Communicable Diseases Intelligence

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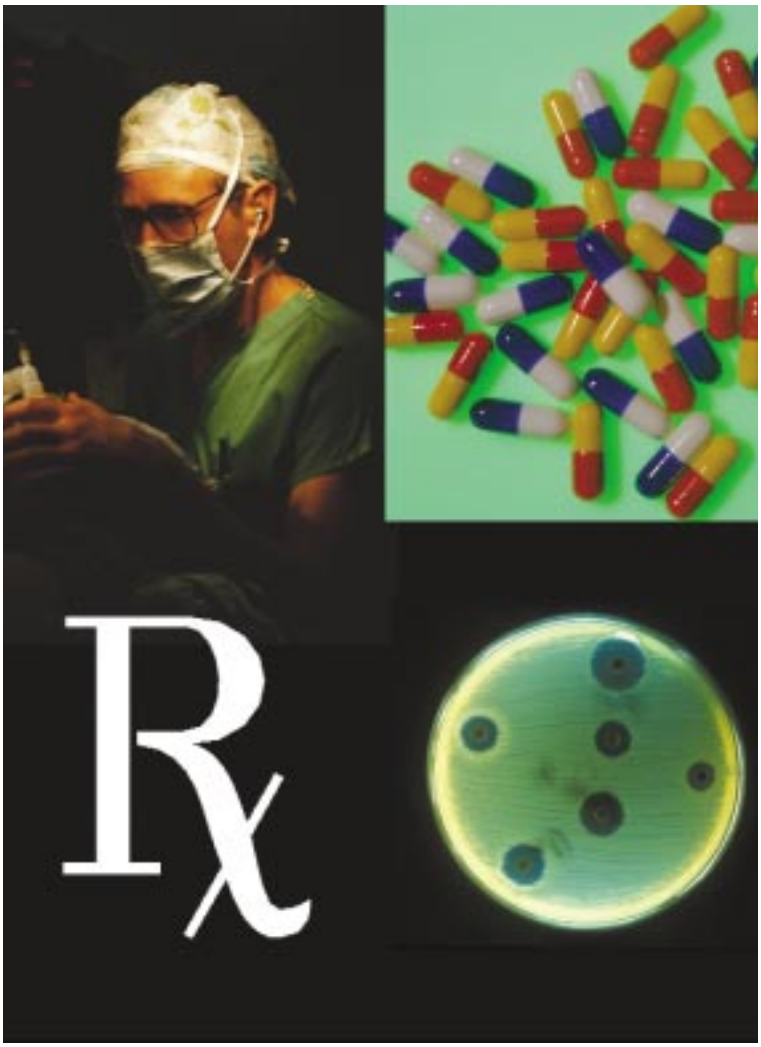

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Surveillance and Epidemiology Section
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Department of Health and Ageing
GPO Box 9848, (MDP 6)
CANBERRA ACT 2601;
Phone: +61 2 6289 8245
Facsimile: +61 2 6289 7791
E-mail: cdi.editor@health.gov.au.

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Contents

Editorial: Antimicrobial resistance in Australia

Paul Roche, Jenean Spencer

Surveillance and Epidemiology Section, Department of Health and Ageing, Canberra, Australian Capital Territory

This supplement of *Communicable Diseases Intelligence* contains articles describing various aspects of the problem of antimicrobial resistance (AMR) in Australia. Three years ago, the Joint Expert Committee on Antibiotic Resistance (JETACAR) released a landmark report entitled *The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans*. This report reviewed the scientific evidence on the link between the use of antibiotics in food-producing animals, the emergence and selection of antibiotic resistant bacteria and their spread to humans. In addition, evidence based recommendations were made for the future management of antibiotic use in Australia. In all, 22 recommendations covering areas such as regulatory controls, monitoring and surveillance, infection prevention, education, research, communication and coordination were made. This supplement is an attempt to inform Australian prescribers, regulators and stakeholders on the current state of knowledge about various aspects of antimicrobial use, resistance and surveillance in humans and animals.

Articles were invited from recognised experts in January 2002. Thirty-two abstracts were received of which 28 were peer-reviewed and accepted for this supplement. Papers have been grouped under the following themes.

Introduction

Alexandra Geue, former Director of the Infection Management Section, Department of Health and Ageing, describes the progress towards a national antibiotic resistance management program since the JETACAR report. Tim Dyke from the National Registration Authority for Agricultural and Veterinary Chemicals, describes the regulation of veterinary antibiotics in Australia.

Education and prescribing

Management of antibiotic resistance starts with rational and appropriate use of antibiotics. The *Antibiotic Guidelines* has been an essential resource for Australian physicians to prescribe according to best practice. Harvey and colleagues describe 25 years of development of the *Guidelines* and innovations designed to improve access to the *Guidelines*, for example by integration into clinician's electronic desktops.

Promotion of best practice prescribing guidelines in a tertiary hospital setting is described in the paper by Tiley and colleagues. Guidelines for appropriate antibiotic use in the management of pneumonia, surgical prophylaxis and wound infection were developed with restrictions on the use of certain antibiotics. Implementation of these guidelines in a variety of novel ways with regular reviews seems to have already had an impact on the prevalence of vancomycin resistant enterococci and *Clostridium difficile* infection in this hospital.

Innovative methods to measure antibiotic usage in South Australian hospitals are described by Dollman and Cooper. Eight metropolitan public and private hospitals now electronically provide data on antibiotic prescribing for four major classes of antibiotics to the Communicable Disease Control Branch of the Department of Human Services, South Australia. These data will be used to monitor trends in antibiotic usage and to compare with trends in AMR. This experience will be useful in developing similar surveillance systems in other Australian jurisdictions.

Thomas and Riley provide evidence that restriction in the use of third generation cephalosporins can reduce the prevalence of *Clostridium difficile* associated diarrhoea, an indicator of inappropriate antibiotic use and antibiotic resistant bacteria. Rational use of antibiotics can control and even reverse levels of antibiotic resistance in hospital settings.

Changing antibiotic prescribing practices in general practitioners (GPs) in Canberra was assessed by means of a randomised control trial conducted by Wilson and colleagues. Involving GPs in the development of evidence-based clinical guidelines for the treatment of acute respiratory infections led to a significant decrease in the rate of prescribing. The National Prescribing Service offers GPs education and audit of antibiotic prescribing. Patterson and colleagues describe the results of two audits of GP prescribing practices for otitis media (in 1999) and sinusitis (in 2000). Rates of inappropriate antibiotic prescribing for upper respiratory tract infections by Australian GPs, however, remains high at around 50 per cent.

Consumer education programs through National Medicines Weeks (1996–1998) are described by Donovan. Consumer education has also been incorporated into the recent National Prescribing Service campaign *Common colds need common sense*, which aims to discourage inappropriate antibiotic prescribing and consumption in people with common colds. Consumer education is an important contribution to the appropriate consumption of antibiotics in Australia.

Surveillance

Several groups and networks have been, and continue to be active in the surveillance of AMR in Australia. The Australian Group for Antimicrobial Resistance have provided data on the prevalence of AMR in important pathogens in Australia for the past 15 years. The paper by Nimmo and colleagues provides important high quality data on the prevalence of resistance to major antibiotics in important pathogens in Australia.

The Australian Hospital Morbidity Database managed by the Australian Institute of Health and Welfare is a source of important data on antimicrobial resistance in Australian hospitals. An analysis of these data by International Classification of Disease codes specific for AMR infections between 1994–1995 and 1998–1999 is given in the paper by Hargreaves and Kok.

Australian laboratories are part of regional surveillance networks monitoring AMR in the Asia Pacific region and South Africa through the SENTRY antimicrobial surveillance program. The paper by Bell and Turnidge shows relatively moderate prevalence of antimicrobial resistance in Australia compared with other regional countries. The SENTRY program has published a number of significant reports over the years and this paper provides regional data of importance to the management of antibiotic resistance in Australia.

Rapid and timely data on antimicrobial resistance has been difficult to achieve in Australia. Turnidge and members of the Surveillance Network (TSN), describe a recent development in the automatic collection and analysis of data from Australian laboratories. TSN has accumulated more than 14 million results since 1996 and provides subscribers with an interactive access to a database which is growing at 300,000 records per month. Unfortunately access to these data are limited, although the collection is now undoubtedly the most comprehensive in Australia.

John Tapsall describes the role of surveillance in the management of AMR illustrating this with data on quinolone resistant gonococci and penicillin resistant meningococci in New South Wales between 1995 and 2001. Development of resistance to quinolones in the gonococci has impacted on the treatment of these infections, while penicillin remains a useful first-line treatment for meningococcal infections since resistance to this antibiotic has not developed to the same extent.

A similar picture of increasing resistance to ciprofloxacin in gonococcal isolates in Victoria since the late 1990s, with a particularly large increase in resistance in gonococcal infections acquired outside Australia, is shown in the paper by Veitch. Similarly, higher rates of resistance in *Campylobacter* infections acquired overseas were observed by Sharma *et al* in their study of isolates from residents of the Hunter region of New South Wales. This paper also provides evidence of the utility of 'resisto-typing' for describing the epidemiology of this common cause of bacterial gastroenteritis.

Surveillance of major nosocomial infections are described in a trio of papers. Cooper describes another innovative surveillance system from South Australia where state-wide monitoring of methicillin resistant *Staphylococcus aureus* has been in place since December 2000. Pearman describes an outbreak of vancomycin resistant *Enterococcus faecium* in a Western Australian hospital in 2001 and novel contact tracing and screening methods. An analysis of five years of data on quinolone resistance in *E. coli* in Australia from the TSN database is presented by Turnidge *et al*. Levels of resistance to these antibiotics in this organism remain at low levels in Australia.

Rapid methods of identifying resistant organisms are urgently needed. Jones and colleagues describe polymerase chain reaction methods that screen for antibiotic resistance genes in integrons. Polymerase chain reaction methods may allow the rapid identification of resistance and aid in timely surveillance.

Antibiotic resistance in animals

The JETACAR report confirmed that there was evidence of the spread of antibiotic resistant bacteria from animals to humans and recommended that the use of antibiotics in animals as growth promotants be limited. Further, JETACAR recommended the surveillance of antibiotic resistance bacteria in food-producing animals and veterinary areas. Four papers in this supplement address the surveillance of antibiotic resistant bacteria in animals.

Webber and Valois survey the recommendations of the JETACAR report as regards surveillance in animals, review surveillance programs in other countries and discuss strategies to implement surveillance in Australia. Jordan discusses sampling methodologies for the surveillance of antibiotic resistant *Escherichia* in food animals and describes a novel sampling method that has been successfully trialed in dairy cattle in New South Wales.

Barton and colleagues review Australian data on resistance in bacteria from food producing and veterinary animals. Although data are sparse the resistance patterns detected are similar to those overseas and reflect antibiotics used for growth promotion and treatment in animals. Veterinary data from a regional laboratory on cattle and pigs in Queensland (1999 to 2001) are presented in the paper by Stephens. This laboratory services an area that has 45 per cent of the State's cattle and more than half of Queensland's pigs. Patterns of resistance detected in this setting need, however, to be interpreted with caution because of the small and selective sample of animals tested.

Infection control

Two papers discuss methods and policies to reduce health care acquired infections. Nosocomial infections in hospitals are frequently resistant to multiple antibiotics and are increasingly untreatable with available medications. Prevention of such infections is a high priority in the management of antibiotic resistance in Australia.

Richards and colleagues describe the work of the Australian Council on Healthcare Standards (ACHS) which has been developing infection control indicators in collaboration with medical associations and the Australian Infection Control Association. These have been published in the 2002 edition of the ACHS clinical indicators users' manual. Standardised indicators aid surveillance and allow comparisons of rates of antibiotic resistance over time and between institutions.

The Australian Council for Safety and Quality in Health Care provides a summary of the outcomes from the April 2002 *National workshop to reduce health care associated infection*. Five priority areas identified by the workshop have been passed on to the Council and Australian Health Ministers to guide policy in reducing health care associated infections.

Vaccines and alternative approaches to treatment.

The supplement concludes with two papers which discuss the potential impacts of vaccines and alternative therapies on the prevalence of AMR. Dagan discusses the potential for new seven-valent conjugate pneumococcal vaccines to reduce the levels of penicillin resistant *Streptococcus pneumoniae*. As this vaccine was recently introduced into Australia in a program aimed at children with very high rates of disease and a substantial proportion of isolates from these cases are resistant to treatment with penicillin, the potential for this vaccine to control antibiotic resistance is of great interest.

Finally, Carson and Riley review non-antibiotic approaches to the treatment of infectious diseases. Probiotics, bacteriophages and phytomedicines are all approaches with potential for the control of antibiotic resistance and there will be much activity in developing these therapies in the future.

The editors thank all contributors to this supplement on antibiotic resistance in Australia. We would like to thank Alexandra Geue, Robyn Leader and Lindsay Blackburn of the Infection Management and TSE Section, Department of Health and Ageing, for initiating and coordinating the contributions for this supplement. The editors believe this collection of articles will be an important reference collection as national surveillance for antibiotic resistance commences and the management of antibiotic resistance in Australia moves forward.

Introduction: progress in the development of a national antibiotic resistance management program

Alexandra Geue, Infection Management Section, Department of Health and Ageing, Canberra, Australian Capital Territory

Since the release of *The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Group on Antibiotic Resistance* (JETACAR) in October 2000, the government has continued its work toward the development of a national antibiotic resistance management program.[113] Two committees were established to further this aim:

- The Expert Advisory Group for Antimicrobial Resistance (EAGAR), was set up in April 2001 under the auspices of the National Health and Medical Research Council, to provide continuing advice on antibiotic resistance and related matters; and
- The Commonwealth Interdepartmental JETACAR Implementation Group was established in November 2000, to oversee and coordinate the continuing government response to JETACAR, to respond to the policy advice received from EAGAR and to seek funding for implementation purposes.

During 2001, EAGAR developed and commenced the use of a protocol to assess the risk of antibiotic resistance developing in new and existing antibiotics.

Activities undertaken by the Commonwealth Interdepartmental JETACAR Implementation Group and its member agencies in 2001 include:

- an informal consultation meeting in March—The Monitoring of the Distribution of Antibiotics for Veterinary and Human Use in Australia; and
- the release in April of the draft report, *National surveillance of healthcare associated infection in Australia*, for consultation.

Other important activities included:

- the workshop on *Antibiotic Resistance Surveillance* (4 May);
- the *National Summit on Antibiotic Resistance* (30 and 31 May);
- a nationwide consultation toward *Development of a National Antibiotic Resistance Surveillance System for Antibiotic Resistance Management* (July to September); and
- the initiation of the EAGAR website—http://www.health.gov.au/pubhlth/strateg/jetacar/eagar.htm.

Progress reports on implementation of the Government Response are available on the implementing JETACAR website—http://www.health.gov.au/pubhlth/strateg/jetacar/index.htm.

Through the *National Summit on Antibiotic Resistance*, representatives from governments, health, agricultural, industry and consumer groups identified priorities for action. In particular, the need for the development of a national system of surveillance for antibiotics was recognised. This system will inform improvements in current practice and health outcomes, including:

- improved education and awareness, leading to more appropriate use of antibiotics;
- clearer research focuses, and better communication and regulation;
- more effective linkages between corporate and peak organisational bodies;
- measurable reductions in prevalence of antibiotic resistance; and
- reduced incidence of health care–associated infections in Australia.

The Commonwealth Department of Agriculture, Fisheries and Forestry—Australia and the Department of Health and Ageing undertook a collaborative consultation process to develop a national system of surveillance for antibiotic resistance.

Regulation of veterinary antibiotics in Australia

TM Dyke

Abstract

The Australian Pesticides and Veterinary Medicines Authority (APVMA)* registers veterinary antibiotic products before they can be supplied, distributed or sold in Australia. Extensive scientific assessment on all new veterinary antibiotic products is undertaken for the APVMA by experts in other government agencies including the Therapeutic Goods Administration (toxicology), the National Occupational Health and Safety Commission (occupational health and safety), Environment Australia (environmental hazards) and state departments of agriculture or primary industry (efficacy and safety) as well as APVMA assessments on food residues, trade and manufacturing. The National Health and Medical Research Council Expert Advisory Group on Antimicrobial Resistance provides advice to the APVMA on the potential transfer of antibiotic resistance from the use of antibiotics in animals to humans, and the impact transfer may have on public health. Food Standards Australia New Zealand (previously Australia New Zealand Food Authority) set maximum residue levels for human foods. The APVMA monitors registered product use through compliance activities and an adverse experience reporting program, and reviews registered products as necessary. The import, manufacture, supply and use of veterinary antibiotics are regulated by Commonwealth and State governments in Australia. *Commun Dis Intell* 2003;27 Suppl:S6–S8.

Keywords: veterinary antibiotics, Australian Pesticides and Veterinary Medicines Authority

Import

All antibiotics must be imported since no antibiotics are manufactured in Australia. Antibiotics may be imported in bulk or as a final product. Imported antibiotics, considered prohibited imports under Customs legislation, can only pass border controls if accompanied by an import permit, issued by the Therapeutic Goods Administration. Data on imports are collected.

Manufacture

The Australian Pesticides and Veterinary Medicines Authority (APVMA) licenses all manufacturers of products containing antibiotics for animal use, provided manufacturers demonstrate compliance with the Good Manufacturing Practice principles.

Registration

The APVMA registers veterinary antibiotic products before they can be supplied, distributed or sold in Australia. In basic terms the APVMA receives, evaluates and finalises applications to:

- approve active constituents;
- register products;
- approve labels; and
- vary particulars of active constituents, products or labels e.g., to allow use in another animal species.

Correspondence: Dr Timothy Dyke, Principal Scientist, Veterinary Medicines, Australian Pesticides and Veterinary Medicines Authority, PO Box E240, Kingston ACT 2604. Telephone: +61 2 6272 5870. Facsimile: +61 2 6272 5249.
Email: tdyke@apvma.gov.au.

Extensive scientific assessment is undertaken for the APVMA by experts in other government agencies including the Therapeutic Goods Administration (toxicology, scheduling, and determining an acceptable daily intake), the National Occupational Health and Safety Commission (occupational health and safety), Environment Australia (environmental hazards) and State departments of agriculture or primary industry (efficacy and safety). In addition, the APVMA assesses residues in food. Maximum residue limits are established and are nominated to the Food Standards Australia New Zealand for inclusion in the Foods Standards Code. The National Health and Medical Research Council Expert Advisory Group on Antimicrobial Resistance provides advice to the APVMA on the potential for transfer of antibiotic resistance from the use of antibiotics in animals to humans, and the impact that such transfer may have on public health. A risk assessment approach for new antibiotics and significant extensions to the use of registered antibiotics is used. The important concepts of this risk assessment approach are:

1. Hazard: Antibiotic resistant microorganisms or plasmids coding for antibiotic resistance within an animal species, arising from the use of an antibiotic in an animal species, have the potential to transfer to humans.
2. Exposure: the degree and frequency of exposure of susceptible humans to antibiotic-resistant microorganisms (or their plasmids) from animal sources;
3. Impact: the impact of infections caused by antibiotic-resistant pathogens of animal origin in susceptible humans;
4. Risk: the probability of infections caused by antibiotic-resistant pathogens of animal origin in susceptible humans AND the impact of such infections.

The focus is on commensals and enteric pathogens (and transferable genetic elements) that may be important to susceptible humans, not on target animal pathogens. Further development of this approach will occur as a result of an initiative to develop an internationally harmonised guideline for data required for such risk assessments.

In order to register a product, the APVMA must be satisfied that the product is in accordance with the recommendations for its use that the APVMA proposes to approve:

- would not be an undue hazard to the safety of people exposed to it during its handling or to people using anything containing its residues; and
- would not be likely to have an effect that is harmful to human beings; and
- would not be likely to have an unintended effect that is harmful to animals, plants, or to the environment; and
- would not unduly prejudice trade or commerce between Australia and places outside Australia;
- would be effective according to criteria determined by the APVMA for the product.

Post-registration

After product registration, the APVMA monitors product use through compliance activities and an adverse experience reporting program, and reviews registered products as necessary. In 2002, the APVMA began reviewing the registration of products containing virginiamycin, tylosin, oleandomycin and kitasamycin, as recommended by the Joint Technical Expert Technical Advisory Committee on Antibiotic Resistance report.

Most veterinary antibiotic products are prescription remedies, restricting supply by veterinarians to farmers and animal owners. While general medical practitioners must prescribe through pharmacists, veterinarians are allowed to supply antibiotics without pharmacist involvement. Selected antibiotics for certain purposes are open sellers when incorporated in stock feed e.g., ionophores for disease prevention.

Further information on APVMA activities can be found at the APVMA website from: http://www.apvma.gov.au.

Use

State and territory governments regulate the use of veterinary antibiotic products after retail sale. State and territory legislation are currently being amended with the intent that similar laws will apply across Australia.

Alternatives to antibiotics

The APVMA considers registration of all veterinary chemical products in Australia. The registration of products undergoes scientific assessment with respect to safety in humans, animals and the environment and to efficacy in target animals. Evaluation of applications for alternatives to antibiotics such as vaccines and probiotics are similar to other veterinary chemical products, and the APVMA needs to be satisfied as to such products' efficacy and safety, irrespective of their potential use as antibiotic alternatives.

Improving antibiotic use: 25 years of antibiotic guidelines and related initiatives

Ken Harvey,[1] Jonathan Dartnell,[2] Mary Hemming[3]

Abstract

In the late 1970s concern in Melbourne teaching hospitals over the increasing incidence of antibiotic-resistant microorganisms and inappropriate antibiotic prescribing, led to the establishment of a working party to produce guidelines on appropriate antimicrobial therapy. *Therapeutic Guidelines: Antibiotic* is now produced, marketed and sold by Therapeutic Guidelines Limited, an independent, not-for-profit enterprise that distils best-practice prescribing guidelines for Australian health professionals. Therapeutic Guidelines now cover all major therapeutic areas. Mere distribution of the guidelines had little impact on prescribing habits. However, targeted education campaigns have helped to improve antibiotic prescribing. The Antibiotic title remains the flagship of Therapeutic Guidelines Limited with sales, surveys and endorsements over 11 editions attesting to its wide acceptance and use. *Therapeutic Guidelines: Antibiotic* is one of many initiatives that have contributed to improving antibiotic use and it serves as a valuable foundation on which to build other strategies. There is demand for a consumer friendly version of the guidelines. In addition, the increasing use of computerised prescribing programs has highlighted the need for electronic guidelines to be closely integrated with decision support software. *Commun Dis Intell* 2003;27 Suppl:S9–S11.

Keywords: antibiotic guidelines, antibiotic resistance

History

The Therapeutic Guidelines story started in Australia in the late 1970s. There was concern in Melbourne teaching hospitals that an increasing incidence of antibiotic-resistant microorganisms reflected inappropriate antibiotic prescribing.[1] A working party was set up to produce concise guidelines on appropriate antimicrobial therapy. The aim was to improve patient outcomes by distilling the world literature on best-practice management of common clinical conditions, tempered by the experience and wisdom of Australian experts.

The first edition of *Antibiotic Guidelines* was a slim booklet of 30 pages designed to fit into a hospital doctor's white coat pocket. A modest grant from the Hospitals and Charities Commission made the publication available free of charge to Victorian resident medical officers. Twenty-five years later, the 11th edition of *Therapeutic Guidelines: Antibiotic* has grown to 330 pages; addresses clinical problems in both hospital and general practice; and has national authorship together with the approval of many professional organisations.

Therapeutic Guidelines: Antibiotic is now produced, marketed and sold by Therapeutic Guidelines Limited, a self-sufficient, independent, not-for-profit enterprise that distils best-practice prescribing guidelines for Australian health professionals. Therapeutic Guidelines now covers all major therapeutic areas.[2] While print versions are still produced, there are now electronic versions for installation on personal computers, for use on health department Intranets, and for integrating with prescribing software. Preliminary versions have also been developed for use on hand-held computers (e.g., Palm Pilots and Pocket PCs).

1. Board Member, Therapeutic Guidelines Limited and Senior Lecturer, School of Public Health, La Trobe University, Bundoora, Victoria
2. Production Manager, Therapeutic Guidelines Limited, North Melbourne, Victoria
3. Chief Executive Officer, Therapeutic Guidelines Limited, North Melbourne, Victoria

Corresponding author: Dr Ken Harvey, Senior Lecturer, School of Public Health, La Trobe University, Bundoora Vic 3086. Telephone: +61 3 9479 1750. Facsimile: +61 3 9479 1783. Mobile: 0419 181 910. Email: k.harvey@latrobe.edu.au

As many studies have noted, initial audits of antibiotic prescribing showed that the mere distribution of Therapeutic Guidelines had little impact on prescribing habits.[3] However, when specific education campaigns targeted the discrepancy between what was practised and what the guidelines recommended, antibiotic prescribing improved.[4,5,6] These concepts were ultimately incorporated into the Quality Use of Medicines pillar of Australian Medicines Policy and put into operation by the Pharmaceutical Health and Rational Use of Medicines committee and later the National Prescribing Service.[7] National indicators show that antibiotic use in Australia is now slowly improving.[8] *Therapeutic Guidelines: Antibiotic* though only one of many initiatives that has contributed to this result, is a foundation upon which other strategies have built.

While the Antibiotic title remains the flagship of Therapeutic Guidelines Limited the sales of other titles are now approaching that of *Therapeutic Guidelines: Antibiotic*. Clinicians, endorsements, and sales attest to the wide acceptance, use and perceived value of Therapeutic Guidelines.[9] This has been recognised by groups in Japan, China, Spain and Russia who have adapted the Australian Therapeutic Guidelines content in order to improve prescribing in their countries.

The business model for this international exchange is as follows. While the distillation of best-practice therapeutic guidelines has international applicability, disease patterns vary in different countries, as do the drugs available, their prices and local prescribing habits. In addition, if Therapeutic Guidelines is to have an impact, there is a need for local endorsement and ownership by respected opinion leaders. Furthermore, Therapeutic Guidelines need to be incorporated into broader programs including drug utilisation studies and targeted educational campaigns. Thus, there is a need for local groups to adapt overseas guidelines to their local situation. To assist this process, Therapeutic Guidelines Limited makes available Australian guideline content in electronic format for modification by organisations having similar aims in other countries. A modest licence fee is charged depending on the country's circumstances. This process avoids duplication of effort while maintaining local autonomy.

Current challenges

Integration of Therapeutic Guidelines with computerised prescribing programs

The increasing use of computerised prescribing programs in Australia has highlighted the need for electronic Therapeutic Guidelines (and other resources) to be closely integrated with decision support software and ultimately with the emerging electronic record.[10] The long-term goal is to provide succinct advice, tailored to a particular patient at the time of prescribing, together with automated monitoring of prescribing habits for self-audit and education. The literature shows that such systems can substantially improve patient safety, assist best-practice prescribing and be cost-effective. Despite these benefits, Australian hospitals have been slow to implement such systems and the software currently available in general practice lacks many desirable features.[11]

Therapeutic Guidelines Limited has won competitive research grants to pursue the integration of its electronic products into computerised prescribing and decision support systems. The Antibiotic title is currently partially integrated into Medical Director (HCN) prescribing software and it has previously been integrated with MIMS Script.

Some software groups have indicated a desire to integrate the complete electronic therapeutic guidelines suite into their products. However, a number of barriers exist including uncertainty over whether an integrated product will generate additional revenue and questions about who will pay for the development work required. Another problem is the different business models used. Some prescribing software vendors generate revenue by displaying advertisements for the drugs but this is a practice not undertaken by Therapeutic Guidelines Limited. Other barriers to integration include the lack of agreed coding systems (for clinical problems and drugs) and common decision support and data interchange standards.

Improving versatility

Our initial title, *Antibiotic Guidelines*, was designed to fit into a doctor's white coat pocket thus information access by mobile clinicians was relatively assured. Today, most Australian doctors do not wear white coats, the Therapeutic Guidelines series (and other evidence-based information) have proliferated, and the numerous resources necessary for good clinical practice no longer fit into pockets. Therapeutic Guidelines is now available on state health department intranets such as the New South Wales Clinical Information Access Program and the Victorian Clinician's Health Channel, but access to these services is still not available in many busy clinical settings.

One modern equivalent of the health workers white coat pocket is the handheld computer Personal Digital Assistant.[12] These devices are getting cheaper, they still fit into pockets, they have substantial memory and computing power, they can be radio-linked to hospital networks and the Internet, and future versions are likely to become the computing platform of choice for mobile health care workers. Consequently, we have already converted several Guideline titles to Personal Digital Assistant format (for both Palm and MS Pocket PC operating systems).

There is also demand for a consumer friendly version of the guidelines to perhaps be made available over the Commonwealth Web Portal. These initiatives await further development.

Conclusion

Therapeutic Guidelines Limited has a long track record of producing best-practice evidence-based therapeutic guidelines for both general and hospital practices. The organisation has also been proactive in developing a variety of electronic formats of the guidelines with the aim of integrating these into computerised prescribing and decision support programs. Currently, a number of barriers are impeding these developments. These could be overcome by cooperation and collaboration between the government and relevant organisations. There has been agreement for at least the last 10 years as to what constitutes a core set of knowledge resources for the therapeutic domain. It only remains to integrate this knowledge into the clinician's electronic desktop; such an investment would improve patient safety and facilitate best-practice drug therapy.

Acknowledgments

We thank our colleagues: microbiologists, clinical pharmacologists, physicians, surgeons, paediatricians, general practitioners, dental surgeons, pharmacists, administrators and computer scientists, who have shared the vision and helped Therapeutic Guidelines Limited become a self-sustaining reality.

References

1. Pavillard R, Harvey K, Douglas D, Hewstone A, Andrew J, Collopy B, *et al*. Epidemic of hospital-acquired infection due to methicillin-resistant *Staphylococcus aureus* in major Victorian hospitals. *Med J Aust* 1982;1:451–454.
2. Therapeutic Guidelines Limited. http://www.tg.com.au/home/index.html.
3. Harvey K, Stewart R, Hemming M, Moulds R. Use of antibiotic agents in a large teaching hospital. The impact of Antibiotic Guidelines. *Med J Aust* 1983;2:217–222.
4. Harvey KJ, Stewart R, Hemming M, Naismith N, Moulds RF. Educational antibiotic advertising. *Med J Aust* 1986;1:28–32.
5. Landgren FT, Harvey KJ, Mashford ML, Moulds RF, Guthrie B, Hemming M. Changing antibiotic prescribing by educational marketing. *Med J Aust* 1988;149:595–599.
6. De Santis G, Harvey KJ, Howard D, Mashford ML, Moulds RF. Improving the quality of antibiotic prescriptions in general practice. The role of educational intervention. *Med J Aust* 1994;1:502–505.

7. Harvey K, Murray M. Medicinal drug policy. In: Gardner H, ed. *The Politics of Health*, 2nd edition. Churchill Livingstone, Melbourne, 1995;238–283.

8. Roughead EE, Gilbert AL, Primrose JG, Harvey KJ, Sansom LN. Report of the national indicators: Evaluating the quality use of medicines component of Australia's National Medicines Policy. Publications Production Unit, Commonwealth Department of Health and Aged Care, Canberra, 1999.

9. Hemming M. Therapeutic Guidelines: an Australian experience. *International Journal of Pharmaceutical Medicine*. 2000;14:259–264.

10. Nolan AM, Norquay CA, Dartnell JGA, Harvey KJ. Electronic prescribing and computer-assisted decision support systems. *MJA* 1999;171:541–543.

11. Harvey K. Medication management 2000: e-Scripts, e-Promotion. e-Health? *Health Issues* 2000;63:10–14.

12. Wilcox RA, La Tella RR. The personal digital assistant: a new medical instrument for the exchange of clinical information at the point of care. *Med J Aus*t 2001;175:659–662.

Active promotion of antibiotic guidelines: an intensive program

Susan M Tiley,[1] Jennifer J MacDonald,[2] Paula L Doherty,[2] John K Ferguson,[1,3] John E Fergusson[2]

Abstract

John Hunter Hospital, a 600 bed tertiary referral centre, has an antimicrobial working party comprising representatives from pharmacy, microbiology and infectious diseases areas, which is responsible for the development, implementation and evaluation of guidelines for the appropriate use of antimicrobials. Activities include the development and promotion of a restricted antimicrobial policy, and specific guidelines for the management of pneumonia, and surgical prophylaxis and wound infection. These guidelines are available on the hospital intranet, in hard copies in all wards, and on laminated cards (10 x 6.5 cm) attached to the hospital identification tag. Active promotion of the guidelines is undertaken at orientation and via a 2 week intensive period four times per year (corresponding with the registrar rotation), weekly meetings and follow up of non-compliance courses directly with the attending medical officer. Education and feedback to specific groups is provided as required. Other projects include a campaign to encourage oral antibiotics where indicated. Regular drug utilisation evaluations are undertaken to measure outcomes, along with other indicators of antibiotic use such as the prevalence of antimicrobial resistance. Appropriate prescribing of third generation cephalosporins has increased from 21 per cent to 52 per cent (p = 0.008) of courses between December 1999 and June 2001. *Commun Dis Intell* 2003;27 Suppl S13–S18.

Keywords: antibiotic guidelines, antibiotic resistance

Introduction

The John Hunter Hospital, which is a 600 bed tertiary referral centre, has an antimicrobial working party (AWP) comprising representatives from pharmacy, microbiology and infectious diseases fields of knowledge. This group, which reports to the Hunter Area Health Service Quality Use of Medicines Committee, is responsible for the monitoring of antibiotic usage and the development, implementation and evaluation of guidelines for the appropriate use of antimicrobials. Activities include the development and promotion of a restricted antimicrobial policy including specific guidelines for the management of pneumonia, surgical prophylaxis and wound infection and approved indications for antibiotics identified as requiring restrictions. The Hunter Area Health Service adopted this restricted anti-infective policy in 2001. Support for the implementation of this policy at smaller hospitals within the area is provided by members of the AWP.

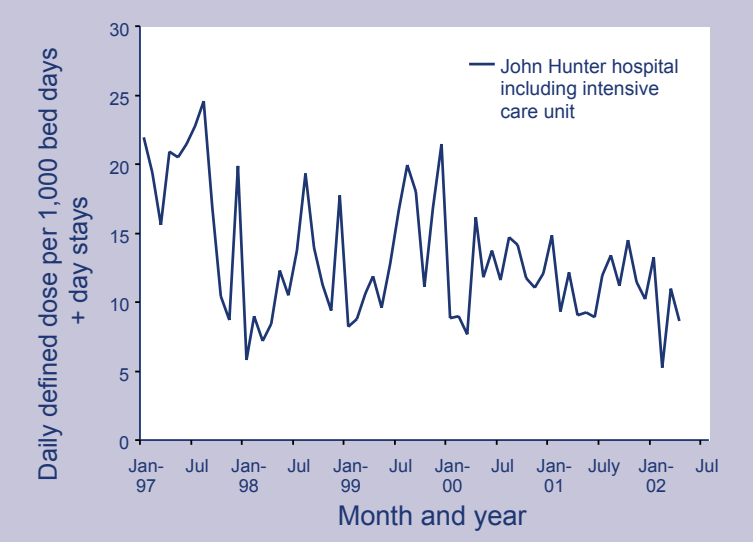
Monitoring

Antibiotic utilisation is monitored using World Health Organization Defined Daily Dose measures per 1,000 bed days and trends are evaluated at the end of each month. Increases in usage are investigated and interventions developed as necessary. A template of the spreadsheet is available on request by sending an email to jmacdonald@hunter.health.nsw.gov.au. Data can be entered into the spreadsheet to produce graphs such as the example shown (Figure).

1. Department of Microbiology, Hunter Area Pathology Service, John Hunter Hospital, New Lambton, New South Wales
2. Department of Pharmacy, John Hunter Hospital, New Lambton, New South Wales
3. Department of Infectious Disease and Immunology, John Hunter Hospital, New Lambton, New South Wales

Corresponding author: Dr Susan Tiley, Department of Microbiology, Hunter Area Pathology Service, John Hunter Hospital, Lookout Road, New Lambton NSW 2135. Telephone: +61 2 4921 4423. Facsimile: +61 2 4921 4440. Email: stiley@hunter.health.nsw.gov.au

Figure. Third generation cephalosporin usage at John Hunter Hospital, January 1997 to April 2002, example of graphs which can be produced by the John Hunter Hospital spreadsheet



Drug Utilisation Evaluation (DUE) is a structured ongoing system for monitoring drug use through comparisons with existing standards and guidelines. DUE is a cycle of audit, educational intervention and review, which aims to measure prescribing of target drugs and provide feedback to prescribers. The Greater Newcastle Sector has a dedicated team who conducts DUE projects throughout the region.

Promotion of guidelines

Restricted antibiotic guidelines

Hospital specific guidelines have been developed, in line with the *Therapeutic Guidelines: Antibiotic*,[1] taking into consideration input from relevant clinical units, published evidence (where available) and local resistance data. The main aims of the guidelines are to promote appropriate use of broad-spectrum antimicrobials in order to limit the development and spread of antimicrobial resistance, and to ensure appropriate use of specific agents. These guidelines are available on the hospital intranet, the VAX network system and in hard copy on all wards. The guidelines are reviewed regularly according to clinical needs and formulary changes. Active promotion of the guidelines is undertaken at medical staff orientation and during a 2 week intensive audit and intervention period four times per year, corresponding with the registrar rotation. Education and feedback to specific groups is undertaken as required. Clinical pharmacists consult with prescribing doctors regarding their choice of antibiotic and the Infectious Diseases (ID) service is available around the clock to review requests outside of the guidelines.

Table 1. Use of restricted antibiotics, 2 January to 15 February 2001

Division	Courses of restricted antibiotics	Approved (% for Division)	Not approved (% for Division)	Approved but used outside guidelines
Medicine	51 (39.5%)	42 (82.3%)	9 (17.7%)	13 (25.5%)
Obstetrics and Gynaecology	1 (0.7%)	0	1	0
Paediatrics	24 (18.6%)	21 (87.5%)	3 (12.5%)	6 (25.0%)
Surgery	53 (41.1%)	41 (77.4%)	9 (17.0%)	11 (20.8%)

Adherence to the guidelines for prescribing of restricted antimicrobials is monitored rather than policed, and feedback is intended to be educational. Clinical pharmacists review all restricted antimicrobials dispensed (capturing about 85% of all courses) daily, and note non-compliance with the guidelines. If the clinical pharmacist considers it necessary, the prescribing team is contacted and the issue is discussed. Reference is made to the hospital guidelines and the *Therapeutic Guidelines: Antibiotic*. If, however, the clinical team is reluctant to change their anti-infective choice then a consultation with the ID service can occur. Clinical pharmacists undertake this level of intervention as part of their ward-based service. Having the support of the ID team allows the pharmacists to avoid a proscriptive approach. Members of the AWP meet weekly and review the use of restricted antimicrobials outside the guidelines, and feedback to individual medical officers is undertaken where necessary. Specific education and feedback to a particular clinical unit or group of prescribers has also occurred as required. Over time, this united, educative approach has reinforced the importance of appropriate anti-infective prescribing and improved discussion surrounding prescribing choices.

During the quarterly audit and intervention period, all courses of restricted antimicrobials are reviewed, including those non-dispensed, i.e., from imprest stocks. Non-adherence to the guidelines is addressed by members of the AWP within 24 hours. The ID consultant, after reviewing the indication for antibiotic therapy, contacts the prescribing team, suggests alternative therapy if indicated and explains the guidelines. The emphasis is on education. Data collected on the use of restricted antibiotics between 2 and 15 February 2001 is presented in the Table. Of the 22 courses of antibiotics not approved, 7 (32%) were for (suspected or proven) intra-abdominal sepsis, 6 (27%) for respiratory tract infection, 3 (14%) for urinary tract infection, and 6 (27%) for other reasons (including surgical prophylaxis, cellulitis, surgical wound infection). The main reasons for non-concordance with the hospital guidelines were either the availability of less broad-spectrum antimicrobials that would provide adequate cover for the condition or organism concerned, or that antibiotic therapy was not considered necessary by the ID team.

Pneumonia guidelines

The *Pneumonia Guidelines* were developed by the AWP in September 1998 in conjunction with the evidence-based review of pneumonia management that took place for the *Therapeutic Guidelines: Antibiotic*, edition 10.[2] Consultation was undertaken with the Respiratory Medicine, Accident and Emergency and Intensive Care units at John Hunter Hospital, and the guidelines were updated and ratified in May 2001. The pneumonia card (Box), was developed as a tool for ready reference by clinical staff. This card is small enough to attach to the hospital identification tag and has been distributed widely amongst medical officers. Every junior medical officer is given a card with education at orientation. Active promotion of the card is undertaken, including intensive promotion each year leading into the winter months. Anecdotal feedback and requests for cards from clinicians indicate that this is a worthwhile method of information dissemination.

At the John Hunter Hospital DUE projects have been conducted twice yearly (in June and December) since 1998, to assess utilisation of third generation cephalosporins and the appropriateness of prescribing. Inappropriate prescribing is defined as that which is outside the hospital anti-infective guidelines and where the infectious diseases physician considers that an alternative anti-infective should have been used. Appropriate prescribing of third generation cephalosporins has increased from 21 per cent to 52 per cent (p=0.008) of courses between December 1999 and June 2001. Whilst this may seem a modest improvement it is in line with the compliance achieved by other workers.[3]

Surgical prophylaxis

Surgical prophylaxis and wound infection antibiotic guidelines were developed in 2001 after consultation between the AWP and Surgery. These guidelines detail the choice of antibiotic, timing for surgical prophylaxis and the appropriate length of treatment. A laminated card for quick reference was also developed and is promoted and distributed within Surgery. An audit of surgical prophylaxis practices was conducted by the DUE team in March 2000. As a result of this audit agreements have been developed with Gynaecology, relating to cefotetan usage, and with the Cardiac Surgery team regarding vancomycin prophylaxis.

Box. The pneumonia card, (front and back)

HOSPITAL-ACQUIRED PNEUMONIA (HAP)

EMPIRIC ANTIBIOTIC THERAPY

See JCLIN(VAX) or the HAHS intranet for dosages, advice on investigation and other alternatives for ß-lactam allergic patients

Mild/moderate

No risk factors: *penicillin G + gentamicin (IV) OR amoxycillin/clavulanate (oral)*

Witnessed aspiration: pen G + gentamicin + metronidazole

Head injury, coma, diabetes, dialysis: pen G + gentamicin + di/flucloxacillin

OR if MRSA proven: vancomycin + gentamicin

ICU cases or Severe

Onset less than 5 days post admission & no risk factors:

penicillin G + gentamicin. If severe, add erythromycin as per severe CAP

Other cases:

gentamicin + ticarcillin/clavulanate (gent + cefepime if minor ß-lactam allergy)

IMPORTANT:

1. Review empiric therapy at 48 hours: it may be possible to cease gentamicin or switch to oral therapy.
2. DO NOT USE third generation cephalosporins in HAP.

COMMUNITY-ACQUIRED PNEUMONIA (CAP)

EMPIRIC THERAPY (immunocompetent host)

See JCLIN(VAX) or the HAHS intranet for dosages, advice on investigation and other alternatives for ß-lactam allergic patients.

Mild/moderate (pneumococcal cover essential)

Oral amoxycillin or doxycycline (not in children aged <8yrs or pregnant women) or roxithromycin

Parenteral penicillin G

Severe (cover for Legionella and aerobic Gram negatives essential)

Adults, children >10yrs

penicillin G + gentamicin (once daily) + erythromycin (intravenous, central line)

Children < 10yrs

penicillin G + gentamicin (once daily) + consider flucloxacillin

IMPORTANT:

1. Review empiric therapy at 48 hours: it may be possible to cease gentamicin or switch to oral therapy.
2. A third generation cephalosporin is only indicated in severe CAP when minor ß-lactam allergy or established renal failure is present.

These consensus guidelines have been reviewed and accepted by Paediatric & Adult Respiratory Medicine, ID and Intensive Care specialists at JHH May 2000.

Switch to oral campaign

The increasing trend for antibiotic use overall, and the concern over the complications of intravenous administration, prompted a campaign to encourage the use of oral antibiotics where indicated. 'The Switch to Oral' campaign involved a DUE performed over a 3 week period in November 2001 assessing adult in-patients in non-intensive care wards. Agreed criteria for oral antibiotic use were developed and disseminated to medical staff. Promotional activities included posters and postcards distributed to individual doctors and bright orange stickers placed in the medical charts of patients on intravenous antibiotic orders.

The criteria for eligibility for a switch to oral antibiotics or ceasing of therapy included the following:

- the patient was improving clinically;
- a temperature <38˚C for 2 consecutive days;
- oral fluids and food tolerated;
- no ongoing or potential absorption problems;
- no unexplained tachycardia;
- the patient did not have a condition that required high tissue antibiotic concentrations e.g., endocarditis or meningitis; or
- a suitable oral formulation was available.

Of 55 patients fulfilling these criteria, 27 (49%) ceased antibiotics altogether and 18 (33%) switched to a suitable oral form within 3 days. The remaining 10 patients (18%) could have been switched but were not. This is an improvement on a small pilot audit conducted earlier in September 2001 where 74 per cent of 16 eligible patients were switched to an oral alternative. The promotion of the appropriate switch from parenteral to oral antibiotics is ongoing. Outcome measures such as prevalence of antimicrobial resistant organisms within the hospital, monthly antibiotic utilisation data and data relating to complications of parenteral administration (e.g., line sepsis) are being monitored to determine the long-term effects.

Nosocomial infection

The prevalence of certain organisms associated with nosocomial infection has dropped since the commencement of intervention to promote appropriate use of antimicrobials at John Hunter Hospital. Between 1997 and 2000, the nosocomial *Clostridium difficile* infection rate fell from 9.8 per 10^5 patient days to 4.0 cases per 10^5 patient days (incidence rate ratio 0.41, 95% CI 0.21–0.80).[4] Vancomycin resistant enterococci were first isolated at John Hunter Hospital in 1996. Fourteen isolates occurred in Hunter Area Health hospitals in 1997. Since then, the numbers have decreased, with one urinary vancomycin resistant enterococci isolate in May 2001, and none reported since. Although other factors may be involved, the control of broad-spectrum antibiotic use instituted at John Hunter Hospital may have limited this problem.[5]

Healthcare-associated acquisition and morbidity due to multiple antibiotic-resistant organisms is closely monitored within the hospital by the Infection Control service. By regular review of the data on antibiotic use and the prevalence of multiple antibiotic-resistant organisms, it was noted that there appeared to be a relationship between the incidence of multi-resistant *Acinetobacter baumannii* isolation (defined as resistant to gentamicin, ciprofloxacin and carbapenems) and the use of imipenem or meropenem. These antibiotics were being overused in surgery (as empiric treatment for severe pancreatitis), or for severe sepsis in intensive care units. Through an education program, the development of specific guidelines for the use of carbapenems, and strict limitations on the availability of these antibiotics, the use of these agents has decreased. The association between carbapenem (and other antibiotic) usage and multi-resistant *Acinetobacter baumannii* emergence is being examined further with a formal case-control study.

Conclusions

The John Hunter Hospital sought to develop antibiotic guidelines using a multi-disciplinary evidence based approach. With approval from the relevant clinical units, regular evaluations were carried out and individual were feedback was given. The guidelines were disseminated in multiple ways to maximise access by clinical staff. Implementation of the guidelines was via drug bulletins, clinical meetings, educational sessions, and individual contact. Regular review and update of the guidelines was undertaken to ensure relevance. Promotion of appropriate prescribing is an ongoing activity.

This report has described how active promotion of antibiotic guidelines along with educational activities leads to more appropriate prescribing.

References

1. Therapeutic Guidelines Limited. *Therapeutic Guidelines: Antibiotic*. 11th edition. North Melbourne, Australia, 2000.
2. Therapeutic Guidelines Limited. *Therapeutic Guidelines: Antibiotic*. 10th edition. North Melbourne, Australia, 1998.
3. Robertson MB, Korman TM, Dartnell JG, Ioannides-Demos LL, Kirsa SW, Lord JA, *et al*. Ceftriaxone and cefotaxime use in Victorian hospitals. *Med J Aust* 2002:176;524–529.
4. MacDonald J, Ferguson JK. How education influences prescribing at John Hunter Hospital. *Australian Prescriber* 2001;24:32.
5. Quale J, Landman D, Saurina G, Atwood E, DiTore V, Patel K. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. *Clin Infect Dis* 1996;23:1020–1025.

State-wide surveillance of in-hospital antimicrobial utilisation in South Australia

Catherine M Dollman,[1] Celia M Cooper[2]

Abstract

In late 2001, a group of South Australian metropolitan public and private hospitals commenced voluntary contribution of data on in-hospital utilisation of antimicrobials to the Communicable Disease Control Branch of the Department of Human Services. Where possible, hospitals contributed data on all antimicrobials dispensed for use within the institution each month. These data were stratified into antimicrobials issued to intensive care units and antimicrobials issued to all other areas within the hospital. In the first instance, only data relating to four antimicrobial classes have been analysed. These classes are third or fourth generation cephalosporins, carbapenems, glycopeptides and fluoroquinolones. Utilisation of these four classes was presented as a monthly utilisation rate i.e., total defined daily doses for each antimicrobial class per month per 1,000 occupied bed days. These utilisation rates were calculated for each individual hospital and for the combined group of contributing hospitals (state-wide rate). Although limited data are currently available, results to date demonstrate a much higher antimicrobial usage rate in intensive care units than other in-patient areas for the classes currently analysed. Considerable variation in the usage of various antimicrobials has been noted for individual hospitals, and analysis of trends over a longer time period, in conjunction with resistance surveillance data, will be required. *Commun Dis Intell* 2003;27 Suppl:S19–S27.

Keywords: antimicrobial utilisation, cephalosporin, carbapenem, glycopeptide, fluoroquinolone, antibiotic resistance

Introduction

Antimicrobial resistance is now regarded as a significant and growing threat to public health worldwide. The emergence and dissemination of antimicrobial resistant organisms are known to be associated with antimicrobial use, and various strategies have been developed in recent years to alter antibiotic usage patterns to assist in the containment of this problem.

Educational programs, including the development and promulgation of evidence-based clinical guidelines; continuing education sessions and media-based programs aimed at promoting more rational antibiotic use and feedback on prescribing to individual clinicians have been developed for use in both community and health-care settings, with variable success.[1,2,3,4,5,6] In some institutions, restrictive measures such as antibiotic cycling, formulary restriction of certain antibiotics and the implementation of stop-orders and 'prior approval' requirements, either involving computer-based programs or requiring specialist consultation, have also been employed in an attempt to modify prescribing patterns.[7,8,9] Dosing based on pharmacokinetic and pharmacodynamic parameters has also been proposed as a potential tool to minimise resistance to some antimicrobial classes.[10,11]

Broad-based surveillance of both antimicrobial resistance and antimicrobial consumption has now been recognised as essential for planning future strategies aimed at controlling resistance. Programs for the surveillance of antimicrobial resistance and antimicrobial usage have been recommended by the World Health Organization,[12,13] the European Union[14] and the Centers for Disease Control and

1. Project Pharmacist, Communicable Disease Control Branch, South Australian Department of Human Services, Adelaide, South Australia
2. Head of Infection Control Service, Communicable Disease Control Branch, South Australian Department of Human Services, Adelaide, South Australia

Corresponding author: Dr Celia M Cooper, Head of Infection Control Service, Communicable Disease Control Branch, South Australian Department of Human Services, 162 Grenfell Street, Adelaide SA 5000. Telephone: +61 8 226 7177. Facsimile: +61 8 226 7187. Email: cdcb@dhs.sa.gov.au

Prevention[15] in the United States of America USA). The European Surveillance of Antibiotic Consumption project has recently been set up to co-ordinate international surveillance and promote world-wide collaboration.[16] In the USA, the Centers for Disease Control and Prevention Hospital Infections Program began Project ICARE (Intensive Care Antibiotic Resistance Epidemiology) in 1994 to provide data on the prevalence of antibiotic resistance and antibiotic use in USA hospital settings.[17]

In Australia, the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR), a group of 15 experts from public health, human medicine, veterinary medicine, molecular biology and primary industries, was formed by the Commonwealth Government in December 1997. The final JETACAR report,[18] released in October 1999, concluded that the use and overuse of antibiotics in human medicine is the major factor contributing to the development of antibiotic resistance. The *Commonwealth Government Response to the Report of the JETACAR*,[19] published in August 2000, supported the surveillance of both antimicrobial-resistant organisms and antimicrobial consumption at a national level, and invited proposals for the development of such programs.

In response to recommendations resulting from the JETACAR report, surveillance systems for antimicrobial utilisation, multi-resistant organisms, and other organisms linked to antimicrobial use, were established within the Communicable Disease Control Branch of the Department of Human Services in South Australia in late 2001. These surveillance systems incorporate data from major metropolitan public and private hospitals in South Australia, and will allow antimicrobial utilisation data to be linked with the incidence of particular organisms within the same institution. Published data suggest that concomitant surveillance of both antibiotic resistance and antimicrobial use is helpful in interpreting resistance patterns within a particular unit or hospital.[20]

This paper describes the methods used and problems encountered in setting up an antimicrobial surveillance program to monitor in-patient antibiotic usage in major South Australian metropolitan hospitals. A brief summary of preliminary data obtained from contributing hospitals is provided, however, interpretation of these data is at present limited by the short time period over which data has been collected and a correlation with resistance surveillance data has not yet been examined.

Methods

The antimicrobial utilisation surveillance program in South Australia was initially modelled on Project ICARE[17] in the USA, with data submitted by contributing hospitals stratified into use by the intensive care unit (ICU) and pooled use by other in-patient areas (non-ICU). Outpatient use, and use by day-stay or home treatment units are not included. ICU data have not been stratified by ICU type, as in Project ICARE, due to the small number of ICUs involved. Stratification of non-ICU data by clinical unit is limited by the ability of pharmacy service providers to provide accurate unit specific data, and in most contributing institutions this is not possible.

All contributors supply antimicrobial usage data on a voluntary basis. Usage reports for all antimicrobials are generated each month by the pharmacy departments of public hospitals or contracted pharmacy service providers for private hospitals. Details of the in-hospital consumption of oral and parenteral antimicrobials are provided, in terms of units or packs used for each dosage form and strength.

For larger hospitals with ICUs, data are supplied separately for this area, and pooled for other in-patient areas (non-ICU). Where a small number of designated ICU beds are incorporated into the same area as high dependency or coronary care beds, specific data relating to ICU use cannot be obtained, and all usage is pooled to provide total hospital usage rates.

