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Antimicrobial susceptibility of anaerobic bacteria

Antimicrobial susceptibility profiles of anaerobic bacteria, isolated from human clinical specimens, within different European and surrounding countries. A joint ESGAI study

A.C.M. Veloo [a,*], H. Bahar Tokman [b], H. Jean-Pierre [c,d], Y. Dumont [c,d], S. Jeverica [e], R. Lienhard [f], A. Novak [g], A. Rodloff [h], V. Rotimi [i], I. Wybo [j], E. Nagy [k], on behalf of the ESGAI study group

[a] University of Groningen, University Medical Center Groningen, Department of Medical Microbiology and Infection Prevention, Groningen, the Netherlands
[b] Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Department of Medical Microbiology, Istanbul, Turkey
[c] Laboratoire de Bactériologie, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
[d] MIVEGEC, IRD, CNRS, Université de Montpellier, Montpellier, France
[e] Institute for Microbiology and Immunology, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia
[f] Analyses et Diagnostics Médicaux (ADMed) Microbiologie, La Chaux-de-Fonds, Switzerland
[g] University Hospital Center of Split, University of Split, School of Medicine, Split, Croatia
[h] Institute for Medical Microbiology and Epidemiology of Infectious Diseases, Leipzig University Hospital, Leipzig, Germany
[i] Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait
[j] Department of Microbiology and Infection Control, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel (VUB), Brussels, Belgium
[k] Institute of Clinical Microbiology, Faculty of Medicine, University of Szeged, Szeged, Hungary

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ABSTRACT

Objectives: Studies on the antimicrobial susceptibility profile of anaerobic bacteria are underrepresented in the literature. Within this study we aim to give an extensive overview of the differences in antimicrobial susceptibility profiles between different European and surrounding countries.
Methods: Minimal inhibitory concentration (MIC) data of different antibiotics were collected from 10 participating laboratories, representing an equal number of countries. All MIC's were determined using Etest, according to the protocol used by the participating laboratory. Anaerobic genera represented by at least 10 clinical isolates were included in the study.
Results: Each country tested different antibiotics, sometimes depending on the kind of infection and/or the anaerobic species isolated. All countries tested clindamycin and metronidazole. Resistance rates differed remarkably between the different countries. Especially in Kuwait, resistance was high for all tested antibiotics. Unexpected metronidazole resistance was observed for *Finegoldia magna* isolates, *Peptoniphilus* isolates and *Eggerthella lenta* isolates.
Conclusions: Due to the extensive differences in antimicrobial susceptibility profile of anaerobic bacteria isolated within different countries, we strongly recommend to perform this kind of study on a regular basis.
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1. Introduction

Anaerobic bacteria are a major part of the human commensal microbiota and play a role in a variety of human infections. When applying proper culture conditions, they are isolated from about 30% of the clinical specimens [1]. The most common isolated anaerobic genera are *Bacteroides* spp., the different genera of gram-positive anaerobic cocci (GPAC), *Prevotella* spp., *Parabacteroides* spp., *Porphyromonas* spp., *Fusobacterium* spp., *Actinomyces* spp., *Cutibacterium* spp. and *Clostridium* spp. [1,2]. The antibiotic susceptibility profile of anaerobic bacteria differs per country due to differences in antibiotic consumption [3]. Unfortunately, not all bacteriology laboratories are equipped with facilities to perform

* Corresponding author. University Medical Center Groningen, Department Medical Microbiology and Infection prevention, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands.
E-mail address: a.c.m.veloo@umcg.nl (A.C.M. Veloo).

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proper anaerobic culture of clinical specimens. Therefore, antibiotic susceptibility testing is not performed and treatment of patients suffering from an infection in which anaerobic bacteria are involved is often empirical.

Within this ESCMID Study Group for Anaerobic Infections (ESGAI) study we aim to provide insight in the current status of the antibiotic susceptibility profile, by showing the resistance rates of different anaerobic genera, isolated in different European and surrounding countries.

