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Original Article

Trend in healthcare-associated infections due to vancomycin-resistant *Enterococcus* at a hospital in the era of COVID-19: More than hand hygiene is needed

Mizuho Fukushige ^{a,b}, Ling-Shang Syue ^{b,c}, Kazuya Morikawa ^a, Wen-Liang Lin ^d, Nan-Yao Lee ^{b,c,e}, Po-Lin Chen ^{b,c,e}, Wen-Chien Ko ^{b,c,e,*}

^a Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
^b Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
^c Center for Infection Control, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

^d Department of Pharmacy, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

^e Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

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KEYWORDS

Healthcareassociated infections; Vancomycin resistance; *Enterococcus*; Prevention measures; COVID-19; Taiwan **Abstract** *Background*: Variable control measures for vancomycin-resistant *Enterococcus* (VRE) infections were adopted among different hospitals and areas. We investigated the burden and patient characteristics of healthcare-associated VRE infections in 2018–2019 and 2020, when multiple preventive measures for COVID-19 were taken.

Methods: During the COVID-19 pandemic, mask waring and hand hygiene were enforced in the study hospital. The incidence densities of healthcare-associated infections (HAIs), including overall HAIs, methicillin-resistant *Staphylococcus aureus* (MRSA) HAIs, VRE HAIs, and VRE healthcare-associated bloodstream infections (HABSIs), consumption of broad-spectrum antibiotics and hygiene products, demographic characteristics and medical conditions of affected patients, were compared before and after the pandemic.

Results: The incidence density of both VRE HAIs and VRE HABSIs did not change statistically significantly, however, the highest in 2020 than that in 2018 and 2019. This was in spite of universal mask waring and increased consumption of 75% alcohol in 2020 and consistent implementation of an antibiotic stewardship program in three observed years. The increased

* Corresponding author. Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, Tainan, 704, Taiwan. Fax: +886 6 2752038.

E-mail address: winston@mail.ncku.edu.tw (W.-C. Ko).

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prescriptions of broad-spectrum cephalosporins might partially explain the increase of VRE infection.

Conclusion: Increased mask wearing and hand hygiene may not result in the decline in the development of VRE HAIs in the hospital during the COVID-19 pandemic, and continued monitoring of the dynamics of HAIs remains indispensable.

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Introduction

Vancomycin-resistant *Enterococcus* healthcare-associated infections (VRE HAIs) are of great health importance, since they have been associated with a high mortality rate, longer hospital-stay days, and higher healthcare cost.¹ Approximately 30% in the US, \geq 20% in Europe and Africa, clinical *Enterococcus* isolates have been resistant to vancomycin.^{2–4} In Taiwan, the first VRE case was reported in 1996,⁵ and currently >20% of clinical *Enterococcus* isolates were VRE.⁶

VRE has the ability to survive on hospital environmental surfaces in dry conditions for longer than seven days.⁷ Therefore, the environmental cleaning is one of the keys for a successful control of VRE HAIs.⁸ Besides this, there have been many studies to investigate the effectiveness of infection control measures against VRE infections. These measures included hand hygiene, patient cohorting,⁹ chlorhexidine gluconate bathing, contact precautions,¹⁰ and antimicrobial stewardship.^{11,12} The effectiveness of control measures was diverse among studies.¹⁰ This variability might be related to hospital and/or patient characteristics and suggested the control measures unique to the country- or hospital-level be essential to be useful control strategies. However, the feasibility of hospital-level interventions for VRE HAIs in Taiwan has rarely been reviewed.

In the end of 2020, Taiwan did not experience an abrupt upsurge of COVID-19 patients, with a total case number of 797,¹³ and was likely to be related to early preventive interventions, such as border control, traveler quarantine, social distancing, mask wearing in general population, and health promotion were initiated in Jan. 2020-Feb. 2020.¹⁴⁻¹⁶ The COVID-19 burden in 2020 was limited with only in a total of 10 patients admitted to the study hospital. At Taiwan hospitals, hand hygiene, universal masking, environmental cleaning, social distancing, restriction of visitors and attendants, and body temperature monitoring in the entry, have been implemented.^{14,15} Some of COVID-19 control measures are common with those for VRE HAI. and theoretically may result in a decrease of VRE incidence. Echoing this hypothesis, one study from a hospital in southern Taiwan during the first half of 2020 experienced a reduction of incidence density of nosocomial VRE infection, which was associated with more consumption of 75% alcohol and soaps for hand hygiene, both widely used to prevent COVID-19¹⁷. On the other hand, an extra workload to response towards the COVID-19 pandemic, which might reduce the staff resources for antimicrobial stewardship program might contribute the increase of VRE HAIs.¹⁸ These

contradictory findings motivated us to evaluate the recent trend in VRE infections in association with potential predisposing and protective factors. The objective of the current work was to investigate the impact of COVID-19 control measures and/or related factors on VRE HAIs through the analysis of patient and hospital data at the study hospital from 2018 to 2020.

