ERADICATION OF A LARGE OUTBREAK OF A SINGLE STRAIN OF vanB VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM* AT A MAJOR AUSTRALIAN TEACHING HOSPITAL

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ABSTRACT

OBJECTIVE: To demonstrate that nosocomial transmission of vancomycin-resistant enterococci (VRE) can be terminated and endemicity prevented despite widespread dissemination of an epidemic strain in a large tertiary-care referral hospital.

INTERVENTIONS: Two months after the index case was detected in the intensive care unit, 68 patients became either infected or colonized with an epidemic strain of vanB vancomycin-resistant *Enterococcus faecium* despite standard infection control procedures. The following additional interventions were then introduced to control the outbreak: (1) formation of a VRE executive group; (2) rapid laboratory identification (30 to 48 hours) using culture and polymerase chain reaction detection of *van*A and *van*B resistance genes; (3) mass screening of all hospitalized patients with isolation of carriers and cohorting of contacts; (4) environmental screening and increased cleaning; (5) electronic flagging of medical records of contacts; and (6) antibiotic restrictions (third-generation cephalosporins and vancomycin).

RESULTS: A total of 19,658 patient and 24,396 environmental swabs were processed between July and December 2001. One hundred sixty-nine patients in 23 wards were colonized with a single strain of vanB vancomycin-resistant *E. faecium*. Introducing additional control measures rapidly brought the outbreak under control. Hospital-wide screening found 39 previously unidentified colonized patients, with only 7 more nonsegregated patients being detected in the next 2 months. The outbreak was terminated within 3 months at a cost of $2.7 million (Australian dollars).

CONCLUSION: Despite widespread dissemination of VRE in a large acute care facility, eradication was achievable by a well-resourced, coordinated, multifaceted approach and was in accordance with good clinical governance (*Infect Control Hosp Epidemiol* 2004;25:384-390).

Vancomycin-resistant enterococci (VRE) are recognized as significant nosocomial pathogens. The National Nosocomial Infections Surveillance (NNIS) System of the Centers for Disease Control and Prevention reported a vancomycin resistance rate of 26.3% for enterococci isolated from patients in intensive care units (ICUs) with nosocomial infections in 2000.[1] The clinical impact of this resistance has been variably reported. Small studies[2-5] have not demonstrated an increase in mortality rates, although they have shown a longer duration of hospitalization and antibiotic therapy. Three larger studies[6-8] controlled for disease severity found that vancomycin resistance was predictive of increased mortality. Measures to control VRE in hospitals have been promulgated[9] and adopted by many hospitals.

Once VRE is endemic in a hospital, efforts to eradicate it have been unsuccessful.[10,11] Maintenance of low-level endemicity after a large outbreak has been achieved[12,13] as has eradication following a small outbreak[14] and in specific units.[15-17] Successful control has also been reported in a healthcare region that included long-term–care facilities.[18] In that report, however, only 38 patients were found to be colonized during a 2-year period. We report the first successful eradication of VRE following a major hospital-wide outbreak in a large tertiary-care referral hospital.

The decision to mount an extreme effort to eradicate VRE from the hospital was based on several reasons. The organism was not endemic in Royal Perth Hospital or any other hospital in Western Australia. The first isolation of VRE in Western Australia occurred in 1996, and screening of high-risk areas and renal, intensive care, and hematology–oncology units, introduced at Royal Perth Hospital in 1998 on a quarterly basis, had revealed colonization of only four patients by May 2001. All had acquired VRE from outside Western Australia and there was no evidence

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of horizontal transmission. These four isolates were not related to the outbreak strain. Vigorous screening and control measures had been successful in keeping multidrug-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) from becoming endemic in all hospitals in Western Australia despite a high prevalence in many teaching hospitals in the rest of Australia.[19] The alternative was to accept that VRE would remain endemic in the hospital, with associated patient morbidity and mortality. The hospital management found this to be unacceptable.

METHODS

Facility Characteristics

Royal Perth Hospital has two campuses. The main campus, the largest adult tertiary-care referral hospital (694 beds in 33 wards) in Perth, has heart, renal, and bone marrow transplant units; the State adult burns unit; a 22-bed ICU; general medical and surgical units; and cardiovascular surgical, acute orthopedic, and major trauma services. The Shenton Park campus (200 beds in 8 wards) has the State spinal injury service and elective orthopedic surgery and neurologic and orthopedic rehabilitation units.