2. Material and methods

2.1. Bacterial strains

All included anaerobic strains were isolated in the period of one year, 2017, from a variety of clinical specimens, in the country of origin. Participating laboratories originate from: Split, Croatia; Kuwait City, Kuwait; Leipzig, Germany; Brussels, Belgium; Montpellier, France; Istanbul, Turkey; Ljubljana, Slovenia; Szeged, Hungary; La Chaux-de-Fonds, Switzerland and Groningen, the Netherlands. All strains were identified, at the laboratory of isolation, by Matrix Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS), using either the Biotyper system (Bruker Daltonics, Germany) or the Vitek MS system (bioMerieux, France). Only genera represented with at least 10 isolates were included.

2.2. Antibiotic susceptibility testing

All participating laboratories determined the MIC-values for the different antibiotics using Etest (bioMerieux, France and Liofilchem, Italy), according to their own guidelines. Resistance was interpreted using EUCAST breakpoints. For cefoxitin and tigecycline no EUCAST breakpoints were available, for these antibiotics CLSI breakpoints were applied. An overview of all tested antibiotics, including breakpoints, for each laboratory is given in Table 1. The participating laboratories each applied their own guidelines to determine which isolates were tested for certain antibiotics, therefore the antibiotics tested could depend on the kind of species isolated and/or the type of infection. MIC values of metronidazole for the genera *Cutibacterium* and *Actinomyces* isolates were excluded from the study because of natural resistance. Within the genus *Clostridium*, *Clostridioides* (*Clostridium) difficile* was excluded from this study, since its susceptibility profile, in general, is assessed for other antibiotics than the other anaerobic bacteria.

3. Results

3.1. Gram-negative anaerobic bacteria

The percentage resistance for the tested antibiotics, if performed in at least two countries, in the different countries is represented in Fig. 1. Further results, range, MIC_{50} and MIC_{90}, are shown in Table 1 of the supplementary data.

All countries determined the MIC-value of an antibiotic belonging to the class of penicillin's using Etest, except for France where antibiotic disks were used. Penicillin was tested by 7 different countries, but not for all gram-negative genera. The resistance for the *Bacteroides* group varied from 90.6% (68/75) in Turkey to 100% (n = 196) in Kuwait. The percentage resistance varied most within the genus *Prevotella* and was lowest among *Fusobacterium* isolates. Ampicillin was only tested in Germany, amoxicillin only in the Netherlands and piperacillin only in Kuwait. Percentage resistance within the *Bacteroides* group in these three countries was 73.4% (138/188), 96.5% (167/173) and51.6%) (101/196), respectively.

An antibiotic belonging to the class of penicillin antibiotics together with a beta-lactamase inhibitor (amoxicillin-clavulanic acid or piperacillin-tazobactam) was tested in all countries. Resistance for amoxicillin-clavulanic acid was relatively high (≈20%) for *Parabacteroides* isolates in France (21.7%, 5/23) and Slovenia (17.3%, 14/81), while it was relatively high for *Bacteroides* isolates in Kuwait and Belgium, 32.6% (64/196) and 21.3% (32/150), respectively.

Clindamycin was tested in all countries, with the exception of France where the MIC value for clindamycin was only tested on a selection of anaerobic isolates, while for *Bacteroides* isolates an antibiotic disk was used, yielding an insufficient number of isolates per genus. Resistance for clindamycin was roughly similar for *Bacteroides* in all countries (≈25%), with the exception of Belgium and Kuwait where the resistance was 41.9% (62/148) and 84.2% (165/196), respectively. This high rate of resistance for clindamycin was also observed for *Prevotella* isolates in Kuwait, namely 89.2% (64/72). *Fusobacterium* isolates showed the lowest resistance rate in all countries which tested a sufficient number of isolates.

Cefoxitin was tested in France, Kuwait and Turkey. *Bacteroides* isolates from Kuwait showed the highest resistance, 73.8% (145/196), while in France the resistance to cefoxitin was 7.8% (32/409). Resistance rates among *Parabacteroides* isolates from France were

Table 1
An overview of the tested antibiotics for each country.

