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Abstract

Tigecycline is a broad-spectrum antimicrobial agent that has been approved for the treatment of skin and soft-tissue infections as well as intra-abdominal infections. The Tigecycline Evaluation and Surveillance Trial (TEST) is a global, longitudinal surveillance study established in 2004 to monitor the in vitro activity of tigecycline and comparator agents against key Gram-negative and Gram-positive pathogens. This report examines data obtained for 24 748 isolates collected across 24 European countries between 2004 and 2007. Tigecycline, meropenem and imipenem were the most active antimicrobial agents against most Gram-negative isolates including multidrug-resistant *Acinetobacter baumannii* (15.7% of the *A. baumannii* isolates in this study), extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* (8.5% of *E. coli*) and ESBL-producing *Klebsiella pneumoniae* (13.6% of *K. pneumoniae*). Only amikacin was active against >90% of *Pseudomonas aeruginosa* isolates (92.8% susceptible). Tigecycline, linezolid and vancomycin were the most active agents against Gram-positive agents across Europe between 2004 and 2007, with tigecycline displaying the lowest MIC₉₀ values (minimum inhibitory concentration for 90% of the organisms) against methicillin-resistant *Staphylococcus aureus* (26.5% of the collected *S. aureus* isolates), vancomycin-resistant *Enterococcus faecium* (15.7% of the *E. faecium* strains) and penicillin-resistant *Streptococcus pneumoniae* (9.3% of the *S. pneumoniae* strains). Longitudinal analysis showed no increase in tigecycline MIC values over the 4-year study period, whilst increased resistance was noted for several comparator agents.

1. Introduction

The prevalence of antimicrobial resistance among bacterial pathogens has increased to worrying levels in recent years, resulting in more complicated treatment challenges and increased healthcare burdens [1,2]. Novel resistance mechanisms have evolved that can counter the effects of newer antimicrobial agents, such as the development of metallo- β -lactamases with activity against carbapenems [3]. The development of new antimicrobial agents active against emerging resistant pathogens is thus an essential process.

Tigecycline is a broad-spectrum antimicrobial agent and is the first member of a new class of antimicrobial agents, the glycylcyclines (derived from the tetracycline nucleus), to be made commercially available. Tigecycline is unaffected by most bacterial resistance mechanisms, including tetracycline resistance [4]. It is, however, susceptible to the multidrug efflux systems found in *Pseudomonas aeruginosa* and some *Proteus* spp. [5]. Tigecycline is active in vitro against diverse Gram-negative and Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and extended-spectrum β -lactamase (ESBL)-producing bacteria (including *Escherichia coli* and *Klebsiella pneumoniae*) [6]. Tigecycline is approved for the treatment of intra-abdominal infections and complicated skin and skin-structure infections [7].

This study reports on the antimicrobial susceptibility of a wide range of nosocomial and community organisms, including resistant pathogens, collected throughout Europe between 2004 and 2007 as a part of the Tigecycline Evaluation and

Surveillance Trial (TEST). Rodloff et al. [8] have previously reported on tigecycline activity in Europe, examining data from isolates collected in France, Germany, Italy, Spain and the UK between 2004 and 2006. This report expands on that study by incorporating isolates from these same five countries plus several other European countries, bringing the total number of participating countries to 24; data are also expanded to include 2007 isolates, bringing the number of studied isolates to 24 748.

2. Materials and methods

2.1. Collection of bacterial isolates

Bacterial isolates were consecutively collected between 2004 and 2007 from the following European countries (number of centres in parentheses): Austria (2); Belgium (7); Croatia (2); Czech Republic (3); Denmark (3); Finland (3); France (16); Germany (13); Greece (5); Hungary (5); Ireland (4); Italy (21); Latvia (2); Lithuania (1); Norway (1); Poland (1); Portugal (1); Slovak Republic (1); Slovenia (2); Spain (9); Sweden (4); Switzerland (2); The Netherlands (2); and the UK (4). Not all centres contributed isolates in all years.

Participating laboratories annually provided up to 200 isolates for extended susceptibility testing. Isolates were collected from inpatients and outpatients with community-acquired or nosocomial infections where the pathogen collected was identified as the probable infecting organism. All body sites were considered acceptable sources for collection, including blood, respiratory tract, intra-abdominal material, wounds and urine (accounting for no more than 25% of all isolates from each centre). Only one isolate per patient was accepted into this study; inclusion was

independent of medical history, age, gender or previous antimicrobial usage. Each participating centre was required to submit the following isolates in each year of participation in the TEST study: (number of isolates in parentheses): *Acinetobacter* spp. (15); *Enterococcus* spp. (15); *Enterobacter* spp. (25); *E. coli* (25); *Klebsiella* spp. (25); *P. aeruginosa* (20); *S. aureus* (25); *Serratia* spp. (10); *Haemophilus influenzae* (15); *Streptococcus agalactiae* (10); and *Streptococcus pneumoniae* (15).

A single laboratory [Laboratories International for Microbiology Studies, a division of International Health Management Associates, Inc. (IHMA), Schaumburg, IL] was responsible for the co-ordination of isolate collection, transport and confirmation of isolate identification. Quality control checks were carried out on ca. 10% of contributed isolates.

2.2. Susceptibility testing

Minimum inhibitory concentrations (MICs) were established at collecting medical centres using Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards) broth microdilution methodology [9], using either MicroScan[®] panels (Dade Behring Inc., Sacramento, CA) or Sensititre[®] plates (TREK Diagnostic Systems, East Grinstead, UK). Gram-negative organisms were investigated against the following antimicrobial agents (concentration ranges in mg/L in parentheses): amikacin (0.5–64); amoxicillin/clavulanic acid (0.12/0.06–32/16); ampicillin (0.5–32); cefepime (0.5–32); ceftriaxone (0.06–64); ceftazidime (8–32); imipenem (0.06–16; MicroScan[®] only); meropenem (0.06–16; Sensititre[®] only); levofloxacin (0.008–8); minocycline (0.5–16); tigecycline (0.008–16); and piperacillin/tazobactam (0.06/4–128/4). Gram-

positive organisms were tested against: amoxicillin/clavulanic acid (0.03/0.015–8/4); ampicillin (0.06–16); penicillin (0.06–8); linezolid (0.5–8); ceftriaxone (0.03–64); imipenem (0.12–16; MicroScan[®] only); meropenem (0.12–16; Sensititre[®] only); levofloxacin (0.06–32); minocycline (0.25–8); tigecycline (0.008–16); piperacillin/tazobactam (0.25/4–16/4); and vancomycin (0.12–32). In 2006, imipenem was replaced by meropenem in the TEST antimicrobial panel owing to imipenem stability issues. Quality control testing was carried out on each day of MIC testing using *E. coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619 (as appropriate). Susceptibility was determined using CLSI interpretive criteria [10], with the exception of tigecycline for which European Committee on Antimicrobial Susceptibility Testing (EUCAST) (<http://www.srga.org/eucastwt/MICTAB/index.html>) breakpoints were used (Enterobacteriaceae, susceptible ≤ 1 mg/L, resistant ≥ 4 mg/L; *S. aureus*, susceptible ≤ 0.5 mg/L, resistant ≥ 1 mg/L; *Enterococcus* spp., susceptible ≤ 0.25 mg/L, resistant ≥ 1 mg/L).

2.3. Resistance determination

Meticillin resistance among isolates of *S. aureus* was detected using local methodologies; subsequent confirmation was carried out using the cefoxitin disk diffusion method (30 μ g disks) (Remel Inc., Lenexa, KS) at the central laboratory. Penicillin-resistant *S. pneumoniae* (PRSP) are defined as having an MIC ≥ 2 mg/L and penicillin-intermediate *S. pneumoniae* as isolates with MICs >0.06 mg/L and <2 mg/L.