Data collection has been complicated by the four different computerised pharmacy dispensing systems used by contributors, with the reporting format depending on the system used by the pharmacy. Datasets are transmitted electronically to the Communicable Disease Control Branch each month and centrally loaded into a FoxPro database for calculation of usage density rates. The database has been specifically designed to accept data generated by different pharmacy systems, whether dispensing is by individual unit of use or by manufacturer's pack, as is the case where the

Pharmaceutical Benefits Scheme is involved. Usage density rates for each antimicrobial agent are calculated using the total number of grams of the antimicrobial used, the defined daily dose for that antimicrobial, and the number of occupied bed days as provided by the contributor.

The usage density rate is defined as the number of defined daily doses used per 1,000 occupied bed-days and is calculated as follows:

$$\text{Antimicrobial usage rate} = \frac{\text{total grams for the particular antimicrobial x 1,000}}{\text{defined daily dose for the particular antimicrobial x OBD}}$$

Defined daily doses assigned by the WHO[21] have been used to enable benchmarking with European centres in the future, although some values may not be consistent with common clinical practice in Australia.

Although most contributing hospitals have supplied data for a broad range of antimicrobials, usage rates are currently reported for only four antimicrobial classes: third or fourth generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime, cefepime), carbapenems (meropenem, imipenem), glycopeptides (vancomycin, teicoplanin) and fluoroquinolones (ciprofloxacin, gatifloxacin, moxifloxacin, norfloxacin). Rates are reported both for individual antimicrobial agents and pooled rates for antimicrobial classes. Reporting of additional classes will be undertaken as required by participating hospitals.

Although formal reports had not been distributed at the time of submission of this paper, discussions with interested clinicians had taken place and a format for data presentation was agreed upon. Programming to enable automated monthly reporting is now underway. Monthly reports will be forwarded to each contributor, displaying hospital and state-wide usage for total hospital, ICU and non-ICU for each of the four antimicrobial classes, and will also provide usage rates for individual agents within classes.

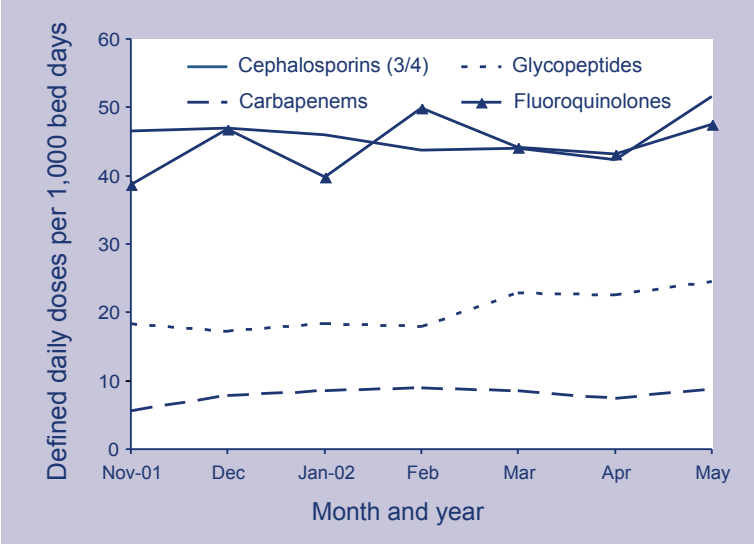
State-wide utilisation rates are calculated for the total group of contributing hospitals for the purpose of comparison. Individual contributing hospitals, however, have access only to their own rates and to the pooled state-wide rate to ensure confidentiality. Benchmarking with other Australian or overseas antimicrobial utilisation data is planned for the future.

Results

The limited results presented in this report have been calculated from antimicrobial utilisation data supplied by the eight hospitals for the period November 2001 to May 2002. Five of these hospitals had ICUs. Six public and two private hospitals are included. One paediatric hospital and two private hospitals with incomplete datasets for that time period have been excluded.

The state-wide rates for the period November 2001 to May 2002 for each of the four reported antimicrobial classes are shown in Figure 1. Monthly state-wide usage rates have not shown large variations to date.

Figure 1. State-wide usage rates for total hospital use of third or fourth generation cephalosporins, glycopeptides, carbapenems and fluoroquinolones



Comparative state-wide rates for ICU and non-ICU usage for the four classes are shown in Figures 2, 3, 4 and 5. Antimicrobial usage rates for ICUs in all contributing hospitals are markedly higher than rates for pooled usage in other hospital areas for the antibiotic classes currently reported.

Figure 2. State-wide usage rates for Intensive Care Unit and non-Intensive Care Unit use of third or fourth generation cephalosporins (includes ceftriaxone, cefotaxime, ceftazidime and cefepime)

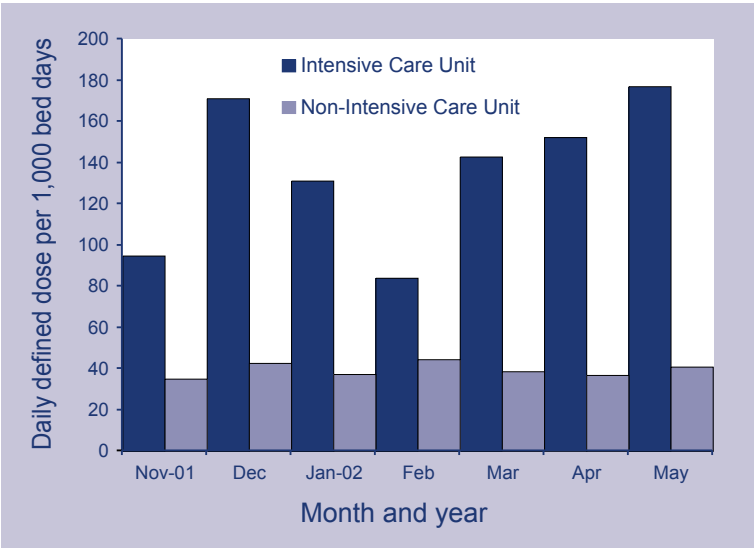


Figure 3. State-wide usage rates for Intensive Care Unit and non-Intensive Care Unit use of glycopeptides (includes vancomycin and teicoplanin)

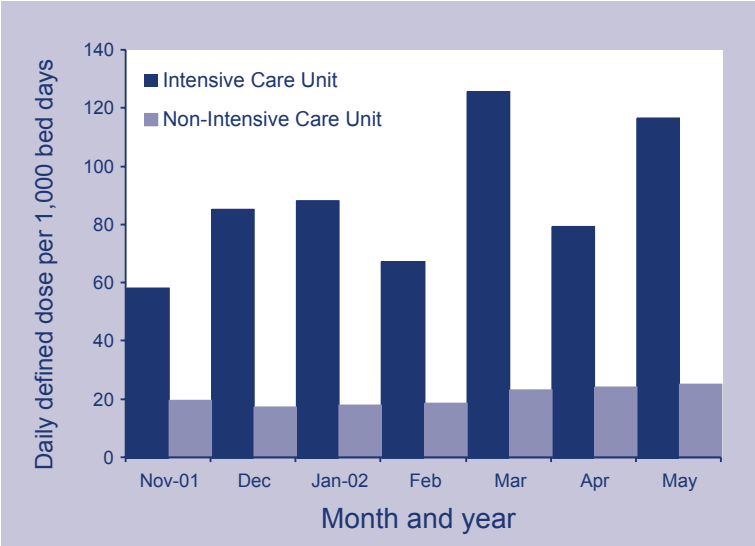


Figure 4. State-wide usage rates for Intensive Care Unit and non-Intensive Care Unit use of carbapenems (includes meropenem and imipenem-cilastatin)

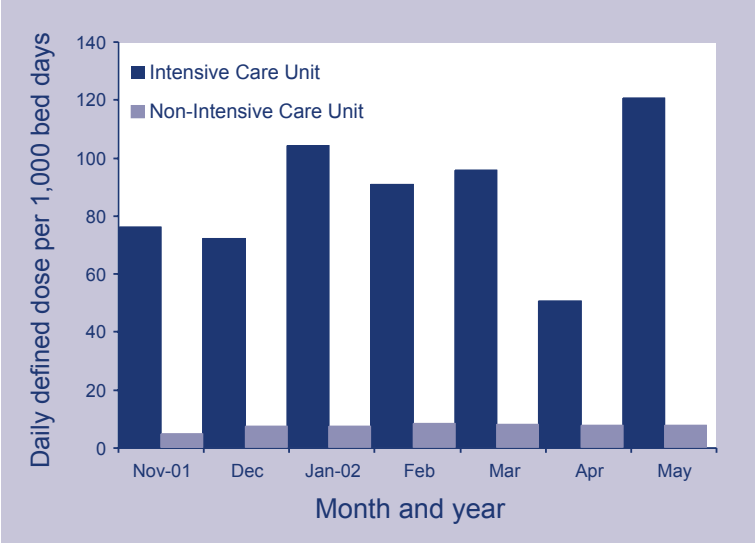
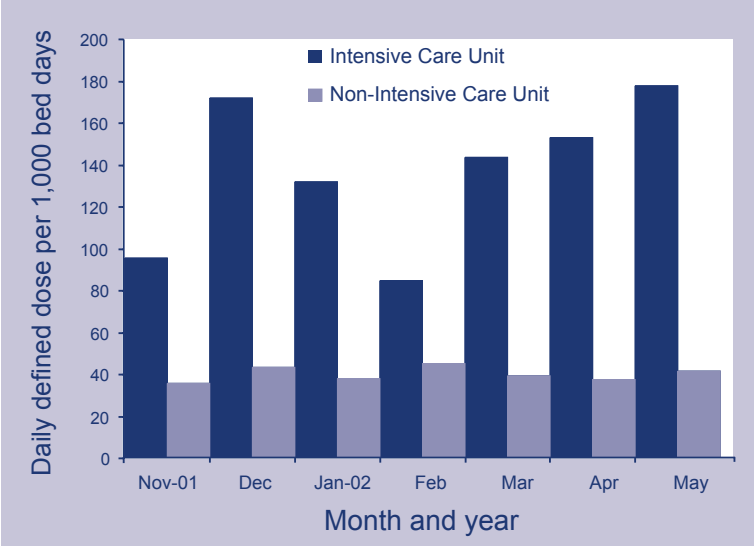


Figure 5. State-wide usage rates for Intensive Care Unit and non-Intensive Care Unit use of fluoroquinolones (includes ciprofloxacin, gatifloxacin, moxifloxacin and norfloxacin)



Figures 6 and 7 show comparative usage rates for third or fourth generation cephalosporin and fluoroquinolone classes for public and private hospitals, as well as corresponding state-wide rates, with preliminary data suggesting higher usage rates in some private hospitals in comparison with public hospitals for some antimicrobials, as shown in Figures 6 and 7. These rates have been calculated using pooled preliminary data for the six public and two private hospitals included in this report.

Figure 6. Usage rates for individual third and fourth generation cephalosporins in a public hospital Intensive Care Unit

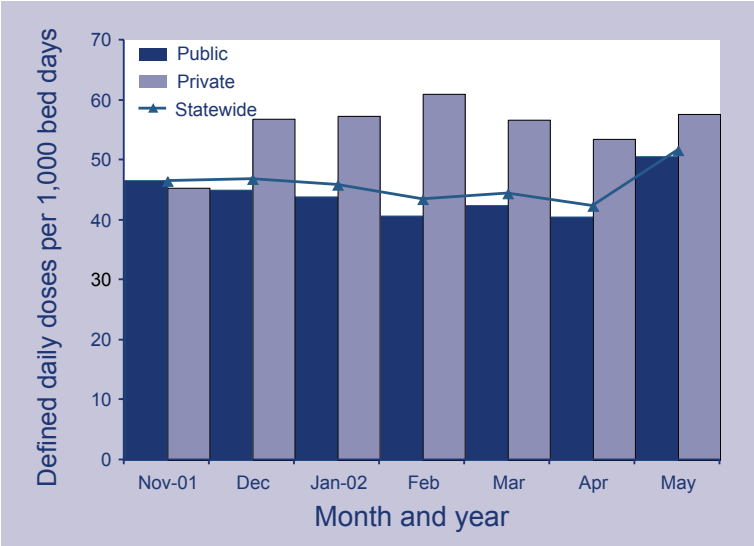
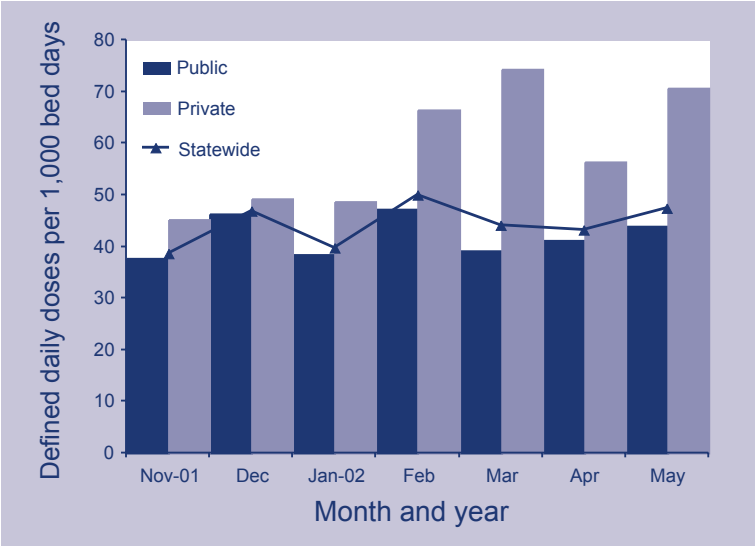


Figure 7. Usage rates for individual third and fourth generation cephalosporins in a private hospital Intensive Care Unit



Discussion

It is anticipated that complete data will be available for 13 hospitals in the near future. Although paediatric usage data has been submitted by one specialist paediatric hospital, analysis of such data is difficult due to the lack of standard defined daily doses applicable to the paediatric population. Usage is therefore reported as total grams used per month for particular antimicrobials. While utilisation rates are currently presented in the form of simple charts showing both hospital and statewide usage rates over time, it is anticipated that more sophisticated models may be used when a larger pool of data is available for analysis. Use of these models may enable linking of both antimicrobial usage and resistance surveillance data.[22,23] Comparison of South Australian usage with European and possibly other Australian centres is planned, however, differences in antimicrobial groupings analysed and defined daily doses used in other centres have made this impractical at present.

As limited data are available for analysis at this stage and no specific recommendations for intervention programs have as yet been made, some areas for future consideration have been identified. The high usage rates for third generation cephalosporins, particularly ceftriaxone and cefotaxime, by most contributors, may require the introduction of intervention programs on a statewide basis.

Further comparisons between prescribing patterns in the private and public sectors are also planned for the future. It should be noted, however, that complete data for only two private hospitals were available for analysis at the time of preparation of this paper. While mechanisms such as restricted formularies and prior approval requirements may be implemented in public hospitals to influence prescribing, in the private sector the Pharmaceutical Benefits Scheme restrictions are currently the only regulatory mechanism in place. Interventions to modify prescribing practices in the private sector are therefore limited to education. A regulatory mechanism at state level may be necessary in the future if antimicrobial use is to be successfully controlled in both the public and private settings.

Reporting of antimicrobial usage rates for specific hospital areas or units would enable greater comparison between similar hospitals, or particular units within hospitals. The identification of specific wards or units such as haematology or specialised transplant units, where there is high usage of antimicrobials, may be a future focus for collection and analysis of unit-specific data where this can be accurately provided. For general surgical or medical wards, accurate data are difficult to obtain due to the complex or diverse patient mix within these areas. At present in South Australia, no hospital is able to provide complete, accurate data for antimicrobial consumption at the individual patient level.

The expansion of resistance and antimicrobial utilisation surveillance programs to include data from regional centres may reveal differences in the prevalence of resistance and antimicrobial usage patterns compared with metropolitan hospitals.

The initial phase of the program has highlighted many problems relating to the availability of the required data. The use of the Pharmaceutical Benefits Scheme by private hospitals, the diversity of computer systems and methods of cataloguing drugs within the participating group of hospitals, have necessitated the design of a central program to accept and analyse data presented in a number of different formats. If larger programs involving both hospital and community use are to be instituted in the future it will be necessary to ensure that data can be collected in a standardised format. Future introduction of new pharmacy computer systems in the public or private sectors may represent an opportunity to institute standardisation of drug cataloguing, perhaps using the World Health Organization Anatomical Therapeutic Chemical code.[21] Incorporation of a standard reporting function into such systems would facilitate regular reporting of usage data for antimicrobials and other drug groups.

Hospitals are encouraged to use caution when comparing their own usage rates with those for the pooled state-wide data, as significant differences exist in casemix complexity and in the burden of multi-resistant organisms between hospitals contributing data to this program.

It is hoped that this program will assist participating hospitals identify areas where quality improvements in antimicrobial use can be made, and encourage restraint in the use of certain antimicrobial classes, particularly within the ICU setting. Analysis of antimicrobial usage data in conjunction with resistance surveillance data may enable planning of more effective strategies to combat antimicrobial resistance.

Acknowledgments

Mr Chris Horwood for developing and managing the database and assisting with other aspects of the project.

References

1. Centers for Disease Control and Prevention campaign to prevent antimicrobial resistance in health-care settings. *MMWR Morb Mortal Wkly Rep* 2002;51:343.
2. Emmer CL, Besser RE. Combating antimicrobial resistance: intervention programs to promote appropriate antibiotic use. *Infect Med* 2002;19:160–173.
3. Sbarbaro JA. Can we influence prescribing patterns? *Clin Infect Dis* 2001;33 Suppl 3:S240–S244.
4. Watson DA. Antibiotic guidelines: improved implementation is the challenge. *Med J Aust* 2002;176:513–514.
5. Bell DM. Promoting appropriate antimicrobial drug use: perspective from the Centers for Disease Control and Prevention. *Clin Infect Dis* 2001;33;Suppl 3:S245–S250.
6. Wilton P, Smith R, Coast J, Millar M. Strategies to contain the emergence of antimicrobial resistance: a systematic review of effectiveness and cost-effectiveness. *J Health Serv Res Policy* 2002;7:111–117.
7. Empey KM, Rapp RP, Evans ME. The effect of an antimicrobial formulary change on hospital resistance patterns. *Pharmacotherapy* 2002;22;81–87.
8. Lawton RM, Fridkin SK, Gaynes RP, McGowan JE Jr. Practices to improve antimicrobial use at 47 US hospitals: the status of the 1997 SHEA/IDSA position paper recommendations. Society for Healthcare Epidemiology of America/Infectious Diseases Society of America. *Infect Control Hosp Epidemiol* 2000;21:256–259.
9. Landman D, Chockalingam M, Quale JM. Reduction in the incidence of methicillin-resistant S*taphylococcus aureus* and ceftazidime-resistant *Klebsiella pneumoniae* following changes in a hospital antibiotic formulary. *Clin Infect Dis* 1999;28:1062–1066
10. MacGowan AP. Role of pharmacokinetics and pharmacodynamics: Does the dose matter? *Clin Infect Dis* 2001;33 Suppl 3:S238–S239.
11. Craig WA. Does the dose Matter? *Clin Infect Dis* 2001;33 Suppl 3:S233–S237.

12. World Health Organization consultation on global principles for the containment of antimicrobial resistance due to antimicrobial use in livestock. Geneva, June 2000. Available from: http://www.who.int./emc/diseases/zoo/drafting.html

13. World Health Organization global strategy for containment of antimicrobial resistance. Geneva, June 2001. Available from: http://www.who.int/emc/amrpdfs/WHO_Global_Strategy_English.pdf

14. The Copenhagen Recommendations: Report from the Invitational European Union Conference on The Microbial Threat. Copenhagen: Ministry of Food, Agriculture and Fisheries. September 1998:1-52. Available from: http://www.tour.info.fr/tours/pap/articles/copen2.htm

15. Centers for Disease Control and Prevention. A public health action plan to combat antibiotic resistance. June 2000. Available from: http://www.cdc.gov/drugresistance/actionplan/html/index.htm

16. European Surveillance of Antimicrobial Consumption. ESAC project description. Laboratory of Microbiology, University of Antwerp. Available from: http://www.uia.ac.be/esac/ESAC_project.htm. Accessed: 2002.

17. Fridkin SK, Steward CD, Edwards JR, Pryor ER, McGowan JE Jr, Archibald Lk, et al. Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: project ICARE phase 2. Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) hospitals. *Clin Infect Dis* 1999;29:245–252.

18. Commonwealth Department of Health and Aged Care. *The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans*. Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia. October 1999.

19. Commonwealth Department of Health and Aged Care. Commonwealth Government response to the report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR). Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Canberra, August 2000.

20. Monnet DL, Archibald LK, Phillips L, Tenovar FC, McGowan JE Jr, Gaynes RP. Antimicrobial use and resistance in eight US hospitals: complexities of analysis and modelling. Intensive Care Antimicrobial Resistance. Epidemiology Project and National Nosocomial Infections Surveillance System Hospitals. *Infect Control Hosp Epidemiol* 1998;19:388–394.

21. World Health Organization Collaborative Centre for Drug Statistics Methodology. Available from: http://www.whocc.no/atcddd. Accessed: 2002.

22. Monnet DL, Lopez-Lozano JM, Campillos P, Burgos A, Gonzalo N. Making sense of antimicrobial use and resistance surveillance data: application of ARIMA and transfer function models. *Clin Microbiol Infect* 2001;7 Suppl 5: S29–S36

23. Lopez-Lozano JM, Monnet DL, Yague A, Burgos A, Gonzalo N, Campillos P, *et al*. Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. *Int J Antimicrob Agents* 2000;14:21–31.

Restriction of third generation cephalosporin use reduces the incidence of *Clostridium difficile*–associated diarrhoea in hospitalised patients

Claudia Thomas,[1,2] Thomas V Riley[1,3]

Abstract

Third generation cephalosporin antibiotics (3GC) have become the antibiotics of choice in many hospitals in recent years for the treatment of infections such as community-acquired pneumonia. However, increased use of 3GCs has also been associated with a rise in the occurrence of antibiotic-associated diarrhoea due to *Clostridium difficile*, as well as an increase in the prevalence of antibiotic resistant organisms such as methicillin resistant *Staphylococcus aureus*, vancomycin resistant entrococci, and extended-spectrum beta-lactamase–producing gram negative bacilli. In Western Australia, greater use of 3GCs was shown to correlate with more *Clostridium difficile*–associated diarrhoea (CDAD) in a large acute care teaching hospital during the 1980s. During the 1990s, the use of 3GCs in this hospital remained high and, at the end of 1998, a policy was introduced to prevent the use of ceftriaxone (the only 3GC in use) without prior approval. This resulted in a decline in 3GC use and a 50 per cent reduction in the incidence of CDAD during 1999 and 2000. To strengthen these observations, the impact of the 3GC policy on the occurrence of CDAD was analysed using time-series intervention analysis that showed a statistically significant decrease in the occurrence of CDAD during the post-intervention period after controlling for exogenous factors. Thus, changes in antibiotic prescribing practices can influence the incidence of CDAD and, potentially, antibiotic resistant pathogens. *Commun Dis Intell* 2003;27 Suppl:S28–S31.

Keywords: Clostridium difficile, Staphylococcus aureus, *antibiotic resistance*

Introduction

Clostridium difficile is an anaerobic toxin–producing bacterium, with an ability to form spores that allow it to survive in the environment for extended periods of time. Exposure to *C. difficile* can result in asymptomatic carriage or produce clinically apparent disease ranging from mild to acute diarrhoea, or the more severe pseudomembranous colitis. Mortality associated with CDAD is usually low, due to clinicians' widespread knowledge of the illness, resulting in prompt diagnosis and treatment. Information regarding the pathogenesis and clinical manifestation of CDAD is available from several reviews.[1,2,3]

The main risk factor for *C. difficile* colonisation and disease is prior exposure to antibiotics, particularly clindamycin and broad-spectrum antibiotics such as the cephalosporins.[4] Biological evidence indicates that antibiotics disrupt the normal gut flora allowing subsequent colonisation and/or infection with *C. difficile*.[3] However, not all hospitalised patients exposed to *C. difficile* become ill, or even colonised. These differences have still not been clearly explained.[5] There are different levels of risk associated with different antibiotic classes, the number of antibiotics used and the duration of antibiotic exposure, however, a paucity of good quality studies prevents firm conclusions from being drawn.[4] Increased age, patient length of hospital stay and underlying co-morbidities are important confounders

1. Department of Microbiology, The University of Western Australia, Queen Elizabeth II Medical Centre, Perth, Western Australia
2. Department of Public Health, The University of Western Australia, Perth, Western Australia
3. Division of Microbiology, The Western Australian Centre for Pathology and Medical Research, Perth, Western Australia

Corresponding author: Professor Thomas V Riley, Department of Microbiology, Queen Elizabeth II Medical Centre, Nedlands, Perth WA 6009. Telephone: +618 9346 3690. Facsimile: +618 9382 8046. Email: triley@cyllene.uwa.edu.au

to be considered for all hospital-acquired infections,[6] and these risk factors, in addition to the virulence of specific *C. difficile* strains,[7] may determine whether a patient develops clinical disease. The ecology and epidemiology of *C. difficile* diarrhoea are similar to that of antibiotic resistant bacteria and the incidence of CDAD may be a good surrogate measure for the impact of interventions aimed at reducing antibiotic resistance through restricting antibiotic use.

Methods and results

The Sir Charles Gairdner Hospital (SCGH) in Perth, Western Australia, is a 560-bed teaching hospital with specialist services that include neurosurgery and liver transplantation. The epidemiology of CDAD has been studied at SCGH since the early 1980s when it became apparent that this was an important hospital pathogen with the potential to cause considerable morbidity.[8] Early work showed that CDAD increased substantially during the 1980s, from 23 cases per 100,000 patient days in 1983 to 50 cases per 100,000 patient days in 1992, equating to approximately 100 cases per year.[9] At the same time third generation cephalosporin (3GC) use rose and there appeared to be a relationship between the increase in 3GC use and the incidence of CDAD.[9,10] During most of the 1990s, the incidence of CDAD remained at approximately 50 cases per 100,000 patient days annually, but unexpectedly fell to 20 cases per 100,000 patient days in 1999 and fell further still in 2000.[11] This suggested that a significant event(s) with a lasting effect took place at the end of 1998 which dramatically reduced the incidence of CDAD. No changes were made to infection control procedures at this time. While some investigators have reported significant reductions in the incidence of CDAD following changes in infection control practices,[12,13] others have found infection control strategies are relatively ineffective in reducing endemic *C. difficile* transmission.[14]

Given the previously demonstrated relationship between 3GC use and CDAD at SCGH, this relationship was re-examined. Some important changes had occurred during the period of time under investigation. A hospital-wide restriction policy on the prescription of 3GC antibiotics was introduced by the hospital Drug and Therapeutics Committee in October 1998. This involved getting approval from a clinical microbiologist or infectious diseases physician before prescribing 3GCs. Prior to this change, from 1997, ceftriaxone was the only 3GC in use at the hospital. Despite the removal of other 3GCs and the introduction of a 72-hour stop order policy at the end of 1996, the overall gram amounts of 3GCs fell no more rapidly than the decreasing trend seen since 1993. After the introduction of the restriction policy in 1998, ceftriaxone use fell from 8,000 g in 1998 to 1,400 g in 1999 and 1,200 g in 2000.[11] Although the use of 3GCs had been falling gradually during the 1990s, the introduction of the restriction policy resulted in an immediate fall to almost negligible levels. It was only when 3GC use had reached such low levels that the incidence of CDAD also fell.[11]

Time series analysis

Time series analysis is a method suitable for analysing ecologic-level data over time, which has recently been used to study the relationship between antimicrobial consumption and the evolution of resistant organisms.[15] We used time series analysis to test the effect of the change in antibiotic policy on the subsequent monthly count of CDAD episodes from 1993 to 2000.[16] Consumption of 3GC fell from 28.95 defined daily doses per 1,000 patient days (95%CI 28.63-29.26) prior to October 1998 to 3.29 defined daily doses per 1,000 patient days (95%CI 3.12-3.46) after the policy was introduced. The average incidence of CDAD during the pre-intervention period was 0.61 episodes per 1,000 patient days (95% CI 0.56-0.65). During the post-intervention period, the average incidence was 0.28 episodes per 1,000 patient days (95% CI 0.23-0.33), a statistically significant reduction. Based on our previous estimations of the cost of CDAD to SCGH,[17] such a reduction would result in a potential saving, either real or opportunity, of more than A$800,000 annually.

Discussion

Several others have reported falls in CDAD after reduced use of antibiotics known to be associated with *C. difficile* infection, such as clindamycin,[18] and cephalosporins, particularly 3GCs.[19,20,21] The aim of the policy restricting 3GC use in SCGH was not primarily to control CDAD. The policy was introduced due to concerns about increased numbers of antibiotic resistant microorganisms within the hospital. Cephalosporin use has been implicated in the increased prevalence of methicillin resistant *Staphylococcus aureus*,[22,23] vancomycin resistant enterococci,[24] and extended-spectrum beta-lactamase producing gram-negative organisms.[25] There is now increasing evidence that reduction in the use of this class of antibiotics can lead to reduced rates of methicillin resistant *Staphylococcus aureus*,[22] vancomycin resistant enterococci[25] and extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*.[25] The effectiveness of the policy introduced in SCGH is currently being evaluated regarding these types of organisms.

Although evidence from the literature indicates that a reduction in the use of antibiotics results in decreased rates of resistant organisms, the exact approaches to antibiotic control are being debated.[26,27] The requirement for approval of orders for ceftriaxone at SCGH resulted in a sustained reduction in ceftriaxone use over the 2-year period following implementation of the policy. The success of this policy must be attributed to the hospital Drug and Therapeutic Committee that regularly audits and reviews antibiotic use in the hospital. However, methods to assess the effectiveness of such interventions are contentious.[28] Using a time series approach not only accounts for auto-correlation of the data, but also controls for exogenous factors that influence the data series.[29] We have demonstrated that a restrictive prescribing policy for 3GCs can significantly reduce the incidence of CDAD and may, potentially, reduce antibiotic resistant organisms.

References

1. Kelly CP, LaMont JT. *Clostridium difficile* infection. *Annu Rev Med* 1998;49:375–390.
2. Riley TV. *Clostridium difficile*: a pathogen of the nineties. *Eur J Clin Microbiol Infect Dis* 1998;17:137–141.
3. Borriello SP. Pathogenesis of *Clostridium difficile* infection. *J Antimicrob Chemother* 1998;41:13–19.
4. Bignardi GE. Risk factors for *Clostridium difficile* infection. *J Hosp Infect* 1998;40:1–15.
5. Johnson S, Gerding DN. *Clostridium difficile*–associated diarrhea. *Clin Infect Dis* 1998;26:1027–1034.
6. Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. *Clin Infect Dis* 2001;32:1055–1061.
7. Poxton IR, McCoubrey J, Blair G. The pathogenicity of *Clostridium difficile. Clin Microbiol Infect* 2001;7:421–427.
8. Riley TV, Bowman RA, Carroll SM. Diarrhoea associated with *Clostridium difficile* in a hospital population. *Med J Aust* 1983;1:166–169.
9. Riley TV, O'Neill GL, Bowman RA, Golledge CL. *Clostridium difficile*–associated diarrhoea: epidemiological data from Western Australia. *Epidemiol Infect* 1994;113:13–20.
10. Golledge CL, McKenzie T, Riley TV. Extended spectrum cephalosporins and *Clostridium difficile. J Antimicrob Chemother* 1989;23:929–931.
11. Thomas C, Stevenson M, Williamson DJ, Riley TV. *Clostridium difficile*–associated diarrhea: epidemiological data from Western Australia associated with a modified antibiotic policy. *Clin Infect Dis* 2002;35:1457–1462.
12. Johnson S, Gerding DN, Olson MM, Weiler MD, Hughes RA, Peterson LR. Prospective controlled study of vinyl glove use to interrupt *Clostridium difficile* nosocomial transmission. *Am J Med* 1990;88:137–140.
13. Zafar AB, Gaydos LA, Furlong WB, Nguyen MH, Mennonna PA. Effectiveness of infection control program in controlling nosocomial *Clostridium difficile. Am J Infect Control* 1998;26:588–593.
14. Sanderson PJ. What should we do about patients with *Clostridium difficile*? *J Hosp Infect* 1999;43:251–253.
15. López-Lozano JM, Monnet DL, Yagüe A, Burgos A, Gonzalo N, Campillos P, *et al*. Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. *Int J Antimicrob Agents*, 2000;14:21–31.

16. Thomas C, Beyaert A, López-Lozano J-M, Stevenson M, Riley TV. Evaluation of a hospital-wide policy restricting 3rd generation cephalopsorin use to reduce *Clostridium difficile*–associated diarrhoea: a time-series analysis. In press.

17. Riley TV, Codde JP, Rouse IL. Increased length of stay due to *Clostridium difficile*–associated diarrhoea. *Lancet* 1995;345:455–456.

18. Climo MW, Israel DS, Wong ES, Williams D, Coudron P, Markowitz SM. Hospital-wide restriction of clindamycin: effect on the incidence of *Clostridium difficile*–associated diarrhea and cost. *Ann Intern Med* 1998;128:989–995.

19. Ludlam H, Brown N, Sule O, Redpath C, Coni N, Owen G. An antibiotic policy associated with reduced risk of *Clostridium difficile*–associated diarrhoea. *Age Ageing* 1999;28:578–580.

20. Jones EM, Kirkpatrick BL, Feeney R, Reeves DS, MacGowan AP. Hospital-acquired *Clostridium difficile* diarrhoea. *Lancet* 1997;349:1176–1177.

21. McNulty C, Logan M, Donald IP, Ennis D, Taylor D, Baldwin RN, *et al*. Successful control of *Clostridium difficile* infection in an elderly care unit through use of a restrictive antibiotic policy. *J Antimicrob Chemother* 1997;40:707–711.

22. Fukatsu K, Saito H, Matsuda T, Ikeda S, Furukawa S, Muto T. Influences of type and duration of antimicrobial prophylaxis on an outbreak of methicillin-resistant *Staphylococcus aureus* on the incidence of wound infection. *Arch Surg* 1997;132:1320–1325.

23. Hill DA, Herford T, Parratt D. Antibiotic usage and methicillin-resistant *Staphylococcus aureus*: an analysis of causality. *J Antimicrob Chemother* 1998;42:676–677.

24. Schentag JJ, Hyatt JM, Carr JR, Paladino JA, Birmingham MC, Zimmer GS, *et al*. Genesis of methicillin-resistant *Staphylococcus aureus* (MRSA), how treatment of MRSA infections has selected for vancomycin-resistant *Enterococcus faecium*, and the importance of antibiotic management and infection control. *Clin Infect Dis* 1998;26:1204–1214.

25. Patterson JE. Antibiotic utilization. Is there an effect on antimicrobial resistance? *Chest* 2001;119 Suppl 2:S426–S430.

26. Shlaes DM, Gerding DN, John JF Jr, Craig WA, Bornstein DL, Duncan RA, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Clin Infect Dis* 1997;25:584–599.

27. Cunha BA. Effective antibiotic-resistance control strategies. *Lancet* 2001;357:1307–1308.

28. McGowan JE Jr. Strategies for study of the role of cycling on antimicrobial use and resistance. *Infect Control Hosp* Epidemiol 2000;21 Suppl:S36–S43.

29. Morrell S. Time series (Box-Jenkins) analysis. In: Kerr C, Taylor R, Heard G, eds. *Handbook of Public Health Methods*. Sydney: McGraw-Hill Book Company Australia Pty Ltd; 1998:354–371.

Changing GPs' antibiotic prescribing: a randomised controlled trial

Eileen J Wilson,[1] Dilruba Nasrin,[1] Keith B G Dear,[2] Robert M Douglas[3]

Abstract

A randomised controlled trial involving 54 general practitioners (GPs) was conducted in Canberra, Australian Capital Territory from September 1997 to November 1999. In the first year of the study, 24 GPs, who constituted the active arm of the intervention group, were involved in the consideration of evidence and the development and implementation of a set of clinical guidelines for the treatment of acute respiratory infections. These guidelines were then endorsed in a meeting together with specialist colleagues. In the second year of the study the group of GPs who had been acting as controls, received a moderate intervention consisting of a brief educational event and distribution of the locally developed guidelines. We obtained data from January 1997 to December 1999 from the Health Insurance Commission on prescribing rates for 40 of the doctors in the study. The rate of prescribing was calculated as the number of antibiotic prescriptions per 100 Medicare services. The average yearly prescribing decreased significantly in the intensive intervention group and increased in the moderate intervention group, (p=0.026). A mixed effects longitudinal time series model was fitted to the data to account for seasonal variation of antibiotic prescribing and trends over time. The intensive intervention group significantly reduced their antibiotic prescribing over time compared to the moderate intervention group, (p<0.001). This study has shown that an intensive intervention in which general practitioners were actively engaged in development and consideration of the evidence base for the guidelines resulted in a significant fall in general antibiotic prescribing. *Commun Dis Intell* 2003;27 Suppl:S32–S38.

Keywords: acute respiratory infections, antibiotic prescribing, antibiotic resistance

Introduction

Acute respiratory infections (ARI) are a very significant part of the workload of general practitioners (GPs). Antibiotics are frequently used to treat these generally self-limiting infections. For different types of respiratory infections, the antibiotic prescribing rate in general practice ranges from 50 to 90 per cent.[1]

Numerous studies have demonstrated that antibiotics offer at best a modest benefit for most acute respiratory infections. Antibiotics are not indicated for simple upper respiratory tract infections.[2,3,4] However, upper respiratory tract infection is often associated with bronchitis, pharyngitis, otitis media or sinusitis. These conditions can sometimes benefit from antibiotic treatment in a subset of patients.[5,6,7,8,9,10,11,12,13] The difficulty for the clinician is to distinguish, at the time of the consultation, which subset of patients would benefit from antibiotics and which would not. The signs and symptoms of these illnesses may not clearly differentiate between these groups of patients. A watchful approach may often be justified,[14,15] but the pressures of modern practice are such that clinicians currently tend to overuse these drugs.

1. PhD Scholar, National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory
2. Senior Fellow, National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory
3. Director, National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory

Corresponding author: Dr Eileen J Wilson, Epidemiologist, Defence Links Branch, Department of Veterans' Affairs, Canberra ACT 2602. Telephone: +61 2 6289 1110. Facsimile: +61 2 6289 6173. Email: eileen.wilson@dva.gov.au

In light of growing antibiotic resistance and the modesty of the clinical benefit[16] calls have been made for a more judicious use of antibiotics for the treatment of acute respiratory infections.[17] Yet the task of altering established practices of antibiotic use remains an unmet challenge.[18]

This paper reports on the effect on general prescribing practices of a randomised controlled trial that tested two different approaches to the implementation of clinical guidelines for antibiotic use in management of childhood respiratory infections.

Methods

We undertook a two year randomised controlled trial to explore the effects of a unique method of clinical practice guideline development and implementation on antibiotic use for acute respiratory infections in young children. The recruitment of participants and methods of guideline development are described fully elsewhere.[19] Briefly, 54 GPs from practices in Canberra, Australian Capital Territory (one GP per practice) were recruited into the study beginning in September 1997. GPs were randomly allocated into an intensive intervention group or a moderate intervention group. The intensive intervention consisted of a series of focus groups with parents of young children and workshops with the study GPs (beginning in the first quarter of 1998). Clinical practice guidelines for the management of childhood ARI were collaboratively developed in these focus groups and workshops. Evidence for antibiotic treatment of ARI from Cochrane reviews and other studies was explored and examined in light of the experiences and expectations of GPs and consumers in the management of these illnesses. Barriers to the judicious use of antibiotics for ARI were identified and discussed and an implementation package developed which addressed these barriers to change. This package consisted of:

- Guidelines for GPs: The guidelines were entitled *Principles of Practice* and stated the principles of management of ARI that the GPs had agreed upon during the development process. The guidelines were flexible and allowed for the realities of general practice and patient preference. They incorporated the evidence and were tailored to GP and patient concerns to allow for ownership of the guidelines.
- Information sheets on otitis media and sore throat: Copies of these sheets were given to GPs to distribute to patients. The sheets were developed by Dr Chris Del Mar, one of the authors for the Cochrane review on antibiotic treatment of otitis media[11] and sore throat[8] and kindly given to us for use in this study. The information sheets allowed for the education of patients in a time efficient manner.
- ARI management prescription pad: These prescription-like pads allowed the GP to tick a series of boxes that explained the diagnosis, recommended symptomatic treatment, and caution on the warning signs if the patient did not have any improvement. The prescription pads also contributed to the education of the patient by providing clear advice on self-management.
- Poster: We developed a colourful poster to be displayed in the GPs surgery that advocated the judicious use of antibiotics. The poster helped to market the new way of practice.

The implementation package was distributed to the intensive intervention group in the first year of the study shortly after the last workshop session (April 1998). The moderate intervention group acted as a control for the ensuing year.

In the second quarter of 1999, the moderate intervention group was provided with the locally developed guidelines and implementation package at an evening educational event. At this time the intensive intervention group received prescribing feedback and reinforcement of the guideline principles at a follow-up evening group meeting. Thus the study tested the comparative effects over time of two levels of intervention, an intensive intervention and a moderate intervention. Although not part of this analysis, the study also provided guidelines to parents and education through newsletters.

GP antibiotic prescribing was monitored using Health Insurance Commission (HIC) data obtained with GP's permission from 40 of the 49 GPs still active in the study by the end of 1999, 20 from each intervention group. The total number of antibiotic prescriptions filled for patients eligible for Pharmaceutical Benefits Scheme subsidy and total number of Medicare services provided by the GPs in the two groups were calculated by calendar quarter from 1997 through 1999 and by calendar year. The variable of interest was the number of subsidised antibiotic prescriptions per 100 Medicare services.

A mean rate of prescribing was calculated for each year of the study and the change in prescribing from the baseline year (1997) to the intervention years of 1998 and 1999 were compared using t-tests. To account for the seasonal variation in antibiotic prescribing, detail which is lost using a yearly mean rate, a mixed effects longitudinal time series model was fitted to the HIC data using Stata version 7 software.[20] The model incorporated a random effect clustered by GP and fixed effects of intervention group and sine and cosine terms to account for the seasonal variation of antibiotic prescribing. In addition, a linear term in time was added to measure trend within the intervention groups.

Results

Antibiotic prescribing followed a cyclical seasonal pattern. Prescribing was lowest in the summer months (first quarter) and highest in the winter months (third quarter). Table 1 details the number of antibiotic prescriptions per 100 Medicare services by intervention group and quarter.

Table 1. Mean number of antibiotic prescriptions per 100 Medicare services by intervention group and yearly quarter

Quarter*	Group	Mean ± SD	95% CI
Q1 – 1997	IIG	6.67 ± 2.7	5.4, 7.9
	MIG	5.68 ± 1.7	4.8, 6.5
Q2 – 1997	IIG	7.66 ± 2.6	6.4, 8.9
	MIG	7.61 ± 3.3	6.1, 9.1
Q3 – 1997	IIG	8.73 ± 2.8	7.4, 10.1
	MIG	8.39 ± 2.5	7.2, 9.6
Q4 – 1997	IIG	7.01 ± 2.4	5.9, 8.1
	MIG	6.96 ± 1.9	6.1, 7.8
Q1 – 1998	IIG	5.92 ± 2.1	4.9, 6.9
	MIG	5.82 ± 1.7	5.0, 6.6
Q2 – 1998	IIG	6.16 ± 2.3	5.1, 7.2
	MIG	7.14 ± 2.2	6.1, 8.2
Q3 – 1998	IIG	8.00 ± 3.3	6.5, 9.5
	MIG	7.92 ± 2.1	6.9, 8.9
Q4 – 1998	IIG	7.53 ± 2.8	6.2, 8.8
	MIG	7.61 ± 2.4	6.5, 8.7
Q1 – 1999	IIG	6.43 ± 2.4	5.3, 7.6
	MIG	6.33 ± 2.4	5.2, 7.4
Q2 – 1999	IIG	6.47 ± 2.3	5.4, 7.5
	MIG	7.14 ± 2.5	6.0, 8.3
Q3 – 1999	IIG	7.16 ± 3.5	5.5, 8.8
	MIG	8.60 ± 2.5	7.4, 9.8
Q4 – 1999	IIG	6.90 ± 3.1	5.5, 8.3
	MIG	8.00 ± 2.6	6.8, 9.2

* Recruitment into the study started at the end of Q3 1997. Intensive intervention began from Q1 1998 and moderate intervention began from Q2 1999.

IIG Intensive intervention group.

MIG Moderate intervention group.

Antibiotic prescribing during the baseline year of 1997 was not significantly different between the intensive and moderate intervention groups as shown in Table 2. Over the course of the study the mean rate of prescribing for the intensive intervention group decreased by –0.78 prescriptions per 100 Medicare services whereas the mean rate of prescribing increased by 0.35 prescriptions in the moderate intervention group, a difference of –1.13, 95 per cent CI (-2.1, –0.1) and p=0.026 (Table 2).

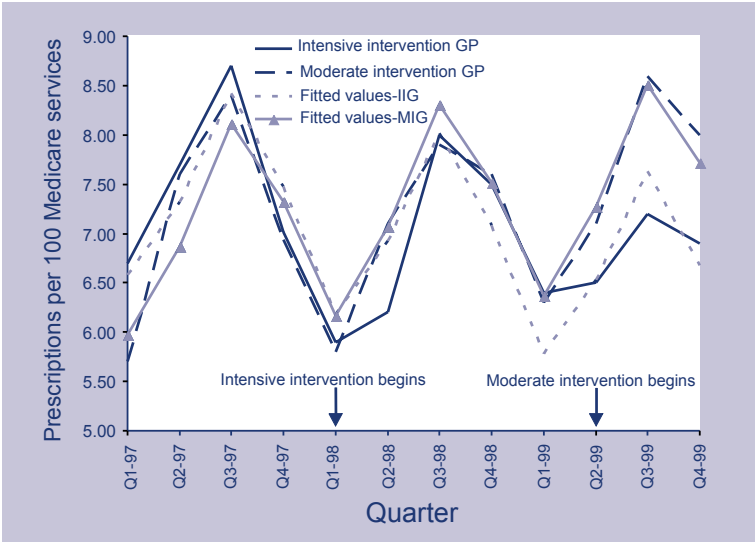
Table 2. Baseline level of antibiotic prescribing and mean yearly change

Group	Baseline prescribing in 1997 (number of prescriptions per 100 Medicare services)	Mean change* from 1997 to 1998	Mean change from 1997 to 1999
Intensive intervention group	7.52 ± 2.4	–0.62 ± 1.3	–0.78 ± 1.3
Moderate intervention group	7.16 ± 2.2	–0.04 ± 0.8	0.35 ± 1.7
p value 95% confidence interval	0.630 (–1.1, 1.8)	0.100 (–1.3, 0.1)	0.026 (–2.1, –0.1)

* Mean yearly difference ± standard deviation.

The seasonal pattern of prescribing was accounted for by a mixed effects longitudinal time series model fitted to the HIC data. There was a highly significant interaction between intervention group and time, p<0.001, whereby the intensive intervention group reduced their antibiotic prescribing over time compared to the moderate intervention group (ß coefficient = –0.15, 95% CI –0.22, –0.07). The Figure shows the fitted curve of the model with the data for mean rates of prescribing by quarter for each intervention group.

Figure. Prescriptions per 100 Medicare services in groups of GPs before and after intensive or moderate interventions to revise prescribing practices for upper respiratory tract infections, means and fitted values



Source: Data from the Health Insurance Commission

Discussion

A detailed analysis of the randomised trial that involved 54 general practitioners and 502 of their child patients has been presented elsewhere.[21] That report showed that GPs in the intensive intervention group changed their prescribing practices in relation to the study children. The analysis in the present paper was undertaken to test whether this change in prescribing behaviour, which was evident for children enrolled in the study, carried over into the overall practices of the doctors, including patients who were not enrolled in the very intense diary keeping study. This study has shown that a multi-faceted evidence-based approach to guideline development and implementation was effective in reducing general antibiotic prescribing.

The use of the Pharmaceutical Benefits Scheme and Medicare data involved some limitations but provided an objective measure of prescribing behaviour over time. The Health Insurance Commission will hold a record of a prescription only if the cost of the drug is higher than the patient contribution, approximately A$21.00 at the time of the study. However, prescriptions from pensioners and holders of concession cards is recorded. Thus the data capture for antibiotic prescriptions, which generally cost less than the patient contribution, was incomplete. This incomplete data capture, however, would have been equal for both intervention groups and not a source of bias. Furthermore, HIC data has been used previously to monitor antibiotic prescribing.[28] Only 40 of the 49 GPs active at the end of the study gave written permission to obtain their prescribing information from the HIC. Those that did not comply, however, were equally distributed between the two groups.

Clinical practice guidelines have long been seen as a way to enhance best practice in health care. The National Health and Medical Research Council has published a series of handbooks detailing the main stages of clinical practice guideline development and implementation.[22] However, observed change in studies of guideline development and implementation have often been modest.[23,24,25] Single interventions frequently resulted in little or no change in behaviour but complex interventions using several methods had a better chance of producing change.[26,27] Nevertheless, all make it clear that, as Oxman *et al* declare, 'there are no magic bullets'.[25] There is no one method that will effectively change clinical behaviour.

Grol and Grimshaw[18] provide a general framework for integration of evidence with clinical practice. They advocate an evidence-based multi-faceted approach, the careful assessment of barriers to change, and tailoring interventions to specifically address the barriers. This general framework was used to guide the approach of guideline development and implementation described in this study. We first started with the evidence for the judicious use of antibiotics for ARI. Then the barriers to incorporating the evidence into practice for GPs and consumers were assessed through the process of guideline development using focus groups and workshops. The identification of these barriers have been presented previously.[19] Discussing the evidence, identifying the barriers to incorporate the evidence into practice, openly exploring these issues with the GPs in a collaborative peer environment, and devising an implementation package to address these barriers contributed to the development of guidelines that were effective for changing practice in the intensive intervention group of GPs. Furthermore, ongoing contact was maintained with the intensive intervention group through feedback reports and reinforcement of guidelines. A moderate intervention of distribution of the locally developed guidelines and implementation package with a brief educational component was not sufficient to reduce antibiotic prescribing in the moderate intervention cohort of GPs.

Although labour intensive, the workshops, which were the main difference between the intensive and moderate interventions, were effective in changing clinical behaviour. The process of examining the evidence and discussing this with their colleagues during several sessions, with the support of academic GPs to clarify the evidence, was more influential in changing GP behaviour than distribution of the evidence-based guideline package with a brief educational event (moderate intervention).

Others have shown that passive dissemination of guidelines,[23] unsolicited feedback reports,[28] or didactic continuing medical education[28] are generally ineffective in changing clinical behaviour. This study has shown that antibiotic prescribing can be significantly reduced using methods that discuss

the evidence in a peer-supported environment. The need for effective methods to reduce antibiotic prescribing becomes more urgent in light of the results from companion research to this study that has shown antibiotic use in the community directly correlates with the level of antibiotic resistance.[29] In Australia there may be a role for the Divisions of General Practice, in conjunction with academic institutions, to organise workshop series with GPs and focus groups with consumers for the open examination of evidence, experiences, and preferences to enhance the practice of evidence-based health care.

Acknowledgments

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References

1. Bridges-Webb C, Britt H, Miles DA, Neary S, Charles J, Traynor` V. Morbidity and treatment in general practice in Australia 1990–1991. *Med J Aust* 1992;157 Suppl:S1–S56.
2. Rosenstein N, Phillips WR, Gerber MA, Marcy SM, Schwartz B, Dowell SF. The common cold — principles of judicious use of antimicrobial agents. *Pediatrics* 1998;101 Suppl:S181–S184.
3. Mashford ML, Beaves M, Hogg G, Kucers A, Robinson G, Spicer JW, *et al*. *Antibiotic Guidelines* 9th edition. Victorian Medical Postgraduate Foundation Inc; Melbourne, 1996.
4. Arroll B, Kenealy T. *Antibiotics versus placebo in the common cold (Cochrane review)*. In: *The Cochrane Library*. Oxford, Issue 1, 1999.
5. Becker L, Glazier R, McIsaac W, Smucny J. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 1997;4.
6. Orr PH, Scherer K, Macdonald A, Moffatt ME. Randomized placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. *J Fam Pract* 1993;36:507–512.
7. O'Brien K, Dowell S, Schwartz B, Marcy S, Phillips W, Gerber M. Cough illness/bronchitis — principles of judicious use of antimicrobial agents. *Pediatrics* 1998;101 Suppl:S178–S181.
8. Del Mar C, Glasziou P. Antibiotics for the symptoms and complications of sore throat. In: *The Cochrane Library*. Oxford, 1996.
9. Zwart S, Sachs AP, Ruijs GJ, Gubbels JW, Hoes AW, de Melker RA. Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. *BMJ* 2000;320:150–154.
10. Froom J, Culpepper L, Jacobs M, DeMelker RA, Green LA, van Buchem L, *et al*. Antimicrobials for acute otitis media? A review from the International Primary Care Network. *BMJ* 1997;315:98–102
11. Glasziou P, Hayem M, Del Mar C. Treatments for acute otitis media in children: antibiotic versus placebo. In: *The Cochrane Library*. Oxford, 1996.
12. O'Brien KL, Dowell SF, Schwartz B, Marcy SM, Phillips WR, Gerber MA. Acute sinusitis — principles of judicious use of antimicrobial agents. *Pediatrics* 1998;101 Suppl:S174–S177.
13. Winther B, Brofeldt S, Gronborg H, Mygind N, Pedersen M, Vejlsgaard R. Study of bacteria in the nasal cavity and nasopharynx during naturally acquired common colds. *Acta Otolaryngol* 1984;98:315–320.
14. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;322:336–342.
15. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth A. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997;315:350–352.
16. Turnidge JD, Bell JM, Collignon PJ. Rapidly emerging antimicrobial resistances in *Streptococcus pneumoniae* in Australia. *Med J Aust* 1999;170:152–155.

17. The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic resistance (JETACAR). Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia, Canberra, 2000:39.

18. Grol R, Grimshaw J. Evidence-based implementation of evidence-based medicine. *Jt Comm J Qual Improv* 1999;25:503–513.