Antibiotic	breakpoint >R mg/L (G-/G+)[a]	FR	SU	BE	DE	KW	TR	NL	SL	HR	HU
penicillin	0.5			x	x	x	x		x	x	x
amoxicillin	2/8							x			
ampicillin	2/8				x						
piperacillin	16					x					
amoxicillin-clavulanic acid	8	x	x	x		x	x	x	x	x	x
piperacillin-tazobactam	16				x		x			x	x
cefoxitin	64[b]	x				x	x				
imipenem	8		x		x	x	x		x	x	x
ertapenem	0.5									x	
meropenem	8			x		x	x	x		x	x
tigecycline	8[b]	x									
vancomycin	-/2	x								x	
tetracycline	8[b]										
clindamycin	4	x	x	x	x	x	x	x	x	x	x
metronidazole	4	x	x	x	x	x	x	x	x	x	x

Abbreviations: FR, France; SU, Switzerland, BE, Belgium; DE, Germany; KW, Kuwait; TR, Turkey; NL, the Netherlands; SL, Slovenia; HR, Croatia; HU, Hungary.
[a] Breakpoints differ for gram-negative (G-) and gram-positive (G+) anaerobic bacteria.
[b] CLSI breakpoints are used.

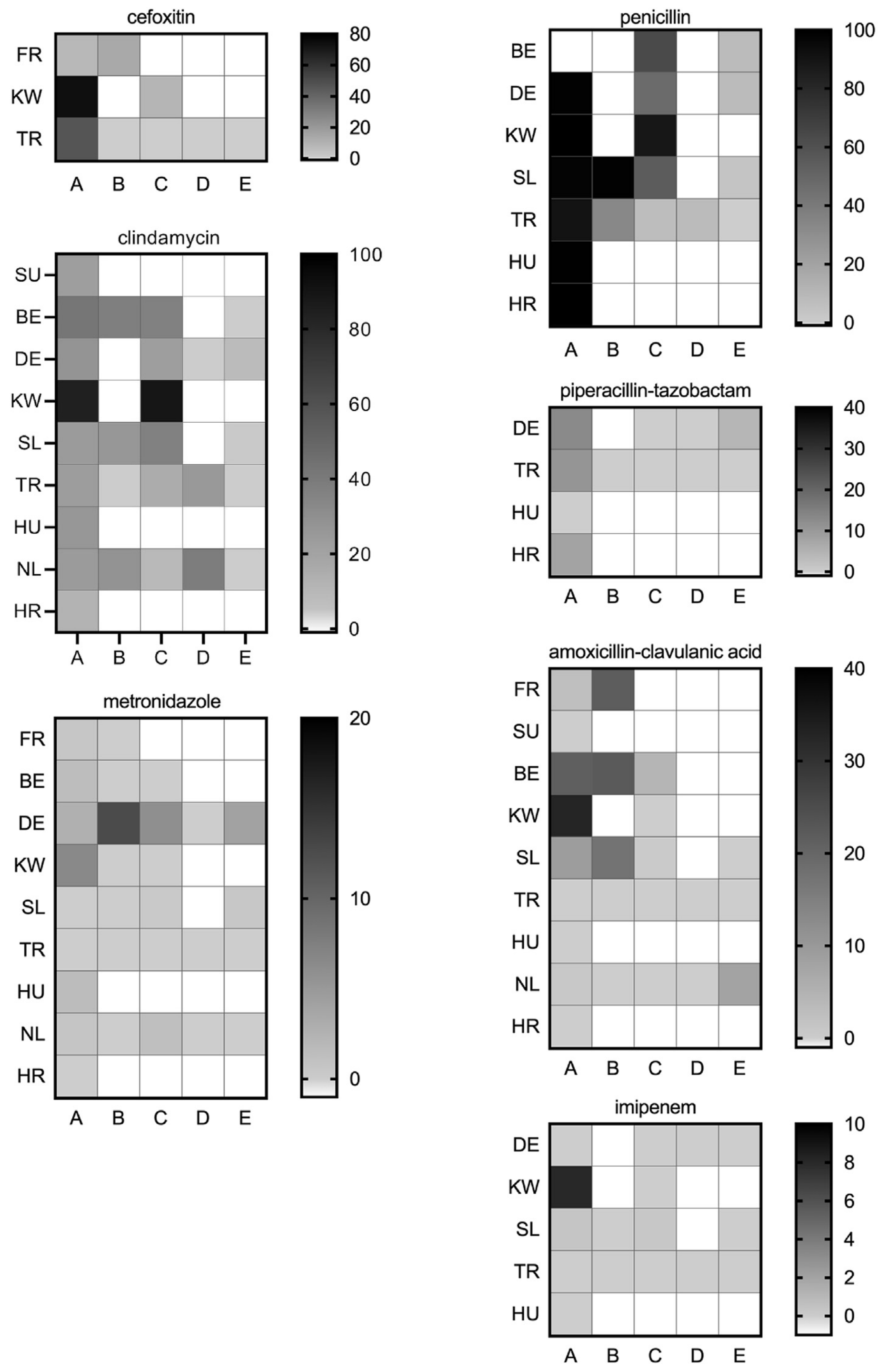

Fig. 1. Heatmaps of the percentage resistance per antibiotic of gram-negative anaerobic bacteria, shown in a grey-scale. A white block indicates that that specific antibiotic is not tested by the participating laboratory or the entity was present with <10 isolates. Abbreviations: Countries, FR: France; SU: Switzerland; BE: Belgium; DE: Germany; KW: Kuwait; SL: Slovenia; TR: Turkey; HU: Hungary; NL: the Netherlands; HR: Croatia. Anaerobic genera, A: *Bacteroides*; B: *Parabacteroides*; C: *Prevotella*; D: *Porphyromonas*; E: *Fusobacterium*.

13% (3/23), while none of the isolates of Turkey (n = 12) showed resistance.

As for clindamycin, metronidazole was also tested by all participating countries, even though Switzerland is missing due to an insufficient number of isolates tested with Etest within a genus. Resistance was highest in Kuwait and Germany. In Germany the resistance was relatively high among isolates of the genera *Fusobacterium* and *Prevotella*, 4.2% (1/24) and 5.9% (5/85). In Kuwait the resistance among *Bacteroides* isolates was 6.5% (13/196). Only in Turkey and Croatia, there were no isolates resistant to metronidazole.