Multidrug resistance among isolates of *Acinetobacter baumannii* was defined as resistance to fluoroquinolones (levofloxacin) and aminoglycosides (amikacin) plus carbapenems (imipenem/meropenem) and/or third-generation cephalosporins (ceftazidime/ceftriaxone).

β -Lactamase production among *H. influenzae* isolates was determined using local methodologies. IHMA confirmed β -lactamase production in *H. influenzae* [using the CefinaseTM disk test (BD Diagnostics, Sparks, MD)] only if an investigator's β -lactamase detection result and ampicillin or amoxicillin/clavulanic acid MICs were contradictory or when an investigator did not perform a β -lactamase determination. ESBL production was identified among *E. coli* and *K. pneumoniae* using the CLSI phenotypic disk test [10]; ESBL production was confirmed at IHMA by the double-disk synergy test using disks containing cefotaxime (30 μ g), cefotaxime/clavulanic acid (30/10 μ g), ceftazidime (30 μ g) and ceftazidime/clavulanic acid (30/10 μ g). Phenotypic identification of ESBL production was not confirmed using molecular tools. Antimicrobial disks were manufactured by Oxoid Inc. (Ogdenburg, NY), whilst Mueller–Hinton agar was produced by Remel Inc. An inhibition zone size increase of ≥ 5 mm on the combination disk indicated a positive result for the presence of ESBL [10]. Quality control strains in this study included *K. pneumoniae* ATCC 700603 (used as a positive ESBL control) and *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922 (used as a negative ESBL controls).

3. Results

3.1. Gram-negative isolates

Susceptibility testing was performed on 16 760 isolates across nine Gram-negative taxa; pooled data for these isolates are listed in Table 1. The most active agents against *A. baumannii* were tigecycline [MIC for 90% of the organisms (MIC_{90}) = 1 mg/L] and minocycline (MIC_{90} = 4 mg/L; 94.2% susceptible) (Table 1). Low MIC_{90} values (≤ 2 mg/L) were noted for tigecycline, imipenem and meropenem against *Enterobacter aerogenes* and *Enterobacter cloacae* (Table 1). *Escherichia coli* isolates were highly susceptible to tigecycline, imipenem and meropenem, with MIC_{90} values < 1 mg/L. *Escherichia coli* resistance to tigecycline and imipenem did not change, whilst small increases in resistance [ranging from 0.1% (amikacin) to 6.6% (minocycline)] were noticed among all other agents (Table 1). Low MIC_{90} values (≤ 2 mg/L) were noted for tigecycline, imipenem and meropenem against *K. pneumoniae*, and resistance to all antimicrobial agents increased during the study period with the exception of meropenem and tigecycline (for which decreases were noted) (Table 1). Low MIC_{90} values (≤ 2 mg/L) were noted for levofloxacin, cefepime, tigecycline, imipenem and meropenem against *Klebsiella oxytoca*. MIC_{90} values for *Serratia marcescens* were ≤ 2 mg/L for tigecycline, cefepime, imipenem, meropenem and levofloxacin, whilst high susceptibilities were noted for cefepime, imipenem, meropenem and amikacin (Table 1). *Serratia marcescens* resistance to minocycline increased by 6.0%, with a corresponding decrease in susceptibility from 85.1% in 2004 to 68.8% in 2007 (data not shown); susceptibility to tigecycline was stable. *Haemophilus influenzae* isolates were highly susceptible to most test agents (Table

1). Few agents showed notable activity against *P. aeruginosa*, with amikacin the only agent inhibiting >90% of isolates (Table 1).

Summary data (pooled) for important resistant Gram-negative pathogens are provided in Table 2. Multidrug-resistant (MDR) isolates represented 15.7% of all *A. baumannii* isolates, with the lowest MIC₉₀ reported for tigecycline (2 mg/L) (Table 2). A large decrease (45.4%) in imipenem susceptibility was seen between 2004 and 2005, likely due to the low number of isolates tested for imipenem in 2005 ($n = 16$). ESBLs were produced by 289 *E. coli* isolates (8.5%); low MIC₉₀ values were observed for meropenem (0.12 mg/L), tigecycline and imipenem (both 0.5 mg/L) (Table 2). Tigecycline MIC₉₀ values were stable over the 4 study years (0.5 mg/L or 1 mg/L) (Table 2). ESBLs occurred in 316 *K. pneumoniae* isolates (13.6%) (Table 2); the most active agents against these isolates were imipenem (MIC₉₀ = 0.5 mg/L), meropenem and tigecycline (both = 2 mg/L) (Table 2). ESBL-positive *K. pneumoniae* showed increasing resistance to amoxicillin/clavulanic acid (18.4%), levofloxacin (17.5%) and piperacillin/tazobactam (15.1%) (Table 2) and increasing susceptibility to tigecycline (12.5%). Low MIC₉₀ values were reported for most agents against β -lactamase-positive *H. influenzae* with the exception of ampicillin (≥ 64 mg/L) and amikacin (8 mg/L) (Table 2).

3.2. Gram-positive isolates

Susceptibility testing was carried out on 7988 Gram-positive isolates spread over five species collected across Europe from 2004–2007. Pooled data are presented in Table 1. Tigecycline was the most active agent against both *Enterococcus* spp., with stable MIC₉₀ values reported over the 4-year study period (0.25 mg/L for *E. faecalis*

and 0.12 mg/L for *Enterococcus faecium*). Minocycline resistance among isolates of *E. faecalis* increased by 18.3% during this study. Low linezolid MIC₉₀ values were also noted for *E. faecium* (2 mg/L) during the study period but notable resistance increases were noted among several agents (Table 1). All *S. aureus* isolates were susceptible to linezolid and vancomycin; low MIC₉₀ values were recorded for tigecycline (0.25 mg/L), minocycline (0.5 mg/L) and vancomycin (1 mg/L). *Staphylococcus aureus* resistance decreased against most antimicrobials during this study (Table 1). *Streptococcus agalactiae* isolates were highly susceptible to most agents on the test panel, with the exception of minocycline (against which resistance increased by 14.5%). *Streptococcus pneumoniae* MIC₉₀ values of ≤ 1 mg/L were recorded for all antimicrobials with the exception of ampicillin and minocycline; high susceptibilities were noted to amoxicillin/clavulanic acid, ceftriaxone, levofloxacin, linezolid and vancomycin (Table 1).

Pooled summary data for key resistant Gram-positive pathogens are listed in Table 2. Of 491 *E. faecium* isolates, 77 (15.7%) were vancomycin-resistant (Table 2); for this resistant subpopulation, the lowest MIC₉₀ was reported for tigecycline (0.12 mg/L overall, ranging from 0.06 mg/L in 2005 to 0.25 mg/L in 2007), whilst 71.4% and 79.2% were susceptible to minocycline and linezolid, respectively. Resistance to ampicillin increased by 23.1% among vancomycin-resistant *E. faecium* isolates, whilst levofloxacin resistance increased by 15.4% (Table 2). MRSA accounted for 26.5% of *S. aureus* isolates (Table 2) and were highly susceptible to tigecycline (MIC₉₀ = 0.25 mg/L), linezolid (MIC₉₀ = 4 mg/L) and vancomycin (MIC₉₀ = 1 mg/L) (Table 2). MRSA prevalence ranged from 0% (0/24) in Norway and The Netherlands (0/49) to 48.8% in Greece (Table 3) and 58.3% in Poland (14/24) in this study. PRSP

represented 9.3% (149/1602) of *S. pneumoniae* isolates (Table 3). Low MIC₉₀ values (≤ 1 mg/L) of tigecycline, imipenem, meropenem, levofloxacin, linezolid and vancomycin were noted for PRSP.