Outbreak

In July 2001, an ICU patient was found to have a positive blood culture for vanB vancomycin-resistant *Enterococcus faecium*. The organism was amoxicillin resistant and had minimum inhibitory concentrations (MICs) for vancomycin and teicoplanin of more than 256 mg/L and 1.0 mg/L, respectively. The index patient was isolated under strict contact precautions. Contact patients, defined as all patients on the same ward (not just those sharing the same room), were screened for VRE. Those screened included patients in both the ICU and the dialysis unit as the index patient had been receiving hemodialysis prior to his admission to the ICU. As a precaution, patients in the nephrology ward were also screened. The testing resulted in the detection of another positive patient in the ICU and additional colonized patients in the two renal areas. The index patient lived in a hostel with other patients receiving renal dialysis and, through them, transmission to the nephrology ward is postulated to have occurred. Spread occurred through 11 wards despite the isolation of known carriers (including the use of gown and glove precautions), screening of contact patients, introduction of antiseptic hand hygiene, reinforcement of standard infection control practices, and intensified cleaning as recommended by Hospital Infection Control Practices Advisory Committee guidelines.[9] By late September 2001, 68 patients had become colonized. At that time, it was decided that more intensive intervention was needed to prevent the organism from becoming endemic.

Intensified Outbreak Control Measures

Formation of a VRE Executive Group. The VRE executive group was composed of the Chief Executive, the Director of Clinical Services, the Director of Nursing Services, a hospital epidemiologist, the chief executive of another teaching hospital who had outbreak management expertise, a clinical microbiologist, and an infection control nurse. The group met daily for the next 3 months to make all decisions regarding outbreak control. A dedicated cost center was established to record all costs associated with the outbreak.

Rapid Laboratory Identification of VRE. New laboratory procedures were introduced to enable the detection of VRE in most patients within 30 to 48 hours of receipt of the screening specimens. Previously, it had taken up to 5 days, thus the period during which environmental contamination and nosocomial transmission could occur was reduced.

Widespread Patient Screening. Every inpatient, regardless of exposure status, was screened during a 1-week period to identify the total reservoir of VRE carriage. Previously, only known ward contacts had been screened. Subsequently, every hospital patient was screened on admission and on discharge.

Environmental Screening. Initially, wards with a VRE-positive patient had environmental sampling prior to extensive cleaning. As early results indicated that there was a high level of environmental contamination, sampling was changed to after cleaning only to measure the adequacy of the cleaning process. Swabs were taken from the immediate vicinity of the patient (ie, the locker, telephone, over-bed table, bedside chair, bed, mattress, pillow, over-bed fixtures such as the oxygen supply and suction, and horizontal surfaces) and general areas (ie, the floors, bathroom, toilet, commodes, equipment, lotion rooms, storerooms, offices, nurses' station, computer terminals, and handwash basins).

Establishment of a Dedicated Cleaning Team. Wards with positive patients were closed for intensive two-step cleaning (ie, an anionic detergent followed by a phenolic disinfectant) and not reopened to new admissions until the environmental screening was negative for VRE. All wards in the hospital received at least two intensive cleanings.

Cohorting of All Positive and Contact Patients. Three cohorts of patients were established. Positive patients were transferred into dedicated isolation wards where strict contact gown and glove precautions were maintained. Patients who had been in the same ward as positive patients were accommodated in designated "contact" wards. Patients who had not been admitted to Royal Perth Hospital previously during the outbreak, those who had not been in contact with a carrier, and those who had had four negative rectal swabs were placed in designated "clean" wards. Standard precautions were practiced in the latter two patient cohorts. Each cohort had dedicated nursing staff, thus ensuring that movement of nursing staff between VRE-positive and VRE-negative patients did not occur. Transfer of patients within the hospital was not allowed unless approved by the VRE executive group. Discharge of VRE-positive geriatric patients to long-term–care facilities was suspended and a separate