Resistance to a carbapenem antibiotic was tested in all countries using Etest, except in France where antibiotic disks were used. The highest resistance rates were encountered in Belgium and Kuwait. The resistance for meropenem was 9.6% (19/196) for *Bacteroides* isolates from Kuwait and 4% (6/150) for Belgian isolates. In Kuwait and Slovenia also one *Prevotella* isolate showed resistance to a carbapenem. None of the clinical isolates from Germany, Turkey, Hungary, Croatia and the Netherlands showed resistance to a carbapenem antibiotic.

3.2. Gram-positive anaerobic bacteria

The percentage resistance, of gram-positive anaerobic bacteria which were isolated in 10 different countries, for the different antibiotics is presented in Fig. 2. More extensive data, range, MIC_{50} and MIC_{90}, are presented in Table 2 in the supplementary data.

Of the beta-lactam antibiotics, most countries tested penicillin (Fig. 2). In Germany, ampicillin was tested and resistance was found only among the peptostreptococci (11.1% (3/27); supplementary data, Table 2). In the Netherlands, amoxicillin resistance was encountered only among the clostridia (2.7% (1/37); supplemental data, Table 2). Piperacillin was only tested in Kuwait. Resistance was found among different GPAC genera. Resistance towards penicillin varied among the anaerobic genera (Fig. 2). In each country several genera showed resistance against penicillin, with a resistance of 35% (7/20) for peptostreptococci isolates in Kuwait being the highest.