19. Wilson EJ, Nasrin D, Banwell C, Broom D, Douglas RM. Realities of practice. Engaging parents and GPs in developing clinical practice guidelines. *Aust Fam Physician* 2000;29:498–503.

20. Stata Statistical Software 6.0 version. College Station, TX: Stata Corporation, 1999.

21. Wilson E. Realities of practice: development and implementation of clinical practice guidelines for acute respiratory infections in young children (PhD thesis). The Australian National University, 2002.

22. National Health and Medical Research Council. Series of handbooks on the main stages involved in the development of clinical practice guidelines. Biotex Canberra, 2000. Available from: http://www.health.gov.au/nhmrc/publications/synopses/cp65syn.htm. Accessed 2001.

23. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *CMAJ* 1997;157:408–416.

24. Lomas J. Words without action? The production, dissemination, and impact of consensus recommendations. *Annu Rev Public Health* 1991;12:41–65.

25. Oxman A, Thomson M, Davis D, Haynes B. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *CMAJ* 1995;153:1423–1431.

26. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: reviews of interventions to promote implementation of research findings by health care professionals. In: Haines A, Donald A, editors. *Getting Research Findings into Practice*. London: *BMJ* Publishing, 1998:160.

27. Grol R. Successes and failures in the implementation of evidence-based guidelines for clinical practice. *Med Care* 2001;39 Suppl 2:II46–II54.

28. O'Connell DL, Henry D, Tomlins R. Randomised controlled trial of effect of feedback on general practitioners' prescribing in Australia. *BMJ* 1999;318:507–511.

29. Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM. Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. *BMJ* 2002;324:28–32.

Antibiotic prescribing for upper respiratory-tract infections in primary care

Craig A Patterson,[1] Judith M Mackson,[2] Lynn M Weekes[3]

Abstract

The use and overuse of antibiotics in humans is a major contributor to the selection of antibiotic resistance organisms. Recent evidence has shown that primary care prescribing selects for resistances of clinical importance. The National Prescribing Service runs both educational and audit activities. The latter provide some insight into general practice attitudes toward antibiotic prescribing. *Commun Dis Intell* 2003;27 Suppl:S39–S41.

Keywords: antibiotic resistance, upper respiratory-tract infections, antibiotic prescribing, primary care

Introduction

The use and overuse of antibiotics in humans is a major contributor to the selection of antibiotic resistant organisms. Recent evidence has shown that primary care prescribing selects for resistances of clinical importance.[1]

Managing upper respiratory-tract infections (URTIs) in general practice is very common; second behind hypertension as the most frequently managed problem and the most common 'new problem' seen by general practitioners (GPs).[2] Many URTIs and acute bronchitis are viral in origin and of a self-limiting nature. However, data from the *Bettering the evaluation and care of health* study indicate that antibiotic prescribing for URTIs is inappropriately high: around 50 per cent of patients who present with an URTI to their GP receive an antibiotic, a rate of prescribing which has remained virtually unchanged in the last few years.[3]

The National Prescribing Service (NPS) is an independent organisation promoting quality use of medicines in Australia. To encourage rational antibiotic prescribing, the NPS provides both educational and audit activities to primary care practitioners and has conducted an antibiotics program each year during the winter months from 1999 to 2001. These programs have offered an insight into general practice attitudes and barriers to optimising antibiotic prescribing for URTI and acute bronchitis.

Methods

In addition to print materials circulated to GPs (e.g., *NPS News, Prescribing Practice Review*, individual prescribing feedback, and educational visits), the NPS has offered case studies and clinical audits to GPs as part of their professional development. Participation by GPs in these activities assists them in satisfying the requirements for payment under the Practice Incentives Program for the Commonwealth Government's Quality Prescribing Initiative.

Hypothetical case scenarios were provided for GPs on otitis media in 1999 and sinusitis in 2001. The responses to the case study questions were aggregated and, together with expert commentary discussion of the results, supplied in a report to participating GPs.

1. Information Officer, National Prescribing Service
2. Education, Quality and Prescribing Program Manager, National Prescribing Service
3. Chief Executive Officer, National Prescribing Service

Corresponding author: Mr Craig Patterson, National Prescribing Service, Level 1, 31 Buckingham Street, Surry Hills NSW 2010. Telephone: +612 9699 4499. Facsimile: +61 2 9699 5155. E-mail: cpatterson@nps.org.au

Clinical audits have been offered each winter in 1999, 2000 and 2001. An audit form was designed allowing GPs to record their own prescribing for 20 patients presenting with any of the following: common cold; sore throat; acute otitis media; otitis media with effusion; acute sinusitis; acute bronchitis; or chronic bronchitis. Prescribing was measured for concordance with recommendations in the *Therapeutic guidelines: antibiotic* for the various conditions. A report containing individual responses, together with aggregated results and an expert commentary, was provided to participating GPs.

Results

A small number of GPs (n=107) responded to the first case study on otitis media in 1999. Ninety-two per cent of GPs chose to prescribe an antibiotic in a case which the microbiologist's expert commentary described as not requiring antibiotic therapy. Eighty-six per cent of the prescriptions written were intended for immediate use. Furthermore, while 73 per cent chose amoxycillin as their first-line agent (in line with *Therapeutic guidelines* recommendations), some antibiotics selected were inappropriate for the likely causative pathogens, including cephalexin, co-trimoxazole, penicillin V, and roxithromycin.

In 2001, GP participation in NPS case studies had increased such that 962 responses had been received for the study on sinusitis; the responses from a sample of 150 participants were analysed. Ninety per cent of GPs considered an antibiotic was required; some of this prescribing was accompanied by symptomatic treatments such as a decongestant and an analgesic. Amoxycillin was the first-choice antibiotic in 77 per cent of cases in accordance with *Therapeutic guidelines* recommendations.

The antibiotic clinical audits measured concordance with *Therapeutic guidelines* recommendations. Overall, concordance included occasions when an antibiotic was not indicated and was not prescribed, or when an antibiotic was indicated and the appropriate first-line agent was selected.

Concordance for all conditions (common cold, sore throat, acute otitis media, otitis media with effusion, acute sinusitis, acute bronchitis and chronic bronchitis) was moderately good (around 70%) for the three audits. Certain conditions were managed in accordance with recommendations better than others: that common colds are viral and do not require antibiotics was recognised by over 90 per cent of respondents, yet acute bronchitis was poorly managed with around 50 per cent of respondents prescribing antibiotics despite this condition viral most often having a viral cause.

In general, the levels of antibiotic prescribing were high, particularly for sore throats, acute sinusitis, acute otitis media, and acute bronchitis. The overall amount of antibiotic prescribing was 42.6 per cent, 50.3 per cent, and 50.9 per cent for 1999, 2000, and 2001, respectively. With respect to antibiotic selection, although higher use of the first-line agents amoxycillin and penicillin V, is promising in comparison with other agents, inappropriate choices for treating URTIs such as cephalexin, cefaclor, and macrolides, continues.

Discussion

Results from the case studies and clinical audits are not comparable as some data are derived for hypothetical cases whereas the clinical audits are self-reported with no assurance of standardised diagnostic labelling. However, they do provide an insight into conditions for which GPs are more likely to prescribe antibiotics.

Overall, the antibiotic prescribing rate of around 50 per cent still allows room for improvement given that these conditions are primarily viral or self-limiting in nature. Antibiotic prescribing for these conditions remains high and with only moderate accord with national best practice guidelines. This is despite mounting evidence from systematic reviews and meta-analyses that prescribing antibiotics does little to affect the course of many URTIs.

Some areas pose greater diagnostic and therapeutic dilemmas for prescribers. GPs are aware of the evidence regarding antibiotic prescribing for otitis media and there appears to be a willingness to delay antibiotic use (around 10% of antibiotic prescriptions in the audits were to be filled at a later date), yet there is still an inappropriate level of prescribing for acute bronchitis which is almost always viral in nature. Similarly, acute sore throat was treated with antibiotics too frequently for what is most often a viral infection; an antibiotic is indicated in severe tonsillitis only. Perhaps some conditions present greater diagnostic ambiguity, for example concern that acute bronchitis may be pneumonia, and this concern drives antibiotic prescribing outside evidence-based recommendations.

The NPS receives feedback on GP perceptions of antibiotic prescribing for URTIs via activity reports submitted by NPS facilitators following educational visits and small-group peer discussions with GPs. Through these reports, the NPS has become aware that focusing on resistance patterns can divert the emphasis away from the self-limiting nature of most URTIs and the limited benefit of antibiotics. However, practitioners often receive information concentrating on bacterial sensitivities and resistance to primary care antibiotics, either through pharmaceutical industry detailing or the data presented in product information documents.

An overemphasis on increasing rates of resistance for common respiratory pathogens deflects from the issue of judiciousness in the decision to prescribe (if at all) and can prompt inappropriate responses, for example, selecting second-line antibiotics as first-line choices or using antibiotics in conditions where they are of limited benefit.

Another problem for GPs is reconciling the public health necessity of reduced antibiotic resistance through less prescribing with the potential individual benefits of prescribing antibiotics for the patient before them. GPs need to be able to offer patients alternatives to antibiotics in the management of their URTI to help find this balance should prescribing be deemed unnecessary.

Consequently, the NPS has provided tools for GPs to facilitate alternative approaches to managing URTIs, including symptomatic management 'non-prescription' pads, patient materials on sore throats and acute bronchitis, as well as consumer campaigns (such as the *Common colds need common sense* campaign) that raise community awareness of the limitations of antibiotics for certain infections and highlight the possible side-effects of antibiotics.

In conclusion, activities to address excessive antibiotic use need to include primary care settings as there is evidence that the management of URTIs by this group is less than optimal. However, global arguments on developing resistance can sometimes overwhelm quality issues surrounding antibiotic prescribing in this arena. Messages for general practitioners must focus on the benefits and risk to the patient which can be applied in daily practice. Promoting appropriate prescribing for URTIs will in itself contribute to reducing antibiotic resistance as there is room for improvement in the current attitudes toward the management of these conditions.

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References:

1. Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM. Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. *BMJ* 2002;324:28–30.

2. Britt H, Miller GC, Knox S, Charles J, Valenti L *et al*. General practice activity in Australia 2000–01. AIHW Cat. No. GEP 8. Canberra: Australian Institute of Health and Welfare (General Practice Series No. 8).

3. National Prescribing Service. Antibiotics in primary care. Prescribing Practice Review May 2002;18:2–3.

Consumer activities on antimicrobial resistance in Australia

Jan Donovan
Australian Pharmaceutical Advisory Council (APAC)

Abstract

The focus of this article is the role of consumer education campaigns in Australia and overseas as an important step in helping people develop a more considered use of antibiotics. Evidence of the success of campaigns in Australia, New Zealand and the United Kingdom is presented. On the basis of this evidence, the paper argues that education campaigns are central to reducing inappropriate antibiotic use and lowering the chances of antibiotic resistance building up in the populations of developed countries. *Commun Dis Intell* 2003;27 Suppl:S42–S46.

Keywords: antimicrobial resistance, JETACAR, public health, education campaigns

Introduction

The Pharmaceutical Benefits Scheme provides consumers with equitable and affordable access to necessary antibiotics in the community. This access to antibiotic treatments has worked well for Australians, but many viral infections, such as upper respiratory tract infections are still being inappropriately treated with antibiotics.[1] In the 1940s coinciding with the introduction of penicillin, antibiotic-resistant bacteria were isolated in Australian hospitals. The implications and public health importance of antibiotic resistance have been well understood by health professionals such as microbiologists and infectious disease physicians but consumers lacked information about the health risks associated with antimicrobial resistance. This may partly explain the lack of political will to address this problem until recently.

In the late 1980s, the Consumers Health Forum produced a document titled *Towards a National Medicinal Drug Policy*. This work by consumers stimulated a quality use of medicines policy formulated by the Pharmaceutical Health and Rational Use of Medicines (PHARM) Committee and accepted as part of National Medicinal Drug Policy by government in the early 1990s. In 2000, the National Medicinal Drug Policy was revised and the National Medicines Policy was endorsed by government. The Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) assisted this process, but until recently was not integrated with National Medicines Policy activities.

National focus on antibiotic resistance

The JETACAR, a Commonwealth Government initiative, was a group of experts from human health, veterinary medicine and primary industry. They had the task of assessing the scientific evidence for a link between the use of antibiotics in food producing animals, and the emergence of antibiotic resistant bacteria in humans (JETACAR, 1999).[2] JETACAR reported to Government in 1999 and was then disbanded. A Government response to JETACAR was released in 2000 and this is now being implemented.

In May 2001 the Commonwealth Government sought participation from all of the key stakeholders in a National Summit on antimicrobial resistance, to assist in the implementation and consultation process. Five priority areas for action are: regulatory controls, monitoring and surveillance, infection prevention, and education and research.[3] These issues require governments, health professionals, consumers, veterinary professionals and agriculture producers to work cooperatively towards a solution to the problem.

Correspondence: Ms Jan Donovan, 25 New Street, Brighton Beach VIC 3186. Telephone: +61 3 521 8293.
Email: jdonovan@netspace.net.au

The Summit reinforced the importance of educating the public, as well as the medical and veterinary professions and farmers about the appropriate use of antibiotics and flagged this as a priority. Other priorities identified included the greater involvement of consumer organisations in the development of community education initiatives, and establishing links with general practice and veterinary initiatives. Maintaining Australia's commitment to the World Health Organization's strategy to reduce reliance on antibiotics was also viewed as crucial.[4]

National Medicines Policy

The quality use of medicines component of the National Medicines Policy is now the cornerstone for community action to minimise the inappropriate use of antibiotics in Australia. According to the National Medicines Policy 2000 all medicines should be used;

- judiciously: medicines should be used only when appropriate, with non medicinal alternatives also considered;
- appropriately: choosing the most appropriate medicine taking account of clinical condition, risks and benefits, dose, length of treatment and cost;
- safely: misuse, including overuse and under use should be minimised; and
- efficaciously: the medicines must achieve the goals of therapy by delivering beneficial changes in actual health outcomes.

In March 2002, the National Strategy for the Quality Use of Medicines was released by the Commonwealth Department of Health and Ageing.[5] The National Strategy is an important step forward as it acknowledges that there are still significant problems linked to the use of medicines in Australia. For example, the National Strategy points out that problems remain despite successful initiatives promoting the quality use of medicines in areas such as improved use of antibiotics and non-steroidal anti-inflammatory drugs with fewer hospitalisations and deaths associated with the adverse effects of these medicines. However, there is still no room for complacency as there are now around 140,000 hospital admissions each year associated with problems with the use of medication.[6] Older people on multiple medicines are at increased risk of medication misadventure and increasing risk of antibiotic resistance.[6]

Community use of antibiotics

The number of prescriptions written for antibiotics declined from 26.5 million in 1993–94 to just under 23.3 million in 1998–99. One of the challenges has been to change community attitudes and promote ongoing and regular consumer information and education about the appropriate use of antibiotics. This includes such matters as their ineffectiveness in treating viral infections such as coughs and colds. Since 1992, the Commonwealth Government has actively sought to address the problem of antibiotic prescribing and use in the community, through consumer education campaigns. The National Strategy for the Quality Use of Medicines highlights education as an essential process to increase the awareness of communities, their knowledge and skills and motivation in relation to the quality use of medicines.

Consumer medicines education

Australia has now become a leader in tackling the problems related to appropriate prescribing and use of antibiotics. Early work done by PHARM included the National Medicines Week campaigns on the appropriate use of medicines. The 1996 campaign specifically targeted the appropriate use of antibiotics by consumers. Themes of the 1996 National Medicines Week campaign in Australia were to:

- ask your doctor or your pharmacist about your medicines;

- encourage people to be more aware of the risks and benefits of medicines; and
- ask for and read Consumer Medicines Information.

The National Medicines Week campaign produced a range of promotional materials for use in local communities including a brochure titled *Antibiotics, your questions answered* and a booklet *Be wise with medicines* with a section 'When antibiotics will not help'. (Commonwealth Department of Health and Family Services, 1996).

Other activities included a National Phone-in Medicines Information Service, media and radio campaigns, written information in pharmacies and GPs' surgeries, community grants and educational sessions on the quality use of medicines.

An evaluation of the National Medicines Week campaigns 1996 to 1998 showed they were effective in terms of increasing community awareness of the 'be wise with medicines' messages. Knowledge of the messages increased from 19 per cent in 1996 to 26 per cent in 1998 and rose to 30 per cent in the older population. The evaluation found that the National Medicines Week campaigns had an impact on consumer attitudes, knowledge and behaviour in relation to medicines. Consumers who were aware of the National Medicines Week messages were more likely to take action such as asking questions, discussing the use of their medicines with their doctor or pharmacist and asking for a medicines review.

According to the report evaluating the quality use of medicines component of the National Medicines Policy, over 70 per cent of the population considered it inappropriate to take antibiotics for colds, the flu or a sore throat, while more than 20 per cent of people considered it inappropriate to take antibiotics for bronchitis. In 1999 the National Prescribing Service (NPS) ran its first consumer survey as part of the NPS evaluation activity in order to achieve a better understanding of the attitudes and beliefs of consumers towards the use of antibiotics for coughs and colds. Similar surveys were also conducted in 2000 and 2001. There was a perception in younger people (particularly young males) that antibiotics promote recovery and prevent deterioration. Consequently, the NPS campaigns in 2001 and 2002 developed messages to address this erroneous perception and specifically targeted younger people, those in the workforce and parents of young children.

National Medicines Week consumer projects

As part of the 1996 National Medicines Week consumer activities, the Council on the Ageing (Australia) ran a major national project funded by the Commonwealth Department of Health and Ageing to coincide with National Medicines Week. Eighty peer educators were trained to disseminate information on the appropriate use of medicines including antibiotics. Peer educators held local discussion groups using the materials provided by the Commonwealth Department of Health and Ageing for National Medicines Week.

The formal evaluation funded by the Department of Health and Ageing identified a number of positive elements of this sort of approach. For example, the evaluation found that:

'Important processes were established through the peer education program that continue to yield benefits …a significant feature of the program was the extent to which resources were maximised… the grass roots networking and promotion that occurred would have been costly to run otherwise.'

The evaluation of the 1996 consumer project also made the general point that the projects were a community development activity bringing together community members and professionals in a way that encouraged partnerships.

A more recent project conducted by Council on the Ageing in 2000–2001, focused on all medicines (including complementary). It adopted a community/business partnership approach to work with health professionals through the involvement of pharmacists in training older people about the wise use of medicines.

Outcomes of consumer campaigns

There are major advantages for health professionals and government working in partnership with consumer organisations on antimicrobial resistance. The materials produced for consumers such as those produced for the National Medicines Week campaigns are widely disseminated at the local level. With input from the target groups, written information is designed to meet the needs of consumers and is widely disseminated and discussed. A more informed network of locally based peer educators is established and awareness is raised about the problem. A better understanding of the problems of antibiotic use and antimicrobial resistance greatly assists in changing attitudes and addressing the issue in the community.

Unfortunately, the National Medicines Week campaigns about the wise use of medicines including antibiotics were not ongoing. However, the NPS has broadened its work, focusing on the community with a 'wise use of antibiotics' message 'common cold needs common sense'. During the winters of 2001 and 2002, this message was widely publicised in local press, community grants enabled local level discussion and the messages were reinforced on billboards in some capital cities. The NPS campaign works with diverse groups of consumers, including non-English speaking consumers. Consumer activity at the local level is encouraged through a community grants process. The winter 2002 campaign is being evaluated.

Consumer strategies in other countries

Other countries such as the United Kingdom (UK), the USA and New Zealand are also concerned about the appropriate use of antibiotics in the community. Both the United Kingdom and New Zealand run campaigns targeted to both consumers and prescribers on the ineffectiveness of antibiotics for coughs and colds. For example, the UK has recently targeted campaigns on the appropriate use of antibiotics for viral upper respiratory tract infections to both prescribers and consumers. In the UK, a 9 per cent reduction in consumption of anti-microbials was achieved. The UK and New Zealand campaigns produce posters and leaflets for use by consumers and health professionals.

In New Zealand, written materials about colds and flu are also disseminated to the community through general practitioners. The Pharmaceutical Management Agency in New Zealand has run the campaigns in the years 1998–2001 from May to September. The New Zealand campaign aims to educate prescribers, consumers and the general public about the appropriate use of antibiotics in respiratory infections. An evaluation component is included with each campaign. The evaluation of the 2000 campaign showed that prescriptions for antibiotics were reduced by 14.8 per cent from January to December 2000 compared to the same period in 1999. There was also a shift in prescribing from broad spectrum to narrow spectrum antibiotics, improved public understanding of the role of antibiotics and changing consumer expectations about receiving antibiotics.

The future

To be effective, future Australian consumer campaigns need to work in partnership with and engage consumer organisations. Health professionals and other stakeholders need to foster consumer partnerships to ensure antibiotic awareness campaigns are coordinated. Consumer campaigns, such as the National Medicines Week campaigns and the National Prescribing Service *Common colds need common sense* campaign are part of Australia's contribution to the World Health Organization's global strategy to address antimicrobial resistance.

To continue to be effective, these campaigns need to be ongoing, engage consumers and work at the local as well as the national level. The consumer education funding announced in the last Federal budget 2001–02 will be an important resource for additional consumer activity in curbing inappropriate use of antibiotics in the future. The issue of antimicrobial resistance in Australia is a major public health issue and consumers have an important role in ensuring its growth is curbed.

References

1. National Prescribing Service. Evaluation report No. 2. National Prescribing Service; Sydney, November 2000:8.
2. Commonwealth Department of Health and Aged Care. Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR). Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia. Biotex Canberra, 1999.
3. Commonwealth Department of Health and Aged Care. Communique National Summit on Antibiotic Resistance 2001, Commitment and Communication, Issue 1.
4. World Health Organization. Global strategy for containment of antimicrobial resistance. World Health Organization, 2001.
5. Department of Health and Ageing. The National Strategy for Quality Use of Medicines. Department of Health and Ageing, Canberra, 2002:4.
6. Commonwealth Department of Health and Aged Care. National Medicines Policy. Commonwealth Department of Health and Aged Care, 2000:3.

Fifteen years of surveillance by the Australian Group for Antimicrobial Resistance (AGAR)

Graeme R Nimmo,[1] Jan M Bell,[2] Peter J Collignon,[3] on behalf of the Australian Group for Antimicrobial Resistance

Abstract

The Australian Group for Antimicrobial Resistance (AGAR) has played a unique role in surveillance of antimicrobial resistance in Australia. It has a broad laboratory membership representing the major teaching hospitals in all Australian capitals and more recently major private pathology laboratories in most states. The use of an active surveillance strategy with standard methodology for collection and examination of clinically significant isolates has produced data accurately reflecting the changing prevalence of antimicrobial resistance in major hospitals as well as the community. AGAR has documented the spread of methicillin-resistant *Staphylococcus aureus* in Australian hospitals in the late 1980s and throughout the 1990s. Surveys of antimicrobial resistance in enterococci have monitored the emergence of vancomycin-resistant enterococci as an important nosocomial pathogen in Australia. AGAR has also conducted major national surveys of resistance in *Streptococcus pneumoniae*, community isolates of *Staphylococcus aureus, Haemophilus influenzae* and in the *Enterobacteriaceae*. These and other activities have given AGAR a unique perspective on emerging patterns of resistance in key pathogens in Australia. The recent extension of membership to include more private pathology laboratories may provide the opportunity to conduct more representative community based surveys. *Commun Dis Intell* 2003;27 Suppl:S47–S54.

Keywords: methicillin-resistant Staphylococcus aureus, *vancomycin-resistant enterococci,* Streptococcus pneumoniae, *antimicrobial resistance*

Introduction

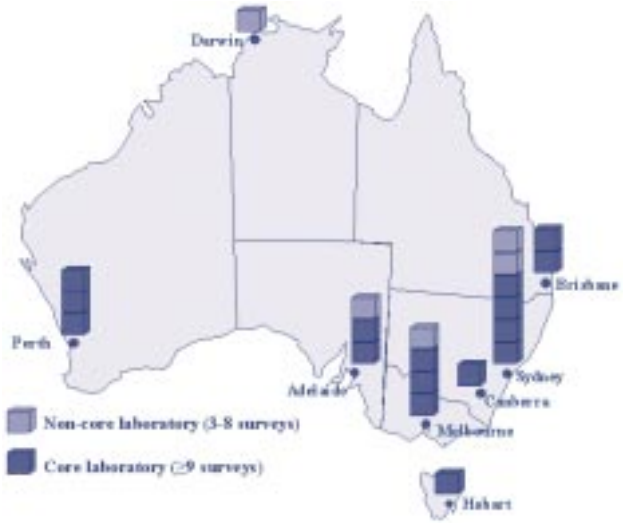
The Australian Group for Antimicrobial Resistance (AGAR) has conducted surveillance of antimicrobial resistance in Australian teaching hospitals since 1986. AGAR membership has always includes very broad representation of the major teaching hospitals in all Australian capitals (Figure 1). The spread of methicillin-resistant *Staphylococcus aureus* (MRSA) was a major concern in the 1980s and surveillance of hospital staphylococcal infections was the first activity of AGAR. Periodic surveys of the prevalence of resistance in hospital isolates of *S. aureus* have now been conducted for 15 years.[1,2] This represents the most complete prospective national description of the evolution of resistance in hospital isolates of *S. aureus*.

1. Director of Mircobiology, Queensland Health Pathology Services, Brisbane, Queensland.
2. Senior Scientist, Mircobiology and Infectious Disease, Women's and Children's Hospital, North Adelaide, South Australia.
3. Director of Microbiology and Infectious Diseases, Canberra Hospital, Garran, Australian Capital Territory.

The Australian Group for Antimicrobial Resistance is (in alphabetical order): John Andrew (Gribbles Pathology Victoria Pty Ltd, Victoria), Jan Bell (Women's and Children's Hospital, South Australia), Richard Benn, Sue Benson (St John of God Pathology, Western Australia), Susan Bradbury (Canberra Hospital, Australian Capital Territory), Keryn Christiansen, Peter Collignon, Geoff Coombs (Royal Perth Hospital, Western Australia), Marion Easton, Joan Faoagali, Clarence Fernandes (Royal North Shore Hospital, New South Wales), Graham Francis (Fremantle Hospital, Western Australia), Glenn Funnell (Concord Repatriation General Hospital, New South Wales), Sue Garland, Narelle George (QHPS, Royal Brisbane Hospital, Queensland), Gena Gonis, Iain Gosbell, Tom Gottlieb, Jacqueline Harper, Linda Joyce (St Vincent's Hospital, Victoria), PC Lee (Gribbles Pathology, South Australia), Irene Lim, Gary Lum (Royal Darwin Hospital, Northern Territory), David McGechie, Alistair McGregor (Royal Hobart Hospital, Tasmania), David Mitchell (Westmead Hospital, New South Wales), Leigh Mulgrave (PathCentre, Western Australia), Stephen Neville (South Western Area Pathology Service, New South Wales), Graeme Nimmo, Miriam Paul (Douglas Henley Moir Pathology, New South Wales), John Pearman, Hendrik Pruul (Flinders Medical Centre, South Australia), Jenny Robson (Sullivan Nicolaides Pathology, Queensland), David Rose (Nepean Hospital, New South Wales), Jacqueline Schooneveldt (QHPS, Princess Alexandra Hospital, Queensland), Denis Spelman (Clare Franklin Alfred Hospital, Victoria), Joanne Stylianopoulos, Anastasia Stylianopoulos (Royal Children's and Women's Hospitals, Victoria), John Turnidge, Alison Vickery, Mary Jo Waters, Bruce Winter (Institute of Medical and Veterinary Science, South Australia), Barbara Yan (Royal Prince Alfred Hospital, New South Wales).

Corresponding author: Dr Graeme Nimmo, Director of Microbiology, Queensland Health Pathology Service, c/– Princess Alexandra Hospital, Brisbane QLD 4102. Telephone: +61 7 3240 2389. Facsimile: +61 7 3240 5786. Email: Graeme_Nimmo@health.qld.gov.au

Figure 1. Distribution of participating teaching hospital laboratories in capital cities



The emergence of resistance in other groups of bacteria has prompted AGAR to conduct a number of organism specific surveys. An extensive study of resistance in *Haemophilus influenzae* was conducted prior to the introduction of vaccination for *H. influenzae* type b.[3] The emergence of antimicrobial resistance in *Streptococcus pneumoniae* has caused worldwide concern and AGAR has been able to demonstrate over four surveys the trend towards multiple antimicrobial resistance and penicillin resistance in pneumococci in Australia.[4,5] Ongoing surveys of antimicrobial resistance in enterococci have also been conducted in response to increasing interest in vancomycin-resistant enterococci. Changing patterns of resistance in the *Enterobacteriaceae* and the emergence of extended-spectrum ß-lactamases (ESBL) led to surveys of resistance trends in *Escherichia coli* and *Klebsiella pneumoniae*.

Methods

The AGAR surveys have been conducted prospectively with standardised methods for data collection, isolate collection and laboratory examination. Collections consisting of unique clinically significant sequential isolates, excluding duplicates and screening isolates, have been stored for future reference. Methods for identification, susceptibility testing and typing have been described in detail elsewhere.[1,2,3,4,5] Standard quality control organisms were included in each susceptibility testing batch with results validated by a coordinating laboratory.

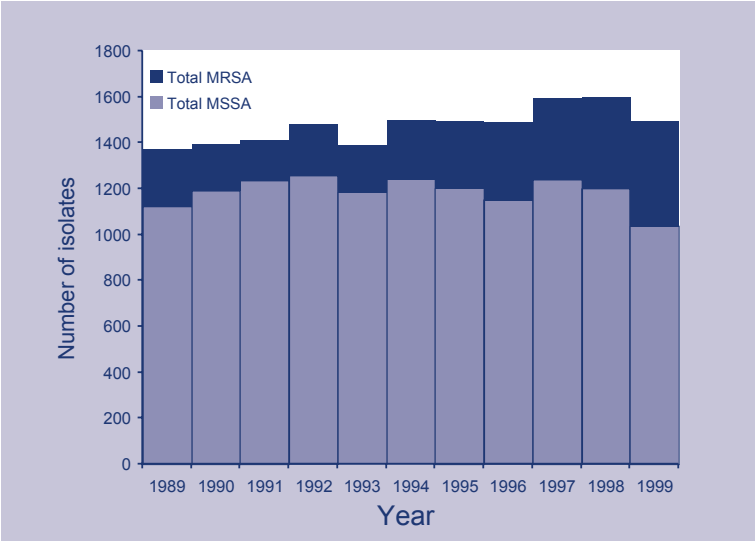
Results

Resistance in *Staphylococcus aureus*

The first three surveys of the prevalence of resistance in teaching hospital isolates of *S. aureus* were conducted during 1986 and 1987.[1] This first national study involved 14 teaching hospital laboratories in the national capital and all mainland state capitals. The study established that the prevalence of MRSA as a proportion of clinically significant isolates of *S. aureus* was 14.4 per cent. Annual surveys were conducted from 1989 to 1999 and the results have been published[2] or submitted for publication. The total number of isolates collected in each year and the number of MRSA isolates are shown in

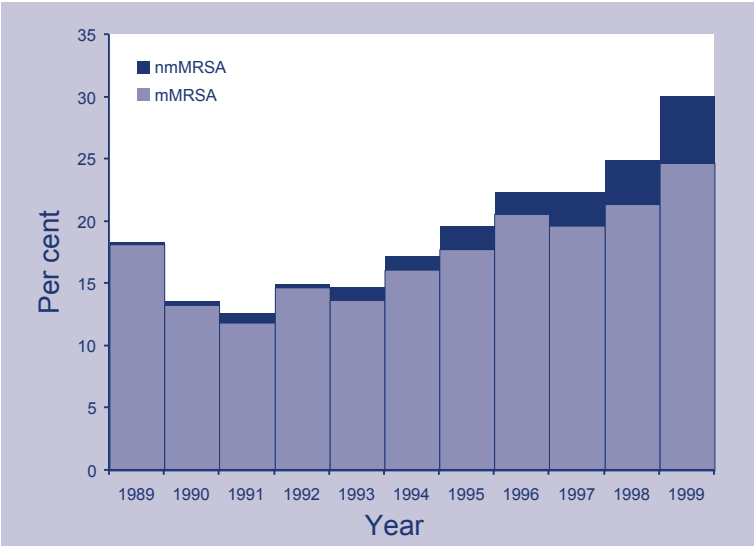
Figure 2. In the initial study most MRSA isolates were multiresistant. In the subsequent annual surveys MRSA was divided into two groups based on resistance to erythromycin, tetracycline, trimethoprim, gentamicin, rifampicin, fusidic acid, ciprofloxacin and mupirocin. Isolates which were resistant to three or more of the above were defined as multiresistant (mMRSA), and those resistant to less than three as non-multiresistant (nmMRSA). Data collected by AGAR and others showed that this latter non-multiresistant group appeared to arise more often in the community setting.[6,7,8] The trends in prevalence of mMRSA and nmMRSA are shown in Figure 3. Both show marked and sustained increases in the late 1990s.

Figure 2. Number of MRSA and MSSA isolates collected from 1989 to 1999



MRSA Methicillin-resistant Staphylococcus aureus.
MSSA Methicillin-senstive Staphylococcus aureus.

Figure 3. mMRSA and nmMRSA isolates collected from 1989 to 1999 as a proportion of all *Staphylococcus aureus* isolates



Resistance in *Haemophilus influenzae*

Thirty-four laboratories were involved in the collection of 970 isolates of *H. influenzae* between 1988 and 1990.[3] Minimal Inhibitory Concentrations (MICs) to 16 different antibiotics were determined. The overall rate of beta-lactamase production was 16 per cent but there was wide variation between the states. In Adelaide the rate was 4.5 per cent and in Canberra 28.6 per cent. There was also a marked difference between invasive strains (e.g., blood) and non-invasive strains (e.g., sputum). In invasive strains beta-lactamase production was 22.3 per cent but in respiratory tract isolates it was 35.3 per cent. Most strains were resistant to erythromycin. Variable resistance was seen to most other antibiotics with geographical differences as well as differences between invasive and non-invasive strains. In non-invasive strains the resistance to amoxicillin-clavulanate, chloramphenicol, tetracycline, trimethoprim and co-trimoxazole were 2.1 per cent, 1.8 per cent, 4.5 per cent, 12.2 per cent and 5.7 per cent respectively.

Resistance in *Streptococcus pneumoniae*

Antimicrobial resistance in *Streptococcus pneumoniae* has been monitored by the AGAR group in three survey periods, 1989, 1994 and 1999. Up to 100 consecutive clinically significant isolates were collected from each participating laboratory. All isolates collected for the 1994 and 1999 surveys had a penicillin MIC determined using Etest strips (AB Biodisk, Solna, Sweden). Erythromycin, tetracycline, chloramphenicol and co-trimoxazole were tested using disc diffusion. Penicillin resistance increased significantly between 1989 and 1994, however, this trend levelled out in 1999. Overall 86 per cent of invasive isolates and 75 per cent of non-invasive isolates were penicillin susceptible (MIC < 0.064 mg/L). High-level penicillin resistance (MIC > 1 mg/L) was found in 2.6 per cent of invasive isolates and 6.9 per cent of non-invasive isolates. Prevalence of penicillin resistance in invasive and non-invasive isolates in each state is shown in Figures 4 and 5. Multi-drug resistant strains were common with over 8 per cent resistant to three or more antimicrobial agents tested in 1994. In 1999, 6.8 per cent of invasive and 16.7 per cent of non-invasive isolates were multi-drug resistant. Another survey was conducted in 2002.

Figure 4. Proportion of penicillin resistance in *Streptococcus pneumoniae* in invasive isolates by state, 1999

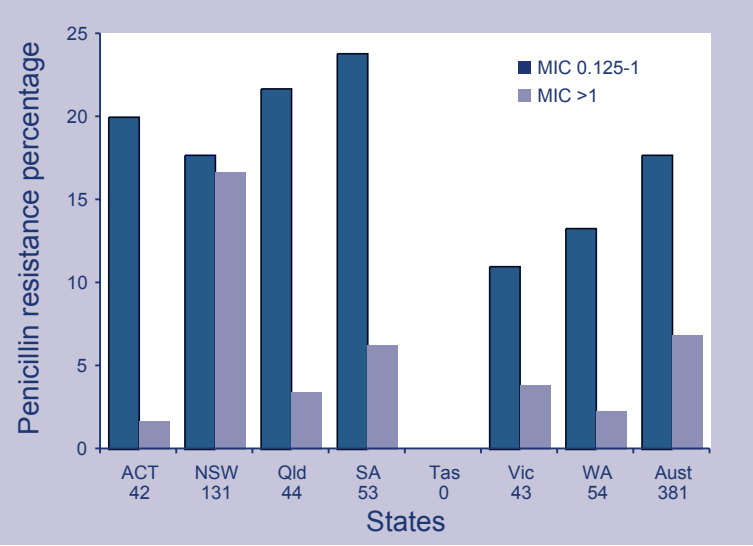
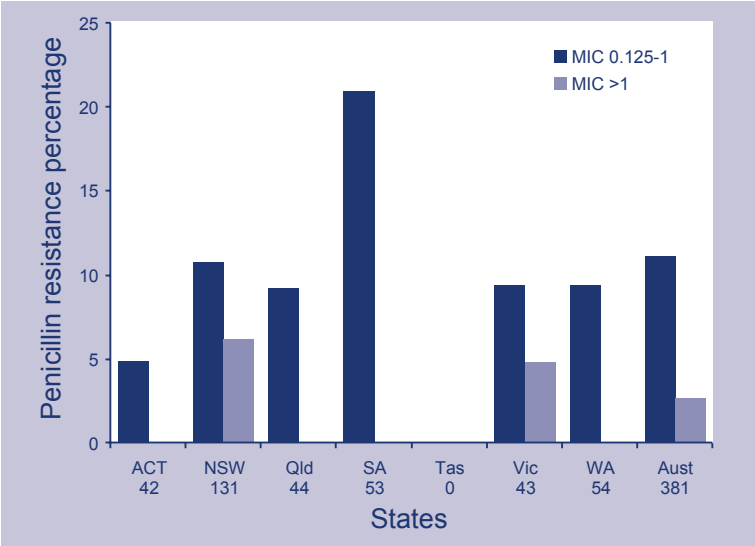


Figure 5. Proportion of penicillin resistance in *Streptococcus pneumoniae* in non-invasive isolates by state, 1999



Resistance in *enterococci*

Two surveys to study the prevalence of antimicrobial resistance in Enterococcus spp. in hospitals were conducted, one in 1995 and another in 1999. For each study period, up to 100 consecutive clinically significant strains were identified and antimicrobial susceptibility tests performed using the participating institutions routine methods. Any strain demonstrating resistance to ampicillin, vancomycin or high level aminoglycoside resistance, and all non *E. faecalis* isolates were referred to a central testing laboratory for confirmation. Correct identification of enterococci to species level was problematic. The proportion of *E. faecium* increased from 5 per cent of all isolates in 1995 to nearly 10 per cent in 1999. No vancomycin resistance was detected in the first study period, however, in 1999, six (0.3%) strains were resistant. Ampicillin resistance in *E. faecium* increased from 57 per cent in 1995 to 77 per cent in 1999. Beta-lactamase production remains uncommon, with only one ß-lactamase producing *E. faecalis* detected.

During 1999, 18 institutions collected all enterococci isolated from blood cultures. Over 370 strains were isolated, of which 74 per cent were *E. faecalis*, and 20 per cent were *E. faecium*. Vancomycin-resistance was detected in 8 per cent of all *E. faecium* isolates. All were *vanB* and were from three institutions.

Resistance in *Escherichia coli* and *Klebsiella* spp.

Surveys of resistance and multi-resistance in *Escherichia coli* and *Klebsiella* spp. have been conducted biannually since 1992. Up to 50 isolates from each species were collected from 14–20 institutions throughout Australia. MICs to 14 antimicrobial agents (from 8 drug classes) were determined using a customised conventional MicroScan broth microdilution panel (Dade Behring, West Sacramento, California). In *E. coli* ampicillin resistance has been prevalent since the beginning of surveillance at approximately 50 per cent, while non-susceptibility to amoxicillin-clavulanate has remained at under 10 per cent. Multi-resistant *E. coli* (resistance to 4 or more drug classes) were uncommon (<4%). *K. pneumoniae* with an extended-spectrum ß-lactamase phenotype were prevalent in some institutions (Figure 6). Overall 8 per cent (range 0–26%) of *K. pneumoniae* were ceftazidime resistant (MIC > 1 mg/L). While most institutions demonstrated a decline in the number of *K. pneumoniae* with ESBL phenotypes since 1992, others have shown a steady increase since 1996. The number of *E. coli* that were ceftazidime resistant has remained steady at less than 1.5 per cent since 1992 (Figure 7). Between

1992 and 1998, the rate of ceftazidime resistant *K. pneumoniae* varied between 6–10 per cent with an increasing proportion of isolates with an MIC > 8 mg/L (Figure 7). Gentamicin resistance was also common in some institutions and closely paralleled ESBLs (Figure 8). Ciprofloxacin non-susceptibility (MIC > 1 mg/L) was uncommon in *E. coli* (< 1%). Ciprofloxacin non-susceptible *K. pneumoniae* decreased from 6–7 per cent in 1992–1996 to less than 3 per cent in 1998 (Figure 9). No carbapenem resistance has been detected. An increase in co-trimoxazole resistance (MIC > 8 mg/L) was observed between 1992 and 1994 (11% to 19%), but the level of resistance has since remained steady at approximately 20 per cent (data not shown).

Figure 6. Extended-spectrum ß-lactamase phenotype in *Escherichia coli* and *Klebsiella pneumoniae* in 20 institutions, 1992 to 1998

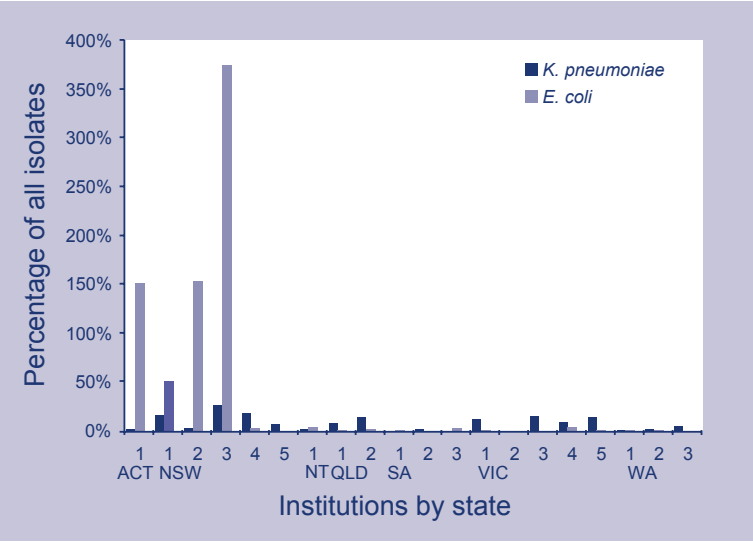


Figure 7. Proportion of ceftazidime resistance in *Escherichia coli* and *Klebsiella pneumoniae*, 1992 to 1998

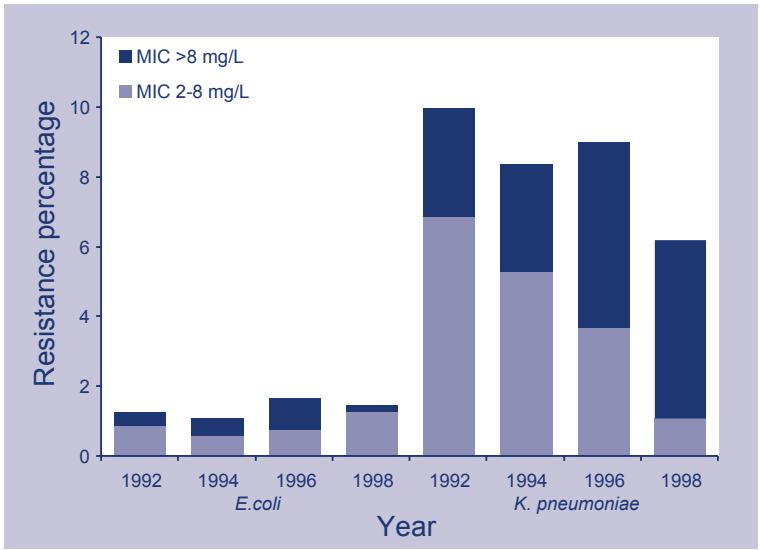


Figure 8. Proportion of gentamicin resistance in *Escherichia coli* and *Klebsiella pneumoniae*, 1992 to 1998

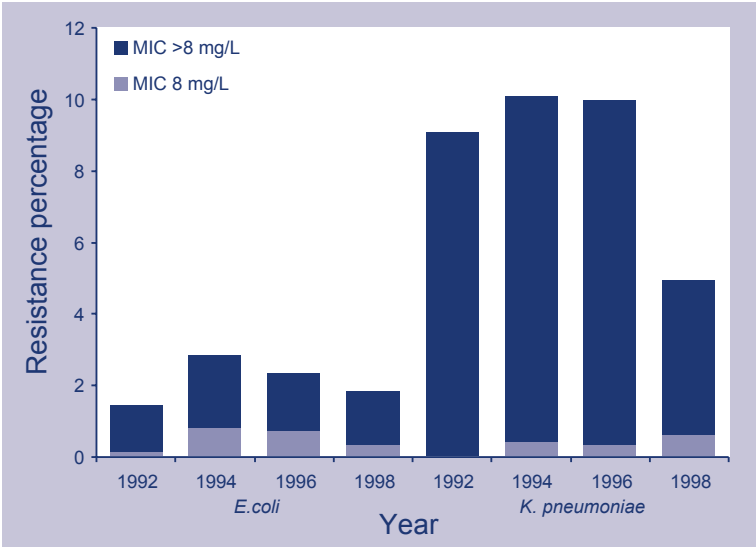
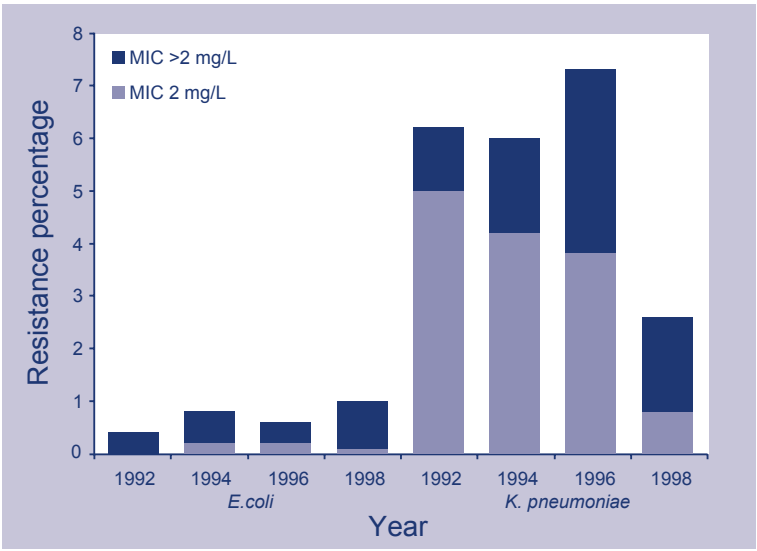


Figure 9. Proportion of ciprofloxacin resistance in *Escherichia coli* and *Klebsiella pneumoniae*, 1992 to 1998



Future directions

AGAR will continue to publish surveys of antimicrobial resistance in bacteria causing serious health problems within Australia. Organisms of interest will include *Staphylococcus aureus*, pneumococcus, *Enterococcus* spp, *E.coli, Klebsiella* spp. and *Enterobacter* spp. As significant problems emerge in other organisms they will also be subject to survey where practicable. AGAR may also test organisms other than bacteria where there is currently little or no data but potential for antimicrobial resistance to compromise clinical care (e.g., fungi).

Additional major private laboratories have joined AGAR recently so that private pathology is now represented in each mainland state. This has given AGAR the ability to conduct valid surveys of community-acquired as well as health care-associated infections. Opportunities also exist for closer liaison with other groups involved in surveillance of health care-associated infections (e.g., with Australian Infection Control Association on national surveillance of wound and blood stream infections). A collaborative approach should provide better quality national data on all aspects of infection including antimicrobial resistance. AGAR surveys to date have mainly been limited to major teaching hospitals in capital cities. While we believe those results reflect the situation in those institutions, we have not attempted any population based surveys. Recent consolidation of pathology service provision and the availability of more flexible information technology may both serve to make such surveys a more practical possibility. Matching of data from such surveys to other information such as antimicrobial consumption may also be possible in future creating a powerful tool for monitoring the effectiveness of initiatives aimed at encouraging rational prescribing.

Continued funding of AGAR is a vexed issue. While funding for the survey activities of AGAR has been primarily by the participating laboratories, one major pharmaceutical company sponsored biannual meetings of participants from 1986 to May 2002. AGAR must now identify stable ongoing sources of funds to enable it to continue its current program and where appropriate broaden the scope of its activities, for example in the area of community-acquired infection. Whether funding can be sourced from the pharmaceutical industry or from government remains to be seen. The former possibility may be problematic given the reduction in development and marketing of antimicrobials in recent years.

For 15 years AGAR has provided data on the evolution of antimicrobial resistance in major pathogens in Australia. In the future it is hoped AGAR will not only continue this important task but also broaden the range of its surveys to cover emerging resistance in all organisms of importance in community and health care-associated infection. Efforts need to be made to ensure sampling is representative of hospital and community trends, to correlate results with other relevant data and to disseminate results widely in a more timely manner.

Acknowledgment

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References

1. Turnidge J, Lawson P, Munro R, Benn R. A national survey of antimicrobial resistance in *Staphylococcus aureus* in Australian teaching hospitals. *Med J Aust* 1989;150:65–72.

2. Turnidge JD, Nimmo GR, Francis G. Evolution of resistance in *Staphylococcus aureus* in Australian teaching hospitals. *Med J Aust* 1996;164:68—71.

3. Collignon P, Bell J, MacInnes S, Gilbert G, Toohey M. A national collaborative study of resistance to antimicrobial agents in *Haemophilus influenzae* in Australian hospitals. *J Antimicrob Chemother* 1992;30:153–163.

4. Collignon P, Bell J. *Streptococcus pneumoniae*: How common is penicillin resistance in Australia? *Aust N Z J Med* 1992;22:473.

5. Collignon P, Bell J. Drug-resistant *Streptococcus pneumoniae*: The beginning of the end for many antibiotics? *Med J Aus*t 1996;164:64–67.

6. Collignon P, Gosbell I, Vickery A, Nimmo G, Stylianopoulos T, Gottlieb T. Community-acquired methicillin-resistant *Staphylococcus aureus* in Australia. *Lancet* 1998;352:146–147.

7. Nimmo GR, Schooneveldt J, O'Kane G, McCall B, Vickery A. Community acquisition of gentamicin-sensitive MRSA in south-east Queensland. *J Clin Microbiol* 2000;38:3926–3931.

8. Gosbell IB, Mercer JL, Neville SA, Crone SA, Chant KG, Jalaludin BB, *et al*. Non-multiresistant and multiresistant methicillin-resistant *Staphylococcus aureus* in community-acquired infections. *Med J Aust* 2001;174:627–630.

Australian hospital morbidity data on antibiotic resistance

Jenny Hargreaves,[1] Jenny Kok[2]

Abstract

Reports of infections with drug-resistant microorganisms are included in the National Hospital Morbidity Database (NHMD) at the Australian Institute of Health and Welfare. This database includes data on diagnoses of patients admitted to Australian hospitals, recorded using codes from the Australian version of the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), and the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification*. Reports of infections with drug-resistant microorganisms, recorded as either the patient's principal diagnosis, or as a co-morbidity or complication, increased markedly between 1994–95 (when the first reports were included) and 2000–01. Infections resistant to penicillins were the most commonly recorded. The national introduction of the Australian versions of ICD-9-CM in 1995, and of casemix-based funding and management from the mid-1990s, has possibly led to more accurate medical record documentation and improved coding of these infections and are likely explanations for the observed increase in reporting. The NHMD should be considered as a component of a national surveillance system for antibiotic resistance. Its routine data collection covers almost all hospital separations in Australia and is supported by a comprehensive national data collection infrastructure. *Commun Dis Intell* 2003;27 Suppl:S55–S60.

Keywords: hospital morbidity, antibiotic resistance

Introduction

Antibiotic resistance is a public health issue of major importance, with impacts on health costs resulting from consequent needs to use more expensive antibiotics, multiple courses of antibiotics, increased length of hospital stay, and increased morbidity and mortality.[1] Systems for resistance surveillance in human bacterial isolates seem to be well established.[1] However, efforts to reduce the occurrence and impact of antibiotic resistance, such as those coordinated by the Commonwealth Interdepartmental JETACAR Implementation Group, could usefully be additionally informed by other monitoring activities.

Hospital morbidity data are routinely collected for all patients admitted in Australian hospitals. These data, which include codes for infections with antibiotic resistant organisms, have the advantage of essentially fully covering hospital separations (discharges, deaths or changes in type of care) throughout Australia, and being supported by substantial national data collection infrastructures. These data (collated nationally as the Australian Institute of Health and Welfare's National Hospital Morbidity Database, NHMD) could therefore potentially be used as a component of a national surveillance system for antibiotic resistance. However, the nature of this data collection, and its limitations, need to be taken into consideration.

1. Head, Hospitals and Mental Health Services Unit, Australian Institute of Health and Welfare, Canberra, Australian Capital Territory
2. Hospitals and Mental Health Services Unit, Australian Institute of Health and Welfare, Canberra, Australian Capital Territory

Corresponding author: Ms Jenny Hargreaves, Head, Hospitals and Mental Health Services Unit, Australian Institute of Health and Welfare, GPO Box 570, Canberra ACT 2601. Telephone: +61 2 6244 1121. Facsimile: +61 2 6244 1299.
Email: jenny.hargreaves@aihw.gov.au.

The National Hospital Morbidity Database

The NHMD is a compilation of electronic summary records collected in admitted patient morbidity data collection systems in almost all Australian hospitals.[2] The data are provided by state and territory health authorities and are based on the agreed National Minimum Data Set for Admitted Patient Care endorsed by the National Health Information Management Group and detailed in the *National Health Data Dictionary*.[3]

The data relate to hospital episodes of care or separations (discharges, deaths or changes in type of care), compiled by the date of separation: data for 1997–98, for example, include separations from 1 July 1997 to 30 June 1998. As the records relate to separations, rather than to individual patients, a patient who had been hospitalised more than once will have more than one record in the database.

