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Epidemiology of vancomycin-resistant enterococci in the United Arab Emirates: a retrospective analysis of 12 years of national AMR surveillance data

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Introduction: Enterococci are usually low pathogenic, but can cause invasive disease under certain circumstances, including urinary tract infections, bacteremia, endocarditis, and meningitis, and are associated with peritonitis and intra-abdominal abscesses. Increasing resistance of enterococci to glycopeptides and fluoroquinolones, and high-level resistance to aminoglycosides is a concern. National antimicrobial resistance (AMR) surveillance data for enterococci from the Middle East and North Africa (MENA) and the Gulf region is scarce.

Methods: A retrospective 12-year analysis of $N = 37,909$ non-duplicate diagnostic *Enterococcus* spp. isolates from the United Arab Emirates (UAE) was conducted. Data was generated by routine patient care during 2010–2021, collected by trained personnel and reported by participating surveillance sites to the UAE National AMR Surveillance program. Data analysis was conducted with WHONET.

Results: *Enterococcus faecalis* was the most commonly reported species (81.5%), followed by *Enterococcus faecium* (8.5%), and other enterococci species (4.8%). Phenotypically vancomycin-resistant enterococci (VRE) were found in 1.8% of *Enterococcus* spp. isolates. Prevalence of VRE (%VRE) was highest for *E. faecium* (8.1%), followed by *E. faecalis* (0.9%). A significant level of resistance to glycopeptides (%VRE) for these two species has been observed in the majority of observed years [*E. faecalis* (0–2.2%), 2010: 0%, 2021: 0.6%] and *E. faecium* (0–14.2%, 2010: 0%, 2021: 5.8%). Resistance to fluoroquinolones was between 17 and 29% (*E. faecalis*) and was higher for *E. faecium* (between 42 and 83%). VRE were associated with higher patient mortality (RR: 2.97), admission to intensive care units (RR: 2.25), and increased length of stay (six excess inpatient days per VRE case), as compared to vancomycin-susceptible *Enterococcus* spp.

Discussion: Published data on *Enterococcus* infections, in particular VRE-infections, in the UAE and MENA region is scarce. Our data demonstrates that VRE-enterococci are relatively rare in the UAE, however showing an increasing resistance trend for several clinically important antibiotic classes, causing a concern for the treatment of serious infections caused by enterococci. This study also demonstrates that VRE were associated with higher mortality, increased intensive care unit admission rates, and longer hospitalization, thus poorer clinical outcome and higher associated costs in the UAE. We recommend the expansion of current surveillance techniques (e.g., local VRE screening), stricter infection prevention and control strategies, and better stewardship interventions. Further studies on the molecular epidemiology of enterococci are needed.

KEYWORDS

vancomycin-resistant enterococci (VRE), vancomycin, antimicrobial resistance (AMR), United Arab Emirates (UAE), surveillance

1 Introduction

Several dozen species of enterococci are part of the physiological intestinal flora in humans as well as in vertebrate and invertebrate animals (1). Due to a high degree of tenacity, once excreted, the bacteria stay viable or may even proliferate on environmental surfaces, food as well as in surface and waste water (2–8). The bacteria are transmitted between humans and from animals to humans by hand contact as well as by contaminated food and water (9, 10).

In addition to their physiologic role in the human intestinal microbiome, they can cause infections, especially in persons with breaches in their unspecific immune defense, e.g., due to inserted catheters, surgical procedures and medication affecting the mucosal surfaces (11–14). In such persons, enterococci as sole responsible agents can cause urinary tract infections, bacteremia, and endocarditis. In combination with other, more pathogenic bacteria they are associated with wound infections and secondary peritonitis (15–21).

Once causing infections, antibiotic therapy can be challenging, since enterococci are inherently resistant to cephalosporins and often also to penicillins (22–24). So, in severe infections,

glyco- and lipopeptides such as vancomycin and daptomycin, or oxazolidinones such as linezolid are among the few remaining therapeutic options (25, 26). But even to these compounds, enterococci have developed resistance mechanisms encoded on mobile genetic elements or plasmids (27, 28). So far, this type of vancomycin resistance encoded by the *vanA* or *vanB* genes has predominantly been demonstrated in *Enterococcus faecium* but may also be present in *Enterococcus faecalis* (29–33).

There is conflicting data on the role of vancomycin-resistant enterococci (VRE) in severe infections concerning their contribution to increased mortality (34–37). However, there are potentially more tenacious and/or pathogenic VRE clones which remain for extended periods in specific hospitals and as a consequence, are involved in nosocomial outbreaks (38–42) combined with a high economic burden (43–45).

Therefore, important national and international institutions such as the United States Centers for Disease Prevention and Control (CDC) (46) and the European Center for Disease Prevention and Control (ECDC) (47) have included VRE on their lists of potentially harmful microorganisms that should be constantly monitored.

Data from such monitoring programs indicate that the VRE portion among the total number of clinical enterococcal isolates varies between 1 and 50% depending on regional and temporal settings and also across individual medical institutions within a given region and period. Preventive hygiene measures such as contact precautions and isolation of VRE-carrying/infected patients are not necessarily associated with changed VRE portions among enterococci, stressing the importance of individual VRE clones for the regional and temporal VRE prevalence (48–51).

Increasing levels of antimicrobial resistance in healthcare and non-healthcare settings is also increasingly seen as a problem in the Middle East and North African (MENA) region, including the Gulf region (GCC, Gulf Cooperation Council) (52, 53). Several reports from countries belonging to the MENA and GCC region demonstrate the emergence of and increasing interest in VRE. These countries include Morocco (54), Algeria (55–57),

Abbreviations: CDC, United States Centers for Disease Prevention and Control; CLSI, United States Clinical & Laboratory Standards Institute; COVID-19, coronavirus disease 2019; CRE, Carbapenem-resistant Enterobacteriales; ECDC, European Centers for Disease Prevention and Control; EUCAST, European Committee for Antimicrobial Susceptibility Testing; ICU, intensive care unit; GCC, Gulf Cooperation Council; GLASS, Global Antimicrobial Resistance Surveillance System; GRE, glycopeptide-resistant enterococci; HL, high-level; LOS, length of stay; MDR, multidrug-resistant; MDRO, multidrug-resistant organisms; MENA, Middle East and North Africa; MRSA, methicillin-resistant *Staphylococcus aureus*; NRL-AMR, National Reference Laboratory for Antimicrobial Resistance; n.s., not significant; PDR, Pandrug-resistant; SPSS, Statistical Package for the Social Sciences; UAE, United Arab Emirates; UTI, urinary tract infections; VRE, vancomycin-resistant enterococci; WHO, World Health Organization; XDR, extensively drug-resistant.

Tunisia (58, 59), Libya (60), Egypt (61–66), Saudi-Arabia (67–69), Oman (70), Qatar (71), Bahrain (72), Iran (73), and others. However, published epidemiological data from the MENA region on *Enterococcus* spp. and VRE on a national/country level are scarce and outdated, and, to the best of our knowledge, limited to Saudi Arabia (69) and Oman (70).

Surveillance of antimicrobial resistance in the United Arab Emirates (UAE) started in 2010 at Emirate-level (Abu Dhabi). Inspired by the World Health Organization (WHO) global action plan on antimicrobial resistance (GAP-AMR) and especially, the global AMR surveillance system (GLASS), the UAE national antibiotic resistance surveillance program was established in 2015, leading to the present data collection and evaluation.

Here we present the enterococci epidemiology in the UAE in a period ranging from pre-COVID-19 pandemic years to well into the second pandemic year (2021). The successful impact of the UAE health care system on the relatively low VRE prevalence, as well as the impact of VRE on the UAE health care system and health outcomes are discussed. This paper also presents a discussion of the effect that the COVID-19 pandemic had on the surveillance and reporting of *Enterococcus* spp., and related antimicrobial resistance levels during the pre-pandemic and pandemic period. This paper represents the first documentation of a 12-year resistance portfolio for enterococci across the whole country, from 2010 until 2021.

2 Materials and methods

2.1 Study design and data source

A multi-institutional retrospective observational study was conducted between 2010 and 2021 in the UAE using data extracted from the WHONET microbiology laboratory database software (<https://whonet.org/>) supported by the Global AMR Surveillance System protocol (GLASS, World Health Organization). Data was generated, collected, cleaned and analyzed through the UAE national AMR Surveillance programs as described by Thomsen et al. (74).

2.2 Identification and enrollment of national AMR surveillance sites

Starting in 2010, UAE institutions were incorporated into the UAE national AMR surveillance program based on epidemiological needs assessment, readiness and willingness of facilities to participate, availability of high-quality electronic AMR data, lab accreditation status, and qualification of staff. Hospitals, centers, and clinics representing all seven Emirates of the UAE joined the AMR surveillance network gradually over the years.