Methods

Healthcare-associated infections (HAIs)

This study was conducted at a teaching hospital with approximately 1300 beds in southern Taiwan. The definitions of HAIs followed those of Taiwan CDC,¹⁹ and VRE HABSIs included the cases of VRE bacteremia noted at 48 h or later after the admission. The information about the incidence density of overall HAIs, methicillin-resistant Staphylococcus aureus (MRSA) HAIs, VRE HAIs, VRE healthcare-associated bloodstream infections (HABSIs), total inpatient-days, case mix index (CMI) scores, defined daily doses (DDDs) to define the average antibiotic consumption for each year, and 48-h response rates of antibiotic consultations by antimicrobial stewardship program (ASP) team, mainly infectious disease specialists, were collected through the Center for Infection Control. The CMI score reflects the disease complexity of hospitalized patients, and the higher CMI score suggests higher disease complexity.^{20,21} Monthly requests and clinical indications of 75% alcohol, chlorhexidine, chlorhexidine alcohol, from 2018 to 2020 were obtained through the Department of Pharmacy. Chlorhexidine bathing was not adopted as a standard practice for the prevention of the colonization or infection of multidrug-resistant organisms in intensive care units. Annual consumption data of N95 masks and surgical masks were sourced through the Department of General Affairs. The data of annual requests for sodium hypochlorite were retrieved from the Department of Environmental Management and the compliance rates of hand hygiene program were obtained from the Center for Infection Control.

Healthcare-associated bloodstream infections due to VRE

All patients with VRE HABSIs were reviewed for their demographic characteristics and medical conditions through the electronic medical records (EMRs). Underlying diseases of each patient was abstracted from EMRs, and the Charlson comorbidity index (CCI) score was calculated accordingly.²² Data extraction was performed by two of the authors, M.F. and L.S.S., and in the cases of data discrepancy, a consensus would be achieved by EMR recheck.

Statistical analysis

Descriptive statistical analyses were conducted to compare the incidence density of HAIs, patients' demographic characteristics, antibiotic consumption, and disinfection agent consumption among three years. One-way ANOVA or Welch ANOVA was performed to compare patient days, CMI, the incidence density of overall HAIs, VRE HAIs, VRE HABSIs, the 48-h response rate of antibiotic consultations, disinfection agents consumption, and antimicrobial agents consumption in each year from 2018 to 2020 (Table 1). Similarly, one-way ANOVA or Welch ANOVA was also performed to compare age, hospital stay prior to VRE isolation, and CCI score among inpatients with VRE HABSI. Those variables with a significant difference in variances between comparison groups were analyzed with Welch ANOVA. Turkey's HSD test or Games-Howell test was conducted as a post-hoc analysis for statistically significant variables being identified through one-way ANOVA or Welch ANOVA respectively. A chi-square test was used to compare the proportions of gender, ICU stay, and comorbidity.

The annual and monthly requests of disinfection agents from the hospital departments/wards were used as the approximate consumption for the analysis purpose. EMR data were entered in data spreadsheets of the Microsoft Excel version 16.49, which also was used for graphical expressions. IBM SPSS Statistics version 25.0 was used for the statistical analyses.

Only the first episode was included, if a patient had multiple episodes of VRE HABSIs within one year. There were two patients with an episode of VRE HABSI in two consecutive years. To keep the independence between groups for statistical analysis, they were analyzed by two ways, the inclusion of the first or last record, and separate statistical analyses were conducted. The analysis results found there was negligible impact by either approach. Therefore, the current study adopted the inclusion of the first record of each patient.

Ethics approval

This study received an ethical approval from the National Cheng Kung University Hospital: NCKUH-10904009/A-ER-108-373, and the patient consents can be waived.

Results

Hospital-level patient characters and healthcareassociated infections (HAIs)

The one-way ANOVA results showed that there was a statistically significant difference in incidence density of HAIs during the years from 2018 to 2020 [F(2, 33) = 6.09], P = 0.006]. Turkey's HSD test of multiple comparisons showed that the incidence density of HAIs was significantly higher in 2018 than that in 2019 or 2020 (95% confidence interval [CI] 0.091-0.809, P = 0.011; 95% CI 0.075-0.792, P = 0.015, respectively). Although there was no statistically significant difference, the incidence density of MRSA HAIs was the lowest in 2020 (Table 1). On the other hand, although there was no statistically significant difference, the incidence density of VRE HAI or VRE HABSI was the highest in 2020 (Table 1). Welch ANOVA result showed that there was a significant difference in case mix index (CMI) during three years [F (2, 19) = 6.84, P = 0.006]. A Games-Howell test showed the mean CMI in 2020 was significantly lower than that of 2018 (95% CI 0.0092–0.0869, P = 0.015), but there was no statistically significant difference between CMI in 2019 and 2020 (Table 1). The patient-days in 2020 were lower in the first half of the year than those in the same period of 2018 and 2019, which coincided with the emergence and health impact of the COVID-19 pandemic, and then increased in the second half of the year as high as those in the same time period of 2019 (Figure S1).