Included in the NHMD are demographic, administrative and length of stay data, and data on diagnoses, procedures and external causes of injury and poisoning. A principal diagnosis is reported for all separations and is defined as the diagnosis established after study to be chiefly responsible for occasioning the patient's episode of care in hospital.[3]

A majority of records also have one or more additional diagnoses. These are defined as conditions or complaints which either coexisted with the principal diagnosis or arose during the episode of care.[3] For diagnoses of injuries and poisonings (which can include adverse events such as nosocomial infections), 'external causes' are reported, defined as the environmental events, circumstances and conditions as the cause of injury, poisoning and other adverse effects.

Infections (such as those reported with antibiotic resistant organisms) can be recorded as the principal diagnosis or as an additional diagnosis. A secondary code is assigned (as an additional diagnosis) if the infection was caused by an antibiotic resistant organism. More than one drug-resistant organism, or more than one type of antibiotic resistance, can be reported within a single record.

Diagnoses and external causes have been assigned codes based on the International Statistical Classification of Diseases and Health Related Problems, 10th Revision, Australian Modification (ICD-10-AM)[4] since 1998-99 in four states or territories, and since 1999-00 in the other four (Table 1). From 1995-96 to the implementation of ICD-10-AM, the Australian editions of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)[5,6] were used. Various other versions of ICD-9-CM (for example, United States' versions) were used prior to 1 July 1995.

Codes for infections with antibiotic resistant organisms were available in ICD-9-CM versions used since 1994-95, but only in ICD-10-AM since 2000-01. In ICD-9-CM, infections with drug-resistant organisms were classified and coded to V09 (Infection with drug-resistant microorganism), with sub-categories available for different types of antibiotic resistance. In ICD-10-AM, a single code for drug resistance of any type (Z06) was available for data from 1 July 2000,[7] and separate codes for multidrug-resistant *Staphylococcus aureus* and vancomycin resistant enterococci were included from July 2002.[8]

Reports of infections with drug-resistant microorganisms

Between 1994-95 and 1997-98, there were marked increases in reports of infections with drug-resistant microorganisms, and of hospital separations for which they were reported (Table 2). The most common type of antibiotic resistance reported was resistance to penicillins. Reports continued to increase (by 16%) in 1998–99 for the four jurisdictions that continued to use ICD-9-CM in that year (Queensland, Western Australia, South Australia and Tasmania) (data not shown). Nationally, there was a decline between 1997-98 and 1998-99, reflecting the introduction of the first edition of ICD-10-AM (which did not include a relevant code) in four jurisdictions from July 1998. In 2000-01 (in which the second edition of ICD-10-AM was used, with a relevant code), there were 21,704 separations reported nationally with infections with drug-resistant organisms, 25 per cent more than for 1997–98.

Table 1. International classification of disease codes used for infection with drug-resistant microorganisms

ICD version	Edition	Date of effect	Codes	Description
ICD-9-CM Australian version	First	1 July 1995*	V09.0	Infection with microorganisms resistant to penicillins
	Second	1 July 1996	V09.1	Infection with microorganisms resistant to cephalosporins and other ß-Lactam antibiotics
			V09.2	Infection with microorganisms resistant to macrolides
			V09.3	Infection with microorganisms resistant to tetracyclines
			V09.4	Infection with microorganisms resistant to aminoglycosides
			V09.5	Infection with microorganisms resistant to quinolones and fluoroquinolones
			V09.50	Without mention of resistance to multiple quinolones and fluroquinolones
			V09.51	With resistance to multiple quinolones and fluoroquinolones
			V09.6	Infection with microorganisms resistant to sulfonamides
			V09.7	Infection with microorganisms resistant to other specified anti-mycobacterial agents
			V09.70	Without mention of resistance to multiple anti-mycobacterial agents
			V09.71	With resistance to multiple anti-mycobacterial agents
			V09.8	Infection with microorganisms resistant to other specified drugs
			V09.80	Without mention of resistance to multiple drugs
			V09.81	With resistance to multiple drugs
			V09.9	Infection with microorganisms resistant to unspecified drugs
			V09.90	Without mention of multiple drug resistance
			V09.91	With multiple drug resistance
ICD-10-AM	First	1 July 1998†		No codes to indicate infection with drug-resistant microorganisms
	Second	1 July 2000	Z06	Infection with drug-resistant microorganism
	Third	1 July 2002	Z06.1	Infection with multidrug-resistant *Staphylococcus aureus*
			Z06.2	Infection with vancomycin resistant enterococci
			Z06.8	Infection with other drug-resistant microorganism
			Z06.9	Infection with drug-resistant microorganism, unspecified

* Prior to 1 July 1995, ICD-9 and various versions of the United States' ICD-9-CM were used.

† ICD-10-AM first edition was used in New South Wales, Victoria, the Australian Capital Territory and the Northern Territory from 1 July 1998, and in all states and territories from 1 July 1999.

Table 2. Infections with drug-resistant microorganisms reported to the National Hospital Morbidity Database, Australia, 1994–95 to 2000–01

ICD-9-CM Code	Description	1994-95	1995-96	1996-97	1997-98	1998-99†	2000-01
V09.0	Penicillins	2,160	5,901	9,764	12,592	6,532	‡
V09.1	Cephalosporins and other ß-Lactam antibiotics	68	560	1,090	1,459	827	‡
V09.2	Macrolides	9	228	450	544	325	‡
V09.3	Tetracyclines	46	180	385	494	290	‡
V09.4	Aminoglycosides	32	234	331	451	282	‡
V09.5	Quinolones and fluoroquinolones						
V09.50	Without mention of resistance to multiple quinolones and fluroquinolones	7	48	137	166	87	‡
V09.51	With resistance to multiple quinolones and fluoroquinolones	0	39	86	150	41	‡
V09.6	Sulfonamides	35	75	90	85	19	‡
V09.7	Other specified anti-mycobacterial agents						
V09.70	Without mention of resistance to multiple anti-mycobacterial agents	8	28	34	43	22	‡
V09.71	With resistance to multiple anti-mycobacterial agents	9	51	77	164	67	‡
V09.8	Other specified drugs						
V09.80	Without mention of resistance to multiple drugs	20	362	780	1,005	555	‡
V09.81	With resistance to multiple drugs	148	850	1,782	2,283	1,001	‡
V09.9	Unspecified drugs						‡
V09.90	Without mention of multiple drug resistance	19	100	87	131	100	‡
V09.91	With multiple drug resistance	59	416	838	1,157	643	‡
Z06 (ICD-10-AM)	Infection with drug-resistant micro-organism	‡	‡	‡	‡	‡	21,824
	Total infections with drug-resistant microorganisms	2,620	9,072	15,931	20,724	10,791	21,824
	Total separations with infections with drug-resistant organisms	2,451	7,752	13,412	17,350	8,920	21,704

* See Table 1 for information on relevant ICD codes. There was no code available for 1999-00.

† In 1998-99, only Queensland, South Australia, Western Australia and Tasmania were using ICD-9-CM.

‡ Not applicable.

Data for 2000-01 provides an illustration of the other information recorded for the separations for which infections with drug-resistant microorganisms were reported. For example, males accounted for more separations (12,094 separations, 55.7%) than females (9,610 separations). Fifty-six per cent (12,252 separations) were for patients aged over 65 years, with highest numbers reported for males in the 75-79 years age group (1,731 separations) and for females aged over 85 years (1,536 separations).

The principal diagnoses most frequently reported were infection following a procedure, not elsewhere classified (code T81.4, 1,309 separations) and care involving a rehabilitation procedure, unspecified (code Z50.9, 1,289 separations). The organisms (within ICD-10-AM Chapter 1 infectious and parasitic diseases) most commonly reported were *Staphylococcus aureus* (code B95.6, 13,894 separations) and *Pseudomonas* (code B96.5, 2,444 separations).

The complications of surgical and medical care (ICD-10-AM codes T80-T88) reported most frequently as principal or additional diagnosis for these separations were infection following a procedure, not elsewhere classified (code T81.4, 3,813 separations) and infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts (code T82.7, 1,096 separations). External causes relating to complications (ICD-10-AM codes Y60–Y84) that were commonly reported with infections with drug-resistant microorganisms included surgical operation with implant of artificial internal device (code Y83.1, 1,419 separations) and other surgical procedures (code Y83.8, 1,352 separations).

Discussion

As noted above, the NHMD covers essentially all admissions to Australian hospitals, and is supported by substantial national data collection infrastructures. It includes a range of information that could potentially be used to supplement other antibiotic resistance surveillance activities.

However, the data on infections with drug-resistant microorganisms collected to date is of limited use. The antibiotic resistance codes available in ICD-9-CM may not have matched priority needs for surveillance data, without, for example, a code specific for multidrug-resistant *Staphylococcus aureus*. The first edition of ICD-10-AM (used from July 1998) did not include any codes for antibiotic resistance, and the second edition's single code (used from July 2000 to June 2002) is also unlikely to suit surveillance needs.

The third edition of ICD-10-AM may prove more suitable for monitoring of infections with drug-resistant microorganisms, with its specific codes for infections with multidrug-resistant *Staphylococcus aureus* and vancomycin resistant enterococci. It will be in use from July 2002 to June 2004 (with 2002–03 data available nationally from July 2004), and coders are to be guided in the use of the codes with definitions and examples of the correct coding in an accompanying Australian Coding Standard.

Limitations of the data collected to date also arise from the changes in codes available for infections with drug-resistant microorganisms since 1994–95, which mean that comparison of the data over time is currently problematic. In addition, the increase in separations with antibiotic resistant organisms since 1994-95 is unlikely to represent increased numbers of these infections with these organisms. Improvements in coding quality, associated with the introduction of casemix-based funding and management, the introduction of the Australian editions of ICD-9-CM, major national and state/territory coder and clinician education initiatives and coding audit activities could have played significant roles in the increased reporting of these infections.

Importantly, coding of antibiotic resistance is largely dependant on the accuracy and completeness of entries made by clinical and laboratory staff in patients' medical records. Definitions for drug resistance have not been included within ICD-10-AM, so coding is likely to have reflected the definitions used for clinician documentation of the drug resistance in the medical record. Hence, it is not certain that all the reported resistance was laboratory-confirmed. In addition, although coders are instructed to code infectious organisms only if a clinically significant infection has been documented, some colonisations may also have been included.

Association of the antibiotic resistance information with the principal diagnosis, additional diagnosis or the external cause information in a record cannot be assumed. More detailed analysis of the data (using information on the sequencing of the codes) could allow associations to be clarified, as would better linkage of these data within separation records.

Hence, whilst increased numbers of reports provide some indication of increased coding quality in relation to infections with drug-resistant microorganisms, and the introduction of the new codes for 2002 may better reflect surveillance needs, the use of these data will continue to require caution, and further refinements to data collection may be required. ICD-10-AM is revised every two years, so refinement of relevant codes and coding standards could be sought as necessary. In addition, the Australian Council for Safety and Quality in Health Care is working to improve the use of morbidity data sets for adverse event monitoring,[9] and this work could encompass enhancements relating to infections with antibiotic resistant organisms. With such alterations, hospital morbidity data collections such as the NHMD could be considered as potential components of a national surveillance system for antibiotic resistance in Australia.

References

1. Joint Expert Technical Advisory Committee on Antibiotic Resistance 1999. The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth Department of Health and Aged Care and Commonwealth Department of Agriculture, Fisheries and Forestry.
2. Australian Institute of Health and Welfare (AIHW) 2002. Australian hospital statistics 2000–01. AIHW Cat. No. HSE 20 (Health Services Series). Canberra: AIHW.
3. Australian Institute of Health and Welfare (AIHW) 2002. National health data dictionary version 11. AIHW Cat. No. HWI 36. Canberra: AIHW.
4. National Centre for Classification in Health 1998. International statistical classification of diseases and related health problems, 10th revision, Australian modification. First edition. Sydney: University of Sydney.
5. National Coding Centre 1995. The Australian version of the International Classification of Diseases, 9th Revision, Clinical modification (ICD-9-CM), first edition. Sydney: University of Sydney.
6. National Coding Centre 1996. The Australian version of the International Classification of Diseases, 9th Revision, Clinical modification (ICD-9-CM), second edition. Sydney: University of Sydney.
7. National Centre for Classification in Health 2000. International statistical classification of diseases and related health problems, 10th revision, Australian modification. Second edition. Sydney: University of Sydney.
8. National Centre for Classification in Health 2002. International statistical classification of diseases and related health problems, 10th revision, Australian modification. Third edition. Sydney: University of Sydney.
9. Australian Council for Safety and Quality in Health Care. Safety through action. Third report to the Australian Health Ministers' Conference 19 July 2002.

SENTRY Antimicrobial Surveillance Program Asia-Pacific region and South Africa

Jan Bell,[1] John Turnidge[2]

Abstract

The SENTRY Antimicrobial Surveillance Program was initiated in January 1997 and was designed to monitor the predominant pathogens and antimicrobial resistance for both nosocomial and community-acquired infections globally by using validated, reference-quality identification and susceptibility testing methods performed in a central laboratory. Consecutive bacterial or fungal isolates, deemed clinically significant by local criteria, are forwarded to the local reference laboratory from various study objectives. The major objectives include blood stream infections, community-acquired respiratory tract infections (*Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*), pneumonias in hospitalised patients, skin and soft tissue infections, and urinary tract isolates from hospitalised patients. In 2001, special objectives were introduced to examine gastroenteritis pathogens and ß-haemolytic streptococcal isolates. Over 22 nations participate in SENTRY surveillance globally. The Women's and Children's Hospital, Adelaide has been the reference centre for the Asia-Pacific region and South Africa since 1998, and three other Australian institutions, from Brisbane, Perth, and Adelaide, are part of the global network. All isolates received from our region are tested against up to 29 antimicrobial agents using custom-made broth microdilution panels. The data generated from SENTRY allows Australia to compare our antimicrobial resistance patterns and trends with our regional neighbours. *Commun Dis Intell* 2003;27 Suppl:S61–S66.

Keywords: antimicrobial surveillance

Introduction

Surveillance programs are necessary to identify changes in the spectrum of microbial pathogens causing serious infection and to monitor trends in antimicrobial resistance patterns in nosocomial and community-acquired infections.[1,2] The information gleaned from surveillance efforts is integral to the design of empirical approaches to the therapy of serious infection and also to defining appropriate control measures for antimicrobial-resistant pathogens.[1] Such information has been provided in recent years by programs such as the National Nosocomial Infection Surveillance (NNIS) system,[3] the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) program, and the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) project.[4] Australia currently has no formal mechanism for national antimicrobial resistance surveillance. The National Antimicrobial Resistance Surveillance Program (NARSP) was set up in 1991[1] but funding and contribution has been intermittent. Other surveillance is also being conducted on targeted pathogens by the Australian Group on Antimicrobial Resistance. These programs have been limited by their focus on nosocomial infections (NNIS and SCOPE) and by the lack of validated identification and antimicrobial susceptibility testing performed in a central laboratory (NNIS, ICARE and NARSP).

The SENTRY Antimicrobial Surveillance Program was initiated in January 1997 and was designed to monitor the predominant pathogens and antimicrobial resistance for both nosocomial and community-acquired infections globally by using reference quality identification and susceptibility testing methods performed in a central laboratory.

1. Microbiology and Infectious Diseases, Women's and Children's Hospital, Adelaide, South Australia
2. Director of Microbiology and Infectious Diseases, Women's and Children's Hospital, Microbiology Department, North Adelaide, South Australia

Corresponding author: Ms Jan Bell, Microbiology and Infectious Diseases, Women's and Children's Hospital, Adelaide SA 5006. Telephone: +61 8 8161 6359. Facsimile: +61 8 8161 6051. Email: bellj@mail.wch.sa.gov.au

Methods

Consecutive bacterial or fungal isolates, deemed clinically significant by local criteria, are forwarded to the local reference laboratory from five study objectives (Table 1). SENTRY sentinel sites for the Asia-Pacific and South Africa region (APAC) are shown in Table 2. The Women's and Children's Hospital, Adelaide has been the reference centre for the SENTRY-APAC since 1998. Recent publications from the SENTRY-APAC group have appeared elsewhere.[5,6,7,8,9,10,11,12] All isolates were tested against more than 25 antimicrobials by the broth microdilution method using commercially prepared trays (TREK™ Diagnostic Systems Limited, United Kingdom), according to National Committee for Clinical Laboratory Standards (NCCLS).[13] Breakpoints for resistance were those recommended by the NCCLS.[14] During the first four years, over 21,500 isolates from our region were tested.

Table 1. Major objectives under SENTRY surveillance, 1998 to 2001

Objective	Infections and organisms
A	Blood stream infections (bacteria and yeast)
B	Community-acquired respiratory tract infections (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*)
C	Pneumonias in hospitalised patients
D	Skin and soft tissue infections from hospitalised patients
E	Urinary tract infections in hospitalised patients
Special objectives (2001)	
G	Pathogens causing gastroenteritis
H	ß-haemolytic *Streptococci*
I	Pathogens from infected intensive care patients
NM	*Neisseria meningitidis*

Table 2. SENTRY sentinel sites (Asia-Pacific Region and South Africa)

Country	Site location
Australia	Princess Alexandra Hospital, Brisbane; Royal Perth Hospital, Perth; Royal Adelaide Hospital, Adelaide; Women's and Children's Hospital, Adelaide
Mainland China	Beijing Medical University, Beijing; First Municipal Peoples Hospital of Guangzhou, Guangzhou; Guangzhou Medical College First Affiliated Hospital, Guangzhou
Hong Kong China	Queen Mary Hospital, Hong Kong
Japan	Kitasato University Hospital, Kitasato; Nagasaki University Hospital, Nagasaki; Teikyo University Hospital, Tokyo
Philippines	Mataki Medical Centre, Manila
Singapore	Singapore General Hospital (till 1999); Tan Tock Seng Hospital (since 2000)
Taiwan	Chang Gung Memorial Hospital, Taoyuan; National Taiwan University Hospital, Taipei; Veterans General Hospital, Taipei
South Africa	Drs du Buisson, Bruinette and Partners, Johannesburg

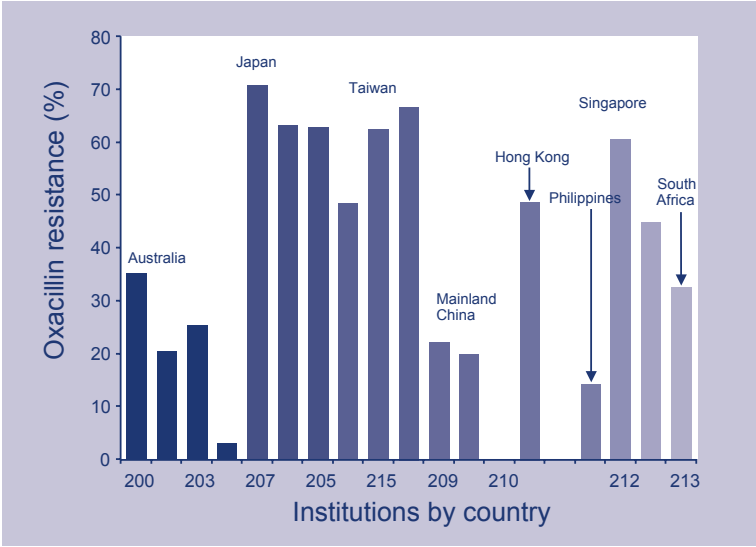
Results

A snapshot of some key findings from our region is as follows:

Oxacillin-resistant *Staphylococcus aureus*

Oxacillin-resistant *Staphylococcus aureus* (ORSA) comprised more that 44 per cent of all *S. aureus* isolates from 17 of the 19 institutions participating since 1998. There is considerable regional variation in the prevalence of ORSA in our region. The prevalence of ORSA from blood stream infections from isolates collected from 1998 to 2001 is shown in Figure 1. Only one glycopeptide-intermediate (vancomycin MIC 8 mg/L) strain, from Hong Kong, has been detected to date.

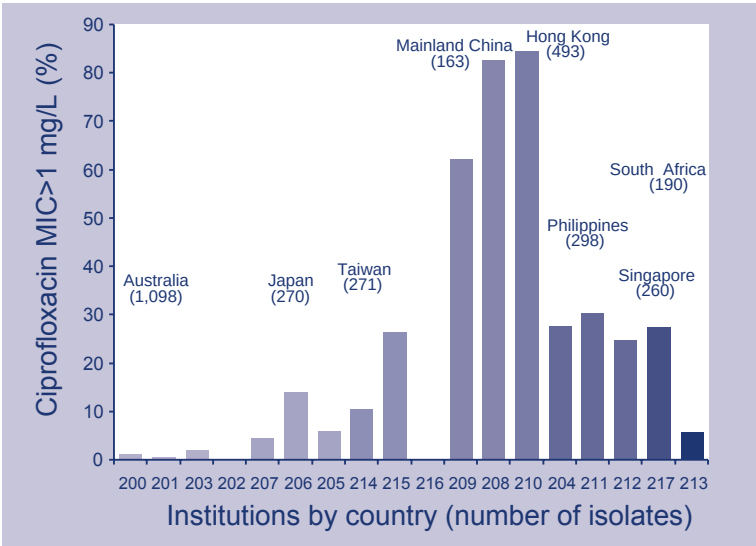
Figure 1. Oxacillin-resistant *Staphylococcus aureus* blood stream infections, 1998 to 2001



Fluoroquinolone resistance

There were significant levels of fluoroquinolone resistance. The one exception is Australia where quinolone use in the community has been quite restricted. In the other countries there are high levels of resistance demonstrable in *Enterobacteriaceae*, non-fermentative Gram-negatives and oxacillin-resistant *S. aureus*. For some countries, the prevalence of ciprofloxacin resistance in *Enterobacteriaceae* is amongst the highest in the world. The prevalence of ciprofloxacin non-susceptible (MIC > 1 mg/L) *Escherichia coli* is shown in Figure 2.

Figure 2. Prevalence of ciprofloxacin non-susceptible *Escherichia coli*, 1998 to 2001



Respiratory tract pathogens

Our region has some of the highest rates of penicillin resistance in *Streptococcus pneumoniae* in the world. Resistance was more prevalent in isolates from patients with respiratory tract infections (Figure 3) than those with blood stream infections (Figure 4). High-level resistance (MIC > 1 mg/L) was common in all participating countries except the Philippines, where *S. pneumoniae* were rarely recovered.

Figure 3. Respiratory tract isolates for penicillin resistant *Streptococcus pneumoniae*, 1998 to 2001

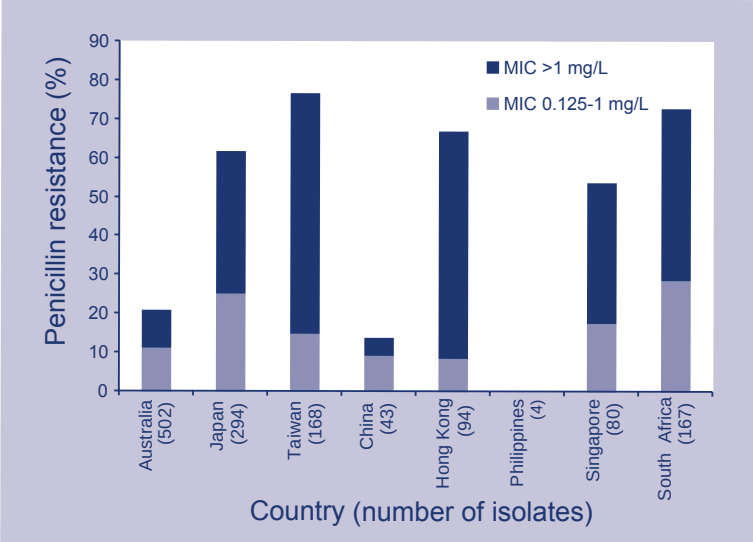
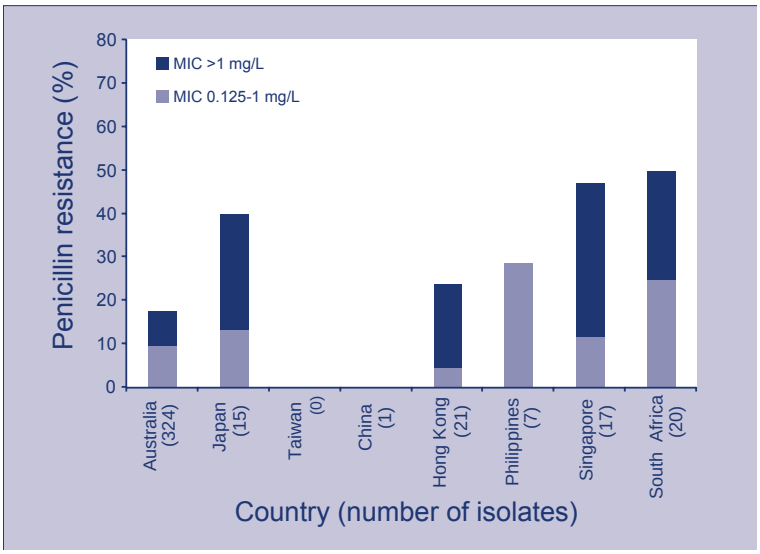


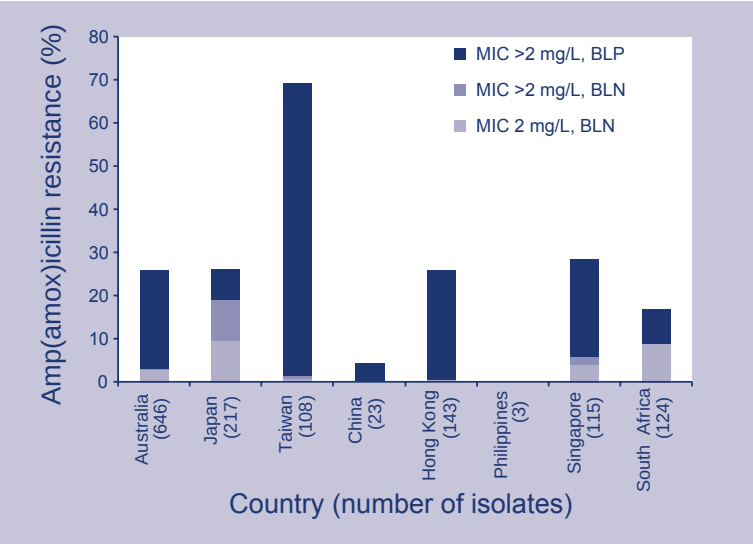
Figure 4. Penicillin resistant *Streptococcus pneumoniae*, blood stream isolates, 1998 to 2001



Twenty-eight *S. pneumoniae* isolates, 15 of 130 (11.5%) from Hong Kong, 8 of 215 (3.7%) from one institution in Australia, 4 of 201 (2%) from two institutions in Japan and one from China, demonstrated high level resistance to fluoroquinolones (defined as an MIC > 32 mg/L). All isolates were resistant to all the recent agents (gatifloxacin, trovofloxacin, grepafloxacin, ofloxacin, levofloxacin).

Of interest is the increasing incidence of ampicillin-resistant ß-lactamase negative *Haemophilus influenzae* (BLNAR) (Figure 5). In Japan, these isolates account for nearly 10 per cent of all respiratory isolates and 58 per cent of those strains that were ampicillin resistant. BLNAR have now been detected in Australia. Alarming levels of resistance are seen in Taiwan, with many of the isolates being multi-drug resistant.

Figure 5. Respiratory tract isolates for amp(amox)icillin resistant *Haemophilus influenzae*, 1998 to 2001



Extended-spectrum ß-lactamases

Australia had the lowest incidence of extended-spectrum ß-lactamase (ESBL) producing *K. pneumoniae* and *E. coli* in the APAC region. Over 30 per cent of *K. pneumoniae* isolates from patients with blood stream infection from Mainland China, Philippines, Singapore and South Africa were confirmed as having an ESBL (Table 3). Mainland China and Hong Kong China also had significant numbers of ESBL-producing *E. coli* (24% and 13% respectively). Although multi-resistance was common, no carbapenem resistance was detected. More than one third of isolates were also resistant to cefoxitin, consistent with them also possessing Class 1 cephalosporinases. Nearly half of these isolates were from a single institution, and in two species, (*E. coli* and *K. pneumoniae*) suggesting both clonal dissemination and plasmid transfer of resistance. Over 75 per cent of cefoxitin-resistant ESBL isolates were found in three countries (Philippines, China and Hong Kong).[15]

Table 3. Variation in rates of extended spectrum ß-lactamase production among *Escherichia coli* and *Klebsiella pneumoniae* blood isolates by region at SENTRY-APAC centres, 1998 to 1999

Country	*E. coli*		*K. pneumoniae*	
	n	%*	n	%*
Australia	286	0.0	51	2.0
Hong Kong	138	13.0	38	7.9
Japan	74	1.4	44	15.9
Mainland China	75	24.0	23	65.2
Philippines	65	6.2	44	31.8
Singapore	50	4.0	39	41.0
South Africa	30	3.3	22	45.5
Taiwan	29	13.8	56	5.4
Total	**774**	**6.1**	**290**	**24.1**

* Reduction in ceftazidime, ceftriaxone or aztreonam MIC in presence to 4 mg/L clavulanate.

Discussion

The global nature of antimicrobial resistance requires that resistance data from both developed and developing countries be collected. New resistance phenotypes remain on the rise while multidrug-resistant pathogens continue to spread. The data generated from SENTRY allows Australia to compare our antimicrobial resistance patterns and trends with our regional neighbours, who have some of the highest reported resistances in the world. Ongoing surveillance such as obtained by the SENTRY program is essential to monitor the emerging resistances, and also to evaluate new antimicrobial agents as they become available.

Acknowledgment

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References

1. Turnidge J, Bell J, Collignon P. The battle against antibiotic resistance. *Microbiology Australia* 1996;17:27-31.
2. Jones RN. The emergent needs for basic research, education, and surveillance of antimicrobial resistance. Problems facing the report from the American Society for Microbiology Task Force on Antibiotic Resistance. *Diagn Microbiol Infect Dis* 1996;25:153-161.
3. Emori TG, Culver DH, Horan TC, Jarvis WR, White JW, Olson DR, *et al*. National nosocomial infections surveillance system (NNIS): description of surveillance methods. *Am J Infect Control* 1991;19:19–35.
4. Archibald L, Phillips L, Monnet D, McGowan JE, Tenover F, Gaynes R. Antimicrobial resistance in isolates from inpatients and outpatients in the United States: increasing importance of the intensive care unit. *Clin Infect Dis* 1997;24:211–215.
5. Diekema DJ, Pfaller MA, Turnidge J, Verhoef J, Bell J, Fluit AC, *et al*. Genetic relatedness of multidrug-resistant, methicillin (oxacillin)-resistant *Staphylococcus aureus* bloodstream isolates from SENTRY antimicrobial resistance surveillance centers worldwide, 1998. *Microb Drug Resis* 2000;6:213–221.
6. Turnidge JD, Bell JM. Methicillin-resistant *Staphylococcus aureus* evolution in Australia over 35 years. *Microb Drug Resis* 2000;6:223–229.
7. Diekema DJ, Pfaller MA, Schmitz FJ, Smayevski J, Bell JM, Jones RN, *et al*. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe and the western Pacific for the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin Infect Dis* 2001;32 Suppl 2:S114–S132.
8. Bell JM, Turnidge JD, SENTRY APAC. High prevalence of oxacillin-resistant *Staphylococcus aureus* isolates from hospitalised patients in Asia-Pacific and South Africa: Results from the SENTRY Antimicrobial Surveillance Program, 1998–1999. *Antimicrob Agents Chemother* 2002;46:879–881.
9. Bell JM, Turnidge JD, Gales AC, Pfaller MA, Jones RN, the SENTRY APAC Study Group. Prevalence of extended spectrum beta-lactamase (ESBL)-producing clinical isolates in the Asia-Pacific region and South Africa: regional results from SENTRY Antimicrobial Surveillance Program, (1998–99). *Diagn Microbiol Infect Dis* 2002;42:193–198.
10. Bell JM, Turnidge JD, Jones RN, the SENTRY Regional Participants Group. Antimicrobial resistance trends in community-acquired respiratory tract pathogens in the Western Pacific Region and South Africa: report from the SENTRY Antimicrobial Surveillance Program, (1998–1999) including an *in vitro* evaluation of BMS284756. *Int J Antimicrob Agents* 2002;19:125–132.
11. Bell JM, Turnidge JD, Pfaller MA, Jones RN. *In vitro* assessment of gatifloxacin spectrum and potency tested against *Haemophilus influenzae, Moraxella catarrhalis*, and *Streptococcus pneumoniae* isolates from the Asia-Pacific component of the SENTRY Antimicrobial Surveillance Program (1998–1999). *Diagn Microbiol Infect Dis* 2002;43:315–318.
12. Turnidge JD, Bell JM, Biedenbach DJ, Jones RN. Pathogen occurrence and antimicrobial resistance trends among urinary tract infection isolates in the Asia-Western Pacific Region: Report from the SENTRY Antimicrobial Surveillance Program, 1998–1999. *Int J Antimicrob Agents* 2002;20:10–17.
13. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved Standard–Fifth Edition [M7–A5]. National Committee for Clinical Laboratory Standards, Wayne, Pennsylvania, 2000.
14. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing; Twelfth informational supplement [M100–S12]. National Committee for Clinical Laboratory Standards, Wayne, Pennsylvania, 2002.
15. Bell JM, Turnidge JD, the SENTRY Western Pacific Plus Participants. Paper C2–1477 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, 26–29 September 1999, San Francisco.

TSN® Database Australia, a new tool to monitor antimicrobial resistance in Australia

John Turnidge,[1] Laurence R McCarthy,[2] Ronald N Master,[3] Douglas E Kepner,[4] James Weslock[5]

Abstract

An electronic network of Australian microbiology laboratories was established to monitor the emergence and occurrence of antimicrobial resistance among clinically relevant bacteria. It is believed that the data network collected approximately 42 per cent of all antibacterial susceptibility test results generated by Australian laboratories. The network comprised 94 hospitals and 9 private commercial laboratories. Selected data elements were extracted and electronically transmitted to a central location. Upon receipt, all data were first normalised and thereafter examined for errors. Duplicate results for the same patient were identified to prevent skewing of the data toward resistance. All data passing quality assessment was staged for release of a new database release that occurred monthly. Unusual test results were first validated prior to their inclusion into the database. Using an Internet-based query tool, individual institutions could query their own data, but could only query aggregated data for other regional or national analyses. Individual patient results could be examined nor could the results of any individual institution other than their own. As of March 2002, TSN Database Australia contained 14,648,752 test results, from 2,000,394 strains (453 different taxa) and 1,213,605 patients. Since the same database concept has been established in 10 other countries (United States of America, Europe, and Canada), observations made in Australia may be compared to those observed elsewhere in the world. This article will describe TSN in greater detail, describe the query tool and some of the analyses that are possible. *Commun Dis Intell* 2003;27 Suppl:S67–S69.

Keywords: antimicrobial resistance, TSN database, monitoring

Introduction

Several years before the beginnings of TSN in Australia, the infectious disease community, concerned about growing antimicrobial resistance formed a program called the National Antibiotic Resistance Surveillance Program (NARSP). This program was directed by a NARSP committee, a group of leading experts in the field of infectious diseases including government representation from the Commonwealth Department of Health and Ageing. This national program was constructed to act as an antibiotic resistance surveillance system capturing susceptibility testing results from approximately 50 private and public infectious disease testing laboratories across the country. The program was voluntary and with government funding the program was able to compile data, mostly manually and publish the combined data yearly (usually from 1–2 years earlier). The testing sites involved with the NARSP program acted as the foundation for the automation of the surveillance system (TSN Database Australia).

1. Director of Microbiology and Infectious Diseases, Women's and Children's Hospital, Microbiology Department, North Adelaide, South Australia
2. President and CEO, Focus Technologies Inc, Virginia, United States of America
3. Director, TSN Operations, Focus Technologies Inc, Virginia, United States of America
4. TSN Microbiology Analyst, Focus Technologies Inc, Virginia, United States of America
5. Country Manager Australasia and Canada, Focus Technologies Inc, Ontario, Canada

Corresponding author: Associate Professor John Turnidge, Director of Microbiology and Infectious Diseases, Women's and Children's Hospital, Microbiology Department, 72 King William Road North Adelaide SA 5006. Telephone: +61 8 8161 6873.
Email: turnidgej@wch.sa.gov.au.

In 1998, the NARSP committee was contacted by Focus Technologies (owners of TSN) and consulted on the development of an automated resistance surveillance system. The goal was to capture a balanced dataset: a representative percentage of the susceptibility testing to effectively monitor antimicrobial resistance in Australia. NARSP suggested the sites to be approached and provided guidance on the development of TSN Database Australia in the very early stages. Subsequently, Focus formed a TSN Australian Advisory Board to assist in the process. The pool of approximately 50 NARSP testing laboratories were reviewed and 30 geographically and demographically diversified TSN testing sites (e.g., public, private, hospital and pathology services) were selected across Australia. The TSN data were divided into 4 distinct regional datasets as was advised by the TSN Australian Advisory Board. Focus incorporated a sufficient number of sites in each region to provide a representative regional sample and to maintain TSN site anonymity.

Each testing site was visited and received a formal presentation about the goals and details of the TSN program. Interested sites were required to complete a comprehensive evaluation questionnaire to establish the use of acceptable microbiology practices, quality control and their information technology capabilities in providing the necessary data for capture. Upon an acceptable evaluation review, each testing laboratory signed a written TSN Participation Agreement indicating their commitment to the program and terms for data and site confidentiality. In all, 30 sites signed on. Sites not signing on were usually unable to provide susceptibility testing data electronically through a Laboratory Information System and were subsequently considered ineligible. Replacement sites from the original list of 30 were chosen with the consultation of TSN Advisory Board members.

Installation of TSN in Australian sites began in August 1998. The national TSN Database Australia was released to participants in November 2000. At the time of writing it was estimated that TSN Database Australia captured approximately 42 per cent of all susceptibility testing done in the country annually.

Methods

The participant's susceptibility results were gathered from either a laboratory information system or directly from an automated susceptibility testing instrument through an extraction program. Patient privacy and the anonymity of each institution's data were ensured by encryption of files prior to transmission and the exclusion of patient names. Each institution's data was maintained anonymously within the TSN database. Only the submitting institution had access to its own segregated data. All files were further encrypted prior to transmission to Focus Technologies in Herndon, Virginia USA.

In Herndon, VA the data were normalised. Normalisation subjects the data to a number of processes including validating each line of data, and cross referencing the significant parts of each data line with a master data dictionary provided by the participant. The master data dictionary includes definitions for patient wards, specimen source, organism name, antimicrobial agent name, patient type (ICU, in-patient, outpatient), test method, and sub-institution. The result is two types of files, a *mrg* file and/or *rpr* file. The *mrg* file contains data ready for merging into the participant's main database. The *rpr* file contains data that requires manual resolution by a TSN Site Analyst or Microbiology Analyst. Upon resolution of the manual issues, the *rpr* file is re-entered into the normalisation process and becomes an *mrg* file.

Each month, newly created *mrg* files were loaded into the TSN database and software programs were applied. The programs eliminated duplicates, address interpretation or test method issues and review critical organism-antimicrobial agent issues. Critical organism-antimicrobial agent issues involved those instances where a particular organism-antimicrobial agent result was unusual, or hadn't been reported in the clinical literature. Examples such as vancomycin-resistant *Staphylococcus aureus* or fluoroquinolone-resistant *Streptococcus pneumoniae* would be flagged and withheld from the database pending confirmation of the result by the participating laboratory.

When these issues were resolved, the data was finally released into the TSN database and became available for use by the participant to perform queries. There were six different query types available using the Query III tool. The most common type of query was the 'SIR' query, which provided susceptible, intermediate and resistant results for a single organism-antimicrobial agent combination or to a group of organisms versus a group of antimicrobial agents over time. Trending provided the opportunity to examine the data by month, by quarter or by year. An antibiogram in which the user defined the susceptibility interpretation (S only, R only, S and I, R and I) was also available. Antibiograms could also be exported to Excel, Word, Crystal Reports, or Rich Text Format. Minimum Inhibitory Concentrations (MIC) and zone size data distribution reports were also available, as were Incidence reports.

Three datasets were defined, national, regional and institutional. All participants could look at the national data and their individual institutional data, but security programs prevented one participant from looking at another individual participant's data.

Nine different query parameters provided a wide range of criteria available to generate queries. S,I,R Sub-select offered the opportunity to look at the susceptibility patterns of alternative antimicrobial agents against organisms such as MRSA or gentamicin-resistant *Pseudomonas aeruginosa*. Specimen, patient type (ICU, in-patient, outpatient), ward, age, gender, institution type, bed size and test method were the other parameters available. Selection of organisms and antimicrobial agents were available from two different tables, a 'Top 25' list or a more comprehensive list. The query and the parameters used to generate the query could be saved for future reference. Each query could be customised in the Select Query Output Parameters window.

Results

The TSN Database Australia contained data from 103 sites, 453 taxa, and 99 antimicrobial agents. There were 14,648,752 results from 2,000,394 strains obtained from 1,213,605 patients. Each month approximately 300,000 records were entered into the database. The data could be analysed by multiple factors including any combination of the following: age and gender of the patient, specimen source, organism, susceptibility test method, drugs tested, and quantitative and qualitative test results. An example of data generated by the Query III SIR tool is shown in the Table.

Table. Trends in the susceptibility of *Staphylococcus aureus* to methicillin/oxacillin, Australia, 1996 to 2001

		S		I		R	
Year	**Total**	**N**	**%**	**N**	**%**	**N**	**%**
1996	16,972	15,277	90.0	0	0.0	1,695	10.0
1997	36,596	32,951	90.0	0	0.0	3,645	10.0
1998	54,542	48,667	89.2	0	0.0	5,875	10.8
1999	71,995	62,366	86.6	1	0.0	9,628	13.4
2000	93,104	80,026	86.0	2	0.0	13,076	14.0
2001	98,490	83,655	84.9	1	0.0	14,834	15.1

S Susceptible.
I Intermediate.
R Resistant.

Discussion

TSN Database Australia has demonstrated the feasibility and utility of an electronic surveillance system. The system monitors the trends of resistance in key organisms to provide timely information that can be used by physicians and pharmacists to guide patient management decisions. Data are provided to all laboratories participating in the system in the form of queries that can be performed on their own information, that of their region, and nationally. The proprietary nature of the system does not allow wider dissemination of data at this stage, although discussions are ongoing to make this data available nationally.

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Monitoring antimicrobial resistance for public health action

John W Tapsall

Abstract

Antibiotics are used both to treat infections in individual patients and in public health interventions to control disease outbreaks. In both circumstances the outcome, as measured by morbidity and mortality, is compromised by antimicrobial resistance (AMR) in the causative organism. Of necessity, antibiotics are frequently given empirically and their selection is based on presumptions of efficacy and the susceptibility of the infecting agent. AMR surveillance provides reassurance with regard to efficacy and guides the formulation of standard treatment regimens. However, AMR surveillance is not always appropriately performed nor are the data generated necessarily used to best advantage. Optimal use of AMR surveillance data requires for each disease of importance: an understanding of the applications of AMR surveillance and a clear definition of the type of data required: the 'triggers for surveillance'; construction of AMR surveillance programs appropriate to differing requirements; and better linkages between AMR surveillance data and disease control functions so that the thresholds for initiating public health action are clearly defined. Examples which illustrate the application of these principles are provided from experience with surveillance of AMR in the pathogenic *Neisseria* (*N. gonorrhoeae* and *N. meningitidis*). *Commun Dis Intell* 2003;27 Suppl:S70–S74.

Keywords: Neisseria gonorrhoeae, Neisseria meningitidis, *antibiotic resistance*, *gonococci, meningococci*

Introduction

The most obvious application of antibiotic susceptibility testing and surveillance is to facilitate use of the most appropriate treatment in infected individuals. Equally relevant is the role of antibiotics in public health interventions in infectious disease control. Control of certain diseases of public health importance is materially assisted by the ability of antibiotic treatment, either therapeutic or prophylactic, to decrease transmission between individuals and reduce the duration of infectiousness of affected patients. Conversely, increasing or high levels of resistance to the antibiotics used for these purposes pose the very real prospect of increased morbidity and mortality and prolongation of disease outbreaks. This is not to suggest that antibiotic treatment alone is the sole or even major intervention required, but rather that it is one component, albeit a key one, of an integrated public health approach to infectious disease management and control.[1]

Treatment of an individual infection or use of an antibiotic in a disease outbreak is often commenced before the diagnosis is confirmed and almost always before the susceptibility or resistance to the pathogen can be fully ascertained. In either circumstance, treatments are based on an assumed response to the antibiotic chosen. One important consideration in this choice of agent is the level of resistance to that antibiotic that is likely to be encountered. For example, the use of antibiotics such as rifampicin or ciprofloxacin for prophylaxis in an outbreak of meningococcal disease is predicated on the assumption that the meningococcus remains susceptible to their action. Similarly where a case of invasive meningococcal disease occurs, reassurance that there is no clinically significant resistance in Australia to the penicillins[2] means that, in keeping with current recommendations, treatment with this antibiotic can be initiated in general practice before transfer to hospital.

Correspondence: Assoc. Professor John Tapsall, Director, WHO Collaborating Centre for STD and HIV, Microbiology Department, The Prince of Wales Hospital, Randwick NSW 2031. Telephone: +61 2 9382 9079. Facsimile: +61 2 9398 4275. Email: j.tapsall@unsw.edu.au

Antimicrobial resistance surveillance thus has an integral place in helping to determine the most appropriate choice of antibiotics for both individual and public health management. It also follows that for public health purposes, this surveillance should be of high quality so that data generated are accurate, and focussed on those diseases and organisms where therapeutic options may be severely limited by antimicrobial resistance (AMR). Further, AMR surveillance for broader public health purposes should be linked with public health disease surveillance and control functions i.e., an effector arm, if value from surveillance is to be fully realised.[1]

The need for AMR surveillance for public health purposes is therefore based on certain 'triggers' including among others, the importance of the disease in terms of mortality and morbidity, the disease incidence in Australia, and the potential for disease transmission in Australia. The diseases involved would be those where the public health response (in the broad sense) is important and where therapeutic options and disease control are affected by AMR. There are many well established laboratory based programs in Australia for AMR surveillance at a local, national and even international level. What is sometimes lacking however, is a link between these programs and disease surveillance and control. Even when these AMR surveillance systems are in place and links between AMR and disease surveillance are established, there is still a requirement for a definition of 'thresholds for action'. That is, at certain defined and established stages in the evolution of antibiotic resistance, interventions with regard to treatment options, as opposed to separate issues of control of AMR, must be commenced.

To illustrate these principles and their differential applications in various diseases, the example of the place of AMR surveillance in the treatment and control of gonococcal and meningococcal infection in Australia will be used. For *Neisseria gonorrhoeae*, the specific instance of the emergence and spread of quinolone resistant gonococci in New South Wales is examined. For *Neisseria meningitidis* the consequences of resistance to antibiotics used for either treatment or prophylaxis would be significant. Examples of surveillance of antibiotic resistance are drawn from published studies, including those of the National Neisseria Network.

Methods

Data were derived from the New South Wales component of the Australian Gonococcal Surveillance Programme and the National Neisseria Network. The program of surveillance of antimicrobial resistance in *N. gonorrhoeae* has been established for over 20 years and is based on the results of examinations of gonococci obtained from public and private sectors.[3,4] Quinolone resistant gonococci (QRNG) were subdivided into 'less sensitive' and 'resistant' subgroups on the basis of MIC levels and correlation with patient demographics were as previously described.[4,5] The World Health Organization criteria of critical levels of antibiotic resistance in gonococcal populations, namely, a resistance level of 5 per cent or more,[6] was used in this example. Meningococcal resistance data for invasive isolates of *N. meningitidis* in Australia were recently reviewed[2] and were also based on data gathered since 1999.[7,8] Methods and criteria of resistance have also been previously published.[2]

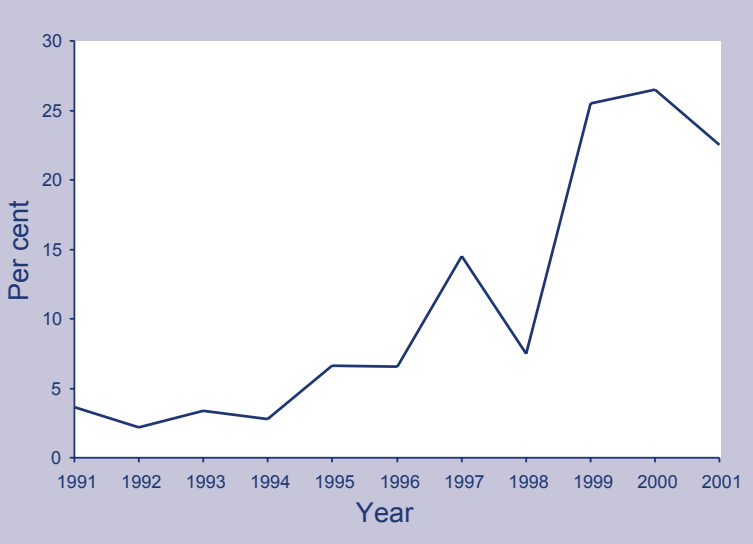
Results

Surveillance of quinolone antibiotic resistance in *N. gonorrhoeae* in New South Wales

Quinolone resistance in gonococci was first detected in New South Wales in 1984 but for the next decade generally remained at a low level, was seen almost exclusively in gonococcal infection acquired overseas and was not associated with sustained domestic transmission.[9] Quinolone antibiotics, especially ciprofloxacin, were increasingly used successfully in the management of gonorrhoea despite occasional instances of treatment failures.[10,11] These cases of treatment failure were infections with gonococci with higher levels of quinolone resistance and again were isolated examples of imported gonococcal disease.

From 1995 to the end of 2001 considerable volatility in the patterns of quinolone resistance was observed in gonococci isolated in New South Wales (Figure) and sustained endemic transmission of QRNG became established. There were several subsets of patients identified with domestic dissemination of QRNG at different times including clients of sex workers and homosexually active males.[4,11] The effect of the emergence and local spread of QRNG in New South Wales since 1995 has been a rapid escalation of the rate of QRNG and maintenance of this rate well above the 'critical' 5 per cent level for many years. As a consequence quinolone antibiotics are no longer recommended treatments for gonococcal infection in New South Wales.

Figure. Quinolone resistant gonococci as a percentage of all gonococci isolated in New South Wales, 1991 to 2001



Surveillance of antibiotic resistance in *N. meningitidis* in Australia

The data obtained by the National Neisseria Network from 1994 to 1999[2] showed a trend towards decreased sensitivity to penicillin in invasive meningococcal isolates in Australia between 1994 and 1996, but no further decrease in sensitivity thereafter.[2,7,8] This decrease in susceptibility did not indicate clinical resistance and only two isolates which would be regarded as potentially resistant to the penicillin group of antibiotics were isolated between 1994 and 2001. All isolates examined remained susceptible to the third generation cephalosporin antibiotics. Nine instances of *N. meningitidis* resistant to rifampicin[2,8] and a single quinolone resistant isolate were identified between 1994 and 2001.[12]

Discussion

There are several criteria to be met for establishing meaningful AMR surveillance for public health purposes. The disease must be of public health importance e.g., readily transmissible and of sufficient incidence; therapeutic options and disease control must be affected by AMR and measures must be in place to alter antibiotic treatments when surveillance data reveal a significant change in AMR.

Both of the pathogenic *Neisseria*, the gonococcus and the meningococcus, warrant active surveillance for emergence and spread of antibiotic resistant strains for public health purposes by the above criteria. Both are of obvious public health importance in terms of incidence, transmissibility, potential morbidity and, in the case of the meningococcus, mortality. Antibiotic therapy is important not only for their treatment but is also integral for disease control. In gonorrhoea, effective antibiotic treatment

decreases the duration of infectiousness and the transmissibility of the organism, both key factors in disease control. Public health management of invasive meningococcal disease is heavily reliant on early treatment with an effective antibiotic if the disease is suspected clinically. In Australia, this is with penicillin. Antibiotic prophylaxis is one means of reducing secondary cases of invasive meningococcal disease in close contacts of an index case. However, other agents used for chemoprophylaxis such as sulphonamides have had to be discarded for this application because of antibiotic resistance.[2]

Australia has well established systems for surveillance of AMR in these two closely related organisms.[4,8] Results and analyses of AMR surveillance of both of these organisms are published regularly in *Communicable Diseases Intelligence* and elsewhere. Despite these similarities, there are important differences in the approaches, principles and methods of AMR surveillance and the public health responses that follow detection of AMR in these two organisms.

With regard to the gonococcus, it is well established that a level of resistance of 5 per cent to an antibiotic in prevalent strains of *N. gonorrhoeae* should result in that antibiotic being removed from recommended treatment schedules.[6] The gonococcus has a particular capacity to become resistant to antibiotics and this has seen the progressive removal of penicillins, tetracyclines and now quinolones from treatment regimens in New South Wales. In other parts of Australia, penicillins continue to be standard treatment because AMR surveillance continues to demonstrate susceptibility to these agents. This '5 per cent' tolerance level is indicative only and in many instances a change in standard treatment would occur at a lower level and in 'high frequency transmitters' of the disease or in small communities, any level of resisitance warrants an alteration of recommendations.[6] In general, the threshold levels for action as currently defined are such that it is considered sufficient to sample a representative number and distribution of gonococci for public health purposes.

In contrast with gonococci, antibiotic resistance in meningococci in Australia has been slower to develop. Penicillin resistance in meningococci would have wide ranging consequences. Instances of beta-lactamase producing *N. meningitidis* have been reported overseas and on occasion chemoprophylaxis has been rendered ineffectual.[2] *In vitro* models have revealed the potential for meningococci to become resistant to quinolone antibiotics.[13] For these reasons and because of the relatively low number of isolates involved, it is necessary to examine all available isolates from invasive cases of meningococcal disease for AMR. and to alter treatment schedules sooner rather than later i.e. a ‘zero tolerance’ approach.