As for the gram-negative anaerobic bacteria, amoxicillin-clavulanic and/or piperacillin-tazobactam were tested in several of the participating countries. Surprisingly, a relatively high percentage of resistance for amoxicillin-clavulanic was encountered for peptostreptococci in Kuwait and Slovenia, 45% and 8.6%, respectively. Also, *Eggerthella lenta* isolates from Germany showed a relatively high percentage of resistance for piperacillin-tazobactam, 12.5% (2/16).

Cefoxitin was only tested in Kuwait and Turkey. Isolates belonging to the GPAC genera, *Peptostreptococcus*, *Peptoniphilus* and *Finegoldia*, showed resistance for this antibiotic. *Cutibacterium* and *Clostridium* isolates were susceptible to cefoxitin.

Carbapenem antibiotics, imipenem, meropenem and ertapenem, were tested by about half of the participating countries (supplementary data, Table 2). Resistance among *F. magna* and *Peptostreptococcus* isolates was only observed in Kuwait. Of the *F. magna* isolates 5.5% (1/18) was resistant to imipenem and 5.5% (1/18) for meropenem. Meropenem resistance was also observed among 5% (1/20) of the peptostreptococci isolates. In Slovenia 1% (2/208) of the clostridia isolates showed resistance to imipenem.

Clindamycin was tested in all countries. *F. magna* and *Peptoniphilus* isolates from Kuwait showed the highest rate of resistance, 50% (9/18) and 53.8% (7/13), respectively. *Cutibacterium* isolates were most resistant in Kuwait and Turkey, 36.7% (4/11) and 32.8% (21/64), respectively. Resistance rates of almost 30% were encountered for clostridia isolated in Belgium (6/21, 28.6%),