In the study hospital, both 75% alcohol and 4% chlorhexidine solutions were primarily used for hand hygiene and occasionally skin antisepsis prior to intramuscular injection (75% alcohol) and wound cleaning (4% chlorhexidine). Chlorhexidine alcohol solutions, regardless of chlorhexidine concentration, were mainly used for skin antisepsis before invasive procedures, including catheter insertion. The annual consumption of 75% alcohol for hand hygiene or

Variables (monthly)	Year			F value	P value
mean \pm standard deviation	2018	2019	2020		
Patient days	32,891 ± 1927	33,238 ± 1816	31,666 ± 1509	2.64	0.086
Case mix index	$\textbf{1.422} \pm \textbf{0.046}$	$\textbf{1.418} \pm \textbf{0.055}$	$\textbf{1.374} \pm \textbf{0.023}$	6.84	0.006
Incidence density (‰)					
Overall HAIs	$\textbf{3.77} \pm \textbf{0.33}$	$\textbf{3.32} \pm \textbf{0.44}$	$\textbf{3.33} \pm \textbf{0.28}$	6.09	0.006
MRSA HAIs	$\textbf{0.07} \pm \textbf{0.06}$	$\textbf{0.10}\pm\textbf{0.06}$	0.05 ± 0.03	2.27	0.119
VRE HAIs	$\textbf{0.22}\pm\textbf{0.09}$	$\textbf{0.24} \pm \textbf{0.08}$	$\textbf{0.28} \pm \textbf{0.07}$	1.86	0.172
VRE HABSIs ^a	$\textbf{0.13} \pm \textbf{0.07}$	$\textbf{0.12} \pm \textbf{0.06}$	$\textbf{0.18} \pm \textbf{0.07}$	2.34	0.112
48-h response rate (%)	$\textbf{77.5} \pm \textbf{9.3}$	$\textbf{74.6} \pm \textbf{10.4}$	75.6 ± 7.9	0.30	0.741

Table 1 The incidence density of healthcare-associated infections (HAIs), vancomycin-resistant *Enterococcus* (VRE) HAIs, and variables that related to the characteristics of the study hospital from 2018 to 2020.

^a HABSI, healthcare-associated bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*.

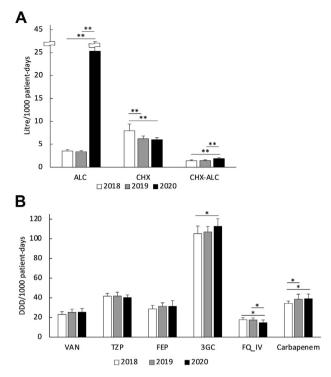


Figure 1. The monthly consumption quantity of disinfection agents and antimicrobial agents from 2018 to 2020. **A**) average monthly consumption of 75% alcohol (ALC), 4% chlorhexidine (CHX), and chlorhexidine-alcohol solutions (CHX-ALC) from 2018 to 2020. **B**) average monthly consumption of different types or class of antibiotics. Note: VAN = vancomycin; TZP = piperacillin/tazobactam; FEP = cefepime; 3 GC = third-generation cephalosporins; FQ_IV = intravenous fluoroquinolone. **: p < 0.001; *: p < 0.005.

environmental disinfection in 2020 was approximately 14,000 L, and was 1.64 and 1.77 times higher than that in 2019 and 2018, respectively (Fig. 2). In line with this, the Welch ANOVA and Games-Howell test results showed that the requests from departments/wards on 75% alcohol in litre/1000 patient-days were significantly higher in 2020 compared to 2018 and 2019 [F(2, 19) = 10.4, P = 0.001] (95% CI 8.51-35.1, P = 0.003 between 2018 and 2020, and 95% CI 8.66-35.2, P = 0.003 between 2019 and 2020) (Fig. 1A). In addition, there were high overall compliance rates of hand hygiene, 96%-99%, between 2018 and 2020, suggestive of acceptable adherence to the hand hygiene program promoted even in the hospital in 2020, when the hospital was fighting against the COVID-19 pandemic.