2.3 Bacterial population and variables of the study

All *Enterococcus* spp. isolated from clinical samples at the National AMR surveillance sites from January 2010 to December

2021 were included in this study. Only the first reported isolate per patient was included in the surveillance analysis.

The associated patient demographic information, clinical data, and microbiologic laboratory results were extracted from the national WHONET laboratory database software. The demographic variables included age, sex, nationality, clinical variables revealed the type of facility reporting the isolate (hospital/center/clinic), patient location, location type, specimen collection date, types of infection/specimen source, and microbiology variables revealed types of organism and antibiotic susceptibility testing results. The infection was considered as community-acquired if the patient presented at an outpatient setting (center, clinic), emergency department or urgent care center, or a clinic or outpatient department of a hospital. The infection was considered healthcare-associated if the isolate was reported from an inpatient setting (inpatient ward, ICU).

2.4 Bacterial identification

The participating centers used at least one commercial, automated system for identification of bacteria, including VITEK[®] (BioMérieux SA, Craponne, France), BD Phoenix[™] (Becton Dickinson, New Jersey, USA) and MicroScan WalkAway (Beckman Coulter, Brea, CA, USA). Only one lab relied on manual systems like API[®] (Analytical Profile Index, BioMérieux SA, Craponne, France) solely for identification.

2.5 Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed at the National AMR surveillance sites using at least one commercial, automated system for routine antimicrobial susceptibility testing. Only two laboratories used manual testing methods (disc diffusion/Kirby Bauer). All laboratories followed Clinical & Laboratory Standards Institute (CLSI) guidelines for antimicrobial susceptibility testing (75). The criteria of the susceptibility of tigecycline were adapted from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (76). Any *Enterococcus* spp. phenotypically resistant to either vancomycin, or teicoplanin, or both, was considered as vancomycin-resistant *Enterococcus* spp. (VRE). To assess the multidrug-resistant (MDR) phenotype of the isolates the standard definition by Magiorakos et al. (77) was used. To assess the extensively drug-resistant (XDR) and pandrug-resistant (PDR) phenotypes, a slightly modified version of the standard definition by Magiorakos et al. (77) was used. Magiorakos' et al. definitions for XDR and PDR phenotypes for *Enterococcus* spp. includes 11 antimicrobial categories with 17 antibiotic agents. For technical reasons, associated costs, and local formulary requirements, participating laboratories would not routinely test all 17 antibiotics, i.e., some antibiotics were only very rarely (minocycline, meropenem) or not at all (doripenem) tested.

As such, the following, slightly modified definitions were used for "possible XDR" and "possible PDR" isolates (modifications highlighted in *italics*):

- **“Possible XDR”**: Non-susceptibility to at least one agent *routinely tested by clinical labs* in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories).
- **“Possible PDR”**: Non-susceptibility to all agents *routinely tested by clinical labs* in all antimicrobial categories (i.e., no agents were tested as susceptible for that organism).

2.6 Statistical tests

Significant temporal trends for antimicrobial resistance were assessed if at least five years of data were available to perform such an analysis. Trend analysis was not done when <30 isolates per year were reported. Extended Mantel-Haenszel Chi-square test for trend was done using SPSS version 29.0.1.0. Statistically significant differences in mortality among patients admitted in the intensive care unit (ICU) were assessed and $p < 0.05$ was considered significant. To assess differences in the length of stay between those patients with and without VRE, we performed a weighted log-rank test, and a $p < 0.05$ was considered statistically significant.

3 Results

3.1 Distribution of reporting sites for national AMR surveillance

The UAE national AMR surveillance program was initiated in 2010 in the Abu Dhabi Emirate with 6 hospitals and 16 centers/clinics enrolled. Additional sites were recruited over the years, starting with 22 participating sites located only in the Emirate of Abu Dhabi in 2010, which is the first year during which the study was initiated, and reaching in 2021 a total of 317 surveillance sites, including 84 hospitals and 233 centers/clinics and representing all seven Emirates of the country. [Figure 1](#) represents the distribution of reporting sites by Emirate from 2010 to 2021.

3.2 Bacterial population

From 2010 to 2021, a total of 37,909 non-repetitive *Enterococcus* spp. were isolated from an equivalent number of patients over the surveillance period. [Figure 2](#) represents the number of *Enterococcus* spp. included per year.

3.3 Species distribution

Among the 37,909 *Enterococcus* spp. analyzed, *E. faecalis* was the most commonly reported species (81.5%), followed by *E. faecium* (8.5%), and other enterococci species (4.8%). The species distribution over the surveillance period is shown in [Figure 3](#) and the overall percentages over the study period are shown in [Supplementary Table 1](#).

3.4 Distribution of *Enterococcus* spp. patients by age, gender, nationality status, and emirate

Enterococcus spp. strains were mostly associated with adults ([Figure 4](#)). It is noteworthy that the proportion of inpatient and outpatient surveillance sites changed during 2010–2021. While in 2010 inpatient sites accounted for 67.5% of all reported isolates of *Enterococcus* spp., this percentage decreased to 31.8% in 2021, due to the enrollment of more outpatient sites over time, as compared to inpatient sites. Accordingly, during the same period (2010–2021), the percentage of *Enterococcus* spp. isolates from outpatient sites increased from 31.7% (2010) to 56.1% (2021). As all newborn and most pediatric samples likely originate from several inpatient sites, a “decrease” of percentage of infections in the newborn and pediatric population over time is observed, however this is a statistical artifact due to the change in proportions of sites over time.

Enterococcus spp. was more commonly found in females (61.2%), as compared to males (38.8%), with a predominance of younger females (age 15–44), which was not observed in the male patient population ([Figure 5](#)).

Among those patients for whom the nationality status was available ($n = 21,975$, 59.7%), 41.5% of these patients were UAE nationals, while 58.5% were expatriates. For the remaining 40.3% of patients the nationality status was missing. Non-nationals were from a total of 136 countries, most commonly from Asian and Arab countries (India, 8.7%; Pakistan, 6.7%; Egypt, 4.6%; Yemen, 3.7%; Syria, 3.6%; Jordan, 3.1%, others, 27.9%).

