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Original Research

Antibiotic resistance rates in Enterococcus spp. in Turkey; a meta-analysis research

Meta-analysis of resistance in Enterococci in Turkey

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Abstract

Aim: Inappropriate use of antibiotics cause resistance to vancomycin (VAN) and other antibiotics, and infections with resistant enterococci have high mortality. The aim of this study is to reveal the resistance rate of enterococci in Turkey to VAN and the other antibiotics at antibiotic stewardship program by meta-analysis of the studies from various regions in Turkey.

Material and Methods: The clinical enterococci isolates from Turkey between 2007-2016 were evaluated according to inclusion criteria based on the PRISMA.

Results: Totally, 37 different data series of 33 articles were included in the study. Data between 2007 and 2016 were divided into two groups as Group-1; 2007-2011 and Group-2; 2012-2016. The differences in antibiotic resistance rates between Group-1 and Group-2 were analyzed. The pooled analysis of 9208 enterococci isolates revealed that the overall VAN resistance rate in enterococci in Turkey is 4.374%. The heterogeneity analysis of the study was determined as Cochrane-Q test (457.6370), I^2=91.91 and p<0.0001. When the group 1 (2007-2011) and group 2 (2012-2016) were analyzed separately, VRE rate between 2012 and 2016 was detected significantly higher than between 2007 and 2011 (6.531%, p<0.001 and 3.393%, p <0.000, respectively). Linezolid (LNZ) resistance rate was found as 0.835% in the 4478 enterococci isolates analyzed at the study. There was more than 3 fold increase (0.578%, to 1.846%) in LNZ resistance in Group-2-period.

Discussion: VRE rate in Turkey is still lower than the World's average, while it is close to the rates in European countries. In Turkey, there is a significant increase in resistance rates in enterococci to almost all the antibiotics.

Keywords

Antibiotic resistance; Enterococci; Meta-Analysis; Turkey

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Introduction

Enterococci, member of the gastrointestinal tract flora in human beings and animals, can also colonize in genitourinary system and biliary tract. They have been recognized as an important cause of infections such as urinary tract infections (UTI), wound infections, sepsis and endocarditis in human beings [1].

Vancomycin, discovered in the 1950s, is one of the main antibiotics used for serious gram-positive infections. Widely use of vancomycin in late 1970s for methicillin resistant Staphylococcus aureus (MRSA) infections is considered as the cause of development of vancomycin resistance in Enterococci (VRE) [2]. Prolonged length of hospital stay, broad-spectrum antibiotic use, increased numbers of immunocompromised patients are other important reasons for the increase in vancomycin resistance in the United States and worldwide [3]. It is also known that the use of avoparcin, a glycopeptide used to accelerate growth in animals in European farms, is also responsible for the increase in VRE [4]. The first glycopeptide-VRE resistance in the world was reported in 1988 by Uttley AHC et al.[4, 5]. Ten years later, VAN resistance was demonstrated first time in Turkey in *Enterococcus casseliflavus*, which was isolated from a child with malignant histiocytosis by Vural et al [6].

There are generally two mechanisms in the development of antibiotic resistance in *Enterococcus* species [7]. The first one is structural (intrinsic) and the second one is acquired resistance. Intrinsic resistance; naturally existed on chromosomes in enterococci, is responsible for resistance to beta-lactam antibiotics like penicillin and cephalosporin, also aminoglycosides and clindamycin. Acquired resistance is variable, but mostly occurred by mutations in the enterococcal DNA or transmitted by plasmids or transposons, and it is the prevalent one observed in recent years [7-9].

In the last 20 years, inadequate infection control measures and inappropriate use of antibiotics have led to the acquisition of significant antibiotic resistance in enterococci [10]. Therefore, determining resistance profile in enterococci obtained from clinical isolates is highly critical in determining treatment strategies. The goal of the present work is to reveal the resistance profile of *Enterococcus* spp. in Turkey.

Material and Methods

In this meta-analysis, antibiotic resistance status in clinical isolates of *Enterococcus* spp. in studies published between the years of 2007-2016 in Turkey was analyzed. For this purpose, statistical analysis was carried out by separating the data in the scientific studies according to the inclusion and exclusion criteria based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) flow diagram (Figure 1).