However, due to supply shortage during the COVID-19 pandemic, the annual consumption of 4% chlorhexidine solution in 2020 was approximately 5000 L, and 0.66 and 0.67 times lower than that in 2019 and 2018, respectively (Fig. 2). The Welch ANOVA Games–Howell test results showed requests on 4% chlorhexidine solution from departments/wards were significantly lower in 2019 and 2020 compared to that in 2018 [F(2, 20) = 9.9, P = 0.001] (95% CI 0.572–2.93, P = 0.004 between 2018 and 2019, and 95% CI 0.823–3.14, P = 0.002 between 2018 and 2020) (Fig. 1A). On the other hand, the quantity of requests from departments/wards on chlorhexidine alcohol (a total

consumption of 0.5%, 2%, and 5% solutions) in 2020 was significantly higher in 2020 compared to 2018 and 2019 [F(2, 22) = 27.6, P = 0.001] (95% CI 0.296-0.637, P < 0.001 between 2018 and 2020, and 95% CI 0.266-0.588, P < 0.001 between 2019 and 2020) (Fig. 1A).

Sodium hypochlorite in different concentrations depending on the target pathogens (e.g., 1000 ppm for SARS-CoV-2 virus or 5000 ppm for *Clostridium difficile*) was used as a main detergent for environmental cleaning at the study hospital. There was a high variability of the intervals between the requests of sodium hypochlorite from different departments. Therefore, no statistical comparisons of monthly consumption of sodium hypochlorite could be made in the study period. However, the annual consumption of sodium hypochlorite in 2020 was approximately 13,600 L, which was 1.29 and 1.06 times higher than that in 2019 and 2018, respectively.

The one-way ANOVA results showed that there was no statistically significant difference in vancomycin use at the study hospital from 2018 to 2020 [F(2, 33) = 1.88]P = 0.168]. Vancomycin usage in 2020 was 25.2 DDDs/1000 patient-days which is 0.1% lower than that in 2019 and 2.2% higher than that in 2018 (Fig. 1B). The average use of piperacillin/tazobactam and cefepime were also no statistically significant difference during the studied three years. In contrast, monthly average use of third-generation cephalosporins and carbapenems in 2020 were statistically significantly higher than in 2018 [F(2, 33) = 3.69, P = 0.036](95% CI 0.387-14.6, P = 0.037)] and [F(2, 19) = 7.11,P = 0.005 (95% CI 0.922 - 8.71, P = 0.015)] respectively (Fig. 1B). The 48-h response rate, which reflects the working efficacy of ASP members, in 2020 was 76%, similar to that in 2019 and 2018, 75% and 74%, and there was no statistically significant difference among study years (Table 1).

Healthcare-associated bloodstream infections due to VRE (VRE HABSIs)

As for the cases of VRE HABSIs in three calendar years, oneway ANOVA analyses showed there were no significant differences, in terms of age, gender, Charlson comorbidity index, the duration of hospital stay prior to the onset of HABSIs, and the need of ICU care (Table 2). Among the patients' comorbidities, only peptic ulcer disease was most common in 2018 and less common in 2020 [X²(2, 164) = 7.74, P = 0.021]. For other types of comorbidities, such as diabetes mellitus, solid tumor with or without metastasis, chronic heart, renal, lung or liver disease, or cerebrovascular disease or dementia, there were no significant differences among three study years (Table 2).

Overall trend

There were several factors that have been consistent during three years (with no statistically significant change):48h response rate, hand hygiene compliance rate, CCI of VRE HABSI patients, and vancomycin consumption (Fig. 2). On the other hand, average consumption of third generation cephalosporin, sodium hypochlorite, 75% alcohol, N95 mask, and surgical mask usage increased by statistically

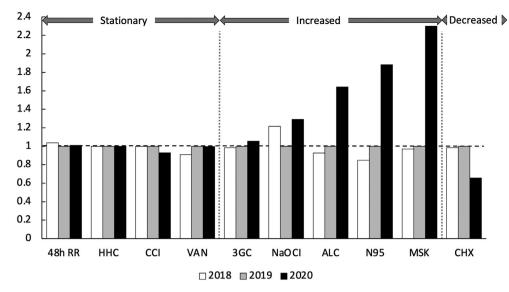


Figure 2. The relative changes of several variables associated with healthcare-associated vancomycin-resistant *Enterococcus* bloodstream infections from 2018 to 2020. The data in 2019 are regarded as the reference value. The annual hospital-wide consumption/compliance data of parenteral vancomycin, third-generation cephalosporins, sodium hypochlorite, 75% alcohol, 4% chlorhexidine, N95 mask, surgical mask, and hand hygiene compliance rate were used for analyses. Note: 48h RR = 48-h response rate; HHC = hand hygiene compliance rate; CCI = Charlson comorbidity index score; VAN = vancomycin; 3 GC = third-generation cephalosporins; NaOCI = sodium hypochlorite; ALC = 75% alcohol, N95 = N95 mask, MSK = surgical mask, and CHX = 4% chlorhexidine.

significantly or for more than 10% in 2020 compared to previous two years (Fig. 2). A decline of 4% chlorhexidine annual consumption for more than 10% in 2020 was also noted (Fig. 2).