From these examples, it would seem necessary to have in place active surveillance of AMR in the causative organisms of those diseases meeting the criteria outlined above. Just as importantly it is necessary to have the data so gathered, critically analysed and interpreted and integrated into wider public health control effective mechanism, which includes a plan for action once defined thresholds of AMR are reached. While some of these thresholds of AMR for action have been determined and used for some time e.g., in gonorrhoea, in most instances they remain intuitive and variable e.g., in meningococcal disease. The nature and amount of AMR define these thresholds and predicate the requirements of optimal AMR surveillance for a particular organism, disease and antibiotic combination. For optimal use of AMR surveillance in a public health context, definition and implementation of these thresholds for action is required.

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Athena Limnios, Tiffany Hogan and members of the National Neisseria Network of Australia generated data used in the references below.

References

1. World Health Organization. Surveillance standards for antimicrobial resistance. 2001. WHO/CDS/CSR/DRS/2001.5P.

2. Tapsall JW, Shultz T, Limnios E, Munro R, Mercer J, Porritt R, *et al*. Surveillance of antibiotic resistance in invasive isolates of *Neisseria meningitidis* in Australia, 1994–1999. Pathology 2001;33:359–361.

3. Tapsall JW, Phillips EA, Cossins YM *et al*. Penicillin sensitivity of gonococci in Australia: the development of an Australian Gonococcal Surveillance Programme. *Br J Vener Dis* 1984,60:226–230.

4. Australian Gonococcal Surveillance Programme. Annual report of the Australian Gonococcal Surveillance Programme, 2001. *Commun Dis Intell* 2002;26:242-247.

5. Tapsall JW, Limnios EA, Shultz TR. Continuing evolution of the pattern of quinolone resistance in *Neisseria gonorrhoeae* isolated in Sydney, Australia. *Sex Transm Dis* 1998;25:415–417.

6. World Health Organization. Guidelines for the management of sexually transmitted infections. WHO/HIV_AIDS/2001.01 WHO/RHR/01.10:pp 1–5. World Health Organization, Geneva; 2001.

7. Australian Meningococcal Surveillance Programme. Annual report of the Australian Meningococcal Surveillance Programme, 2000. *Commun Dis Intell* 2001;25:113–121.

8. Australian Meningococcal Surveillance Programme. Annual report of the Australian Meningococcal Surveillance Programme, 2001. *Commun Dis Intell* 2002;26:407–418.

9. Tapsall JW, Shultz TR, Phillips EA. Characteristics of *Neisseria gonorrhoeae* isolated in Australia showing decreased sensitivity to quinolone antibiotics. *Pathology* 1992,24:27–31.

10. Tapsall JW, Shultz TR, Lovett R, Munro R. Failure of 500 mg ciprofloxacin therapy in male urethral gonorrhoea. *Med J Aust* 1992;156:143.

11. Tapsall JW, Limnios EA, Thacker C, Donovan B, Lynch SD, Kirby LJ, *et al*. High level quinolone resistance in *Neisseria gonorrhoeae*: a report of two cases. *Sex Transm Dis* 1995;22:310–311.

12. Shultz TR, Tapsall JW, White PA, Newton PJ. An invasive isolate of *Neisseria meningitidis* showing decreased susceptibility to quinolones. *Antimicrob Agents Chemother* 2000;44:1116.

13. Shultz TR, Tapsall J. GyrA and ParC changes in ciprofloxacin resistant meningococci parallel those seen in gonococci. Abstract 217, Abstract guide of the Twelfth International Pathogenic Neisseria Conference Galveston USA; 12–17 November 2000.

Ciprofloxacin resistance emerges in *Neisseria gonorrhoeae* in Victoria, 1998 to 2001

Mark G K Veitch,[1] Julia M Griffith,[1] Melissa L Morgan,[2]

Abstract

Notifications of gonorrhoea in Victoria increased suddenly in the late 1990s, from an average of 375 cases per year from 1993 to 1997, to over 700 cases in 2000. This paper describes the susceptibility to ciprofloxacin of isolates of *N. gonorrhoeae* in Victoria from 1998 to 2001, and relates these to the reported epidemiologic characteristics of the cases. The proportion of all isolates of *N. gonorrhoeae* that was resistant to ciprofloxacin rose from 3 per cent in 1998 to 11 per cent in 2001. Among homosexual and bisexual men, resistant isolates remained rare (< 1 per cent). Among heterosexual men and women whose infection was acquired overseas, the proportion of resistant isolates increased from 14 per cent to 51 per cent. Among heterosexual men and women whose infection was acquired in Australia, the proportion of resistant isolates increased from 6 per cent to 14 per cent, and disproportionately involved persons born overseas. Patterns of antibiotic resistance are intimately linked to epidemiological characteristics of cases. Clinical treatment and public health and control strategies for resurgent sexually transmitted infections benefit from the insights of collaborative microbiological and epidemiological surveillance. *Commun Dis Intell* 2003;27 Suppl:S75–S79.

Keywords: Neisseria gonorrhoeae, *ciprofloxacin, antibiotic resistance*

Introduction

Notifications of gonorrhoea in Victoria in the late 1990s echoed worldwide trends. Numbers of cases of gonorrhoea in Victoria declined from the mid-1980s and were relatively low (averaging 375 cases per year) from 1993 to 1997, but then surged to 552 cases in 1998, 742 cases in 2000 and 718 cases in 2001.[1,2]

A widely used Australian guideline[3] recommends a single dose of either 500 milligrams of orally administered ciprofloxacin or a 250-milligram intramuscular injection of ceftriaxone to treat suspected or proven uncomplicated urogenital gonorrhoea. Epidemiologically relevant trends in antimicrobial susceptibility should guide this choice.[4] Treatment should also include azithromycin or doxycycline to treat co-existing *Chlamydia* infection.

The proportion of Australian isolates of *Neisseria gonorrhoeae* with reduced susceptibility to ciprofloxacin increased from 5 per cent in 1998 to 17 per cent in 1999 and 18 per cent in 2000.[5] In 2000, the prevalence of reduced susceptibility to ciprofloxacin exceeded 50 per cent in most of the larger countries of the Western Pacific Region.[6]

This review describes the susceptibility to ciprofloxacin of isolates of *N. gonorrhoeae* in Victoria from 1998 to 2001, and relates these to the reported epidemiologic characteristics of the cases.

1. Microbiological Diagnostic Unit, Public Health Laboratory, Department of Microbiology and Immunology, the University of Melbourne, Victoria
2. Sexually Transmissible Infections and Hepatitis C Program, Communicable Diseases Section, Victorian Department of Human Services, Victoria

Corresponding author: Dr Mark Veitch, Public Health Physician, Microbiological Diagnostic Unit, Public Health Laboratory, Department of Microbiology and Immunology, the University of Melbourne, Melbourne VIC 3010. Telephone: +61 3 8344 7735. Facsimile: +61 3 8344 7833. E-mail: mgkv@unimelb.edu.au

Methods

The Communicable Diseases Section of the Victorian Department of Human Services (DHS) and the Microbiological Diagnostic Unit of the University of Melbourne (MDU) collaborate in surveillance of gonorrhoea in Victoria. Legislation requires that cases of gonorrhoea in Victoria be notified to the DHS both by the diagnosing clinician, and by the laboratory that makes the diagnosis. Information in the notification includes an anonymous identifier (first two letters of last and first names), sex, date of birth or age, residential postcode and details of the diagnosing doctor or laboratory. Further details, including sexual orientation, and putative source of infection are routinely sought from the notifying clinician.

Primary diagnostic laboratories send cultures of *N. gonorrhoeae* to the MDU, where antibiotic susceptibility is determined by agar plate dilution methods developed by the Australian National Neisseria Network.[5,7]

We defined the ciprofloxacin susceptibility of isolates of *N. gonorrhoeae* as fully sensitive (minimum inhibitory concentration (MIC) less than or equal to 0.03 mg/L), less sensitive (MIC 0.06 to 0.5 mg/L) or resistant (MIC equal to or greater than 1 mg/L).

This review examined cases of gonorrhoea infections for which the specimens were: collected between 1 January 1998 and 31 December 2001; diagnosed by culture in Victoria; and for which ciprofloxacin susceptibility was established.

Results

N. gonorrhoeae was identified by Victorian diagnostic laboratories in 2,827 cultures from one or more anatomic sites of persons between 1 January 1998 and 31 December 2001 and referred to the MDU for antibiotic susceptibility testing. Twenty-eight cultures were not tested for ciprofloxacin susceptibility. When multiple cultures from the same or different anatomic site of the same person within 28 days were identified, the isolate least susceptible to ciprofloxacin was retained and the others (163 isolates) were excluded, leaving isolates from 2,636 cases for this analysis.

Almost all isolates (97 per cent) from heterosexual men and women were from urogenital anatomic sites. Seventy-five per cent of isolates from homosexual men were urethral, 18 per cent rectal and 7 per cent pharyngeal.

The proportion *N. gonorrhoeae* isolates resistant to ciprofloxacin rose from 3 per cent in 1998 to 11 per cent in 2001 (Table 1).

Table 1. Ciprofloxacin susceptibility of cases of culture-proven gonorrhoea in Victoria, 1998 to 2001

Year	Fully sensitive (%)	Less sensitive (%)	Resistant (%)	Total number of isolates
1998	95	2	3	535
1999	77	18	5	700
2000	79	14	7	756
2001	84	5	11	645

In mid-1999, locally acquired isolates of *N. gonorrhoeae* that were less sensitive (but not fully resistant) to ciprofloxacin emerged suddenly, concentrated in, but not limited to, homosexual and bisexual men. These persisted during 2000 and then declined in 2001.

Over the four years, the prevalence of ciprofloxacin-resistant *N. gonorrhoeae* among heterosexual men and women was 16 per cent (155/942), far greater than among homosexual and bisexual men (0.4 per cent, 6/1,501, Chi-square=240, p<0.001) (Table 2). Only one of 287 male rectal isolates was resistant to ciprofloxacin.

Table 3 describes the ciprofloxacin susceptibility of the 2,358 (89 per cent) isolates with complete data on the sexual orientation of the case and the location where the infection was reportedly acquired.

Table 2. Ciprofloxacin susceptibility of cases of culture-proven gonorrhoea in Victoria, 1998 to 2001, by sex and reported sexual orientation

Sex	Sexual orientation	Fully sensitive (%)	Less sensitive (%)	Resistant (%)	Total number of isolates
Male	Heterosexual	74	10	16	806
	Homosexual or bisexual	89	11	<1	1,501
	Not reported	80	14	6	177
Female	Heterosexual	76	5	18	136
	Homosexual or bisexual	100	0	0	4
	Not reported	67	8	25	12

Table 3. Temporal trends in ciprofloxacin susceptibility of cases of culture-proven gonorrhoea in Victoria, 1998 to 2001, by sex, sexual orientation and location where the infection was reported to have been acquired

Sex and sexual orientation	Location acquired	Year	Fully sensitive (%)	Less sensitive (%)	Resistant (%)	Total number of isolates
Male and female, heterosexual	Australia	1998	93	1	6	114
		1999	79	12	9	178
		2000	76	10	14	184
		2001	83	3	14	206
	Overseas	1998	72	14	14	50
		1999	57	18	24	49
		2000	44	16	40	55
		2001	37	12	51	57
Male, homosexual and bisexual	Australia	1998	>99	0	<1	306
		1999	79	20	<1	418
		2000	86	14	<1	434
		2001	94	6	<1	282
	Overseas	1998	83	17	0	6
		1999	83	0	17	6
		2000	33	67	0	6
		2001	86	0	14	7

Among heterosexual men and women whose infection was acquired overseas, the proportion of ciprofloxacin-resistant isolates increased from 14 per cent in 1998 to 51 per cent in 2001 (Chi-square for trend=18.97, p<0.001). Eighty-three per cent (148/179) of the overseas-acquired infections of heterosexual men and women for which a country or region was specified were acquired in Asia. Of these, 39 per cent were resistant to ciprofloxacin.

Among heterosexual men and women whose infection was acquired in Australia, the proportion of ciprofloxacin-resistant isolates of *N. gonorrhoeae* increased from 6 per cent in 1998 to 14 per cent in 2001 (Chi-square for trend=5.94, p=0.015). Of infections acquired heterosexually by Australian-born persons, 7 per cent (34/518) were ciprofloxacin-resistant. In contrast, 30 per cent (35/118) of infections acquired heterosexually in Australia by overseas-born persons were ciprofloxacin-resistant (Chi-square=53, p<0.001).

From 1998 to 2001, ciprofloxacin-resistant isolates remained rare among homosexual and bisexual men. Four (one each year) were acquired in Australia, and two were acquired overseas.

Three of 2,636 isolates (0.1 per cent) demonstrated clinically insignificant slightly altered susceptibility to ceftriaxone (MIC 0.06 mg/L). Two of these were acquired in Asia.

Discussion

From 1998 to 2001 the annual incidence of ciprofloxacin resistant *N. gonorrhoeae* in Victoria tripled. However, the distribution of ciprofloxacin-resistant isolates of *N. gonorrhoeae* differed markedly in persons of different sexual orientation.

The increase in clinically significant ciprofloxacin resistance was entirely due to infections among heterosexual men and women. The high prevalence of resistance among infections acquired by Victorian travellers to Asia is typical of infections in this region.[6,8]

The high prevalence of ciprofloxacin resistance among infections acquired in Australia by persons who were born outside Australia may be due to misclassification of the source of the infection, or to chains of transmission and sexual networks that were several links from an imported resistant infection.

Regardless of the specific source of the infection, the overall prevalence of ciprofloxacin resistance among heterosexually acquired gonorrhoea diagnosed in Victoria is sufficiently high to render ciprofloxacin inappropriate for presumptive therapy of such infections.[5]

In contrast, less than one per cent of locally acquired infections of homosexual and bisexual men were resistant to ciprofloxacin. Ciprofloxacin therefore remains useful as first-line therapy for uncomplicated urogenital gonorrhoea acquired locally by homosexual and bisexual men.

The wave of ciprofloxacin-'less sensitive' *N. gonorrhoeae* that peaked in 1999 and ebbed in 2000 demonstrates the vulnerability of this population to the emergence of resistant strains. Infections with strains with reduced susceptibility to ciprofloxacin are more likely to fail treatment with the conventional single-dose therapy,[5] and may be precursors to highly resistant strains.[9]

New methods are being used to diagnose gonorrhoea by nucleic acid amplification.[4] These currently provide no information about the antimicrobial susceptibility of the organism causing the infection. Diagnostic strategies that recover isolates for antimicrobial susceptibility testing will be needed to ensure that the shifting patterns of antimicrobial susceptibility of *N. gonorrhoeae* are monitored.

The antimicrobial susceptibilities of isolates of *N. gonorrhoeae* are intimately linked to epidemiological characteristics of cases, and illuminate the transmission dynamics of this resurgent infection. Collaborative microbiological and epidemiological surveillance guide the choice of antibiotics that will efficiently cure uncomplicated gonorrhoea at first presentation, and may help avoid the clinical and public health consequences of selection and dissemination of resistant strains.

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References

1. O'Grady K-A, Tallis G, eds. *Surveillance of Notifiable Infectious Diseases in Victoria 2000*. Communicable Diseases Section, Public Health Division, Victorian Department of Human Services; 2001.
2. Surveillance report. *Victorian Infectious Diseases Bulletin* 2002;5:7–15.
3. Spicer J. (Chairman of Writing Group) *Therapeutic guidelines: antibiotic*. (Version 11) North Melbourne: Therapeutic Guidelines Limited; 2000.
4. Bowden FJ, Tabrizi SN, Garland SM, Fairley CK. Sexually transmitted infections: new diagnostic approaches and treatments. *Med J Aust* 2002;176:551–557.
5. Australian Gonococcal Surveillance Programme. Annual report of the Australian Gonococcal Surveillance Programme, 2000. *Commun Dis Intell* 2001;25:59–63.
6. WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme. Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2000. *Commun Dis Intell* 2001;25:274–276.
7. Australian Gonococcal Surveillance Programme. Use of a quality assurance scheme in a long-term multicentric study of antibiotic susceptibility of *Neisseria gonorrhoeae*. *Genitourin Med* 1990;66:437–444.
8. Berglund T, Unemo M, Olcen P, Giesecke J, Fredlund H. One year of *Neisseria gonorrhoeae* isolates in Sweden: the prevalence study of antibiotic susceptibility shows relation to the geographic area of exposure. *Int J STD AIDS* 2002;13:109–114.
9. Tapsall JW. The biology of *Neisseria gonorrhoeae*: a model of adaptation and survival. *Venereology* 2000;13:63–69.

Antibiotic resistance in *Campylobacter jejuni* isolated from humans in the Hunter Region, New South Wales

Hemant Sharma,[1] Leanne Unicomb,[2] Wendy Forbes,[3] Steve Djordjevic,[3] Mary Valcanis,[4] Craig Dalton,[5] John Ferguson[1]

Abstract

***Campylobacter* is a common cause of bacterial gastroenteritis in Australia. Antibiotic resistance among *Campylobacter* is an emerging problem in Europe and the United States of America. Monitoring may detect emerging resistance. Since there is no epidemiologically validated subtyping system for *Campylobacter*, antimicrobial resistance patterns may prove useful as an epidemiological marker. *Campylobacter* isolates from residents of the Hunter region were differentiated by PCR into two categories: *C. jejuni* and non-*C. jejuni*. Minimal inhibitory concentrations (MIC) were determined for 10 antibiotics using the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution methodology. Risk factor information including travel history were obtained as part of a case-control study by conducting telephone interviews with infected individuals. Sixty-four per cent, 3.4 per cent, 3.4 per cent and 11.2 per cent of *C. jejuni* isolates were resistant to ampicillin (at MIC > 8 mg/L), erythromycin (> 8 mg/L), nalidixic acid (> 32 mg/L) and tetracycline (> 8 mg/L), respectively. A diverse pattern of antibiotic resistance ('resistotypes') was detected with some change occurring over time. Several possible clusters of *Campylobacter* infections were identified based on resistotype. Of seven infections acquired during overseas travel, 57 per cent (4/7) were resistant to more than one antibiotic class compared to 10 per cent (14/144) of locally-acquired isolates (p=0.004, Fisher exact). The potential usefulness of resistotyping as an epidemiological marker is worthy of further exploration. *Commun Dis Intell* 2003;27 Suppl:S80–S88.**

Keywords: antibiotic resistance, Campylobacter jejuni

Introduction

Campylobacter is the most common bacterial cause of foodborne disease in Australia. More than 15,000 cases of *Campylobacter* infection are reported in Australia each year, excluding New South Wales where the disease is not notifiable (Communicable Diseases Network Australia — National Notifiable Diseases Surveillance System, personal communication). Antibiotic therapy is generally not recommended for the treatment of campylobacteriosis, however, antimicrobials are prescribed at times (Hunter Public Health Unit, 2002, unpublished data) and therapy is warranted in some circumstances.[1]

Antimicrobial resistance among *Campylobacter* isolates was first observed in the early 1990s.[2] Resistance among *Campylobacter* isolates has been reported from the United States of America (USA),[3] Europe,[4,5,6] the United Kingdom,[7,8] Asia,[9,10] the Middle East[11] and Australia.[12] In particular, resistance to quinolones has been widely observed.[4,5,6,13,14] Recently, reports describing increasing prevalence of quinolone resistances have been made in the Netherlands,[6] the USA[3] and the United Kingdom.[7,8] However, resistance to macrolides such as erythromycin remains low among isolates from humans[9] and animals.[5]

1. University of Newcastle and Hunter Area Pathology Service, Newcastle, New South Wales
2. Coordinator, OzFoodNet, Wallsend, New South Wales
3. Elizabeth Macarthur Agricultural Institute, Camden, New South Wales
4. Microbiological Diagnostics Unit, University of Melbourne, Melbourne, Victoria
5. Hunter Public Health Unit, Wallsend, New South Wales

Corresponding author: Dr John Ferguson, HAPS, Locked Bag 1, Newcastle Mail Centre NSW 2310. Telephone: +61 2 4921 4422. Facsimile: +61 2 4921 4440. Email: jferguson@hunter.health.nsw.gov.au

There have been at least two previous surveys of *Campylobacter* resistance in Australia. Huysman and Turnidge[15] examined 79 clinical strains of *C. jejuni* from South Australian patients isolated prior to 1997. Riley (personal communication T. Riley, University of Western Australia, 2001) examined 50 clinical and 50 environmental strains of *Campylobacter* species isolated in Western Australia between 1999 and 2000. These studies were descriptive only and did not explore the use of resistance typing as an epidemiological marker.

Antibiotics are used in the livestock industry and it has been suggested that their use in food animals has contributed to the development of antibiotic resistance in human isolates. Increases in the detection of quinolone resistant *Campylobacter* were reported from the UK after licensing of enrofloxacin for veterinary use[16] and experimental evidence suggests that the use of quinolones in broiler chickens leads to the selection of resistant *Campylobacter* organisms.[17] In Australia, legislation limits the use of particular antibiotics such as fluoroquinolones, cephalosporins, gentamicin, and chloramphenicol in food producing animals.[18] However, use of these agents is widespread in some countries and therefore imported foods may be a source of resistant organisms.

With the global concern with the increasing prevalence of resistance among clinically important bacterial pathogens, the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) examined the use of antibiotics in food producing animals and its association with emergence of resistance. The JETACAR report made several recommendations for regulatory control of antibiotic use, monitoring and surveillance of resistance in clinical isolates, strategies for antibiotic use, infection prevention and hygiene, education, research, communication and coordination of resistance management programs.[18]

A study of antibiotic resistance among *Campylobacter* isolates from residents of the Hunter region was initiated as part of monitoring and surveillance efforts. This report describes antibiotic resistance profiles of human *Campylobacter* isolates and is part of an evaluation of multiple typing methods for their usefulness to examine specific risk factors for *Campylobacter* infection.

Methods

Epidemiological methods

A case control study was conducted in the Hunter region of New South Wales, which has a population of 570,000 and includes urban, rural and semi-rural areas. Cases were recruited using voluntary notifications from two participating laboratories of the three major pathology service providers for the population. A total of 355 cases were enrolled between January 1999 and July 2001. Telephone interviews were conducted after verbal consent was given and information on illness, travel, foods consumed, dining locations, drinking and recreational water sources, animal contact and demographics was obtained.

Isolates

Of the 355 enrolled cases, 240 *Campylobacter* isolates were detected at the public laboratory (Hunter Area Pathology Service, HAPS). Of these, 171 stored isolates were available for inclusion in this study. An additional 29 Hunter isolates obtained between July to September 2001 from patients not enrolled in the case control study were included to bring the total tested up to 200.

Laboratory methods

Diarrhoeal stool was cultured on charcoal blood-free agar with cefoperazone and amphotericin B (Biomerieux). Plates were incubated microaerobically at 42˚C for 48 hrs. *Campylobacter* species were motile isolates with characteristic gram stain appearance and oxidase positivity. Isolates were stored at –70˚C in glycerol broth until analysed.

Speciation of each isolate was determined by hippurate hydrolysis and polymerase chain reaction (PCR) targeted at *C. jejuni* specific hippuricase and putative oxidoreductase genes as described previously.[19,20,21] There was complete concordance between tested hippurate and PCR species status. Template DNA for PCR was prepared using Instagene matrix as outlined in the manufacturer's instructions (BioRad, California, USA). PCR amplifications were performed by previously described methods[19,20,21] and the amplification products were analysed on one per cent agarose gels. This enabled classification of the isolates as either *C. jejuni* or non-*C. jejuni*.

Susceptibility testing was performed by agar dilution methodology utilising Mueller-Hinton agar with 5 per cent lysed sheep blood in accord with National Committee for Clinical Laboratory Standards (NCCLS) methodology for *Helicobacter* species.[22] The inoculum was prepared as a saline suspension equivalent to a 2.0 McFarland standard from a 48-hour blood agar subculture and inoculated with a replicator machine. This technique places 1 µl of suspension per spot onto the agar dilution medium. Media were prepared containing doubling dilutions through a full range of concentrations for quinolone agents (nalidixic acid, norfloxacin and ciprofloxacin), tetracycline, ampicillin, gentamicin and macrolide agents (erythromycin, azithromycin, clarithromycin, roxithromycin). The inoculated plates were incubated microaerobically for 48 hours. The Minimal Inhibitory Concentration (MIC) was defined as the lowest concentration giving complete inhibition of visible growth on the plate. Interpretation of MIC levels were made with reference to accepted breakpoint values where available. *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 were used as quality control strains. The MIC_{50} and MIC_{90} values for each antibiotic were calculated from the distribution of the MIC values of all isolates. MIC_{50} values represent the concentration of antibiotic below which growth of 50 per cent of isolates were inhibited and MIC_{90} value represent the concentration of antibiotic below which growth of 90 per cent of isolates were inhibited.

Statistical methods

Comparison of the proportions was performed using the Fisher exact test or Yates corrected X^2 test as appropriate and comparison of proportion of resistance over time was performed using X^2 for trend using Epi Info version 6.04c.

Results

The isolates included in this report comprised those stored at one of the two participating laboratories. HAPS is the public laboratory for the Hunter Health Area, and services a different population from many of the private laboratories. Of the 240 HAPS-identified cases that participated in the case control study, 90 (37.5%) were admitted to hospital compared to three (3%) hospitalised cases of the 115 identified through the other pathology service provider (Yates corrected Chi-square=47.2, $p<0.001$). Thus, cases of *C. jejuni* included in this study probably represent more severe cases.

PCR analysis confirmed 180 of the 200 isolates to be *C. jejuni* (151 of which were enrolled in the case control study) and only the susceptibility results for the *C. jejuni* isolates are described in this paper.

MIC_{50} and MIC_{90} values for each antibiotic are shown in Table 1 together with resistance levels for those agents with accepted breakpoint values. Ampicillin resistance was common (64%) with tetracycline resistance at 11 per cent. Levels of erythromycin and quinolone resistance were low. Sixty-eight per cent of locally acquired isolates were resistant to at least one class of antibiotic.

Figures 1a and 1b show the MIC distributions for macrolide and quinolone antibiotics respectively. The MIC distribution curves were bimodal with a small outlying peak made up of high-level resistant isolates. For macrolides, the isolates were most susceptible to azithromycin and least susceptible to roxithromycin. All the erythromycin resistant isolates were pan-resistant to other macrolides.

Table 1. Resistance of *Campylobacter jejuni* isolates in Hunter region (n =180)

	MIC50 mg/L	MIC90 mg/L	Breakpoint	Resistant %		
				All Isolates	Locally-acquired	Overseas acquired†
Nalidixic acid	4	8	> 32 mg/L	3.4	1.4	43*
Norfloxacin	0.5	1.0				
Ciprofloxacin	0.25	0.5	> 4 mg/L	2.9	0	43*
Tetracycline	0.25	8	> 8 mg/L	11	10	43*
Ampicillin	8	64	> 8 mg/L	64	66	57
Erythromycin	1	2	> 8 mg/L	3.4	3	0
Azithromycin	0.125	0.25				
Clarithromycin	1	4				
Roxithromycin	4	16	> 8 mg/L	48	40	57
Gentamicin	0.5	1.0	> 8 mg/L	0	0	0
Resistance > 1 class				12	9	43*
Total number of isolates				**n=180†**	**n=148**	**n=7**

* Significant difference ($p<0.05$) local versus overseas-acquired cases. Fisher exact test.

† Travel history information was available for 155 of 180 isolates.

Figure 1a. Macrolide MIC distribution for *C. jejuni* isolates (n=180)

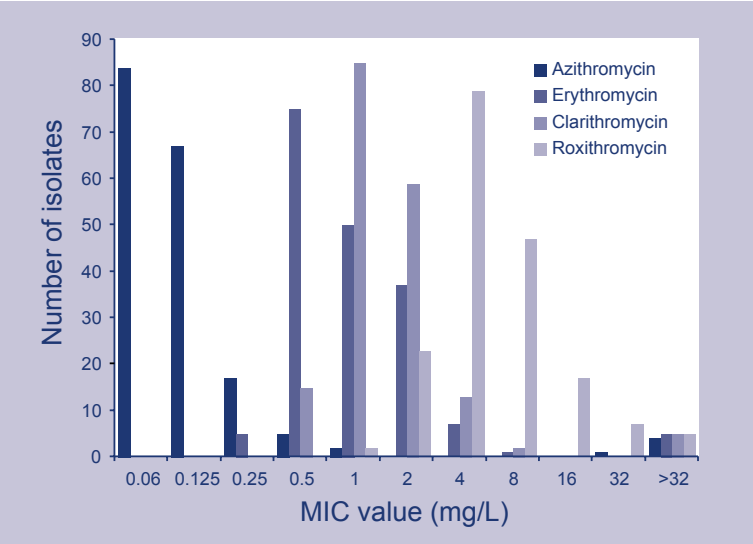
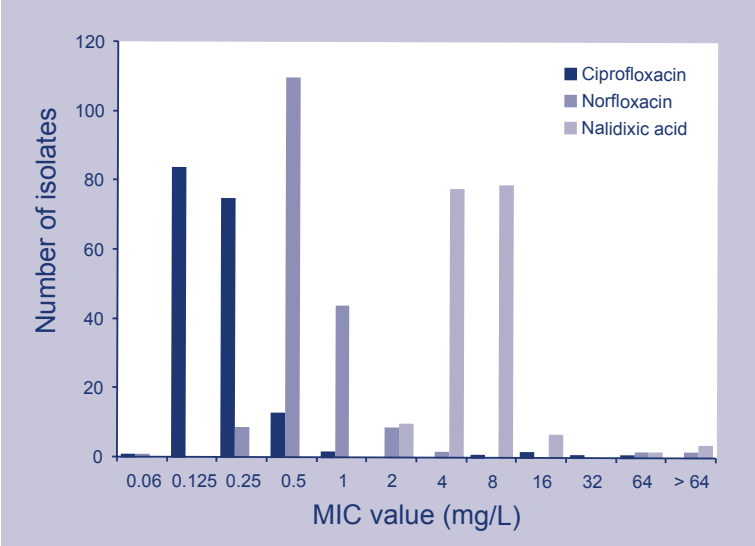


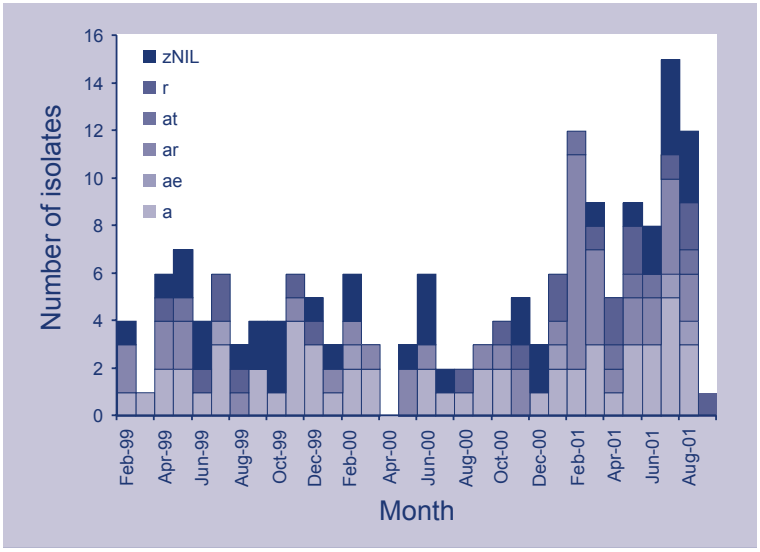
Figure 1b. Quinolone MIC distribution for *C. jejuni* isolates (n=180)



For quinolones, isolates were most susceptible to ciprofloxacin and least susceptible to nalidixic acid. Two isolates with high-level ciprofloxacin resistance were identified (MIC ≥ 32 mg/L), one acquired overseas, one where it was not known whether it was acquired locally or overseas. Two nalidixic acid resistant isolates (both locally-acquired) were susceptible to ciprofloxacin and norfloxacin implying a different resistance genotype.

Table 2 shows the variation in resistance patterns ('resistotypes') that occurred over the three years of this study. Ampicillin resistance increased from 59 per cent in 1999 to 69 per cent in 2001 and roxithromycin resistance from 36 to 51 per cent over the same time, however these trends were not statistically significant. Temporal distribution of resistotypes was examined by year (Table 2) and month (Figure 2). There were 15 unique resistance patterns seen among the 180 isolates. Three dominant resistotypes occurred throughout the years of the study. Resistance to ampicillin, roxithromycin, and ampicillin-roxithromycin was observed in each year. Many resistotypes were found over the study period. Ampicillin-tetracycline resistance was found in May 1999 and then again from February 2001 until the end of the study period (Figure 2).

Figure 2. Temporal distribution of the major resistotypes, February 1999 to December 2001



A = Azithromycin, ae = Azithromycin-Erythromycin, ar = Azithromycin-Roxithromycin, at = Azithromycin-Tetracycline, r = Roxithromycin, zNIL = no resistance.

Table 2. Annual distribution of *C. jejuni* resistotypes, 1999 to 2001

Resistance pattern (resistotype)	Count of resistance patterns by year			Total
	1999	2000	2001	
a	20	14	21	55
act			2	2
ae	1	1	3	5
aet	1			1
ant		1	1	2
ar	8	10	23	41
arc			1	1
art	2		2	4
at	1		4	5
ct	1			1
r	7	3	11	21
rc			1	1
rt	1		1	2
t	1		2	3
Nil	13	12	11	36
Total	**56**	**41**	**83**	**180**

a=ampicillin, c=ciprofloxacin, e=erythromycin, n=nalidixic acid (ciprofloxacin susceptible), r=roxithromycin (erythromycin susceptible), t=tetracycline

Four potential clusters of *Campylobacter* infection were identified on the basis of resistotype. Among the resistotypes of more than 10 isolates (ampicillin (a) resistance, ampicillin-roxithromycin (ar) resistance, and roxithromycin (r) resistance), a cluster was defined as more than two-times the average number of cases in a one month period. One cluster of ampicillin resistant isolates was detected in November to December 1999 (n=7), one from January to March 2001 (n=7) and one in July to August 2001 (n=7). A further cluster of ampicillin-roxithromycin resistance was detected in February to March 2001(n=13) (Figure 2).

All seven isolates acquired during overseas travel were resistant to at least one class of antibiotic. There were two nalidixic acid (one with coincident ciprofloxacin resistance) and three tetracycline resistant isolates. Fifty-seven per cent (4/7) of overseas-acquired isolates were resistant to more than one antibiotic class compared to 10 per cent (14/144) of locally-acquired isolates (p=0.004, Fisher exact). Isolates acquired overseas had similar levels of ampicillin resistance to locally acquired isolates. Quinolone and tetracycline resistance were significantly more frequent in overseas isolates (Table 1).

Eight per cent (12/150) of the patients took antibiotic therapy in the month prior to *Campylobacter* infection. The resistance rates among those exposed to antibiotics (11/12, 92%) was higher compared to unexposed subjects (109/138, 79%; Odds ratio 2.95, 95% CI 0.37–23.8, p=0.46). This was not statistically significant, possibly due to the low power to detect a difference, limited by the small sample size.

Discussion

Patterns of antibiotic resistance among the isolates included in this study were similar to previous studies conducted in Australia. A prevalence of ampicillin resistance of 64 per cent (MIC >8) was similar to the levels seen in South Australia[16] and Spanish paediatric isolates.[23] The majority of this resistance is due to ß-lactamase production in that the majority of resistance is abolished by the addition of clavulanate. In the latter study, amoxycillin/clavulanate resistance began to emerge implying an alternative resistance mechanism.

Seven isolates with quinolone resistance were detected in the current study. Quinolone resistance was more common in the isolates acquired overseas. Binotto *et al*[12] described two cases of quinolone resistant *Campylobacter* infection in travellers returning to Australia from the United Kingdom. Riley found 4 of 50 (8%) Western Australian clinical strains had ciprofloxacin resistance (MIC ≥4) (personal communication T. Riley, University of Western Australia, 2001). Huysman et al found no quinolone resistance in isolates from South Australia.[15]

The usual evolution of quinolone resistance involves mutations in the quinolone resistance-determining region of the *gyrA* (topoisomerase II) gene.[24] Initial mutations produce high-level nalidixic acid resistance, with additional changes leading to increasing ciprofloxacin resistance. Active multi-drug efflux mechanisms for quinolone resistance in *Campylobacter* are also described[25] and may be responsible for reducing susceptibility to quinolones, ß-lactams, tetracycline, chloramphenicol and other agents.[26] The molecular mechanisms of resistance in the present study's isolates are to be confirmed through further study.

Levels of erythromycin resistance were low in the present study (3.4%) as previously described in Australia[16] and other countries.[9] None of the overseas-acquired isolates in the current study showed macrolide resistance. Roxithromycin resistance (48%) was more prevalent and therefore provided a more useful contribution to resistotype diversity than erythromycin.

Gentamicin resistance was not detected among these isolates similar to findings from the other Australian studies. Studies of *Campylobacter* gentamicin susceptibility overseas have mostly shown universal susceptibility.[7,27] However, Reina *et al*,[23] documented 12 resistant isolates (2.2%) in the last two years (1992–93) of that study.

In addition to the descriptive epidemiology of resistotypes, antibiotic resistance was explored for its potential usefulness as an epidemiological marker. Outbreaks of campylobacteriosis are rarely detected, due to the inability to recognise the existence of a cluster by serotype or phage type distributions. The small clusters of resistotypes that were observed in this study possibly represented outbreaks. Furthermore, a temporal trend was detected for one pattern (ampicillin-tetracycline resistance). The diversity of antibiotic resistance found among these isolates suggests that resistance patterns may be useful as an epidemiological marker. Resistotyping is being evaluated for its epidemiological value in comparison with eight *Campylobacter* subtyping methods. Comparison of the major resistotypes with respect to range of food, water and environmental exposures for infection from this case set will also be undertaken. The difference in resistance between overseas and locally acquired isolates in these human isolates further supports its potential use as an epidemiological marker.

The findings outlined in this report suggest that routine antibiotic resistance testing for *Campylobacter* may prove useful to assess emerging resistance and to detect clusters. If resistotyping is to be performed on a routine basis, standardised testing protocols will need to be developed.

Acknowledgements

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References

1. Chin J ed. *Control of Communicable Diseases Manual*, 2000, 17th edition. American Public Health Association.
2. Allos BM. *Campylobacter jejuni* infections: update on emerging issues and trends. *Clin Infect Dis* 2001;32:1201–1206.
3. Smith KE, Besser JM, Hedberg CW, Leano FT, Bender JB *et al*. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992–1998. *N Engl J Med* 1999;340:1525–1532.
4. Sjogren E, Lindblom G-B, Kaijser B. Norfloxacin resistance in *Campylobacter jejuni* and *Campylobacter coli* isolates from Swedish patients. J *Antimicrob Chemother* 1997;40:257–261.
5. Saenz Y, Zarazaga M, Lantero M, Gastanares MJ, Baquero F, Torres C. Antibiotic resistance in *Campylobacter* strains isolated from animals, foods, and humans in Spain in 1997–1998. *J Antimicrob Chemother* 2000;44:267–271.
6. Talsma E, Goettsch WG, Nieste HL, Schrijnemakers PM, Sprenger MJ. Resistance in *Campylobacter* species: increased resistance to fluoroquinolones and seasonal variation. *Clin Infect Dis* 1999;29:845–848.
7. Thwaites RT, Frost JA. Drug resistance in *Campylobacter jejuni*, *C. coli* and *C. lari* isolated from humans in north west England and Wales, 1997. *J Clin Pathol* 1999;52:812–814.
8. Sam WIC, Lyons MM, Waghorn DJ. Increasing rates of ciprofloxacin resistant *Campylobacter*. *J Clin Pathol* 1999;52:709–710.
9. Isenbarger DW, Hoge CW, Srijan A, Pitarangsi C, Vithayasai N, Bodhidatta L, *et al*. Comparative antibiotic resistance of diarrheal pathogens from Vietnam and Thailand, 1996–1999. *Emerg Infect Dis* 2002;8:175–180.
10. Ananthan S, Swarna SR, Alavandi SV. Isolation of nalidixic acid resistant *Campylobacters* from cases of paediatric diarrhoea in Chennai. *J Commun Dis* 1998;30:159–162.
11. Wasfy MO, Oyofo BA, David JC, Ismail TF, el-Gendy AM, Mohran ZS, *et al*. Isolation and antibiotic susceptibility of *Salmonella*, *Shigella*, and *Campylobacter* from acute enteric infections in Egypt. *J Health Popul Nutr* 2000;18:33–38.
12. Binotto E, McIver CJ, Hawkins GS. Ciprofloxacin-resistant *Campylobacter jejuni* infections. *Med J Aust* 2000;172:244–245.
13. Prasad KN, Mathur SK, Dhole TN, Ayyagari A. Antimicrobial susceptibility and plasmid analysis of *Campylobacter jejuni* isolated from diarrhoeal patients and healthy chickens in northern India. *J Diarrhoeal Dis Res* 1994;12:270–273.
14. Hoge CW, Gambel JM, Srijan A Pitarangsi C, Echeverria P. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. *Clin Infect Dis* 1998;26:341–345.
15. Huysmans MB, Turnidge JD. Disc susceptibility testing for thermophilic *Campylobacters*. *Pathology* 1997;29:209–216.
16. World Health Organization. Use of quinolones in food animals and potential impact on human health. Report and proceedings of a WHO meeting, Geneva, Switzerland, 2-5 June, 1998. Geneva: World Health Organization, 1998.
17. McDermott PF, Bodeis SM, English LL, White DG, Walker RD, Zhao S, *et al*. Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. *J Infect Dis* 2002;185:837–840.
18. Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR). The use of antibiotics in food-producing animals: antibiotic resistant bacteria in animals and humans. Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia. Prepared for JETACAR by Biotex Canberra, 1999, Commonwealth of Australia. Available from: http://www.health.gov.au/pubs/jetacar.htm. Accessed: July 2002.

19. Linton D, Lawson AJ, Owen RJ, Stanley J. PCR detection, identification to species level, and fingerprinting of *Campylobacter jejuni* and *Campylobacter coli* direct from diarrhoeic samples. *J Clin Microbiol* 1997;35:2568–2572.

20. Harmon KM, Ransom GM, Wesley IV. Differentiation of *Campylobacter jejuni* and *Campylobacter coli* by polymerase chain reaction. *Mol Cell Probes* 1997;11:195–200.

21. Bolton FJ, Wareing DRA, Skirrow MB, Hutchinson DN. Identification and biotyping of Campylobacters. In: Board GR, Jones D, Skinner FA eds. *Identification methods in applied and environmental microbiology*. Blackwell Scientific Publications, Oxford, United Kingdom, 1992:151–161.

22. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 11th edition. Approved standard. National Committee for Clinical Laboratory Standards document M7–A5. Villanova, Pennsylvania, USA, 2001.

23. Reina J, Ros MJ, Serra A. Susceptibilities to 10 antimicrobial agents of 1,220 *Campylobacter* strains isolated from 1987 to 1993 from feces of pediatric patients. *Antimicrob Agents Chemother* 1994;38:2917–2920.

24. Wang Y, Huang WM, Taylor DE. Cloning and nucleotide sequence of the *Campylobacter jejuni gyrA* gene and characterization of quinolone resistance mutations. *Antimicrob Agents Chemother* 1993;37:457–463.

25. Charvalos E, Tselentis Y, Hamzehpour MM, Kohler T, Pechere JC. Evidence for an efflux pump in multidrug-resistant *Campylobacter jejuni*. *Antimicrob Agents Chemother* 1995;39:2019–2022.

26. Ferguson JK, Dalton CB, McGettigan P, Hill S. Antimicrobial resistance in animal enteric bacteria and human disease — a review of the scientific literature. Commissioned report to the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR). Canberra; National Health and Medical Research Council, 1998.

27. Aquino MH, Filgueiras AL, Ferreira MC, Oliveira SS, Bastos MC, Tibana A. Antimicrobial resistance and plasmid profiles of *Campylobacter jejuni* and *Campylobacter coli* from human and animal sources. *Lett Appl Microbiol* 2002;34:149–153.

Low levels of fluoroquinolone resistance in *Escherichia coli*. A five-year trend in Australia measured through the use of TSN® Database Australia

John Turnidge,[1] Laurence R McCarthy,[2] Ronald N Master,[3] Douglas E Kepner[4]

Abstract

In many countries, fluoroquinolones are among the most commonly used antibacterial drugs. Concerns about bacterial resistance to these and other frequently used drugs have been raised by the medical and scientific communities. While fluoroquinolone resistance has not yet developed among many bacteria, emergence of resistance in *Escherichia coli* would be a problem as multiple resistances to other antibiotics is now a common problem. This paper examines trends in resistance to fluoroquinolones in *Escherichia coli* through analysis of data collected from Australian institutions between 1997 and 2001. During the study period, norfloxacin and ciprofloxacin were the most frequently tested fluoroquinolones in Australian laboratories. An examination of results for strains tested simultaneously against both drugs indicated that testing against either drug accurately predicted resistance or susceptibility for the other (99.7% agreement). Over 400,000 tests were performed to determine the fluoroquinolone susceptibility of *E. coli*. Data were analysed by the test method used (Calibrated Dichotomous Sensitivity (CDS) or National Committee for Clinical Laboratory Standards (NCCLS)). The data indicate that fluoroquinolone resistance in *E. coli* has not yet emerged as a significant problem in Australia, but there are some indications of low level increases in resistance rates. Norfloxacin results are likely to be a better guide to fluoroquinolone resistance in this species using this method of surveillance. *Commun Dis Intell* 2003;27 Suppl:S89–S91.

Keywords: fluoroquinolone resistance, Escherichia coli, *antibiotic resistance*

Introduction

The fluoroquinolones are a potent class of antimicrobial agents that have a wide range of activity against both gram-negative and gram-positive bacterial pathogens. In many countries, this has resulted in widespread use of these agents as treatment modalities for a broad range of infections. By contrast, in Australia the widespread use of quinolones has been prevented, in part through restricted access on the Pharmaceutical Benefits Scheme. The initial quinolone agents (e.g., norfloxacin and ciprofloxacin) were approved for use mainly against gram-negative pathogens including those in the family *Enterobacteriaceae* and the genus *Pseudomonas*. The more recent derivatives (e.g., moxifloxacin and gatifloxacin) retain much of the gram-negative activity, but have enhanced gram positive activity. Over the years these agents have demonstrated continued success, but there is concern about the development of resistance, especially in *E. coli* where multi-resistance to other antibiotic classes is now seen regularly.

1. Director of Microbiology and Infectious Diseases, Women's and Children's Hospital, Microbiology Department, North Adelaide, South Australia
2. President and CEO, Focus Technologies Inc, Virginia, United States of America
3. Director, TSN Operations, Focus Technologies Inc, Virginia, United States of America
4. TSN Microbiology Analyst, Focus Technologies Inc, Virginia, United States of America

Corresponding author: Associate Professor John Turnidge, Director of Microbiology and Infectious Diseases, Women's and Children's Hospital, Microbiology Department, 72 King William Road, North Adelaide, SA 5006. Telephone: +61 8 8161 6873.
Email: turnidgej@wch.sa.gov.au

It is important to monitor the activity of fluoroquinolones using a strategy that provides an accurate and timely picture. TSN Database Australia was used as the system to monitor the activity of two fluoroquinolones; ciprofloxacin and norfloxacin, against *Escherichia coli* in Australia over the past five years.

Methods

The Surveillance Network (TSN) Database was first initiated in 1994 by Focus Technologies, Inc. (formerly 'MRL,' Herndon, Virginia). TSN assimilates antimicrobial susceptibility testing and patient demographic data from over 100 laboratories across Australia, into a database. Laboratories are included in TSN based on factors such as hospital bed size, patient population, geographic location, and the antimicrobial susceptibility test methods used. Antimicrobial susceptibility testing of patient isolates is conducted onsite by each participating laboratory as a part of their routine diagnostic testing. TSN uses a series of quality-control filters (i.e., critical rule sets) to screen susceptibility test results for patterns suggestive of testing error and 'quarantines' such results pending laboratory confirmation. TSN Database Australia reflects current testing practices in Australian laboratories and connects a significant number of laboratories in the country in an automated surveillance effort. As of 31 March 2002 TSN Database Australia contained more than 15 million antimicrobial agent/organism susceptibility test results. These results are from approximately 2 million bacterial strains isolated from 1.2 million patients across Australia since 1995.

For analysis of trends, all strains of *E. coli* tested were included. Significance of trends in rates of resistance was analysed using the Chi-square test for linear trend.

Isolates tested concurrently against ciprofloxacin and norfloxacin were also analysed to examine the degree of concordance.

Results

Data from TSN Database Australia demonstrated continued excellent activity of both ciprofloxacin and norfloxacin against *E. coli*, with a small but steady decrease in susceptibility over five years, as shown in Table 1. Both drugs showed increasing trends to resistance, and both trends were significant at $p<0.0001$; but more than 97 per cent of isolates were susceptible. This was true for isolates tested by both CDS and NCCLS methods. The ciprofloxacin rate of resistance changed from 1.7 per cent in 1997 to 4.7 per cent in 2001, and the norfloxacin resistance rate increased from 0.3 per cent in 1997 to 1.1 per cent in 2001.

There appear to be differences in the resistance rates between ciprofloxacin and norfloxacin tested by either CDS or NCCLS test methods. These differences are likely to be due to selective testing of ciprofloxacin, in strains demonstrating intermediate or resistant result to norfloxacin. There are large differences in the number of tests with norfloxacin being tested significantly more frequently than ciprofloxacin. For the CDS test method in 2001 there were 1,654 ciprofloxacin results versus 67,320 norfloxacin results. For the NCCLS test methods in 2001 there were 13,643 ciprofloxacin results versus 69,535 results for norfloxacin. Norfloxacin is the fluoroquinolone most frequently routinely tested in Australia and as such is the better indicator of resistance trends using this method of surveillance. We do not believe that the ciprofloxacin results from the TSN Database Australia provide an accurate guide to true rates of fluoroquinolone resistance in *E. coli* at this time.

The activities of the two fluoroquinolones were compared using 3 by 3 analyses for data from both 2000 and 2001. Of the 11,225 strains of *E. coli* examined in 2000 for this study, 99.7 per cent were concordant (data not shown), and for the 13,445 strains examined in 2001, the same percentage were concordant (Table 2). The rates of concordance were high and no differences were observed between the CDS and NCCLS methodologies.

Table 1. Ciprofloxacin and norfloxacin against *E. coli*, number and per cent susceptible, intermediate and resistant

Year	Drug	S		I		R	
		n	%	n	%	n	%
1997	Ciprofloxacin	4,987	99.5	0	0	25	0.5
	Norfloxacin	45,307	99.7	0	0	121	0.3
1998	Ciprofloxacin	6,480	99.2	0	0	53	0.8
	Norfloxacin	61,834	99.6	0	0	234	0.4
1999	Ciprofloxacin	11,054	98.7	3	0	145	1.3
	Norfloxacin	84,044	99.5	16	0	380	0.5
2000	Ciprofloxacin	15,697	98.4	2	0	260	1.6
	Norfloxacin	126,325	99.3	20	0	851	0.7
2001	Ciprofloxacin	18,240	97.8	1	0	409	2.2
	Norfloxacin	138,202	99.0	34	0	1,306	0.9

Table 2. *E. coli*, ciprofloxacin versus norfloxacin, 2001

			Norfloxacin		
			S %	I %	R %
Ciprofloxacin	S	%	97.11	0.00	0.19
		n	(13,057)	(0)	(25)
	I	%	0.02	0.00	0.01
		n	(3)	(0)	(1)
	R	%	0.13	0.01	2.54
		n	(17)	(1)	(341)

S Susecptible.
I Intermediate.
R Resistant

Discussion

This study demonstrates several interesting findings. Firstly, both ciprofloxacin and norfloxacin remain highly active against *E. coli* in Australia. Secondly, a direct comparison of ciprofloxacin and norfloxacin tested concurrently demonstrates a high degree of concordance between the two when tested against Australian isolates of *E. coli*. Testing either drug predicted resistance or susceptibility for the other drug. Thirdly, while fluoroquinolone resistance in Australia has not yet emerged as a significant problem, there are indications of increasing resistance rates at low levels. The overall rate of resistance to norfloxacin increased from 0.3 per cent in 1997 to 0.9 per cent in 2001. This trend of increasing resistance rates suggests the need for continued surveillance.

Acknowledgments

We would like to thank the members of the TSN Australia Advisory Board and the participating institutions.

Surveillance of hospital-acquired methicillin-resistant *Staphylococcus aureus* in South Australia

Celia Cooper,[1] Meredith A Ochota[2]

Abstract

In September 2001, the South Australian state-wide methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance system was expanded to include three surveillance indicators namely: estimated MRSA burden, MRSA morbidity and estimated MRSA acquisition. The last two indicator rates have been stratified into intensive care unit (ICU) versus non-ICU. Between September 2001 and March 2002, state-wide MRSA burden rates (prevalence) ranged from 27.5 to 39.8 per 10,000 occupied bed days (OBDs). Acquisition rates ranged from 28.2 to 69.0 per 10,000 OBDs (ICU) and 6.3 to 10.1 per 10,000 OBDs (non-ICU). Morbidity rates ranged from 12.9 to 43.1 per 10,000 OBDs (ICU) and 3.0 to 5.0 per 10,000 OBDs (non-ICU). In association with the changes to surveillance indicators, a new monthly surveillance report was developed. Assuring confidentiality to individual contributing hospitals has been a major consideration in the development of the data collection system. Individual contributors have access only to their own indicator rates and pooled state-wide indicator rates. Contributing institutions are urged to use great caution if wishing to compare their own rates with state-wide rates. In particular, contributors are asked to take inter-institutional differences in MRSA burden and casemix complexity into account when making such comparisons. *Commun Dis Intell* 2003;27 Suppl:S92–S96.

Keywords: methicillin-resistant Staphylococcus aureus, *antibiotic resistance*

Introduction

Antibiotic-resistant organisms are now regarded as a significant and growing threat to public health worldwide.[1] In October 2000, the Australian Commonwealth Government released its response to the report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) in which it supported surveillance of antibiotic-resistant organisms at the national level and at the level of individual states and territories.[2]

In response to the Commonwealth Government recommendations, the surveillance system for methicillin-resistant *Staphylococcus aureus* (MRSA) established in South Australia (December 2000), incorporating all the major public and private hospitals, was expanded in September 2001. The primary aim of this enhanced surveillance is to better understand the epidemiology of MRSA infection and colonisation in South Australia; this is seen as an important first step towards the development of effective local control programs.