Data-search

For this purpose, the searches were performed by writing the words "*Enterococcus*", "Enterokok", "Vancomycin resistance", "Vankomisin direnci", "Turkey", "Turkiye" as the keyword to Google Scholar, PubMed, Web of Science, Turkish Medline and Higher Educational Institution of Turkey (YOK) thesis center databases.

Inclusion and exclusion criteria

Enterococcus species, isolated from various clinical specimens from adult patients in Turkey between the years 2007-2016, were included in the study.

The number of isolates tested, the number and the ratio of resistant isolates, the antibiogram method of at least one of the criteria of the Clinical and Laboratory Standards Institute (CLSI) and/or European Committee on Antimicrobial Susceptibility Testing (EUCAST), the minimum inhibition concentration technique used were required to be included in the study. Original articles which have at least ten isolate data, and with full text in Turkish or English were recorded. Other exclusion criteria are presented at Figure1.

Literature search and collection of data

Studies including *Enterococcus* spp., *Enterococcus faecalis* and *Enterococcus faecium*, were included in data pool. The author surname, date of publication, years of collection of isolates, number of isolates, number (n) and ratio (%) of resistant isolates, cities where the isolates collected were recorded. Disputes between the ones who gather work data were resolved through discussion.

Two groups were formed in the study according to the years of collection of the data; the first group included the years between 2007 and 2011 and the second group between 2012 and 2016.

Groups were classified according to the antibiotic stewardship program (ASP) of the US Centers for Disease Control and Prevention (CDC); group A: Ampicillin (AMP) and Penicillin (PEN), group B: Vancomycin (VAN), Linezolid (LNZ), group C: high level gentamicin (HLG) and high-level streptomycin (HLS), group U: Ciprofloxacin (CIP), Levofloxacin (LVX), and Tetracycline (TET). Other antibiotic groups were classified as Teikoplanin (TEC), Erythromycin (ERY), Imipenem (IPM), Moxifloxacin (MFX), Trimethoprim/Sulfamethoxazole (SXT) and Tigecycline (TIG) (Table 1, 2, 3).

Statistical analysis

Study design was created through the Medical Research Support (MedicReS) e-picos assistant program. The data included in the study was recorded in the Microsoft Office 2016 Professional Plus excel program. The data were sorted by years in excel program. Medcalc © software version 17.9.7 program was used for meta-analysis. Author surnames, total number of isolates, number of isolates resistant to antibiotics indicated in the ASP were transferred from excel to Medcalc © for analysis. During the analysis procedure, first, the ten-years-period data between 2007 and 2016 were obtained. Second, the period between 2007 and 2011 were classified as Group 1, 2012 and 2016 as Group 2, and then the change in antibiotic resistance rates was analyzed over five-year periods

Statistical test for heterogeneity was performed to measure the heterogeneity of data. According to this; $I^2 \leq 25\%$ heterogeneity was assumed to be insignificant and Fixed effect was used. $I^2 > 25\%$ heterogeneity was assumed to be significant; the study data were considered as nonhomogeneous and the random effect value was used. $p < 0.01$ was considered to be no need to add more studies, and $0.01 < p < 0.05$ was statistically significant but it was accepted that the results could change with new studies to be added.

A funnel plot was used to evaluate possible bias and the results were interpreted.

Results

In this study, 1205 articles were reached in accordance with the research criteria (Figure 1). After removing 228 duplicated articles from different databases, 997 studies were displayed. 762 of them were excluded after an evaluation process of the title, summary and manuscript of studies. Of these, 182 of 215 studies of which the full texts were reached were excluded from the study (Figure 1). As a result, 37 data series of 33 articles with antibiotic resistance in enterococci were taken into process of study. The majority of the work was done in İzmir (n:6) and Istanbul (n:5). Other studies were conducted in Ankara (n:4), Erzurum (n:3), Adana (n:2), Afyon (n:2), Balıkesir (n:2), Kahramanmaraş (n:2), Rize (n:2), Amasya (n:1), Isparta (n:1), Konya (n:1), Tokat (n:1) and Van (n:1). The highest and lowest VRE prevalence rates were in studies conducted in Izmir. As a result, meta-analysis of a total of 9208 isolates revealed that, overall VAN resistance rate in *Enterococcus* spp. in Turkey was 4.37% (95% CI: 2.91-6.11). The study heterogeneities were high and Cochrane Q test (457.63), I^2 = 91.91 and p <0.001 were found (Table 1). Also, VRE ratio was found to be 3.39 (95% CI: 1.94-5.22) and 6.53 (95% CI: 3.55-10.33) in Group 1 and Group 2 years, respectively. An increase in the resistance rates

