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Near Absence of Vancomycin-Resistant Enterococci but High Carriage Rates of Quinolone-Resistant Ampicillin-Resistant Enterococci among Hospitalized Patients and Nonhospitalized Individuals in Sweden

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Rates of colonization with enterococci with acquired resistance to vancomycin (vancomycin-resistant enterococci [VRE]) and ampicillin (ampicillin-resistant enterococci [ARE]) were determined by using fecal samples from 670 nonhospitalized individuals and 841 patients in 27 major hospitals. Of the hospitalized patients, 181 (21.5%) were carriers of ARE and 9 (1.1%) were carriers of VRE. In univariate analyses, length of hospital stay (odds ratio [OR], 4.6; 95% confidence interval [CI], 2.5 to 8.9) and antimicrobial therapy (OR, 4.7; 95% CI, 3.3 to 6.7) were associated with ARE colonization, as were prior treatment with penicillins (OR, 3.1; 95% CI, 1.8 to 5.5), cephalosporins (OR, 2.9; 95% CI, 1.7 to 5.0), or quinolones (OR, 2.7; 95% CI, 1.5 to 4.7). In logistic regression analysis, antimicrobial therapy for at least 5 days was independently associated with ARE carriage (adjusted OR, 3.8; 95% CI, 2.6 to 5.4). Over 90% of the ARE isolates were fluoroquinolone resistant, whereas 14% of the ampicillin-susceptible *Enterococcus faecium* isolates were fluoroquinolone resistant. ARE carriage rates correlated with the use of fluoroquinolones ($P = 0.04$) but not with the use of ampicillin ($P = 0.68$) or cephalosporins ($P = 0.40$). All nine VRE isolates were *E. faecium vanB* and were found in one hospital. Seven of these isolates were related according to their types as determined by pulsed-field gel electrophoresis. Among the nonhospitalized individuals, the ARE carriage rate was lower (6%; $P < 0.05$), and only one person, who had recently returned from Africa, harbored VRE (*E. faecium vanA*). The absence of VRE colonization in nonhospitalized individuals reflects an epidemiological situation in Sweden radically different from that in countries in continental Europe where glycopeptides have been widely used for nonmedical purposes.

During the last decade, enterococci with acquired high-level resistance to antimicrobial agents have emerged as nosocomial pathogens worldwide (25). Strains with acquired ampicillin resistance (ampicillin-resistant enterococci [ARE]) and high-level aminoglycoside resistance cause considerable therapeutic problems in patients with severe infections like endocarditis, and since 1989, strains with acquired resistance to glycopeptides (vancomycin-resistant enterococci [VRE]) have further emphasized these problems (17). A majority of reports on VRE carriage and infections have originated from the United States (12, 17, 28, 29), but several also originated from Europe (18, 22, 31). Heavy use of antimicrobial agents such as vancomycin and cephalosporins, prolonged hospital stays, immunosuppression, physical location in the hospital, and gastrointestinal colonization with VRE are all factors associated with VRE infection (13). The spread of resistant enterococcal strains in hospitals has been described (17, 23, 29). The epidemiology of resistant strains of enterococci seems to differ between the United States and Europe. In the United States clonal spread of endemic VRE strains of both the *vanA* and the *vanB* genotypes within and between hospitals was demonstrated (12, 28, 29), but VRE colonization among nonhospitalized persons has so far not been found (5, 33). In contrast, studies from European countries have revealed a surprisingly high prevalence of VRE, mainly *Enterococcus faecium* of the *vanA* genotype, among nonhospitalized citizens (1, 37, 39), among farmers, farm animals, and meat products (2, 4, 24, 36), and from sewage treatment plants (20). Moreover, genetic fingerprinting of European nosocomial VRE isolates has often shown polyclonality, indicating the import of various *vanA* strains from the community (3, 22).

In most European countries the glycopeptide avoparcin has been widely used as a growth promoter in animal husbandry, whereas this agent has not been licensed for use in the United States. On the other hand, the rate of use of vancomycin in U.S. hospitals has increased dramatically over the last 15 years

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(19) but has probably increased less so in European hospitals, although reliable data on European antibiotic consumption is not available. These differences in the use of glycopeptides in hospitals and in animal husbandry have been proposed as explanations for the different epidemiologies of VRE on the two continents (14). Three major reasons prompted us to study the epidemiology of drug-resistant strains of enterococci. First, data on VRE carriage rates in Sweden were lacking and only one limited VRE outbreak had been described (35). Second, there has been a contrasting increase in the incidence of clinical ARE isolates in many Swedish hospitals during the 1990s (16). Third, since January 1986, a national feedstuffs act has prohibited administration of all antimicrobial agents as growth promoters to livestock, and thus, Sweden is one of the rare countries in the world that lacks this major risk factor for the emergence of antimicrobial drug resistance.