3.3. Longitudinal analysis

The yearly prevalence of key resistant Gram-negative and Gram-positive isolates for countries contributing ≥ 10 isolates in at least 3 study years is presented in Table 3.

Overall, MDR *A. baumannii* percentages were stable, with the highest levels occurring in Greece (50.0%) and Italy (36.0%); rates increased in Italy (19.1% in 2004 to 53.3% in 2007) but decreased in Spain (35.7% in 2004 to 15.1% in 2007). Across Europe, ESBL-positive *E. coli* increased from 6.3% in 2004 to 10.4% in 2007. The highest levels were reported in Greece (21.7% over 2004–2007), ranging annually from 8.3% to 27.8% (Table 3). Notable ESBL-positive *E. coli* increases were reported for strains collected from Germany (5.0% to 16.0%), Ireland (0.0% to 20.0%) and Spain (1.0% to 12.9%). ESBL-positive *K. pneumoniae* increased in the UK from 24.2% (16/66) in 2004 to 80.0% (16/20) in 2007. β -Lactamase-positive *H. influenzae* levels were stable across Europe, ranging from 14.6% in 2004 to 14.4% in 2007 (Table 3).

Only 17 (1.2%) of 1433 *E. faecalis* isolates recorded across Europe were vancomycin-resistant; 13 of these were recovered in Italy, 6 of which were reported in 2004 (Table 3). The remaining vancomycin-resistant *E. faecalis* isolates were reported from the Czech Republic ($n = 1$, collected in 2007), Greece ($n = 1$, 2006), Ireland ($n = 1$, 2007) and Latvia ($n = 1$, 2005). Vancomycin-resistant *E. faecium* accounted for 15.7% (77/491) of all *E. faecium* isolates; again, the biggest

contributor was Italy (29 isolates), with 19 isolates collected in 2006. MRSA rates were highest in Poland (58.3%; data available for 2004 only, no isolates were contributed between 2005 and 2007), Greece (48.8%) and Croatia (48.6%; data available for 2006 and 2007 only, no MRSA isolates were contributed in 2004 or 2005), although Italy and France contributed the highest numbers of MRSA isolates (205 and 160, respectively). MRSA prevalence in Italy decreased (from 45.1% to 27.8%), whilst rates in France were relatively stable (ranging from 35.8% in 2004 to 30.0% in 2007) (Table 3). PRSP prevalence increased from 7.1% (28/396) in 2004 to 11.2% (53/475) in 2007: levels increased most noticeably in Ireland (from 0.0% in 2004 to 29.2% in 2007), although total *N* values were relatively low (*N* = 15 in 2004 and 24 in 2007). PRSP levels were highest overall in Finland (data not shown), occurring in 8 (20.5%) of 39 *S. pneumoniae* isolates during the study period.

4. Discussion

TEST was initiated to monitor the presence and development of resistance to tigecycline among important bacterial pathogens globally, including various European countries [8]. Some general trends in resistance to antimicrobials in Europe are apparent from the data presented in the current study. For example, resistance among isolates of *Acinetobacter* spp. are on the increase. *Acinetobacter* spp. are opportunistic pathogens that commonly infect immunocompromised patients, causing an array of infections including nosocomial pneumonia, skin and soft-tissue infections and bacteraemia. *Acinetobacter* spp. (particularly *A. baumannii*) have become resistant to most of the major antimicrobial agents in widespread use, including aminoglycosides, quinolones, β -lactams, cephalosporins and also carbapenems [11,12]. *Acinetobacter baumannii* resistance rates are higher for

piperacillin/tazobactam (+5.2%), ceftazidime (+6.5%) and meropenem (+12.4%) in the current study than indicated by Turner et al. [11]. Although EUCAST has not designated *Acinetobacter* breakpoints for tigecycline, the MIC₉₀ of 1 mg/L reported in the current study is the lowest of all antimicrobial agents tested, including the carbapenems. Tigecycline may thus be one of the few antimicrobial agents available today with good in vitro activity against this increasingly common MDR pathogen. Clinical data are currently lacking for tigecycline in the treatment of infections caused by *Acinetobacter* spp., although initial clinical results for tigecycline used in the treatment of complicated skin and soft-tissue infections due to *A. baumannii* are promising [13].

Similarly, *E. coli* susceptibility to fluoroquinolones and cephalosporins is lower in the current study than in other recent surveillance studies in Europe. As part of The Surveillance Network (TSN) study in 2000–2001, Wenzel et al. [14] reported ceftriaxone susceptibility ranging from 96.7% (Italy) to 99.8% (Germany); this decreased to 89.3% across Europe in the current study. Reduced susceptibility can also be seen among isolates of *E. coli* to ceftazidime (up to 5.7%) and levofloxacin (as much as 14.7%), although levofloxacin susceptibility was already decreasing in some European countries by 2000–2001 (e.g. only 75.2% of isolates were susceptible in Spain) [14]. However, the in vitro susceptibility of *E. coli* to tigecycline and the carbapenems was high in the TEST study.

The decreased *E. coli* susceptibility to cephalosporins may be due to increases in the prevalence of the CTX-M ESBLs among *E. coli* isolates across Europe [15]. These ESBLs, particularly CTX-M-15, have been detected in various members of the

Enterobacteriaceae family [16]. Similarly, decreased susceptibility of *K. pneumoniae* to third-generation cephalosporins over the study period, together with the increasing rate of ESBL-producing strains particularly observed in France and Ireland, may be attributed to the spread of ESBL-producing clones [15]. The dramatic increase in ESBL-positive *K. pneumoniae* reported in the UK in this study, rising from 24.2% in 2004 to 80.0% in 2006, may be due in large part to the relatively low numbers of isolates collected (66 and 20, respectively). Introduction of β -lactamase genotyping to the TEST study would help to reveal whether CTX-M-15 is responsible for changing patterns of resistance among *E. coli* and other Enterobacteriaceae across Europe.

β -Lactamase production is not the only route by which isolates of *H. influenzae* may develop resistance to ampicillin or other β -lactam antimicrobials: amino acid substitutions in penicillin-binding protein 3 (PBP3) also confer low-level resistance to β -lactam antimicrobials. Recent reports suggest that PBP3 amino acid substitutions are increasing among isolates of *H. influenzae* in Europe, resulting in increased occurrences of β -lactamase-negative, ampicillin-resistant (BLNAR) isolates [17–19]. *Haemophilus influenzae* resistance is low against all agents in this study with the exception of ampicillin, against which 13.7% resistance was reported. Previous studies have shown that changes to PBP3 can result in large-scale increases in imipenem resistance in *H. influenzae* [20]. Although no imipenem-resistant *H. influenzae* isolates were identified in this study, β -lactamase-negative isolates with an imipenem MIC of 4 mg/L have been identified. These indicate that BLNAR *H. influenzae* are most likely present among the isolates collected during this study; the

MIC distribution of imipenem could possibly be used as an indicator of the prevalence of BLNAR *H. influenzae* in Europe.

MRSA prevalence is typically highest in southern and western Europe, with lower rates seen in northern Europe [21]. This trend generally holds true in the current study. National MRSA prevalence varied widely in this study, ranging from 0% in Norway and The Netherlands to 48.8% in Greece and 58.3% in Poland. Large variations in national MRSA prevalence across Europe have previously been reported. Sader et al. [22] noted MRSA occurrence ranging from 2.1% in Sweden to 54.7% in Ireland as part of the SENTRY study in 2005. Similarly, Tiemersma et al. [21] described MRSA levels between 0.5% in Iceland and 44.0% in Greece between 1999 and 2002. The relative prevalence of MRSA isolates is still very low in several European countries, which may result in large year-to-year fluctuations in MRSA levels [21]. Regardless of their country of origin, MRSA isolates were highly ($\geq 99.9\%$) susceptible to tigecycline, linezolid and vancomycin in this European study.