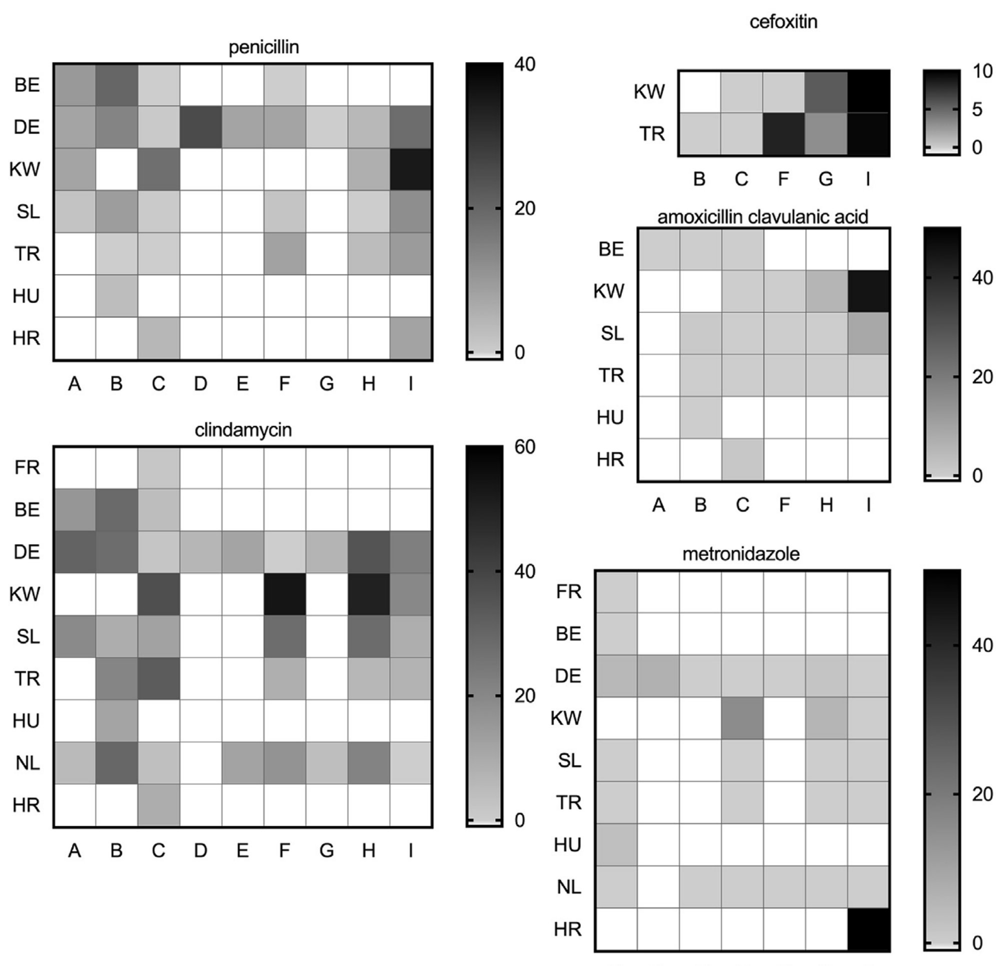

Fig. 2. Heatmaps showing the percentage resistance for the different antibiotics, for the gram-positive anaerobic genera. A white block indicates that that specific antibiotic is not tested by the participating laboratory or that the entity was present with <10 isolates. Abbreviations: countries, FR: France; SU: Switzerland; BE: Belgium; DE: Germany; KW: Kuwait; SL: Slovenia; TR: Turkey; HU: Hungary; NL: the Netherlands; HR: Croatia. Anaerobic genera, A: *Actinomyces*; B: *Clostridium*; C: *Cutibacterium*; D: *Eggerthella lenta*; E: *Anaerococcus*; F: *Peptoniphilus*; G: *Parvimonas micra*; H: *Finegoldia magna*; I: *Peptostreptococcus*.

Germany (12/43, 27.9%) and the Netherlands (11/37, 29.7%). *Actinomyces* isolates from Germany had the highest resistance rate, 30.8% (4/13), compared with 15.8% (3/19) in Belgium, 19.2% (36/188) in Slovenia and 5.2% (9/172) in the Netherlands.

As with clindamycin, metronidazole was also tested by all participants. None of the genera tested in France, Belgium, Slovenia, Turkey and the Netherlands showed resistance to metronidazole. In the other countries, resistance was observed among genera belonging to the GPAC group, among *Clostridium* isolates and in Germany among *E. lenta* isolates, 6.3% (1/16). Remarkable are the 50% (6/12) resistance of peptostreptococci isolates from Croatia and the 15.4% (2/13) resistance among *Peptoniphilus* isolates from Kuwait.

4. Discussion

In this study, we compared the antibiotic susceptibility profile of different anaerobic genera isolated in 10 different European and surrounding countries. As described in several other studies these profiles differ per country [3,4]. Klein et al. [5] analyzed the trends in antibiotic consumption between 2000 and 2015 and concluded that the antibiotic usage increased mostly due to an increase in consumption in low- and middle-income countries. According to the study by Klein et al. [5], Turkey has the highest antibiotic consumption per 1000 inhabitants per day. This fact is not reflected in the antibiotic susceptibility profile of anaerobic bacteria of Turkey compared with the other countries participating in this study. The highest resistance rates were observed for isolates of Kuwait, which actually is a country with a relatively low antibiotic consumption. Ulger-Toprak et al. [6] determined the antibiotic susceptibility of *Prevotella* isolates derived from different countries. They also showed that there is no relation between the antibiotic consumption and rates of resistance found in *Prevotella* isolates. These findings contradict what is described by Boyanova et al. [3], in which a relation was observed between resistance rates and antibiotic consumption.

Boyanova et al. [3] described the trends in antibiotic resistance in anaerobes over a few decades and concluded that the rates of resistance are diverse and dynamic. Our data shows that there are differences between countries and some remarkable resistance rates are notable. For example, in Germany and Turkey high resistance rates for piperacillin-tazobactam were observed and in Croatia 50% (6/12) of the peptostreptococci isolates were resistant to metronidazole. High resistance rates for amoxicillin-clavulanic acid were observed for *Parabacteroides* isolates in France (5/23, 21.7%) and Slovenia (14/81, 17.3%), the latter was also observed in a previous study from Slovenia by Jeverica et al. [7].

