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# Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the *in vitro* activity of tigecycline

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***Objectives*: To describe antimicrobial susceptibility among bacterial isolates associated with hospital infections collected from 266 centres in Asia/Pacific Rim (*n* = 1947), North America (*n* = 24 283), Latin America (*n* = 1957) and Europe (*n* = 8796).**

***Methods*: Isolates were collected from blood, respiratory tract, urine, skin, wound, body fluids and other defined sources between January 2004 and August 2006. Only one isolate per patient was accepted. *In vitro* MICs for the isolates were determined according to the CLSI (formerly NCCLS) guidelines.**

***Results*: Key organisms collected were *Acinetobacter baumannii* (*n* = 2902), *Enterobacter* spp. (*n* = 5731), *Escherichia coli* (*n* = 6504), *Klebsiella pneumoniae* (*n* = 4916), *Pseudomonas aeruginosa* (*n* = 5128), *Serratia marcescens* (*n* = 2313), *Enterococcus faecalis* (*n* = 2701), *Enterococcus faecium* (*n* = 1035) and *Staphylococcus aureus* (*n* = 5753). Rates of methicillin resistance among *S. aureus* and of vancomycin resistance among enterococci were highest in North America (2016/3809, 52.9% and 571/2544, 22.4%, respectively) and lowest in Europe (337/1340, 25.1% and 36/916, 3.9%, respectively). Tigecycline was the only antimicrobial to maintain activity against all Gram-positive isolates ($MIC_{90}$ values of $\leq$0.25 mg/L). Overall, tigecycline and imipenem were the most active (>93% susceptibility in all regions) antimicrobials against the Gram-negative species, except for *A. baumannii* and *P. aeruginosa*. Piperacillin/tazobactam and amikacin were the most active against *P. aeruginosa*. Extended-spectrum β-lactamase producers among *K. pneumoniae* occurred most frequently in Latin America (124/282, 44.0%).**

***Conclusions*: Tigecycline is a novel broad-spectrum antimicrobial that is active against the common organisms associated with infections.**

Keywords: global, hospital infections, surveillance, resistance

## Introduction

Significant changes in causative organisms of nosocomial bacterial infections have been observed globally over the past 100 years. In the first half of the 20th century, Gram-positive cocci, particularly *Staphylococcus aureus* and streptococci, were of primary concern. By the end of the 1970s, Enterobacteriaceae (mainly *Escherichia coli*, *Enterobacter* spp. and *Klebsiella* spp.) and *Pseudomonas aeruginosa* had gained prominence as nosocomial pathogens; however, methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci had also emerged. More recently, *Acinetobacter* spp. have become important pathogens in intensive care units (ICUs), with increasing resistance to most antimicrobial agents.[1]

Widespread inappropriate use of antimicrobial agents in the hospital setting has resulted in the emergence of resistance in

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nosocomial organisms, and lack of adherence to hygiene practices has facilitated their dissemination.[2] Clinical success is much more likely if the pathogen is susceptible to the chosen antimicrobial; however, there are no agents available that are fully effective against all the common pathogens. The key to antimicrobial development has been to design agents that elude the main bacterial resistance mechanisms. One such agent is tigecycline, a tetracycline analogue in the new antimicrobial class of glycylcyclines. Like the tetracyclines, tigecycline binds to the 30S subunit of bacterial ribosomes and inhibits protein synthesis by preventing the incorporation of amino acid residues into elongating peptide chains.[3,4] Tigecycline, however, can overcome two major tetracycline resistance mechanisms (ribosomal protection and active efflux), and this is thought to be due to steric hindrance by a large substituent at position 9 of the molecule.[5] In addition, tigecycline binds 5-fold more effectively than related compounds to the ribosomal site.[6] The activity of tigecycline is also unaffected by other mechanisms such as β-lactamase production, penicillin-binding protein alterations, macrolide efflux pumps and DNA gyrase mutations. Consequently, tigecycline has a broad spectrum of *in vitro* activity, including most organisms of importance in nosocomial infections. However, it should be noted that the activity of tigecycline is affected by the intrinsic multidrug pumps of *P. aeruginosa*, *Proteae* and some isolates of *Acinetobacter* spp.[7–9]

The Tigecycline Evaluation and Surveillance Trial (TEST) is a global multicentre study designed to compare the *in vitro* activity of tigecycline with established antimicrobial agents against a range of clinically important organisms. In this article, we report the TEST data for a range of common organisms collected between January 2004 and August 2006, from patients with hospital-associated infections in four geographic regions: Asia/Pacific Rim, North America, Latin America and Europe.

## Materials and methods

### *Bacterial isolates*

A total of 266 centres, located in Asia/Pacific Rim (15 centres), North America (176), Latin America (13) and Europe (62), participated in TEST (Table 1). Each study centre was required to collect, identify and test the antimicrobial susceptibility of a maximum of 200 consecutive fresh clinically significant isolates (defined by institutional criteria) from patients with documented infections. Isolates from hospital- and community-acquired infections were permitted into the study. A hospital infection was defined as occurring more than 48 h after admission. Isolates, restricted to one per patient, were obtained from blood, respiratory tract, urine (limited to no more than 25% of all isolates), skin, wound, fluids and other defined sources.

Species requested by the protocol included (number of isolates requested appear in parentheses) *Acinetobacter* spp. (15), *Enterococcus* spp. (15), *Enterobacter* spp. (25), *E. coli* (25), *Klebsiella* spp. (25), *P. aeruginosa* (20), *S. aureus* (25) and *Serratia* spp. (10).

### *Antimicrobial susceptibility testing*

MICs were determined at the local laboratory using broth microdilution methodology with either MicroScan® panels (Dade Behring Inc., Sacramento, CA, USA) or Sensititre® plates (TREK Diagnostic Systems, West Sussex, UK), according to guidelines published by the CLSI (formerly NCCLS).[10] Antimicrobial agents tested against Gram-negative organisms (with concentrations expressed in mg/L) were: 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); levofloxacin (0.008–8); minocycline (0.5–16); tigecycline (0.008–16); and piperacillin/tazobactam (0.06/4–128/4). Antimicrobial agents tested against Gram-positive organisms (with concentrations expressed in mg/L) were: amoxicillin/clavulanic acid (0.03/0.0015–8/4); ampicillin (0.06–16); penicillin (0.06–8); linezolid (0.5–8); ceftriaxone (0.03–64); imipenem (0.12–16; MicroScan® only); levofloxacin (0.06–32); minocycline (0.25–8);

