ESBL (CDS 100% and others 82%, *2011, 6:1b*); and (iv) detection of meropenem resistance in *Citrobacter freundii* mediated by a carbapenemase (CDS method 95%, other methods 71%, *2013, 4:1b*).

The future of the CDS

Registrants as CDS users continue to grow and number over 200 at present. The CDS method is now being used by laboratories in South East Asia, India and South Africa. It is unfortunate that a number of Australian public laboratories have changed from using the CDS method to other methods as a result of executive decisions apparently based on reasons other than scientific merit. As long as antimicrobial susceptibility testing is performed in diagnostic laboratories the CDS will continue to provide a service to Australasian and a number of overseas laboratories. The original CDS team has been joined by younger scientific and medical staff who will carry on the tradition of supporting a high-performance national antibiotic susceptibility test method well into the future.

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Vancomycin-resistant enterococci in hospitals

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Control measures for vancomycin-resistant enterococci (VRE) should be determined by the current epidemiology of infection and must be practical and effective. It is essential that emphasis is placed on consistent implementation of enhanced standard precautions (horizontal measures) in healthcare that reduce infections caused by all organisms, not just VRE. Effective antimicrobial stewardship programs are paramount and should target reduction in the use of extended-spectrum cephalosporins, carbapenems and fluoroquinolones. VRE causes marked morbidity in a limited range of at-risk patient groups who require additional active measures to prevent their acquisition of virulent strains. The use of additional measures for patients at low risk from VRE morbidity is unlikely to be cost-effective and should be reserved for outbreak situations or for patients who are more likely to transmit VRE.

Epidemiology

Infectious agent and clinical significance

Enterococci are Gram-positive cocci that colonise the intestinal tract of humans and animals. They can persist on inanimate objects for weeks, have intrinsic resistance to many antibiotics and a capacity to develop multiresistance. Generally they have low virulence.

Colonisation may precede infection by months to years. Most colonised patients do not develop infection. This is influenced by patient risk factors detailed below and enterococcal strain type.

Some strains adhere to uroepithelium and endocardium and may cause infection in patients without marked immunosuppression. Device-associated infection also occurs. Enterococci can be found in mixed cultures from intra-abdominal and pelvic infections but recovery usually occurs without targeted enterococcal treatment in uncomplicated cases[1]. Most often, isolation of enterococci, including VRE from the urine is not clinically significant[2]. Compared with vancomycin susceptible enterococci (VSE), VRE infections cause more severe disease, increased mortality and have a significant additional economic burden. Antibiotic treatment options for VRE are limited and pan-resistance can occur[3].

Occurrence

Enterococci with acquired, transferrable high level resistance to vancomycin were first detected in faeces from two leukaemia patients from Europe in 1986[4]. Hospital outbreaks were increasingly described over the next decade across Europe and the USA. Internationally, the important resistance genotypes of VRE have been either *vanA* or *vanB* operons usually carried by *Enterococcus faecium* in a transposon located within a large transferrable plasmid. There is evidence of global spread of a clonal complex of hospital-associated ampicillin-resistant *E. faecium* (CC17) that includes both VSE and VRE (either *vanA* or *vanB*) and has a number of putative virulence factors for hospital adaption and spread[5,6].

In Australia, *vanB-E. faecium* has predominated since the late 1990s. A 2010 Australian VRE survey indicated increasing prevalence of VRE *vanB E. faecium* from the CC17 in a number of States[7]. Only Western Australia has conducted consistent long-term VRE surveillance. Of 1182 VRE patient isolates over 15 years, 89% were *vanB-E. faecium*[8]. Seven hundred of these isolates came from three single strain, multiple institution outbreaks. Unexpectedly in 2012, 32% (41 isolates) of the 129 *E. faecium* VRE strains harboured the *vanA* operon. These isolates were polyclonal and found across six hospitals.

Recent whole genome sequencing of Australian invasive VRE and VSE isolates indicates that non-clonality indicated by multilocus sequencing typing is unreliable and that *de novo* generation of polyclonal *vanB*-VRE by transfer of elements from non-enterococcal strains has been frequent[9]. This study and others[5,6,9] suggests that control of hospital-associated VSE may also be important in VRE control efforts. The multi-locus sequence type ST203 from CC17 caused an extensive outbreak in at least one hospital in Victoria from 2007. A marked increase in VRE bacteraemia due to ST203 was preceded by occurrence in other patients of similar ST203 VSE implying lateral transfer of the *vanB* locus into VSE to create VRE[6].