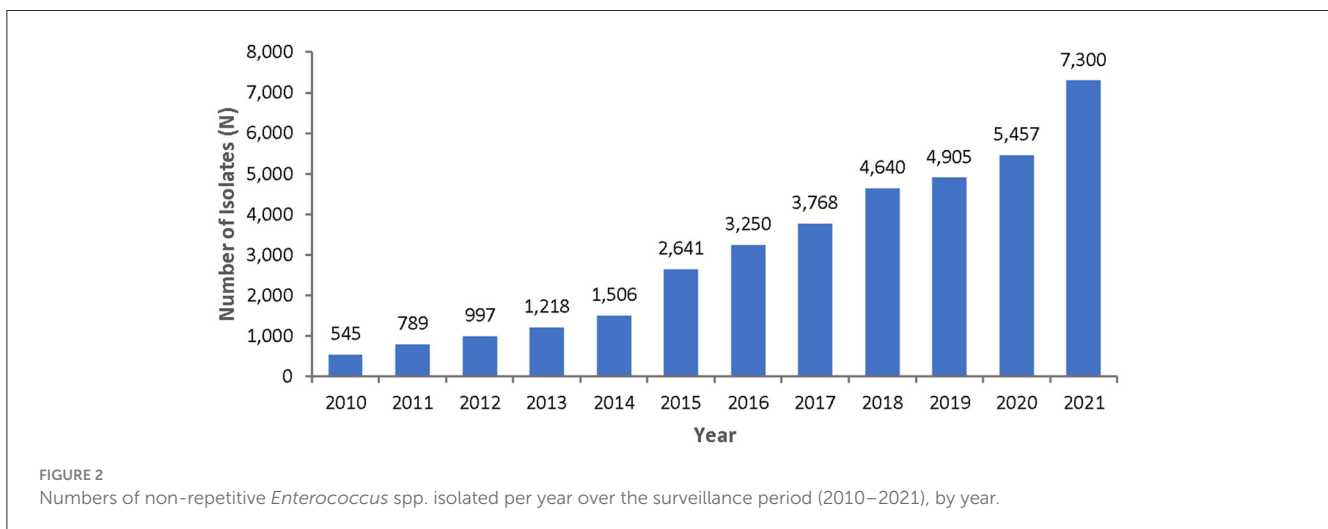
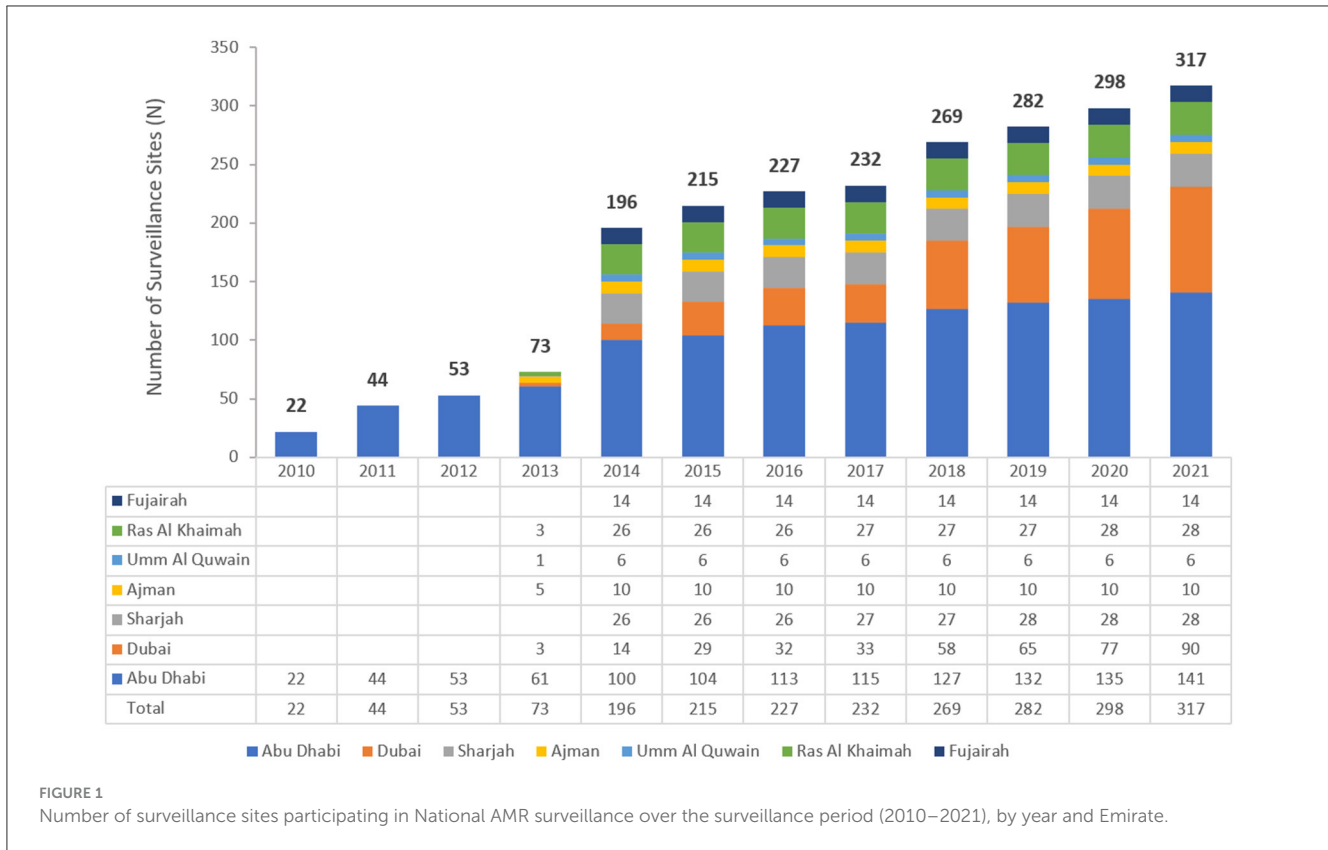
3.5 Distribution of *Enterococcus* spp. by sample type group

Most of the *Enterococcus* spp. strains were isolated from urine (60.9%), followed by soft tissue (23.0%, including wound swabs: 5.5%), blood (6.0%), and genital (5.5%, including vaginal swabs: 4.6%), and other groups. The distribution of *Enterococcus* spp. isolates by clinical sample type is shown in [Figure 6](#).

3.6 Distribution of *Enterococcus* spp. by location type (inpatients/outpatients/ICU), and department

Enterococcus spp. isolates/patients were primarily detected in community settings (outpatient clinics and emergency wards, 54.0%), whereas 46.0% were found in inpatient settings (including ICU: 10.7%).

By clinical specialty/department, *Enterococcus* spp. isolates/patients were associated with internal medicine (17.9%), obstetrics and gynecology (14.9%), surgery (12.7%), and various other disciplines (32.9%). For the remaining 21.6% the department was not known.



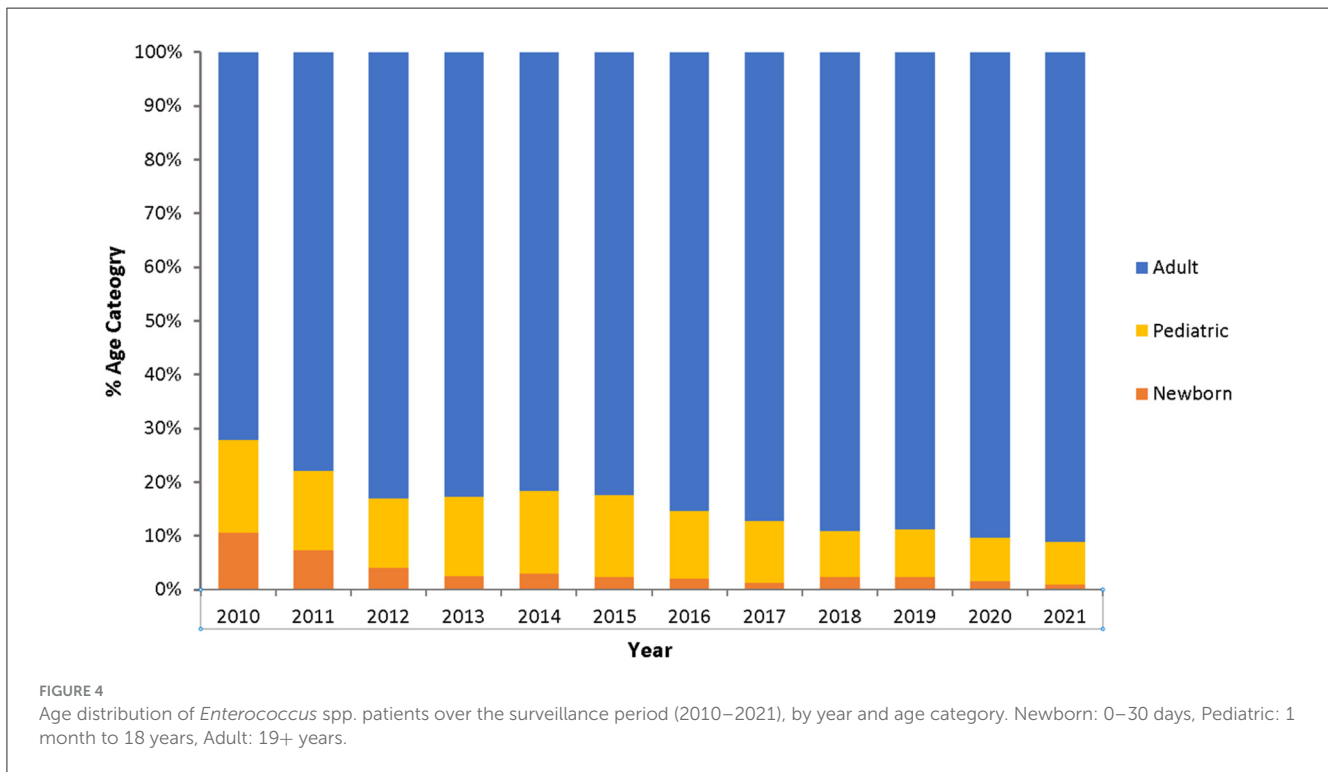
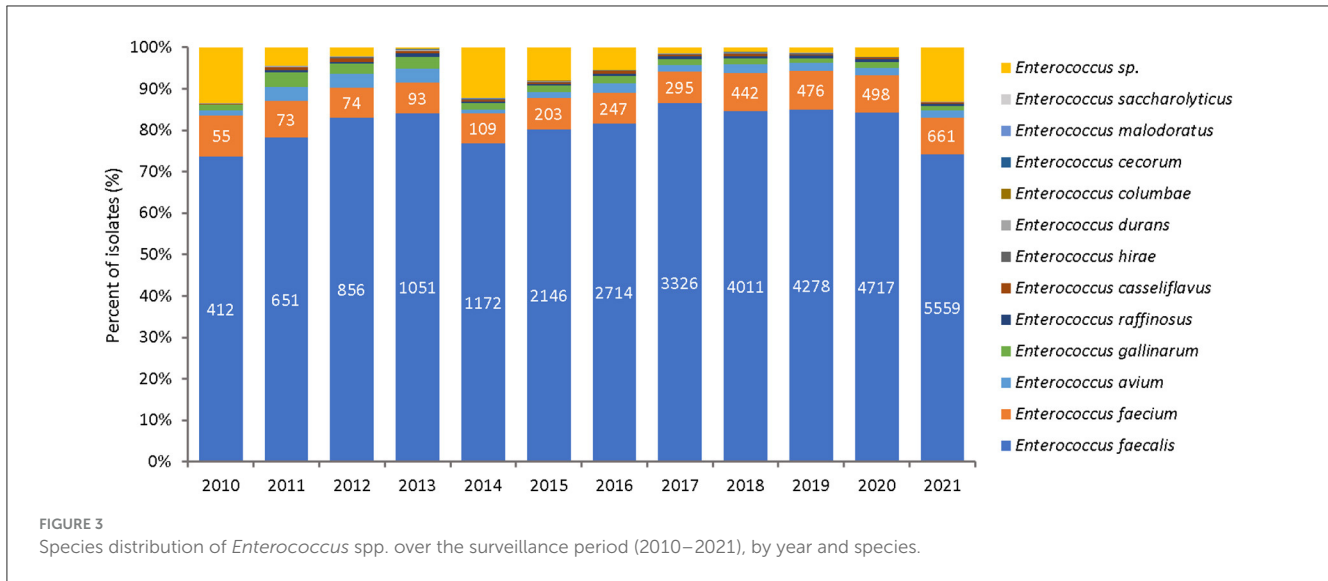
3.7 Trend of antimicrobial susceptibility profiles of *Enterococcus* spp.