MATERIALS AND METHODS

Study group. In February 1997 an offer to join a national enterococcal study group was sent to departments of infectious diseases and departments for hospital infection control at all 28 secondary-care (county) hospitals and all 7 tertiary-care (university) hospitals in Sweden. A majority of these hospitals (n = 27), including all university hospitals, agreed to participate. Local ethical committees throughout Sweden approved of the studies, and informed consent was obtained from all patients and nonhospitalized individuals included in the studies.

Hospitalized patients (study A). Study A was carried out from September through November 1997. During 1 day, rectal swabs were taken from all inpatients at two separate wards in each hospital, resulting in a total of 841 fecal samples. Patients with granulocyte counts below 1.0×10^9/liter or with rectal bleeding disorders were not included. To ensure that the wards chosen had different levels of antimicrobial agent consumption, the local study groups were asked to include both intensive care units (ICUs) and wards that consume low levels of antimicrobial agents. Each patient record was reviewed with respect to antibiotic treatment during the previous 2 weeks. Other patient characteristics recorded were age, sex, period of hospitalization, prior hospitalization within 6 months, and recent travel outside Scandinavia. The selection of two wards with presumed different levels of consumption of antimicrobial agents, collection of information about the patients, collection of rectal swabs specimens, and collection of patient data were carried out by each local study group. The actual level of antimicrobial agent consumption on each ward could not be recorded, and instead, the drug deliveries to each ward during 1997 were obtained through the kind cooperation of the hospital pharmacies that delivered the drugs. The number of patient bed days for each ward during 1997 was obtained from hospital administration records. These data were used to calculate antibiotic consumption rates, expressed as defined daily doses (DDDs) per bed day.

Since only three renal units were included during the first phase of the study and all nine VRE carriers found in the study originated from one of these units (see Results), we considered the risk of selection bias. Therefore, 113 additional inpatients in renal units at five additional tertiary-care hospitals were included in the study. Their fecal samples were screened for VRE only, and no further characteristics of these patients were recorded.

Nonhospitalized individuals (study B). Study B was carried out in cooperation with members of the study group at 20 major outpatient clinics throughout Sweden. Individuals who attended these clinics from March through May 1998 were asked to participate in the study, and 670 agreed to be included. A rectal swab specimen was taken, and a patient record form similar to that used for study A was used. Individuals who had been hospitalized within 30 days prior to attendance at the outpatient clinics were not included in the study.

Culture techniques. All swabs were promptly transported to the Swedish Institute for Infection Disease Control for selective culture for ARE and VRE. Rectal swabs in transport medium were put into 1 ml of nutrient broth and were vigorously shaken for 10 s. A total of 50 μl of the resulting suspension was used for screening for ARE and 200 μl was used for screening for VRE. The remaining part was supplemented with 20% glycerol and was kept at −70°C for later use. Screening for ARE was performed by direct plating of the suspension on cephalexin-aztreonam-arabinose (CAA) agar (11) containing cephalexin (10 μg/ml), aztreonam (75 μg/ml), amphotericin B (5 μg/ml), and with ampicillin (30 μg/ml) added. Screening for VRE was performed in two steps. The suspension was first inoculated into 5 ml of Enteroccosel enrichment broth (BBL, Becton Dickinson Microbiology Systems) containing vancomycin (8 μg/ml) and aztreonam (60 μg/ml) (21), and the mixture was incubated at 37°C and examined at 72 h. Tubes in which growth was indicated by even the slightest color change to black were subcultured by inoculating 50 μl onto CAA agar to which vancomycin (8 μg/ml) was added. These plates were incubated for 24 h at 37°C, and colonies were further identified as enterococci by colony morphology, Gram staining, and catalase and pyroglutamyl-β-naphthylamide tests. *E. faecium* colonies were identified as colonies that were surrounded by a zone of color change from red to yellow, which indicated the fermentation of arabinose.

A reference material of ampicillin-susceptible *E. faecium* was collected from the study A patients. These isolates were obtained by picking colonies from around the inhibition zone around a 10-μg ampicillin disc (>20 mm) placed on a CAA agar plate.