Reservoirs

In Australia, non-enterococcal genera (predominantly anaerobes) in human faeces frequently carry an identical or related *vanB*-containing Tn*1549* mobile element[10] and similar organisms have also been detected in Canada and France. Low rates of polyclonal *vanB-VRE* carriage have also been detected in various community populations, including residential aged care residents[8,11,12]. No animal reservoir has been identified in recent surveys.

In New Zealand, detection of VRE is rare[13]. Significant *VanA*-VRE hospital outbreaks occurred in 2007 and 2008 and were well controlled. Since 2010, *vanB-Enterococcus faecium* has predominated. In 2012, a total of 38 VRE strains were detected with the majority (87%) isolated from patients in Auckland hospitals[14]. Community faecal carriage of *vanA* -VRE is common in Europe, but not in Australia or the USA. *vanA*-VRE have also caused outbreaks in Australia[15] but it is not endemic in most regions.

Patient characteristics (Table 1) and antibiotic exposure may markedly increase the faecal VRE load and/or capacity to disseminate VRE, increasing the risk of hospital transmission and

Table 1. VRE risk areas and at-risk patients in hospitals (after Mutters *et al*.[16]).

Risk areas: high risk of VRE morbidity	Patients at high risk of transmitting VRE
Hematology/oncology units (patients with severe or extreme immunosuppression/immunodeficiency) Transplantation units	VRE colonisation of secreting wounds (e.g. decubitus ulcers, severe burn injuries, other open chronic wounds)
Liver transplantation units ICU/HDU with a high percentage of general surgical or gastroenterological patients Neonatal ICU	VRE colonisation with diarrhoea, *C. difficile* infection, stool incontinence (also enterostomies etc.)
Dialysis stations	VRE-colonised patients with inadequate compliance/cooperation

ICU, intensive care unit; HDU, high dependency/intermediate care unit.

outbreaks[16]. Detection of VRE from clinical samples alone, without active screening, markedly underestimates the reservoir. Whilst transient staff hand VRE colonisation is not uncommon, long-term staff faecal colonisation has not been studied.

VRE persists for prolonged periods on inanimate objects. Cultures from frequently touched surfaces in rooms and toilets of VRE-colonised patients reveal high levels of contamination that may persist following conventional room disinfection[17,18]. Presence of VRE-containing biofilm enhances environmental persistence, complicating the cleaning process[19].

Mode of transmission

VRE is transmitted by hands or from the environment. To break transmission, both hand and environmental hygiene are critical. Airborne dissemination is not important: throat, nasal and airway colonisation with VRE is rare.

A recent modelling paper demonstrates how patient transfer amongst different hospitals within a single region may significantly influence the VRE burden. A sustained increase of 10% in VRE colonisation prevalence in one hospital resulted in a calculated 2.8% (range 0–58%) relative increase in prevalence in other hospitals. The effects took from 1.5 to more than 10 years to manifest. This delay must be considered in research that analyses the impact of control efforts[20]. McBryde used a 'Hidden Markov Model' applied to serial prevalence data to estimate the characteristics of acquisition of VRE and distinguish epidemic versus sporadic acquisition. Using hospital data from Melbourne, this model estimated that 89% of acquisitions were due to ward cross-transmission[21].

Period of colonisation

Prolonged faecal colonisation is usual and relapse or reacquisition of VRE is often reported after apparent clearance, often triggered by antibiotic therapy. From a retrospective cohort from Melbourne, a study group of 103 colonised patients were resampled by faecal culture. The proportion of colonised patients fell to 23% by year 4 and none of 40 patients in whom VRE had been detected >4 years prior was found to be colonised. It was suggested that in the absence of recent risk factors, such as hospitalisation or antibiotic use, that patients with a remote history of colonisation may be considered 'cleared'[22].