Discussion

COVID-19 prevention measures, such as hand hygiene, universal mask wearing, and enhanced environmental cleaning, are partially in common with the recommended prevention measures for HAIs, and therefore may modify the incidence of VRE HAIs. However, one size does not fit all, since our hospital data show no statistically significant decline in the incidence density of MRSA HAIs, VRE HAIs and VRE HABSIs in 2020, with wide adoption of COVID-19 control measures in the study hospital. The present study identified other variables, such as the decreased yearly consumption of 4% chlorhexidine solution and the increased use of third generation cephalosporins,^{23,24} which might be related to the increase of VRE HAI in the era of COVID-19.

A number of infection control polices for the COVID-19 outbreak in Taiwan have been implemented in the beginning of 2020. Health promotion, hand hygiene, universal masking, a surface cleaning, social distancing, restriction of the number of visitors, and body temperature monitoring at the entry, have been widely implemented in the hospitals.^{14,15} Some interventions, for example hand hygiene, are in common with the commonly recommended measures for HAI prevention.^{25,26} At the study hospital, the increased consumption of 75% alcohol solution in 2020 could reasonably be linked to enhanced hand hygiene. Nevertheless, our results were not in

accordance with a decline in VRE HAI, as noted in the Lo's study.¹⁷ There are multiple possible concerns, for example, VRE might be less susceptible to 75% alcohol, as reported from Australia,²⁷ VRE also might be transmitted mainly through health equipment or environmental surfaces at the study hospital, comparable to the report from German.²⁸

In another aspect, the supply shortage and decreased usage of 4% chlorhexidine in 2020 due to COVID-19 outbreak deserved some concerns. An in vitro study found repeating exposure to sub-inhibitory concentrations of chlorhexidine induced a reduced susceptibility among VRE population.²⁹ Strikingly, there were Enterococcus faecium populations in the community and hospital settings tolerant against low concentration chlorhexidine.³⁰ Furthermore, in the Denmark hospitals VRE isolates were less susceptible to chlorhexidine than VSE isolates.³¹ The chlorhexidine susceptibility of VRE in the Taiwan hospitals is not well studied. The previous studies suggested the interaction of reduced consumption of 4% chlorhexidine and chlorhexidine susceptibility of VRE isolates in the hospital environments may influence the occurrence of VRE HAIs.^{29,31} The monitoring of chlorhexidine consumption and susceptibility among the environmental and HAI-related VRE isolates is warranted. Antimicrobial and chlorhexidine susceptibility testing and genotyping of identified VRE strains will be continued at the study hospital.

Annual consumption of sodium hypochlorite used for environmental cleaning in 2020 was not less than that in 2019 and 2018, suggestive of no major change in the practice of environmental cleaning. Likewise, the average compliance rate of hand hygiene program was 98% during the study period. Both environmental cleaning and hand

Patients' characteristics and		Year	Year	
comorbidities	2018	2019	2020	
Age range (mean), years	39-93 (68)	16-91 (67)	20-94 (69)	0.812
Male sex (%)	28 (51)	26 (55)	41 (62)	0.671
ICU stay (%)	21 (41)	12 (26)	24 (36)	0.251
Hospital stay before VRE isolation, range (mean), days	3-467 (36)	6-261 (33)	4-213 (32)	0.891
Charlson comorbidity index, range (mean)	0-16 (5.7)	0-10 (5.7)	0-11 (5.3)	0.643
Comorbidities (%)				
Diabetes mellitus without end organ damage/ complications	24 (47)	17 (36)	24 (36)	0.426
Diabetes mellitus with end organ damage/ complications	2(4)	0 (0)	2 (3)	0.418
Metastatic tumor	20 (39)	17 (36)	22 (33)	0.805
Moderate to severe renal disease	16 (31)	14 (30)	16 (24)	0.696
Peptic ulcer disease	14 (27)	6 (13)	6 (9)	0.021
Chronic pulmonary disease	10 (20)	15 (32)	12 (18)	0.189
Congestive heart failure	9 (17)	11 (23)	16 (24)	0.670
Cerebrovascular disease	9 (18)	5 (11)	7 (11)	0.460
Dementia	4 (8)	6 (13)	5 (8)	0.594
Tumor without metastasis	4 (8)	7 (15)	10 (15)	0.442
Mild liver disease	4 (8)	5 (11)	9 (14)	0.608
Moderate to severe liver	3 (6)	9 (19)	6 (9)	0.090
disease				
Peripheral vascular disease	3 (6)	0 (0)	3 (5)	0.266
Leukemia	3 (6)	3 (6)	11 (17)	0.094
Hemiplegia	2 (4)	0 (0)	4 (6)	0.237
Transplantation	2 (4)	2 (4)	2 (3)	0.936
Myocardial infarction	2 (4)	2 (4)	3 (5)	0.986
Connective tissue disease	1 (2)	2 (4)	3 (5)	0.736
Lymphoma	1 (2)	4 (9)	1 (2)	0.110

Table 2Clinical characteristics and numbers of patients with healthcare-associated bacteremia due to vancomycin-resistantEnterococcus from 2018 to 2020.

hygiene have been reported as key factors of HAI control. Therefore, our data suggested that the study hospital at least kept similar standards of HAI control during the COVID-19 pandemic.