**Table 1.** Distribution of centres participating in TEST in Asia/Pacific Rim, North America, Latin America and Europe

| Region and country | Number of centres |
|---|---|
| **Asia/Pacific Rim** | **15** |
| Australia | 3 |
| China | 2 |
| India | 2 |
| Korea | 2 |
| Pakistan | 2 |
| Philippines | 2 |
| Singapore | 2 |
| **North America** | **176** |
| Canada | 4 |
| USA | 172 |
| **Latin America** | **13** |
| Argentina | 9 |
| Brazil | 1 |
| Chile | 2 |
| Mexico | 1 |
| **Europe** | **62** |
| Austria | 1 |
| Belgium | 4 |
| Czech Republic | 1 |
| Denmark | 1 |
| Finland | 1 |
| France | 9 |
| Germany | 7 |
| Greece | 3 |
| Hungary | 1 |
| Ireland | 2 |
| Italy | 11 |
| Latvia | 2 |
| Poland | 1 |
| Portugal | 1 |
| Spain | 8 |
| Sweden | 2 |
| Switzerland | 2 |
| The Netherlands | 1 |
| UK | 4 |
| **Total number of centres** | **266** |

tigecycline (0.008–16); piperacillin/tazobactam (0.25/4–16/4); and vancomycin (0.12–32). MIC breakpoints followed published CLSI guidelines.[11] For tigecycline, the US Food and Drug Administration (FDA) breakpoints were applied for *S. aureus* (susceptible ≤0.5 mg/L), vancomycin-susceptible *Enterococcus faecalis* (susceptible ≤0.25 mg/L) and Enterobacteriaceae (susceptible ≤2 mg/L), where applicable.[12]

Broth microdilution panels inoculated with Gram-negative organisms were incubated in ambient air at 35°C for 16–20 h. *S. aureus* and *Enterococcus* spp. were incubated in ambient air at 35°C for 20–24 h. Quality control of panels was performed using *E. coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853 and *E. faecalis* ATCC 29212, when appropriate.

All isolates and data were sent to a central laboratory, International Health Management Associates, Inc. (Schaumburg, IL, USA), for confirmation of identity and inclusion into a centralized database. The data were collected using the proprietary OptiScan™ data collection form. Organism identification was carried out according to the American Society for Microbiology methodology[13] and the Remel RapidID system (Remel, Lenexa, KS, USA).

### *Extended-spectrum β-lactamase (ESBL) determination*

*E. coli* and *Klebsiella* spp. were screened and confirmed for ESBL activity, according to CLSI guidelines.[11] The discs used were cefotaxime (30 μg), cefotaxime/clavulanic acid (30/10 μg), ceftazidime (30 μg) and ceftazidime/clavulanic acid (30/10 μg). Discs were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). The Mueller–Hinton agar was used in testing was manufactured by Remel, Inc. Quality control was performed using *Klebsiella pneumoniae* ATCC 700603 (ESBL-positive) and *E. coli* ATCC 25922 (ESBL-negative). In addition, *P. aeruginosa* ATCC 27853 was used for the quality control of the ceftazidime and cefotaxime discs.

### *Methicillin resistance determination*

*S. aureus* were screened using local methodology to identify isolates that were methicillin-resistant. On receipt at the central laboratory, the cefoxitin disc (30 μg discs; Remel) diffusion method was used to confirm methicillin resistance.

## Results

### *Demographic description*

Bacterial isolates were collected between January 2004 and August 2006 and comprised a wide range of aerobic organisms cultured from a variety of sources (mainly respiratory, cardiovascular and genito-urinary). Of the isolates, 65.7% were collected in North America and 74.4% were Gram-negative. Isolates were collected from more male patients than female, typically in the ratio 3:2, with the exception of *E. coli* (60.2% collected from female patients). Approximately half of the isolates were collected from adult patients aged between 18 and 64 years, whereas <15% of isolates were from paediatric patients. At least 70% of the isolates came from hospitalized patients, mainly from non-ICU wards. Only Latin America contributed more isolates from the ICU than from non-ICU. Specifically, 67.0% of *Acinetobacter baumannii* from Latin America came from the ICU, 54.9% of *P. aeruginosa* and 64.3% of vancomycin-resistant *Enterococcus faecium*.

### *Gram-positive isolates*

Overall, the susceptibility results of 9489 Gram-positive isolates are reported. A total of 5753 isolates of *S. aureus* were collected from the four geographical regions, 1035 *E. faecium* and 2701 *E. faecalis*.

### *S. aureus*

The prevalence of MRSA was lowest in Europe (25.1%), while approximately half of the *S. aureus* isolates from North America were methicillin-resistant (Figure 1). In Europe, Greece and Poland had the highest levels of MRSA (55.6% and 60.9%, respectively), followed by Italy and Portugal (36.4% and 37.5%, respectively). No MRSA isolates were collected from the Czech Republic, Denmark, Finland and the Netherlands, while Latvia and Sweden had low MRSA rates (6%). The MRSA rates varied in North America (Canada, 21.6% and the USA, 53.7%) and the Asia/Pacific Rim region, where Australia, Pakistan, the Philippines and Singapore had the lowest rates (~20%), compared with China (59.1%), India (50%) and Korea (85%). In Latin America, the MRSA rates in Argentina, Brazil and Chile were more consistent, ranging between 43.5% and 51.1%; whereas the rate in Mexico was notably higher (86.4%).

All isolates of methicillin-susceptible *S. aureus* and MRSA were susceptible to tigecycline, linezolid and vancomycin (Tables 2 and 3).

### *Enterococcus spp.*

Vancomycin resistance was seen in <5% of *E. faecalis* isolates: North America 4.6%; Europe 1.5%; Latin America 1.4%; and Asia/Pacific Rim 0%. Vancomycin resistance in *E. faecium* varied widely among regions: North America 65.6%; Latin America 46.7%; Asia/Pacific Rim 31%; and Europe 12%. In terms of country distribution, only 14 of the 29 countries submitted more that 10 *E. faecium* isolates and among these, the numbers of vancomycin-resistant isolates were small, except in the USA ($n = 477$). The USA, Argentina and Korea had the highest percentages of vancomycin-resistant *E. faecium* (>60%) (Figure 2).

*E. faecalis* isolates were largely susceptible to the panel of antimicrobials, with the exception of levofloxacin (56.5% to 77.9% susceptible) and minocycline (30.8% to 47.9% susceptible) (Table 2). All isolates were susceptible to penicillin and ampicillin, and tigecycline was the most active compound. The four regions were comparable in terms of $MIC_{90}$ values of all antimicrobials.

Irrespective of vancomycin susceptibility, *E. faecium* isolates showed poor antimicrobial susceptibility, except tigecycline and linezolid (Tables 2 and 3). $MIC_{90}$s of tigecycline were 0.12 mg/L, irrespective of susceptibility to vancomycin. For linezolid, the $MIC_{90}$ values were 2 mg/L (>90% susceptible).

### *Gram-negative isolates*

Results from 27 494 Gram-negative isolates are presented. In the four regions, 4916 *K. pneumoniae*, 6504 *E. coli*, 5731 *Enterobacter* spp., 2313 *Serratia marcescens*, 2902 *A. baumannii* and 5128 *P. aeruginosa* were submitted.