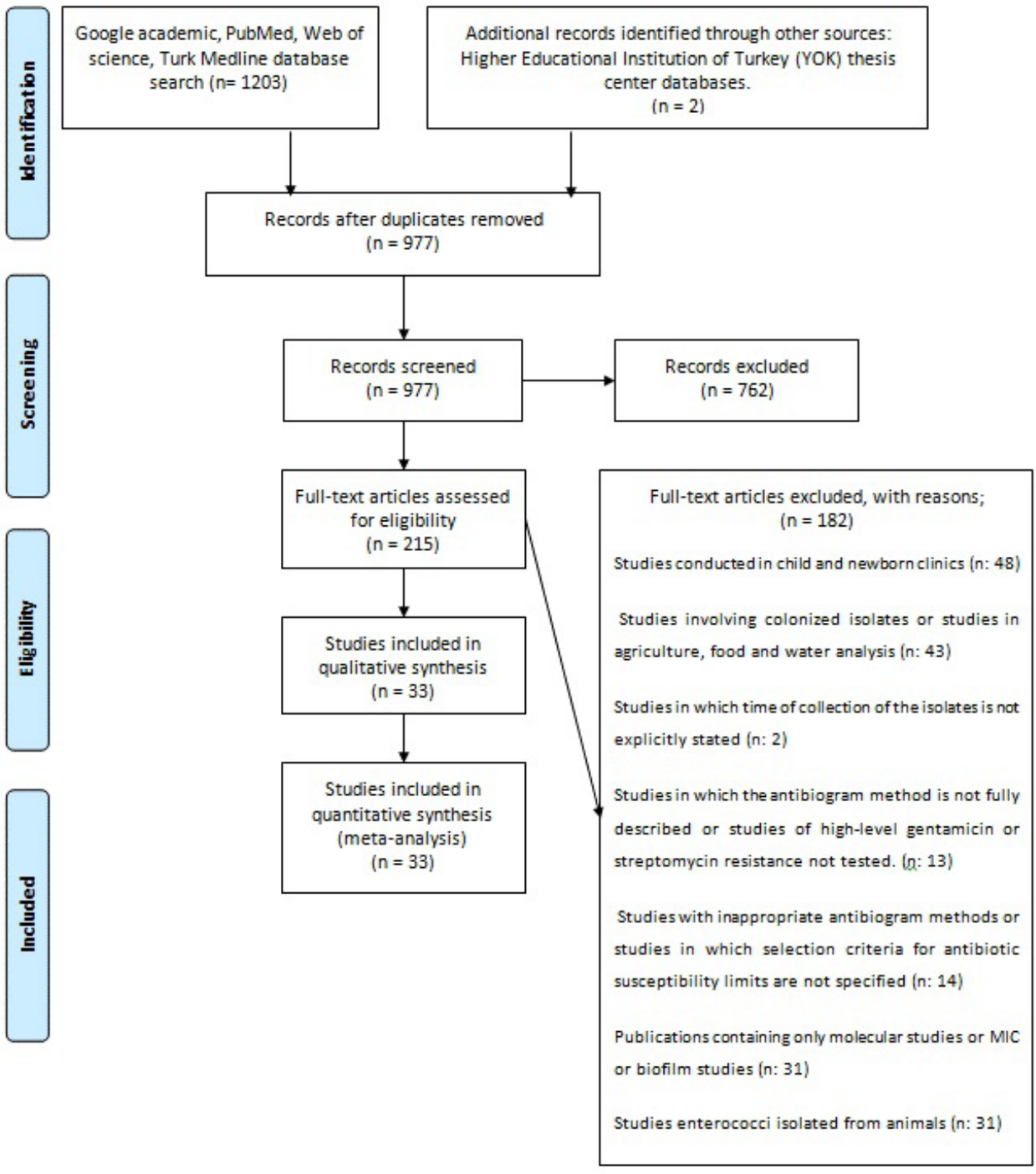

Figure 1. Flow chart for study selection and literature review. Summary of the literature search and study selection

Table 1. Meta-analysis of vancomycin resistance in *Enterococcus* spp. between 2007-2016.

