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# Antimicrobial Susceptibility among Gram-Positive Organisms Collected from Pediatric Patients Globally between 2004 and 2011: Results from the Tigecycline Evaluation and Surveillance Trial

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**The Tigecycline Evaluation and Surveillance Trial (TEST) was designed to monitor global longitudinal changes in bacterial susceptibility to a panel of antimicrobial agents, including tigecycline. In this study, we examine susceptibility among Gram-positive isolates collected from pediatric patients globally between 2004 and 2011. A total of 9,422 Gram-positive isolates were contributed by 1,255 centers, predominantly from Europe and North America. One-third of *Staphylococcus aureus* isolates were methicillin resistant, peaking in prevalence in 2007. All *S. aureus* isolates ($n = 3,614$) were susceptible to linezolid, tigecycline, and vancomycin; minocycline, imipenem, and meropenem were also highly active (>92% susceptibility). Ampicillin and penicillin susceptibility increased significantly during the study period ($P < 0.0001$ for both). *Streptococcus pneumoniae* isolates ($n = 3,373$) were highly susceptible to vancomycin (100%), linezolid (>99%), and levofloxacin and tigecycline (both >96%); imipenem susceptibility was low (32%) in Africa while minocycline susceptibility was low in Asia-Pacific Rim (38%). Penicillin resistance occurred in one-fifth of all *S. pneumoniae* isolates, with penicillin susceptibility ranging from 14% in Africa to 65% in Europe. *Streptococcus agalactiae* isolates ($n = 1,056$) were highly susceptible to most antimicrobials, although only 16% were susceptible to minocycline. *Enterococcus faecalis* isolates ($n = 1,112$) were highly susceptible (>97%) to ampicillin, linezolid, penicillin, tigecycline, and vancomycin globally, but only 34% were minocycline susceptible; minocycline susceptibility decreased significantly from 2004 to 2011 ($P < 0.001$). Tigecycline and linezolid were highly active against *Enterococcus faecium* ($n = 267$) globally (100% and 98% susceptible, respectively). Tigecycline and linezolid were highly active against Gram-positive pathogens from pediatric patients in TEST 2004 to 2011, with vancomycin and the carbapenems performing well against most pathogens.**

The endurance of drug-resistant Gram-positive pathogens, particularly the staphylococci, streptococci, and enterococci, is a continuing global health care issue. *Streptococcus pneumoniae* has been estimated to cause over 800,000 deaths per year in children under 5 years of age (1). *Streptococcus agalactiae* is a group B streptococcus that can cause pneumonia, meningitis, and sepsis in newborn infants (2). One 2003-2007 U.S. study found that *S. agalactiae* caused one-third of all bacterial meningitis cases in children aged from less than 2 months up to 17 years of age (3).

Drug resistance among methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP) is caused by the production of supplementary, low-affinity penicillin-binding proteins (PBPs) and has existed over the last few decades. Vancomycin resistance among enterococci (mostly *Enterococcus faecium*) emerged more recently, during the 1990s, and occurs through mutations in the bacterial peptidoglycan precursors that bind vancomycin (4, 5). There are six vancomycin-resistant phenotypes known to date: VanA, VanB, VanD, VanE, VanG, and VanL (6).

For *S. pneumoniae*, antimicrobial resistance is linked with community-acquired (CA) infections, whereas for vancomycin-resistant enterococci (VRE), infections are mostly hospital acquired (HA). HA-MRSA infections were the first to occur, but more recently, MRSA infections in the community have emerged (4, 6). In the last decade, the prevalence of CA-MRSA has increased in children under the age of 18 years (7).

Tigecycline is a novel glycylcycline antimicrobial that has activity against a broad spectrum of pathogens, including drug-resistant organisms such as MRSA, PRSP, and VRE. The Tigecycline Evaluation and Surveillance Trial (TEST) is a global surveillance study that was established in 2004 to monitor the *in vitro* activity of tigecycline, and a range of other antimicrobial agents, against a variety of pathogens with clinical importance. This paper examines the *in vitro* activity of a panel of antimicrobials against Gram-positive isolates from pediatric patients, collected globally between 2004 and 2011.