1. Head, Infection Control Service, Communicable Disease Control Branch, South Australian Department of Human Services, Adelaide, South Australia
2. Infection Control Practitioner, Infection Control Service, Communicable Disease Control Branch, South Australian Department of Human Services, Adelaide, South Australia

Corresponding author: Dr Celia Cooper, Infection Control Service, Communicable Disease Control Branch, South Australian Department of Human Services, 162 Grenfell Street, Adelaide SA 5000. Telephone: +61 8 226 7177. Facsimile: +61 8 226 7187. Email: cdcb@dhs.sa.gov.au

Methods

Sixteen hospitals (eight public and eight private) currently contribute MRSA infection and colonisation data to the South Australian Department of Human Services (SADHS). The definitions and methodology used are based on those for multi-resistant organisms developed by the Australian Infection Control Association National Advisory Board, which are currently published in draft form.[3] MRSA is defined as *Staphylococcus aureus* with acquired resistance to methicillin (usually reported as flucloxacillin- or oxacillin-resistant).

Each month the infection control practitioner responsible for MRSA surveillance at each contributing hospital supplies the following data about discharged patients.

Documented as infected or colonised:

- The number of patients with previously diagnosed MSRA. These patients may either have an infection (defined as an event associated with a sterile site isolate or an event associated with a non-sterile site clinical isolate where MSRA-specific antibiotic therapy was administered by a clinician) or colonisation (defined as a non-sterile site isolate and specific MRSA therapy has not been instituted).
- The number of patients with newly-acquired, healthcare-related MRSA (either colonised or infected). Newly-acquired is defined as, not previously documented as infected or colonised, first detected more than 48 hours after admission or within 48 hours of discharge from the healthcare facility.
- The number of newly-acquired healthcare-related MRSA infections (these may occur in patients previously known to be colonised) where the infection is first detected more than 48 hours after admission or within 48 hours of discharge from the healthcare facility.

For newly-acquired, healthcare-related MRSA cases (infected or colonised) the following patient data is also collected: medical record number; specialty unit (i.e., ICU or non-ICU); processing laboratory and laboratory identification number of isolate; infection status (i.e., infected or colonised); and infection site (i.e., sterile or non-sterile).

In order to calculate rates, the following hospital separations data are also captured each month (excluding day cases): the number of inpatient separations; the number of inpatient occupied bed days (OBDs); and the number of ICU OBDs.

Upon receipt of a hospital dataset at the SADHS, the data are manually entered into a Microsoft Excel 97 workbook. When all the MRSA and separations data for a month have been entered, the new data are then processed to calculate the following three rates, firstly for each individual hospital, and then for all the hospitals combined.

Estimated MRSA burden (estimated prevalence), calculated as follows:

$$\frac{\text{The number of patients (infected or colonised) with MRSA (previously diagnosed) x 10,000}}{\text{OBD}}$$

Estimated MRSA acquisition (estimated incidence), calculated as follows:

$$\frac{\text{The number of patients (infected or colonised) with newly-acquired, healthcare-related MRSA x 10,000}}{\text{OBD}}$$

MRSA morbidity calculated as follows:

$$\frac{\text{The number of newly-acquired MRSA infections x 10,000}}{\text{OBD}}$$

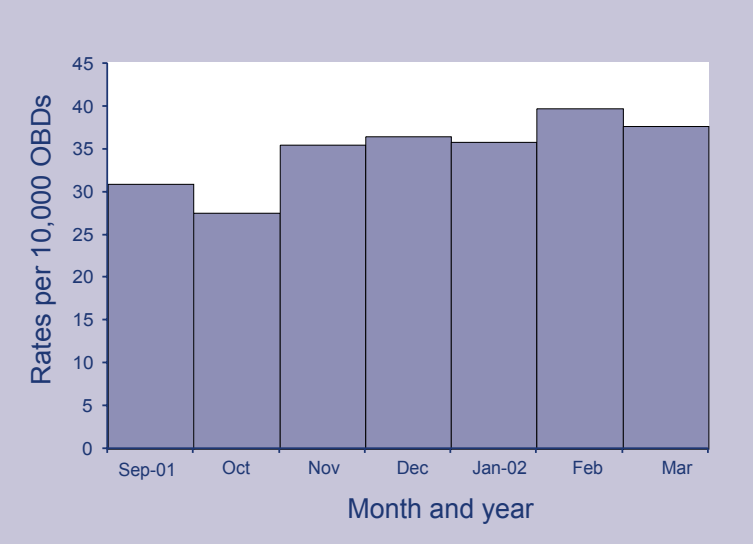
The incidence and morbidity rates are also stratified by ICU or non-ICU.

These rates, along with those for previous months, are incorporated into individual hospital reports, which allow readers to both assess changes over time within their own hospitals and to compare their own rates for the three surveillance indicators with those for all hospitals combined. The highly-automated production of these reports (by way of Excel 'Automation'[4]) helps to ensure that reports are delivered to contributors in a timely manner.

Results

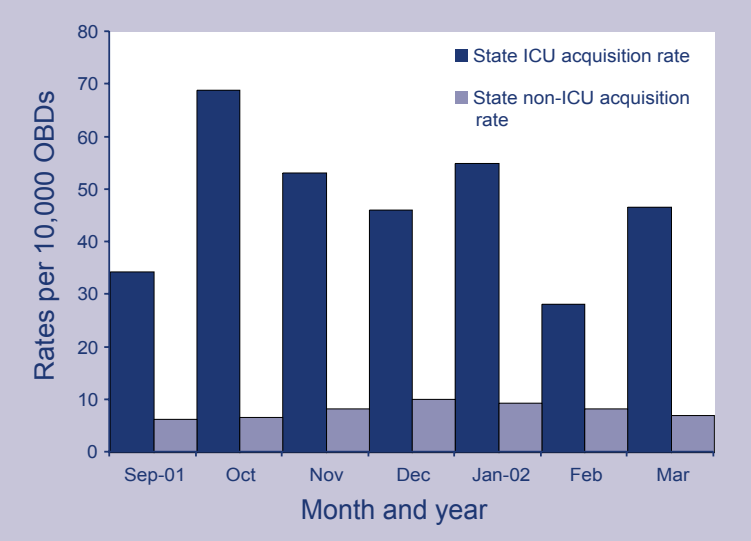
Using combined hospital data for the period 1 September 2001 to 31 March 2002, estimated burden rates range from 27.5 to 39.8 per 10,000 OBD per month (Figure 1). Estimated acquisition rates for the same period range from 28.2 to 69.0 per 10,000 OBD per month (for ICU) and from 6.3 to 10.1 per 10,000 OBD per month (non-ICU) (Figure 2). Morbidity rates range from 12.9 to 43.1 per 10,000 OBD per month (ICU) and from 3.0 to 5.0 per 10,000 OBD per month (non-ICU) (Figure 3).

Figure 1. State-wide estimated methicillin-resistant *Staphylococcus aureus* burden rates for the period 1 September 2001 to 31 March 2002



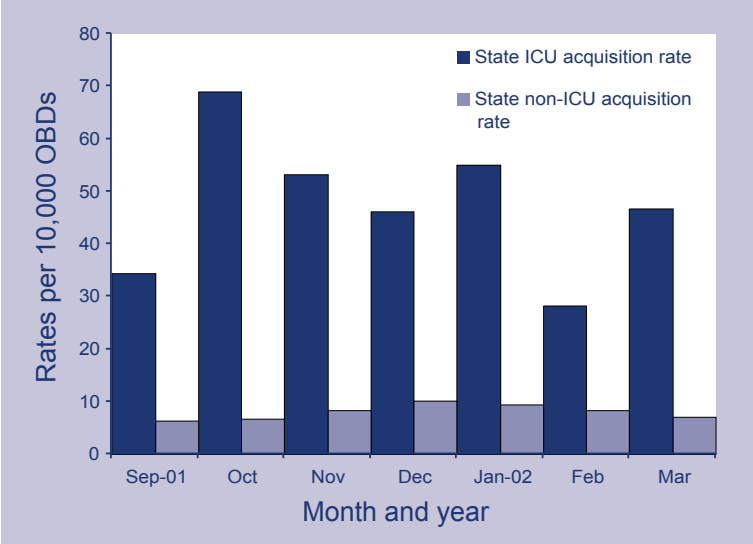
OBD Occupied bed days

Figure 2. State-wide estimated methicillin-resistant *Staphylococcus aureus* acquisition rates for the period 1 September 2001 to 31 March 2002



OBD Occupied bed days
ICU Intensive care unit

Figure 3. State-wide methicillin-resistant *Staphylococcus aureus* morbidity rates for the period 1 September 2001 to 31 March 2002



OBD Occupied bed days

ICU Intensive care unit

Discussion

The release of the JETACAR report and the Commonwealth Government response to JETACAR heralded increased national concern over the public health threat posed by antibiotic-resistant bacteria. This is particularly the case for South Australia, where in 2002, media attention focused on several investigations into antibiotic-resistant bacteria in major public hospitals, helping to highlight the concern that rates of hospital-acquired infection due to antibiotic-resistant bacteria (including MRSA) may be increasing. Information from the Australian Group for Antimicrobial Resistance shows that the proportion of methicillin-resistant *Staphylococcus aureus* isolates in South Australia increased from 4 per cent in 1995 to 23 per cent in 1999 (Dr Peter Collignon, Chair of the Australian Group for Antimicrobial Resistance, personal communication).

Surveillance forms the cornerstone of control programs for all antibiotic-resistant organisms, including MRSA. The surveillance system described in this article has established baseline rates of MRSA acquisition and infection, and is enabling a better understanding of the epidemiology of this organism within South Australian public and private hospitals. We are now better positioned to both monitor the effects of new control measures, such as the use of new hand-hygiene products, or the use of antibacterial coated intravascular catheters, and to deal with new challenges, such as the introduction of new epidemic clones. Data collected will enable us to determine the common antibiotic resistance patterns in hospital-acquired MRSA in South Australia. This analysis has not yet been performed.

With regards to the reports produced by this surveillance system, the advice given by the SADHS to hospital staff is to focus primarily on improving their own rates over time. While there is a place for comparison with state-wide rates, at least in establishing whether or not a hospital's baseline rates are high, hospital staff are urged to do so with great caution. One factor affecting comparability is that South Australian hospitals vary with respect to factors known to influence rates of MRSA acquisition, such as the casemix and the burden of MRSA within the hospital. We are currently working with the contributing hospitals to develop a measure of relative casemix complexity, with the view to possibly adjusting rates according to this measure.

In order to generate high-quality information from this system, it is important to ensure that the contributing hospitals all implement the same surveillance methodology. The SADHS has confirmed that surveillance case definitions and MRSA screening policies (such as screening transfers from other healthcare institutions) are effectively the same for all the contributing hospitals; however, it is important to ensure that hospitals continue to comply with these policies over time.

Involvement in the South Australian MRSA surveillance system is voluntary. This decision was based on the view that mandatory data collection (particularly if attached to punitive consequences) may lead to under-reporting. The SADHS has implemented several strategies in order to encourage hospitals to contribute monthly data. Firstly, regular meetings are convened involving both SADHS staff and hospital infection control staff; these have helped to establish a collaborative relationship with contributing hospitals. Secondly, the system has been designed to ensure that information generated relating to individual hospitals remains confidential. Thirdly, contributors receive feedback in a timely manner, in part due to the high degree of automation achieved in the generation of reports.

Another strength of the South Australian MRSA surveillance system is the inclusion of private hospitals. These hospitals account for a large percentage (32%) of the total number of beds across all the contributing hospitals, and are undertaking increasingly complex procedures. Furthermore, the movement of patients and staff between public and private hospitals in South Australia is such that it makes little epidemiological sense to examine either system in isolation.

In conclusion, this recently-established enhanced surveillance system has improved our understanding of the epidemiology of hospital-acquired MRSA infections in South Australia. Our plan is now to develop similar systems in South Australia to study other resistant organisms, and to look at ways of relating resistance rates to rates of antibiotic usage.

Acknowledgments

We would like to thank the following people for their assistance; members of the South Australian Nosocomial Infection Taskforce and the 16 contributing public and private hospitals for assisting with the development of the surveillance system, Mr Chris Horwood for developing and managing the database and assisting with other aspects of the project and Ms Caroline Gale for assisting with data collection.

References

1. World Health Organization. World Health Organization consultation on global principles for the containment of antimicrobial resistance due to antimicrobial use in livestock, 5–6 June 2000, Geneva, Switzerland. Available from: http://www.who.int/emc/diseases/zoo/drafting.html.
2. Commonwealth Department of Health and Aged Care. *The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR)*. Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia, Canberra 2000.
3. Australian Infection Control Association National Advisory Board. Draft surveillance indicator definitions: multi-resistant organisms. *Australian Infection Control* 2001;6:136–139.
4. McFedries P. Visual basic for applications unleashed. SAMS publishing; Indianapolis, 1997:1000.

Screening and electronic labelling of ward contacts of vancomycin–resistant *Enterococcus faecium vanB* carriers during a single-strain hospital outbreak and after discharge from hospital

John W Pearman,[1] Peta L Perry,[2] Frank P Kosaras,[3] Charles R Douglas,[4] Rosie C Lee,[5] Allison Peterson,[6] C Terri Orrell,[5] Claire H Khinsoe,[2] Christopher H Heath,[7] Keryn J Christiansen[8]

Abstract

A large single-strain outbreak of vancomycin–resistant *Enterococcus faecium* (VREF) *vanB* occurred in Royal Perth Hospital from July to December 2001. When a VREF–carrying patient was discovered on a ward, all patients on the ward were screened with rectal swabs. A total of 172 patients were colonised, four with infections, but no deaths were attributable to VREF. The number of rectal swabs required to detect each carrier was recorded. On average four rectal swabs, each collected on separate days, were needed to detect more than 90 per cent of the 172 VREF carriers who were epidemiologically linked to the Royal Perth Hospital outbreak. An electronic alert system (Micro-Alert) was used to identify ward contacts of VREF carriers and enabled those who had not been screened before discharge to be followed-up and screened. Ninety-six contacts were actively followed-up in October 2001 and 32 (33.3%) were found to be VREF carriers. From 28 September 2001 to 30 April 2002, a total of 1,977 ward contacts were screened after discharge from hospital and 54 (2.73%) were found to be carrying VREF. We conclude that during single-strain outbreaks of vancomycin-resistant enterococci in hospitals, patient contacts need to be screened on more than three occasions in order to detect most of the carriers and control the outbreak. Secondly, electronic labelling and active follow-up of patients with VREF resulted in a significant number of carriers being detected who otherwise posed a risk of initiating further outbreaks in hospitals if they were readmitted. *Commun Dis Intell* 2003;27 Suppl:S97–S102.

Keywords: vancomycin-resistant enterococci, Enterococcus faecium vanB, *alert systems, screening*

Introduction

The control of spread of vancomycin-resistant enterococci (VRE) in hospitals depends largely on the prompt detection of asymptomatic carriers which, in turn, depends on two factors; the collection of a sufficient number of specimens from exposed individuals and the laboratory's ability to promptly and accurately detect VRE. The sensitivity of a single rectal swab is low, being only 79 per cent in one recent study[1] and 58 per cent in another.[2] Since the diagnostic accuracy of one rectal swab is poor, the Division of Public Health, Georgia, United States of America, has recommended that three negative rectal swabs are needed before isolation precautions are discontinued.[3]

1. Head, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Western Australia
2. Senior Medical Scientist, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Western Australia
3. Senior Medical Scientist in charge, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Western Australia
4. Director, Eastern Perth Public and Community Health Unit, Perth, Western Australia
5. Clinical Nurse Specialist, Infection Control, Royal Perth Hospital, Perth, Western Australia
6. Clinical Nurse, Infection Control, Royal Perth Hospital, Perth, Western Australia
7. Infectious Diseases Physician and Clinical Microbiologist, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Western Australia
8. Clinical Microbiologist, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Western Australia

Corresponding author: Professor John W Pearman, Head, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth WA 6000. Telephone: +61 8 9224 2442. Facsimile: +61 8 9224 1989. Email: john.pearman@health.wa.gov.au

On 18 July 2001, a 58-year-old male was admitted to Royal Perth Hospital (RPH) Intensive Care Unit (ICU) with pneumococcal pneumonia. The man had been receiving haemodialysis in the RPH In-centre Dialysis Unit (IDU) three times a week during the previous six weeks. A central venous catheter was inserted on 18 July 2001 and he was given benzylpenicillin intravenously. Five days later he developed bacteraemia and blood cultures collected on 23 July 2001 yielded vancomycin–resistant *Enterococcus faecium* (VREF) *vanB* which was susceptible to teicoplanin. He was treated with teicoplanin 400 mg intravenously after each haemodialysis from 28 July 2001 to 20 August 2001 and survived.

The index patient was a resident of a hostel for people from country areas receiving specialised medical treatment in Perth. Twenty-five residents of the hostel who attended Perth hospitals from 28 July 2001 to 31 December 2001 were screened and 10 of them were found to be carrying the outbreak strain of VREF. All 10 carriers were being dialyzed; nine at RPH and one at another hospital.

Screening of 589 patients on the ICU, IDU, Nephrology ward and Satellite Dialysis Unit (SDU) on multiple occasions from 28 July 2001 to 31 December 2001 detected a total of nine VREF carriers on the ICU, four carriers attending the IDU, 13 carriers on the Nephrology ward and four carriers attending the SDU. Swabbing of these areas demonstrated environmental contamination with VREF on the ICU and Nephrology ward.

Patients carrying VREF were strictly isolated and ward contacts were segregated, cohorted and screened. Wards where carriers were detected were closed and thoroughly cleaned and disinfected in two steps with an anionic detergent followed by a phenolic disinfectant. The wards were then swabbed and not reopened until all environmental swabs were negative for VREF. Despite these measures, transmission of VREF between patients within the RPH continued for five months. Twenty-three wards or units in the hospital and one outpatient unit (SDU) were involved.

As previous studies[1,2] had reported the low sensitivity of a single rectal swab for detecting the carriage of VRE, patients who had been on wards where VREF carriers had been detected (ward contacts) were screened on multiple occasions during their in-patient stay. Screening of patients while they were in RPH detected a total of 118 carriers. The last hospital-acquired colonisation by the outbreak strain of VREF of an in-patient in RPH was detected on 28 December 2001.

It was of concern that many ward contacts of VREF carriers had been discharged from hospital before they had been screened on at least four occasions and it was decided to screen as many discharged ward contacts as possible by collecting at least four rectal swabs on separate days from each of them. Screening of ward contacts after they had been discharged from hospital detected a further 54 carriers, making a total of 172 patients who were colonised.

As a result of the outbreak, four patients were clinically infected with VREF; bacteraemia associated with an intravenous catheter, urinary tract infection associated with an indwelling urethral catheter, peritonitis associated with continuous ambulatory peritoneal dialysis and deep wound infection and subphrenic abscesses following abdominal surgery. No deaths were attributable to VREF but 53 patients have died from causes unrelated to VREF, indicating that many of those who became carriers were suffering from terminal illnesses. Pulsed–field gel electrophoresis of all the isolates and plasmid analysis of 13 isolates demonstrated a single-strain outbreak.

Methods

Screening specimen

The screening specimen used was the rectal swab, which was obtained by dipping a cotton wool tipped swab into sterile water and then gently inserting the swab into the rectum. When the first swab was negative for VREF, further swabs were collected on separate days until at least four negative swabs were obtained. Some patients whose first four swabs were negative had further swabs collected and some of the later swabs were positive. (Table 1).

Table 1. Sensitivity of single and multiple rectal swabs for detecting vancomycin–resistant *Enterococcus faecium* carriers

	Number of carriers						
Number of rectal swabs	1	2	3	4	5	6	7 or more
VREF carriers detected for first time	96	31	17	15	4	2	7
Cumulative number of carriers detected	96	127	144	159	163	165	172
Cumulative percentage of carriers detected (sensitivity)	56	74	84	92	95	96	100

VREF vancomycin–resistant *Enterococcus faecium*.

Contact

A contact was defined as a patient who had been on the same ward as a known carrier of VREF.

Negative contact

A negative contact was defined as a contact who had subsequently had at least four negative rectal swabs collected on separate days.

Laboratory methods

Rectal swabs were first inoculated directly onto CHROMagar®, Orientation medium[4,5] (CHROMagar, Paris, France) containing added vancomycin 6 mg/L and gentamicin 8 mg/L and then placed in Enterococcosel™ broth (BBL Products, Becton Dickinson Microbiology Systems, Maryland, USA) containing added vancomycin 8 mg/L. CHROMagar®, was incubated in air at 35 ± 1ºC for 36 hours (first examined at 24 hours). Enterococcosel™ broth was incubated in air at 35 ± 1ºC for a minimum of 24 hours. Blue colonies resembling enterococci on CHROMagar®, were assayed for *vanA* and *vanB* genes by polymerase chain reaction (PCR). Brown/black Enterococcosel™ broths were subcultured onto CHROMagar®, not containing added antibiotics and incubated in air at 35 ± 1ºC for 24 hours. Blue colonies resembling enterococci on CHROMagar®, were screened for vancomycin resistance using brain heart infusion agar (BHIA)(CM375, Oxoid Ltd, Basingstoke, England) containing added vancomycin 6 mg/L and BHIA containing added vancomycin 16 mg/L. Both BHIA plates were incubated in air at 35 ± 1ºC for 48 hours (first examined at 24 hours). If there was growth on the BHIA vancomycin screening plates, the colonies were Gram-stained and Gram-positive coccal colonies were tested for pyrrolidonyl-ß-naphthylamide production and were assayed for *vanA* and *vanB* genes by PCR. Isolates which were likely to be VRE were identified using motility and standard biochemical tests. Antimicrobial susceptibility tests for ampicillin, gentamicin and vancomycin were performed by disk diffusion according to the National Committee on Clinical Laboratory Standards guidelines.[6] Minimum inhibitory concentrations of vancomycin and teicoplanin for each VRE isolate were determined by Etest®, (AB Biodisk, Sola, Sweden).

Electronic alert system

All public hospitals in the Perth metropolitan area use the same medical record numbering system. Each patient attending a public hospital in Perth is given a unique medical record number which applies in all other Perth public hospitals. The system has several alerts, including Micro-Alert which identifies known carriers of antibiotic-resistant organisms, including methicillin–resistant *Staphylococcus aureus* (MRSA). Micro-Alert was established in 1981 and VRE was included from 1996.

Screening of VREF contacts after discharge from hospital

On 28 September 2001 a new category of Micro-Alert (Micro-Alert 'F') was introduced to identify patients who had been ward contacts of patients found to be VREF carriers and who therefore required four negative swabs to be cleared. These patients were labelled Micro-Alert 'F' and during the outbreak 4,155 contacts were discharged from hospital before they had been swabbed four times.

A program to actively follow-up discharged ward contacts of VREF carriers was undertaken. The aim was to screen as many discharged ward contacts as possible by collecting at least four rectal swabs on separate days from each of them. The swabs were collected in one or more of the following places; the RPH outpatient clinics, on readmission to RPH or on admission to other hospitals. In addition, swabs were collected at the VRE Screening Clinic as described below.

A database was set up which provided demographic details of all VREF carriers and contacts, their admission history by ward and speciality and the number and results of rectal screening swabs collected. From this database all patients from specialities considered high-risk or who had been in high risk wards were identified. The high-risk units were the Nephrology ward and Dialysis Units, Haematology ward and Bone Marrow Transplant Unit and the Intensive Care Unit. In addition, from the database which records the information about all admissions to public hospitals in the Perth metropolitan area, all VREF contacts were stratified according to the number of times they had been admitted to hospital in the previous 12 months. Combining these two lists, patients from high-risk specialities who were frequent attenders were given the highest priority, whilst those who had been admitted to low-risk specialities only once or twice were considered to be very low-risk. A VRE Screening Clinic (VSC) was set up to screen patients on an outpatient basis, to complement the other screening programs which included the screening of inpatients and those attending the pre-admission clinics for routine procedures. Patients were grouped according to priority, and between the months October 2001 to March 2002 letters were sent to patients, starting with the highest priority group. The letters provided them with information about VREF, informed them that they had been in contact with a carrier and offered them four appointments to be screened and, if all swabs were negative, cleared of their 'contact' status. The hospital's voluntary transport scheme was made available for patients who were unable to get to the hospital by themselves. The clinic operated on Monday to Friday from 22 October 2001 to 19 April 2002. In February 2002, those patients on Category 1 and 2 surgical wait lists were included in the program. (The urgency categories for elective admission were: Category 1, within 30 days; Category 2, within 90 days; Category 3, beyond 90 days.) Over the period 22 October 2001 to 19 April 2002, a total of 4,561 appointments were made and 3,241 appointments were kept (response rate 71.06%).

Results

Screening for VRE carriage with rectal swabs

The number of negative rectal swabs collected from each of the 172 VREF carriers before the first positive rectal swab was used to estimate the sensitivity of single and multiple rectal swabs for detecting the gastrointestinal carriage of VREF (Table 1).

Screening of ward contacts after discharge from hospital

From 28 September 2001 to 30 April 2002, 1,977 discharged ward contacts of VREF carriers were screened. The number of negative contacts and the number of contacts found to be carrying VREF each month are listed in Table 2.

Table 2. Vancomycin-resistant *Enterococcus faecium* vanB carriers detected by screening after discharge from hospital

Period	Total number of ward contacts VREF carriers screened afterdischarge or on subsequent presentations to RPH or other hospitals	Number of negative contacts	Number of VREF carriers detected	VREF acquisition rate (%)
2001				
28 Sep –31 Oct	96	64	32	33.3
November	349	340	9	2.6
December	351	345	6	1.7
2002				
January	403	402	1	0.25
February	331	330	1	0.3
March	290	288	2	0.7
April	157	154	3	1.9
Total	**1,977**	**1,923**	**54**	**2.73**

RPH Royal Perth Hospital.
VREF vancomycin–resistant *Enterococcus faecium*.

Discussion

Screening for VRE carriage with rectal swabs

In small outbreaks of VRE, three consecutive negative rectal swabs may be sufficient to discontinue isolation, as recommended by the Division of Public Health, Georgia, USA.[3] However, in larger or prolonged outbreaks, ward contacts of VRE carriers need to have rectal screening swabs collected on more than three separate days before they can be considered not to have acquired VRE.

Screening of ward contacts after discharge from hospital

During previous single-strain MRSA outbreaks in the RPH, a special category of Micro-Alert was used to identify unscreened discharged ward contacts. The alert facilitated their recognition on subsequent presentations to RPH or other hospitals and assisted in successful termination of MRSA outbreaks in the RPH.[7] This technique has now been used for identifying unscreened, discharged, ward contacts during a single-strain hospital outbreak of VREF.

Of the 96 contacts screened at the height of the outbreak (28 September to 31 October 2001), 32 (33.3%) were found to be carrying VREF. In the following months the yields were progressively lower. In the first four months of 2002, 1,181 contacts were screened, resulting in the detection of seven carriers (0.6%) (Table 2). Since the yield declined over time, the VRE Screening Clinic was closed on 19 April 2002 and the Micro-Alert 'F' label will be removed from contacts who have not been screened within 12 months of being labelled.

The post-hospitalisation screening program detected a significant number of carriers who would otherwise have posed a risk to other patients on subsequent admission to hospital, however, the declining yield over time as lower risk patients were being screened allowed the program to be wound down. Active screening of ward contacts after discharge was shown to be a valuable strategy that contributed to the control of this outbreak.

Acknowledgments

We thank Ms Myra Book, Nurse in Charge of the VRE Screening Clinic, and her staff for their dedicated work, the staff of the Royal Perth Hospital Department of Microbiology and Infectious Diseases for their expertise and commitment, Ms Julie Pearson for performing PFGE and Ms Frances O'Brien at the Molecular Genetics Research Unit, Curtin University of Technology, for performing the plasmid analyses.

References

1. Weinstein JW, Tallapragada S, Farrel P, Dembry LM. Comparison of rectal and perirectal swabs for detection of colonisation with vancomycin-resistant enterococci. *J Clin Microbiol* 1996;34:210–212.
2. D'Agata EM, Gautam S, Green WK, Tang YW. High rate of false-negative results of the rectal swab culture method in detection of gastrointestinal colonisation with vancomycin-resistant enterococci. *Clin Infect Dis* 2002;34:167–172.
3. Recommendations for the control of vancomycin-resistant *Enterococcus* (VRE) in healthcare facilities in Georgia. The Georgia VRE Task Force in conjunction with the Division of Public Health, Georgia Department of Human Resources, 1998:6.
4. Merlino J. Detecting enterococci and vancomycin resistance. *Today's Life Science* 1998;10:37–39.
5. Ohkusu K. Cost-effective and rapid presumptive identification of Gram-negative bacilli in routine urine, pus and stool cultures : evaluation of the use of CHROMagar Orientation Medium in conjunction with simple biochemical tests. *J Clin Microbiol* 2000;38:4586–4592.
6. National Committee on Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Tests; Approved Standard – Seventh edition. Document M2–A7 (ISBN 1–56238–393–0). National Committee on Clinical Laboratory Standards; Wayne, Pennysylvania USA, 2000.
7. Pearman JW, Christiansen KJ, Annear DI, Goodwin CS, Metcalf C, Donovan FP, *et al*. Control of methicillin–resistant *Staphylococcus aureus* (MRSA) in an Australian metropolitan teaching hospital complex. *Med J Aust* 1985;142:103–108.

Polymerase chain reaction screening for integrons can be used to complement resistance surveillance programs

Louisa A Jones,[1,2] Christopher J McIver,[1,2,3] William D Rawlinson,[1,2,3] Peter A White[1,2]

Abstract

Integrons have been recognised as important contributors to the acquisition and dissemination of antibiotic resistance in Gram-negative bacteria. In a collection of 19 multi-antibiotic resistant Gram-negative clinical isolates, 47 per cent (9/19) of strains were found to contain one or more integron, using a polymerase chain reaction (PCR) based screening method. Resistance gene cassettes within the integrons were amplified, sequenced and characterised. Antibiotic susceptibility testing demonstrated that resistance phenotypes correlated with the resistance conferred by gene cassettes identified. PCR-screening for integrons and gene cassettes provides a rapid technique for the identification of genetic determinants of resistance in Gram-negative bacteria. Such screening could assist in guiding treatment regimens and complement existing antibiotic resistance surveillance programs by providing information on molecular mechanisms of both resistance and resistance dissemination. *Commun Dis Intell* 2003;27 Suppl:S103–S110.

Keywords: antibiotic resistance, polymerase chain reaction screening, integrons resistance surveillance programs

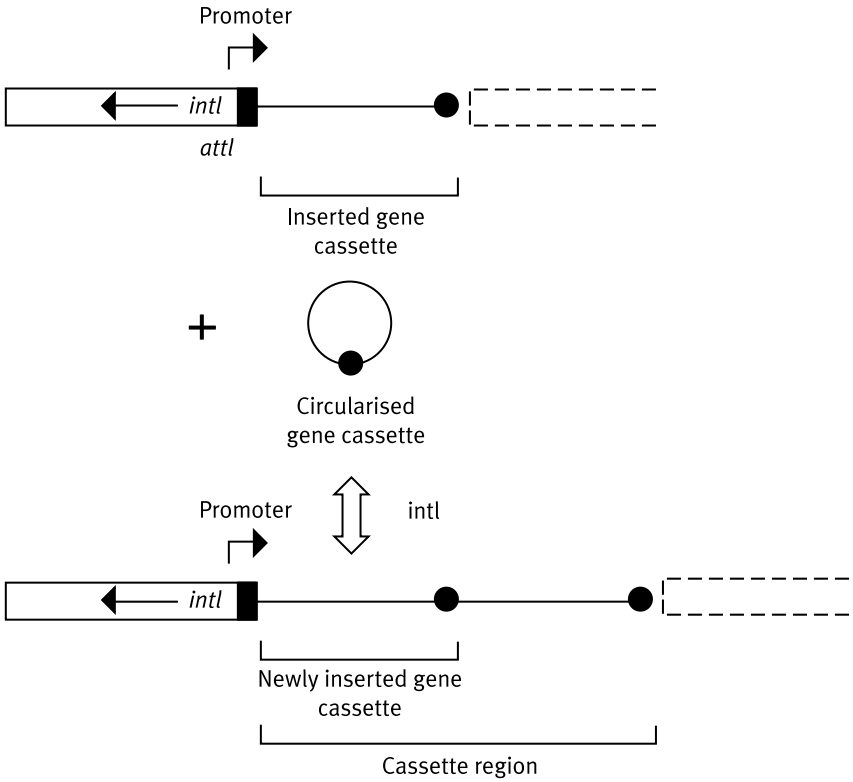
Introduction

Antibiotic resistance is a serious clinical problem worldwide. Acquisition of resistance genes in Gram-negative bacteria is facilitated by mobile genetic elements called integrons, which are associated with resistance plasmids and transposons.[1] Integrons encode an enzyme, termed integrase, which allows them to capture antibiotic resistance gene cassettes (Figure).[2,3] Over 80 cassettes have been identified to date, conferring resistance to almost all classes of antibiotic. The length of gene cassettes varies considerably from 262 base pairs (bp) to 1,549 bp,[4,5] however, a common feature of all gene cassettes is a specific recombination site [termed 59-base element (59–be)], located downstream of the gene. The 59–be is recognised by the integron-encoded integrase (IntI),[6] which enables the gene cassette to be inserted into the integron at a second recombination site (*attI*), located immediately upstream of the integrase gene (*intI*) (Figure).[7,8,9,10] Gene cassette arrays in integrons can consist of up to nine cassettes,[11] which are expressed from an upstream promoter (Figure).[2,12,13] Integrons involved in antibiotic resistance can be divided into three classes, class 1, 2 and 3, based on the amino acid sequence of their respective integrases.

1. Virology Division, Department of Microbiology, SEALS, Prince of Wales Hospital, Randwick, New South Wales
2. Department of Microbiology and Immunology, School of Biotechnology and Biomolecular Sciences, Faculty of Science, The University of New South Wales, Randwick, New South Wales
3. School of Medical Sciences, Faculty of Medicine, The University of New South Wales, Randwick, New South Wales

Corresponding author: Dr Peter White, Virology Division, Department of Microbiology, SEALS, Prince of Wales Hospital, Randwick NSW 2031. Telephone: +61 2 9382 9096. Facsimile: +61 2 9398 4275. Email: whitepa@sesahs.nsw.gov.au

Figure. The insertion of a gene cassette into an integron



The preferential integration of gene cassettes at the *attI* recombination site (indicated by a black box), is catalysed by the product of *intI*, the integrase gene (open box). Two gene cassettes are indicated in the cassette region after the integration event. The filled circle represents the recombination site (59–be) of the gene cassette. A promoter for the expression of integrated gene cassettes, found upstream of the cassette region is also shown.

Integrons are prevalent amongst Gram-negative bacteria and have been associated with antibiotic resistance in clinical isolates.[14,15,16,17,18,19] In a previous study we showed that integrons are significantly associated with multi-resistance in urinary isolates of *Enterobacteriaceae*.[14] Investigations into the prevalence of integrons and characterisation of gene cassettes in clinical isolates provide information on the evolution of multiple-antibiotic resistant strains, the prevalence of antibiotic resistance genes and the molecular mechanisms of antibiotic resistance. This is important when considering strategies for effective antibiotic treatment of bacterial infections.

The present study investigates integrons and gene cassettes in a random selection of Gram-negative clinical isolates that were identified as multi-drug resistant. The presence of antibiotic resistance gene cassettes was correlated with the phenotypic antibiotic resistance profiles to evaluate the contribution of integrons to resistance.

Materials and methods

Clinical isolates

Nineteen randomly selected multi-resistant strains of Gram-negative bacteria from a laboratory collection of clinical isolates were examined (Table 1). All isolates were obtained in 2000 and were considered multi-resistant if resistant to more than four classes of antibiotic. *Escherichia coli* Top 10 and *E. coli* NCTC 10418 were used as integron negative controls, while strains containing class 1, 2 and 3 integrons were also included as positive controls in all experiments.

Table 1. Integron status of bacterial strains studied

Strain	Organism*	Source of isolation†	Integron
INSJ04	*Proteus mirabilis*	N/A	+
INSJ07	*Klebsiella* sp.	Urine	–
INSJ08	*Klebsiella* sp.	Urine	–
INSJ09	*Klebsiella* sp.	Urine	–
INSJ10	*Proteus mirabilis*	Urine	+
INSJ11	*Klebsiella* sp.	Blood	+
INSJ12	*Enterobacter cloaceae*	Wound	–
INSJ14	*Stenotrophomonas maltophilia*	Wound	–
INSJ15	*Acinetobacter baumanii*	Sputum	–
INSJ16	*Klebsiella* sp.	Urine	+
INSJ17	*Acinetobacter baumanii*	Urine	–
INSJ18	*Acinetobacter baumanii*	Urine	–
INSJ19	*Acinetobacter baumanii*	Sputum	–
INSJ20	*Proteus mirabilis*	Urine	+
INSJ21	*Escherichia coli*	Blood	+
INSJ22	*Pseudomonas* sp.	Sputum	–
INS95	*Salmonella typhimurium*	Stool	+
INSTR2	*Citrobacter freundii*	Urine	+
INSTR5	*Enterobacter cloaceae*	Urine	+

* Classification based on standard biochemical criteria.

† N/A: information not available.

Antibiotic susceptibility testing

Susceptibility to antimicrobial agents was determined using the Calibrated Dichotomous Sensitivity method.[20] The antibiotics tested included: aminoglycosides (amikacin, gentamicin, kanamycin, netilmicin, streptomycin and tobramycin), ß-lactams (ampicillin, augmentin, cefotaxime, cefotetan, cephalexin, imipenem and timentin), quinolones (nalidixic acid, norfloxacin), chloramphenicol, nitrofurantoin, sulphafurazole, tetracycline, and trimethoprim.

Detection and classification of integrons and gene cassettes

Methods used to extract bacterial DNA and detect integrons were as previously described by our group.[14,21] Briefly, integrons were detected using polymerase chain reaction (PCR), with primers targeting conserved regions of integron-encoded integrases *intI1*, *intI2*, and *intI3*.[14,21] Integrase PCR products were subjected to restriction fragment length polymorphism (RFLP) analysis, using *Hin*fI and *R*sal to determine integron class as previously described.[14] Gene cassette regions were amplified by PCR and characterised by sequencing and RFLP.[14,21] Analysis of sequence data was performed using programs provided in WebANGIS, by the Australian National Genomic Information Service.

Results

Resistance profiles

All strains tested were resistant to ampicillin, while 18 of 19 (95%) organisms were resistant to cefotaxime, 17 of 19 (89%) organisms were resistant to cephalexin, streptomycin, tobramycin and nitrofurantoin (Table 2). Most strains were susceptible to imipenem, with only 37 per cent of organisms resistant to this antibiotic (Table 2). All strains were resistant to at least 50 per cent of the range of antibiotics tested and one strain, *Acinetobacter baumanii* INSJ18, was resistant to all antibiotics tested (data not shown).

Table 2. Percentage of organisms resistant to antibiotics tested

Antibiotic	Resistant organisms %
Amikacin	63
Gentamicin	79
Kanamycin	84
Netilmicin	68
Streptomycin	89
Tobramycin	89
Ampicillin	100
Augmentin	74
Cefotaxime	95
Cefotetan	47
Cephalexin	89
Imipenem	37
Timentin	84
Nalidixic acid	68
Norfloxacin	58
Chloramphenicol	84
Nitrofurantoin	89
Sulphafurazole	74
Tetracycline	79
Trimethoprim	74

Integron detection and classification

Organisms were screened for the presence of integrase genes by PCR in order to determine the prevalence of integrons in the multi-resistant collection. Nine of 19 (47%) strains contained at least one integron. RFLP analysis revealed that six isolates contained a single class 1 integron, one strain contained two class 1 integrons, one strain contained both a class 1 and a class 2 integron, and in one other strain, a single class 2 integron was detected (Table 3). Class 3 integrons were not detected in this study.

Table 3. Integron cassette arrays and integron-associated antibiotic resistance profiles of integrase positive organisms

Strain	Cassettes contained by integron 1†	Cassettes contained by integron 2†	Resistant to antibiotics*								
			AK	CN	K	NET	S	TOB	AMP	SF	W
P. mirabilis INSJ04	*aacA4, aacC1, orfXa, orfXb, aadA1*	***dfrA1, sat1, aadA1‡***	R	R	R	R	R	R	R	R	R
P. mirabilis INSJ10	***dfrA1, sat1, aadA1‡***	–	R	R	R	R	R	R	R	R	R
Klebsiella sp. INSJ11	*oxa1, aadA1*	–	S	R	R	R	R	R	R	R	R
K. pneumoniae INSJ16	*aadB*	–	R	R	R	R	S	R	R	R	S
P. mirabilis INSJ20	*aacA4, oxa2, orfD*	*aadB, aadA1*	S	R	R	R	R	R	R	R	R
E. coli INSJ21	*dfrA1, aadA1*	–	R	S	S	S	R	S	R	R	R
S. typhimurium INS95	*aadA2*	–	S	R	S	S	R	R	R	R	S
C. freundii INSTR2	NA	–	R	S	R	R	R	R	R	R	R
E. cloaceae INSTR5	*aadA1*	–	R	R	R	R	R	R	R	S	S

* Abbreviations given as standard Calibrated Dichotomous Sensitivity codes: AK amikacin; CN gentamicin; K kanamycin; NET netilmicin; S streptomycin; TOB tobramycin; AMP ampicillin; SF sulphafurazole; W trimethoprim. Resistance (R) and sensitivity (S) are based on interpretation of the Calibrated Dichotomous Sensitivity method of sensitivity testing. Resistance phenotypes encoded by integron-associated resistance genes are underlined.

† Arbitrarily denoted as integron 1 and 2 in the case of strains containing more than one integron. Cassettes are indicated as inserted into the integron from 5' to 3'. NA: not amplified.

‡ Class 2 integrons are indicated in bold type.

Gene cassette characterisation

Analysis of the cassette regions revealed class 1 integrons contained between one and five different gene cassettes (Table 3). Class 2 integrons contained the three gene cassettes associated with Tn*7*, namely *dfrA1* (trimethoprim resistance),[22] *sat1* (streptothricin resistance)[4] and *aadA1* (streptomycin/spectinomycin resistance).[23] A predominance (15/23) of gene cassettes were identified that confer resistance to the aminoglycosides (Table 3). These cassettes were identified as *aadA1* and *aadA2,*[24] *aadB* (resistance to gentamicin, kanamycin and tobramycin),[12] *aacA4* (resistance to amikacin, netilmicin and tobramycin),[25] and *aacC1* (resistance to gentamicin, astromicin and sisomicin).[26] Gene cassettes conferring resistance to trimethoprim (*dfrA1*) and the ß-lactams (*oxa1* and *oxa2*) (i.e., oxacillin and ampicillin resistance)[27,28] were also identified (Table 3). Resistance conferred by the gene cassette correlated with phenotypic resistance as determined by susceptibility testing (Table 3). In addition, all strains containing a class 1 integron with the exception of *Enterobacter cloaceae* INSTR5, were resistant to sulphonamides (Table 3). This sulfonamide resistance is probably due to the presence of a *sul1* gene that is nearly always found downstream of the cassette array in class 1 integrons.

Discussion

Integrons have been recognised as important contributors to antibiotic susceptibility profile of Gram-negative isolates.[14,15,16,17,18,19] Nine of 19 (47%) multi-resistant Gram-negative clinical isolates contained at least one integron, and 2 of 19 (11%) strains contained two integrons. The proportion of strains in this collection of bacteria carrying integrons is comparable to other studies. For example, 49 per cent of 120 urinary isolates of *Enterobacteriaceae* in Sydney were found to carry integrons,[14] 52 per cent of 54 clinical isolates of *E. coli* in Taiwan,[15] and 43 per cent of 163 Gram-negative isolates in European hospitals contained class 1 integrons.[18]

Integrons have not only been found in isolates from human infection. They have also been reported in environmental and animal isolates, for example, integrons have been reported in bacteria from diseased poultry,[29] fish,[30] pigs and cattle[31] and retail ground meats.[32] Thus, there is potential for the transfer of integron-carrying bacteria from these sources to humans.

Up to 50 per cent of multi-resistant strains of *A. baumanii* have been previously reported to carry class 1 and 2 integrons.[33] However, integrons were not detected in the four strains of *Acinetobacter baumanii* in this study although they were resistant to most antibiotics tested (data not shown). These strains, along with the 53 per cent of bacteria that were integron negative, demonstrate that although integrons are significantly associated with a multi-resistance phenotype,[14] multi-resistance in some isolates appears to be mediated by other mechanisms.

In 2000, an outbreak of shigellosis spread rapidly through a community of homosexual men in Sydney and was attributed to a *Shigella sonnei* biotype g strain.[34] Retrospective PCR screening of outbreak strains by our group revealed that they all harboured class 2 integrons that contain resistance genes to streptomycin, streptothricin and trimethoprim.[34] This study highlighted the need for improved control of the spread of resistance-carrying bacteria and demonstrates usefulness of molecular screening techniques for rapid identification of resistance genes. Information provided could have been used to alter the continuation of ineffective antibiotic treatments that occurred during the outbreak.

Integron-screening and gene cassette characterisation can potentially be utilised as a rapid PCR-based method of resistance profile analysis that allows the identification of genetic resistance determinants. Integrons are a marker for multi-resistance, hence integron screening can be used to predict phenotypic antibiotic resistance. The presence of integrons in clinical isolates is of concern due to their ability to capture further gene cassettes. This gives the host organism the potential to acquire resistance against a wide variety of antibiotics, since gene cassettes exist to nearly all classes of antibiotic. Additionally, integron-screening provides the potential for identification of new

resistance gene cassettes, demonstrated by characterisation of two novel gene cassettes *aadA5* and *dfrA17* by our group in 2000.[35] In the present study of Gram-negative multi-resistant bacteria, we have found that integrons contribute considerably to the resistance profiles of nearly 50 per cent of these organisms. This information complements antibiotic resistance surveillance programs, providing information on the molecular mechanisms of resistance in addition to elucidating means of resistance gene acquisition.

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References

1. Hall RM, Collis CM. Antibiotic resistance in Gram-negative bacteria—the role of gene cassettes and integrons. *Drug Resist Updat* 1998;1:109–119.
2. Stokes HW, Hall RM. A novel family of potentially mobile DNA elements encoding site-specific gene-integration functions: integrons. *Mol Microbiol* 1989;3:1669–1683.
3. Hall RM, Collis CM. Mobile gene cassettes and integrons: capture and spread of genes by site-specific recombination. *Mol Microbiol* 1995;15:593–600.
4. Wohllenben W, Arnold W, Bissonnette L, Pelletier A, Tanguay A, Roy PH, *et al*. On the evolution of Tn*21*-like multiresistant transposons: sequence analysis of the gene (*aacC1*) for gentamicin acetyltransferase-3–I (AAC–(3)–I), another member of the Tn*21*-based expression cassette. *Mol Gen Genet* 1989;217:202–208.
5. Bissonnette L, Champetier S, Buisson JP, Roy PH. Characterisation of the nonenzymatic chloramphenicol resistance (*cmlA*) gene of the In4 integron of Tn*1696*: Similarity of the product to transmembrane transport proteins. *J Bacteriol* 1991;173:4493–4502.
6. Hall RM, Brookes DE, Stokes HW. Site-specific insertion of genes into integrons: role of the 59-base element and determination of the recombination cross-over point. *Mol Microbiol* 1991;5:1941–1959.
7. Collis CM, Hall RM. Gene cassettes from the insert region of integrons are excised as covalently closed circles. *Mol Microbiol* 1992;6:2875–2885.
8. Collis CM, Hall RM. Site-specific deletion and rearrangement of integron insert genes catalysed by the integron DNA integrase. *J Bacteriol* 1992;174:1574–1585.
9. Collis CM, Grammaticopoulos G, Briton J, Stokes HW, Hall RM. Site-specific insertion of gene cassettes into integrons. *Mol Microbiol* 1993;9:41–52.
10. Recchia GD, Stokes HW, Hall RM. Characterisation of specific and secondary recombination sites recognised by the integron DNA integrase. *Nucleic Acids Res* 1994;22:2071–2078.
11. Naas T, Mikami Y, Imai T, Poirel L, Nordmann P. Characterisation of In53, a class 1 plasmid-and composite transposon-located integron of *Escherichia coli* which carries an unusual array of gene cassettes. *J Bacteriol* 2001;183:235–249.
12. Cameron FH, Groot Obbink DJ, Ackerman VP, Hall RM. Nucleotide sequence of the AAD(2'') aminoglycoside adenylyltransferase determinant *aadB*. Evolutionary relationship of this region with those surrounding *aadA* in R538–1 and *dhfrII* in R388. *Nucleic Acids Res* 1986;14:8625–8635.
13. Collis CM, Hall RM. Expression of antibiotic resistance genes in the integrated cassettes of integrons. *Antimicrob Agents Chemother* 1995;39:155–162.
14. White PA, McIver CJ, Rawlinson WD. Integrons and gene cassettes in the *Enterobacteriaceae*. *Antimicrob Agents Chemother* 2001;45:2658–2661.
15. Chang C, Chang L, Chang Y, Lee T, Chang S. Characterisation of drug gene cassettes associated with class 1 integrons in clinical isolates of *Escherichia coli* from Taiwan, ROC. *J Med Microbiol* 2000;49:1097–1102.

16. Lee JC, Oh JY, Cho JW, Park JC, Kim JM, Seol SY, *et al*. The prevalence of trimethoprim-resistance-conferring dihydrofolate reductase genes in urinary isolates of *Escherichia coli* in Korea. *J Antimicrob Chemother* 2001;47:599–604.

17. Levesque C, Piche L, Larose C, Roy PH. PCR mapping of integrons reveals several novel combinations of resistance genes. *Antimicrob Agents Chemother* 1995;39:185–191.

18. Martinez-Freijo P, Fluit AC, Schmitz FJ, Grek VSC, Verhoef J, Jones ME. Class I integrons in Gram-negative isolates from different European hospitals and association with decreased susceptibility to multiple antibiotic compounds. *J Antimicrob Chemother* 1998;42:689–696.

19. Senda K, Arakawa Y, Ichiyama S, Nakashima K, Ito H, Ohsuka S, *et al*. PCR detection of metallo-beta-lactamase gene (bla_{IMP}) in gram-negative rods resistant to broad-spectrum ß-lactams. *J Clin Microbiol* 1996;34:2909–2913.

20. Bell SM, Gatus BJ, Pham JN. Antibiotic susceptibility testing by the CDS method. A concise laboratory manual. Arthur Productions Pty Ltd, Sydney. NSW: The antibiotic reference laboratory, South Eastern Area Laboratory Services; 1999.

21. White PA, McIver CJ, Deng YM, Rawlinson WD. Characterisation of two new gene cassettes, *aadA5* and *dfrA17*. *FEMS Microbiol Lett* 2000;182:265–269.

22. Fling ME, Richards C. The nucleotide sequence of the trimethoprim-resistant dihydrofolate reductase gene harbored by Tn*7*. *Nucleic Acids Res* 1983;11:5147–5158.

23. Sundstrom L, Radstrom P, Swedberg G, Skold O. Site-specific recombination promotes linkage between trimethoprim– and sulfonamide resistance genes. Sequence characterization of *dhfrV* and *sulI* and a recombination active locus of Tn*21*. *Mol Gen Genet* 1988;213:191–201.

24. Bito A, Susani M. Revised analysis of *aadA2* gene of plasmid pSa. Antimicrob. *Agents Chemother* 1994;38:1172–1175.

25. Tolmasky ME. Sequencing and expression of *aadA*, *bla*, and *tnpR* from the multiresistance transposon Tn*1331*. *Plasmid* 1990;24:218–226.

26. Tenover FC, Phillips KL, Gilbert T, Lockhart P, O'Hara PJ, Plorde JJ. Development of a DNA probe from the deoxyribonucleotide sequence of a 3–N–aminoglycoside acetyltransferase [AAC(3)–I] resistance gene. *Antimicrob Agents Chemother* 1989;33:551–559.

27. Ouellette M, Bissonnette L, Roy PH. Precise insertion of antibiotic resistance determinants into Tn*21*–like transposons: nucleotide sequence of the oxa–1 ß-lactamase gene. *Proc Natl Acad Sci USA* 1987;84:7378–7382.

28. Hall RM, Vockler C. The region of the IncN plasmid R*46* coding for resistance to ß-lactam antibiotics, streptomycin/spectinomycin and sulphonamides is closely related to antibiotic resistance segments found in IncW plasmids and in Tn*21*-like transposons. *Nucleic Acids Res* 1987;15:7491–7501.

29. Bass L, Liebert CA, Lee MD, Summers AO, White DG, Thayer SG, *et al.* Incidence and characterisation of integrons, genetic elements mediating multiple-drug resistance, in avian *Escherichia coli*. *Antimicrob Agents Chemother* 1999;43:2925–2929.

30. Schmidt AS, Bruun MS, Larsen JL, Dalsgaard I. Characterisation of class 1 integrons associated with R-plasmids in clinical *Aeromonas salmonicida* isolates from various geographical areas. *J Antimicrob Chemother* 2001;47:735–743.

31. Sandvang D, Aarestrup FM. Characterisation of aminoglycoside resistance genes and class 1 integrons in procine and bovine gentamicin-resistant *Escherichia coli*. *Microb Drug Resist* 2000;6:19–27.

32. White DG, Zhao S, Sudler R, Ayers S, Friedman S, Chen S, *et al*. The isolation of antibiotic-resistant *Salmonella* from retail ground meats. *N Engl J Med* 2001;345:1147–1154.

33. Koeleman JG, Stoof J, Van der Bijl MW, Vadenbrouke-Grauls CMJE, Savelkoul PHM. Identification of epidemic strains of Acinetobacter baumanii by integrase gene PCR. *J Clin Microbiol* 2001;39:8–13.

34. McIver CJ, White PA, Jones LA, Karagiannis T, Harkness J, Marriott D, et al. Epidemic strains of *Shigella sonnei* Biotype g carrying integrons. *J Clin Microbiol* 2002;40:1538–1540.

35. White PA, Rawlinson WD. Current status of the *aadA* and *dfr* gene cassette families. *FEMS Microbiol Lett* 2001;182:265–269.