VRE clearance criteria within published guidelines vary widely and no consensus has been reached in Australia or internationally. Queensland and South Australia have different clearance criteria while NSW, Victoria and WA have none. Case-by-case risk-based decisions are made to clear patients in New Zealand. Eradication of VRE carriage by active treatment has not been conclusively demonstrated. Short-term clearance of VRE has been demonstrated in two small randomised trials of probiotic *Lactobacillus rhamnosus* GG administration.

From a risk point of view, well, continent, VRE-colonised patients who have not been recently hospitalised or given antibiotics will usually revert to undetectable levels residual colonisation, significantly reducing the risk of transmission. Maintaining such patients under transmission-based precautions during representations is unlikely to be cost-effective. Furthermore, given the high prevalence of *vanB* operons in non-enterococcal isolates, community VRE carriage and the lack of systematic screening for VRE colonisation, there will likely be large numbers of unsuspected VRE carriers. Therefore, the priority must be to target screening and isolation to patient groups that are at high risk from VRE disease (see below).

Risk factors

Risk factors for healthcare-associated colonisation and/or infection with VRE have been identified[16]. They include:

- previous antibiotic exposure
- patient characteristics
- colonisation pressure
- exposure to contaminated surfaces.

Previous antibiotic therapy

Initial case-control study evidence implicated vancomycin, broad spectrum cephalosporins and anti-anaerobic agents including metronidazole, clindamycin and ticarcillin+clavulanate. In a landmark study from 1996 of a persistent VRE outbreak , restricted use of cefotaxime, vancomycin and clindamycin and the substitution of pipercillin+tazobactam was followed by a reduction of point prevalence of faecal colonisation with VRE from 47% to 15% . Clinical isolate numbers also decreased[23]. More recent data examining whether the relative risk of pipercillin+tazobactam use is low are less convincing[24]. The association with vancomycin use with VRE risk is much weaker when controls are selected with an equivalent time of risk and comorbidity[25].

Ceftriaxone has no enterococcal action and achieves high biliary and bowel concentrations with associated marked increase in faecal VRE load in both humans and mice. Time series analysis of antibiotic use and VRE bacteraemia at one location found a significant association between prior month ceftriaxone use but no association with cephalosporin class drugs as a whole or other agents including vancomycin[26].

Carbapenems may select for VRE[27]. A case control study from the Alfred Hospital found that antibiotic selection pressure had a larger role in determining VRE colonisation than cross-transmission. In

Table 2. Control measures for VRE.

Standard precautions (horizontal measures)	Targeted additional (vertical) measures
Surveillance	Surveillance: active screening for VRE colonisation
Antimicrobial stewardship	Isolation of VRE-colonised patients under transmission-based contact precautions
Hospital design	Outbreak interventions
Hand hygiene	Advanced environmental decontamination measures for high-risk units
Control of potential fomites	Chlorhexidine-containing wash cloths for patient bathing
Enhanced environmental cleaning and disinfection	
Aseptic practices	

multivariate analysis, exposure to antibiotics, particularly meropenem was strongly associated with VRE colonisation as was age >65 years and length of stay >7 days[28].

Extensive evidence associates use of fluoroquinolones with emergence of MRSA, resistant Gram negatives and *C. difficile*. There are limited data concerning risk of VRE acquisition risk.

Patient characteristics frequently reported include older age, prolonged hospitalisation and significant other medical conditions[16].

Colonisation pressure, defined as the daily point prevalence of VRE-colonised patients, is an important risk factor for acquisition of VRE and may outweigh other risk factors once 50% or more of patients in a location have been colonised[29].

Exposure to contaminated surfaces includes rooms previously occupied by VRE colonised patients and exposure to contaminated reused equipment including commodes, shower chairs, thermometers and many other items.

Control of VRE

Control measures for VRE must be practical and effective and take in to account the current epidemiology of infection[16]. Large prospective studies of control approaches are not available and resources are limited. Selection and likely cost-effectiveness of measures must be considered with care. Emphasis must be on consistent implementation of standard precautions (horizontal measures) in healthcare that reduce infections caused by all organisms, not just VRE. In order to control VRE, standard precautions need to be enhanced to deal more effectively with the environmental reservoir. Typing of VRE strains provides important guidance: if clonality is demonstrated, then infection control is the answer whereas if polyclonality is demonstrated, antimicrobial stewardship is needed.

