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# Emergence of Vancomycin Resistant Enterococci in Australia

Endorsed at the 122nd session of the National  
Health and Medical Research Council

National Health and Medical Research Council

**NHMRC**

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RESEARCH  
RECOMMENDED

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RESISTANCE

# Preface

The emergence of vancomycin resistant enterococci (VRE) in hospital patients is a significant international concern. It threatens to compromise effective treatment of infections caused by multi-resistant gram-positive bacteria, particularly in seriously ill hospitalised patients, who may need treatment with vancomycin where other antibiotics have failed

Following several outbreaks of VRE in Australian hospitals, between October 1994 and October 1996, the NHMRC's Working Party on Antibiotics were asked to investigate the issue of VRE in Australia.

The Working Party considered local and international evidence and formulated a set of recommendations that aim to:

- increase awareness and understanding of VRE; and
- combat the spread of VRE in Australia.

# NHMRC Working Party on Antibiotics

## Terms

1. Provide expert advice to government, health professionals, and the community on the public health implications for the use of antibiotics and the effects of their use in human and veterinary medicine, primary industry (including medicated stockfeeds, agronomy, horticulture, aquaculture and apiculture). Monitor and develop strategies to minimise the rate of development of microbial resistance and the impact of antibiotic use on the environment.
2. Report to the NHMRC Communicable Disease Standing Committee.

## Membership

Associate Professor John Turnidge (Chairman)	Microbiology and Infectious Diseases Department, Womens and Childrens Hospital, SA
Dr Douglas Bryden	Post Graduate Foundation in Veterinary Science, University of Sydney, NSW
Dr Richard Benn	Microbiology, Prince Alfred Hospital, NSW
Dr Lindsay A Herbert	Chemical Standards Branch, Department of Agriculture, Energy and Minerals, VIC
Dr Derk Jan Groot-Obbink	Pathology Services, Royal North Shore Hospital, NSW
Dr Rodney Scott Dyson	Kyabram Veterinary Clinic, VIC
Dr Nicholas Zwar	RACGP Training program, NSW
Ms Susan Powter	Consumers' Health Forum representative
Mr Roger Howard (Secretary/Convener)	Therapeutic Goods Administration, ACT
Ms Maureen Kaupins (Executive Secretary)	Therapeutic Goods Administration, ACT.

# Recommendations

The NHMRC Working Party on Antibiotics makes the following recommendations:

1. Health care establishments to be encouraged to maintain a program of ongoing improvement in infection control practices.
2. Development of specific measures to combat the spread of VRE in health care establishments, to be included in the update of the NHMRC/ANCA publication *Infection Control in the Health Care Setting - Guidelines for the Prevention of Transmission of Infectious Diseases*. A separate document to all health care establishments may also be of value.
3. Hospitals and community-based prescribers to be asked to severely restrict the oral use of vancomycin.
4. Support to be given to ongoing professional education and public awareness campaigns about the risk of VRE and the effect of excessive antibiotic prescribing to humans.
5. Support to be given to the maintenance of the National Antimicrobial Resistance Surveillance Program (NARSP).
6. Urgent research to be encouraged into the prevalence of VRE in Australia through the use of screening tests in hospitalised patients, and studies on risk factors for their emergence and transmission.
7. 'Based on current evidence, there are insufficient grounds to recommend a ban on the use of avoparcin in Australia, at this time.

# Background

Enterococci (*Enterococcus* spp.) are common Gram-positive cocci that colonise the gastrointestinal tract of man and many other animals. All humans and many animals carry enterococci in normal intestinal flora. Enterococci are only pathogenic to humans in specific circumstances. They can cause minor urinary tract infections, wound infections especially after surgery (usually in combination with other bacteria), septicaemia and endocarditis.

Enterococci are bacteria that are naturally resistant to a number of antibiotics, including all cephalosporins, aminoglycosides and clindamycin. In addition they are often resistant to tetracyclines and erythromycin. Treatment of serious infection requires the use of penicillin/ampicillin/amoxycillin or a glycopeptide antibiotic such as vancomycin or teicoplanin. Of all the infections caused by enterococci, endocarditis is the most difficult to treat, requiring a combination of a cell-wall active agent such as penicillin or vancomycin, and an aminoglycoside (usually gentamicin) for synergy to ensure cure.

The first resistance problem to emerge in enterococci was high-level aminoglycoside resistance (normal resistance is at a low level). This type of resistance only affects the treatment of endocarditis and is therefore not a major clinical problem. Aminoglycoside resistance was followed by the emergence of resistance to penicillin/ampicillin/amoxycillin in *E.faecalis* and especially *E.faecium*. This type of resistance is more significant, as it eliminates the drug of choice, and in serious infection means that a glycopeptide must be used. However, this resistance has remained at a fairly low level. Three types of vancomycin resistance have been found in enterococci:

Table 1: Types of vancomycin resistance enterococci (VRE)

Type	Level	X-resistance with teicoplanin	Plasmid-borne, transmissible	Commonest species harbouring
VanA	High	Yes	Yes	<i>E.faecium</i>
VanB	Low	No	Yes	<i>E.faecalis</i>
VanC	Low	No	No - intrinsic	<i>E.gallinarum</i> (C1) <i>E.casselinayus</i> (C2)

*VanA* and *VanB* type resistances found in *E.faecium* and *E.faecalis* account for almost all of the important resistances in clinical settings. VanC resistance is low level intrinsic resistance that is naturally found in the rarer species of enterococci. These species are rarely major pathogens and thus this type of resistance is of little clinical importance.