STUDY NAME		SAMPLE SIZE	PREVALENCE OF VRE (%)	95% CI	WEIGHT (%)	
					FIXED	RANDOM
Kalayci [13]		293	0.00	0.00 to 1.25	3.18	3.06
Aktepe [25]		137	0.00	0.00 to 2.65	1.49	2.85
Aral [26]		158	4.43	1.80 to 8.91	1.72	2.90
Ozseven [27]		380	0.52	0.063 to 1.88	4.12	3.10
Iraz [28]		129	11.62	6.65 to 18.45	1.41	2.83
Erturk [29]		297	0.00	0.00 to 1.23	3.22	3.06
Altun [30]		179	2.79	0.91 to 6.39	1.95	2.94
Ergin [11]		47	21.27	10.70 to 35.66	0.52	2.29
Samlıoğlu [31]		151	13.24	8.28 to 19.71	1.64	2.88
Berktas [12]		113	19.46	12.62 to 27.97	1.23	2.77
Gozubuyuk [32]		93	8.60	3.78 to 16.24	1.02	2.69
Kose [33]		25	0.00	0.00 to 13.71	0.28	1.83
Incecik [34]		35	8.57	1.80 to 23.05	0.39	2.09
Baylan [35]		91	9.89	4.62 to 17.94	1.00	2.68
Guckan [36]		117	0.00	0.00 to 3.10	1.28	2.79
Kara [37]		10	0.00	0.00 to 30.85	0.12	1.15
Etiz [14]		536	14.73	11.84 to 18.02	5.81	3.15
Dinc [38]		100	0.00	0.00 to 3.62	1.09	2.72
Bilici [39]		98	4.08	1.12 to 10.12	1.07	2.71
Er [40]		54	5.55	1.16 to 15.38	0.59	2.38
Barıs [41]		111	3.60	0.99 to 8.97	1.21	2.77
Cicek [15]		10	0.00	0.00 to 30.85	0.12	1.15
Gulmez [42]		1248	2.24	1.49 to 3.22	13.51	3.22
Dagı [43]		306	9.15	6.16 to 12.95	3.32	3.06
Mete [44]		229	13.10	9.01 to 18.17	2.49	3.00
Agus 2011 [45]		1088	3.67	2.63 to 4.97	11.78	3.21
Agus 2012 [45]		1133	3.88	2.83 to 5.17	12.26	3.21
Agus 2013 [45]		1004	2.19	1.37 to 3.29	10.87	3.20
Kucukates [46]		30	0.00	0.00 to 11.57	0.34	1.97
Cetin [47]		147	13.60	8.51 to 20.22	1.60	2.87
Ozkaya [48]		22	4.54	0.11 to 22.84	0.25	1.73
Cakirlar [49]		464	13.14	10.20 to 16.56	5.03	3.13
Hanci [50]		64	4.68	0.97 to 13.09	0.70	2.49
Yenisehirli 2011-12 (Hospital) [51]		81	0.00	0.00 to 4.45	0.89	2.62
Yenisehirli 2012-13 (Hospital) [51]		75	0.00	0.00 to 4.80	0.82	2.58
Yenisehirli 2011-12 (Community) [51]		43	0.00	0.00 to 8.22	0.48	2.23
Yenisehirli 2012-13 (Community) [51]		38	0.00	0.00 to 9.25	0.42	2.15
Soner Yilmaz [52]		72	1.38	0.035 to 7.49	0.79	2.56
Overall results Total	Total (fixed effects)	9208	4.13	3.73 to 4.56	100.0	100.0
	Total (random effects)	9208	4.37	2.91 to 6.11	100.0	100.0
2007-2011 (Group 1)	Total (fixed effects)	5308	2.89	2.46 to 3.37	100.0	100.0
	Total (random effects)	5308	3.39	1.94 to 5.22	100.0	100.0
2012-2016 (Group 2)	Total (fixed effects)	3900	6.16	5.42 to 6.96	100.0	100.0
	Total (random effects)	3900	6.53	3.55 to 10.33	100.0	100.0

Table 2. Antibiotic resistance profile of *Enterococcus* spp. according to ASP.