There have been several antibiotics in association with increased VRE prevalence of incidence in the hospital settings. Increased vancomycin consumption has been contributed to the increased VRE infections in Taiwan.⁶ However, vancomycin consumption at the study hospital was stable in three years. On the other hand, the increased use of third generation cephalosporins was evident from 2018 to 2020, which have also been reported to increase the risk of VRE infections.^{23,24} These broad-spectrum cephalosporins do not directly promote the growth of *Enterococcus*, but they eradicate competitive organisms and lead to the overgrowth of *Enterococcus*.^{32,33}

There was no difference in the 48-h response rates of antibiotic consultations by AST team members in three years. This result could reflect the stable and constant effort for ASP, even during the period when there was extra workload of the ASP team members, especially the infectious disease specialists, to respond to the COVID-19 outbreak. Moreover, the annual consumption of key antibiotics was consistent if not decreased in three years, except the increased consumption of third generation cephalosporins and carbapenem. Further investigations to identify factors related to the increase usage in third generation cephalosporins and to clarify the magnitude of its impact on VRE HAIs should be considered.

The decline in the patient days and case mix index of hospitalized patients in the study hospital in 2020 probably reflect the hesitancy of the hospital visits among general population in the period of the COVID-19 pandemic. In accordance with the majority of other countries where an upsurge of COVID-19 patients occurred, there was often a decline in overall hospital admissions, for example in Denmark from Mar. 2020 to Jan. 2021.³⁴ However, these changes in patient loads and disease severity in the hospital seem to be limited in Taiwan. With unique implementation of multidiscipline preventive measures for COVID-19, this

setting provided us an opportunity to evaluate the real impact of infection control interventions on HAIs in 2020.

The emerging and current levels of VRE endemicity differ among countries. This in part could be relate to the variations in the practices of antibiotic usage not only in healthcare facilities, but also in agriculture, antimicrobial resistance survey systems, and accessibility to antibiotics.³⁵ Taiwan follows medical education systems of American and British standards, and medical colleges adopt medical textbooks from these countries.³⁶ This western standard medical practice may be related to the high prevalence of vancomycin resistance among Enterococcus isolates, similar to that in UK (>20%) and USA (30%). In contrast, a low prevalence of VRE prevalence was noted in Japan, for example <0.1% in 2019.³⁷ Although Japan is geographically, culturally, and climatically closer to Taiwan than Western and European countries, the vast gap in the VRE prevalence between two countries probably reflects the diversity in medical practices, patient-physician relationship, health insurance, etc.

There are multiple factors with potential influence on MRSA HAIs and VRE HAIs but not considered in our study. This includes the frequency of invasive treatment procedures, including central venous catheters which could increase the risk of VRE HAIs and HABSIs.³⁸ Neither the method of hospital environmental cleaning, nor the effectiveness of hand washing and hand sanitizer usage among hospital patients and visitors, were assessed. Although there was a significant reduction in number of visitors during COVID-19 due to the restrictions, we could not quantify the degree of reduction in the visitors. The methodology of bacterial identification was modified for some bacterial species at the study hospital during 2018-2020. Therefore, our study exclusively focused on MRSA HAIs, VRE HAIs and HABSIs, and other clinically important multidrug-resistant organisms, such as carbapenem-resistant Acinetobacter baumannii (CRAB) and carbapenem-resistant Enterobacterales (CRE), were not included. Detailed systematic data collection by the administration regulation of hospital management would be valuable.

Conclusion

An increase in the incidence density of VRE HAIs and HABSIs was noted at a hospital in southern Taiwan in 2020 during the first year of COVID-19 pandemic, in spite of increased consumption of 75% alcohol and persistent efforts for antibiotic stewardship program. However, the decreasing consumption of 4% chlorhexidine solutions and increasing usage of third generation cephalosporins may favor the occurrence of VRE HAIs. Our results highlight the importance of continued surveillance of HAIs in the COVID-19 era, even under the implementation of multiple preventive measures for both COVID-19 and HAIs.