The MIC results presented/discussed here should not be interpreted as recommendations for clinical treatment; clinicians should always follow CLSI guidelines for treatment of infections.

## MATERIALS AND METHODS

**Sample collection.** A total of 1,255 centers worldwide provided clinically significant bacterial isolates from 2004 to 2011. The distribution according to region was as follows: Europe, 500 centers; North America, 442; Latin America, 164; Asia-Pacific Rim, 83; the Middle East, 43; and Africa, 23. Each center was requested to submit a minimum number of Gram-positive organisms each year, including *S. aureus* (25 isolates), *S. pneumoniae* (15 isolates), *S. agalactiae* (10 isolates), and *Enterococcus* species

Received 21 January 2013 Returned for modification 1 February 2013
Accepted 9 May 2013
Published ahead of print 15 May 2013
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Supplemental material for this article may be found at http://dx.doi.org/10.1128/JCM.00157-13.

doi:10.1128/JCM.00157-13

(*E. faecium* and *E. faecalis*) (10 isolates). Only one isolate per patient was permitted, and inclusion of any isolate was independent of patient medical history, previous antimicrobial use, gender, or age (only isolates from patients aged 0 to 18 years were included in the current study). Acceptable sources included bodily fluid; central nervous system (CNS); cardiovascular system (CVS); gastrointestinal (GI) tract; genitourinary (GU) tract; head, ears, eyes, nose, and throat (HEENT); medical instruments (including catheters, surgical instruments, and prostheses); integument; lymph; and the muscular, reproductive, respiratory, or skeletal system.

**Antimicrobial susceptibility testing and determination.** All centers measured MICs using broth microdilution methods (Sensititre plates [Trek Diagnostic Systems, West Sussex, United Kingdom] or MicroScan panels [Siemens Healthcare Diagnostics Inc., Sacramento, CA]) in accordance with the guidelines published by the Clinical and Laboratory Standards Institute (CLSI) (8). Gram-positive isolates were tested against the following panel of agents: amoxicillin-clavulanate, ampicillin, ceftriaxone, imipenem, levofloxacin, linezolid, meropenem, minocycline, penicillin, piperacillin-tazobactam, tigecycline, and vancomycin. In 2006, meropenem replaced imipenem in the TEST panel due to stability issues, and the use of Sensititre plates was discontinued in favor of MicroScan panels. In 2008, the panel of antimicrobial agents tested against *S. pneumoniae* was extended to include azithromycin, clarithromycin, clindamycin, and erythromycin, and isolates have been tested retrospectively.

Laboratories International for Microbiology Studies, a division of International Health Management Associates, Inc. (IHMA; Schaumburg, IL), were responsible for isolate collection and transport, confirmation of isolate identification, and management of a centralized database. The IHMA also carried out quality control (QC) checks on approximately 10% to 15% of isolates, as recommended in the CLSI guidelines (10). Gram-positive QC strains used during testing were *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. MIC data were included in this analysis only if the corresponding daily QC isolate test results for each antimicrobial agent were within the MIC ranges accepted by the CLSI (9).

Antimicrobial susceptibility was assessed according to CLSI interpretive criteria (9). For tigecycline, the criteria as approved by the U.S. Food and Drug Administration (provided in the tigecycline package insert) were used (10).

## RESULTS

Between 2004 and 2011, 1,255 centers worldwide contributed data on Gram-positive isolates to the TEST study, with the majority of centers being located in Europe and North America (39.8% and 35.2%, respectively) (Table 1). A total of 9,422 Gram-positive isolates were collected from 2004 to 2011. The majority of isolates submitted were *S. aureus* (3,614), followed by 3,373 *S. pneumoniae* isolates, 1,112 *E. faecalis* isolates, 1,056 *S. agalactiae* isolates, and 267 *E. faecium* isolates.