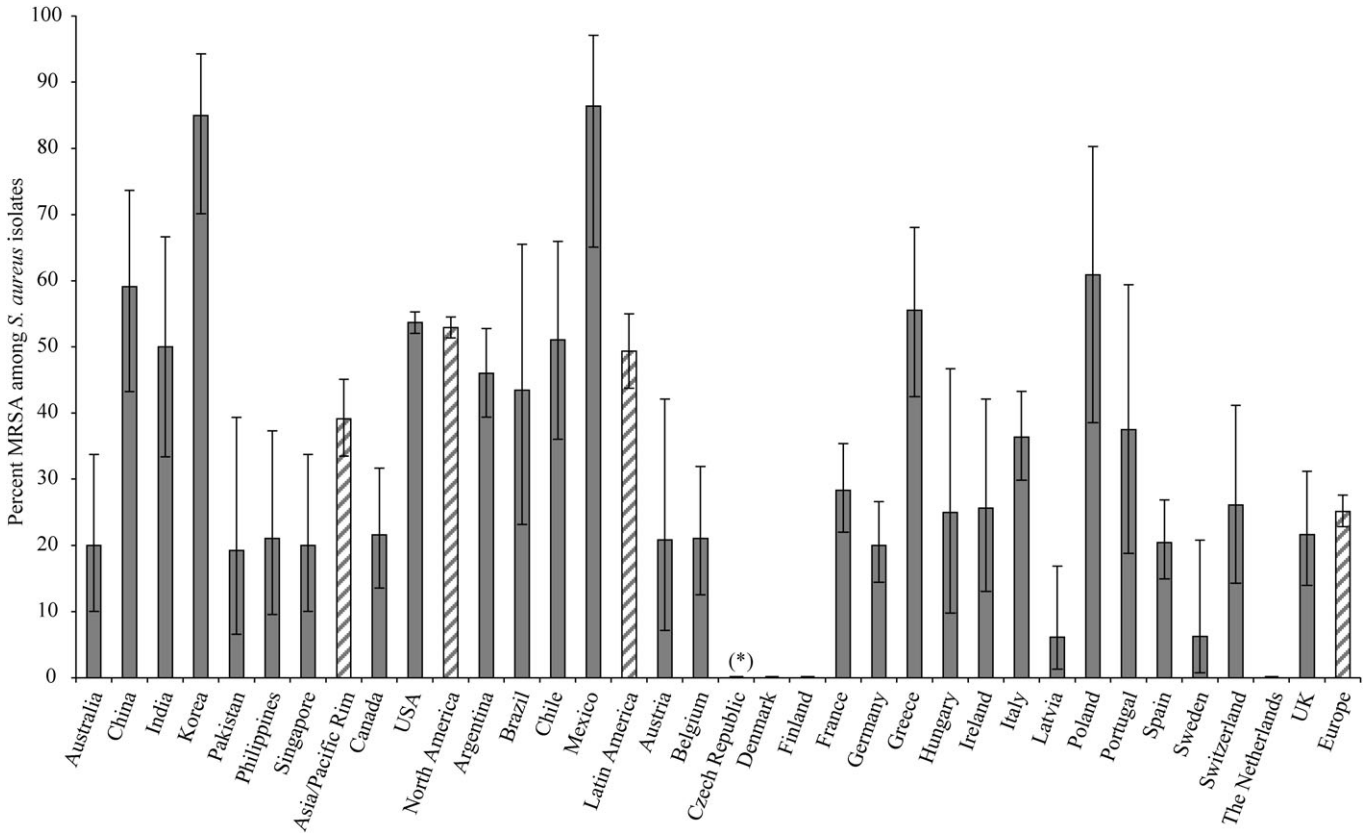


**Figure 1.** Frequency of methicillin-resistant strains (MRSA) among *S. aureus* isolates (January 2004–August 2006), by country submitting ≥10 isolates (with 95% confidence intervals). *Indicates data not shown as country submitting <10 *S. aureus* isolates.

### *K. pneumoniae*

The occurrence of ESBL producers among *K. pneumoniae* isolates collected over 3 years was highest in Latin America (44%), compared with Asia/Pacific Rim (22.4%), North America (7.5%) and Europe (13.3%) (Figure 3). By country, the highest ESBL rates occurred in India (72%) and Mexico (71.4%). Also notable were the rates in the other Latin American countries (37.8% to 55.3%), Greece (43.1%) and Poland (37.5%). No ESBL-producing isolates were reported in Austria, Czech Republic, Denmark, Finland, Ireland, Switzerland and the Netherlands.

Against all *K. pneumoniae* collected, imipenem was the most active antimicrobial, with >99% susceptibility in each region. This was followed by tigecycline (>94% of isolates susceptible in each region) (Table 4). Imipenem and tigecycline were also the most active agents against the subpopulation of ESBL-producing *K. pneumoniae* (Table 3). The susceptibility rates for β-lactams and levofloxacin varied widely among the regions and were markedly lower in Latin America than the other regions in the cases of amoxicillin/clavulanate and piperacillin/tazobactam.

### *E. coli*

ESBL production among *E. coli* was variable among the regions; Asia/Pacific Rim and Latin America had the highest rates (12.0% and 13.5%, respectively) and North America had the lowest rate (2.2%). In Europe, 7.6% of *E. coli* were ESBL producers. *E. coli* isolates showed 100% susceptibility to tigecycline and imipenem and >90% susceptibility to piperacillin/tazobactam and amikacin in the four regions (Table 4). Overall, antimicrobial susceptibility was comparable in the four regions; however, the $MIC_{90}$ values varied widely for ceftriaxone (0.25 to ≥128 mg/L) and cefepime (≤0.5–32 mg/L). Ampicillin, amoxicillin/clavulanic acid and levofloxacin showed poor activity against *E. coli*.

### *Enterobacter spp.*

These isolates comprised mostly *Enterobacter aerogenes* (25.5%) and *Enterobacter cloacae* (71.2%); both species had similar antimicrobial susceptibility profiles (data not shown). Susceptibilities to tigecycline, imipenem and amikacin ranged between 89.8% and 100% among the *Enterobacter* spp. isolates in all four regions (Table 4). The *Enterobacter* spp. were totally or almost totally resistant to ampicillin and amoxicillin/clavulanic acid. Latin America had the lowest susceptibility rates among the regions for the remaining β-lactams (piperacillin/tazobactam, ceftazidime, ceftriaxone and cefepime), levofloxacin and minocycline.

### *S. marcescens*

With the exception of ampicillin and amoxicillin/clavulanic acid, *S. marcescens* was largely susceptible to the panel of antimicrobials (Table 4). Imipenem was the most active antimicrobial (100% susceptibility), followed by tigecycline (>96%

