Top End hospitals<br>CARPA Standard Treatment Manual (STM) to support remote clinicians |
| New South Wales (NSW) | State AMS expert advisory committee terms of reference<br>AMS toolkit: sample terms of reference for AMS committees, sample AMS policy, list of antimicrobial restrictions, fact sheets<br>Other resources: hospital-level cumulative antibiograms, e-learning module on AMR, mobile applications |
| Queensland | Statewide formulary (MedTRx)<br>Statewide AMS program offering a range of educational activities and skills sessions with video conference access available |
| South Australia | South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR)<br>Statewide antimicrobial formulary management and surveillance of antimicrobial use<br>AMS self-evaluation toolkit |
| Tasmania | State Health Service AMS committee<br>Online state medicines formulary with comprehensive antimicrobial component<br>Regional AMS committees reporting to the statewide committee with primary health and GP liaison |
| Victoria | Support for AMS through Safer Care Victoria, with regular email updates to AMS hospital contact list<br>Annual forum for Antibiotic Awareness Week<br>VICNISS (Victorian Healthcare Associated Infection Surveillance System) activities available to all acute and some non-acute health services in Victoria |
| Western Australia (WA) | WA Committee for Antimicrobials<br>Statewide medicines formulary |