The trend of antimicrobial sensitivity of all *Enterococcus* spp. recovered during the period of the study (2010 to 2021) is shown in Figure 7.

As shown in Figure 7, *E. faecium* showed an overall higher level of antimicrobial resistance during the study period (2010–2021), as compared to *E. faecalis*; in particular for aminopenicillins (ampicillin), fluoroquinolones (levofloxacin, moxifloxacin), aminoglycosides (gentamicin-HL, streptomycin-HL), and glycopeptides (vancomycin, teicoplanin).

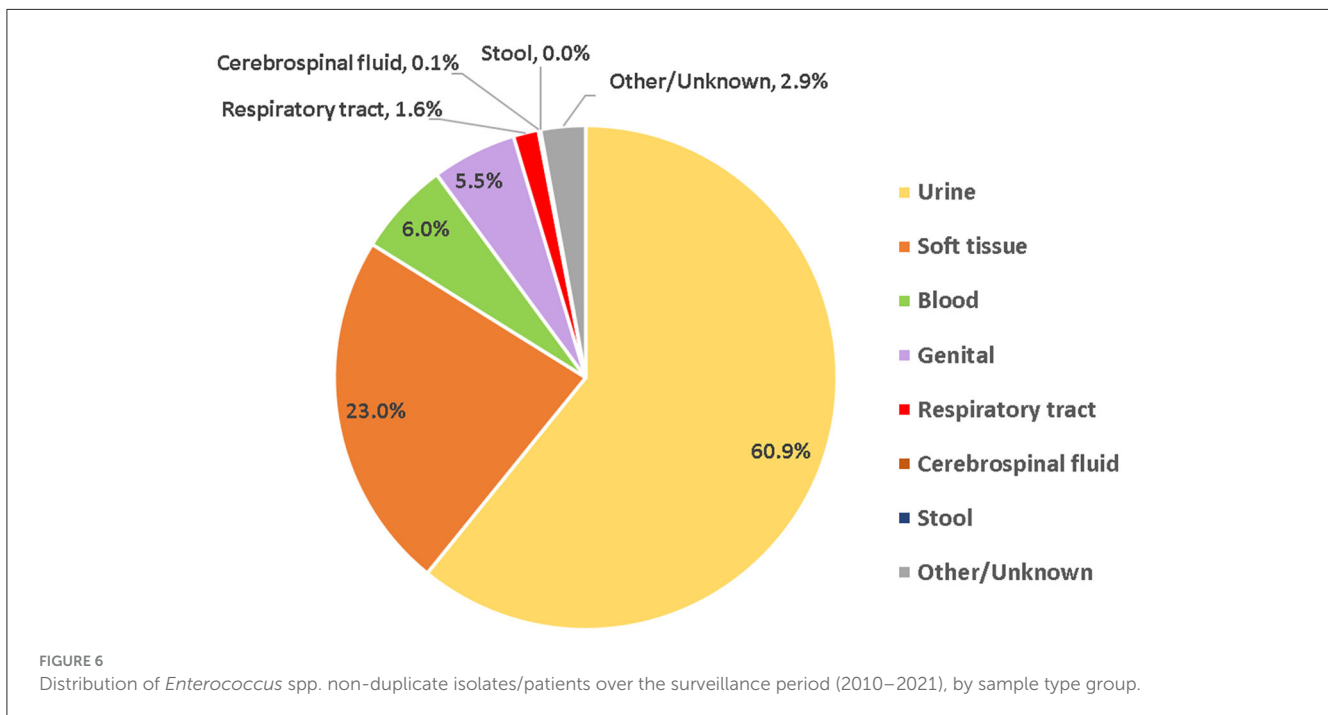
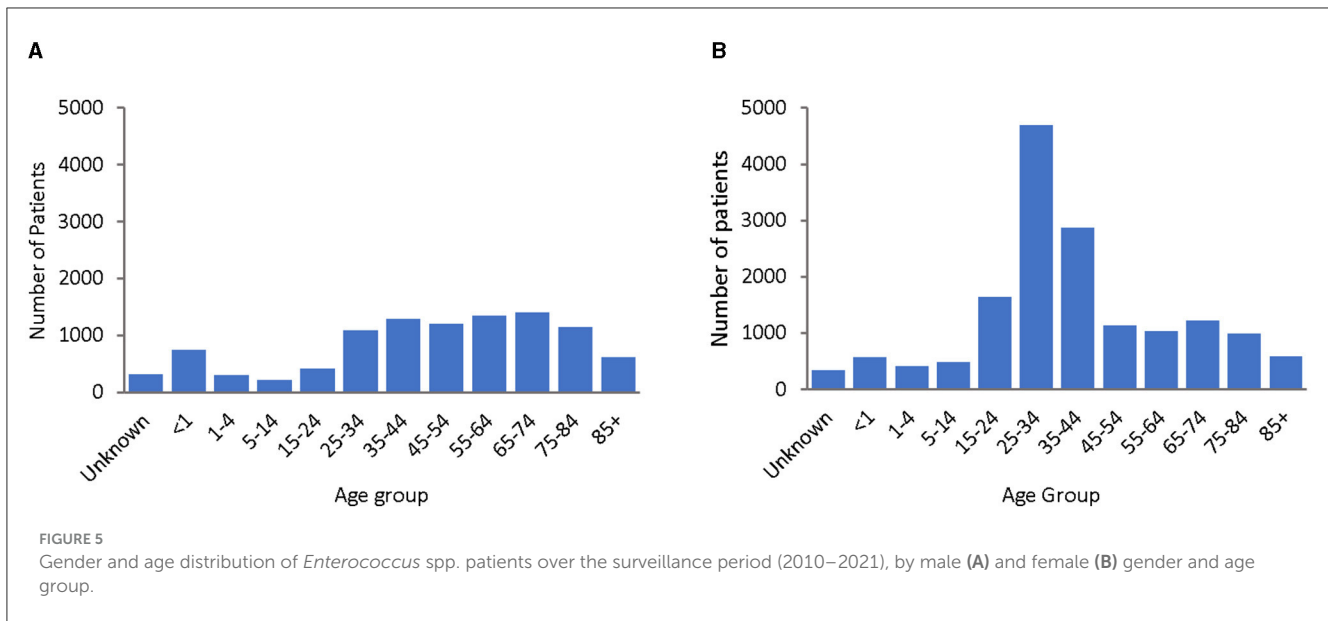
Resistance to **aminopenicillins** (ampicillin) ranged from 0–1.4% (*E. faecalis*, average: 0.8%) to 63.0%–77.7% (*E. faecium*, average: 70.5%). An increasing trend of resistance to ampicillin was observed for *E. faecalis* (from 0% in 2010 to 0.4% in 2021), and for *E. faecium* (from 63.0% in 2010 to 77.7% in 2021; $p < 0.001$).

Resistance to fluoroquinolones (levofloxacin, moxifloxacin) was in the range of 20%–28% (*E. faecalis*, average: 24.2%) to 42%–83% (*E. faecium*, average: 67.3%), showing a largely horizontal trend (n.s.). Susceptibility to fluoroquinolones was in the range of 68%–78% (*E. faecalis*, average: 72.3%) and 7%–45% (*E. faecium*, average: 25.6%) during the study period.



Resistance to high-level **aminoglycosides** (gentamicin-HL, streptomycin-HL) has not been observed in the UAE during the early years of AMR surveillance (2010–2015), however has emerged since then, with current (2021) levels at 12.5% and 2.5% (*E. faecalis*), and 12.6% and 2.2% (*E. faecium*), respectively. A statistically significant overall increase of resistance to streptomycin-HL has been observed for *E. faecalis*, from 0% (2012) to 2.5% (2021; $p < 0.001$), as well as for *E. faecium*, from 0% (2013) to 2.2% (2021), with a peak of 11.5% in 2018 ($p = 0.014$). Resistance to gentamicin-HL increased from 0% (2013) to 12.5% (2021) for *E. faecalis* ($p < 0.001$), and from 0% (2013) to 12.6% (2021), with a peak of 34.5% (2017) for *E. faecium* (n.s.).