Antibiotic susceptibility testing of VRE and ARE isolates. The following antimicrobial agents were used and were kindly provided by the respective manufacturers: ampicillin and teicoplanin (Astra), vancomycin (Eli Lilly), imipenem (Merck Sharpe & Dohme), ciprofloxacin (Bayer), netilmicin, (Schering-Plough), and erythromycin (Abbott). MICs were determined by agar dilution on PDM Antibiotic Sensitivity Medium (AB Biodisk, Solna, Sweden). Resistance to vancomycin was defined by an MIC of ≥8 μg/ml (27), and resistance to ampicillin was defined by an MIC of ≥16 μg/ml (26, 27).

Genetic analyses. The resistance genotypes (*vanA*, *vanB*, *vanC1*, and *vanC2*) and species (*E. faecium*, *Enterococcus faecalis*, *Enterococcus casseliflavus*, and *Enterococcus gallinarium*) of all VRE were confirmed by PCR (9). Pulsed-field gel electrophoresis (PFGE) was performed by preparation of chromosomal DNA (8), digestion with *Sma*I, loading of sample plugs containing digested DNA on a 1% SeaKem Gold gel (FMC Bioproducts, Rockland, Maine), and electrophoresis by using the autoalgorithm mode (20 to 300 kb) of CHEF-mapper (Bio-Rad Laboratories, Richmond, Calif.) equipment with a ramping factor of 0.55, an initial switch time of 2.98 s, a final switch time of 26.29 s, and a running time 14 h and 50 min. The gels were stained with ethidium bromide, and DNA bands were visualized with UV light. For interpretation, we divided the restriction endonuclease digest patterns into four categories, indistinguishable, closely related, possibly related, and unrelated, as suggested by Tenover et al. (34).

Control samples and strains. The ability of our screening method to detect VRE was tested with the kind assistance of A. E. van den Bogaard, University Hospital, Maastricht, The Netherlands, who provided us with seven human fecal samples about whose VRE infection status we were blinded. We accurately found five of the samples to contain *E. faecium vanA* and two to be negative for VRE. The control strains used throughout our own screening procedure were *E. faecium* BM4147 *vanA* and *E. faecalis* V583 *vanB*, kindly provided by P. Courvalin, Institute Pasteur, Paris, France. For antibiotic susceptibility testing, *E. faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Staphylococcus aureus* ATCC 29213 were used as control strains.

Statistics. Microsoft Access 97 (Microsoft Corp.) was used to create the database, and univariate analyses (two-by-two tables) of odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by using the statcalc mode of the EPI info, version 6, software (6). For logistic regression analysis SPSS, release 8.0, for Windows (SPSS Inc., Chicago, Ill.) was used. The Spearman rank correlation test was used for calculation of correlations between sales of antimicrobial agents and rates of carriage of resistant enterococci in the participating hospital wards.

RESULTS

VRE and ARE carriage rates among hospitalized patients (study A). The 841 patients studied were hospitalized in ICUs (22%) and in surgical-orthopedic (9%), internal medicine (15%), renal (7%), infectious disease (5%), geriatric rehabilitation (38%), and other (4%) units. Other patient characteristics are presented in Table 1. ARE were found in the fecal flora of 181 patients (median, 21% per ward; range 0 to 56%). Nine patients (1.1%) carried both VRE and vancomycin-susceptible ARE. All ARE and VRE isolates were *E. faecium*. The VRE-infected patients were all hospitalized at Umeå University Hospital in northern Sweden: five in a renal unit and four in a geriatric unit. All VRE isolates were *E. faecium vanB*, and seven of the nine isolates were identical or closely related according to PFGE. Three of the geriatric patients were colonized with indistinguishable *E. faecium vanB* isolates (outbreak strain), and one was colonized with a closely related strain. Three of the VRE-positive patients in the renal unit harbored isolates closely related to the outbreak strain, and two carried VRE isolates indistinguishable by PFGE but different from the outbreak strain (Fig. 1). One of the patients in the geriatric unit who was colonized with the outbreak VRE strain regularly attended the renal unit for dialysis. This patient also had diarrhea and may have contributed to the spread of VRE between the renal and the geriatric units. Among the additional 113 patients from renal units from other tertiary-care hospitals studied, only one VRE carrier (*E. faecium vanB*)

TABLE 1. Characteristics of hospitalized patients (study A) and nonhospitalized individuals (study B)

Study and characteristic	ARE	No ARE
Study A		
No. of patients studied	181	660
No. (%) of male patients	98 (54)	301 (45)
Mean age (yr)	73	67
No. (%) of patients who traveled outside Scandinavia[a]	4 (2)	46 (7)
No. (%) of patients with previous hospitalization[b]	71 (39)	159 (24)
Study B		
No. of patients studied	40	630
No. (%) of male patients	18 (45)	298 (47)
Mean age (yr)	54	48
No. (%) of patients who traveled outside Scandinavia[c]	7 (18)	247 (39)
No. (%) of patients with previous hospitalization[d]	29 (73)	106 (17)

[a] Previous 6 months.
[b] Hospitalization in the preceding 3 months.
[c] Previous 12 months.
[d] Previous 12 months; significantly associated with ARE carriage ($P < 0.005$).

was found, and this was a patient in a hospital in southern Sweden.