Group	Antibiotics	Resistance Rate (%)								
		Total			Group 1 (2007-2011)			Group 2 (2012-2016)		
		Number of isolates (n)	Resistance rates (%)	95% CI	Number of isolates (n)	Resistance rates (%)	95% CI	Number of isolates (n)	Resistance rates (%)	95% CI
A	AMP	5258	53.79	44.22 to 63.22	4086	51.51	41.61 to 61.34	1172	59.20	40.71 to 76.44
	PEN	2431	66,48	53,25 to 78,51	1890	67,59	49,72 to 83,15	541	64,58	47,15 to 80,22
B	VAN	9208	4.37	2.91 to 6.11	5308	3.39	1.94 to 5.22	3900	6.53	3.55 to 10.33
	LNZ	4478	0.83	0.35 to 1.52	3324	0.57	0.19 to 1.16	1154	1.84	0.41 to 4.25
C	YDG	5079	43.96	37.69 to 50.33	3996	42.50	34.68 to 50.52	1083	47.84	38.81 to 56.94
	YDS	4397	45.75	39.56 to 52.00	3430	44.75	37.18 to 52.44	967	49.98	40.87 to 59.08
U	CIP	2947	53.70	43.78 to 63.47	1948	50.56	36.53 to 64.54	999	61.58	51.27 to 71.38
	LVX	542	41.87	27.03 to 57.49	542	41.87	27.03 to 57.49	NA	NA	NA
	TET	1682	52.21	43.79 to 60.56	934	45.69	37.22 to 54.29	748	67.53	60.44 to 74.23
Other	TEC	5057	3.40	1.70 to 5.65	4092	3.62	1.62 to 6.38	965	2.80	0.28 to 7.80
	ERY	2721	73.01	66.12 to 79.38	2099	71.97	63.87 to 79.41	622	77.42	63.87 to 88.53
	MFX	804	71.20	44.15 to 91.88	NA	NA	NA	653	56.61	38.82 to 73.55
	SXT	1315	90.29	75.94 to 98.54	662	84.83	55.76 to 99.47	653	98.18	96.84 to 99.06
	TIG	1119	0.35	0.092 to 0.78	NA	NA	NA	NA	NA	NA

AMP: Ampicillin, PEN: Penicillin, VAN: Vancomycin, LNZ: Linezolid; YDG: High Level Gentamycin, YDG: High Level Streptomycin, CIP: Ciprofloxacin, LVX: Levofloxacin, TET: Tetracycline, TEC: Teicoplanin, ERY: Erythromycin, MFX: Moxifloxacin, SXT: Trimethoprim/sulfamethoxazole, TIG: Tigecycline. n: Number, 95% CI: 95 % confidence interval, NA: Not analyzed. ASP: Antibiotic stewardship program

Table 3. Antibiotic resistance profile of *Enterococcus faecalis* according to ASP.

Group	Antibiotics	Resistance Rate (%)								
		Total			Group 1 (2007-2011)			Group 2 (2012-2016)		
		Number of isolates (n)	Resistance rates (%)	95% CI	Number of isolates (n)	Resistance rates (%)	95% CI	Number of isolates (n)	Resistance rates (%)	95% CI
A	AMP	4678	28.83	16.95 to 42.41	2433	17.05	6.56 to 31.16	2245	49.99	23.69 to 76.30
	PEN	795	45.90	25.03 to 67.56	579	37.63	13.84 to 65.16	216	64.82	32.14 to 91.16
B	VAN	4928	0.68	0.33 to 1.16	2683	0.57	0.17 to 1.20	2245	0.85	0.32 to 1.62
	LNZ	4026	2.18	1.40 to 3.12	1781	1.75	0.92 to 2.84	2245	2.87	1.38 to 4.87
C	YDG	4887	28.20	23.17 to 33.53	2642	21.77	15.23 to 29.11	2245	38.80	32.75 to 45.04
	YDS	7087	29.33	18.16 to 41.92	4950	23.29	10.11 to 39.89	2137	41.86	36.49 to 47.34
U	CIP	3795	35.93	27.19 to 45.16	1581	28.49	14.37 to 45.20	2214	44.50	32.91 to 56.40
	LVX	613	48.18	27.65 to 69.03	204	52.19	8.05 to 94.16	409	42.34	37.52 to 47.28
	TET	912	71.43	63.61 to 78.66	456	66.46	54.47 to 77.46	456	77.72	67.72 to 86.33
Other	TEC	4718	0.65	0.44 to 0.93	2611	0.50	0.27 to 0.85	2107	0.88	0.52 to 1.37
	ERY	995	58.73	48.34 to 68.74	610	53.77	40.27 to 67.00	385	69.26	55.01 to 81.85
	MFX	409	42.34	37.52 to 47.28	NA	NA	NA	409	42.34	37.52 to 47.28
	SXT	471	98.89	97.48 to 99.62	NA	NA	NA	409	98.75	97.14 to 99.58
	TIG	NA	NA	NA	NA	NA	NA	NA	NA	NA