Resistance levels to **glycopeptides** (vancomycin, teicoplanin) were very low for *E. faecalis* (0–2.2%, average: 0.9%), however as high as 0–14.2% (average: 8.1%) for *E. faecium*, with both antibiotics showing a slightly increasing trend over the study period (2010–2021) for both pathogens (statistically not significant, n.s.). Across all *Enterococcus* species, 1.5% of isolates were fully resistant to both, vancomycin and teicoplanin, 0.7% of isolates were resistant to vancomycin and susceptible to teicoplanin, while 97.4% of isolates were fully susceptible to both (co-susceptibility). For *E. faecalis*, 0.8% of isolates were fully resistant to both, vancomycin and teicoplanin (probably *vanA* phenotype), 0.4% of isolates were resistant to vancomycin and susceptible to teicoplanin (probably

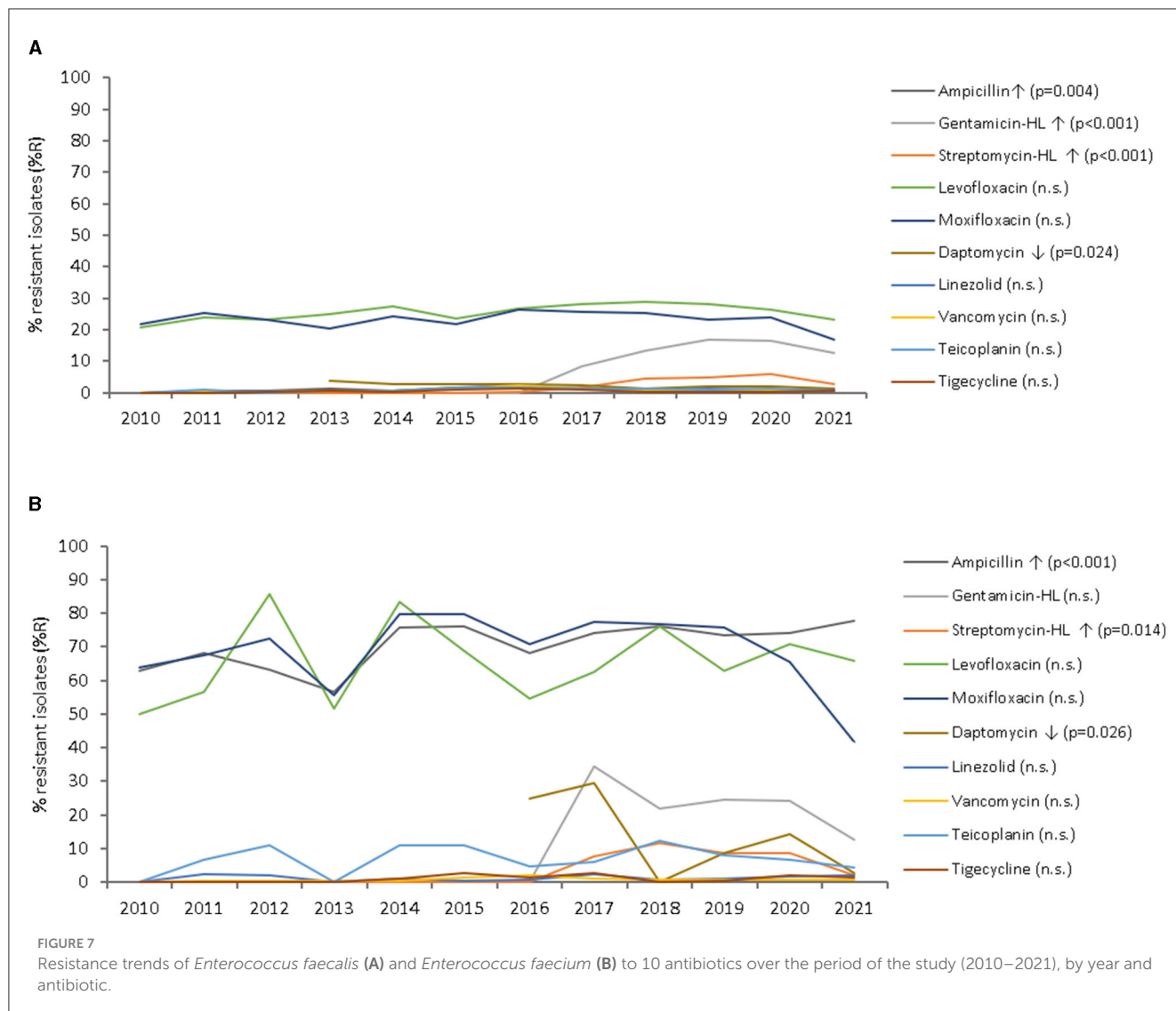


vanB phenotype), while 98.5% of isolates were fully susceptible to both (co-susceptibility). For *E. faecium*, 6.2% of isolates were fully resistant to both, vancomycin and teicoplanin (probably *vanA* phenotype), 1.9% of isolates were resistant to vancomycin and susceptible to teicoplanin (probably *vanB* phenotype), while 91.6% of isolates were fully susceptible to both (co-susceptibility).

Resistance data for **lipopeptides** (i.e., daptomycin) has been available since 2013 for *E. faecalis* and since 2016 for *E. faecium*. Both organisms have shown a decline in resistance to daptomycin. For *E. faecalis*, there was a significant decline in antimicrobial resistance from 3.8 to 1.4% between 2013 and 2021 ($p = 0.024$), and for *E. faecium* from 25.0 to 2.6% between 2016 and 2021 ($p = 0.026$).

Both **linezolid** and **tigecycline** remained highly susceptible over the study period for both pathogens (0–2.8 %R, 94–100 %S).

The impact of the Coronavirus Disease 2019 (COVID-19) pandemic on incidence of multidrug-resistant infections and antimicrobial resistance levels and trends has been subject to scientific debate (78–82). **Supplementary Figure 2** shows the number of non-duplicate isolates/patients reported to the national AMR surveillance system during the pre-pandemic period (2010–2019), as compared to the COVID-19 pandemic period (2020–2021). Results are presented for (a) all organisms (A), and (b) all *Enterococcus* spp. isolates/patients (B). The number of reported isolates (all organisms, A) increased during the pre-pandemic period (2010–2019) consistently, from 11,698 (2010) to 105,096



(2019), in line with the increasing number of surveillance sites being enrolled into the program during this pre-pandemic period. For 2020, this number then decreased to $n = 95,502$, and increased again to an all-time high ($n = 130,750$) in 2021, reflecting a short-term negative impact of COVID-19 on national AMR surveillance reporting. The number of isolates reported for *Enterococcus* spp. (B) increased consistently during the whole study period (2010–2021), suggestive of only a minor negative impact of COVID-19 on reporting rates for *Enterococcus* spp., including VRE.

As shown in Figure 7 and Table 1, the percentage of *E. faecalis* and *E. faecium* isolates resistant to antibiotics (%R) was lower, or did not further increase, for most antibiotics (with few exceptions) during the early years of the Coronavirus Disease 2019 (COVID-19) pandemic (2020 and 2021), as compared to the average resistance level during the pre-pandemic period (2010–2019). Resistance to glycopeptides was reduced by 0.3–0.4 (*E. faecalis*) and 2.7 (*E. faecium*) percentage points during COVID-19, as compared to the pre-COVID period. Similarly, resistance to moxifloxacin was reduced by 4.1 (*E. faecalis*) and 19.1 (*E. faecium*) percentage points during COVID-19, as compared to the pre-COVID period, whereas

levofloxacin showed a mixed pattern. For daptomycin, resistance was reduced by 0.3 (*E. faecalis*) and 5.9 (*E. faecium*) percentage points during COVID-19, as compared to the pre-COVID period.