The numbers of VRE by country were insufficient in the current study to draw meaningful conclusions regarding local changes in distribution. However, levels appear to be stable across Europe: Sader et al. [22] noted vancomycin-resistant *E. faecalis* and *E. faecium* levels of 0.9% and 17.9%, respectively in 2005, whilst 1.2% of *E. faecalis* and 15.7% of *E. faecium* isolates were vancomycin-resistant in the current study. Enterococci are often intrinsically resistant to many clinically important antimicrobial agents and are commonly implicated in nosocomial infections and bacteraemia [23]. Tigecycline had a MIC₉₀ of 0.12 mg/L against vancomycin-

resistant *E. faecium*, making it the most active agent against this pathogen in this study.

The frequency of occurrence of penicillin resistance among *S. pneumoniae* also appears to be stable across Europe. *Streptococcus pneumoniae* is an important pathogen in respiratory tract pathogens worldwide, with therapeutic options often limited by the presence of resistant or MDR strains [24]. Isolates of PRSP account for 9.3% of *S. pneumoniae* in the current study, only slightly lower than the 12.1% reported across Europe by Reinert et al. [25] between 2001 and 2003. Reinert et al. [25] also described 24.6% of *S. pneumoniae* isolates as being penicillin non-susceptible, similar to the 27.6% non-susceptibility seen in the current study. The lowest PRSP MIC₉₀ seen in this study was for tigecycline (0.12 mg/L).

Surveillance studies are crucial elements in monitoring trends in antimicrobial resistance on local, national and global scales today. The information gathered during these studies is essential in preparing evidence-based guidelines for the treatment of bacterial infections [25,26]. TEST is one such study, designed to longitudinally monitor the susceptibilities of numerous key pathogens to tigecycline (plus several comparators) on a global scale. Previous reports from the TEST study have indicated good in vitro activity for tigecycline against most of the pathogens in the TEST panel [27]. In the current study, which includes data collected from 24 European countries over a 4-year period, tigecycline was highly active in vitro against most of the pathogens monitored, including MDR pathogens. This activity was stable over the study period, whilst increasing resistance was noted for several comparator agents during the same period. Tigecycline is approved for the treatment

of intra-abdominal and complicated skin and soft-tissue infections and retains potential to be a valuable part of the armamentarium used to combat MDR pathogens.

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Competing interests: NN-L has lectured at educational meetings sponsored by Wyeth and other pharmaceutical companies and has received sponsorship from Wyeth to attend an educational meeting. MJD is an employee of Wyeth Pharmaceuticals.

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Table 1

Minimum inhibitory concentrations (MICs) and antimicrobial susceptibility of pooled Gram-negative and Gram-positive organisms

Organism	N	MIC (mg/L)			Susceptibility		
		MIC ₅₀	MIC ₉₀	Range	%S	%R	ΔR (%) ^a
Gram-negative	16 760						
<i>Acinetobacter baumannii</i>							
Tigecycline	1560	0.25	1	≤0.008–16	N/A	N/A	–
Minocycline	1560	≤0.5	4	≤0.5 to ≥32	94.2	2.1	–2.0
Ampicillin	1560	≥64	≥64	≤0.5 to ≥64	N/A	N/A	–
AMC	1560	32	≥64	0.25 to ≥64	N/A	N/A	–
PIP/TAZ	1560	16	≥256	≤0.06 to ≥256	56.0	33.2	0.0
Ceftazidime	1560	≤8	≥64	≤8 to ≥64	52.3	39.5	–2.4
Ceftriaxone	1560	16	≥128	≤0.06 to ≥128	31.9	42.8	–1.3
Cefepime	1560	8	≥64	≤0.5 to ≥64	56.6	28.7	–0.4
Imipenem	919	0.5	16	≤0.06 to ≥32	85.2	12.6	–13.0
Meropenem	641	1	16	≤0.06 to ≥32	68.5	23.4	–8.2
Levofloxacin	1560	2	≥16	≤0.008 to ≥16	55.0	32.1	–4.7
Amikacin	1560	4	≥128	≤0.5 to ≥128	71.4	23.7	1.0
<i>Enterobacter aerogenes</i>							
Tigecycline	682	0.5	2	0.03–8	88.7	2.9	–2.4
Minocycline	682	2	8	≤0.5 to ≥32	81.2	7.3	3.8
Ampicillin	682	≥64	≥64	1 to ≥64	0.1	95.2	–4.1
AMC	682	≥64	≥64	≤0.12 to ≥64	2.8	93.1	4.3
PIP/TAZ	682	4	64	≤0.06 to ≥256	74.5	7.6	1.2
Ceftazidime	682	≤8	≥64	≤8 to ≥64	61.1	31.4	–10.6
Ceftriaxone	682	0.5	64	≤0.06 to ≥128	74.9	10.3	–0.9
Cefepime	682	≤0.5	8	≤0.5 to ≥64	93.5	4.3	–5.9
Imipenem	443	0.5	2	≤0.06–8	99.5	0.0	0.0
Meropenem	239	≤0.06	0.25	≤0.06–16	97.9	0.4	0.0
Levofloxacin	682	0.06	≥16	≤0.008 to ≥16	74.3	22.4	3.3
Amikacin	682	2	8	≤0.5 to ≥128	97.4	1.3	0.9

<i>Enterobacter cloacae</i>							
Tigecycline	2364	0.5	2	0.06–8	87.3	5.6	–2.4
Minocycline	2364	4	8	≤0.5 to ≥32	78.4	9.9	5.8
Ampicillin	2364	≥64	≥64	2 to ≥64	0.8	91.9	–2.2
AMC	2364	≥64	≥64	0.25 to ≥64	1.6	96.7	–1.6
PIP/TAZ	2364	4	128	≤0.06 to ≥256	69.9	17.8	4.7
Ceftazidime	2364	≤8	≥64	≤8 to ≥64	64.0	29.5	3.3
Ceftriaxone	2364	0.5	≥128	≤0.06 to ≥128	67.2	21.8	4.2
Cefepime	2364	≤0.5	8	≤0.5 to ≥64	92.9	5.0	–0.5
Imipenem	1422	0.5	1	≤0.06 to ≥32	99.3	0.4	0.6
Meropenem	942	≤0.06	0.25	≤0.06 to ≥32	99.2	0.4	0.4
Levofloxacin	2364	0.06	8	≤0.008 to ≥16	85.8	12.1	6.3
Amikacin	2364	2	4	≤0.5 to ≥128	98.4	1.1	–0.5
<i>Escherichia coli</i>							
Tigecycline	3403	0.12	0.5	≤0.008–8	99.2	0.03 ^b	0.0
Minocycline	3403	1	16	≤0.5 to ≥32	79.5	10.3	6.6
Ampicillin	3403	≥64	≥64	≤0.5 to ≥64	39.8	59.4	4.2
AMC	3403	8	32	0.5 to ≥64	69.6	12.3	0.6
PIP/TAZ	3403	1	16	≤0.06 to ≥256	92.0	4.3	1.3
Ceftazidime	3403	≤8	≤8	≤8 to ≥64	93.4	4.5	2.0
Ceftriaxone	3403	≤0.06	16	≤0.06 to ≥128	89.3	9.1	3.0
Cefepime	3403	≤0.5	4	≤0.5 to ≥64	92.7	5.7	3.5
Imipenem	2093	0.25	0.5	≤0.06 to ≥32	99.9	0.1	0.0
Meropenem	1310	≤0.06	≤0.06	≤0.06–8	99.8	0.0	0.0
Levofloxacin	3403	0.03	≥16	≤0.008 to ≥16	75.1	21.6	5.8
Amikacin	3403	2	8	≤0.5 to ≥128	98.6	0.7	0.1
<i>Haemophilus influenzae</i>							
Tigecycline	1634	0.12	0.5	≤0.008–2	N/A	N/A	–
Minocycline	1634	≤0.5	1	≤0.5 to ≥32	97.3	0.7	–0.5
Ampicillin	1634	≤0.5	16	≤0.5 to ≥64	83.6	13.7	–0.4
AMC	1634	0.5	1	≤0.12–32	99.6	0.4	0.2
PIP/TAZ	1634	≤0.06	≤0.06	≤0.06–16	99.8	0.2	0.0
Ceftriaxone	1634	≤0.06	≤0.06	≤0.06–32	99.9	N/A	–