**Table 2.** Antimicrobial susceptibility and $MIC_{90}$ values for Gram-positive isolates, by region

| Antimicrobial | Asia/Pacific Rim | | North America | | Latin America | | Europe | |
|---|---|---|---|---|---|---|---|---|
| | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S |
| **Methicillin-susceptible *S. aureus*** | $n = 174$ | | $n = 1793$ | | $n = 161$ | | $n = 1003$ | |
| Tigecycline | 0.25 | 100 | 0.12 | 100 | 0.25 | 100 | 0.12 | 100 |
| Penicillin[a] | ≥16 | 10.9 | ≥16 | 17.9 | ≥16 | 10.6 | ≥16 | 18.5 |
| Amoxicillin/clavulanate | 2 | 100 | 2 | 100 | 1 | 100 | 1 | 100 |
| Piperacillin/tazobactam | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 |
| Ceftriaxone | 4 | 98.3 | 4 | 99.3 | 4 | 100 | 4 | 99.6 |
| Imipenem[b] | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 |
| Levofloxacin | 0.25 | 98.9 | 0.25 | 95.3 | 0.25 | 98.1 | 0.25 | 98.3 |
| Minocycline | ≤0.25 | 100 | ≤0.25 | 99.4 | 0.5 | 99.4 | ≤0.25 | 99.4 |
| Linezolid | 4 | 100 | 2 | 100 | 4 | 100 | 4 | 100 |
| Vancomycin | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 |
| ***E. faecalis*** | $n = 130$ | | $n = 1753$ | | $n = 140$ | | $n = 678$ | |
| Tigecycline[c] | 0.12 | 100 | 0.12 | n/a | 0.25 | n/a | 0.25 | n/a |
| Penicillin | 4 | 100 | 4 | 100 | 4 | 100 | 4 | 100 |
| Ampicillin | 2 | 100 | 1 | 100 | 2 | 100 | 2 | 100 |
| Amoxicillin/clavulanate | 1 | n/a | 1 | n/a | 1 | n/a | 1 | n/a |
| Piperacillin/tazobactam | 8 | n/a | 4 | n/a | 4 | n/a | 8 | n/a |
| Ceftriaxone | ≥128 | n/a | ≥128 | n/a | ≥128 | n/a | ≥128 | n/a |
| Imipenem[d] | 4 | n/a | 2 | n/a | 4 | n/a | 4 | n/a |
| Levofloxacin | 32 | 68.5 | ≥64 | 56.5 | 32 | 77.9 | 32 | 69.3 |
| Minocycline | ≥16 | 30.8 | 8 | 47.9 | ≥16 | 47.1 | ≥16 | 39.2 |
| Linezolid | 2 | 96.9 | 2 | 99.0 | 2 | 95.0 | 2 | 96.8 |
| Vancomycin | 2 | 100 | 2 | 95.0 | 2 | 98.6 | 2 | 98.5 |
| ***E. faecium*** | $n = 58$ | | $n = 727$ | | $n = 30$ | | $n = 220$ | |
| Tigecycline | 0.12 | n/a | 0.12 | n/a | 0.12 | n/a | 0.12 | n/a |
| Penicillin | ≥16 | 17.2 | ≥16 | 11.7 | ≥16 | 46.7 | ≥16 | 20.0 |
| Ampicillin | ≥32 | 20.7 | ≥32 | 13.2 | ≥32 | 33.3 | ≥32 | 24.5 |
| Amoxicillin/clavulanate | ≥16 | n/a | ≥16 | n/a | ≥16 | n/a | ≥16 | n/a |
| Piperacillin/tazobactam | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a |
| Ceftriaxone | ≥128 | n/a | ≥128 | n/a | ≥128 | n/a | ≥128 | n/a |
| Imipenem[e] | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a |
| Levofloxacin | ≥64 | 8.6 | ≥64 | 8.9 | ≥64 | 23.3 | ≥64 | 26.8 |
| Minocycline | 8 | 70.7 | 8 | 74.0 | 8 | 70.0 | ≥16 | 75.5 |
| Linezolid | 2 | 100 | 2 | 97.0 | 2 | 93.3 | 2 | 93.6 |
| Vancomycin | ≥64 | 69.0 | ≥64 | 33.1 | ≥64 | 53.3 | ≥64 | 87.3 |

[a]Ampicillin susceptibility should be inferred from penicillin susceptibility.
[b]Overall 96.0% of isolates were tested against imipenem: Asia/Pacific Rim, 172; North America, 1681; Latin America, 160; Europe, 993.
[c]Susceptibility breakpoint applies only to vancomycin-susceptible isolates.
[d]Overall 95.0% of isolates were tested against imipenem: Asia/Pacific Rim, 129; North America, 1636; Latin America, 136; Europe, 666.
[e]Overall 93.0% of isolates were tested against imipenem: Asia/Pacific Rim, 56; North America, 659; Latin America, 30; Europe, 218.
n/a, CLSI susceptibility breakpoints not available.

susceptibility across the regions). Levofloxacin and minocycline susceptibility rates were moderately consistent across the regions (87.9% to 95.6% and 88.5% to 90.9%, respectively). For the remaining antimicrobials, however, the susceptibility rates were lower in Latin America than the other regions.

### *A. baumannii*

With the exception of minocycline and tigecycline, *A. baumannii* isolates exhibited relatively poor antimicrobial susceptibility (Table 4). The susceptibility of imipenem and amikacin varied across the regions, from fairly good in North America and Europe (≥74%) to poor or moderate in Latin America (60.6% and 23.4%, respectively) and Asia/Pacific Rim (69.2% and 59.6%, respectively). Susceptibility rates for those antimicrobials with breakpoints (except minocycline) were markedly lower in Latin America than the other regions.

### *P. aeruginosa*

Among the *P. aeruginosa* collected, >85% susceptibility to piperacillin/tazobactam was seen for isolates from all regions

**Table 3.** Antimicrobial susceptibility and $MIC_{90}$ values for resistant organisms, by region

| | Asia/Pacific Rim | | North America | | Latin America | | Europe | |
|---|---|---|---|---|---|---|---|---|
| Antimicrobial | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S |
| **MRSA**[a] | $n = 112$ | | $n = 2016$ | | $n = 157$ | | $n = 337$ | |
| Tigecycline | 0.5 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 |
| Levofloxacin | ≥64 | 21.4 | ≥64 | 21.4 | 16 | 10.2 | 32 | 10.4 |
| Minocycline | 8 | 80.4 | 0.5 | 99.1 | 4 | 98.7 | 4 | 97.3 |
| Linezolid | 2 | 100 | 2 | 100 | 4 | 100 | 2 | 100 |
| Vancomycin | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 |
| **Vancomycin-resistant *E. faecium*** | $n = 18$ | | $n = 477$ | | $n = 14$ | | $n = 26$ | |
| Tigecycline[b] | 0.12 | n/a | 0.12 | n/a | 0.12 | n/a | 0.12 | n/a |
| Penicillin | ≥16 | 5.6 | ≥16 | 1.3 | ≥16 | 7.1 | ≥16 | 3.9 |
| Ampicillin | ≥32 | 0.0 | ≥32 | 2.5 | ≥32 | 0.0 | ≥32 | 11.5 |
| Amoxicillin/clavulanate | ≥16 | n/a | ≥16 | n/a | ≥16 | n/a | ≥16 | n/a |
| Piperacillin/tazobactam | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a |
| Ceftriaxone | ≥128 | n/a | ≥128 | n/a | ≥128 | n/a | ≥128 | n/a |
| Imipenem[c] | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a |
| Levofloxacin | ≥64 | 0.0 | ≥64 | 0.4 | ≥64 | 0.0 | ≥64 | 7.7 |
| Minocycline | 8 | 83.3 | 8 | 71.9 | ≥16 | 78.6 | 4 | 92.3 |
| Linezolid | 2 | 100 | 2 | 96.4 | 2 | 100 | 2 | 92.3 |
| Vancomycin | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 |
| **ESBL-producing *K. pneumoniae*** | $n = 62$ | | $n = 246$ | | $n = 124$ | | $n = 142$ | |
| Tigecycline | 2 | 96.8 | 2 | 90.7 | 2 | 95.2 | 4 | 87.3 |
| Ampicillin | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 |
| Amoxicillin/clavulanate | 32 | 27.4 | ≥64 | 33.7 | ≥64 | 4.0 | ≥64 | 27.5 |
| Piperacillin/tazobactam | 32 | 82.3 | 128 | 45.5 | 128 | 25.0 | 128 | 57.0 |
| Ceftazidime[d] | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 |
| Ceftriaxone[d] | ≥128 | 0.0 | ≥128 | 0.0 | ≥128 | 0.0 | ≥128 | 0.0 |
| Cefepime[d] | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 |
| Imipenem[e] | 1 | 100 | 4 | 94.9 | 1 | 100 | 0.5 | 100 |
| Levofloxacin | ≥16 | 64.5 | ≥16 | 24.8 | ≥16 | 32.3 | ≥16 | 47.9 |
| Amikacin | ≥128 | 83.9 | 32 | 86.6 | ≥128 | 77.4 | 32 | 89.4 |
| Minocycline | 16 | 69.4 | ≥32 | 64.6 | 8 | 74.2 | ≥32 | 53.5 |