One particular problem of VRE is that they are usually multi-resistant, ie they are resistant not only to vancomycin but also to penicillin/ampicillin/amoxycillin and to high levels of aminoglycosides. This makes serious infection with these strains very difficult to treat. The main drugs used to treat these organisms are experimental, such as the combination streptogramin agent, quinupristin-dalfopristin, the oxazolidinones and possibly in future the ketolides, as well as many combinations of older drugs even in the face of resistance, hoping for some synergy. VanB resistant organisms can be treated with teicoplanin.

# International emergence of VRE

VRE were first found in the late 1980s in the United States of America (USA). As with many types of resistance these were at first considered to be a rarity. However, over the next few years they were found to be a significant cause of cross-colonisation and infection in tertiary care hospitals in the USA, particularly in Intensive Care units. More recently they have been described with increasing frequency in Europe, especially Britain.

RESISTANCE

# VRE in Australia

There have been 15 confirmed isolates (13 strains) of VRE in Australia as at 28 October 1996. The first isolate was in 1994 from a patient who had undergone a liver transplant at the Austin Hospital in Melbourne. Extensive investigations at the time did not find any other strains in the hospital. There have been a further 14 isolates in Australia, 13 since April 1996, as shown in the following table. There may well have been other isolates about which we have not heard.

Table 2: Australian VRE - as at 28 October 1996

Site	Number	Time	Species	Phenotype	Genotype
A	1	October 1994	<i>E. faecium</i>	VanA	van A -
B	1	1995	<i>E. faecalis</i>	VanA	van A
C	3 (in one ward)	April 1996	<i>E. faecium</i>	VanA	van A
D	1	May 1996	<i>E. faecalis</i>	VanB	van B
E	1	June 1996	<i>E. faecalis</i>	VanB	van B
F	1	August 1996	<i>E. faecium</i>	VanA	van A
D	1 (?2)	August 1996	<i>E. faecium</i>	VanB ->?VanA	van B/van B
G	1	August 1996	<i>E. faecium</i>	VanB	van B
A	1	September 1996	<i>E. faecium</i>	VanB	van B
H	1	September 1996	<i>E. faecium</i>	VanB	van B
I	1	September 1996	<i>E. faecalis</i>	VanB	van B
D	1	October 1996	<i>E. faecium</i>	VanB	van B
E	1	October 1996	<i>E. faecium</i>	VanA	Pending

# Risk factors for VRE acquisition and spread

Experience in the USA suggests that VRE have emerged as a result of antibiotic pressure generated on normal gut flora by the clinical use of vancomycin, particularly in the oral form used for the treatment of *Clostridium difficile* (antibiotic-associated) colitis. Oral vancomycin is used widely in the USA for this condition, but is reserved for relapsing infection in Australia. In Australia, metronidazole is the preferred agent principally because of cost. Other treatments that can and have been used include oral bacitracin and oral sodium fusidate. Vancomycin has also been used extensively in the USA and Europe for suppression of Gram-positive gut flora in the setting of cancer chemotherapy and intensive care to prevent infection. These practices have not become common in Australia. The following have been identified as risk factors for VRE in the USA:

- prolonged hospitalisation;
- immunocompromised host;
- neutropenia;
- prior antimicrobial therapy (especially with cephalosporins and vancomycin);
- admission to an intensive care unit;
- renal failure.

The USA experience suggests that the propensity for cross-infection with VRE is very high, and of a similar order of magnitude to multi-resistant *Staphylococcus aureus* (MRSA). However, unlike MRSA, the clinically manifest infection rate is low compared to the rate of asymptomatic colonisation, possibly of the order of one in 100.

Of particular interest are the results of a study from Belgium, where vancomycin and teicoplanin were given orally to healthy volunteers from 1989-91 and VRE emerged in 64 per cent. A subsequent investigation in 1992, included in the same study, revealed that 11 of 40 (28%) healthy individuals and 4 of 33 (12%) cancer patients who had never received any glycopeptides before were colonised with low numbers of VRE (*VanA E.faecium*, see below). The source of these colonising strains was unclear.

# Possible role of animal glycopeptide use

Studies in three European countries: Germany, Britain and Denmark, have shown that VanA strains of *E.faecium* can be found in intensively-farmed pigs and poultry. One controlled study in Denmark has shown that the presence of these type of VRE in the gut of pigs and poultry is statistically-significantly associated with the use of the growth promotant antibiotic, avoparcin. Avoparcin is in the same antibiotic class as vancomycin (the glycopeptide class). The same European investigators have also found these types of VRE in occasional samples of prepared pork and chicken meat or carcasses, raising the possibility of transmission by the food chain. It is conceivable that these strains could colonise vulnerable humans, especially those with depressed immunity or those prescribed antibiotics to which the organism is naturally resistant such as cephalosporins.