Antimicrobial therapy and antimicrobial resistance (study A). The nine VRE isolates were all resistant to ampicillin, ciprofloxacin, and netilmicin but were susceptible to teicoplanin. All five VRE carriers in the renal unit in Umeå had received more than one antimicrobial agent during the previous 2 weeks (vancomycin, $n = 5$; fluoroquinolones, $n = 3$; cephalosporins, $n = 2$; penicillins, $n = 2$; imipenem, $n = 1$; a macrolide, $n = 1$). One patient had been treated with ciprofloxacin for 33 days and with vancomycin both orally and intravenously for 7 days before VRE was isolated. Also, all four geriatric patients had recently received antimicrobial agents (trimethoprim-sulfamethoxazole, cephadroxil, metronidazole, or penicillin G). Due to the low number of VRE carriers found, no further analysis of risk factors for VRE colonization could be performed.

A majority (80%) of the 181 hospitalized ARE carriers had also received antimicrobial therapy. By univariate analysis, both length of hospital stay and any antimicrobial therapy for 5 days or longer during the previous 2 weeks were strongly associated with ARE colonization (Table 2). When the patients treated for more than 5 days with each group of antimicrobial agents were compared with all the other treated and nontreated patients, cephalosporin, fluoroquinolone, and penicillin therapies were associated with ARE carriage. After adjustment of antimicrobial agent therapy for length of hospital stay by logistic regression, antimicrobial agent therapy for at least 5 days was found to be independently associated with ARE colonization (adjusted OR, 3.8; 95% CI, 2.6 to 5.4; $P < 0.001$).

Antimicrobial sales and correlation with ARE carriage rates (study A). Data on antimicrobial agent deliveries expressed as DDDs and numbers of patient bed days per year was available for 35 of the 53 wards sampled. The median consumption of antimicrobial agents in these wards was 0.35 DDD/bed day (range, 0.09 to 1.40 DDDs/bed day) during 1997. Glycopeptide usage was low; only 17 wards used more than 0.01 DDD/bed day (median, 0.01 DDD/bed day; range, 0.01 to 0.50 DDD/bed day). The prevalence of ARE carriers was correlated neither with total antimicrobial agent consumption ($P = 0.42$) nor with usage of cephalosporins ($P = 0.40$) or ampicillin and its derivatives ($P = 0.68$). In contrast, ARE carriage rates were correlated with fluoroquinolone usage ($P = 0.09$). After exclusion of wards with small patient samples (<10 and <15 patients) and, thus, the risk of a large random error in ARE carriage rates, this correlation was even stronger ($P = 0.04$ and 0.05, respectively).

VRE and ARE carriage rates among nonhospitalized individuals (study B). ARE were found in the fecal flora of 40 (6%) of the 670 individuals studied, but only 1 carried VRE (Table 1). The VRE strain was *E. faecium vanA* and was isolated from a man who had recently returned from travel in Africa. He was included in the study when he attended a hospital in the south of Sweden. He was admitted and treated for acute malaria. Of the 40 ARE carriers, 37 (93%) had been treated with antimicrobial agents during the preceding 12 months on at least one occasion, whereas 305 of 630 (48%) of the ARE noncarriers had been treated with antimicrobial agents during the preceding 12 months on at least one occasion ($P < 0.001$). ARE carriage was also associated with hospitalization during the previous year ($P < 0.005$).

Antimicrobial agent resistance of ARE and ampicillin-susceptible *E. faecium*. Except for glycopeptides, most of the ARE strains (80 to 99%) were also resistant to the other antimicrobial agents tested, with a high degree of similarity between the isolates from study A and study B (Table 3). The ampicillin-susceptible *E. faecium* strains isolated from the study A patients had much lower rates of resistance to ciprofloxacin (14