Cefepime	1634	≤0.5	≤0.5	≤0.5–32	99.0	N/A	–
Imipenem	993	0.25	1	≤0.06–4	100	N/A	–
Meropenem	641	≤0.06	0.12	≤0.06–0.5	100	N/A	–
Levofloxacin	1634	0.015	0.03	≤0.008–1	100	N/A	–
Amikacin	1634	4	8	≤0.5–64	N/A	N/A	–
<i>Klebsiella oxytoca</i>							
Tigecycline	922	0.25	1	≤0.008–8	93.5	1.8	–0.2
Minocycline	922	1	8	≤0.5 to ≥32	88.3	5.3	6.2
Ampicillin	922	≥64	≥64	1 to ≥64	1.1	87.7	3.6
AMC	922	4	32	0.5 to ≥64	79.3	13.3	0.5
PIP/TAZ	922	1	≥256	≤0.06 to ≥256	83.6	14.4	–1.7
Ceftazidime	922	≤8	≤8	≤8 to ≥64	94.3	3.4	–1.9
Ceftriaxone	922	≤0.06	8	≤0.06 to ≥128	90.1	4.8	0.5
Cefepime	922	≤0.5	2	≤0.5 to ≥64	96.2	2.3	–2.3
Imipenem	552	0.25	0.5	≤0.06–8	99.8	0.0	0.0
Meropenem	370	≤0.06	0.12	≤0.06–8	99.7	0.0	0.0
Levofloxacin	922	0.06	1	≤0.008 to ≥16	93.3	4.9	1.2
Amikacin	922	2	4	≤0.5 to ≥128	98.7	0.8	0.0
<i>Klebsiella pneumoniae</i>							
Tigecycline	2331	0.5	2	0.015–16	88.0	4.7	–5.4
Minocycline	2331	2	16	≤0.5 to ≥32	75.6	16.0	4.4
Ampicillin	2331	≥64	≥64	≤0.5 to ≥64	0.6	86.2	2.8
AMC	2331	4	32	0.5 to ≥64	72.7	15.0	3.0
PIP/TAZ	2331	2	128	0.12 to ≥256	84.4	10.3	2.8
Ceftazidime	2331	≤8	≥64	≤8 to ≥64	82.4	14.8	2.1
Ceftriaxone	2331	≤0.06	≥128	≤0.06 to ≥128	82.2	13.8	5.4
Cefepime	2331	≤0.5	16	≤0.5 to ≥64	88.8	8.5	5.0
Imipenem	1403	0.25	0.5	≤0.06 to ≥32	99.7	0.3	0.0
Meropenem	928	≤0.06	0.25	≤0.06 to ≥32	98.3	1.2	–1.7
Levofloxacin	2331	0.06	8	≤0.008 to ≥16	85.7	10.9	6.9
Amikacin	2331	2	8	≤0.5 to ≥128	96.9	1.9	0.7
<i>Pseudomonas aeruginosa</i>							
Tigecycline	2653	8	≥32	0.06 to ≥32	N/A	N/A	–

Minocycline	2653	≥32	≥32	≤0.5 to ≥32	5.9	77.6	−0.8
Ampicillin	2653	≥64	≥64	≤0.5 to ≥64	N/A	N/A	−
AMC	2653	≥64	≥64	0.5 to ≥64	N/A	N/A	−
PIP/TAZ	2653	4	128	≤0.06 to ≥256	86.8	13.2	3.1
Ceftazidime	2653	≤8	32	≤8 to ≥64	76.6	14.8	1.8
Ceftriaxone	2653	64	≥128	≤0.06 to ≥128	15.3	55.9	−9.7
Cefepime	2653	4	32	≤0.5 to ≥64	76.4	12.2	−1.7
Imipenem	1624	1	8	≤0.06 to ≥32	82.6	9.7	−4.2
Meropenem	1029	1	16	≤0.06 to ≥32	79.4	13.8	−8.4
Levofloxacin	2653	1	≥16	≤0.008 to ≥16	66.2	27.1	0.0
Amikacin	2653	4	16	≤0.5 to ≥128	92.8	4.2	0.1
<i>Serratia marcescens</i>							
Tigecycline	1211	1	2	0.06–16	81.6	3.2	−1.3
Minocycline	1211	4	8	≤0.5 to ≥32	80.8	4.8	6.0
Ampicillin	1210	≥64	≥64	2 to ≥64	0.5	91.3	−4.7
AMC	1211	≥64	≥64	2 to ≥64	1.0	96.9	−2.3
PIP/TAZ	1211	2	32	≤0.06 to ≥256	89.5	3.3	2.2
Ceftazidime	1211	≤8	≤8	≤8 to ≥64	92.3	6.1	1.5
Ceftriaxone	1211	0.25	16	≤0.06 to ≥128	89.4	4.6	0.9
Cefepime	1211	≤0.5	1	≤0.5 to ≥64	97.3	2.2	0.3
Imipenem	729	0.5	1	≤0.06 to ≥32	98.9	0.7	0.0
Meropenem	482	≤0.06	0.25	≤0.06 to ≥32	97.9	1.5	0.5
Levofloxacin	1211	0.12	2	≤0.008 to ≥16	93.0	4.0	1.9
Amikacin	1211	2	8	≤0.5 to ≥128	97.9	1.1	−0.3
Gram-positive 7988							
<i>Enterococcus faecalis</i>							
Tigecycline	1433	0.12	0.25	≤0.008–0.5	N/A	N/A	−
Minocycline	1433	8	≥16	≤0.25 to ≥16	38.0	27.8	18.3
Penicillin	1433	2	4	≤0.06 to ≥16	99.9	0.1	−0.3
Ampicillin	1433	1	2	≤0.06 to ≥32	99.9	0.1	−0.3
AMC	1433	0.5	1	≤0.03 to ≥16	N/A	N/A	−
PIP/TAZ	1433	2	8	≤0.25 to ≥32	N/A	N/A	−
Ceftriaxone	1433	≥128	≥128	≤0.03 to ≥128	N/A	N/A	−