***Staphylococcus aureus.*** Linezolid, tigecycline, and vancomycin were highly active against *S. aureus* isolates from all regions participating in TEST (100% susceptibility for each region in all years) (Table 2 and 3). Global susceptibility of *S. aureus* to minocycline, imipenem, and meropenem was 98.4%, 95.9%, and 92.4%, respectively, during all TEST years. Susceptibility of *S. aureus* to amoxicillin-clavulanate, ceftriaxone, levofloxacin, and piperacillin-tazobactam appeared to vary by region but was high in Europe and the Middle East (≥87.5%). Asia-Pacific Rim, Latin American, and North American *S. aureus* isolates had lower susceptibility to these agents (65% to 80%) over all years. Ampicillin and penicillin had little activity against *S. aureus* globally: overall bacterial susceptibility to these antimicrobials during TEST was 11.5% and 9.8%, respectively. European isolates were marginally more susceptible to both antimicrobials, with higher susceptibility for all years than the pooled global figures.

**TABLE 1** Number of centers by geographical region during all years of TEST[a]

| Yr | Africa | Asia-Pacific Rim | Europe | Latin America | Middle East | North America | Global |
|---|---|---|---|---|---|---|---|
| 2004 | 1 | 6 | 30 | 4 | 0 | 64 | 105 |
| 2005 | 4 | 6 | 20 | 12 | 3 | 92 | 137 |
| 2006 | 4 | 16 | 46 | 23 | 4 | 84 | 177 |
| 2007 | 6 | 21 | 65 | 25 | 5 | 80 | 202 |
| 2008 | 4 | 12 | 96 | 34 | 7 | 35 | 188 |
| 2009 | 3 | 12 | 106 | 33 | 11 | 36 | 201 |
| 2010 | 0 | 10 | 89 | 25 | 9 | 26 | 159 |
| 2011 | 1 | 0 | 48 | 8 | 4 | 25 | 86 |
| 2004–2011 | 23 | 83 | 500 | 164 | 43 | 442 | 1,255 |

[a] Africa = Mauritius, Namibia, South Africa, and Tunisia; Asia-Pacific Rim = Australia, China, Hong Kong, India, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan, and Thailand; Europe = Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, The Netherlands, and United Kingdom; Latin America = Argentina, Brazil, Chile, Colombia, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Puerto Rico, and Venezuela; Middle East = Israel, Jordan, Lebanon, Oman, Saudi Arabia, and Turkey; and North America = Canada and United States.

Methicillin resistance was observed in approximately 1 in 3 *S. aureus* isolates globally between 2004 and 2011 (see Table S1 in the supplemental material). The number of global MRSA isolates peaked in 2007 (32.0%) but decreased in each subsequent year, such that it reached 21.7% in 2011 (data not shown). North America had the highest proportions of MRSA during TEST: the 2004-2011 value was 40.7%, which exceeded the global study average (27.2%). The lowest percentage of MRSA over all years was found in Europe (12.0%). Statistically significant decreases in susceptibility to amoxicillin-clavulanate were reported in Latin America ($P < 0.01$) and North America ($P < 0.0001$), while susceptibility to ampicillin and penicillin increased significantly globally ($P < 0.0001$ for both) (see Table S2).

Source data were available for 3,614 isolates of *S. aureus*, with integument isolates being the most common (1,038/3,614). Susceptibility to amoxicillin-clavulanate, ceftriaxone, levofloxacin, meropenem, and piperacillin-tazobactam was lowest among isolates derived from instruments (Table 4). Susceptibility to amoxicillin-clavulanate, ceftriaxone, levofloxacin, minocycline, and piperacillin-tazobactam was lower among patients aged 1 to 5 years in the Asia-Pacific Rim than in older patients from the same region (see Table S3a in the supplemental material). In the Middle East, susceptibility to amoxicillin-clavulanate, ceftriaxone, levofloxacin, meropenem, and piperacillin-tazobactam was reduced among 13- to 17-year-old patients.