3.8 Trend of MDR, XDR, and PDR phenotypical resistance profiles of *Enterococcus* spp.

The overall percentage of *E. faecalis* and *E. faecium* isolates that exhibited a multidrug-resistant (%MDR) phenotype, possibly extensively resistant (%possible-XDR), and possibly pandrug-resistant (% possible-PDR) phenotype over the study period is shown in Table 2, whereas Figure 8 presents the trends of such phenotypes over the study period. Overall, multi-, extensively-, and pandrug-resistant phenotypes were more frequently found in *E. faecium* (MDR: 42.7%, possible-XDR: 11.3%, possible PDR: 0.3%), as compared to *E. faecalis* (MDR: 13.9%, possible-XDR: 1.0%, possible PDR: 0.04%; Table 2). As shown in Figure 8, an increasing trend of %MDR and %possible-XDR isolates over the

TABLE 1 Percentage of *Enterococcus faecalis* and *Enterococcus faecium* isolates resistant to antibiotics (%R), during the pre-COVID-19 pandemic period (2010–2019), and the early COVID-19 pandemic period (2020–2021).

| Organism | Antibiotic | %R pre-COVID-19 (2010–2019)* | %R during COVID-19 (2020–2021)* | Difference (%R) |
|------------------------------|-----------------|------------------------------|---------------------------------|-----------------|
| <i>Enterococcus faecalis</i> | Ampicillin | 1.0 | 0.6 | −0.4 |
| | Gentamicin-HL | 10.2 | 13.9 | 3.7 |
| | Streptomycin-HL | 2.2 | 4.2 | 2.0 |
| | Levofloxacin | 26.7 | 24.4 | −2.3 |
| | Moxifloxacin | 23.6 | 19.5 | −4.1 |
| | Daptomycin | 2.0 | 1.7 | −0.3 |
| | Linezolid | 1.3 | 0.9 | −0.4 |
| | Vancomycin | 1.0 | 0.6 | −0.4 |
| | Teicoplanin | 1.2 | 0.9 | −0.3 |
| <i>Enterococcus faecium</i> | Ampicillin | 71.8 | 76.7 | 4.9 |
| | Gentamicin-HL | 19.9 | 19.5 | −0.4 |
| | Streptomycin-HL | 5.9 | 5.5 | −0.4 |
| | Levofloxacin | 65.6 | 67.9 | 2.3 |
| | Moxifloxacin | 73.6 | 54.5 | −19.1 |
| | Daptomycin | 13.6 | 7.7 | −5.9 |
| | Linezolid | 1.1 | 2.0 | 0.9 |
| | Vancomycin | 9.1 | 6.4 | −2.7 |
| | Teicoplanin | 7.6 | 4.9 | −2.7 |

*%R: weighted average across the respective period.

TABLE 2 *Enterococcus* species: percent MDR (%MDR), % possible XDR, and % possible PDR, as an average over the study period (2010–2021).

| Organism | Isolates (N) | MDR | Possible XDR | Possible PDR |
|------------------------------|--------------|---------------|--------------|--------------|
| <i>Enterococcus faecalis</i> | 30,893 | 4,287 (13.9%) | 307 (1.0%) | 12 (0%) |
| <i>Enterococcus faecium</i> | 3,226 | 1,376 (42.7%) | 365 (11.3%) | 11 (0%) |

study period has been observed for *E. faecium*, and for *E. faecalis*. For *E. faecium*, %MDR increased from 20.0% (2010) to 66.6% (2021; $p < 0.001$), and % possible-XDR increased from 0% (2010) to 5.9% (2021; n.s.). *Enterococcus faecalis* showed an increasing trend for % possible-XDR, from 0% (2010) to 0.4% (2021; $p < 0.001$).

3.9 Mortality rate

A subgroup analysis including the nine clinical institutions that reported mortality was performed. In these institutions, a total of 12,372 patients were associated with *Enterococcus* spp. (non-VRE) of whom 787 patients died (mortality rate: 6.4%), while a total of 127 patients were associated with *Enterococcus* spp. (VRE), of whom 24 patients died (mortality rate: 18.9%). The difference in mortality between VRE patients (18.9%) and non-VRE patients (6.4%) is statistically highly significant (RR 2.97, 95% CI 2.06, 4.29, $p < 0.001$).

3.10 Admission to intensive care unit

A total of 27,839 patients were associated with *Enterococcus* spp. (non-VRE) of whom 2,854 patients were admitted to ICU (ICU admission rate: 10.3%), while a total of 430 patients were associated with *Enterococcus* spp. (VRE), of whom 99 patients were admitted to ICU (ICU admission rate: 23.0%). The difference in ICU admission rate is statistically highly significant (RR 2.25, 95% CI 1.88, 2.69, $p < 0.001$).

3.11 Length of stay

A subgroup analysis including those patients for whom the date of admission as well as the date of discharge was known was performed. For those patients who were associated with non-VRE *Enterococcus* spp. ($n = 3,824$) the median length of stay was 7 days, while for those patients who were associated with VRE *Enterococcus* spp. ($n = 715$) the median length of stay was 13 days (Supplementary Figure 3). The weighted log-rank test was done to assess the difference in length of stay (LOS) between patients infected with VRE and those infected with non-VRE. The data showed that there was a statistically significant difference in the length of stay between the two groups, Chi square 5.8, $p = 0.02$ (Supplementary Figure 4).

Based on a total of $n = 687$ patients with infections associated with VRE during the observation period (2010–2021), a total of 4,122 excess days of hospitalization were observed, attributable to

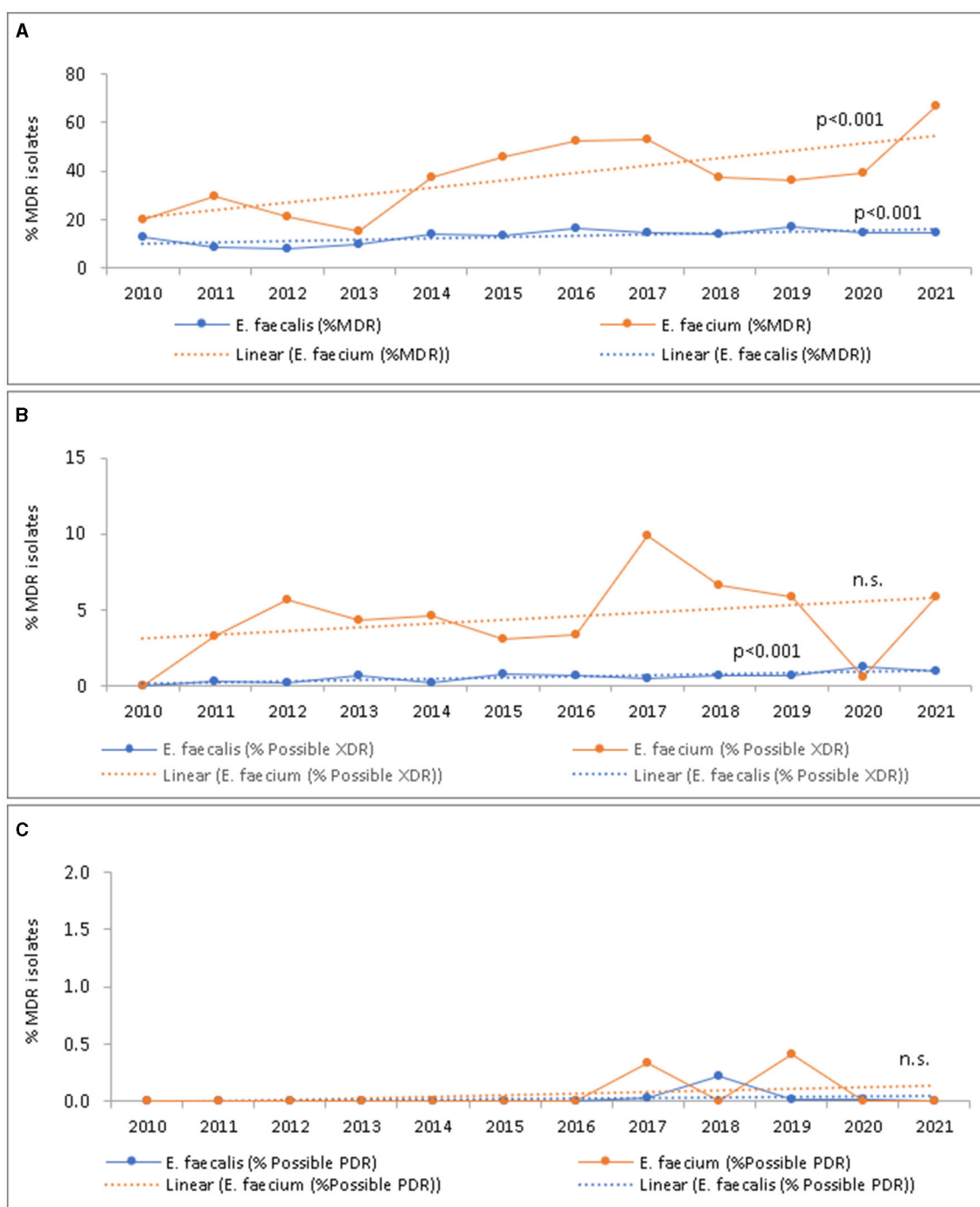


FIGURE 8 *Enterococcus* species: trend of percent MDR (% MDR) (A), % possible XDR (B), and % possible PDR (C) over the study period (2010–2021), by year.

VRE. For the year 2021 only, a total of 732 excess hospitalization days were observed, attributable to VRE.