Towards a national surveillance program for antimicrobial resistance in animals and animal-derived food

Jonathan Webber, Angelo Valois

Abstract

One of the major recommendations of the JETACAR report was that a comprehensive national surveillance system be established to measure antimicrobial resistance to cover medical, food-producing and veterinary areas. While there are a number of existing passive surveillance programs on a national, regional and state basis in the medical field, there are few analogous programs in the veterinary area, and none with a particular emphasis on the food chain. The Commonwealth Interdepartmental JETACAR Implementation Group is working with stakeholders to develop this aspect of the national surveillance program based on the Guidelines published by the world organisation for animal health, the Office International des Épizooties. *Commun Dis Intell* 2003;27 Suppl:S111–S116.

Keywords: antimicrobiotic resistance, surveillance programs

Introduction

The Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) made 22 recommendations[1] for an antimicrobial resistance management program that focuses on the use of antimicrobials in both animals and humans. The proposed program covers regulatory controls; monitoring and surveillance; infection prevention strategies; education; and research; communication; and implementation.

A key component of the national program is monitoring and surveillance for antimicrobial resistance—this was addressed in recommendation 10:

> *'That a comprehensive surveillance system be established to measure antibiotic-resistance covering all areas of antibiotic use, including medical, food-producing animal and veterinary areas. Where possible, this should use, enhance and extend currently available systems and organisational structures'.*

The Commonwealth Government response to the report in August 2000 largely supported the JETACAR recommendations and supported the development of a national antimicrobial resistance management program.[2] An important component of the Government's response was to institute a review of existing systems of surveillance and monitoring of antimicrobial resistant bacteria in the human and animal health fields. Tenders were advertised in February 2001 and contractors have been working with departmental officers in the Commonwealth as well as holding consultations with industry and State government stakeholders to develop a national antimicrobial surveillance program.

The consultations identified few antimicrobial resistance surveillance programs in the veterinary area that could be readily adapted into a national surveillance program. There is limited passive surveillance of veterinary pathogens via diagnostic submissions, some passive surveillance of zoonotic organisms (*Salmonella*) and some targeted surveillance undertaken by some industries. The main limitations to using existing veterinary data as the basis of a national program are:

- the existing antimicrobial susceptibility test data has not been generated using standardised test methods;

Correspondence: Dr Jonathan Webber, Principal Research Scientist, Office of the Chief Veterinary Officer, Department of Agriculture, Fisheries and Forestry—Australia, GPO Box 858, Canberra ACT 2601. Telephone: +61 2 6272 5975. Facsimile: +61 2 6272 3150. Email: jonathan.webber@affa.gov.au

- most of the available data are for antimicrobial resistance in clinically significant animal pathogens covering therapeutic antimicrobials used in veterinary medicine;
- there is a lack of data on resistance in commensal bacteria and to those antimicrobials that are used for growth promotant purposes and for some classes of antimicrobials that are not used in food animals in Australia (e.g., fluoroquinolones), but for which resistance is a particular human health concern.

Monitoring and surveillance of antimicrobial resistance derived from the veterinary and agricultural use of antimicrobials will require a new approach. Existing systems are unlikely to meet the animal health and welfare requirements of the animal industries and do not address the public health concerns about resistance that originates from antimicrobial use in animals.

International monitoring and surveillance programs

A number of programs have been instituted in other countries in the past 10 years.

DANMAP (Denmark)[3]

DANMAP which is a collaborative project between the Danish Veterinary Laboratory, the Danish Veterinary and Food Administration, the Statens Serum Institut and the Danish Medicines Agency commenced in 1995. Annual reports cover antimicrobial resistance in bacteria from humans, food and food animals as well as statistics on the consumption of antimicrobials in humans and animals.

National Antimicrobial Resistance Monitoring System (USA)[4]

The National Antimicrobial Resistance Monitoring System was established in 1996 as a collaborative project involving the Food and Drug Administration's Center for Veterinary Medicine, US Department of Agriculture and the Centers for Disease Control and Prevention. The program monitors changes in the susceptibilities of human and animal enteric bacteria to a range of antimicrobials. It is designed to address equally the human and the animal components with bacterial isolates collected from human and animal clinical specimens, from healthy farm animals and from raw products derived from food animals.

Swedish Veterinary Antimicrobial Resistance Monitoring (Sweden)[5]

The Swedish Veterinary Antimicrobial Resistance Monitoring program focuses on both antimicrobial usage statistics as well as on resistance of bacteria of animal origin. To obtain samples representative of the animal population, the number collected at each abattoir is determined in proportion to the number of animals slaughtered at the abattoir each year.

RESABO (France)[6]

RESABO is a network of regional veterinary laboratories in France. The program is managed by a central reference laboratory (CNEVA, Lyon). Features of the program include standardised methods for all laboratories, collation and reporting of data on resistance and undertaking specific studies on mechanisms for resistance.

The appropriate aspects of these programs, together with the international standard developed by the world organisation for animal health, the Office International des Épizooties (OIE), could form the basis for the design of an Australian program.

The international standard

The OIE is the international standards setting organisation recognised by the World Trade Organization for the elaboration of international standards, guidelines and recommendations on matters of animal health and zoonoses relevant for trade in animals and animal products. The OIE has produced a number of guideline documents[7] outlining a comprehensive strategy that can form the blueprint for member countries to manage antimicrobial resistance arising from the agricultural and veterinary use of antimicrobials. The guidelines cover:

- risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin;
- prudent and responsible use of antimicrobial agents in veterinary medicine;
- monitoring the quantities of antimicrobials used in animal husbandry;
- standardisation and harmonisation of laboratory methodologies used for the detection and quantification of antimicrobial resistance; and
- harmonisation of national antimicrobial resistance monitoring and surveillance programs in animals and animal derived food.

Application of the OIE Guideline on monitoring and surveillance to Australia

The OIE Guideline was developed by an ad hoc group of experts on antimicrobial resistance of the OIE. The objective is to allow the generation and consolidation of comparable results on a national level and to compare the situations on a national, regional and international level. National systems should be able to detect the emergence of resistance and to determine the prevalence of resistant bacteria. The resulting data can then be used in the assessment of risks to public health and form the basis of risk management policy. Specific factors identified for harmonisation include antimicrobial usage patterns, animal species, food commodities, bacterial species, antimicrobials to be tested, laboratory methods, and data reporting.

Risk assessment

A comprehensive risk assessment should take account of agricultural production systems, animal husbandry and antimicrobial usage patterns in Australia. This, together with the subsequent issues discussed in this paper, will be used in the development of a surveillance program for antimicrobial resistance of food-animal origin.

Antimicrobial usage patterns

Acquired antimicrobial resistance arises from the selection pressure exerted on bacteria by antimicrobials in their immediate environment. The types of antimicrobials used and the extent, quantities and patterns of their use should be taken into account in designing a surveillance program. Mechanisms to collect these data objectively are needed.

Animals to be sampled

A risk assessment should take account of the relative importance of the various categories of livestock in potentially contributing to antimicrobial resistance. A key consideration will be knowledge of antimicrobial use patterns in the various livestock industry sectors. Categories of livestock that should be considered for sampling include cattle and calves, slaughter pigs, broiler chickens, layer hens, and farmed aquatic animals.

Food to be sampled

Contaminated food is the principal route of transmission of antimicrobial resistance from animals to humans, either by pathogens or by transfer of resistance genes carried by commensal bacteria. The earlier in the processing chain that samples can be taken, the more likely it is that susceptibility test results can be associated with on-farm management issues.

Sampling strategies

Once the objectives of any program are decided, an early decision is whether reliance can be made on existing passive surveillance programs (usually based on data from veterinary diagnostic submissions), whether existing programs need to be modified or whether a new active surveillance program should be undertaken to meet the objectives.

The sampling strategy should ensure the representativeness of the population of interest. Options for sampling[8] are simple random, random systematic, stratified random collection (e.g., by age group or production system) or purposive sampling (targeted at specific groups e.g., cull dairy cows) with random sampling within each group. If the sampling strategy is robust then use of statistically based sample sizes will allow a more accurate estimate of the prevalence of antimicrobial resistance in the population of interest.

Some knowledge of the expected prevalence of resistance will allow decisions to be made on the number of samples that will be required to give the desired level of precision of the prevalence estimate. For example, if the expected prevalence in a large population were 10 per cent, then the number of samples required to give a statistically valid estimate of the prevalence with 5 per cent precision and 95 per cent level of confidence would be 138 samples.

Sample specimens to be collected

Ideally samples should be taken on-farm. While this may be an option for individual sick animals, the most practical point of sampling is at the abattoir or processing plant where animals from a number of properties can be sampled over a relatively short period of time. In these circumstances, the best specimen for investigating resistance is faeces (10–50 gm) in livestock and whole caeca in poultry. If the interest is surveillance of resistance in the food chain after slaughter, then tissue or swab samples should be taken from the carcass or food product.

Bacteria to be tested

The bacteria of interest are listed in Table 1 and can be divided into three groups.

Table 1. Bacteria for potential inclusion in a surveillance program

Target animals	Pathogens	Zoonotics	Commensals
Cattle	*Pasteurella* spp. *Haemophilus somnus* *Staphylococcus aureus* *Streptococcus agalactiae/uberis*	*Salmonella* spp.	*Escherichia coli* *Enterococcus faecium/faecalis*
Pigs	*Actinobacillus pleuropneumoniae* *Brachyspira* *Streptococcus suis*	*Salmonella* spp.	*Escherichia coli* *Enterococcus faecium/faecalis*
Poultry	*Escherichia coli*	*Campylobacter* *Salmonella* spp.	*Escherichia coli* *Enterococcus faecium/faecalis*
Fish	*Vibrio* spp. *Aeromonas* spp.		

Animal pathogens

Monitoring of resistance in animal pathogens will allow early detection of the emergence of resistance that could be of animal (and human) health concern. The results can be used by veterinarians to make informed prescribing decisions and in developing prudent use guidelines.

Zoonotic bacteria

Samples for isolation of *Salmonella* can either be taken at the abattoir, or isolates originating from other sources can be obtained from national laboratories such as the National Enteric Pathogens Surveillance Scheme and the Australian Salmonella Reference Centre. Isolates should be identified and serotyped according to international methods. *Campylobacter* isolates should be identified to species level.

Commensal/indicator bacteria

Escherichia coli and enterococci are regarded as commensal bacteria common to all animals and man. They constitute a reservoir of resistance genes that are capable of transmission to pathogens or to other commensals. It is particularly important that the various enterococcus species are correctly identified, as there are differences in innate resistance to some antimicrobials among the different species.

Antimicrobials to be used in susceptibility testing

It would be cost-prohibitive to monitor all clinically important antimicrobials used in animals and humans. Table 2 contains a list of antimicrobial groups that could be considered for inclusion in a national surveillance program. Priority should be given to monitoring those antimicrobials identified in the risk assessment as having the greatest public or animal health concern in Australia.

Table 2. Antimicrobials that may be included in an antimicrobial resistance surveillance program

Antimicrobial class	Animal pathogens Gram –ve	Animal pathogens Gram +ve	*Salmonella/ Escherichia coli*	*Campylobacter*	*Enterococcus*
Aminoglycosides	+	+	+		+
Amphenicols	+	+	+		
Beta-lactams	+	+	+	+	+
Cephalosporins	+		+		
Glycopeptides		+			+
Lincosamides		+			
Macrolides		+		+	+
Quinolones	+	+	+	+	+
Streptogramins					+
Sulfonamides	+		+		
Tetracyclines	+	+	+	+	+

Standardised testing methods and quality control

A wide variety of antimicrobial sensitivity test (AST) methods are used around the world. The most commonly used methods are disk diffusion, broth dilution and agar dilution. Regardless of the AST method used, all aspects of the method must be rigorously standardised to ensure accurate and reproducible results. Appropriate reference organisms should be included in every AST run as a quality control measure to ensure the accuracy of the test results. Where a number of laboratories are involved in a testing program, it is advisable that the same method is used in all laboratories and that the performance of laboratories is monitored through regular participation in a proficiency testing program.

Data collation and reporting

In choosing an AST method, it is preferable that the result can be recorded quantitatively (minimum inhibitory concentration in mg/Litre or inhibition zones in millimetres) rather than qualitatively as 'resistant' or 'susceptible'. This will allow the early detection of emerging resistance and trends to be followed. Consideration needs to be given to having the raw data sent to a central point for entry into a national database to facilitate evaluation of the data in response to various questions and for the generation of regular reports for the information of national regulatory agencies and the public.

Conclusion

This paper has provided some background and made recommendations for factors to be considered in the development of an antimicrobial resistance surveillance program for Australia. It may be necessary to develop the program in an incremental way based on priorities established through a risk assessment that considers animal husbandry conditions in Australia and their associated antimicrobial use patterns.

References

1. Commonwealth Department of Health and Aged Care. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). *The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans*. Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia. September 1999. Available from: http://www.health.gov.au/pubs/jetacar.pdf.
2. Commonwealth Department of Health and Aged Care. *Commonwealth Government response to the report of the JETACAR*. Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia. August 2000. Available from: http://www.health.gov.au/pubhlth/publicat/document/jetacar.pdf.
3. Danish Veterinary Institute. The Danish Integrated Antimicrobial resistance Monitoring and Research Programme (DANMAP) 2001. Available from: http://www.vetinst.dk/high_uk.asp?page_id=180.
4. US Food and Drug Administration. National Antimicrobial Resistance Monitoring System. US Food and Drug Administration, Center for Veterinary Medicine. Available from: http://www.fda.gov/cvm/index/narms/narms_pg.html.
5. National Veterinary Institute of Sweden. Swedish Veterinary Antimicrobial Resistance Monitoring, 2001. National Veterinary Institute, Uppsala, Sweden. Available from: http://www.sva.se/dokument/stdmall.html?id=341&lang=e.
6. Martel J-L, Brisabois A, Tardy F, Chaslus-Dancla E. The French Antibiotic Resistance Monitoring Programmes. Antibiotic Resistance in Bacteria from Animal Origin, Concerted action FAIR5-CT97-3654. European Symposium. Institut Pasteur Paris 29–30 November 1999. French Agency for Food Safety. Available from: http://www.fougeres.afssa.fr/arbao/martel.html.
7. Office International des Épizooties. OIE guidelines. 2nd OIE International Conference on Antimicrobial Resistance. Use of antimicrobials and protection of public health. 2001. Available from: http://www.anmv.afssa.fr/oiecc/conference/guidelines.htm.
8. Graat EAM, Frankena K, Bos H. Principles and methods of sampling in animal disease surveys. In: Noordhuizen JPTM, Frankena K, Van der Hoofd CM, Graat EAM editors. *Application of Quantitative Methods in Veterinary Epidemiology*. Wageningen, The Netherlands: Wageningen Press, 1997:33–36.

Surveillance for antibiotic resistant *Escherichia coli* in food animals

David Jordan

Abstract

A successful surveillance program for antibiotic resistant *Escherichia coli* in Australia should account for the heterogenous nature of the food-animal population. Studies that rely on measurements made on several hundred isolates can only satisfy limited objectives because they risk imprecise and biased estimation of the presence and distribution of resistance traits. Observations on a larger number of isolates are needed to ensure animal, herd and region effects are adequately represented so that findings can be extrapolated to the appropriate population of interest. An efficient methodology for measuring the resistance traits of a large number of isolates is described. *Commun Dis Intell* 2003;27 Suppl:S117–S120.

Keywords: Escherichia coli, *antibiotic resistance, food animals, livestock*

Introduction

Generic indicator organisms such as *Escherichia coli* play a prominent role in many existing surveillance systems for antibiotic resistance in animals.[1] *E. coli* is regarded as a useful indicator of antibiotic resistance in the bacterial flora of livestock and food because it responds to the selective pressures of antibiotics, because it is ubiquitous in the gut of food animals, and because it readily persists in raw foods and the environment. Individual *E. coli* isolates are easily studied in the laboratory to yield results that can be interpreted using standard criteria. *E. coli* is therefore a strong candidate for inclusion in future studies of the spatial and temporal distribution of antibiotic resistance in Australian livestock and livestock products.

Practical considerations

Future surveillance systems for antibiotic resistance will need to allow for the extreme heterogeneity that characterises livestock production in Australia. There are a plethora of animal species, animal breeds and management systems located within many different climatic regions. Hence, food-animal production occurs in diverse environments resulting in variable degrees of exposure to possible sources of resistant organisms (other herds or flocks, humans, wildlife and environmental contamination). Even at a particular locality and within a specific industry there can be large differences in husbandry practices. Antibiotic usage patterns range from continuous inclusion of low-concentrations in rations in some intensive production systems to extremely rare, highly selective or even absent in the extensive beef and sheep grazing industries.

The underlying complexity of the animal industries impacts on the ways in which surveillance for resistant *E. coli* could be conducted. In particular, the low profitability of some production systems and the low monetary value of most individual animals explains why veterinary laboratories receive only a small number of requests for antibiotic resistance testing of *E. coli* isolates from food animals. Moreover, the selective nature of veterinary diagnostic submissions means that the *E. coli* isolates obtained from diagnostic testing are not likely to be representative of those entering the food chain. Thus, passively acquired data appear to be poorly suited to accommodating the complexity present in the underlying population of *E. coli* derived from animals. Purposefully designed surveys of the livestock population and livestock products are best suited to providing data forming a basis for national policies.

Correspondence: Dr David Jordan, Senior Research Scientist, New South Wales Agriculture, Bruxner Highway Wollongbar NSW 2477. Telephone: +61 2 6626 1240. Facsimile: +61 2 6628 1744. Email: david.jordan@agric.nsw.gov.au

Implementation of active surveillance

Active surveillance for resistant *E. coli* in animal populations should be designed and analysed to account for the sources of variation in the population of isolates and valid confidence limits for the proportion of *E. coli* with a specific resistance trait can be generated. Confidence limits need only be as narrow as required by the study objectives which in turn should reflect how the surveillance findings will contribute to decision making. It is also a requirement that the strength of association between risk factors and the occurrence of resistance be estimated without bias. To meet these aims a number of sampling issues need to be addressed. One of these is the requirement to test a sufficient number of isolates, a sufficient number of animals, herds (flocks), and at a sufficient number of points in time to allow firm inferences to be made about the distribution of resistance and sources of variation. A second requirement is the need to ensure that sampling is performed to account for the likely 'contagious' or 'clustered' pattern of distribution of resistant isolates. A third consideration is to design sampling methods that allow confidence interval estimates of prevalence to be produced that are based on all of the sources of variation in the population. The latter requirement can usually be satisfied by using statistical techniques for estimation of variance components provided an appropriate study design is implemented.[2] However, the first two of these requirements have hitherto been difficult to satisfy because the high cost of assessing a large number of *E. coli* isolates has restricted the options available for study design. Thus, only small numbers of herds, product consignments, or regions appear to be represented in most existing data and it is difficult to extrapolate the findings beyond those animals or products included in the study.

To illustrate the importance of sample size and sampling error one can make the simplifying assumption that the resistance phenotypes of interest occur at random throughout the populations of *E. coli*, animals and herds. The required sample size for estimating prevalence can then be calculated from the binomial probability distribution. If the objective is to estimate the prevalence of tetracycline resistance (at a particular concentration) amongst *E. coli* isolates from intensively-raised animals, such that the 95 per cent confidence limits are each within 5 per cent of the point estimate, then about 400 isolates would require evaluation (this assumes the expected prevalence is close to 50 per cent — an assumption that is justified on the basis of published estimates from pigs and poultry,[3,4,5] and because it is appropriate to err closer to 50 per cent to ensure a sufficient sample size). The required sample size is between 1.3 and 2 times greater that number relied upon in various national surveys to assess the proportion of resistant *E. coli* from a single animal species or product.[4,5,6] Moreover, this sample size calculation is probably an underestimate because it assumes that the only variation is due to random error, that is, it takes no account of the likely non-random distribution of resistance isolates in the population of interest.

'Clustering' (likeness amongst observations close in time or space) is a term used to describe the non-random source of variation that is commonly associated with the distribution of infectious agents or disease events. In the case of antibiotic resistance in animal populations, clustering could feasibly be induced by a range of determinants of resistance (known or unknown) such as exposure to antibiotics in rations or exposure to human effluent contaminating the environment. In veterinary epidemiology clustering is often exaggerated because of the way that animals are managed in commercial units (herds or flocks), and by the way that herds and flocks at a similar geographic location tend to have a common set of risk factors.[7] Sometimes clustering occurs for no obvious reason and this has been shown to be the case for the clustering of particular resistant *E. coli* phenotypes within individual pigs housed in the same pen.[8] The pervasiveness of clustering prevents the indiscriminate use of binomial probabilities (or any approximations thereof) for generating confidence limits or sample sizes. Unfortunately, the estimation of sample sizes (number of isolates, number of animals, number of herds or flocks etc.) is difficult in the absence of any estimates of variance. The number of isolates required to be evaluated could be several times greater than what is predicted by the approach described above. Consequently, during the initial phases of surveillance there is a need to estimate components of variance attributable to the different levels of sampling (isolates, animals, herds, or flocks etc.) to aid in the design of subsequent sampling plans.

New methodology

To overcome the difficulties of study design and sampling, a laboratory technique for assessing large numbers of *E. coli* isolates per specimen has been adopted in a pilot study of dairy cattle in north-eastern New South Wales. The aims are to develop methodology that could be used to efficiently study the distribution of resistance in animals, humans and environmental samples. The approach has been adapted from work on *E. coli* in pig populations in Canada[3] and is based on hydrophobic grid membrane filtration (HGMF). Key elements of the procedure are: the growth of *E. coli* by filtering diluted animal faeces through HGMF grids, incubation of grids on selective agar, replication of colonies onto HGMF grids that are either incubated on chromogenic agar (for *E. coli* identification) or on agar containing antibiotics and made to standard specifications.[9] The final and critical step for achieving economy of scale is to use computer software to perform image analysis of HGMF grids to detect the growth of *E. coli*, to compute multiple resistance patterns for each isolate, and to incorporate the findings for each specimen in a surveillance database. The process is summarised in the Table.

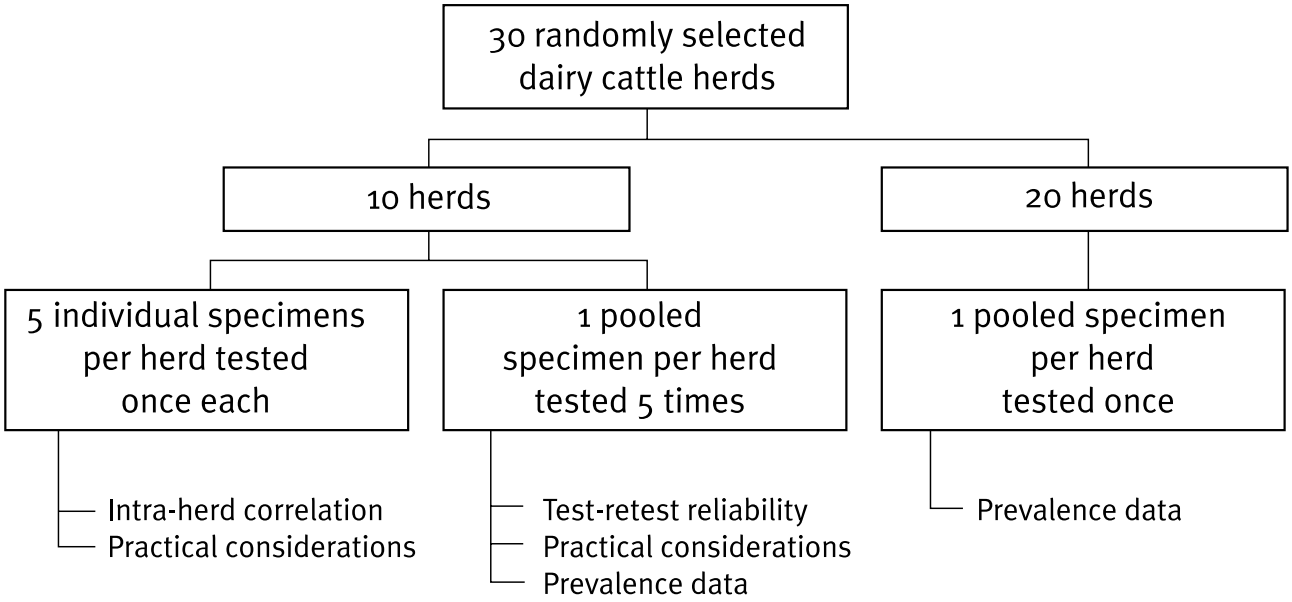
Table. Summary of steps performed during antibiotic resistance testing of *Escherichia coli* derived from cattle faeces using the HGMF procedure and image analysis

Step 1.	Fresh cattle faeces obtained during farm visits.
Step 2.	Tenfold serial dilution of specimens prepared and stored.
Step 3.	Preliminary estimation of the concentration of *E. coli* per gram of faeces determined by spread plate or HGMF enumeration technique.
Step 4.	A master HGMF grid is produced by filtering an appropriate volume of diluted cow faeces to provide 100 to 200 colonies following incubation.
Step 5.	Colonies are replicated from the master grid onto grids placed on chromogenic agar for presumptive identification of *E. coli*.
Step 6.	Colonies are replicated from the master grid onto grids placed on agar containing antimicrobials at National Centre for Clinical Laboratory Standards (NCCLS) recommended concentrations. A copy is also placed on agar containing no antimicrobials.
Step 7.	Chromogenic, antimicrobial and control agar plates are incubated overnight.
Step 8.	Consistent interpretation of colony growth is achieved by capturing digital images of HGMF grids and analysing using specific software.
Step 9.	Collation and standardised reporting of single and multiple resistance traits is achieved within the software.

The advantages of the HGMF approach are that it can be used to appraise single and multiple resistance traits of up to 200 colonies per specimen. The use of image analysis provides a standard interpretation of results and avoids errors encountered with manual data recording. In the New South Wales study this has enabled deployment of a study design for deriving variance components followed by calculation of intracluster (intra-herd) correlation. The latter is useful for quantifying the extent of likeness within groups (in this case the clustering of *E. coli* resistance trait within herds of cattle) which impinges on the interpretation and analysis of data and is of interest in the design of future studies.[10] The study will also provide prevalence estimates (proportion of isolates, proportion of herds) for single and multiple resistance traits for four antibiotics (gentamycin, ampicillin, tetracycline and sulfamethoxazole) at NCCLS 'intermediate' concentrations[9] based on observations made on approximately 10,000 isolates from 30 randomly-selected dairy herds. Test-retest reliability[11] is also being evaluated on pooled faecal samples from 20 dairy farms. Overall, the study will help generate the statistical assumptions required for a more comprehensive survey of livestock. The Figure summarises the design of this study.

Conventional approaches to surveillance for antimicrobial resistance in livestock and food usually rely on disk diffusion, agar dilution or broth dilution techniques. These methods are suited to comprehensive screening of individual isolates against a large number of drugs and drug concentrations. They are often chosen because they can provide data for commensals, animal pathogens, and zoonotic pathogens that can be compared to the data being obtained for human pathogens. Furthermore, because many technicians are familiar with these methods they are a convenient basis for standardisation of measurement systems. However, because these techniques are costly on a per isolate basis they are less appealing for ecological and population based studies that demand the evaluation of resistance traits of a large number of indicator organisms, such as *E. coli*.

Figure. Design of the pilot study for assessing prevalence of resistance, intra-herd clustering, and test-retest reliability



Although there is no limit to the number of antibiotics or concentrations that may be evaluated in the HGMF resistance test, restricting the number of antibiotics avoids the difficulty of having to interpret data for a large number of resistance patterns (if *a* is the number of antibiotics evaluated then the test produces information on 2^a resistance patterns). HGMF resistance testing is therefore suited to screening a very large number of isolates against a panel of the most important antibiotics. It is attractive to combine HGMF testing with other research on the biology of resistance by removing a sub-sample of screened isolates for more detailed analysis by conventional resistance tests or molecular techniques.

References

1. Wray C, Gnanou JC. Antibiotic resistance monitoring in bacteria of animal origin: analysis of national monitoring programmes. *Int J Antimicrob Agents* 2000;14:291–294.
2. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS system for mixed models. Cary, N.C.: SAS Institute Inc.; 1996.
3. Dunlop RH, McEwen SA, Meek AH, Clarke RC, Friendship RM, Black WD *et al*. Measurement of antimicrobial-resistant *Escherichia coli* in pig feces with a hydrophobic grid membrane filter interpreter system. *Appl Environ Microbiol* 1998;64:366–369.
4. Barton MD, Wilkins J. Antibiotic resistance in bacteria isolated from poultry. Canberra: Rural Industries Research and Development Corporation; 2001.
5. Barger F Editor. DANMAP 99 — Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. Copenhagen: Danish Veterinary Laboratory; 1999.
6. Bengtsson B, Franklin A, Greko C, Karlsson MWC. SVARM 2000 — Swedish veterinary antimicrobial resistance monitoring. Uppsala: National Veterinary Institute, Sweden.
7. Bohning D, Greiner M. Prevalence estimation under heterogeneity in the example of bovine trypanosomosis in Uganda. *Prev Vet Med* 1998;36:11–23.
8. Dunlop RH, McEwen SA, Meek AH, Friendship RM, Black WD, Clarke RC. Sampling considerations for herd-level measurement of faecal *Escherichia coli* antimicrobial resistance in finisher pigs. *Epidemiol Infect* 1999;122:485–496.
9. National Centre for Clinical Laboratory Standards, Document M07-A5 'Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically', Approved Standard. 5th edition; 2000.
10. Baskerville NB, Hogg W, Lemelin J. The effect of cluster randomization on sample size in prevention research. *J Fam Pract* 2001;50:W241–W246.
11. Streiner DL, Norman GR. Health Measurement Scales. Second edition. Oxford, UK: Oxford University Press; 1995:231.

Antibiotic resistance in animals

Mary D Barton,[1] Rachael Pratt,[2] Wendy S Hart[3]

Abstract

There is currently no systematic surveillance or monitoring of antibiotic resistance in Australian animals. Registration of antibiotics for use in animals is tightly controlled and has been very conservative. Fluoroquinolones have not been registered for use in food producing animals and other products have been removed from the market because of human health concerns. In the late 1970s, the Animal Health Committee coordinated a survey of resistance in *Salmonella* and *Escherichia coli* isolates from cattle, pigs and poultry and in bovine *Staphylococcus aureus*. Some additional information is available from published case reports. In samples collected prior to the withdrawal of avoparcin from the market, no vancomycin resistant *Enterococcus faecium* or *Enterococcus faecalis* were detected in samples collected from pigs, whereas some *vanA* enterococci, including *E. faecium* and *E. faecalis*, were found in chickens. No *vanB* enterococci were detected in either species. Virginiamycin resistance was common in both pig and poultry isolates. Multiple resistance was common in *E. coli* and salmonellae isolates. No fluoroquinolone resistance was found in salmonellae, *E. coli* or *Campylobacter*. ß-lactamase production is common in isolates from bovine mastitis, but no methicillin resistance has been detected. However, methicillin resistance has been reported in canine isolates of *Staphylococcus intermedius* and extended spectrum ß-lactamase producing *E. coli* has been found in dogs. *Commun Dis Intell* 2003;27 Suppl:S121–S126.

Keywords: antibiotic resistance, food-producing animals

Introduction

There is no formal system for monitoring or surveillance of antibiotic resistance in animal bacterial isolates in Australia. Although some investigations were conducted in the late 1970s and into the 1980s, there was little standardisation of sensitivity testing methods so it is difficult to compare this historical data with that which may be produced in the future. The lack of historical data is compounded by the fact that little, if any was published in readily available form and/or was lost with the rationalisation of veterinary laboratories that began in the late 1980s and continues to this day. However, in response to the JETACAR report[1] there is an opportunity to establish *de novo*, a new system of antibiotic resistance surveillance, if agreement can be reached between the relevant government and industry stakeholders on how it should be funded.

Background

Australia has had a conservative approach to registration of antibiotics for use in food-producing animals, particularly since the Swann report[2] recommended that antibiotics important in animal and human health not be used as growth promotants or production enhancers. Initially, the main purpose of controls was to ensure minimal antibiotic (chemical) residues in meat and dairy products, but since the early 1980s the potential for transfer of resistant bacteria and genes from animals to humans has been taken into account. As a result of this approach, neither fluoroquinolones nor gentamicin have been registered for use in food-producing animals and chloramphenicol, furazolidone and carbadox were removed from use in food-producing animals because of human toxicity concerns. Only one third or fourth generation cephalosporin (Ceftiofur) has been registered for use in animals. This product was

1. Professor and Head of School of Pharmaceutical, Molecular and Biomedical Sciences, University of South Australia, Adelaide, South Australia
2. Hospital Scientist, Institute of Medical and Veterinary Science, Rundle Mall, Adelaide, South Australia
3. PhD Student, University of South Australia, Adelaide, South Australia

Corresponding author: Professor Mary D Barton, Professor and Head of School of Pharmaceutical, Molecular and Biomedical Sciences, University of South Australia, GPO Box 2471, Adelaide SA 5001. Telephone: +61 8 8302 2933. Facsimile: +61 8 8302 2389. Email: mary.barton@unisa.edu.au

registered specifically for treatment of respiratory infections in cattle, but inconsistencies in state and territory 'control of use' legislation has meant that in some states and territories it has been used in other food-producing animals. Work is underway to have uniform 'control of use' legislation operating in most states and territories by mid-2003.

Antibiotics are used in animals to treat and prevent infections. In food-producing animals, antibiotics have also been used for growth promoting or production enhancing purposes. Antibiotics used in this way are fed to animals at subtherapeutic concentrations for extended periods of time. Invariably, such use is not under the control of a veterinary surgeon—farmers and stock feed manufacturers purchase these products direct from retailers and wholesalers. A restricted range of products is registered for 'growth promotant' use, with the most contentious (from a human health perspective) being avoparcin (a glycopeptide), virginiamycin (a streptogramin) and tylosin (a macrolide). Such antibiotics are used in Australia primarily for the control of chronic enteric infections such as necrotic enteritis in meat chickens and swine dysentery and ileitis in pigs, rather than as 'pure' growth promotants. In addition, ionophores, which are not used in human medicine, are used for control of coccidiosis in chickens and lactic acidosis in cattle and sheep fed high grain rations. Ionophores account for a very large proportion of growth promotant antibiotics used in Australia.

Intensively farmed pigs, poultry, feedlot cattle and sheep account for most antibiotic use in food-producing animals. Therapeutic and prophylactic use (as well as growth promotant use) is often by mass medication through feed or water because of the numbers of animals involved. Antibiotics are rarely used in extensively grazed beef cattle or sheep but individual dairy cows may be treated on occasion and in-feed products can be used to control lactic acidosis. Mass medication (intramammary) can be used at the end of lactation to help control mastitis. Intramammary use during lactation is contra-indicated and is obvious in milk of treated animals through the presence of a blue dye which is a mandatory inclusion in these products.

The extent to which antibiotics are used in aquaculture in Australia is largely unknown. In line with international trends, there is increasing pressure being brought to bear on industry and regulators to use antibiotics to minimise the adverse effects of bacterial and protozoan diseases. Interestingly, Codex Alimentarius, the joint World Health Organization and Food and Agriculture Organization body charged by the World Trade Organization with developing *de facto* international food standards, including maximum residue limits (MRLs), has not yet addressed the issue of MRLs for antibiotics in aquaculture. Nationally, the National Residue Survey (NRS)* has initiated, primarily for market protection purposes, a series of programs to monitor for the presence of antibiotics (and other chemical residues) in a variety of predominantly wild-caught seafood. Reports of these monitoring programs can be found on the NRS website (www.affa.gov.au/nrs).

A wider range of antibiotics is registered for the treatment of disease in cats, dogs and horses with human products frequently used off-label (at least in cats and dogs). Animals are treated individually.

Enteric bacteria

Information on resistance in enteric bacteria isolated from animals is limited. In the late 1970s the then Animal Health Committee (AHC) coordinated a survey of antibiotic resistance in *Escherichia coli* and salmonellae isolates from livestock, and bovine mastitis *Staphylococcus aureus* isolates. The previously unpublished results for *E. coli* from pigs, cattle and miscellaneous sources are shown in Table 1. The results are difficult to interpret and presumably reflect the variation in sources of isolates between years. However, it is clear that in both cattle and pigs resistance to streptomycin and tetracycline was prevalent even 25 years ago. In cattle isolates particularly, there was significant resistance to ampicillin. One thousand two hundred and eighty-seven *Salmonella* isolates from cattle, pigs and poultry were tested between 1975 and 1982.[3] The same antibiotics were used as in the *E. coli* study—resistance to streptomycin and tetracycline was most common. A number of isolates were resistant to more than one antibiotic with the co-resistant combinations of tetracycline and streptomycin (6%) or tetracycline, streptomycin and ampicillin (2%) being the most common.

* The National Residue Survey is part of the Department of Agriculture Fisheries and Forestry—Australia; see: http://www.affa.gov.au/nrs

Table 1. Frequency of antibiotic resistance in Escherichia coli (%)

Species	Antibiotic	Antibiotic concentration*	1976	1977	1978	1979	1980	1981
Pig†			(227)	(196)	(248)	(289)	(270)	(201)
Ampicillin	10 µg/ml	7	12	8	9	6	7	
Chloramphenicol	25 µg/ml	5	3	2	2	3	8	
Furazolidone	25 µg/ml	19	12	18	17	11	12	
Neomycin	4 µg/ml	7	8	7	8	7	13	
Streptomycin	10 µg/ml	50	49	60	56	59	66	
Tetracycline	5 µg/ml	75	82	86	73	72	73	
Bovine†			(91)	(66)	(31)	(89)	(46)	(23)
Ampicillin	10 µg/ml	8	8	23	29	28	9	
Chloramphenicol	25 µg/ml	4	3	24	10	11	4	
Furazolidone	25 µg/ml	19	15	6	4	9	14	
Neomycin	4 µg/ml	4	6	16	24	15	5	
Streptomycin	10 µg/ml	32	45	45	42	39	22	
Tetracycline	5 µg/ml	63	79	71	60	57	39	
Miscellaneous origin†			(17)	(7)	(3)	(1)	(8)	(6)
Ampicillin	10 µg/ml	12	0	0	0	13	0	
Chloramphenicol	25 µg/ml	12	0	0	0	0	0	
Furazolidone	25 µg/ml	24	0	67	0	25	50	
Neomycin	4 µg/ml	12	0	0	0	0	17	
Streptomycin	10 µg/ml	24	29	67	0	25	17	
Tetracycline	5 µg/ml	65	86	100	100	50	50	

* Organisms grew on agar plates containing this concentration of drug.

† Figures in brackets indicate the number of isolates tested.

Source: Animal Health Commission study. J Craven, Director Attwood Veterinary Research Laboratory, Victoria (unpublished results).

Results from the National Enteric Pathogen Surveillance Scheme testing of bovine, chicken and porcine strains of *Salmonella* between 1990 and 1997 are shown in Table 2. The results suggest an increase in prevalence of resistance since the AHC survey in the 1970s (Table 1). There are also differences in the prevalence of resistance in bacteria isolated from different host species, reflecting differences in antibiotic use (e.g., streptomycin was used more commonly in cattle than in pigs and tetracycline is used very commonly in pigs). Fewer isolates from chicken were resistant than isolates from cattle or pigs. Multi-resistant *S.* Typhimurium have been isolated from dairy cattle in Victoria.[4,5] For example, 10 isolates of *S.* Typhimurium PT44 were all resistant to ampicillin, chloramphenicol, kanamycin, neomycin, streptomycin, sulphonamide, tetracycline and trimethoprim but none were resistant to gentamicin or spectinomycin.[5] Interestingly, S. Dublin isolates from the same herds were fully sensitive to the antibiotics tested. It is important to note that the multi-drug resistant serovar *S.* Typhimurium DT104 has not yet been isolated from animals in Australia.

Table 2. Frequency of resistance in *salmonella* 1990 to 1997 (%)a

Chemotherapeutic concentration	Bovine (396)	Chicken (108)	Porcine (51)
Ampicillin 32 µg/ml	31	17	35
Chloramphenicol 10 µg/ml	18	5	10
Streptomycin 25 µg/ml	86	5	10
Tetracycline 20 µg/ml	47	44	92
Sulphathiazole 550 µg/ml	70	19	41
Trimethoprim 50 µg/ml	29	17	35
Kanamycin 10 µg/ml	28	15	31
Nalidixic acid 50 µg/ml	0.5	0	0
Spectinomycin 50 µg/ml	0.6	4	5
Gentamicin 25 µg/ml	0.6	4	5
Ciprofloxacin 0.06 µg/ml	0	5	7

Figures extracted from results provided to the AHC from National Enteric Pathogen Surveillance Scheme by the Microbiological Diagnostic Unit, Department of Microbiology and Immunology, University of Melbourne.

Anecdotal accounts indicate that treatment failure, in part due to antibiotic resistance, is not uncommon in neonatal enteritis in calves and post-weaning diarrhoea in pigs.

The JETACAR report[1] included some results of testing by the Central Veterinary Diagnostic Laboratory of small numbers of *Salmonella* isolates from a range of species with resistance more apparent in cattle and equine isolates than in chicken, cat or dog isolates. Multiple resistance was noted in *Salmonella* isolates from several cattle and one equine isolate. The JETACAR report[1] also included an account of resistance patterns of avian *E. coli* from three chicken meat production companies (T Grimes, personal communication), with widespread resistance to tetracycline and significant resistance to ampicillin and sulphonamides-trimethoprim evident. A study of *E. coli* and *Salmonella* isolates from horses[6] found all 39 isolates resistant to streptomycin and 7 resistant to multiple antibiotics. Resistance to streptomycin was also widespread in *E. coli* isolates and a number of isolates were resistant to at least three antibiotics.

There is very little published Australian information on antimicrobial resistance in *Campylobacter*. A study of 79 chicken isolates[7] found widespread resistance to erythromycin and significant resistance to doxycycline but no resistance to enrofloxacin. Similarly unpublished studies (R Pratt, WS Hart and MD Barton, personal communication) have found significant rates of resistance to erythromycin, tylosin, lincomycin, ampicillin and tetracycline (but no resistance to ciprofloxacin) in pig, pig carcass and pig meat isolates. A study of chickens[8] has reported significant resistance to ampicillin, ceftazidime and tetracycline in *C. jejuni* and *C. coli* isolates. No fluoroquinolone resistance was detected and there was relatively little resistance to erythromycin or tylosin. This study also noted differences in resistance patterns in isolates from different sources, reflecting differences in antibiotics used.

There are no published Australian reports of antibiotic resistance patterns in animal isolates of enterococci. A conference poster[9] reported isolation of one *van*A and one *van*B isolate from animals in the Hunter Valley. Pratt, Hart and Barton (unpublished data) did not detect any *van*A or *van*B *E. faecium* or *E. faecalis* in isolates from pigs, pig carcasses or pig meats. Virginiamycin resistance was found in *E. faecium* isolates, however, no resistance to ampicillin was detected. In the study of chickens mentioned previously[8] about 10 per cent of chicken carcass rinse samples contained *van*A positive enterococci. In keeping with overseas findings that *van*B vancomycin resistance is not associated with avoparcin use in animals, no *van*B resistance was detected in the isolates from chickens. Virginiamycin resistance was detected in *E. faecium* isolates in this study.

Staphylococcus aureus

Frost and Boyle[10] reported the results of testing the 1,657 bovine mastitis *S. aureus* isolates collected in the AHC survey mentioned previously. Sixty-two per cent of the isolates produced penicillinase and around 10 per cent were resistant to streptomycin. Resistance to other antibiotics was negligible and no isolates were resistant to methicillin.

A Tasmanian study of *S. aureus* isolates from bovine milk (Mark Broxton, unpublished results) found 49 per cent of 133 isolates collected in 1992-93 were resistant to penicillin, 11 per cent resistant to streptomycin and none resistant to methicillin. Similarly, Barton (unpublished data) found that of 144 *S. aureus* isolates from South Australian bovine milk samples collected in 1993-94, 54 per cent were resistant to penicillin, 9 per cent were resistant to streptomycin and none were resistant to methicillin.

Bacterial isolates from cats and dogs

Documentation of antimicrobial resistance in isolates from cats and dogs is very limited. A 1995 study[11] of staphylococcal isolates from dogs found that a very high proportion of *S. aureus* and *S. intermedius* isolates were ß-lactamase producers, but all isolates were sensitive cloxacillin/oxacillin. There was considerable resistance to trimethoprim, sulphamixazole and lincomycin. More recently, methicillin resistant *S.* intermedius have been isolated from infections in dogs (J Lucas, personal communication). A Queensland clinic[12] has recently reported isolation of multi-drug resistant *E. coli* with extended spectrum ß-lactamase activity and fluoroquinolone resistance from a nosocomial outbreak of infections in dogs.

Conclusion

Data on antimicrobial resistance in bacterial isolates from Australian animals is sparse but resistance patterns are not dissimilar from those reported from overseas countries and reflect the antibiotics which have been used for treatment. The situation relating to antibiotic resistance in aquaculture needs investigation. It is critical for Australian animal production that there is continued access to antibiotics for treatment and prevention of disease. Use of antibiotics must however, be in accordance with guidelines that minimise the risk of emergence or amplification of resistant bacteria.

References

1. Commonwealth Department of Health and Aged Care. Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR). Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia. Prepared for JETACAR by Biotex Canberra. 1999.
2. Swann MM. Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine. Cmnd. 4190. London: Her Majesty's Stationery Office, 1969.
3. Murray CJ, Ratcliff RM, Cameron PA, Dixon SF. The resistance of antimicrobial agents in *Salmonella* from veterinary sources in Australia from 1975 to 1982. *Aust Vet J* 1986;63:286–292.
4. Valcanis M, Lightfoot D, Li H, Powling J, Truong B, Forsyth JRL. Multi-resistance in enzootic strains of *Salmonella* Typhimurium. In: Goldsmid JM, editors. Proceedings of the Annual Scientific Meeting of the Australian Society for Microbiology, Melbourne, 1994. Hobart: Australian Society for Microbiology; 1994;15:56.
5. Mackie JT, Lightfoot D, Adamson M, Wishart M. Antibiotic resistant phage types of *Salmonella* Typhimurium in dairy cattle. *Aust Vet J* 1996;73:194–195.

6. Bucknell DG, Gasser RB, Irving A, Whithear K. Antimicrobial resistance in *Salmonella* and *E. coli* isolated from horses. *Aust Vet J* 1997;75:355–356.

7. Korolik V, Chang J, Coloe PJ. Variation in antimicrobial resistance in *Campylobacter* spp. isolated from animals in the last 5 years. In: Newell DG, Ketley J, Feldman RA, editors. *Campylobacters*, helicobacters, and related organisms. New York; Plenum Publishing Corporation, 1996.

8. Barton MD, Wilkins J. Antibiotic resistance in bacteria isolated from poultry. A report for the Rural Industries Research and Development Corporation. RIRDC Publication No 01/105, Canprint. 2001.

9. Butt H, Bell J, Ferguson J. Are vancomycin-resistant enterococci prevalent in Hunter region farm animals? Australian Society for Microbiology Annual Conference; October 1997. Adelaide, South Australia. Abstract PO4.8, 1997.

10. Frost AJ, O'Boyle D. The resistance to antimicrobial agents of *Staphylococcus aureus* isolated from the bovine udder. *Aust Vet J* 1981;57:262–267.

11. Barrs VR, Malik R and Love DN. Antimicrobial susceptibility of staphylococci isolates from various disease conditions in dogs: a further survey. *Aust Vet Pract* 1995;25:37–42.

12. Warren A, Townsend K, King T, Moss S, O'Boyle D, Yates M, *et al*. Multi-drug resistant *Escherichia coli* with extended-spectrum beta-lactamase activity and fluoroquinolone resistance isolated from clinical infections in dogs. *Aust Vet J* 2001;79:621–623.

Surveillance for antibiotic resistance in veterinary pathogens from the perspective of a regional diagnostic laboratory

Carol P Stephens

Abstract

The Toowoomba Veterinary Laboratory tests for antibiotic resistance through passive surveillance of bacterial pathogens from diseased, frequently intensively managed, animals. Testing is carried out on the basis of the number of animals involved, the nature and severity of the disease and the identity and significance of the bacterium, the results guiding the submitting veterinarian in implementing appropriate treatment. The antibiotics chosen for testing are those that are currently registered for veterinary use and are considered effective in the given situation. Testing is carried out according to the current National Committee for Clinical Laboratory Standards Approved Standard for Disc Susceptibility Tests. This paper presents some results of testing bacterial pathogens from cattle and pigs. *Commun Dis Intell* 2003;27 Suppl:S127–S131.

Keywords: antibiotic resistance, veterinary pathogens, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa

Introduction

The Toowoomba Veterinary Laboratory is operated by the Animal and Plant Health Service of the Queensland Department of Primary Industries. The laboratory provides a comprehensive disease investigation and surveillance service for commercial livestock producers throughout South-East Queensland and receives approximately 4,000 accessions per year. Samples may be submitted to the laboratory from either live or dead animals or whole animals may be brought to the laboratory for necropsy. Diagnostic testing of commercial livestock is provided free of charge to primary producers and veterinarians. The diagnostic service provided by the laboratory assists producers to maintain sustainable production levels by implementation of appropriate treatment and control programs. The laboratory maintains a surveillance program for both exotic and endemic disease, helping to ensure market access for animals and animal products and the provision of wholesome animal products to consumers.

As the area serviced by the Toowoomba Veterinary Laboratory contains 45 per cent of the State's cattle and more than half of Queensland's pigs, bacterial pathogens from these animals are of major interest. The laboratory routinely carries out susceptibility testing on bacterial pathogens isolated from diseased tissues. Susceptibility testing of organisms involved in mastitis is also performed.

Methods

The Toowoomba Veterinary Laboratory is accredited for Veterinary Testing by the National Association of Testing Authorities to Australian Standard AS ISO/IEC 17025. The method used for susceptibility testing is that specified by the National Committee for Clinical Laboratory Standards for disc susceptibility tests.[1,2] Quality control is carried out weekly using the type strains *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

Correspondence: Ms Carol Stephens, Senior Microbiologist, Toowoomba Veterinary Laboratory, Animal and Plant Health Service, Department of Primary Industries, PO Box 102, Toowoomba, QLD 4350. Telephone: +61 7 4688 1355 Facsimile: +61 7 4688 1195. Email carol.stephens@dpi.qld.gov.au

Antibiotic susceptibility testing is not carried out on all bacteria isolated from diseased animals. The decision to proceed with susceptibility testing is based on the number and value of animals involved, the nature and severity of the disease and the identity and significance of the bacterium isolated. A susceptibility result is only provided for isolates obtained in pure or almost pure culture that are considered to be primary or significant contributing factors in the disease syndromes under investigation. Susceptibility testing is only carried out on rapidly growing, aerobic bacteria. Antibiotic susceptibility test results are generally provided within 48 hours of receipt of the submission.

The antibiotics chosen for testing reflect those drugs that are currently registered for veterinary use in Australia and are considered most effective by veterinarians. A panel of antibiotics is tested against each of the pathogen groups. While reasonably stable, the composition of these panels may change from time to time according to the registration or de-registration of particular antibiotics and their availability, cost and effectiveness in the field. The Toowoomba Veterinary Laboratory runs between 400 and 450 susceptibility test panels per annum, each consisting of from seven to nine antibiotics.

Currently enteric pathogens are tested against the antibiotics ampicillin, apramycin, ceftiofur, cotrimoxazole, lincospectin, neomycin and tetracycline. Non-enteric pathogens are tested against ampicillin, ceftiofur, cotrimoxazole, lincospectin, neomycin, tetracycline and penicillin. Organisms isolated from cases of mastitis are tested against ampicillin, cefuroxime, clindamycin, cloxacillin, neomycin, novobiocin, penicillin and tetracycline.

Results

Bovine

Mastitis is an ongoing problem in dairy cows, from which the most frequently isolated aetiological agent is *Staphylococcus aureus*. Nine antibiotics, listed above, are routinely tested against bacterial isolates from bovine mastitis (Table 1). Over a three-year period, from 1999 to 2001, one third of isolates were found to be resistant to ampicillin and penicillin, while a small number were resistant to novobiocin. No other resistance was detected.

Table 1. Results of antibiotic susceptibility testing of strains of *Staphylococcus aureus* isolated from bovine mastitic milk between 1999 and 2001

Antibiotic	AMP10	CXM30	DA2	N30	NV30	OB5	P10	TE30
Number of strains tested	121	107	121	121	120	121	121	121
Number of strains resistant	40	0	0	0	3	0	40	0
Strains resistant (%)	33.1	0	0	0	2.5	0	33.1	0

AMP10 = ampicillin (10 µg); CXM30 = cefuroxime (30 µg); DA2 = clindamycin 2 µg); N30 = neomycin (30 µg); novobiocin (30 µg); OB5 = cloxacillin (5 µg); P10 = penicillin (10 i.u.); TE30 = tetracycline (30 µg).

Scours as a result of non-haemolytic *Escherichia coli* infection is a common problem in young calves. For the purposes of comparison, the results of antibiotic testing of these isolates in 1999 and 2001 in are given in Table 2. Resistance was detected in tetracycline, ampicillin and cotrimoxazole, with levels appearing to increase, particularly against tetracycline. Levels of resistance to neomycin appear stable, while a single isolate demonstrated resistance to apramycin in 2001.

Table 2. Results of antibiotic sensitivity testing of strains of non-haemolytic *Escherichia coli* isolated from the intestine of calves with scours between 1999 and 2001

	1999			2001		
	Tested	Resistant	Resistant %	Tested	Resistant	Resistant %
AMP10	11	4	36.3	18	11	61.1
APR15	11	0	0.0	18	1	5.6
EFT30	11	0	0.0	18	0	0.0
N30	11	6	54.5	18	9	50.0
SXT25	11	3	27.2	18	8	44.4
TE30	11	4	36.3	18	14	77.8

AMP10 = ampicillin (10 µg); CXM30 = cefuroxime (30 µg); DA2 = clindamycin 2 µg); N30 = neomycin (30 µg); novobiocin (30 µg); OB5 = cloxacillin (5 µg); P10 = penicillin (10 i.u.); TE30 = tetracycline (30 µg).

Salmonellosis is also diagnosed in cattle, in calves as well as mature animals. Results of testing between 1999 and 2001, presented in Table 3, reveal that half of the isolates of *Salmonella* tested were resistant to tetracycline, while one isolate was resistant to cotrimoxazole.