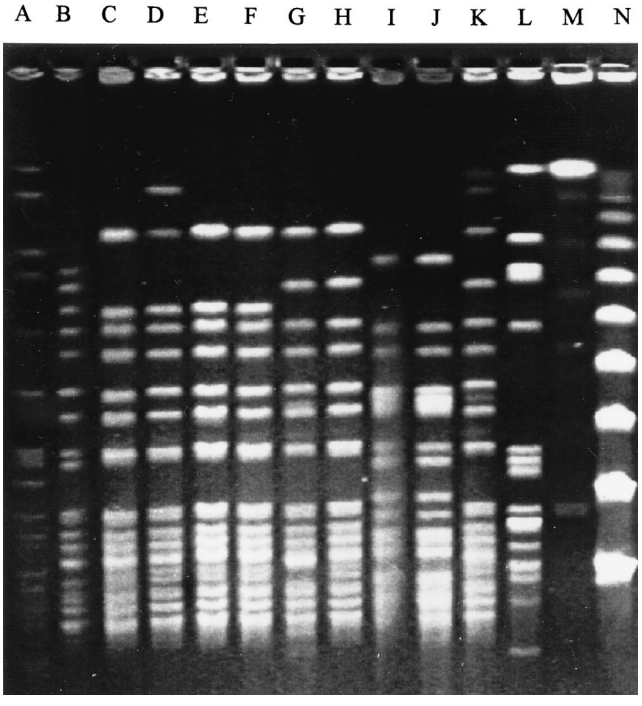

FIG. 1. PFGE patterns of *E. faecium vanB* isolates from nine patients hospitalized in Umeå University Hospital. Lanes A and B, control strains *E. faecalis* EKKR 070 *vanB* and *E. faecium* EKKR 220 *vanB*, respectively; lanes C to J, *E. faecium vanB* isolates from four patients in the geriatric unit with pattern A (lanes C, E, and F) and A_1 (lane D) and five patients in the renal unit with patterns A_2 and A_3 (lanes G and H), A_4 (lane K), and B (lane I and J); lane L clinical *E. faecalis vanA* isolate; lane M, yeast; lane N, bacteriophage lambda ladder standard.

TABLE 2. Association between length of hospital stay, antimicrobial therapy, and ARE colonization in hospitalized patients by univariate analysis (study A)

Characteristic	No. (%) of patients		OR	95% CI	*P* value
	ARE	No ARE			
Patients studied[a]	181	645			
Length of hospital stay (days)					
1–2[b]	14	141	1.0	0.4–2.3	1.0
3–7	35	167	2.1[c]	1.1–4.3	0.02
8–14	39	135	2.9[c]	1.5–5.9	<0.001
>14	93	202	4.6[c]	2.5–8.9	<0.001
>5 days treatment with[d]:					
Any antibiotic[e]	110 (61)	164 (25)	4.7[c]	3.3–6.7	<0.001
Cephalosporins	28 (15)	39 (6)	2.9[c]	1.7–5.0	<0.001
Fluoroquinolones	24 (13)	36 (5)	2.7[c]	1.5–4.7	<0.001
Penicillins	27 (16)	35 (5)	3.1[c]	1.8–5.5	<0.001
Carbapenems	10 (6)	19 (3)	2.0[f]	0.9–4.6	0.08
Macrolides	9 (5)	5 (<1)			
Metronidazole	9 (5)	14 (2)			
Glycopeptides	5 (6)	9 (3)			

[a] Data are missing for 15 patients.
[b] One to 2 days was defined to represent basic risk of colonization.
[c] Significant OR.
[d] During preceding 2 weeks.
[e] Also significant by logistic regression analysis (adjusted OR, 3.8; $P < 0.001$, see text).
[f] Nonsignificant OR.

versus 91%) and erythromycin (45 versus 80%) than the ARE isolates had.

DISCUSSION

The observed prevalence of VRE colonization among 841 hospitalized patients in Sweden was low (1.1%) and was due to a local outbreak originating from a renal unit and a geriatric unit in a teaching hospital. Among 670 individuals attending outpatient clinics, the prevalence was even lower, and only 1 person, who had recently returned from travel in Africa, carried VRE. The near absence of VRE *vanA* in our study was in contrast to the findings in other European countries, where VRE *vanA* has frequently been isolated from hospitalized patients, nonhospitalized persons, and foodstuffs (1, 7, 10, 15, 24, 36, 37). This indicates a markedly different epidemiological situation concerning glycopeptide-resistant enterococci in Sweden compared to that in countries in continental Europe. A small study from The Netherlands suggested that meat consumption was associated with VRE colonization (32), and another recent study has pointed out the striking difference in VRE carriage rates between pigs from The Netherlands (39%) and Sweden (0%) (38). Recently, VRE *vanA* strains were found in Danish but not in Swedish retail chicken (30). The most likely explanation for these differences is that the use of antimicrobial agents, including glycopeptides, as growth promoters for livestock has been prohibited in Sweden since 1986.