AMP: Ampicillin, PEN: Penicillin, VAN: Vancomycin, LNZ: Linezolid; YDG: High Level Gentamycin, YDG: High Level Streptomycin, CIP: Ciprofloxacin, LVX: Levofloxacin, TET: Tetracycline, TEC: Teicoplanin, ERY: Erythromycin, MFX: Moxifloxacin, SXT: Trimethoprim/sulfamethoxazole, TIG: Tigecycline. n: Number, 95% CI: 95 % confidence interval, NA: Not analyzed. ASP: Antibiotic stewardship program

Table 4. Antibiotic resistance profile of *Enterococcus faecium* according to ASP.

Group	Antibiotics	Resistance Rate (%)								
		Total			Group 1 (2007-2011)			Group 2 (2012-2016)		
		Number of isolates (n)	Resistance rates (%)	95% CI	Number of isolates (n)	Resistance rates (%)	95% CI	Number of isolates (n)	Resistance rates (%)	95% CI
A	AMP	2184	91.57	88.54 to 94.17	1223	90.37	86.93 to 93.34	961	93.27	87.27 to 97.46
	PEN	492	93.21	86.23 to 97.86	439	93.95	86.50 to 98.55	53	91.02	62.30 to 99.72
B	VAN	2458	10.12	6.26 to 14.77	1497	9.72	5.21 to 15.45	961	10.91	4.33 to 20.00
	LNZ	2030	2.58	1.60 to 3.78	1069	1.72	0.66 to 3.27	961	4.11	2.95 to 5.45
C	YDG	2373	58.38	52.01 to 64.61	1412	56.52	46.74 to 66.05	961	59.74	53.86 to 65.48
	YDS	2098	65.20	56.99 to 72.99	1230	60.60	47.93 to 72.57	868	74.24	67.48 to 80.46
U	CIP	1814	72.94	62.89 to 81.92	876	61.94	45.36 to 77.20	938	85.60	75.30 to 93.48
	LVX	196	83.07	61.32 to 96.90	196	83.07	61.32 to 96.90	NA	NA	NA
	TET	792	41.95	28.28 to 56.28	371	26.07	18.36 to 34.62	421	63.80	59.18 to 68.29
Other	TEC	2373	9.59	5.64 to 14.44	1412	9.24	4.49 to 15.47	961	10.18	3.75 to 19.27
	ERY	865	91.51	86.12 to 95.67	513	90.70	82.37 to 96.55	352	93.20	85.75 to 98.04
	MFX	391	82.11	53.30 to 98.54	NA	NA	NA	391	82.11	53.30 to 98.54
	SXT	555	99.06	97.33 to 99.91	164	97.71	87.94 to 99.74	391	99.50	98.20 to 99.94
	TIG	NA	NA	NA	NA	NA	NA	NA	NA	NA

AMP: Ampicillin, PEN: Penicillin, VAN: Vancomycin, LNZ: Linezolid; YDG: High Level Gentamycin, YDG: High Level Streptomycin, CIP: Ciprofloxacin, LVX: Levofloxacin, TET: Tetracycline, TEC: Teicoplanin, ERY: Erythromycin, MFX: Moxifloxacin, SXT: Trimethoprim/sulfamethoxazole, TIG: Tigecycline. n: Number, 95% CI: 95 % confidence interval, NA: Not analyzed. ASP: Antibiotic stewardship programme.

was observed according to the years in which the isolates were studied. It is observed that the 95% CI: 3.55-10.33 confidence interval for Group 2 does not include the value of 3.39 which is the prevalence average of Group 1. It is also observed that the prevalence average value of 6.53 for Group 2 was not within the confidence interval of 95% CI: 1.94-5.22 for Group 1. Therefore, it was concluded that the averages increased within the last 5 years (Table 1).