[a]β-Lactams and β-lactams/inhibitor combinations are not effective clinically against MRSA.
[b]No breakpoints available against vancomycin-resistant *Enterococcus* spp.
[c]Overall 92.1% of isolates tested against imipenem: Asia/Pacific Rim, 18; North America, 435; Latin America, 14; Europe, 26.
[d]All isolates defined as resistant to cephalosporins, according to the CLSI guidelines.
[e]Overall 97.7% of isolates tested against imipenem: Asia/Pacific Rim, 61; North America, 237; Latin America, 121; Europe, 142.
n/a, CLSI susceptibility breakpoints not available.

and to amikacin among isolates from Asia/Pacific Rim, North America and Europe (Table 4). Of the antimicrobials with breakpoints, minocycline had the lowest susceptibility rates (<7%). No breakpoints were available for tigecycline, but the $MIC_{90}$ value was ≥32 mg/L in each region. There was a trend for lower susceptibility rates in Latin America than the other regions.

## Discussion

These TEST data provide information about the distribution of antimicrobial-resistant organisms in four major geographic regions. They demonstrate the large variation in the percentage of resistant organisms among countries and regions. The clinical importance of antimicrobial resistance, among both Gram-positive and Gram-negative organisms, has been demonstrated in a number of studies.[14] MRSA, in particular, is a global problem and as expected, the MRSA isolates collected in the TEST study were largely multiresistant, but remained susceptible to vancomycin and linezolid, as well as tigecycline. Tigecycline is notable as it is the first compound in some time to be licensed that combines activity against MRSA with activity against Gram-negative organisms.

Of the four regions, Europe had the lowest proportion of MRSA among *S. aureus* isolates over the 3 years; the rate (25%) was in line with the findings of the European Antimicrobial Resistance Surveillance System (EARSS) for 2004 (24%).[15] However, large variations in the rates of MRSA within Europe have been reported[15] and are supported by the findings of this study. Greece, Italy and Portugal had rates of >35% in both the TEST data and EARSS.[15] Interestingly, the UK, although

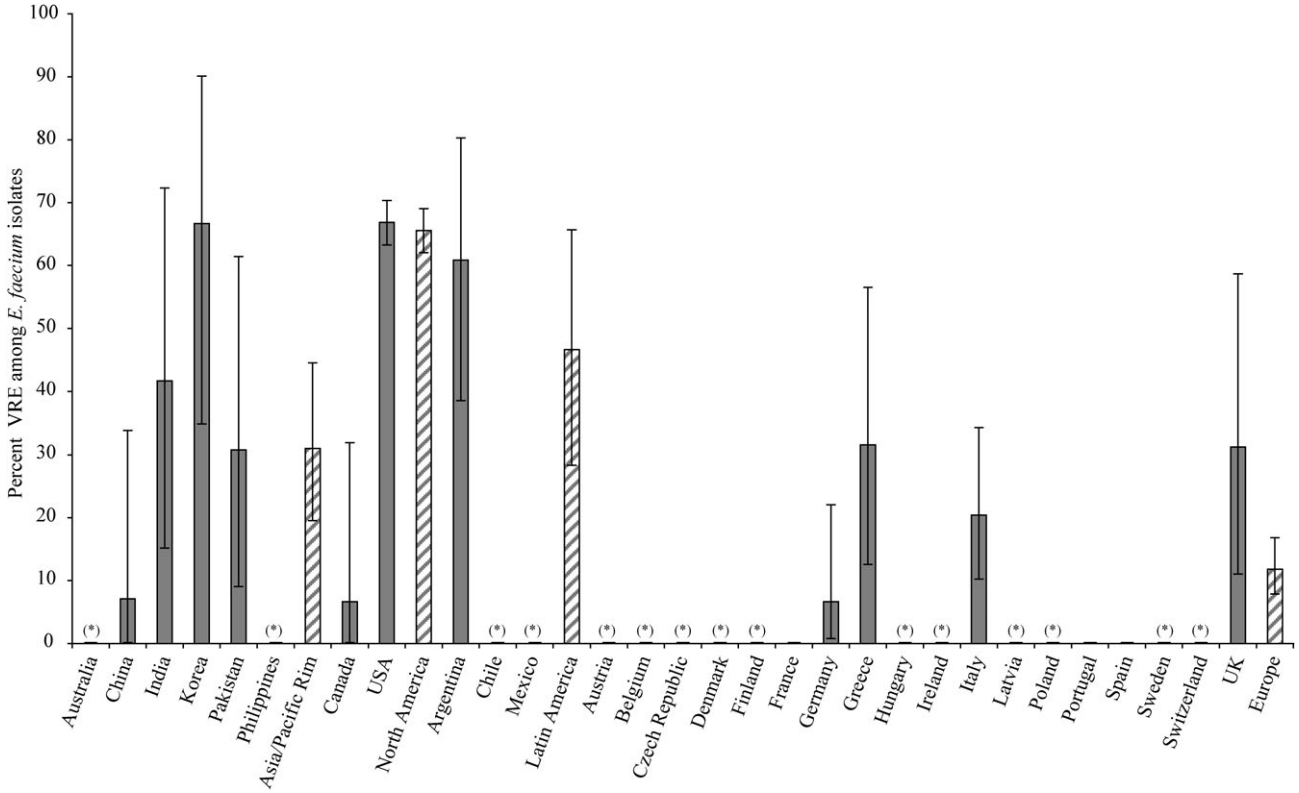


**Figure 2.** Frequency of vancomycin-resistant strains among isolates of *E. faecium* (January 2004–August 2006), by country submitting ≥10 isolates (with 95% confidence intervals). *Indicates data not shown as country submitting <10 *E. faecium* isolates. Data for Singapore, Brazil and the Netherlands are not presented as these countries did not submit *E. faecium* isolates to TEST during the study period.