The clustering in one hospital of nine VRE *vanB* carriers in our study was unexpected. PFGE indicated the nosocomial spread of VRE between the renal and the geriatric units at this hospital. There was no indication of higher overall levels of consumption of antimicrobial agents in these two units than in the other study hospitals (data not shown), but all the VRE carriers had received therapy with single or multiple antimicrobial agents during the previous 2 weeks. None of the carriers had signs of VRE infection. This local outbreak of VRE colonization illustrates the ability of VRE to silently spread into hospital environments.

The high carriage rate of ARE among hospitalized patients in both small and large hospitals nationwide (21.5%) was expected, because such strains have been isolated from clinical specimens at increasing rates in Sweden during the 1990s. Therapy with cephalosporins, quinolones, and penicillins were all risk factors for the acquisition of ARE by univariate analysis. Length of hospital stay was equally associated with ARE colonization, illustrating that other factors like intrahospital transmission between patients may also have affected colonization rates. To evaluate prior antimicrobial therapy, we analyzed the total exposure to antimicrobial agents, adjusted for length of hospital stay, using logistic regression and found that antimicrobial therapy in general was still independently associated with ARE carriage.

Our attempt to correlate the consumption of antimicrobial agents on each ward with the prevalence of ARE carriers on those wards was limited by a lack of accurate data on levels of antimicrobial agent use for some wards and data on number of inpatient bed days for other wards. Nevertheless, we believe that these problems were randomly occurring so that the 36 wards analyzed were representative of all 53 wards included in our study. Surprisingly, ARE carriage was correlated with fluoroquinolone use on the wards but not with the consumption of cephalosporins or ampicillin and its derivatives. Moreover, in contrast to the ampicillin-susceptible *E. faecium* isolates in study A, most of the ARE isolates from both studies were fluoroquinolone resistant (14 versus 91%) (Table 3), enabling fluoroquinolones to select for fluoroquinolone-resistant ARE in the gut flora. In parallel with the increase in ARE in Sweden during the 1990s, the use of fluoroquinolones has increased from none to 1.3 DDDs/1,000 inhabitants/day, whereas the use of cephalosporins and ampicillin has shown little or no increase during this time (from 0.4 to 0.6 and a constant level of 1.4 DDDs/1,000 inhabitants/day, respectively). Another possible explanation for the high percentage of fluoroquinolone resistance among ARE strains might be an exceptional capacity for epidemic spread of certain clones of enterococci with this resistance pattern. Further studies on these matters are of interest.

Surprisingly, as many as 6% of the nonhospitalized individuals in study B carried ARE. However, almost all of these individuals had received antimicrobial agents and 73% had been hospitalized during the previous year (Table 1), indicating possible hospital acquisition of some of these strains.

We conclude that ARE are now endemic in most hospitals but that VRE are still rare both inside and outside hospitals in

TABLE 3. Antimicrobial resistance of ARE and ampicillin-susceptible *E. faecium* isolates

Antimicrobial agent	No. (%) of strains		
	Study A		Study B, ARE[a] (n = 40)
	ARE (n = 181)	ASE[b] (n = 177)	
Imipenem	180 (99)	10 (6)	39 (98)
Vancomycin	0 (0)	0 (0)	0 (0)
Teicoplanin	0 (0)	0 (0)	0 (0)
Ciprofloxacin	164 (91)	25 (14)	37 (93)
Netilmicin	177 (98)	163 (92)	40 (100)
Erythromycin	144 (80)	80 (45)	27 (68)

[a] Ampicillin-susceptible enterococci from study B were not analyzed.
[b] ASE, ampicillin-susceptible enterococci.

Sweden. The absence of VRE of the *vanA* genotype is in contrast to the situation in continental Europe and supports the hypothesis that the use of glycopeptides as growth promoters for livestock may also affect VRE carrier rates in the human population.