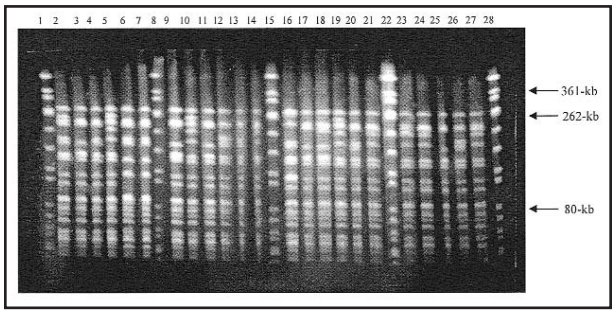

FIGURE 1. Results of pulsed-field gel electrophoresis of *Sma*I enzyme–restricted digests of chromosomal DNA from representative subtypes of the epidemic vancomycin-resistant *Enterococcus faecium* isolates showing the clonal nature of the outbreak. Lanes 21, 23, 24, and 27 = subtype A; lanes 5, 10, and 19 = subtype B; lanes 2, 4, 12, 13, 16, 20, and 26 = subtype C; lanes 3, 9, 11, 17, 18, and 25 = subtype D; lanes 6 and 7 = subtype E; lane 16 = subtype F; lane 14 = subtype G; and lanes 1, 8, 15, 22, and 28 = *Staphylococcus aureus* NCTC8325 size standard.

isolation facility was established and managed at an affiliated hospital.

Electronic Tracking of Contact Patients. An existing system was used to flag ward contacts after discharge, facilitating placement on contact wards if readmitted. Bed management became problematic because of the high number of readmissions of these contact patients. Hence, an active outpatient screening program was initiated to screen flagged patients at high risk of readmission because of either their medical condition or their previous admission history. The flag was removed if four VRE-negative rectal swabs were obtained.

Restriction of Antimicrobials. The use of third-generation cephalosporins ceased. Severe sepsis was treated with piperacillin/tazobactam.[20] Vancomycin use required approval by a clinical microbiologist or infectious diseases consultant.

Laboratory Methods

Rectal swabs were initially plated onto CHROMagar Orientation medium (CHROMagar, Paris, France) containing 6 mg/L of vancomycin and 8 mg/L of gentamicin, followed by inoculation into BBL Enterococcosel broth (Becton Dickinson, Cockeysville, MD) supplemented with 8 mg/L of vancomycin. Environmental swabs were inoculated into broth only. Positive broths were subcultured onto CHROMagar medium containing no antibiotics. All media were incubated for 24 hours at 36°C. A real-time polymerase chain reaction method[21] using the Roche LightCycler platform (Roche Molecular Biochemicals, Mannheim, Germany) was developed for the detection of *van*A and *van*B genes from characteristic colonies growing on CHROMagar. Identification of each isolate was confirmed by Gram stain, colonial morphology, and biochemical and growth characteristics. Kirby–Bauer disk diffusion[22] and the National Committee for Clinical Laboratory Standards 6-mg/L vancomycin screening plate confirmed vancomycin resistance. Vancomycin and teicoplanin MICs were performed by Etest (AB Biodisk, Solna, Sweden) using Mueller–Hinton agar. The VRE isolates were typed using a modified pulsed-field gel electrophoresis (PFGE) technique,[23] plasmid analysis,[24] and ribotyping.[25]

RESULTS

A total of 19,658 patient and 24,396 environmental specimens were screened until the end of December 2001 when the outbreak was terminated. One hundred sixty-nine patients from 23 wards at both campuses were colonized with a clonal vanB *E. faecium* (vancomycin-resistant *E. faecium*). Four patients had the following clinical infections: bacteremia and empyema of the gallbladder, a urinary tract infection associated with an indwelling urinary catheter, peritonitis associated with continuous ambulatory peritoneal dialysis, and a deep wound infection and subphrenic abscess in a patient who had undergone surgery. All 169 patient and 87 environmental isolates underwent analysis by PFGE (Fig. 1) and phylogenetic analysis (Fig. 2) and were closely related by established criteria.[26] The plasmid profile and ribotyping confirmed the clonal nature of the outbreak (data not shown). In addition to the vanB vancomycin-resistant *E. faecium*, the large-scale screening detected other VRE, 5 vanA *E. faecium*, 1 vanB and 5 vanE *E. faecalis*, and 4 vanA *Enterococcus* species, none of which resulted in transmission.