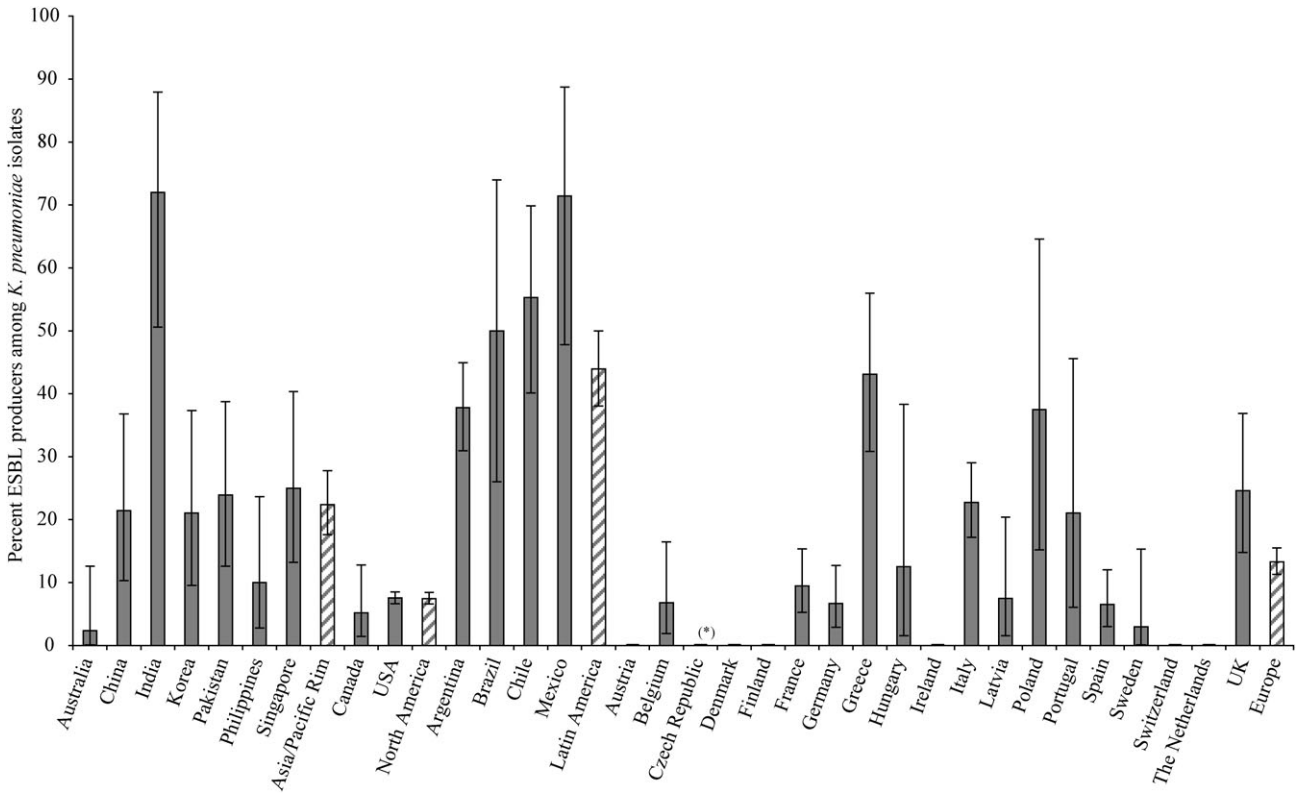


**Figure 3.** Frequency of ESBL producers among *K. pneumoniae* isolates (January 2004–August 2006), by country submitting ≥10 isolates (with 95% confidence intervals). *Indicates data not shown as country submitting <10 *K. pneumoniae* isolates.

**Table 4.** Antimicrobial susceptibility and $MIC_{90}$ values for Gram-negative isolates, by region

| | Asia/Pacific Rim | | North America | | Latin America | | Europe | |
|---|---|---|---|---|---|---|---|---|
| Antimicrobial | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S |
| ***K. pneumoniae*** | $n = 277$ | | $n = 3289$ | | $n = 282$ | | $n = 1068$ | |
| Tigecycline | 1 | 97.1 | 2 | 95.0 | 2 | 96.5 | 2 | 94.3 |
| Ampicillin | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 |
| Amoxicillin/clavulanate | ≥64 | 62.5 | 16 | 86.2 | ≥64 | 43.3 | 32 | 74.3 |
| Piperacillin/tazobactam | 32 | 87.7 | 16 | 92.2 | 128 | 57.1 | 64 | 86.2 |
| Ceftazidime | ≥64 | 72.2 | 16 | 89.1 | ≥64 | 55.0 | ≥64 | 83.3 |
| Ceftriaxone | ≥128 | 67.1 | 4 | 91.8 | ≥128 | 53.2 | 64 | 84.4 |
| Cefepime | 32 | 81.6 | 2 | 95.9 | ≥64 | 58.5 | 8 | 90.3 |
| Imipenem[a] | 0.5 | 99.3 | 0.5 | 99.6 | 1 | 100 | 0.5 | 100 |
| Levofloxacin | ≥16 | 81.6 | 4 | 89.4 | ≥16 | 62.1 | 4 | 86.9 |
| Amikacin | 8 | 92.4 | 2 | 98.5 | 32 | 87.6 | 8 | 96.9 |
| Minocycline | 16 | 80.5 | 8 | 83.9 | 16 | 78.4 | 16 | 78.0 |
| ***E. coli*** | $n = 341$ | | $n = 4265$ | | $n = 326$ | | $n = 1572$ | |
| Tigecycline | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 |
| Ampicillin | ≥64 | 29.3 | ≥64 | 47.2 | ≥64 | 33.1 | ≥64 | 40.8 |
| Amoxicillin/clavulanate | 32 | 65.4 | 32 | 76.6 | 32 | 65.6 | 32 | 71.6 |
| Piperacillin/tazobactam | 8 | 95.9 | 4 | 96.5 | 16 | 92.9 | 8 | 93.6 |
| Ceftazidime | 16 | 88.6 | ≤8 | 95.1 | 16 | 89.3 | ≤8 | 94.0 |
| Ceftriaxone | ≥128 | 77.1 | 0.25 | 95.6 | ≥128 | 82.2 | 16 | 89.9 |
| Cefepime | 32 | 86.5 | ≤0.5 | 97.9 | 16 | 86.5 | 4 | 93.7 |
| Imipenem[b] | 0.5 | 100 | 0.5 | 100 | 0.5 | 100 | 0.5 | 100 |
| Levofloxacin | ≥16 | 61.6 | ≥16 | 76.3 | ≥16 | 66.0 | ≥16 | 77.2 |
| Amikacin | 8 | 97.4 | 4 | 99.5 | 8 | 97.9 | 4 | 98.9 |
| Minocycline | 8 | 74.2 | 8 | 86.5 | 8 | 77.3 | 8 | 83.5 |
| ***Enterobacter*** spp. | $n = 283$ | | $n = 3699$ | | $n = 295$ | | $n = 1454$ | |
| Tigecycline | 1 | 97.2 | 2 | 93.6 | 2 | 96.6 | 2 | 94.6 |
| Ampicillin | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 |
| Amoxicillin/clavulanate | ≥64 | 2.8 | ≥64 | 2.5 | ≥64 | 2.7 | ≥64 | 2.0 |
| Piperacillin/tazobactam | 64 | 79.5 | 64 | 83.8 | 128 | 66.8 | 128 | 72.5 |
| Ceftazidime | ≥64 | 62.2 | ≥64 | 76.2 | ≥64 | 57.6 | ≥64 | 62.7 |
| Ceftriaxone | ≥128 | 66.8 | 64 | 81.3 | ≥128 | 59.7 | 64 | 69.3 |
| Cefepime | 16 | 88.0 | 4 | 96.3 | ≥64 | 76.3 | 8 | 92.9 |
| Imipenem[c] | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 |
| Levofloxacin | 2 | 90.1 | 2 | 91.7 | ≥16 | 77.6 | ≥16 | 83.3 |
| Amikacin | 4 | 95.8 | 4 | 99.5 | 32 | 89.8 | 4 | 98.3 |
| Minocycline | 8 | 83.0 | 8 | 85.3 | 8 | 81.0 | 8 | 82.0 |
| ***S. marcescens*** | $n = 122$ | | $n = 1508$ | | $n = 124$ | | $n = 559$ | |
| Tigecycline | 2 | 97.5 | 2 | 96.6 | 2 | 97.6 | 2 | 97.0 |
| Ampicillin | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 | ≥64 | 0.0 |
| Amoxicillin/clavulanate | ≥64 | 0.0 | ≥64 | 1.0 | ≥64 | 3.2 | ≥64 | 0.5 |
| Piperacillin/tazobactam | 8 | 93.4 | 4 | 96.9 | 64 | 82.3 | 8 | 94.5 |
| Ceftazidime | 32 | 88.5 | ≤8 | 93.8 | 32 | 77.4 | ≤8 | 95.2 |
| Ceftriaxone | 32 | 87.7 | 4 | 93.8 | ≥128 | 76.6 | 8 | 91.2 |
| Cefepime | 4 | 93.4 | 1 | 98.4 | ≥64 | 81.5 | 1 | 98.4 |
| Imipenem[d] | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 |
| Levofloxacin | 0.5 | 94.3 | 1 | 95.6 | 4 | 87.9 | 1 | 95.0 |
| Amikacin | 8 | 94.3 | 4 | 99.6 | 32 | 81.5 | 4 | 97.9 |
| Minocycline | 8 | 88.5 | 4 | 90.9 | 4 | 90.3 | 8 | 88.9 |
| ***A. baumannii*** | $n = 156$ | | $n = 1889$ | | $n = 188$ | | $n = 669$ | |
| Tigecycline[e] | 1 | n/a | 1 | n/a | 1 | n/a | 1 | n/a |
| Ampicillin | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a |