REFERENCES

1. **Bates, J.** 1997. Epidemiology of vancomycin-resistant enterococci in the community and the relevance of farm animals to human infection. J. Hosp. Infect. **37:**89–101.
2. **Bates, J., J. Z. Jordens, and D. T. Griffiths.** 1994. Farm animals as a putative reservoir for vancomycin-resistant enterococcal infection in man. J. Antimicrob. Chemother. **34:**507–514.
3. **Boisivon, A., M. Thibult, R. Leclerc, and the College de Bacteriologie-Virologie-Hygiene des Hospitaux Generaux Francais.** 1996. Colonization by vancomycin-resistant enterococci of the intestinal tract of patients in intensive care units from French general hospitals. Clin. Microbiol. Infect. **3:**175–179.
4. **Chadwick, P. R., N. Woodford, E. B. Kaczmarski, S. Gray, R. A. Barrell, and B. A. Oppenheim.** 1996. Glycopeptide-resistant enterococci isolated from uncooked meat. J. Antimicrob. Chemother. **38:**908–909. (Letter.)
5. **Coque, T. M., J. F. Tomakayo, S. C. Rickie, P. C. Okhuysen, and B. E. Murray.** 1996. Vancomycin-resistant enterococci from nosocomial, community, and animal sources in the United States. Antimicrob. Agents Chemother. **40:**2605–2609.
6. **Dean, A. G., J. A. Dean, D. Coulombier, K. A. Brendel, D. C. Smith, A. H. Burton, R. C. Dicker, K. Sullivan, R. F. Fagan, and T. G. Arner.** 1994. Epi Info version 6: a word processing, database, and statistical program for epidemiology on microcomputers. Centers for Disease Control and Prevention, Atlanta, Ga.
7. **Devriese, L. A., M. Ieven, H. Goossens, P. Vandamme, B. Pot, J. Hommez, and F. Haesebrouck.** 1996. Presence of vancomycin-resistant enterococci in farm and pet animals. Antimicrob. Agents Chemother. **40:**2285–2287.
8. **Donabedian, S. M.** 1992. Molecular typing of ampicillin-resistant non-β-lactamase-producing *Enterococcus faecium* isolates from diverse geographic areas. J. Clin. Microbiol. **30:**2757–2761.
9. **Dutka-Malen, S., E. Evers, and P. Courvalin.** 1995. Detection of glycopeptide resistance genotypes and identification to the species level of clinically relevant enterococci by PCR. J. Clin. Microbiol. **33:**24–27.
10. **Endtz, H. P., N. Van den Braak, A. Van Belkum, J. A. J. Kluytmans, G. M. Koeleman, L. Spanjaard, and A. Voss.** 1997. Fecal carriage of vancomycin-resistant enterococci in hospitalized patients and those living in the community in The Netherlands. J. Clin. Microbiol. **35:**3026–3031.
11. **Ford, M., J. D. Perry, and F. K. Gould.** 1994. Use of cephalexin-aztreonam-arabinose agar for selective isolation of *Enterococcus faecium*. J. Clin. Microbiol. **32:**2999–3001.
12. **Frieden, T. R., S. S. Munsiff, D. E. Low, B. M. Willey, G. Williams, Y. Faur, et al.** 1993. Emergence of vancomycin-resistant enterococci in New York City. Lancet **342:**76–79.
13. **Gin, A. S., and G. G. Zhanel.** 1996. Vancomycin-resistant enterococci. Ann. Pharmacother. **30:**615–624.
14. **Goosens, H.** 1998. Spread of vancomycin-resistant enterococci: differences between the United States and Europe. Infect. Control Hosp. Epidemiol. **19:**546–551.
15. **Gordts, B., H. Van Landuyt, M. Ieven, P. Vandamme, and H. Goosens.** 1995. Vancomycin-resistant enterococci colonizing the intestinal tract of hospitalized patients. J. Clin. Microbiol. **33:**2842–2846.
16. **Hanberger, H., M. Hoffman, S. Lindgren, and L. E. Nilsson.** 1997. High incidence of antibiotic resistance among bacteria in four intensive care units at a university hospital in Sweden. Scand. J. Infect. Dis. **29:**607–614.
17. **Handwerger, S., B. Raucher, D. Altarac, J. Monka, S. Marchione, K. V. Singh, B. E. Murray, J. Wolff, and B. Walters.** 1993. Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin and gentamicin. Clin. Infect. Dis. **16:**750–755.
18. **Jordens, J. Z., J. Bates, and D. T. Griffiths.** 1994. Faecal carriage and nosocomial spread of vancomycin-resistant *Enterococcus faecium*. J. Antimicrob. Chemother. **34:**515–528.
19. **Kirst, H. A., D. G. Thompson, and T. I. Nicas.** 1998. Historical yearly usage of vancomycin. Antimicrob. Agents Chemother. **42:**1303–1304.
20. **Klare, I., H. Heier, H. Claus, and W. Witte.** 1993. Environmental strains of *Enterococcus faecium* with inducible high-level resistance to glycopeptides. FEMS Microbiol. Lett. **106:**23–30.