Bacteroides isolates showed a high rate of amoxicillin-clavulanic resistance in Kuwait. Especially in Kuwait the resistance among *Bacteroides* isolates for meropenem was high, 9.6% (19/196). In this country there seems to be a trend for an increase in meropenem resistance, from 1% in 1999 to 7.9% in 2007 [8], to 9.6% in this study. The high resistance rate of *Bacteroides* and *Prevotella* isolates, 84.2% and 89.2% respectively, for clindamycin was not observed in previous studies on the antibiotic susceptibility profiles on clinical anaerobic isolates from Kuwait [9], in which the antibiotic resistance profile was described per species. Also, in a multicenter study on the antibiotic susceptibility profile of *Prevotella* isolates this high rate of clindamycin resistance was not observed for Kuwait [6]. This might indicate that the resistance for clindamycin is increasing in this country. Among *Bacteroides* isolates from Belgium a relatively high resistance rate of clindamycin was encountered, 41.9% (62/148). This rate of resistance is similar to that described previously by Wybo et al. [10]. A decrease in clindamycin resistance in *Prevotella* isolates is observed for Turkey; 15.6% (15/96) in this study compared to 40.5% in the study by Ulger-Toprak et al. [6]. For other countries participating in both studies no differences were observed.

In general, metronidazole is the drug of choice to treat an infection in which anaerobic bacteria play a role [11], especially as gram-negative anaerobic bacteria are assumed to be susceptible for this drug. Nowadays, more and more metronidazole resistant *Bacteroides* and *Prevotella* clinical isolates, often multidrug resistant, are popping up [12–15]. From the data collected within this study we can conclude that the assumption of susceptibility for this drug for gram-negative anaerobic bacteria is not valid anymore. Resistance for metronidazole was observed among gram-negative anaerobic bacteria derived from all participating countries, except for the isolates from Turkey.

For the gram-positive anaerobic bacteria, isolates belonging to the genera *Cutibacterium*, *Actinomyces* or *Bifidobacterium* are, in general, considered to be resistant to metronidazole. We observed resistance among the GPAC genera, especially *F. magna*. Shilnikova et al. [16] encountered one *F. magna* isolate, which was not only resistant to metronidazole but also multidrug resistant. In a study by Novak et al. [17], in Croatia, metronidazole resistance was reported in 28.6% of the isolated gram-positive anaerobic cocci strains isolated in 2013. In this data set of clinical isolates from 2017, metronidazole resistance was observed among 50% (6/12) of the peptostreptococci isolates. The relatively high resistance rates for *Peptoniphilus* spp. in Kuwait (2/13, 15.4%) has not been described previously, either no resistance was encountered or isolates were included in under the general name gram-positive anaerobic cocci [8,9]. Also, no reports are available describing the metronidazole resistance in *E. lenta* observed among isolates from Germany. Resistance among *C.* non-*difficile* isolates is rare and can be observed among isolates of *Clostridium innocuum*, *Clostridium ramosum* and *Clostridium clostridioforme* [18]. We observed low rates of resistance within the clostridia isolates from Germany and Hungary. These were *C. innocuum*, *Clostridium bifermentans* and *Clostridium perfringens* isolates (data not shown).

Discrepancies were noted regarding the rate of resistance for different kind of antibiotics belonging to the same category. This can indicate that for some antibiotics the breakpoint is incorrect and needs evaluation.

For a number of genera less than 30 isolates were encountered, which can hinder the interpretation of the results presented in this study. Furthermore, no limitation was set for certain groups of patients.

This study shows that the antimicrobial susceptibility profile of anaerobic bacteria differs remarkably between different countries and that unexpected resistance patterns can be observed. This data set confirms that the antimicrobial resistance rates are highest among gram-negative anaerobic bacteria [19,20]. Considering the limited amount of data available, regarding the antimicrobial susceptibility profile of the different European and surrounding countries, we recommend to perform this study on a regular basis, preferably every 5 year, using the data available in the different laboratories. Furthermore, a standardization of antibiotics to be tested for anaerobic bacteria, depending on the isolate and known antibiotic susceptibility profiles, is proposed.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anaerobe.2019.102111.

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