For a possible classification of patients and units by risk for targeting of additional measures see Table 1, but interventions must be guided by local epidemiology including morbidity and outbreak surveillance (Table 2). Other VRE-colonised patients can be managed using standard precautions (horizontal measures) enhanced by including consistent routine surface disinfection (see below).

Surveillance

VRE (and other MRO) morbidity surveillance is essential for guiding the focus of prevention efforts and assessing the impact of interventions. At a minimum, VRE blood stream infections should be documented. In view of the evidence that most nosocomial VRE and VSE are drawn from the same clonal cluster, monitoring of all healthcare-associated enterococcal bacteraemia is advisable. It is essential that the laboratory submits sterile site enterococcal isolates for *vanB* PCR testing as some *vanB* enterococcal isolates are phenotypically susceptible to vancomycin.

Infection control alerting of identified VRE cases (colonised or infected) assists case management and may identify a localised increase in cases.

Standard precautions

Antimicrobial stewardship

Antibiotic stewardship (AMS) is fundamental in the control of major hospital pathogens. In particular, restriction of the use of extended-spectrum cephalosporins, quinolones is of proven worth for VRE, MRSA, MRGN and *C. difficile.* Intervention studies that have had a measured impact on resistance usually have reduced usage below 10 DDDs/1000 patient-days for third generation cephalosporins and below 30 DDDs/1000 for quinolones[30]. In order to achieve such reductions, replacement with antimicrobial agents that have lesser ecological effects is necessary. The relative

ecological effects of cephalosporins are uncertain. Ceftriaxone may be the most important agent to restrict[26].

The new Australian Safety and Quality standards now require all facilities to have in place AMS programs, which is an important first step[31]. These programs now need to drive down unnecessary antimicrobial usage and target drug therapy more effectively, where possible avoiding empiric use of agents associated with adverse MRO and *C. difficile* ecological effects.

Hospital design

There are extensive considerations required in order to optimise infection prevention, such as decisions about the number and type of single rooms and the provision of adequate numbers of toilets. Where possible, dedicated toilets and bathrooms for each patient location are required. All surfaces and equipment must be optimal for routine cleaning and disinfection. Antimicrobial surface materials and coatings require consideration for higher risk locations, including bathrooms and toilets. The Australasian Health Facility Guidelines are an excellent resource[32]. Toilets in hospitals should have lids that automatically close and flush; lidless toilets aerosolise enteric bacteria during flushing causing extensive contamination.

Hand hygiene

There is good evidence showing that healthcare workers can carry VRE on their hands from one patient to another. Such transmission is more likely to occur when healthcare workers are non-compliant with recommended hand hygiene practice. Consistent compliance with all five components of the WHO Standard is essential. Gloves and impervious gown may also be required if contact with body substances is anticipated.

Provision of hand hygiene facilities/materials for patients is important in acute and subacute healthcare, including residential aged care. Facilitation of patient hand hygiene after toileting and at other times is advisable.

Control of potential fomites

Contamination of the environment and equipment occurs from patients colonised or infected with resistant organisms. Staff clothing, stethoscopes, phones, lanyards, gowns and other reused items are frequently contaminated during clinical care. Clothing standards such as bare-below-the-elbow are especially important for high risk locations (Table 1) as clothing sleeves transfer microorganisms as efficiently as hands and the presence of rings, wrist watches and long sleeves or coats impede effective cleaning of hands prior to patient care.

As a minimum, it is essential that all reusable patient equipment is cleaned and disinfected prior to patient use. Use of patient-dedicated equipment is preferred wherever reliable cleaning and disinfection cannot be assured.

Enhanced environmental cleaning and disinfection

Admission to a room previously occupied by a patient with a MRO or *C. difficile* increases the risk of acquisition. More effective systems of room decontamination are required, especially for high risk units (Table 1) and are shown to markedly reduce the risk of VRE (other MROs and *C. difficile*) acquisition compared with conventional methods and should become part of the standard of care for high risk units[33].