21. **Landman, D., J. M. Quale, E. Oydna, B. Willey, V. Ditore, M. Zaman, and K. Patel.** 1996. Comparison of five selective media for identifying faecal carriage of vancomycin-resistant enterococci. J. Clin. Microbiol. **34:**751–752.
22. **Leclerc, R., and P. Courvalin.** 1997. Resistance to glycopeptides in enterococci. Clin. Infect. Dis. **24:**546–556.
23. **McCarthy, A. E., G. Victor, K. Ramotar, and B. Toye.** 1994. Risk factors for acquiring ampicillin-resistant enterococci and clinical outcome at a Canadian tertiary-care hospital. J. Clin. Microbiol. **32:**2671–2676.
24. **Møller Aarestrup, F., P. Ahrens, M. Madsen, L. V. Pallesen, R. L. Poulsen, and H. Westh.** 1996. Glycopeptide susceptibility among Danish *Enterococcus faecium* isolates of animal and human origin and PCR identification of genes within the *van* A cluster. Antimicrob. Agents Chemother. **40:**1938–1940.
25. **Murray, B. E.** 1990. The life and times of the enterococcus. Clin. Microbiol. Rev. **3:**46–65.
26. **National Committee for Clinical Laboratory Standards.** 1997. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: approved standard, 4th ed. NCCLS document M7-A4, vol. 17, no. 2. National Committee for Clinical Laboratory Standards, Wayne, Pa.
27. **Olsson-Liljequist, B., P. Larsson, M. Walder, and H. Miörner.** 1997. Antimicrobial susceptibility testing in Sweden. III. Methodology for susceptibility testing. Scand. J. Infect. Dis. Suppl. **105:**13–23.
28. **Pegues, D. A., C. F. Pegues, P. L. Hibberd, D. S. Ford, and D. C. Hooper.** 1997. Emergence and dissemination of a highly vancomycin-resistant *vanA* strain of *Enterococcus faecium* at a large teaching hospital. J. Clin. Microbiol. **35:**1565–1570.
29. **Quale, J., E. Atwood, B. Kreiswirth, B. M. Willey, V. Ditore, M. Zaman, et al.** 1996. Experience with a hospital-wide outbreak of vancomycin-resistant enterococci. Am. J. Infect. Control **24:**372–379.
30. **Quednau, M., S. Ahrne, A. C. Petersson, and G. Molin.** 1998. Antibiotic-resistant strains of enterococcus isolated from Swedish and Danish retailed chicken and pork. J. Appl. Microbiol. **84:**1163–1170.
31. **Schouten, M. A., J. A. A. Hoogkamp-Korstanje, and A. Voss.** 1997. Controlling glyccopeptide-resistant enterococci. Clin. Microbiol. Infect. **3:**592–593. (Letter.)
32. **Schouten, M. A., A. Voss, and J. A. A. Hoogkamp-Korstanje.** 1997. VRE and meat. Lancet **349:**1258. (Letter.)
33. **Silverman, J., L. A. Thal, B. Perri, G. Bostic, and M. J. Zervos.** 1998. Epidemiologic evaluation of antimicrobial resistance in community-acquired enterococci. J. Clin. Microbiol. **36:**830–832.
34. **Tenover, F. C., R. D. Arbeit, R. V. Goering, P. A. Mickelsen, B. E. Murray, D. H. Persing, and B. Swaminathan.** 1995. Interpreting chromosomal DNA restriction patterns produced by pulse-field gel electrophoresis: criteria for bacterial strain typing. J. Clin. Microbiol. **33:**2233–2239.
35. **Torell, E., H. Fredlund, E. Törnquist, E. B. Myhre, I. Sjöberg, and A. Sundsfjord.** 1997. Intrahospital spread of vancomycin-resistant *Enterococcus faecium* in Sweden. Scand. J. Infect. Dis. **29:**259–263.
36. **Van den Bogaard, A. E., L. B. Jensen, and E. E. Stobbering.** 1997. Vancomycin-resistant enterococci in turkeys and farmers. N. Engl. J. Med. **337:**1558–1559. (Letter.)
37. **Van den Bogaard, A. E., P. Meertens, E. Lon, and E. E. Stobberingh.** 1997. High prevalence of colonization with vancomycin- and pristinamycin-resistant enterococci in healthy humans and pigs in The Netherlands: is the addition of antibiotics in animal feed to blame? J. Antimicrob. Chemother. **40:**454–456. (Letter.)
38. **Van den Bogaard, A. E., N. London, C. Driessen, and E. Stobberingh.** 1998. The effect of antimicrobial growth promoters on the resistance in faecal indicator bacteria of pigs, abstr. C.77, p. 91. *In* Program and abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
39. **Van der Auwera, P., N. Pensart, V. Korten, B. E. Murray, and R. Leclercq.** 1996. Influence of oral glycopeptides on the faecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. J. Infect. Dis. **173:**1129–1136.