Epidemiologic Information

The epidemic curve is shown in Figure 3. Sixty-eight positive patients were detected prior to the establishment of the VRE executive group, and an additional 26 in the following week. With the introduction of hospital-wide screening, another 39 previously unknown positive patients were identified; with their relocation to isolation wards, the outbreak was effectively controlled. Only 7 more positive inpatients were detected during the next 2 months. The last inpatient to be detected was detected at the end of December 2001. The remaining 29 of the 169 VRE-positive patients were detected by the active outpatient screening program. Between October and December 2001, screening of 780 of the 4,155 patients alerted electronically resulted in the detection of 8 VRE-positive patients on readmission and 21 (3.7%) as outpatients. This initial high VRE yield from discharged patients fell rapidly during the program, and in the 4 months following the outbreak (January to April 2002), only 7 of (0.6%) 1,181 screened patients were positive. Two of the 169 positive patients could not be linked epidemiologically to the outbreak; they had positive swabs on admission and had not been hospitalized recently.

With the exception of a small cluster of 5 inpatients linked to the readmission of a previously cleared contact patient in September 2002, the hospital has remained free of VRE through April 2004.

The intensive care, dialysis, and nephrology units and a hostel used by patients receiving dialysis played a central role in the spread of the vanB vancomycin-resistant *E. faecium* throughout the hospital. Throughout the

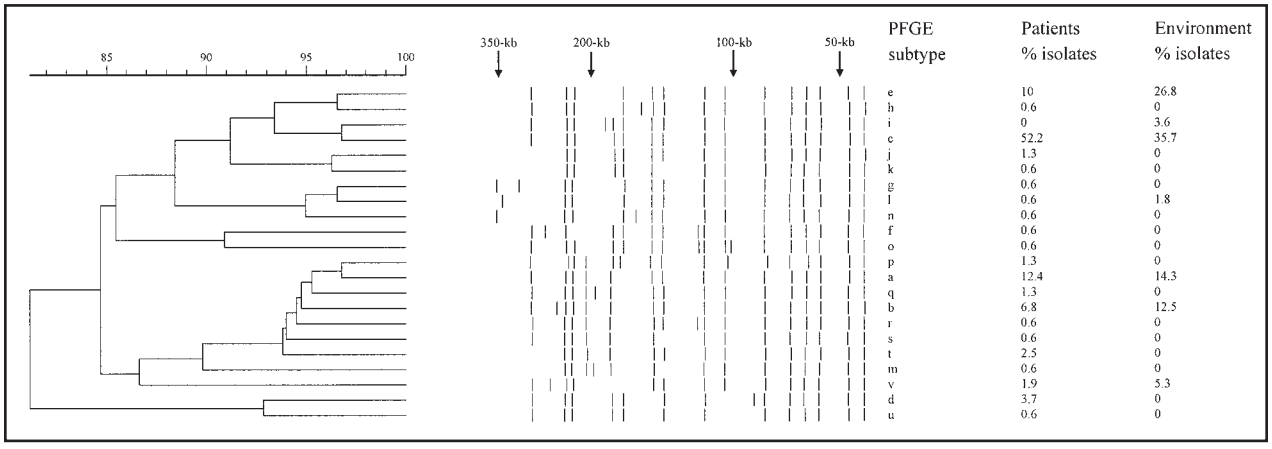

FIGURE 2. Dendrogram, digitized pulsed-field gel electrophoresis (PFGE) patterns, and distribution of the subtypes of the epidemic strain of vancomycin-resistant *Enterococcus faecium* from both the patients and the environment. Note the more than 80% relatedness, only minor band differences on the digitized image, and similar distribution of the various subtypes between patients and the environment. The scale represents the percentage of homology. Molecular weights are shown above the lanes.

first 2 months of the outbreak, 20 VRE carriers were from the two renal areas, 9 of whom had been residents of the hostel. The frequent movement of patients through different wards of the hospital facilitated the spread to 23 wards including general medical, general surgery, orthopedic, neurosurgery, plastic surgery, urology, cardiology, cardiothoracic surgery, vascular surgery, geriatrics, hematology, bone marrow transplant, and spinal injury. At the height of the outbreak, the hospital had 3 isolation wards and 19 contact wards. The remaining 19 wards admitted patients who were considered to be clear of VRE.