Imipenem	852	1	4	≤ 0.12 to ≥ 32	N/A	N/A	–
Meropenem	581	4	8	≤ 0.12 to ≥ 32	N/A	N/A	–
Levofloxacin	1433	1	32	≤ 0.06 to ≥ 64	69.3	29.4	–4.4
Linezolid	1433	2	2	≤ 0.5 –4	97.8	0.0	0.0
Vancomycin	1433	1	2	≤ 0.12 to ≥ 64	98.7	1.2	–0.9
<i>Enterococcus faecium</i>							
Tigecycline	491	0.06	0.12	≤ 0.008 –0.25	N/A	N/A	–
Minocycline	491	≤ 0.25	≥ 16	≤ 0.25 to ≥ 16	72.9	14.9	8.4
Penicillin	491	≥ 16	≥ 16	≤ 0.06 to ≥ 16	14.9	85.1	10.3
Ampicillin	491	≥ 32	≥ 32	≤ 0.06 to ≥ 32	18.1	81.9	16.1
AMC	491	≥ 16	≥ 16	≤ 0.03 to ≥ 16	N/A	N/A	–
PIP/TAZ	491	≥ 32	≥ 32	≤ 0.25 to ≥ 32	N/A	N/A	–
Ceftriaxone	491	≥ 128	≥ 128	≤ 0.03 to ≥ 128	N/A	N/A	–
Imipenem	308	≥ 32	≥ 32	≤ 0.12 to ≥ 32	N/A	N/A	–
Meropenem	183	≥ 32	≥ 32	≤ 0.12 to ≥ 32	N/A	N/A	–
Levofloxacin	491	≥ 64	≥ 64	0.25 to ≥ 64	20.6	75.2	11.2
Linezolid	491	2	2	≤ 0.5 –4	91.6	0.0	0.0
Vancomycin	491	1	≥ 64	≤ 0.12 to ≥ 64	83.1	15.7	3.6
<i>Staphylococcus aureus</i>							
Tigecycline	3218	0.12	0.25	≤ 0.008 –1	99.97 ^b	0.03 ^b	0.0
Minocycline	3218	≤ 0.25	0.5	≤ 0.25 to ≥ 16	98.7	0.2	0.3
Penicillin	3218	8	≥ 16	≤ 0.06 to ≥ 16	14.2	85.8	–3.0
Ampicillin	3218	8	≥ 32	≤ 0.06 to ≥ 32	16.7	83.3	–2.6
AMC	3218	1	≥ 16	≤ 0.03 to ≥ 16	82.8	17.2	–3.4
PIP/TAZ	3218	1	≥ 32	≤ 0.25 to ≥ 32	84.3	15.7	–3.7
Ceftriaxone	3218	4	≥ 128	≤ 0.03 to ≥ 128	77.9	14.2	–5.4
Imipenem	1807	0.25	8	≤ 0.12 to ≥ 32	89.9	9.4	–1.2
Meropenem	1411	≤ 0.12	8	≤ 0.12 to ≥ 32	88.6	8.9	–7.2
Levofloxacin	3218	0.25	16	≤ 0.06 to ≥ 64	74.2	24.1	–0.2
Linezolid	3218	2	4	≤ 0.5 –4	100	N/A	–
Vancomycin	3218	1	1	≤ 0.12 –2	100	0.0	0.0
<i>Streptococcus agalactiae</i>							
Tigecycline	1244	0.03	0.12	≤ 0.008 –0.5	99.9	0.0	0.0

Minocycline	1244	8	≥16	≤0.25 to ≥16	20.9	70.6	14.5
Penicillin	1244	≤0.06	0.12	≤0.06–2	99.8	N/A	–
Ampicillin	1244	0.12	0.12	≤0.06–1	99.8	N/A	–
AMC	1244	0.06	0.12	≤0.03–0.5	N/A	N/A	–
PIP/TAZ	1244	≤0.25	≤0.25	≤0.25–2	N/A	N/A	–
Ceftriaxone	1244	0.06	0.12	≤0.03–8	99.8	N/A	–
Imipenem	620	≤0.12	0.25	≤0.12–8	N/A	N/A	–
Meropenem	624	≤0.12	≤0.12	≤0.12–4	99.7	N/A	–
Levofloxacin	1244	0.5	1	≤0.06–8	99.4	0.2	0.0
Linezolid	1244	1	1	≤0.5–2	100	N/A	–
Vancomycin	1244	0.5	0.5	≤0.12–2	99.8	N/A	–
<i>Streptococcus pneumoniae</i>							
Tigecycline	1602	0.03	0.12	≤0.008–1	N/A	N/A	–
Minocycline	1602	≤0.25	4	≤0.25 to ≥16	84.8	7.8	–3.0
Penicillin	1602	≤0.06	1	≤0.06 to ≥16	72.4	9.3	4.1
Ampicillin	1602	≤0.06	2	≤0.06–8	N/A	N/A	–
AMC	1602	≤0.03	1	≤0.03 to ≥16	98.2	0.7	0.1
PIP/TAZ	1602	≤0.25	1	≤0.25 to ≥32	N/A	N/A	–
Ceftriaxone	1602	≤0.03	0.5	≤0.03 to ≥128	98.4	0.4	0.0
Imipenem	886	≤0.12	0.25	≤0.12 to ≥32	84.5	1.5	0.0
Meropenem	716	≤0.12	0.5	≤0.12 to ≥32	83.7	7.1	–1.5
Levofloxacin	1602	0.5	1	≤0.06–32	99.5	0.3	0.2
Linezolid	1602	≤0.5	1	≤0.5–2	100	N/A	–
Vancomycin	1602	0.25	0.5	≤0.12–2	99.9	N/A	–

MIC_{50/90}, minimum inhibitory concentration for 50% and 90% of the organisms, respectively; %S, % susceptible; %R, % resistant; AMC, amoxicillin/clavulanic acid; PIP/TAZ, piperacillin/tazobactam; N/A, breakpoint not available.

^a Change in resistance between 2004 and 2007, except for imipenem (change in resistance between 2004 and 2005) and meropenem (change in resistance between 2006 and 2007); a negative value indicates a drop in resistance during the corresponding interval.

^b Percentages given to two decimal places where rounding would have erroneously indicated 100% susceptibility or 0.0% resistance.

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Table 2

Minimum inhibitory concentrations (MICs) and antimicrobial susceptibility of pooled resistant Gram-negative and Gram-positive organisms

Organism	N	MIC (mg/L)			Susceptibility		
		MIC ₅₀	MIC ₉₀	Range	%S	%R	ΔR (%) ^a
Gram-negative							
MDR <i>Acinetobacter baumannii</i>							
Tigecycline	245	1	2	≤0.008–8	N/A	N/A	–
Minocycline	245	1	8	≤0.5 to ≥32	86.5	4.9	–7.2
Ampicillin	245	≥64	≥64	2 to ≥64	N/A	N/A	–
AMC	245	≥64	≥64	1 to ≥64	N/A	N/A	–
PIP/TAZ	245	≥256	≥256	0.25 to ≥256	4.9	86.1	–5.2
Ceftazidime	245	≥64	≥64	≤8 to ≥64	1.2	95.5	6.6
Ceftriaxone	245	≥128	≥128	8 to ≥128	0.4	97.1	2.2
Cefepime	245	32	≥64	8 to ≥64	4.9	78.0	10.1
Imipenem	120	16	≥32	0.5 to ≥32	39.2	55.8	–45.4
Meropenem	125	16	≥32	0.5 to ≥32	24.0	66.4	–17.9
Levofloxacin	245	≥16	≥16	8 to ≥16	0.0	100	0.0
Amikacin	245	≥128	≥128	64 to ≥128	0.0	100	0.0
ESBL-positive <i>Escherichia coli</i>							
Tigecycline	289	0.25	0.5	0.03–2	98.3	0.0	0.0
Minocycline	289	4	16	≤0.5 to ≥32	62.6	23.2	4.1
Ampicillin ^b	289	≥64	≥64	2 to ≥64	0.0	100	–
AMC	289	16	32	0.5 to ≥64	25.3	30.8	–11.4
PIP/TAZ	289	8	128	0.25 to ≥256	74.4	12.5	1.6
Ceftazidime ^b	289	16	≥64	≤8 to ≥64	0.0	100	–
Ceftriaxone ^b	289	≥128	≥128	≤0.06 to ≥128	0.0	100	–
Cefepime ^b	289	32	≥64	≤0.5 to ≥64	0.0	100	–
Imipenem	169	0.25	0.5	≤0.06–4	100	0.0	0.0
Meropenem	120	≤0.06	0.12	≤0.06–0.5	100	0.0	0.0
Levofloxacin	289	≥16	≥16	≤0.008 to ≥16	25.3	69.9	0.7
Amikacin	289	4	16	≤0.5 to ≥128	91.3	3.8	–1.2