*Continued*

**Table 4.** *Continued*

| Antimicrobial | Asia/Pacific Rim | | North America | | Latin America | | Europe | |
|---|---|---|---|---|---|---|---|---|
| | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S | $MIC_{90}$ (mg/L) | %S |
| Amoxicillin/clavulanate | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a |
| Piperacillin/tazobactam | 128 | 51.9 | 128 | 59.4 | 128 | 11.2 | 128 | 61.1 |
| Ceftazidime | ≥64 | 44.9 | ≥64 | 49.9 | ≥64 | 7.5 | ≥64 | 54.0 |
| Ceftriaxone | ≥128 | 25.6 | ≥128 | 30.0 | ≥128 | 2.1 | ≥128 | 35.0 |
| Cefepime | ≥64 | 45.5 | ≥64 | 48.8 | ≥64 | 16.5 | 32 | 56.2 |
| Imipenem[f] | ≥32 | 69.2 | 8 | 88.6 | ≥32 | 60.6 | ≥32 | 85.9 |
| Levofloxacin | 8 | 51.9 | ≥16 | 50.4 | ≥16 | 7.5 | ≥16 | 55.3 |
| Amikacin | ≥128 | 59.6 | 32 | 85.0 | ≥128 | 23.4 | ≥128 | 74.9 |
| Minocycline | 4 | 92.3 | 8 | 88.9 | 2 | 99.5 | 4 | 91.8 |
| ***P. aeruginosa*** | $n = 294$ | | $n = 3344$ | | $n = 254$ | | $n = 1236$ | |
| Tigecycline[e] | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a | ≥32 | n/a |
| Ampicillin | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a |
| Amoxicillin/clavulanate | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a | ≥64 | n/a |
| Piperacillin/tazobactam | 128 | 88.8 | 64 | 90.4 | 128 | 86.2 | 128 | 89.4 |
| Ceftazidime | ≥64 | 73.1 | 32 | 82.8 | ≥64 | 59.4 | 32 | 78.2 |
| Ceftriaxone | ≥128 | 11.6 | ≥128 | 17.8 | ≥128 | 16.5 | ≥128 | 18.3 |
| Cefepime | 32 | 70.4 | 16 | 78.2 | 32 | 57.9 | 32 | 75.8 |
| Imipenem[g] | 16 | 81.4 | 8 | 84.6 | 16 | 66.0 | 16 | 82.0 |
| Levofloxacin | ≥16 | 63.6 | ≥16 | 63.3 | ≥16 | 45.3 | ≥16 | 67.0 |
| Amikacin | 32 | 85.7 | 8 | 97.2 | 64 | 72.0 | 16 | 93.5 |
| Minocycline | ≥32 | 5.8 | ≥32 | 4.8 | ≥32 | 3.5 | ≥32 | 6.6 |

[a]Overall 94.5% of isolates tested against imipenem: Asia/Pacific Rim, 269; North America, 3050; Latin America, 278; Europe, 1047.
[b]Overall 95.3% of isolates tested against imipenem: Asia/Pacific Rim, 341; North America, 3963; Latin America, 325; Europe, 1567.
[c]Overall 93.6% of isolates tested against imipenem: Asia/Pacific Rim, 278; North America, 3365; Latin America, 291; Europe, 1428.
[d]Overall 93.6% of isolates tested against imipenem: Asia/Pacific Rim, 114; North America, 1384; Latin America, 120; Europe, 546.
[e]No breakpoints available.
[f]Overall 97.1% of isolates tested against imipenem: Asia/Pacific Rim, 156; North America, 1805; Latin America, 188; Europe, 669.
[g]Overall 95.7% of isolates tested against imipenem: Asia/Pacific Rim, 290; North America, 3136; Latin America, 250; Europe, 1231.
n/a, CLSI susceptibility breakpoints not available.

reported to have a high rate of MRSA,[16] was not among the countries with the highest rates in TEST. The number of centres participating in TEST is low in most countries, and any deviation from EARSS among the TEST data may reflect the local infection control practices and antimicrobial use associated with the limited number of study centres.