Author and contributors

The initial conception and design of the work: MF, LSS, KM, and WCK. Contribution to draft manuscript editing/ reviewing: MF, LHH, KM, WLL, NYL, PLC, and WCK. Data

collection: MF, LSS, WLL, and WCK. Statistical analysis: MF. All authors approved the final version of the manuscript.

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Declaration of competing interest

There was no conflicts of interest in the current study.

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References

- 1. Serra-Burriel M, Keys M, Campillo-Artero C, Agodi A, Barchitta M, Gikas A, et al. Impact of multi-drug resistant bacteria on economic and clinical outcomes of healthcareassociated infections in adults: systematic review and metaanalysis. *PLoS One* 2020;15:e0227139.
- 2. CDC. Antibiotic resistance threats in the United States 2019. Atlanta, GA: U.S.: Department of Health and Human Services, CDC; 2019.
- ECDC. Antimicrobial resistance in the EU/EEA (EARS-Net) annual epidemiological report for 2019. Antimicrobial resistance surveillance in Europe 2020. https://www.ecdc.europa. eu/en/publications-data/surveillance-antimicrobialresistance-europe-2019. [Accessed 19 July 2022].
- 4. Alemayehu T, Hailemariam M. Prevalence of vancomycinresistant *Enterococcus* in Africa in one health approach: a systematic review and meta-analysis. *Sci Rep* 2020;**10**:20542.
- 5. Hsueh PR, Chen WH, Teng LJ, Luh KT. Nosocomial infections due to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci at a university hospital in Taiwan from 1991 to 2003: resistance trends, antibiotic usage and *in vitro* activities of newer antimicrobial agents. *Int J Antimicrob Agents* 2005;26:43–9.
- Lee MC, Lu CH, Lee WY, Lee CM. Correlation between nosocomial carriage of vancomycin-resistant enterococci and antimicrobial use in Taiwan. Am J Trop Med Hyg 2021;104:1131–6.
- 7. Hanczvikkel A, Toth A. Quantitative study about the role of environmental conditions in the survival capability of multidrug-resistant bacteria. *J Infect Public Health* 2018;11: 801–6.
- **8.** Martinez JA, Ruthazer R, Hansjosten K, Barefoot L, Snydman DR. Role of environmental contamination as a risk factor for acquisition of vancomycin-resistant *enterococci* in patients treated in a medical intensive care unit. *Arch Intern Med* 2003;**163**:1905–12.
- 9. Abad CL, Barker AK, Safdar N. A systematic review of the effectiveness of cohorting to reduce transmission of

healthcare-associated *C. difficile* and multidrug-resistant organisms. *Infect Control Hosp Epidemiol* 2020;41:691–709.

- Kleyman R, Cupril-Nilson S, Robinson K, Thakore S, Haq F, Chen LW, et al. Does the removal of contact precautions for MRSA and VRE infected patients change health care-associated infection rate?: a systematic review and meta-analysis. *Am J Infect Control* 2021;49:784–91.
- Remschmidt C, Behnke M, Kola A, Diaz LAP, Rohde AM, Gastmeier P, et al. The effect of antibiotic use on prevalence of nosocomial vancomycin-resistant enterococci-an ecologic study. Antimicrob Resist Infect Control 2017;6:95.
- Webb BJ, Majers J, Healy R, Jones PB, Butler AM, Snow G, et al. Antimicrobial stewardship in a hematological malignancy unit: carbapenem reduction and decreased vancomycinresistant *Enterococcus* infection. *Clin Infect Dis* 2020;71: 960–7.
- 13. Worldometers.info. *COVID-19 coronavirus pandemic*. 2021. https://www.worldometers.info/coronavirus/country/ taiwan/. 19th July, 2022.
- Taiwan CDC. Pretension and control of COVID-19 in taiwan. 2020. https://www.cdc.gov.tw/En/Category/Page/0vq&rsAob_ 9HCi5GQ5jH1Q. 19th July, 2022.
- Taiwan CDC. COVID-19: guidelines for social distancing. 2020. https://www.cdc.gov.tw/En/File/Get/reB429_ 3fV4GulfumH9Vcg. 19th July, 2022.
- Yen MY, Yen YF, Chen SY, Lee TI, Huang GH, Chan TC, et al. Learning from the past: Taiwan's responses to COVID-19 versus SARS. Int J Infect Dis 2021;110:469–78.
- **17.** Lo SH, Lin CY, Hung CT, He JJ, Lu PL. The impact of universal face masking and enhanced hand hygiene for COVID-19 disease prevention on the incidence of hospital-acquired infections in a Taiwanese hospital. *Int J Infect Dis* 2020;**104**: 15–8.
- Monnet DL, Harbarth S. Will coronavirus disease (COVID-19) have an impact on antimicrobial resistance? *Euro Surveill* 2020; 25:2001886.
- Taiwan CDC. Surveillance definitions for healthcareassociated infections (HAI) (Chinese). 2013. https://www. cdc.gov.tw/File/Get/vaCzlSfjhsSg_7siqy44CQ. 19th July, 2022.
- 20. Mendez CM, Harrington DW, Christenson P, Spellberg B. Impact of hospital variables on case mix index as a marker of disease severity. *Popul Health Manag* 2014;17:28–34.
- Horn SD, Sharkey PD, Chambers AF, Horn RA. Severity of illness within drgs - impact on prospective payment. *Am J Publ Health* 1985;**75**:1195–9.
- 22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;40:373-83.
- 23. Dahms RA, Johnson EM, Statz CL, Lee JT, Dunn DL, Beilman GJ. Third-generation cephalosporins and vancomycin as risk factors for postoperative vancomycin-resistant *Enterococcus* infection. *Arch Surg* 1998;133:1343–6.
- 24. Fridkin SK, Edwards JR, Courval JM, Hill H, Tenover FC, Lawton R, et al. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. *Ann Intern Med* 2001;135:175–83.