4 Discussion

This is the first comprehensive analysis across the UAE that shows their relative significance and magnitude of *Enterococcus* spp. infections in clinical settings, their evolution

of antimicrobial resistance over time, and the association of VRE-enterococci with a negative health outcome. The present research utilized an extensive dataset collected over a considerable duration allowing precise observation of subtle variations in antimicrobial resistance among enterococci. This level of inclusive analysis has not been previously replicated in the country. The samples analyzed in this study consisted of non-repetitive enterococcal isolates of laboratory-confirmed identity and antibiotic resistance profile, indicating authenticity

of the microbiological material used and accuracy of the generated data.

The UAE accommodates a diverse community comprising more than 200 nationalities, out of which 136 are represented in this study population. Emirati nationals make up approximately 10% of the overall population, highlighting the UAE's status as one of the countries with a significant expatriate presence. Among the expatriate groups in the UAE, Indians and Pakistanis represent the largest segments, accounting for 27.5 and 12.7% of the total population, respectively (83). However, our results show that about 41.5% of *Enterococcus* samples were recovered from Emirati nationals, while the other 58.5% were expatriates. This can partially be explained with the higher rate of healthcare utilization and more comprehensive health insurance coverage among Emirati nationals.

In our study, among expatriate groups, also Indians and Pakistanis represent the largest segments, accounting for 6.1 and 4.5% of the study population. These proportions of the total sample pool should be interpreted cautiously, since 40.3% of the samples attributed from patients for whom their nationality was not coded in the data, hence not available. With the expatriate-inclusive and multicultural setting expected to prevail for the forthcoming years, the UAE may be an interesting niche to compare how trends of resistance in enterococci differ by nationality, shedding a light on cultural and social factors contributing to resistance in a multidisciplinary research perspective, as previously suggested (84, 85). However, given that a massive 40.3% of our samples originated from patients with unknown nationality, this investigation could not be realized with our data, but remains tempting to explore.

Moreover, the majority of patients (57.8%) from whom samples for the study were recovered were residents of the Emirate of Abu Dhabi, which also included the majority of participating centers (44.5%). Obviously, this conforms with the fact that Abu Dhabi was the first Emirate to start AMR surveillance, and it also is the largest Emirate in terms of area, where it occupies over 80% of the nation's land. However, Dubai, rather than Abu Dhabi, is the most populated Emirate, and samples from Dubai residents accounted for a much lower 24.1% only of those analyzed in this study. As such, these results must be cautiously interpreted.

As shown in Figure 3 and Supplementary Table 1, most recovered species were *E. faecalis* (81.5%), followed by *E. faecium* (8.5%). The remaining proportion was formed collectively from ten other species (4.8%) or has not been identified to the species level (5.3%). The species distribution resembles the historical situation in Europe three to four decades ago, when *E. faecalis* dominated all other species by far. Since then, in Europe *E. faecium* has gained a more important position within etiologically relevant enterococcal species, potentially due to the appearance of more virulent and/or environmentally stable strains (2, 49). Because of the more complex resistance pattern in *E. faecium*, this development has negative consequences in terms of efficient antibiotic therapy regimens.

Although there is frequent exchange of humans and goods between Europe and the UAE, the shift among enterococcal species has not been recorded in the latter, indicating the presence of local factors that stabilize the local species distribution among enterococci (48).

Enterococcus spp. strains were mostly associated with adults, while the percentage of isolates recovered from newborn and pediatric patients declined from 2010 to the end of the study period (Figure 4). As this finding has been observed similarly for several other pathogens under enhanced AMR surveillance in the UAE it is understood that this rather reflects a general demographic trend among the UAE (patient) population and is not particularly associated with *Enterococcus* infections.

Most of the *Enterococcus* spp. strains were isolated from urine (60.9%), followed by blood (6.0%), wound swabs (5.5%), and vaginal swabs (4.6%). In each case, the causative role of the isolates is debatable. In urine and vaginal swabs, enterococci represent parts of the physiological microflora, in most samples. In skin and intraabdominal wounds, enterococci again could be part of the local flora or, alternatively, could aggravate the situation in mixed species infections (86), but an independent causative role has not been demonstrated (87, 88). In many publications, the mere presence of enterococci in such wound samples is equated with a causative role (11), which is not acceptable in the light that the Koch postulates remain to be fulfilled for mixed species infections.

This differs from their responsibility in infections at normally sterile sites, such as endophthalmitis or periprosthetic infections—however, only a minority of isolates result from such sites in the present study. Still in blood cultures, enterococci could be contaminants from the skin microflora or could be involved in transient bacteremia as a result from intestinal translocation processes.

Without clinical details from the patients, neither the general number of isolates nor their association with specific materials necessarily reflect their etiological importance—a qualification that applies to all epidemiological studies on enterococci.

Enterococcus spp. was more frequently found in females (61.2%), as compared to males (38.8%), with a predominance of younger females (age 15–44), which was not equally observed in the male patient population (Figure 5). The predominance of younger females could be explained by the fact that urinary tract infections are more common in females than in males, and *Enterococcus* spp. is a common cause of urinary tract infections in the UAE, with 60.9% of *Enterococcus* spp. isolates being recovered from urinary tract samples (Figure 6). However, enterococcal urinary tract infections are frequently associated with inserted catheters. It is not clear whether the young female patients were more frequently subject to catheterization than other female age groups or males in general.

The proportion of outpatient samples was about 54%, while the remaining 46% of samples were recovered from inpatient settings, including 10.7% from ICU patients.

The evolution of antimicrobial resistance of *Enterococcus* species over the course of this study demonstrated that enterococci in the UAE show either high levels or increasing long-term trends (2010–2021) of acquired resistance to several clinically important antibiotic classes, in particular fluoroquinolones, aminoglycosides (HL) and glycopeptides.

Resistance of enterococci to fluoroquinolones (levofloxacin, moxifloxacin) was between 17 and 29% for *E. faecalis* and between

42 and 83% for *E. faecium*, with both showing a horizontal trend. National AMR surveillance data from a neighboring country (Oman) reported for 2018 a susceptibility level for ciprofloxacin of 34.1% (*E. faecalis*) and 17.4% (*E. faecium*), for blood isolates, but results need to be interpreted with caution due to low sample size (70). Such high level of resistance of enterococci to fluoroquinolones are a concern for the management of urinary tract infections (UTI), especially in the light of the fact that fluoroquinolones (mainly ciprofloxacin) are still the most prescribed empiric antibiotic for common urinary tract infections in the UAE, and despite that national guidelines have been published that do not recommend fluoroquinolones for the empiric treatment of urinary tract infections, due to the high fluoroquinolone resistance levels observed locally for common urinary tract pathogens (89).

Resistance of enterococci to high-level (HL) aminoglycosides has not been observed in the early years of AMR surveillance (2010–2015) and emerged in 2016. Overall, an increasing trend of resistance is observed for high-level gentamicin for *E. faecalis* (from 0% in 2013 to 12.5% in 2021; $p < 0.001$) and *E. faecium* (from 0% in 2010 to 12.6% in 2021; n.s.; Figure 7). Similarly, high-level resistance to streptomycin increased slightly for both pathogens, *E. faecalis* (2010: 0%, 2021: 2.5%; $p < 0.001$) and *E. faecium* (2010: 0%, 2021: 2.2%; $p = 0.014$). The molecular background for this development is unknown. However, it could be genetically linked to the vancomycin resistance phenotype, which would explain a similar increase over time. Enterococcal high level gentamicin resistance associated to vancomycin resistance has been noted elsewhere in Asia (90, 91).

This study demonstrates that vancomycin-resistant (VRE) and glycopeptide-resistant (GRE) enterococci are still relatively rare in the UAE, although slightly increasing over time in prevalence and relative importance. The relatively low numbers of VRE isolates found in this study could perhaps partially be explained by the fact that routine VRE screening procedures seem to be not as widely implemented among participating sites as compared to other MDRO-screening procedures, e.g., for MRSA, CRE, or, more recently, *Candida auris*.

While phenotypically vancomycin-resistant enterococci (VRE) were found in only 1.8% of *Enterococcus* spp. isolates overall, prevalence of VRE (%VRE) was highest for *E. faecium* (8.1%), followed by *E. faecalis* (0.9%). An increasing trend of resistance to glycopeptides (%VRE) has been observed for *E. faecalis* (2010: 0%, 2021: 0.6%; n.s.) and *E. faecium* (2010: 0%, 2021: 5.8%; n.s.). For *E. faecalis*, vancomycin-resistance was usually very low (<1%), with a small peak in 2016 (2.2%). Teicoplanin showed similar resistance levels as compared to vancomycin, 0–1.7% (*E. faecalis*) and 0–12.4% (*E. faecium*), indicating the genomic presence of *vanA* as the responsible resistance genes in the majority of strains. Consecutively, resistance to teicoplanin followed the temporal trend already established for vancomycin resistance, i.e., from 0% (2010) to 0.6% (2021) for *E. faecalis* (n.s.), and from 0% (2010) to 4.3% (2021) for *E. faecium* (n.s.).