Markedly higher rates of methicillin resistance were seen in the other three regions included in this article, with the highest rates in North and Latin America. For the USA, the rate of 53.7% is comparable with the 2006 value (59.5%) from the National Nosocomial Infections Surveillance system.[17] The MRSA rate for Latin America (49.4%) is an appreciable increase from the published rate of 35% for a previous period (1997–99),[18] perhaps a reflection of the rapid rise in antimicrobial resistance in this region. Included in this region is Mexico, the country with the highest MRSA rate (86.4%) in this study. This figure is inconsistent with previous estimates of up to 30% and may represent a clonal outbreak at the single Mexican centre.[19] The wide variation in MRSA prevalence among the Asia/Pacific Rim countries was similar to that reported for the SENTRY Program during 1998–99 (65%).[20]

Enterococci are a predominant cause of nosocomial infections and are intrinsically resistant to many antimicrobial agents. As previously reported for *Enterococcus* spp. by Low *et al*. for 1997–99,[21] the vancomycin resistance rate among *E. faecium* in the USA was the highest. As seen with MRSA, the rate of vancomycin-resistant *E. faecium* is highly variable among countries, although it is important to note that rates of vancomycin-resistant *Enterococcus* have not reached the same levels as seen for MRSA in many parts of the world. Published data are scant for some of the countries involved in TEST. For example, the rate reported here for India is notably higher than local publications, but there are few data available in the wider literature.[22] Against both *E. faecalis* and *E. faecium*, tigecycline was the most active compound and the $MIC_{90}$s reported by this study are similar to those reported for isolates collected from Phase III clinical trials[23] and other studies.[24]

The geographical distribution of the ESBL-producing isolates was reflected in the overall antimicrobial susceptibility profile. Latin America had the highest prevalence of *Klebsiella* ESBL producers (44.0%). Only half of all *K. pneumoniae* isolates from Latin America were susceptible to the cephalosporins and combinations of β-lactam/β-lactamase inhibitor. This is in contrast with the other three regions, in which typically >80% of the isolates were susceptible to these antimicrobials. These results support the findings of Winokur *et al*.[25] The most active agents against *K. pneumoniae* (and the subgroup of ESBL producers) were imipenem and tigecycline. Carbapenem resistance among

*K. pneumoniae* remained low key until an outbreak in several hospitals in New York City in 2003.[26] The *K. pneumoniae* implicated in this outbreak was multiresistant with the $bla_{KPC}$ gene, and the most consistently susceptible agents were tigecycline and polymyxin B/rifampicin.[27] In TEST, imipenem remained >99% active against *K. pneumoniae* in all regions. Susceptibility to tigecycline ranged between 94.3% and 97.1%. With the FDA-approved breakpoints used in this study, a total of 56 isolates were on the tigecycline resistance breakpoint of 8 mg/L. These were isolated in Europe (10 isolates), Latin America (4) and North America (42). Such isolates have been reported previously[28] and the mechanism(s) of resistance warrants further investigation. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) published breakpoints for tigecycline in 2006. For Enterobacteriaceae, they are one doubling dilution lower than those approved by the FDA. Applying the EUCAST breakpoint to the European *K. pneumoniae* isolates collected in this study gave susceptibility rates of 88.9% for all *K. pneumoniae* and 75.4% for ESBL-producing isolates.

ESBL production among isolates of *E. coli* ranged from 2.2% in North America to 13.5% in Latin America. The emergence of strains that produce ESBLs or other β-lactamases and the general increase in multidrug resistance among Gram-negative organisms represent a major threat that affects patient outcomes, particularly in ICUs, although community-acquired ESBL producers, especially among the *E. coli*, are becoming more frequent. So far, carbapenem resistance in *E. coli* remains rare[29] and none was seen in the TEST data. Tigecycline, along with imipenem, was the most active against *E. coli* and all isolates from all four regions were susceptible to these two agents. Applying the EUCAST breakpoints to the collection of isolates from European centres gave a rate of susceptibility of 99.9%, with two isolates on the intermediate breakpoint of 2 mg/L. Isolates with an MIC of 2 mg/L have been reported previously in both European and Global studies.[23,30]

As seen for *K. pneumoniae*, the TEST data showed a trend for lower susceptibility rates in Latin America among isolates of *A. baumannii* and *P. aeruginosa*. These observations are in agreement with published reports.[31,32] Significant increases in antimicrobial resistance, mainly to carbapenems and fluoroquinolones, have also been reported among *P. aeruginosa* isolated in Latin America between 1997 and 2001.[33] However, it is established that antimicrobial resistance rates for most nosocomial organisms are higher among ICU patients than among non-ICU patients.[34] One contributing factor to our observations in TEST may well be that a larger proportion of isolates of *P. aeruginosa* and *A. baumannii* (as well as vancomycin-resistant *E. faecium*) originated from ICU than from non-ICU in Latin America when compared with the other regions.

Among the Gram-negative isolates, *A. baumannii* and *P. aeruginosa* were the most resistant to the antimicrobials tested. *A. baumannii* might be considered to be currently the most troublesome nosocomial pathogen, mainly affecting patients in ICUs. These isolates, largely resistant to the commonly used antimicrobials, have now developed resistance to the carbapenems.[35,36] Treatment options for carbapenem-resistant *A. baumannii* infections are limited and agents such as colistin, a drug that was in clinical use in the 1950s but was abandoned when better-tolerated agents became available, are now being reconsidered.[37,38] The antimicrobial with the lowest $MIC_{90}$s for *A. baumannii* in the TEST panel was tigecycline, and it may be a viable option for the treatment of infections caused by *A. baumannii*, although clinical data are lacking.

The susceptibility profile for *P. aeruginosa* in TEST was similar to that reported by Karlowsky *et al.*,[39] piperacillin/tazobactam and amikacin were comparable in activity and the most active, followed by ceftazidime, cefepime and imipenem. Higgins *et al.*[40] described decreased piperacillin/tazobactam susceptibility among imipenem-resistant isolates and linked imipenem resistance in *P. aeruginosa* with higher rates of resistance to other unrelated antimicrobials. In TEST, imipenem remained fairly active against *P. aeruginosa*, with higher susceptibility rates (>80%, except in Latin America) than ceftazidime, the antipseudomonal cephalosporin. Tigecycline is not considered active against *P. aeruginosa*,[41] and does not have an indication for the treatment of infection caused by this organism.

Surveillance of antimicrobial resistance is essential to understand trends in resistance so as to develop judicious treatment guidelines and to assess the effectiveness of interventions. There are a number of international surveillance studies currently in operation, perhaps the most widely known being The Surveillance Network (TSN) and SENTRY. TEST covers a large geographic area, involves a wide range of Gram-positive and Gram-negative organisms and with 3 years of operation currently contains more than 35 000 isolates in its database. As seen by the data presented here, a large proportion of the isolates collected are from North America (and the USA in particular); however, with the continuation of this study, the contribution from other regions will increase. A possible bias of this study is that it only collected isolates from teaching hospitals and so the results may be an overrepresentation of resistant organisms in the general population. The study would also benefit from the addition of genotyping analysis. As stated by Bax *et al.*,[42] there is no 'ideal' surveillance system, but the data presented by TEST add to the knowledge already available on antimicrobial resistance globally.

Few antimicrobial agents remain that are active against a wide range of organisms. Against Gram-positive organisms, vancomycin and linezolid continue to provide excellent activity, and for Gram-negatives, imipenem is highly active. However, as shown by the data presented here, high rates of resistance have been reported for many antimicrobials, but tigecycline, with its ability to circumvent the common resistance mechanisms and its activity against both Gram-positive and Gram-negative organisms, may make a welcome alternative for the treatment of nosocomial infections.

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