- Allegranzi B, Pittet D. Role of hand hygiene in healthcareassociated infection prevention. J Hosp Infect 2009;73:305–15.
- 26. Sickbert-Bennett EE, DiBiase LM, Willis TM, Wolak ES, Weber DJ, Rutala WA. Reduction of healthcare-associated infections by exceeding high compliance with hand hygiene practices. *Emerg Infect Dis* 2016;22:1628–30.
- Pidot SJ, Gao W, Buultjens AH, Monk IR, Guerillot R, Carter GP, et al. Increasing tolerance of hospital *Enterococcus faecium* to handwash alcohols. *Sci Transl Med* 2018;10. eaar6115.
- Correa-Martinez CL, Tonnies H, Frobose NJ, Mellmann A, Kampmeier S. Transmission of vancomycin-resistant enterococci in the hospital setting: uncovering the patientenvironment interplay. *Microorganisms* 2020;8:203.
- 29. Bhardwaj P, Hans A, Ruikar K, Guan ZQ, Palmer KL. Reduced chlorhexidine and daptomycin susceptibility in vancomycinresistant *Enterococcus faecium* after serial chlorhexidine exposure. Antimicrob Agents Chemother 2018;62. e01235-17.
- Duarte B, Pereira AP, Freitas AR, Coque TM, Hammerum AM, Hasman H, et al. 2CS-CHX^T operon signature of chlorhexidine tolerance among *Enterococcus faecium* isolates. *Appl Environ Microbiol* 2019;85. e01589-19.
- Alotaibi SMI, Ayibiekea A, Pedersen AF, Jakobsen L, Pinholt M, Gumpert H, et al. Susceptibility of vancomycin-resistant and -sensitive *Enterococcus faecium* obtained from Danish hospitals to benzalkonium chloride, chlorhexidine and hydrogen peroxide biocides. *J Med Microbiol* 2017;66:1744–51.
- 32. May AK, Melton SM, McGwin G, Cross JM, Moser SA, Rue LW. Reduction of vancomycin-resistant enterococcal infections by limitation of broad-spectrum cephalosporin use in a trauma and burn intensive care unit. *Shock* 2000;14:259–64.
- Harbarth S, Cosgrove S, Carmeli Y. Effects of antibiotics on nosocomial epidemiology of vancomycin-resistant *enterococci*. *Antimicrob Agents Chemother* 2002;46:1619–28.
- 34. Bodilsen J, Nielsen PB, Søgaard M, Dalager-Pedersen M, Speiser LOZ, Yndigegn T, et al. Hospital admission and mortality rates for non-covid diseases in Denmark during covid-19 pandemic: nationwide population based cohort study. BMJ 2021;373:n1135.
- Chokshi A, Sifri Z, Cennimo D, Horng H. Global contributors to antibiotic resistance. J Global Infect Dis 2019;11:36–42.
- Chou JY, Chiu CH, Lai E, Tsai D, Tzeng CR. Medical education in Taiwan. Med Teach 2012;34:187–91.
- Japan Nosocomial Infections Surveillance. Annual open report 2019 (all facilities). 2020. https://janis.mhlw.go.jp/english/ report/index.html. 19th July, 2022.
- 38. Lopez-Luis BA, Sifuentes-Osornio J, Lambrano-Castillo D, Ortiz-Brizuela E, Ramirez-Fontes A, Tovar-Calderon YE, et al. Risk factors and outcomes associated with vancomycin-resistant *Enterococcus faecium* and ampicillin-resistant *Enterococcus faecalis* bacteraemia: a 10-year study in a tertiary-care centre in Mexico City. J Glob Antimicrob Resist 2021;24:198–204.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.08.003.