Environmental Contamination

Of the 24,396 environmental swabs, 87 were positive. Initially, screening prior to cleaning was performed in 5 wards following detection of a carrier. A high level of environmental contamination was found in all 5 wards with 21 (24.7%) of 85 swabs being positive for VRE. Subsequently, environmental screening was conducted only after intensive cleaning. Environmental contamination was not found on any ward that had not had a known carrier (0 of 6,255 swabs). In areas cleaned after the detection of a carrier, persistent environmental contamination was uncommon (60 [0.3%] of 17,978 swabs). Environmental sites remaining positive after cleaning were those likely to have fecal contamination (ie, commodes, the toilet area, bathrooms, and the immediate patient bed area). Communal areas only were sampled in the isolation wards and had a higher yield with 6 (7.7%) of 78 being positive.

Costs

The costs presented are for the period from July to December 2001 (Table). An additional cost of $440,000 was incurred establishing and maintaining the geriatric isolation facility. The total cost for this period was $2.7 million (Australian dollars).

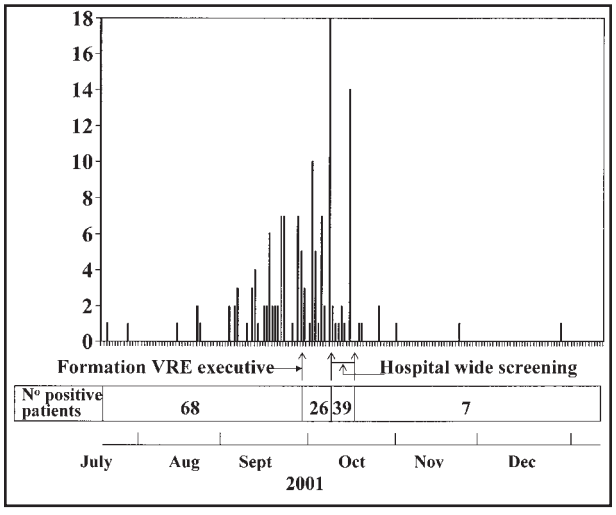

FIGURE 3. The epidemic curve showing the number of patients with vanB vancomycin-resistant *Enterococcus faecium* colonization or infection. This does not include the 29 contact patients detected, as outpatients or on readmission, by the active outpatient screening program. VRE = vancomycin-resistant enterococci.

Antibiotic Use

The use of third-generation cephalosporins decreased dramatically from 3.6 to 0.4 daily defined doses[27] per 100 occupied bed–days between September and December 2001. Vancomycin use declined initially, but, inexplicably, this was not sustained (Fig. 4).

DISCUSSION

The introduction of the epidemic strain of vancomycin-resistant *E. faecium* into Royal Perth Hospital was followed by initial transmission in the ICU and renal dialysis and nephrology units. This was followed by rapid spread through 23 wards of the hospital. This spread was possibly enhanced by the frequent movement of patients

TABLE
COSTS INCURRED DURING THE PERIOD FROM JULY TO DECEMBER 2001 IN THE ERADICATION OF VANCOMYCIN-RESISTANT ENTEROCOCCI

	Cost*
Staffing (ie, nursing, patient care assistants, laboratory staff, and administrative support)	$593,602
Medical, surgical, and diagnostic supplies (ie, drugs, diagnostic supplies, patient appliances, and materials)	$275,153
Contracting (ie, cleaners and other staffing resources)	$584,320
Domestic charges (ie, cleaning and clothing consumables)	$320,594
Building works (ie, electronic taps in the ICU and dispensers for disinfectant and detergents)	$56,749
Other (ie, printing, stationary, and all other consumables)	$381,887
Equipment (ie, LightCycler† [VRE PCR])	$65,000
Total	$2,277,305

ICU = intensive care unit; VRE = vancomycin-resistant enterococci; PCR = polymerase chain reaction.
*Australian dollars.
†Roche LightCycler (Roche Molecular Biochemicals, Mannheim, Germany).