ESBL-positive <i>Klebsiella pneumoniae</i>								
Tigecycline	316	0.5	2	0.06–8	75.9	8.5	–12.5	
Minocycline	316	4	≥32	≤0.5 to ≥32	50.0	34.8	8.9	
Ampicillin ^b	316	≥64	≥64	≥64	0.0	100	–	
AMC	316	16	≥64	4 to ≥64	23.7	40.5	18.4	
PIP/TAZ	316	16	≥256	1 to ≥256	50.3	32.9	15.1	
Ceftazidime ^b	316	≥64	≥64	≤8 to ≥64	0.0	100	–	
Ceftriaxone ^b	316	≥128	≥128	0.12 to ≥128	0.0	100	–	
Cefepime ^b	316	16	≥64	≤0.5 to ≥64	0.0	100	–	
Imipenem	174	0.25	0.5	≤0.06–4	100	0.0	0.0	
Meropenem	142	≤0.06	2	≤0.06–8	99.3	0.0	0.0	
Levofloxacin	316	4	≥16	≤0.008 to ≥16	46.5	42.4	17.5	
Amikacin	316	4	32	≤0.5 to ≥128	88.6	7.6	2.6	
β-Lactamase-positive <i>Haemophilus influenzae</i>								
Tigecycline	239	0.12	0.5	≤0.008–2	N/A	N/A	–	
Minocycline	239	≤0.5	2	≤0.5–4	97.9	0.0	0.0	
Ampicillin	239	32	≥64	2 to ≥64	0.0	93.3	–1.5	
AMC	239	1	2	≤0.12–32	97.5	2.5	1.3	
PIP/TAZ	239	≤0.06	0.12	≤0.06–16	98.7	1.3	0.0	
Ceftriaxone	239	≤0.06	≤0.06	≤0.06–32	99.6	N/A	–	
Cefepime	239	≤0.5	≤0.5	≤0.5–8	98.3	N/A	–	
Imipenem	143	0.25	1	≤0.06–2	100	N/A	–	
Meropenem	96	≤0.06	0.12	≤0.06–0.25	100	N/A	–	
Levofloxacin	239	0.015	0.03	≤0.008–1	100	N/A	–	
Amikacin	239	4	8	≤0.5–32	N/A	N/A	–	
Gram-positive								
Vancomycin-resistant <i>Enterococcus faecium</i>								
Tigecycline	77	0.06	0.12	0.015–0.25	N/A	N/A	–	
Minocycline	77	≤0.25	≥16	≤0.25 to ≥16	71.4	14.3	7.7	
Penicillin	77	≥16	≥16	4 to ≥16	1.3	98.7	7.7	
Ampicillin	77	≥32	≥32	0.5 to ≥32	3.9	96.1	23.1	
AMC	77	≥16	≥16	1 to ≥16	N/A	N/A	–	
PIP/TAZ	77	≥32	≥32	4 to ≥32	N/A	N/A	–	

Ceftriaxone	77	≥128	≥128	4 to ≥128	N/A	N/A	–
Imipenem	48	≥32	≥32	1 to ≥32	N/A	N/A	–
Meropenem	29	≥32	≥32	≥32	N/A	N/A	–
Levofloxacin	77	≥64	≥64	2 to ≥64	2.6	97.4	15.4
Linezolid	77	2	4	≤0.5–4	79.2	0.0	0.0
Vancomycin	77	≥64	≥64	32 to ≥64	0.0	100	0.0
Meticillin-resistant <i>Staphylococcus aureus</i> (MRSA)							
Tigecycline	853	0.12	0.25	0.03–1	99.9	0.1	0.0
Minocycline	853	≤0.25	4	≤0.25 to ≥16	96.1	0.7	1.1
Penicillin ^c	853	≥16	≥16	0.25 to ≥16	0.0	100	–
Ampicillin ^c	853	≥32	≥32	0.5 to ≥32	0.0	100	–
AMC ^c	853	8	≥16	0.25 to ≥16	0.0	100	–
PIP/TAZ ^c	853	≥32	≥32	≤0.25 to ≥32	0.0	100	–
Ceftriaxone ^c	853	64	≥128	0.12 to ≥128	0.0	100	–
Imipenem ^c	441	2	≥32	≤0.12 to ≥32	0.0	100	–
Meropenem ^c	412	2	≥32	≤0.12 to ≥32	0.0	100	–
Levofloxacin	853	8	32	≤0.06 to ≥64	13.1	83.8	4.8
Linezolid	853	2	4	≤0.5–4	100	N/A	–
Vancomycin	853	1	1	≤0.12–2	100	0.0	0.0
Penicillin-resistant <i>Streptococcus pneumoniae</i>							
Tigecycline	149	0.03	0.12	≤0.008–0.12	N/A	N/A	–
Minocycline	149	2	8	≤0.25 to ≥16	63.1	12.1	–8.5
Penicillin	149	2	4	2 to ≥16	0.0	100	0.0
Ampicillin	149	2	4	1–8	N/A	N/A	–
AMC	149	2	4	0.5 to ≥16	81.9	8.1	–3.2
PIP/TAZ	149	2	4	0.5 to ≥32	N/A	N/A	–
Ceftriaxone	149	1	2	0.5 to ≥128	87.2	3.4	–1.7
Imipenem	50	0.5	0.5	0.25–4	0.0	10.0	0.0
Meropenem	99	1	1	≤0.12 to ≥32	4.0	50.5	1.7
Levofloxacin	149	0.5	1	0.25–16	99.3	0.7	0.0
Linezolid	149	1	1	≤0.5–2	100	N/A	–
Vancomycin	149	0.25	0.5	≤0.12–2	98.7	N/A	–

MIC_{50/90}, minimum inhibitory concentration for 50% and 90% of the organisms, respectively; %S, % susceptible; %R, % resistant; MDR, multidrug-resistant; AMC, amoxicillin/clavulanic acid; PIP/TAZ, piperacillin/tazobactam; ESBL, extended-spectrum β -lactamase; N/A, breakpoint not available; CLSI, Clinical and Laboratory Standards Institute.

^a Change in resistance between 2004 and 2007, except for imipenem (change in resistance between 2004 and 2005) and meropenem (change in resistance between 2006 and 2007); a negative value indicates a drop in resistance during the corresponding interval.

^b All ESBL-producers defined as resistant according to CLSI guidelines [10].

^c All MRSA defined as resistant according to CLSI guidelines [10].

Table 3

Prevalence of resistant Gram-negative and Gram-positive organisms collected across Europe (among countries where the total number of isolates collected was ≥ 10 in 3 or 4 years) between 2004 and 2007

Organism	Country	2004		2005		2006		2007		2004–2007	
		<i>N</i>	<i>n</i> (%)	<i>N</i>	<i>n</i> (%)	<i>N</i>	<i>n</i> (%)	<i>N</i>	<i>n</i> (%)	<i>N</i>	<i>n</i> (%)
Gram-negative											
MDR <i>Acinetobacter baumannii</i> ^a											
	Belgium	13	2 (15.4)	18	2 (11.1)	40	1 (2.5)	38	9 (23.7)	109	14 (12.8)
	France	53	2 (3.8)	26	0 (0.0)	102	6 (5.9)	98	6 (6.1)	279	14 (5.0)
	Germany	47	1 (2.1)	21	0 (0.0)	47	2 (4.3)	72	1 (1.4)	187	4 (2.1)
	Greece	20	10 (50.0)	10	4 (40.0)	39	16 (41.0)	25	17 (68.0)	94	47 (50.0)
	Hungary	15	1 (6.7)	14	1 (7.1)	0	0 (–)	10	0 (0.0)	39	2 (5.1)
	Ireland	11	0 (0.0)	11	3 (27.3)	12	1 (8.3)	16	0 (0.0)	50	4 (8.0)
	Italy	47	9 (19.1)	51	8 (15.7)	110	45 (40.9)	75	40 (53.3)	283	102 (36.0)
	Spain	70	25 (35.7)	27	3 (11.1)	1	1 (–)	53	8 (15.1)	151	37 (24.5)
	Europe	371	60 (16.2)	208	21 (10.1)	472	76 (16.1)	509	88 (17.3)	1560	245 (15.7)
ESBL-positive <i>Escherichia coli</i>											
	Belgium	15	0 (0.0)	58	9 (15.5)	51	6 (11.8)	97	2 (2.1)	221	17 (7.7)
	France	100	3 (3.0)	54	1 (1.9)	173	8 (4.6)	204	15 (7.4)	531	27 (5.1)
	Germany	120	6 (5.0)	50	1 (2.0)	128	10 (7.8)	125	20 (16.0)	423	37 (8.7)