Table 3. Results of antibiotic sensitivity testing of strains of *Salmonella* sp. isolated from the intestine of calves diagnosed with salmonellosis between 1999 to 2001

Antibiotic	AMP10	APR15	EFT30	N30	SXT25	TE30
No. of strains tested	21	22	22	22	22	22
No. of strains resistant	0	0	0	0	1	11
Strains resistant (%)	0	0	0	0	9.1	50

AMP10 = ampicillin (10 µg); CXM30 = cefuroxime (30 µg); DA2 = clindamycin 2 µg); N30 = neomycin (30 µg); novobiocin (30 µg); OB5 = cloxacillin (5 µg); P10 = penicillin (10 i.u.); TE30 = tetracycline (30 µg).

Porcine

Scours in neo-natal and young animals due to infection with haemolytic *Escherichia coli* is one of the disease syndromes most frequently diagnosed in pigs and one associated with higher levels of antibiotic resistance. Nonetheless, with the exception of tetracycline to which 100 per cent of isolates obtained in 2001 were resistant, levels of resistance do not appear to have increased between 1999 and 2001. These results are given in Table 4.

Table 4. Results of antibiotic sensitivity testing of strains of haemolytic *Escherichia coli* isolated from the intestine of pigs with enteric disease between 1999 and 2001

	1999			2001		
	Tested	Resistant	Resistant %	Tested	Resistant	Resistant %
AMP10	34	12	35.3	34	8	23.5
APR15	34	13	38.2	34	12	35.3
EFT30	34	0	0.0	34	0	0.0
N30	34	12	35.3	34	15	44.1
SXT25	34	21	61.8	34	16	47.1
TE30	34	30	88.2	34	34	100.0

AMP10 = ampicillin (10 µg); CXM30 = cefuroxime (30 µg); DA2 = clindamycin 2 µg); N30 = neomycin (30 µg); novobiocin (30 µg); OB5 = cloxacillin (5 µg); P10 = penicillin (10 i.u.); TE30 = tetracycline (30 µg).

Antibiotic susceptibility testing is also carried out against respiratory pathogens isolated from pigs. Results of testing *Pasteurella multocida* isolated from cases of porcine respiratory disease are given in Table 5. While levels of resistance to penicillin and tetracycline rose over this time, resistance to other antibiotics was not detected.

Table 5. Results of antibiotic sensitivity testing of strains of *Pasteurella multocida* isolated from the respiratory tract of pigs with pneumonia between March 1998 and March 1999 and between March 2001 and March 2002

	March 1998 to March 1999			March 2001 to March 2002		
	Tested	Resistant	Resistant %	Tested	Resistant	Resistant %
AMP10	20	0	0.0	17	0	0.0
EFT30	20	0	0.0	17	0	0.0
LS109	20	0	0.0	5	0	0.0
N30	20	0	0.0	17	0	0.0
P10	19	3	15.8	16	6	37.5
SXT25	20	0	0.0	17	0	0.0
TE30	20	1	5.0	17	4	23.5

AMP10 = ampicillin (10 µg); CXM30 = cefuroxime (30 µg); DA2 = clindamycin 2 µg); N30 = neomycin (30 µg); novobiocin (30 µg); OB5 = cloxacillin (5 µg); P10 = penicillin (10 i.u.); TE30 = tetracycline (30 µg).

Discussion

The Toowoomba Veterinary Laboratory provides a veterinary diagnostic and disease surveillance service for commercial animal production in south-east Queensland. An integral component of this activity is the provision of antibiotic susceptibility testing of bacteria isolated from diseased livestock and believed to be significant with respect to the disease under investigation. Providing the results of such testing in a timely manner promotes the judicious and targeted use of antibiotics for the treatment of animal disease. Such treatment is necessary in order to contain disease, to maintain production and to ensure the welfare of the animals. The Toowoomba Veterinary Laboratory has actively encouraged the prudent use of antibiotics for animal treatment based on results of *in vitro* testing and field experience. Over the past three years, significant increases in antimicrobial resistance have generally not been observed. Exceptions to this are resistance to tetracycline and to a lesser extent, ampicillin and penicillin.

References

1. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing; twelfth informational supplement, NCCLS M100-S12 Vol 21 No 1 NCCLS, Pennsylvania, USA; 2002.
2. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests; approved standard, 7th edition NCCLS M2-A7 Vol 20 No 1, NCCLS, Pennsylvania, USA; 2000.

Australian Council on Healthcare Standards infection control clinical indicators

Kay L Richards,[1] Dolly Olesen,[2] Michael Whitby[3]

The Australian Council on Healthcare Standards (ACHS) has recently published the *Australian Council on Healthcare Standards Clinical Indicator Users' Manual 2003*, which includes the recently developed Infection Control Indicators. This article describes the indicator development process undertaken with the Australian Infection Control Association (AICA) National Advisory Board.

For over 10 years, the Australian Council on Healthcare Standards has developed speciality specific clinical indicators. The earliest set of Hospital Wide Medical Indicators, measured (among other areas) hospital acquired infections including wound infection and bacteraemia. As clinical practice changed over time, it had become obvious that the indicators were not meeting the needs of clinicians in providing useful information for monitoring or improving infection rates.

From inception, all ACHS indicators have been developed in collaboration with the appropriate medical college, society or association. It was the ACHS and the Australian Infection Control Association that developed a specific set of Infection Control Indicators. Indicators need to be reflective of today's healthcare environment, be easily collectable and assist in providing information that can flag potential areas requiring improvement.

The ACHS has recently published the *Australian Council on Healthcare Standards Clinical Indicator Users' Manual 2003*, which includes the Infection Control Indicators. The indicators are in accord with those developed by the National Advisory Board to the Australian Infection Control Association (AICA-NAB). The AICA-NAB is a multi-disciplinary group with representation of infection control expertise from all regions of Australia and includes representation from the ACHS.

The published AICA indicators[1] were used as the basis for the development of the ACHS indicators. Surgical site infection surveillance targeted specific clinical areas either of high risk for a wound infection or of considerable socioeconomic consequence if infection occurred. These include hip and knee prosthesis, coronary artery bypass grafting, femoro-popliteal bypass procedures, open abdominal aortic aneurysm procedures, lower segment caesarean sections and hysterectomies.

As reported in the *Australian Council on Healthcare Standards Clinical Indicator Users' Manual 2003*, central line-associated blood stream infections (CLAB's) are responsible for 20–40 per cent of healthcare-associated blood stream infections and risk for occurrence differs amongst clinical units dependent on the type of line used and patient intrinsic factors. Therefore, CLAB's were targeted in intensive care units, haematology and oncology units.

The AICA-NAB developed standardised definitions of infection and of clinical indicators with the aim that in-house comparison of rates between surveillance periods could reliably identify a trend in, or maintenance of an acceptable rate. However, the AICA-NAB is mindful that the ACHS Evaluation and Quality Improvement Program members participating in the ACHS Comparative Report Service receive six monthly reports providing national aggregated rates to stimulate quality improvement. Individual results may be compared with the data presented in the ACHS Comparative Report, and the previous surveillance period. The aim is to reduce an organisation's rate to the comparative rate, or to that of

1. Team Leader, Australian Council on Healthcare Standards, Performance and Outcomes Service, Ultimo, New South Wales
2. President, Australian Infection Control Association, on behalf of the National Advisory Board, Wilston, Queensland
3. Chair National Advisory Board; Director, Infection Management Services Southern Queensland, Princess Alexandra Hospital, Brisbane, Queensland

Corresponding author: Ms Kay Richards, Team Leader, Australian Council on Healthcare Standards, Performance and Outcomes Service, Australian Council on Healthcare Standards, 5 Macarthur Street, Ultimo NSW 2007. Telephone: +61 2 8218 2720. Email: krichards@achs.org.au.

the previous surveillance period, whichever is the lowest. As such, comparisons depend on sample size for surgical site infection surveillance, and the ACHS, in accord with the AICA-NAB, recommend that organisations which perform less than 100 major procedures of the same type, use alternative statistical analytical methods, for example process control charts, in conjunction with other quality improvement tools.

These indicators are in a pilot phase and data received will be analysed, taking into consideration issues such as validity, ease of collection and usefulness for quality improvement. The length of the pilot phase will be dependent on the volume and timeliness, which governs time to analyse the data received.

Areas such as multi-resistant organism surveillance have not been included in the 2002 collection period, as definitions are still under development. However, the ACHS have recommended that healthcare organisations continue to monitor those resistant microorganisms that are important to their patient population.

The ACHS have sought feedback and comment from its members regarding the use of the indicators. Health care organisations have received the results for the first half of 2002 and expect to receive the results for the second half of 2002 around April 2003. The indicators are available from the ACHS and member organisations can access the ACHS Clinical Indicator Users' Manual via the ACHS Website (www.achs.org.au). Other interested parties can also obtain copies using the order form found on the ACHS Publications Service section of the Website.

The published indicators have targeted either speciality specific or unit specific areas. Therefore, smaller organisations that do not provide those services will not currently have indicator data to send to the ACHS for comparative reporting. The ACHS are therefore working towards developing indicators that may more accurately reflect the care provided by the smaller organisations. These may take the form of process indicators. The ACHS has advised those organisations with a small volume of cases (i.e., less than 100 surgical procedures of the same type per year) to continue to monitor their infection rates utilising other statistical techniques in preference to rate based indicators. Many organisations regard such infections as sentinel events and perform root cause analysis reviews when an infection occurs.

The ACHS and the AICA-NAB will continue to improve the current indicators and aim to develop future indicators that will assist organisations to collect relevant information, monitor infections within a statistically sound methodology. The process will include steps that identify indicators that measure various dimensions of quality, e.g., safety and effectiveness but also will focus on measuring outcomes. Professor Robert Gibberd at the Health Services Research Group, University of Newcastle, conducts the analysis and review of the ACHS indicator data results. Particular focus is directed at the potential gains that can be made when identifying the difference between the aggregated rate and comparing it to the 20th centile rate. The statistical methodology used for this is outlined in the ACHS publication '*Determining to Improve the Quality of Care in Australian Health Care Organisations Results form the ACHS Clinical Indicators Data 1998 and 1999*'. This type of analysis is dependent upon the size of the dataset and it will only be after the 2002 data becomes available that the ACHS and AICA-NAB will be able to decide on the most appropriate way of reporting the results. The review process also considers the indicator in terms of how easily the data can be collected, how useful the indicator has been for quality improvement, and any other feedback provided by the users. It is envisaged that the indicators will be due for review in 2003–04.

Reference

1. Auricht E, Borgert J, Butler M, Cadwallader H, Collignon P, Cooper C, *et al*. Uniform national denominator definitions for infection control clinical indicators: surgical site and healthcare associated blood stream infection. *Australian Infection Control* 2001;6:47–51.

Antibiotic resistance and the potential impact of pneumococcal conjugate vaccines

Ron Dagan

Abstract

Streptococcus pneumoniae **is a major cause of morbidity and mortality in young children throughout the world, causing both invasive (meningitis, bacteraemia) and non-invasive (pneumonia, acute otitis media, sinusitis) infections. Over the past few decades, the global emergence of antibiotic-resistant pneumococcal strains has complicated disease management. Thus, healthcare practitioners have begun to place more emphasis on the judicious use of antibiotics and prevention of disease through routine immunisation. Researchers have developed several pneumococcal conjugate vaccines, which due to their technology, are effective in infants and young children. Currently, one 7-valent pneumococcal conjugate vaccine (PNCRM7; Prevenar®, Wyeth) is available in various parts of the world and has demonstrated excellent efficacy against vaccine-type invasive disease and efficacy against pneumonia and otitis media caused by the serotypes included in the vaccine. Furthermore, there is evidence suggesting that the use of these conjugate vaccines will reduce the need for antibiotics and the subsequent spread of antibiotic-resistant pneumococci. Ultimately, when routine pneumococcal conjugate vaccination of infants and young children is accompanied by supportive education and active disease surveillance as well as judicious use of antibiotics, there should be a favourable impact on pneumococcal disease incidence in and beyond the vaccinated population.** ***Commun Dis Intell*** **2003;27 Suppl:S135–S143.**

Keywords: Streptococcus pneumoniae, *antibiotic resistance, pneumococcal conjugate vaccine, PNCRM7*

Introduction

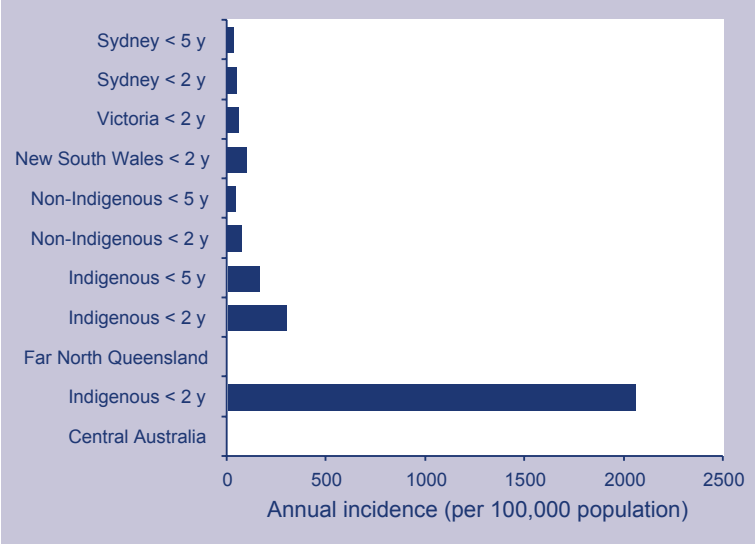
Streptococcus pneumoniae is a major cause of morbidity and mortality in young children throughout the world.[1] The leading cause of bacterial meningitis in infants and children,[2] *S. pneumoniae* also causes other invasive infections, such as bacteraemia and bacteraemic pneumonia. Non-invasive infections commonly caused by *S. pneumoniae* include non-bacteraemic pneumonia, acute otitis media (AOM) and sinusitis.[1]

The annual incidence of invasive pneumococcal disease in Australia ranges from 31.7 to 2,053 cases per 100,000 population, depending on the geographic region, age, and ethnic background of the population studied.[3,4,5,6,7] As shown in Figure 1, the incidence of disease is high among children younger than 2 years, with the highest incidence seen in indigenous children.

Over the past few decades, the global emergence of antibiotic-resistant pneumococcal strains has complicated disease management. Thus, healthcare practitioners have begun to place more emphasis on the judicious use of antibiotics and prevention of disease through routine immunisation.[8,9] This article reviews the increasing incidence of pneumococcal antibiotic resistance and the potential role of pneumococcal conjugate vaccines in reducing antibiotic use and the spread of antibiotic-resistant pneumococcal strains.

Correspondence: Dr Ron Dagan, Pediatric Infectious Disease Unit, Soroka University Medical Center, PO Box 151, Beer-Sheva 84101, Israel. Telephone: +011 972 8 6400547. Facsimile: +011 972 8 6232334. Email: rdagan@bgumail.bgu.ac.il

Figure 1. Annual incidence of invasive pneumococcal disease in various regions of Australia[3,4,5,6,7]

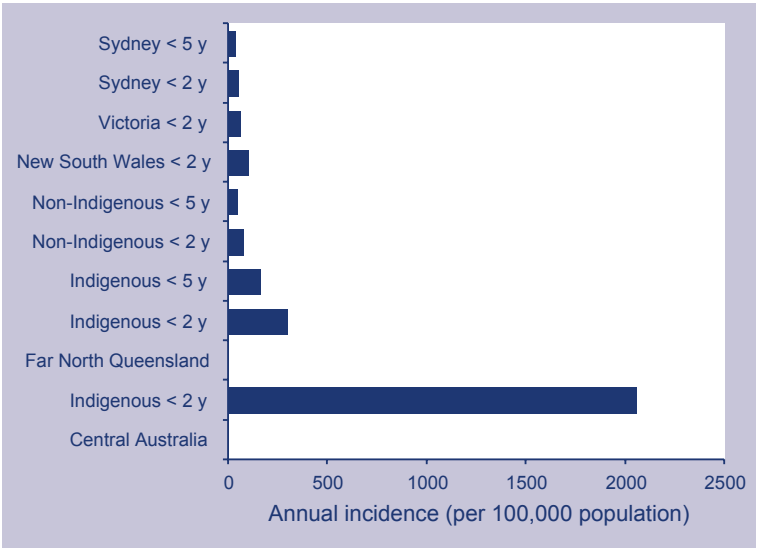


Microbiology, transmission, and carriage of pneumococci

Microbiology

Pneumococci are gram-positive, lancet-shaped bacteria that occur in chains (streptococci) or in pairs (diplococci) and are typically surrounded by a large complex polysaccharide capsule. Based on differences in the composition of the polysaccharide capsule, there are approximately 90 known serotypes of *S. pneumoniae*. The prevalence of different serotypes varies by age, geographic location, and type of disease.[10] In the Australian population, 7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) cause between 62 per cent and 88 per cent of invasive pneumococcal disease among children younger than 5 years (Figure 2).[3,5,6,11] Interestingly, the proportion of invasive pneumococcal disease caused by these serotypes is somewhat lower among young children of indigenous descent.[5,12]

Figure 2. Proportion of invasive pneumococcal disease cases attributed to serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, by region[3,5,6,11]



Nasopharyngeal carriage and transmission

Asymptomatic nasopharyngeal carriage of pneumococci is widely prevalent among young children (ranging from 28% to 86% throughout the United States of America and Europe) and is often the first step in disease transmission.[13,14,15,16] Consequently, young children play an important role in the transmission of pneumococcal disease in the community because of their high carriage rate and the ease with which they can transmit the disease through expulsion of respiratory droplets. Consistent with the findings from other countries, studies in southern Australia among children younger than 5 years of age have found pneumococcal nasopharyngeal carriage rates ranging between 37 per cent and 52 per cent.[17] Of particular note, half of these isolates were resistant to antibiotic treatment.[17]

Pneumococcal antibiotic resistance

Historically, penicillin has been the agent of choice for treatment of pneumococcal disease; however, the widespread use and overuse of penicillin has resulted in the development of penicillin-non-susceptible pneumococcal strains and necessitated changes in treatment.[8,9,18,19,20] Penicillin non-susceptibility—the degree of resistance to treatment—is classified according to minimum inhibitory concentrations (MICs), defined as the minimum concentration of a particular antibiotic needed to stop pneumococcal growth *in vitro* (Table 1).[21,22]

Table 1. Definition of penicillin resistance[21,22]

Level of resistance*	Minimum inhibitory concentration
Susceptible	≤0.06 µg/mL
Intermediate susceptibility	0.1-1 µg/mL
Resistant	≥ 2 µg/mL

* As defined by the United States of America National Committee for Clinical and Laboratory Standards.

Rates of pneumococcal non-susceptibility vary geographically and are rising throughout the world. For example, penicillin non-susceptibility in Spain increased from 6 per cent in 1979 to 44.3 per cent in 1989. By 1999, approximately 60 per cent of all pneumococcal isolates were penicillin non-susceptible.[23,24] Similarly, in the United States of America (USA), an 11-fold increase in the rate of penicillin non-susceptibility was observed between the years 1986 (3.8%) and 1997 (43.8%).[25] The proportion of penicillin-non-susceptible pneumococci has increased in south-eastern Australia as well. In 1990, approximately 2 per cent of isolates were intermediately resistant to penicillin; by 2000, approximately 10 per cent of isolates from blood and cerebrospinal fluid (CSF) cultures and just over 35 per cent of isolates from sites other than blood and CSF exhibited non-susceptibility to penicillin.[19] Further evidence of the dramatic increase in antibiotic resistance is provided by a 1997 Australian-wide surveillance study showing that approximately 25 per cent of the 1,020 isolated strains were non-susceptible to penicillin (16.8% were intermediately resistant and 8.6% were resistant).[26] Rates of resistance to other drugs were also relatively high, with 15.6 per cent of strains resistant to erythromycin, 15.7 per cent resistant to tetracycline, 21.4 per cent resistant to cefaclor, 33.4 per cent resistant to cotrimoxazole, and 3.1 per cent each resistant to amoxicillin-clavulanate and ceftriaxone.[26]

Not surprisingly, the problem of multidrug-resistant strains has been growing at an alarming rate worldwide.[9,19,26] For example, a 1997 USA surveillance study reported that 36.7 per cent of penicillin-intermediate and 65.6 per cent of penicillin-resistant isolates were also resistant to macrolide antibiotics.[27] With respect to Australia, Gratten and colleagues identified 27 cases of multidrug-resistant *S. pneumoniae* in Queensland between 1995 and 1996.[28] All 27 isolates demonstrated resistance to cotrimoxazole, 19 strains (70%) were resistant to chloramphenicol, 25 strains (93%) were resistant to erythromycin, and 25 strains (93%) were resistant to tetracycline. Penicillin-non-susceptible strains were recovered from 18 of the 27 multidrug-resistant cases (66.7%). Furthermore, 14 penicillin-resistant isolates were also resistant to ceftriaxone. The serotype distribution of these multidrug-resistant pneumococci included serotype 19F (15 isolates), serotype 14 (6 isolates), serotype 23F (4 isolates), serotype 6A (1 isolate), and serotype 19A (1 isolate).

The spread of antibiotic-resistant pneumococci has been associated with out-of-home childcare attendance and previous antibiotic use.[29,30,31] Day care attendance increases the risk of resistant pneumococcal disease due to frequent contact with other children, exposure to a greater number of serotypes, and difficulty in maintaining hygienic conditions.[30.31] Furthermore, Levine and colleagues reported that children in day care are more likely to have had a recent ear infection and more likely to have one recent course of antibiotics.[30]

Taken together, the dramatic increase in the prevalence of antibiotic-resistant pneumococci and the persistently high morbidity and mortality associated with pneumococcal infections has shifted the focus of disease management from antibiotic therapy to the prevention of infection through immunisation.[2,8,9]

Role of vaccination in reducing antibiotic resistance

Although pneumococcal polysaccharide vaccines have been available since the 1980s, they are ineffective in children younger than 2 years because they produce a T-cell–independent immune response.[32] To overcome this problem, researchers have developed several pneumococcal conjugate vaccines based on the same principles used to develop the highly successful *Haemophilus influenzae* type b vaccine. Table 2 shows the serotypes and carriers used in the various pneumococcal conjugate vaccines. The only pneumococcal conjugate vaccine available to date is a 7-valent vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) conjugated to a non-toxic diphtheria variant (CRM_{197}) (PNCRM7; Prevenar®; Wyeth).

Table 2. Composition of pneumococcal conjugate vaccines

Vaccine	Protein carrier	Serotypes	Manufacturer
PNCRM7	Non-toxic variant (CRM_{197})	4, 6B, 9V, 14, 18C, 19F, 23F	Wyeth
PNCRM9	CRM_{197}	1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F	Wyeth
PNCOMP7	Outer membrane of *Neisseria meningitidis* group B	4, 6B, 9V, 14, 18C, 19F, 23F	Merck and Co.
PNC–D/T	Diphtheria and tetanus toxoids	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Aventis-Pasteur
PNC–protein D	*Haemophilus influenzae* protein D	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	GlaxoSmithKline

PNCRM7 has demonstrated excellent efficacy against vaccine-type invasive disease and moderate efficacy against vaccine-type AOM. In the first of two safety and efficacy trials, the Northern California Kaiser Permanente (NCKP) study, subjects were randomly assigned to immunisation with PNCRM7 or the meningococcal group C conjugate vaccine (control).[2] Efficacy of PNCRM7 against vaccine-serotype-specific invasive disease was 97.4 per cent in the per-protocol analysis (received ≥ 3 doses) and 93.9 per cent in the intent-to-treat analysis (received ≥ 1 dose). In addition, there was a 6.4 per cent decrease in otitis media episodes, a 9.1 per cent reduction in frequent AOM episodes, and a 20.3 per cent reduction in tympanostomy tube insertions.

Postlicensure surveillance from this trial has shown that the incidence of invasive disease among all children in the NCKP healthcare system (vaccinated and unvaccinated) after licensure and routine use of the vaccine was reduced in children younger than 1 year, 2 years, and 5 years by 87.3 per cent, 58.1 per cent, and 62.4 per cent, respectively, thus suggesting that the benefits of pneumococcal immunisation may extend to the non-vaccinated population as well (i.e., indirect or herd immunity).[33]

The second PNCRM7 study used a vaccination schedule similar to that of the NCKP study; 1,662 subjects were randomly assigned to immunisation with PNCRM7 or the hepatitis B vaccine (control).[34] Similar to the previous study, vaccination with PNCRM7 reduced the incidence of all AOM episodes by 6 per cent, while the incidence of culture-confirmed AOM episodes and vaccine-serotype episodes decreased by 34 per cent and 57 per cent, respectively. However, an increase of 33 per cent was observed for episodes caused by non-vaccine serotypes.

The potential effects of the pneumococcal conjugate vaccines on antibiotic resistance have been examined in 876 children with pneumococcal AOM in southern Israel.[35] Analysis of middle ear fluid isolates showed that 68 per cent were resistant to one or more antibiotic, 61 per cent were resistant to penicillin, and 13 per cent were resistant to three or more antibiotic classes. Taken together with the serotype composition of such isolates (primarily 6B, 9V, 14, 19F, and 23F), it is likely that pneumococcal conjugate immunisation will have a significant impact on the spread of antibiotic resistance, as these five serotypes are included in all of the pneumococcal conjugate vaccines.

Evidence suggesting that the benefits of pneumococcal vaccination extend beyond the prevention of disease to reducing the need for antibiotic treatment has been demonstrated. In the NCKP trial described previously, it was found that PNCRM7 reduced antibiotic use by 5.3 per cent.[36] In another study conducted in children attending day care centers in Israel, researchers compared respiratory morbidity and antibiotic use among children receiving a 9-valent pneumococcal conjugate vaccine (PNCRM9) with that of children immunised with a meningococcal C conjugate (control) vaccine.[37] Overall reductions were seen in the incidence of upper respiratory infections (15% decrease), lower respiratory infections (16% decrease), and AOM (17% decrease). In addition, the overall number of days of antibiotic use was significantly reduced (by 17%, $p \leq 0.005$). When analysed by site of infection, antibiotic use in children with upper respiratory infections, lower respiratory infections, and AOM decreased by 10 per cent, 47 per cent, and 20 per cent, respectively ($p \leq 0.005$ for all comparisons).[37]

Finally, preliminary data from the United States of America (presented at the American Society for Microbiology's Third International Symposium on Pneumococci and Pneumococcal Diseases in Anchorage, Alaska in May of 2002) suggest that the universal immunisation of infants and toddlers has dramatically reduced the incidence of antibiotic-resistant pneumococcal disease among individuals of all ages.

Recommendations for use of PNCRM7 in Australia

PNCRM7 is indicated for the active immunisation of children 6 weeks to 9 years of age against invasive disease, pneumonia, and otitis media caused by those pneumococcal serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). At this time, the Australian Technical Advisory Group on Immunisation (ATAGI) recommends free (federally funded) vaccination with PNCRM7 to those children at greatest risk for pneumococcal disease.[38] All eligible children (Table 3) should receive a 3-dose series, given at 2, 4, and 6 months of age. No booster dose is necessary for the majority of children, with 2 important exceptions: children with impaired immunity should receive a fourth booster dose, and certain Aboriginal and Torres Strait Islander children should receive a booster dose of the 23-valent polysaccharide vaccine (Pneumovax 23®, Merck and Co., West Point, PA). The recommended 'catch-up' schedule for eligible children older than 2 months of age is provided in Table 4.[38] Finally, ATAGI is also currently considering inclusion of a pneumococcal conjugant vaccine as part of the routine, free immunisation schedule for all children, regardless of risk group.

Table 3. Children eligible for free vaccination with PNCRM738

Group	Age limit
All Aboriginal and Torres Strait Islander children	< 24 months
Non-Aboriginal children in Central Australia	< 24 months
Aboriginal children in Central Australia or any region with similarly high incidence of pneumococcal infections	24–59 months
Children with medical risk factors for pneumococcal infection*	< 5 years

* Children with impaired immunity (e.g., hemoglobinopathies, congenital immune deficiency, asplenia, human immunodeficiency virus infection, relapsing or persistent nephrotic syndrome), and anatomical abnormalities predisposing to pneumococcal infection (e.g., congenital cyanotic heart disease, cerebrospinal fluid leak).

Table 4. Recommended catch-up PNCRM7 immunisation schedule[38]

	Age at first dose (months)	Primary schedule (PNCRM7)	Booster
Aboriginal and Torres Strait Islander children in the Northern Territory, the desert and tropical regions of Western Australia and Queensland, and the desert regions of New South Wales and southern Australia	3-6 7-17 18-24	3 doses* 2 doses* 1 dose	23V PS at 18-24 months 23V PS 2 months later
Aboriginal children in Central Australia (and other regions of similarly high pneumococcal disease incidence)	24-59	1 dose	23V PS 2 months later
Aboriginal and Torres Strait Islander children in all other regions, non-Aboriginal children in Central Australia only, and children with anatomical abnormalities	3-6 7-23	3 doses* 2 doses*	None None
Children with impaired immunity	3-6 7-11 12-59	3 doses* 2 doses* 2 doses*	PNCRM7 at 12 months None

* Doses given 2 months apart.

PNCRM7, Prevenar®, Wyeth-Lederle Vaccines; 23V PS, Pneumovax 23®, Merck and Co.

Potential impact in Australia with widespread use of pneumococcal conjugate vaccines

Widespread use of PNCRM7 should lead to a decreased incidence of pneumococcal disease, indirectly reducing antibiotic use and the spread of antibiotic resistance. Epidemiology studies indicate that the seven serotypes included in PNCRM7 are responsible for 62–88 per cent of cases of invasive pneumococcal disease,[3,5,6,11] suggesting that the majority of pneumococcal infections in children could be prevented by vaccination with PNCRM7. Although vaccine coverage would be expected to be lower among indigenous children (62%), the high incidence of disease in this group suggests that the vaccine will still be of substantial value.

In addition to the disease prevention effects in vaccinated individuals, immunisation of infants and young children with pneumococcal conjugate vaccines may indirectly extend disease prevention to a larger population (i.e., indirect or herd immunity), as observed in Northern California.

Conclusions

To realise the full potential of pneumococcal conjugate vaccines, the implementation of vaccination programs must be accompanied by the education of medical practitioners and the public on the appropriate use of antibiotics. Moreover, continued disease surveillance is crucial for understanding whether replacement carriage or disease with non-vaccine serotypes occurs. To date, clinical trials have shown that immunisation with pneumococcal conjugate vaccines has resulted in decreased carriage of vaccine-type pneumococci and increased carriage of non-vaccine-type pneumococci;[39,40,41,42] however, some replacement disease has only been observed for AOM.[34] No replacement disease has been observed for invasive pneumococcal disease.[33]

It also remains to be determined if non-vaccine serotypes will begin to develop antibiotic resistance. Ultimately, when routine pneumococcal conjugate vaccination of infants and young children is accompanied by supportive education and active disease surveillance as well as judicious use of antibiotics, a favourable impact on the incidence of pneumococcal disease in and beyond the vaccinated population should be observed.

References

1. Van Beneden CA, Whitney CG, Levine OS. Preventing pneumococcal disease among infants and young children. *MMWR Morb Mortal Wkly Rep* 2000;49:1–38.
2. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, *et al*. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J* 2000;19:187–95.
3. McIntyre PB, Gilmour RE, Gilbert GL, Kakakios AM, Mellis CM. Epidemiology of invasive pneumococcal disease in urban New South Wales, 1997–1999. *Med J Aust* 2000;173 Suppl:S22–S26.
4. Torzillo PJ, Hanna JN, Morey F, Gratten M, Dixon J, Erlich J, *et al*. Invasive pneumococcal disease in Central Australia. *Med J Aust* 1995;162:182–186.
5. Fagan RL, Hanna JN, Messer RD, Brookes DL, Murphy DM. The epidemiology of invasive pneumococcal disease in children in Far North Queensland. *J Paediatr Child Health* 2001;37:571–575.
6. Hogg GG, Strachan JE, Lester RA. Invasive pneumococcal disease in the population of Victoria. *Med J Aust* 2000;173 Suppl:S32–S35.
7. Liddle JL, McIntyre PB, Davis CW. Incidence of invasive pneumococcal disease in Sydney children, 1991–96. *J Paediatr Child Health* 1999;35:67–70.
8. Dowell SF, Schwartz B. Resistant pneumococci: protecting patients through judicious use of antibiotics. *Am Fam Physician* 1997;55:1647–1648.
9. Collignon PJ, Turnidge JD. Antibiotic resistance in *Streptococcus pneumoniae. Med J Aust* 2000;173 Suppl:S58–S64.

10. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin Infect Dis* 2000;30:100–121.

11. Gratten M, Carlisle J, Hanna J, Bapty G, George N, Nuttall N, *et al*. Seroepidemiology of invasive pneumococcal disease in Queensland, 1990 to 1997. *Commun Dis Intell* 1998;22:265–269.

12. Butler JC, Bulkow LR, Parks DJ, et al. Epidemiology of pneumococcal bacteremia and meningitis during the first 5 years of life in Alaska: implications for conjugate pneumococcal vaccine use [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy 2000;672.

13. Syrjänen R, Kilpi T, Herva E, et al. Pneumococcal carriage during health and respiratory infection [abstract]. International Symposium on Pneumococci and Pneumococcal Disease Abstract Book 1998;29.

14. Appelbaum PC, Gladkova C, Hryniewicz W, Kojouharov B, Kotulova D, Mihalcu F, *et al*. Carriage of antibiotic-resistant *Streptococcus pneumoniae* by children in eastern and central Europe—a multi-center study with use of standardized methods. *Clin Infect Dis* 1996;23:712–717.

15. Garcia-de-Lomas J, Gimeno C, Millas E, Bermejo M, Lazaro MA, Navarro D, *et al*. Antimicrobial susceptibility of *Streptococcus pneumoniae* isolated from pediatric carriers in Spain. *Eur J Clin Microbiol Infect Dis* 1997;16:11–13.

16. Shackley F, Heath PT, Diggle L, *et al*. Carriage of *Streptococcus pneumoniae* (Spn) in Oxford children [abstract]. International Symposium on Pneumococci and Pneumococcal Diseases 1998;36.

17. Skull SA, Shelby-James T, Morris PS, Perez GO, Yonovitz A, Krause V, *et al*. *Streptococcus pneumoniae* antibiotic resistance in Northern Territory children in day care. *J Paediatr Child Health* 1999;35:466.

18. Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM. Effect of beta-lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. *BMJ* 2002;324:28–30.

19. Butler JC, Dowell SF, Breiman RF. Epidemiology of emerging pneumococcal drug resistance: implications for treatment and prevention. *Vaccine* 1998;16:1693–1697.

20. Gosbell IB, Neville SA. Antimicrobial resistance in *Streptococcus pneumoniae*: a decade of results from south-western Sydney. *Commun Dis Intell* 2000;24:340–343.

21. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing; 11th informational supplement. National Committee for Clinical Laboratory Standards, Wayne, Pennsylvania, 2001;21:1–123.

22. American Academy of Paediatrics Committee on Infectious Diseases. Therapy for children with invasive pneumococcal infections. *Paediatrics* 1997;99:289–299.

23. Fenoll A, Martin BC, Munoz R, Vicioso D, Casal J. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979–1989. *Rev Infect Dis* 1991;13:56–60.

24. Fenoll A, Jado I, Vicioso D, Berron S, Yuste JE, Casal J, *et al*. *Streptococcus pneumoniae* in children in Spain: 1990–1999. *Acta Paediatr* 2000;89 Suppl:44–50.

25. Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program. *Clin Infect Dis* 1998;27:764–770.

26. Turnidge JD, Bell JM, Collignon PJ. Rapidly emerging antimicrobial resistance in *Streptococcus pneumoniae* in Australia. *Med J Aust* 1999;170:152–155.

27. Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC, *et al*. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. Surveillance Study. *Antimicrob Agents Chemother* 1999;43:1901–1908.

28. Gratten M, Nimmo G, Carlisle J, Schooneveldt J, Seneviratne E, Kelly R, *et al*. Emergence of further serotypes of multiple drug-resistant *Streptococcus pneumoniae* in Queensland. *Commun Dis Intell* 1997;21:133–136.

29. Arnold KE, Leggiadro RJ, Breiman RF, Lipman HB, Schwartz B, Appleton MA, *et al*. Risk factors for carriage of drug-resistant *Streptococcus pneumoniae* among children in Memphis, Tennessee. *J Pediatr* 1996;128:757–764.

30. Levine OS, Farley M, Harrison LH, Lefkowitz L, McGeer A, Schwartz B, *et al*. Risk factors for invasive pneumococcal disease in children: a population-based case-control study in North America. *Pediatrics* 1999;103:E28.

31. Givon-Lavi N, Dagan R, Fraser D, Yagupsky P, Porat N. Marked differences in pneumococcal carriage and resistance patterns between day care centers located within a small area. *Clin Infect Dis* 1999;29:1274–1280.

32. Black S, Shinefield H. Issues and challenges: pneumococcal vaccination in paediatrics. *Paediatr Ann* 1997;26:355–360.

33. Black SB, Shinefield HR, Hansen J, Elvin L, Laufer D, Malinoski F, *et al*. Postlicensure evaluation of the effectiveness of seven valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2001;20:1105–1107.

34. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, *et al*. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;344:403–409.

35. Dagan R, Givon-Lavi N, Shkolnik L, Yagupsky P, Fraser D. Acute otitis media caused by antibiotic-resistant *Streptococcus pneumoniae* in southern Israel: implication for immunizing with conjugate vaccines. *J Infect Dis* 2000;181:1322–1329.

36. Shinefield H. Pneumococcal conjugate vaccines and ongoing lessons. *Int J Clin Pract* 2001;118 Suppl:23–25.

37. Dagan R, Sikuler-Cohen M, Zamir O, Janco J, Givon-Lavi N, Fraser D. Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care center attendees. *Pediatr Infect Dis J* 2001;20:951–958.

38. Information for Immunisation Providers National Childhood Pneumococcal Vaccination Program. Available from: http://www.health.gov.au/pubhlth/immunise/publications.htm. Accessed: May 2002.

39. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis* 1999;180:1171–1176.

40. O'Brien KL, Bronsdon MA, Carlone GM, *et al*. Effect of a 7-valent pneumococcal conjugate vaccine on nasopharyngeal (NP) carriage among Navajo and White Mountain Apache (N/WMA) infants [abstract]. 19th Annual Meeting of the European Society for Paediatric Infectious Diseases 2001;22.

41. Dagan R, Givon S, Yagupsky P, *et al*. Effect of a 9-valent pneumococcal CRM_{197} vaccine (PncCRM9) on nasopharyngeal (NP) carriage of vaccine type and non-vaccine type *S. pneumoniae* (Pnc) strains among day care center (DCC) attendees (abstract). Program and Abstracts of the 38th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy 1998;299.

42. Obaro SK, Adegbola RA, Banya WAS, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. *Lancet* 1996;348:271–272.

Non-antibiotic therapies for infectious diseases

Christine F Carson,[1] Thomas V Riley[1,2]

Abstract

The emergence of multiple antibiotic resistant organisms in the general community is a potentially serious threat to public health. The emergence of antibiotic resistance has not yet prompted a radical revision of antibiotic utilisation. Instead it has prompted the development of additional antibiotics. Unfortunately, this does not relieve the underlying selection pressure that drives the development of resistance. A paradigm shift in the treatment of infectious disease is necessary to prevent antibiotics becoming obsolete and, where appropriate, alternatives to antibiotics ought to be considered. There are already several non-antibiotic approaches to the treatment and prevention of infection including probiotics, phages and phytomedicines. There is some evidence that probiotics such as *Lactobacillus* spp. or *Saccharomyces boulardii* are useful in the prevention and treatment of diarrhoea, including *Clostridium difficile*-associated diarrhoea that can be difficult to treat and recurs frequently. Bacteriophages have received renewed attention for the control of both staphylococcal and gastrointestinal infections. Phytomedicines that have been utilised in the treatment of infections include artesunate for malaria, tea tree oil for skin infections, honey for wound infections, mastic gum for *Helicobacter pylori* gastric ulcers and cranberry juice for urinary tract infections. Many infections may prove amenable to safe and effective treatment with non-antibiotics. *Commun Dis Intell* 2003;27 Suppl:S144–S147.

Keywords: non-antibiotic therapies, phytomedicines, bacteriophages, probiotics, antimicrobial agents

Introduction

Increased use of alternative medicines has come about largely as a result of the general community's interest in alternative therapies rather than by demand from healthcare professionals for alternative agents. Both groups have their own prejudices; lay people often assume natural products are completely safe and effective while many health professionals dismiss therapeutic agents or methods that do not fit the conventional paradigm. Both groups often maintain their biases in the face of contradictory evidence, or view the absence of evidence as evidence in its own right. A survey published in 1996 indicated that nearly 50 per cent of the Australian population had used at least one non-medically prescribed alternative medicine.[1] With specific regard to antimicrobials, there are several non-antibiotic approaches to the treatment and prevention of infection including probiotics, bacteriophages and phytomedicines.

Probiotics

Probiotics have been suggested as an alternative therapy for the treatment of infectious gastroenteritis, or the treatment and prevention of antibiotic-associated diarrhoea due to *Clostridium difficile*. Probiotics are preparations of ostensibly non-pathogenic organisms known to have a beneficial effect on the digestive and other systems by conferring resistance to infection or eliminating infectious agents. Both bacteria and yeasts have been used as probiotics. The mechanisms of action of probiotics have been summarised by Filho-Lima *et al*.[2] Four possibilities exist: 1. antagonism through production of inhibitory substances; 2. competition with the pathogen for adhesion sites or nutrients; 3. immunomodulation of the host; and 4. inhibition of toxins.

1. Department of Microbiology, The University of Western Australia, Crawley, Western Australia
2. Western Australian Centre for Pathology and Medical Research, Nedlands, Perth, Western Australia

Corresponding author: Professor Thomas V Riley, Department of Microbiology, Queen Elizabeth II Medical Centre, Nedlands, Perth WA 6009. Telephone: +618 9346 3690. Facsimile: +618 9382 8046. Email: triley@cyllene.uwa.edu.au

Lactobacillus GG has been the most widely studied of probiotic agents. In addition to having been used, with varying degrees of success, for treating or preventing urinary tract infections, vulvo-vaginal candidiasis and bacterial vaginosis,[3] *Lactobacillus* GG, in the form of a milk preparation, was recently reported as having some modest but consistent benefits in terms of preventing and reducing the severity of respiratory infections at day care centres.[4] While the relevance of this latter observation to the prevention of antibiotic resistance may not be immediately apparent, any intervention which results in reduced use of antibiotics in a particular setting will eventually lead to a decline in antibiotic resistance. Another well-studied probiotic is *Saccharomyces boulardii*, a yeast that is effective in preventing relapses of *Clostridium difficile*-associated diarrhoea and treating various types of infectious diarrhoea.[5] Several other possible probiotics have been looked at, such as non-toxigenic strains of *C. difficile* and a strain of *Enterococcus faecium*. However, enthusiasm for enterococci as probiotics has waned since the emergence of vancomycin resistant enterococci.

Bacteriophages as antimicrobial agents

An old idea ignored since the beginning of the antibiotic era by all but a few former Soviet bloc countries is bacteriophage therapy where phages are used to lyse bacterial pathogens. There has been renewed interest in bacteriophage therapy with the emergence of antibiotic resistance as a major problem in modern medicine.[6] Several reports from Poland in the 1980s described the treatment of various infections, the majority of which were staphylococcal and included bacteraemia. *In vitro* testing indicated that bacteriophages were active against specific pathogens. Efficacy *in vivo* was assessed on a clinical basis alone and positive results were obtained in over 90 per cent of cases, however, there were no untreated controls.[7] Similar studies were carried out in the former Soviet Union from the early 1970s. In those studies where staphylococci (presumably *Staphylococcus aureus*) were involved, bacteria were eliminated after phage therapy in the majority of cases.[6] Phages were applied either topically, sub-cutaneously, or via irrigation or drains.

Studies in the United Kingdom have predominantly concentrated on the treatment of diarrhoeal disease, mainly caused by *Escherichia coli*, using animal models.[8] Soothill[9] treated experimental *S. aureus* infections in mice with bacteriophage. Bacteriophage and *S. aureus* (the same strains as had been used in some of the Polish studies) were injected intraperitoneally simultaneously. In this situation bacteriophage was not protective although infections involving *Acinetobacter baumanii* and *Pseudomonas aeruginosa* could be prevented by their respective bacteriophages.

As with other alternative therapies, there have been concerns about the safety of bacteriophage therapy. One concern has been the development of antiphage antibody during therapy. This was assessed in Poland in 57 patients following oral administration of bacteriophage and found no measurable antibody in 44 patients during treatment. In two cases high titre antibody developed.[10] Another major problem has been the presence of various toxins in crude phage lysates, however, this can now be addressed during preparative process.[11] The bioavailability of phage administered systematically has also been a concern, with early studies indicating that phage was quickly cleared by the reticuloendothelial system. Mutant phages with the ability to evade the reticuloendothelial system have now been produced.[11] It is possible that bacteria will ultimately become resistant to phage lysis in the same way that antibiotic resistance has emerged. However, phage used as a single dose, may be less likely to result in resistance than using antibiotics for a long period. Other problems include the observation that some methicillin-resistant *S. aureus* (MRSA) seem to be inherently less susceptible to bacteriophages than antibiotic-susceptible *S. aureus*. Finally, there is concern of the possibility of lysogenic conversion, whereby bacteriophage could acquire various toxin genes and introduce these into susceptible bacteria. The likelihood of this occurring, or of virulence genes being introduced by transduction, is unknown.

Phytomedicines

Phytomedicines are plant-derived remedies and many, such as tea tree oil (TTO), honey and cranberry juice, are targeted towards infectious diseases. TTO is the essential oil derived from certain species of Australian native plants in the genus *Melaleuca*, mainly *Melaleuca alternifolia*.[12] Originally developed in the pre-antibiotic era, its antimicrobial properties were first reported in the 1920s when it was shown to be more active than one of the widely used disinfectants of the day, phenol.[12] The antimicrobial activity and tolerability of TTO made it a popular skin antiseptic for the next 20 years. The dawn of the antibiotic era precipitated the demise of interest in TTO which could not compete with the potency and selective toxicity of the new agents. Consequently, TTO was discarded as an antimicrobial agent before its properties could be elucidated fully. Sixty years later, the widespread occurrence of multiple antibiotic-resistant organisms in hospital and community settings suggests new antimicrobial agents, preferably with novel mechanisms of action, are required and it seems prudent to re-examine previously superseded products such as TTO. *In vitro*, TTO has broad spectrum antibacterial activity[13] including activity against MRSA.[14] Antifungal and antiviral properties have also been demonstrated *in vitro* and preliminary *in vivo* work suggests that it may be useful in the treatment of acne[15] and oral candidiasis,[16] and in the decolonisation of MRSA carriage.[17] An understanding of its mechanisms of action against bacteria is being reached[18,19] and it appears that multiple mechanisms are involved, perhaps diminishing the rate at which resistance is likely to develop.

In contrast to TTO, honey has a much longer recorded history of medicinal use. Scattered reports in the medical literature describe the antibacterial properties of honey and honey products, and their potential as antimicrobial agents, particularly in wound care.[20] More recently, *in vitro* antibacterial activity has been described and a wide range of organisms is inhibited by honey including *E. coli*, *Proteus mirabilis*, *Ps. aeruginosa*, *Enterococcus faecalis* [21] and *Helicobacter pylori*.[22] The activity of honey has been attributed to the high osmolarity, the low pH and the presence of hydrogen peroxide. However, these factors alone or in combination do not account for all of the antibacterial activity and the identity of the main antimicrobial component of some honeys and its mechanism of action remains unclear.

Cranberries were used by North American Indians for food and medicine and they still enjoy popularity today. Commercially available cranberry juice may be useful in the treatment and prevention of urinary tract infections. Its putative medicinal properties have been partly investigated with occasional papers appearing in the medical literature. In a recent study, the effect of regular cranberry juice consumption on the recurrence of urinary tract infections was examined.[23] The time to first recurrence of a symptomatic urinary tract infection was compared in three groups of women randomised to receive daily 50 mL of European cranberry juice, 100 mL of a *Lactobacillus* GG drink or no intervention. Of the 50 patients randomised to cranberry juice, the cumulative rate of first recurrence of urinary tract infections during the 12-month follow-up was significantly reduced compared to the 50 patients receiving no intervention. In contrast, consumption of the *Lactobacillus* GG drink offered no benefit. Earlier work by Avorn *et al*.[24] suggested that daily ingestion of 300 mL of cranberry juice reduced the frequency of bacteriuria with pyuria in older women. A number of mechanisms have been postulated although a direct antibacterial effect and acidification of the urine have been excluded as the primary mechanisms of action. Exposure of uropathogenic *E. coli* to cranberry juice or extracts diminishes expression of P-fimbriae and inhibits their adherence to uroepithelial cells.[25] Similar work has shown that a high molecular weight constituent of cranberry juice can inhibit *H. pylori* adhesion to gastric mucosa.[26] While cranberry juice may not prove to be an effective treatment for current urinary tract or *H. pylori* infections, it may prevent *de novo* infections or prevent reinfection.

Conclusions

Alternative therapies are viewed favourably by many patients because they are often not being helped by conventional therapy and they believe there are fewer detrimental side effects. In addition, many report significant improvement while taking complementary and alternative medicines. Unfortunately, the medical profession has been slow to embrace these therapies and good scientific data are scarce at present.[3] However, as we approach the 'post-antibiotic era' the situation is changing. Further research is needed to validate the claims made for alternative therapies.

References

1. MacLennan AH, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. *Lancet* 1996;347:569–573.
2. Filho-Lima JVM, Viera EC, Nicoli JR. Antagonistic effect of *Lactobacillus acidophilus, Saccharomyces boulardii* and *Escherichia coli* combination against experimental infections with *Shigella flexneri* and *Salmonella enteritidis* subsp. Typhimurium in gnotobiotic mice. *J Appl Microbiol* 2000;88:365–370.
3. Golledge CL, Riley TV. 'Natural' therapies for infectious diseases. *Med J Aust* 1996;164:94–95.
4. Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, *et al*. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ* 2001;322;1327–1331.
5. McFarland LV, Bernasconi P. A review of a novel biotherapeutic agent: *Saccharomyces boulardii*. *Microb Ecology Health Dis* 1993;6:157–171.
6. Alisky J, Iczkowski K, Rapoport A, Troitsky N. Bacteriophages show promise as antimicrobial agents. *J Hosp Infect* 1998;36:5–15.
7. Slopek S, Weber-Dabrowska B, Dabrowski M, Kucharewicz-Krukowska A. Results of bacteriophage treatment of suppurative bacterial infections in the years 1981–1986. *Arch Immunol Ther Exp* 1987;35:569–583.
8. Smith HW, Huggins MB. Successful treatment of experimental *Escherichia coli* infections in mice using phage: its general superiority over antibiotics. *J Gen Microbiol* 1982;128:307–318.
9. Soothill JS. Treatment of experimental infections of mice with bacteriophages. *J Med Microbiol* 1992;37:258–261.
10. Kucharewicz-Krukowska A, Slopek S. Immunogenic effect of bacteriophage in patients subjected to phage therapy. *Arch Immunol Ther Exp (Warsz)* 1987;35:553–561.
11. Merril CR, Biswas B, Carlton R, Jensen NC, Creed GJ, Zullo S, *et al*. Long-circulating bacteriophage as antibacterial agents. *Proc Natl Acad Sci USA* 1996;93:3188–3192.
12. Carson CF, Riley TV. Antimicrobial activity of the essential oil of *Melaleuca alternifolia*. *Lett Appl Microbiol* 1993;16:49–55.
13. Hammer KA, Carson CF, Riley TV. Susceptibility of transient and commensal skin flora to the essential oil of *Melaleuca alternifolia* (tea tree oil). *Am J Infect Control* 1996;24:186–189.
14. Carson CF, Cookson BD, Farrelly HD, Riley TV. Susceptibility of methicillin-resistant *Staphylococcus aureus* to the essential oil of *Melaleuca alternifolia*. *J Antimicrob Chemother* 1995;35:421–424.
15. Bassett IB, Pannowitz DL, Barnetson RStC. A comparative study of tea tree oil versus benzoylperoxide in the treatment of acne. *Med J Aust* 1990;153:455–458.
16. Jandourek A, Vaishampayan JK, Vazquez JA. Efficacy of *Melaleuca* oral solution for the treatment of fluconazole refractory oral candidiasis in AIDS patients. AIDS 1998;12:1033–1037.
17. Caelli M, Porteous J, Carson CF, Heller R, Riley TV. Tea tree oil as an alternative topical decolonization agent for methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 2000;46:236–237.
18. Cox S, Mann CM, Markham JL, Bell HC, Gustafson JE, Warmington JR, *et al*. The mode of action of the essential oil of *Melaleuca alternifolia* (tea tree oil). *J Appl Microbiol* 2000;88:170–175.
19. Carson CF, Mee BJ, Riley TV. Mechanism of action of *Melaleuca alternifolia* (tea tree) oil on *Staphylococcus aureus* determined by time-kill, lysis, leakage, and salt tolerance assays and electron microscopy. *Antimicrob Agents Chemother* 2002;46:1914–1920.
20. Cooper RA, Molan PC, Krishnamoorthy L, Harding KG. Manuka honey used to heal a recalcitrant surgical wound. *Eur J Clin Microbiol Infect Dis* 2001;20:758–759.
21. Allen KL, Molan PC, Reid GM. A survey of the antibacterial activity of some New Zealand honeys. *J Pharm Pharmacol* 1991;43:817–822.
22. Al Somal N, Coley KE, Molan PC, Hancock BM. Susceptibility of *Helicobacter pylori* to the antibacterial activity of manuka honey. *J R Soc Med* 1994;87:9–12.
23. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and *Lactobacillus* GG drink for the prevention of urinary tract infections in women. *BMJ* 2001;322:1571–1575.
24. Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994;271:751–754.
25. Foo LY, Lu Y, Howell AB, Vorsa N. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated *Escherichia coli* in vitro. *Phytochemistry* 2000; 54:173–181.
26. Burger O, Ofek I, Tabak M, Weiss E I, Sharon N, Neeman I. A high molecular mass constituent of cranberry juice inhibits *Helicobacter pylori* adhesion to human gastric mucus. *FEMS Immunol Med Microbiol* 2000;29:295–301.

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