The original statement of the standard precautions model required regular (at least daily) cleaning and disinfection of near patient surfaces, bathrooms and toilets regardless of whether the surface appeared clean or not[34]. This is in contrast with the current Australian Infection Control Guidelines that do not specify disinfection except in certain circumstances[35]. Most jurisdictions in Australia have now implemented more stringent routine cleaning and disinfection requirements.

The environmental audit methods for high risk units need to go beyond a visibly clean standard to provide evidence that a surface has actually been cleaned (e.g. by using a fluorescent marker system) and/or whether there is residual bioburden on the surface (e.g. ATPase detection systems or microbiological culture). This information provides essential feedback for all staff who clean and disinfect, which will increase compliance and effectiveness.

The independent importance of the environment is shown by a large recent study from Melbourne; high levels of hand hygiene compliance that were sufficient to reduce hospital MRSA were still associated with continued increases in VRE transmission. VRE control was eventually achieved by an augmented program of routine environmental disinfection with a hypochlorite[36].

Aseptic practices

Invasive infection may be triggered by poor aseptic practice during an invasive procedure, during manipulation of an invasive device or during preparation of parenteral medication. Routine attention to asepsis training and audits of aseptic practice are now required in Australia by the Safety and Quality standards[31] and is an important way to reduce morbidity from MROs including VRE.

Targeted additional (vertical) measures

Additional measures are warranted in high risk units and for VRE-colonised patients at high risk of transmission or infection (Table 1).

The economic, patient and care impacts of isolation are considerable and single room availability is often limited. Optimising local

compliance with enhanced standard precautions and VRE morbidity data should be considered closely before adoption of more targeted controls.

Surveillance: active screening for VRE colonisation

Active screening is often considered in the following situations:

- patient contacts of VRE patients during outbreaks and periods of higher transmission risk to determine extent of transmission and its possible route
- high risk unit patients, dependent on local prevalence
- outbreaks: for detection, monitoring and identification of new and possibly more virulent strains of VRE (sentinel surveillance)
- 'clearance' documentation if that is supported by local guidelines.

Screening plans need to be prepared in the light of the local VRE prevalence situation (colonisation and infection). The usual screening specimen sites are stool, rectal or perianal swab. Optimal collection and laboratory methods are important to ensure adequate test sensitivity and specificity. Early post-exposure screening of contacts has poor sensitivity unless repeated later. Direct PCR methods for VRE have a high false positive rate in regions like Australia where *vanB* carriage by non-enterococcal bacteria is common and are not recommended.

Isolation of VRE-colonised patients under transmission-based contact precautions

This is recommended for VRE-colonised patients in high risk units (Table 1 or however defined).

Dedicated bathroom and toilet facilities are a must and the isolation or cohort areas as a minimum should be subject to daily cleaning and disinfection. Single use glove and gowns should be used by staff upon room entry without neglect of hand hygiene. Patient-dedicated equipment is required where possible.

In outbreak situations, where single rooms or cohort areas are not available, it is worthwhile using gloves and gowns for interactions even with non-colonised neighbouring patients in order to reduce potential patient anxiety and increase the awareness and compliance of clinical staff[16].

Outbreak interventions

Systems need to be in place to detect outbreaks, especially changes in VRE morbidity that may reflect emergence or introduction of a more virulent strain. The comprehensive approach to outbreak investigation and management is well described in other references[35] and well illustrated by the description of the recent WA VRE outbreak[11].

Staff compliance with enhanced standard precautions (above) must be audited at the outset and all efforts made to ensure consistent implementation of hygiene and antimicrobial stewardship measures. Known VRE-colonised patients should be isolated. Patients with contact with VRE should be screened and pre-emptively isolated pending results. One-off patient screening surveys may identify hidden colonised patients. Strain typing provides confirmation of clonality and has the potential to identify transmission linkages.

Use of skin disinfection with chlorhexidine wash cloths can be considered in situations where control is proving difficult. A systematic review by Karki and Cheng included four studies that reported the impact on VRE colonisation; incidence rate ratio (IRR) was 0.43 (95% CI, 0.32–0.59). However, the six studies reporting impact on VRE infection did not show a significant reduction (IRR of 0.90 (95% CI, 0.42–1.93))[37].

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Biography

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