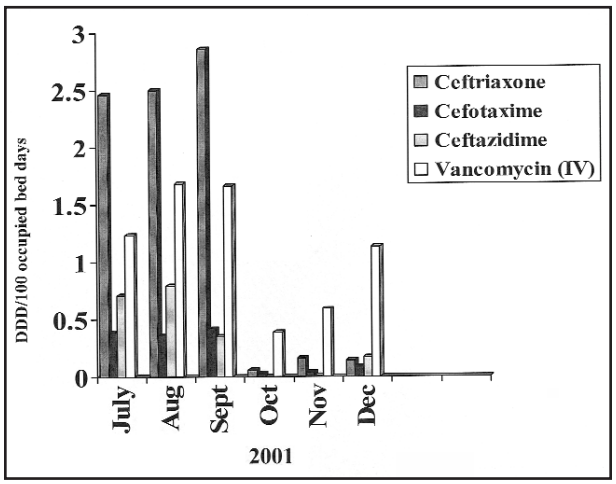

FIGURE 4. Antimicrobial use between July and December 2001 showing a large reduction in the use of third-generation cephalosporins and a temporary decline in the use of vancomycin. Use is expressed as defined daily doses[22] (DDD) per 100 occupied bed–days. IV = intravenous.

between wards, the high use of antimicrobials (particularly third-generation cephalosporins and vancomycin), a limited number of single rooms with en suite facilities, and poor compliance with handwashing. Transmission was also probably facilitated by a relatively high incidence of diarrhea in some of the early positive patients (data not shown) as described by others.[14] Reinforcement of standard infection control procedures[9] early during the outbreak was not successful in containing the outbreak. The decision to attempt eradication of VRE was based on the potential for increased morbidity and mortality,[6] the associated economic cost,[8] the previous absence of the organism within any hospital community in the state, and our previous success with MRSA control.

It is recognized that colonized patients in hospitals are the major reservoir for VRE, with proximity to a previously nonisolated patient being a risk factor for acquisition.[12,14] Previous studies have also demonstrated that VRE is transmitted between patients on the hands and clothing of healthcare workers[14] and indirectly from the contaminated environment.[28] Our early screening revealed heavy environmental contamination associated with positive patients. Thus unidentified, nonisolated positive patients provided a continuing source of vancomycin-resistant *E. faecium* and, therefore, failure of our early control measures. It was therefore crucial to identify the entire reservoir of VRE-colonized patients in the hospital. It was not until every patient in the hospital was screened, allowing isolation of an additional 39 previously unidentified positive patients, that the outbreak was terminated. The rapid laboratory procedures facilitated the early isolation of these positive patients, the intensive cleaning program removed any remaining organisms from the environment, and the cohorting of contact patients reduced the potential for spread prior to clearance swabs.

The identification of the vancomycin-resistant *E. faecium* reservoir in discharged patients was also important in preventing the reintroduction of the organism into the hospital. In the first few months of the active outpatient follow-up program, 3.7% of the contact patients tested positive, affirming the benefit of the electronic flag on patients' records. However, during the 3 months after the outbreak, the number of positive patients declined quickly (0.6%), indicating that many may have detectable carriage for a short period only.

Having a dedicated executive group with the power to make far-reaching decisions was pivotal in ensuring the cooperation of all staff in what was a major exercise involving every ward and clinical and paraclinical service in the hospital during a prolonged period. The executive group was responsible for decisions on funding requirements, complex bed management, cleaning priorities, staffing levels, computing support, and the provision of alternative long-term–care facilities for positive patients. In addition, they provided support to the infection control team and solved many day-to-day problems.

The outbreak was clonal. The first patient became apparent through a positive clinical specimen (bac-

teremia). It is possible that undetected colonized patients were present in the hospital before this event, although the quarterly screening of high-risk areas, performed just 8 weeks prior to the detection of the index case, had failed to yield any positive results. It is therefore unlikely that a widespread long-standing problem had existed in the hospital. The screening of patients on admission to the hospital as part of the outbreak control strategy revealed two patients with the epidemic strain who could not be linked epidemiologically to the outbreak. Similarly, several vanA and vanE VRE strains were identified. The latter strains were heterogeneous and no transmission was detected. The detection of both the epidemic and the unrelated VRE strains from patients on admission suggests that there is low-level prevalence of VRE carriage in the community, highlighting the need for ongoing screening in high-risk units.