In this study, antibiotic resistance status of *Enterococcus* spp. according to ASP was also analyzed (Table 2). Linezolid (LNZ) resistance rate, another antibiotic in ASP Group B, was found to be 0.83 (95% CI: 0.35-1.52) in 4478 analyzed enterococci isolates. In the five-year resistance increase analysis; the resistance rate in Group 1 increased from 0.57 (95% CI: 0.19-1.16) to 1.84 (95% CI: 0.41-4.25) in the last five years. Among the antibiotics analyzed, there was an increase in resistance rates to almost all antibiotics except penicillin and teicoplanin between Group 1 and 2 years (Table 2).

Enterococcus faecalis and *Enterococcus faecium* species were analyzed in the subgroups of this study. In the mixed prediction analysis of *E. faecalis* in 4928 isolates, the VAN resistance rate was found to be about 0.68 (95% CI: 0.33-1.16) (Table 3). The resistance rates of LNZ and TEC were 2.18 and 0.65, respectively, and almost all antibiotics showed a resistance increase according to the pre-determined five-year groups.

In *E. faecium* analysis, VAN resistance rate was 10.12 (95% CI: 6.26-14.77) in 2458 isolates (Table 4). There was a slight increase in VAN resistance in Group 2 compared with Group 1, but the increase in LNZ resistance was found to be higher.

Funnel plot analysis showed negligible asymmetry, asymmetry test did not show any publication bias.

Discussion

Enterococci may be a natural flora element in the gastrointestinal tract in human beings, but in some cases can lead to serious infections. As in the whole world, antibiotic resistance is increasing day by day in our country because of the prolonged and misuse of antibiotics, therefore active surveillance is important [9]. A remarkable increase has been observed in the prevalence of VRE from clinical samples in recent years [10]. Many studies were conducted in different regions of Turkey to demonstrate the increasing resistance of enterococci. In the systematic review and meta-analysis, we conducted in the light of these studies, 37 data series in 33 studies were analyzed.

In our meta-analysis, VRE prevalence was found to be 4.37 and was higher than 54% of studies in Turkey (Table 1). The highest VRE rates were found at the studies of Ergin et al. [11] from İzmir and Berktas et al. [12] from Van; the rates were 21.2 and 19.4, respectively. The rate of VRE was the lowest with 0% in the study of Kalaycı et al. from İzmir [13]. (Weight%: Random: 3.06) (Table 1). When the meta-analysis prevalence rate and the graph of the funnel plot analysis were examined, the two studies were the most distant studies from our results. The first of these studies was done by Etiz P. et al. in which a total of 536 enterococci strains were evaluated [14]. In this study, the VRE ratio was found to be 14.7% and the weight in our meta-analysis was 5.81 (Table 1). All isolates were hospital-derived and obtained from urine specimens. The reason for this high rate was that 97% of the VAN-resistant cases were caused by *E. faecium* and 30.9% of these strains had VAN resistance. In the second study, a total of 10 enterococci were isolated from 900 blood cultures by Copur-Cicek A. et al. from Rize, but no VAN resistance was found [15]. Since the number of enterococci in this study is low, the weight in our meta-analysis is low (0.12%). According to the result of a meta-analysis conducted in Iran in 2016, the prevalence of VRE in all enterococci was reported to be 9.4% [16]. In the literature review; VAN resistance rates in *Enterococcus* spp. were reported to be 11.2%, 8.5-12.5% and 9% in Germany, the United Kingdom and Italy, respectively [9, 16-22]. Although the overall vancomycin resistance rates in those studies were significantly higher than our results, it seems that the situation is not so pleasing for Turkey at all, because of the doubled-increase in resistance rates in the last five years.