Greece	24	2 (8.3)	18	5 (27.8)	82	21 (25.6)	28	5 (17.9)	152	33 (21.7)
Ireland	24	0 (0.0)	28	1 (3.6)	28	6 (21.4)	45	9 (20.0)	125	16 (12.8)
Italy	91	15 (16.5)	139	16 (11.5)	249	22 (8.8)	190	27 (14.2)	669	80 (12.0)
Spain	101	1 (1.0)	102	3 (2.9)	0	0 (–)	101	13 (12.9)	304	17 (5.6)
Sweden	0	0 (–)	25	3 (12.0)	62	1 (1.6)	13	0 (0.0)	100	4 (4.0)
Europe	749	47 (6.3)	501	42 (8.4)	1049	85 (8.1)	1104	115 (10.4)	3403	289 (8.5)
ESBL-positive <i>Klebsiella pneumoniae</i>										
Belgium	28	2 (7.1)	15	2 (13.3)	31	5 (16.1)	63	6 (9.5)	137	15 (10.9)
France	66	5 (7.6)	54	5 (9.3)	87	7 (8.0)	129	16 (12.4)	336	33 (9.8)
Germany	77	4 (5.2)	27	2 (7.4)	62	4 (6.5)	84	7 (8.3)	250	17 (6.8)
Greece	24	7 (29.2)	16	0 (0.0)	69	25 (36.2)	26	4 (15.4)	135	36 (26.7)
Ireland	22	0 (0.0)	26	1 (3.8)	20	0 (0.0)	36	5 (13.9)	104	6 (5.8)
Italy	77	25 (32.5)	86	18 (20.9)	180	12 (6.7)	127	34 (26.8)	470	89 (18.9)
Spain	80	7 (8.8)	64	3 (4.7)	0	0 (–)	69	6 (8.7)	213	16 (7.5)
Europe	564	80 (14.2)	321	32 (10.0)	667	72 (10.8)	779	132 (16.9)	2331	316 (13.6)
β -Lactamase-positive <i>Haemophilus influenzae</i>										
Belgium	15	1 (6.7)	19	1 (5.3)	20	2 (10.0)	59	9 (15.3)	113	13 (11.5)
France	56	13 (23.2)	29	9 (31.0)	57	13 (22.8)	125	23 (18.4)	267	58 (21.7)
Germany	72	7 (9.7)	15	2 (13.3)	36	2 (5.6)	74	3 (4.1)	197	14 (7.1)
Ireland	14	1 (7.1)	0	0 (–)	27	9 (33.3)	25	7 (28.0)	66	17 (25.8)
Italy	45	5 (11.1)	73	13 (17.8)	90	8 (8.9)	63	11 (17.5)	271	37 (13.7)

Spain	60	14 (23.3)	56	9 (16.1)	0	0 (–)	56	10 (17.9)	172	33 (19.2)
Sweden	0	0 (–)	12	3 (25.0)	32	3 (9.4)	15	4 (26.7)	59	10 (16.9)
Europe	431	63 (14.6)	214	40 (18.7)	456	59 (12.9)	533	77 (14.4)	1634	239 (14.6)
Gram-positive										
Vancomycin-resistant <i>Enterococcus faecalis</i> ^b										
Greece	10	0 (0.0)	6	0 (–)	32	1 (3.1)	13	0 (0.0)	61	1 (1.6)
Italy	32	6 (18.8)	53	2 (3.8)	105	3 (2.9)	77	2 (2.6)	267	13 (4.9)
Europe	347	6 (1.7)	205	3 (1.5)	396	4 (1.0)	485	4 (0.8)	1433	17 (1.2)
Vancomycin-resistant <i>Enterococcus faecium</i>										
Germany	14	1 (7.1)	12	1 (8.3)	27	2 (7.4)	23	9 (39.1)	76	13 (17.1)
Italy	22	4 (18.2)	16	4 (25.0)	42	19 (45.2)	16	2 (12.5)	96	29 (30.2)
Europe	104	13 (12.5)	73	9 (12.3)	153	29 (19.0)	161	26 (16.1)	491	77 (15.7)
Meticillin-resistant <i>Staphylococcus aureus</i>										
Belgium	25	9 (36.0)	49	7 (14.3)	33	16 (48.5)	103	23 (22.3)	210	55 (26.2)
France	95	34 (35.8)	63	20 (31.7)	130	40 (30.8)	220	66 (30.0)	508	160 (31.5)
Germany	115	12 (10.4)	46	22 (47.8)	96	15 (15.6)	139	25 (18.0)	396	74 (18.7)
Greece	26	19 (73.1)	24	7 (29.2)	77	36 (46.8)	35	17 (48.6)	162	79 (48.8)
Ireland	25	7 (28.0)	10	0 (0.0)	39	7 (17.9)	41	11 (26.8)	115	25 (21.7)
Italy	91	41 (45.1)	112	44 (39.3)	217	73 (33.6)	169	47 (27.8)	589	205 (34.8)
Spain	99	27 (27.3)	97	13 (13.4)	0	0 (–)	97	32 (33.0)	293	72 (24.6)
Sweden	0	0 (–)	24	2 (8.3)	38	12 (31.6)	20	11 (55.0)	82	25 (30.5)

Europe	744	214 (28.8)	453	121 (26.7)	888	235 (26.5)	1133	283 (25.0)	3218	853 (26.5)
Penicillin-resistant <i>Streptococcus pneumoniae</i>										
Belgium	1	0 (–)	26	1 (3.8)	31	3 (9.7)	56	5 (8.9)	114	9 (7.9)
France	54	10 (18.5)	30	5 (16.7)	66	12 (18.2)	118	18 (15.3)	268	45 (16.8)
Germany	72	0 (0.0)	19	1 (5.3)	62	1 (1.6)	57	2 (3.5)	210	4 (1.9)
Ireland	15	0 (0.0)	1	1 (–)	32	5 (15.6)	24	7 (29.2)	72	13 (18.1)
Italy	43	2 (4.7)	67	3 (4.5)	112	6 (5.4)	62	4 (6.5)	284	15 (5.3)
Spain	57	7 (12.3)	54	12 (22.2)	0	0 (–)	37	6 (16.2)	148	25 (16.9)
Europe	396	28 (7.1)	233	26 (11.2)	498	42 (8.4)	475	53 (11.2)	1602	149 (9.3)

MDR, multidrug-resistant; ESBL, extended-spectrum β -lactamase.

^a ≥ 10 *Acinetobacter baumannii* isolates were contributed from Sweden in 2005, 2006 and 2007 but no MDR isolates were contributed, thus Sweden is not listed here.

^b ≥ 10 *Enterococcus faecalis* isolates were contributed from Belgium, France, Germany and Spain in 3 or 4 years between 2004 and 2007 but no vancomycin-resistant isolates were contributed, thus these countries are not listed here.