However, convincing evidence for transmission of animal VRE to humans is lacking. Using a molecular technique called ribotyping, the Danish investigators initially showed that VRE from animals were identical to strains isolated from patients in Germany. When done subsequently with a different molecular typing technique the strains appeared to all be different. Similar differences were found between a variety of strains from human and animal sources in the German study. There is therefore no certainty at this stage about the similarity of the human and animal isolates of VRE. Another piece of evidence against there being a major role for avoparcin is that in the USA, which has the widest prevalence of VRE, most commonly strains of VanA *E.faecium*, avoparcin has never been licensed or used in any form.

Even if it was proven that there was a connection between avoparcin use in agriculture and transmission of VRE in humans, it would still only provide one possible explanation of the source of some of the types of VRE (VanA *E.faecium* only), and many may still be related to the high usage of vancomycin for the treatment and prophylaxis of human infection, especially when the drug is given orally.

Based on the findings of the European studies; Denmark, Germany and Finland all put a temporary ban on the use of avoparcin in stockfeed. The evidence on which these decisions were based was presented to the Standing Committee on Animal Nutrition (SCAN) of the European Union late last year (1995). In May this year, SCAN concluded that the data against avoparcin did not warrant a ban on its use, and that further investigations were required before a final recommendation could be made one way or the other. This will require Denmark, Germany and Finland to lift their bans.

In a similar manner to Europe, avoparcin has been used extensively in Australia for 19 years. Import figures for 1992 and 1993 show that more than 100 tonnes of avoparcin were imported per annum into Australia for stockfeed use. The figure for 1995 was 150 tonnes. Investigation by the NHMRC Working Party on Antibiotics has shown that it is used mostly as a growth promotant in the intensive animal industries, principally in pigs and poultry. It is also used in calf weaning mixtures to a small extent.

Three strains of VanA *E.faecium* were found at the John Hunter Hospital, Newcastle during May this year. Consequently, Dr John Ferguson of the Hunter Area Pathology Service put forward a joint proposal, with the local Department of Agriculture and Food Hygiene Unit, to screen pigs, poultry, cattle and food samples in the Hunter region for the presence of VRE. Results will be correlated with avoparcin usage. This study has just commenced. Until now there has been no testing of animal enterococci for resistance to avoparcin or vancomycin in Australia. Thus Australia has yet to demonstrate that our situation is the same as that in Europe.

# Action for the NHMRC Working Party on Antibiotics

1. Determine the existence of other isolates of VRE in Australia to date through the National Antimicrobial Resistance Surveillance Program.
2. Alert all microbiology laboratories, via the National Antimicrobial Resistance Surveillance Program, with the assistance of the Quality Assurance Program of the Royal College of Pathologists of Australasia, about the emergence of VRE in Australia, and provide information about methods of detection, confirmation and screening.
3. Ascertain risk factors and clinical significance of the current known isolates of VRE. A short questionnaire has been distributed to the hospitals coded in Table 2: Australian VRE - as at 28 October 1996.
4. Monitor the international and local research into all aspects of the emergence of VRE in humans.
5. Reconvene via teleconference within no more than one month to reconsider any new information about VRE in Australia or overseas.

## Recommendations and reasons

After considering the available evidence, the NHMRC Working Party on Antibiotics makes the following recommendations to the Communicable Diseases Standing Committee, the National Health Advisory Committee, and through them to the National Health and Medical Research Council:

1. Health care establishments to be encouraged to maintain a program of ongoing improvement in infection control practices.

Reason: VRE have a high propensity for cross infection in hospitals,

2. Development of specific measures to combat the spread of VRE in health care establishments, to be included in the update of the NHMRC/ANCA publication *Infection Control in the Health Care Setting - Guidelines for the Prevention of Transmission of Infectious Diseases*. A separate document to all health care establishments may also be of value.

Reason: Specific measures appear to be required to prevent cross infection of VRE. The USA guidelines can serve as a model.

3. Hospitals and community-based prescribers to be asked to severely restrict the oral use of vancomycin.

Reason: oral vancomycin usage appears to be a major factor in amplifying VRE as well as putting patients at risk of colonisation.

4. Support to be given to ongoing professional education and public awareness campaigns about the risk of VRE and the effect of excessive antibiotic prescribing to humans.

Reason: A balanced view of the relative importance of VRE needs to be given to both health care professionals and the public.

5. Support to be given to the maintenance of the National Antimicrobial Resistance Surveillance Program (NARSP).

Reason: NARSP is best placed to monitor trends in the emergence of VRE and other multi-resistant pathogens. At present it is unfunded (apart from temporary salary support from the Women's and Children's Hospital).

6. Urgent research to be encouraged into the prevalence of VRE in Australia through the use of screening tests in hospitalised patients, and studies on risk factors for their emergence and transmission.

Reason: Rapid determination of the risk factors for spread of VRE in Australia will help prevent VRE becoming established in Australia like it has in the USA.

7. Based on current evidence, there are insufficient grounds to recommend a ban on the use of avoparcin in Australia, at this time.

Reason: Self explanatory

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