Several noteworthy issues arose during the outbreak. It is well recognized that hospital staff are potential vectors of resistant organisms such as VRE and MRSA, with documented carriage of both organisms on hands and clothing.[29,30] However, it was decided not to screen nursing staff for hand or clothing carriage given the use of nurses dedicated to each patient cohort (ie, positive, contact, or clean), the use of strict gown and glove precautions, and increased attention to hand hygiene. In addition, VRE bowel colonization among staff has not been demonstrated to be an important reservoir, in contrast to MRSA, in which nasal carriage among staff has been implicated in transmission.[31] Therefore, a conscious decision was made not to screen staff for bowel carriage, which was justified by the ultimate result. There was debate about the number and timing of rectal swabs necessary to clear a contact patient. Initially, 4 swabs were taken at 72-hour intervals, but this was changed to consecutive days to clear patients more quickly and therefore facilitate bed management. Also, there is evidence that fecal specimens have a greater sensitivity than that of rectal swabs.[32] Our experience indicates that rectal swabs are adequate in an outbreak situation.

Antimicrobial restrictions have been successful in reducing VRE isolation rates in endemic situations.[33] Although introduced as part of the overall strategy, the reduction in use did not occur until the outbreak was almost completely controlled. It is possible that continuing restrictions may help maintain control, but its role in the eradication process is uncertain. Finally, a large number of environmental swabs were taken. This added greatly to the laboratory workload and to the cost of controlling the outbreak. In retrospect, our environmental pursuit of VRE was excessive with only 0.3% of swabs being positive after cleaning. Sampling should therefore be targeted to those sites most likely to be fecally soiled, to have had direct patient contact, or to have had a high frequency of healthcare worker manipulations. Our results also indicate that sampling of areas without positive patients is unnecessary provided that patient screening is in place.

Was the cost ($2.7 million Australian dollars; $1.5 million U.S. dollars) of eradication justified? Recently, the costs of endemic VRE have been established. In the study by Carmeli et al.,[8] the overall direct clinical and economic impact of VRE was quantified by comparing a cohort of 233 patients having clinical isolates of VRE with 647 matched controls. The outcome measures were adjusted for confounding in multivariate analysis. The authors reported a 2-fold increased odds of mortality (6% attributable mortality), a 2.7-fold increased odds of a major surgical procedure, a 3.5-fold increased odds of admission to the ICU, a 1.7-fold increase in hospital length of stay, a 1.4-fold increase in the cost of hospitalization, and a 2-fold increased odds of discharge to a long-term–care facility. This translated to 15 cases of in-hospital death, 22 major operations, 26 ICU admissions, 1,445 additional hospitalization days, and excess costs of $2,974,478 (U.S. dollars) during the 4-year study period. The excess costs did not include laboratory and nursing costs of surveillance, isolation supplies, and loss of beds due to isolation needs. Other studies have given higher estimates of the attributable mortality (25%[34] to 37%[35]) and have provided the estimated additional cost for each episode of VRE bacteremia ($13,537[34] to $27,000[35] [U.S. dollars]). Further, the cost-effectiveness of an active surveillance program was determined by Muto et al.,[13] who showed that the number of VRE bacteremias was limited to 1 in the study hospital compared with 29 at the comparator hospital, giving an estimated savings of $508,221 (U.S. dollars) during a 2-year period.

There is a further, less easily quantifiable cost—that of the possibility of gene transfer. Enterococci, although significant nosocomial pathogens, are of relatively low virulence. *S. aureus*, on the other hand, has demonstrated its ability to be virulent, to be persistent, and, for MRSA, to cause major nosocomial infections. Transfer of the vancomycin resistance genes from enterococci to *S. aureus* has previously been demonstrated in vitro.[36] Alarmingly, isolates of vancomycin-resistant MRSA have now been reported from two patients[37,38] with VRE and MRSA co-infections. Every effort should therefore be made to prevent both organisms from becoming endemic in a hospital. Thus, on the basis of mortality, economic cost, and prevention of gene transfer to more virulent organisms, it can be argued that our eradication program was justified and is in accordance with good clinical governance.

It is possible to terminate a clonal outbreak and eradicate VRE from a large tertiary-care hospital provided that there is a well-coordinated program that allows rapid identification and isolation of all positive patients and the segregation of contacts. Intensive cleaning and focused environmental screening also appear to be of importance. Screening of staff for bowel carriage is not necessary.

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