According to data of Turkey in European Antimicrobial Resistance Surveillance Network (EARS-net) system, vancomycin resistance in *E. faecalisstrains* in Turkey were lower than 1.5% [23]. The National Antimicrobial Resistance Surveillance System (UAMDSS) data was last published in 2016; according to this, the vancomycin resistance rate of *E. faecalis* strains in Turkey in 2011, 2012, 2013, 2014, 2015 and 2016 was 0.6%, 0.6%, 0.9%, 3%, 3% and 1.5% respectively. Kilbas and Ciftci showed that the VAN resistance in enterococci in Turkey between the years 2000-2015 was 1% [9]. In the review of O'Driscoll and Crank, *E. faecalis* was reported to have the highest rate of VAN resistance in the USA with 8.5%, VAN resistance rates in *E. faecalis* were 1% in Europe, 3.1% in Latin America and lower than 0.1% in Canada and Asia-Pacific [20]. Both VRE rates and increase rates in vancomycin resistance in *E. faecalis* in our study, 0.57 in Group 1, 0.85 in Group 2 and 0.68 overall, were similar to the results of Europe.

According to EARS-Net system data, the glycopeptide resistance rate in *E. faecium* strains between 2003 and 2008 in Turkey was between 3 and 8%. By 2011, it was found that the VAN resistance ratio was more than doubled, reaching 17% according to UAMDSS data, and it was reported as 16.7% and 22% in 2012 and 2013, respectively [20]. According to our meta-analysis results, VAN resistance in *E. faecium* increased from 9.7% in 2007-2011 to 10.9% in 2012-2016, and the rate of increase was much more limited than the UAMDSS data. Similarly to our results, Kilbas and Ciftci also showed that VAN resistance in enterococci in Turkey between the years 2000-2015 was 9.5% [9].

When EARS Europe 2016 enterococcal resistance report is examined it is seen that VAN resistance rates in *E. faecium* are between 25-50% in the Balkan and East European countries such as Greece, Romania and Poland and Lithuania, and between 10-25% in Bulgaria, Italy and Croatia [20, 24]. In this report, it was given that *E. faecium* VAN resistance rates increased significantly in 7 out of 25 European countries between 2013 and 2016, a common feature of these countries is the fact that these countries have VAN resistance greater than 25%. VAN resistance rates in *E. faecium* were reported to be highest with 79.4% in USA, and it was 22.4% in Canada, 48.1% in Latin America and 14.1% in Asia-Pacific [20]. Turkey seems to be in a better place than European countries in terms of *E. faecium* according to these results.

Another antibiotic, LNZ, is one of the treatment options for gram positive bacterial infections and classified in Group B according to ASP. According to UAMDSS 2013 data, the linezolid resistance rates in our country were reported as 0.8% in *E. faecalis* and 1.1% in *E. faecium* [20]. However, according to our meta-analysis results; resistance rates in *E. faecalis* and *E. faecium* isolates were found to be 2.1% and 2.5%, respectively. Therefore, our results were found to be higher than the national surveillance system data of Turkey. The high rate in our results may be associated with that UAMDSS did not report the results between 2013-2016 period in which the LNZ resistance got higher in Turkey. According to the result of Kilbas et al., the ratio of LNZ resistance in enterococci isolates between 2000 and 2015 were 1.9% in *E. faecalis* and 2.4% in E. *faecium*, which were similar to our results [9].

In general, some limitations must be considered when interpreting our work and all other meta-analysis results. First; it may not be possible to reach the articles that have not yet been published, even though they are covered by the years of study we have planned, or the full text of some works may not be available for other reasons. Second; our study cannot show entirely the result of VRE in Turkey. Third; it should be kept in mind that different phenotypic and genotypic methods may be used in the studies analyzed. And the last one; publications that include both groups, showing changes in antibiotic resistance in five-year-periods within ten years, should be classified by discussing by two different researcher and the person who recorded the data.

Conclusion

All data revealed that the VRE rates can vary between regions, and even between neighboring countries. Our meta-analysis results showed that the VRE ratios in Turkey are close to the average of the European region; even it is much lower than the majority of European countries for E. *faecium*. It can be considered that Turkey is a very low endemic country in terms of resistance in *E. faecalis* and low/middle endemic country in E. *faecium*. However, the rapid increase in VAN resistance especially in *E. faecalis* is remarkable. So, changes in antibiotic resistance profiles should be kept under constant observation; standard guidelines should be established and shared with clinicians. Comprehensive infection control programs should be established, and moreover, existing ones should be developed and maintained.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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