Lipopeptides (daptomycin) show an overall decreasing trend of resistance, from 3.8% (2013) to 1.4% (2021) for *E. faecalis* ($p = 0.024$) and from 25.0% (2016) to 2.6% (2021) for *E. faecium* ($p = 0.026$), which could be an attractive subject for further

investigation as to elucidate the underlying mechanisms. Available national AMR surveillance data from other countries in the GCC region is scarce. Saudi Arabia reported for 2017 an average 90–92% susceptibility level to vancomycin for both, *E. faecalis* and *E. faecium*, with considerable regional variation (52–100%) (69), and Oman reported for 2018 susceptibility levels of 99.1% and 90.7% for *E. faecalis* and *E. faecium*, respectively (70).

Current resistance levels of enterococci in the UAE for oxazolidinones (linezolid), glycylglycines (tigecycline), and lipopeptides (daptomycin) are genetically not associated to the van-genes (92, 93) and thus, fortunately remain very low (linezolid, <2.4%; tigecycline, <2.8%), or are even decreasing (daptomycin), which still provides alternative treatment options for severe infections caused by enterococci (94). While this situation is better as compared to problems in the treatment of VRE strains elsewhere there is still a need to keep monitoring the situation to prevent future more virulent strains causing problems (95).

The percentages of MDR-*E. faecalis* and MDR-*E. faecium* increased during 2010–2021 ($p < 0.001$). A similar increase of the percentages of XDR-*E. faecalis* ($p < 0.001$) and XDR-*E. faecium* (n.s.) was observed. This indicates that there is a small but increasing fraction among the *E. faecium* VRE strains for which little to none therapeutic options are left. So far, none of the reporting hospitals signaled severe problems with such strains. Yet, the present analysis will lead to specific warning notices for hospitals in the UAE. In addition, antiseptic measures and decolonization strategies (96–98) will be considered for their integration into local hospital regimens.

As already discussed in the scientific community for enterococci in general, there is conflicting data on the role of VRE in severe infections concerning their contribution to increased mortality (99–102), possibly since in many studies the net effect of the underlying severe disease(s) are not sufficiently taken into consideration. However, there are potentially more tenacious and/or pathogenic VRE clones which remain for extended periods in specific hospitals and as a consequence, are involved in nosocomial outbreaks (38–40). Our data indicates that VRE infections are potentially associated with poor clinical outcome, in particular mortality rate, ICU admission rate, and excess hospitalization. The overall mortality rate, according to our observations, was about 3.0-fold higher in VRE-patients compared to those associated with non-VRE. In addition, we were able to demonstrate that patients associated with VRE were 2.2-fold more likely to be admitted to ICU, and their median length of stay was increased by 6 days, as compared to patients with non-VRE. This indicates a potential causative role and association with poor clinical outcomes, and is consistent with other findings that indicated high mortality rate and poor outcomes in patients with VRE (41, 103) but contradicts other studies that have not found such an association (12, 104, 105).

The collateral impact of the Coronavirus Disease 2019 (COVID-19) pandemic on AMR surveillance and stewardship, incidence of multidrug-resistant infections and antimicrobial resistance levels and trends has been subject to scientific debate (78–82). On one hand, surges in COVID-19 cases—and associated consequences like abandonment of antibiotic

stewardship programs, high rates of antibiotic prescribing, and disorganization of patient care—were found to favor the spread of resistant bacteria. On the other hand, public health interventions implemented to control COVID-19—including patient lockdowns, universal masking, and reinforcement of hand hygiene—may provide the side-effect benefit of preventing bacterial transmission (78).

This study presents data from the UAE national AMR surveillance program, indicating a temporary negative impact of the COVID-19 early pandemic period (2020) on the total number of reported non-duplicate isolates/patients (all organisms), as compared to the pre-COVID-19 pandemic period (2010–2019), and 2021 (Supplementary Figure 2). The number of isolates reported for *Enterococcus* spp. (C) increased consistently during the whole study period (2010–2021), suggestive for an only minor impact of the COVID-19 pandemic on reporting rates for *Enterococcus* spp., including VRE.

Studies to date report heterogenous impacts of the pandemic on antibiotic-resistant bacteria. One review highlights a decreased incidence of healthcare associated infections caused by vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) relative to pre-pandemic levels (81). Yet in an analysis of microbiological data from 81 hospitals in the United States of America, infections due to MRSA, VRE, and multidrug-resistant gram-negative bacteria all spiked during local surges in COVID-19 cases (82). These conflicting reports suggest that impacts of COVID-19 on antibiotic resistance likely depend on the population, setting, and bacteria in question and may be highly context-specific (78).

This study presents data from the UAE, suggesting overall lower, or not further increasing, average levels of antibiotic resistance for *E. faecalis* and *E. faecium* against several clinically relevant antibiotics during the COVID-19 pandemic period (2020–2021), as compared to the pre-pandemic period (2010–2019; Figure 7, Table 1). *Enterococcus faecalis* showed a reduced average resistance level toward seven out of nine antibiotics (with the exception of HL-aminoglycosides) during the COVID-19 pandemic, as compared to the pre-COVID-19 period. *Enterococcus faecium* showed a reduced average resistance level toward six out of nine antibiotics (except for ampicillin, levofloxacin, and linezolid) during the COVID-19 pandemic, as compared to the pre-COVID-19 period.

5 Conclusion

Data are scarce in the UAE and whole MENA region for VRE-infections. Our data demonstrates that vancomycin-resistant (VRE) and glycopeptide-resistant (GRE) enterococci are relatively rare in the UAE, however, are showing a high, or increasing trend of resistance for several clinically important antibiotics classes, causing a concern for the treatment of serious infections caused by enterococci. This study also demonstrates that VRE are associated with higher mortality, increased ICU admission rates, and longer hospitalization, thus poorer clinical outcome, and higher associated costs in the UAE. We recommend the expansion of current surveillance techniques

(e.g., local VRE screening), stricter infection prevention and control strategies, and better stewardship interventions. Further studies on the genetic and molecular epidemiology of enterococci are needed to characterize in more detail the clonal types circulating in the UAE, and their association with antimicrobial resistance, health outcome, and outbreaks of healthcare-associated infections.

Data availability statement

The national AMR Surveillance database managed by the UAE Ministry of Health and Prevention (MOHAP) contains confidential health information, and as such can only be made available upon reasonable request from the UAE Ministry of Health and Prevention (<https://mohap.gov.ae/>).

Ethics statement

Ethical approval for this study was provided by the Ministry of Health and Prevention Research Ethics Committee (MOHAP/DXB-REC/J.J.J./No. 86/2023), Dubai Scientific Research Ethics Committee (DSREC-GL17-2023), and Abu Dhabi Health Research and Technology Ethics Committee (DOH/ZHCD/2023/1316).

Author contributions

JT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. NA: Funding acquisition, Project administration, Supervision, Writing—review & editing. HA: Funding acquisition, Project administration, Supervision, Writing—review & editing. The UAE AMR Surveillance Consortium: Data curation, Investigation. GM: Conceptualization, Methodology, Supervision, Writing—review & editing. CM: Conceptualization, Methodology, Supervision, Writing—review & editing. DE: Conceptualization, Methodology, Supervision, Writing—review & editing. AS: Conceptualization, Methodology, Supervision, Writing—review & editing. AP: Conceptualization, Formal analysis, Methodology, Supervision, Writing—original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2023.1275778/full#supplementary-material>

SUPPLEMENTARY FIGURE 1

Geographical distribution of *Enterococcus* spp. non-duplicate isolates/patients over the surveillance period (2010–2021), by Emirate.

SUPPLEMENTARY FIGURE 2

Number of non-duplicate isolates/patients reported to National AMR Surveillance program, UAE, 2010–2021, by year.

SUPPLEMENTARY FIGURE 3

Length of inpatient hospitalization (days) for non-VRE patients (A) and VRE patients (B), UAE, 2010–2021.

SUPPLEMENTARY FIGURE 4

Kaplan–Meyer curves for hospitalization duration (length of stay/LOS) of VRE patients vs. non-VRE patients, UAE, 2010–2021.

SUPPLEMENTARY TABLE 1

Enterococcus species distribution as overall percentages across the study period (UAE, 2010–2021).

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| 77 | Rania El Lababidi | Dept. of Pharmacy Services, Cleveland Clinic Abu Dhabi |
| 78 | Saeed Hussein | Erada Center for Treatment and Rehabilitation, Dubai |
| 79 | Stefan Weber | Purelab, Abu Dhabi |
| 80 | Sura Khamees Majeed | Al Gharbia Hospitals - Madinat Zayed Hospital |
| 81 | Syed Irfan Hussein Rizvi | Mediclinic City Hospital, Dubai |
| 82 | Timothy Anthony Collens | Tawam Hospital, Al Ain |
| 83 | Zahir Osman Babiker | Sheikh Shakhbout Medical City (SSMC), Abu Dhabi |