***Streptococcus pneumoniae.*** Regionally, *S. pneumoniae* isolates were most susceptible to vancomycin (100% susceptibility) and linezolid (>99%) over all years (Table 2). Levofloxacin and tigecycline were also highly active, with >96% of isolates susceptible to these agents in all regions each year between 2004 and 2011. *S. pneumoniae* susceptibility to minocycline, meropenem, and ceftriaxone was notably lower in Asia-Pacific Rim (38.2%, 47.3%, and 78.0%, respectively) than in all other regions. Susceptibility to imipenem, minocycline, and meropenem also varied with TEST region. African isolates had the lowest susceptibility to imipenem

**TABLE 2** $MIC_{90}$ and antimicrobial susceptibility for Gram-positive isolates collected from pediatric patients as part of TEST 2004–2011[a]

| | Africa | | Asia-Pacific Rim | | Europe | | Latin America | | Middle East | | North America | | Global | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Species and antimicrobial agent | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S |
| *Staphylococcus aureus* | | | | | | | | | | | | | | |
| AMOX-CLAV | ≥16 | 84.0 | ≥16 | 70.5 | 4 | 91.3 | ≥16 | 67.7 | 4 | 90.4 | 8 | 68.6 | 8 | 78.5 |
| Ampicillin | ≥32 | 4.0 | ≥32 | 6.0 | ≥32 | 16.6 | ≥32 | 7.7 | ≥32 | 9.6 | ≥32 | 9.1 | ≥32 | 11.5 |
| Ceftriaxone | ≥128 | 83.0 | ≥128 | 68.9 | 16 | 89.5 | ≥128 | 66.9 | 16 | 87.5 | 32 | 65.3 | 32 | 76.3 |
| Imipenem | 16 | 81.3 | 1 | 92.9 | 0.5 | 97.7 | ≥32 | 84.2 | — | — | 1 | 97.5 | 1 | 95.9 |
| Levofloxacin | 0.5 | 90.0 | 8 | 76.5 | 1 | 90.8 | 8 | 76.8 | 1 | 91.2 | 4 | 79.6 | 4 | 84.1 |
| Linezolid | 2 | 100 | 4 | 100 | 4 | 100 | 4 | 100 | 4 | 100 | 2 | 100 | 4 | 100 |
| Meropenem | 2 | 91.2 | ≥32 | 75.9 | 1 | 96.3 | ≥32 | 80.1 | 2 | 94.1 | 2 | 95.6 | 2 | 92.4 |
| Minocycline | 4 | 98.0 | 4 | 91.3 | 0.5 | 98.3 | 0.5 | 98.5 | 1 | 99.3 | ≤0.25 | 99.3 | 0.5 | 98.4 |
| Penicillin | ≥16 | 4.0 | ≥16 | 6.0 | ≥16 | 14.4 | ≥16 | 5.8 | ≥16 | 8.1 | ≥16 | 7.7 | ≥16 | 9.8 |
| PIP-TAZ | ≥32 | 86.0 | ≥32 | 72.7 | 4 | 94.0 | ≥32 | 72.5 | 8 | 92.6 | ≥32 | 75.8 | ≥32 | 83.1 |
| Tigecycline | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 |
| Vancomycin | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 |
| *Streptococcus pneumoniae* | | | | | | | | | | | | | | |
| AMOX-CLAV | 4 | 80.6 | 8 | 74.6 | 2 | 94.8 | 2 | 93.0 | 2 | 90.1 | 4 | 83.3 | 4 | 88.9 |
| Ampicillin | 4 | NA | 8 | NA | 2 | NA | 4 | NA | 4 | NA | 8 | NA | 4 | NA |
| Ceftriaxone | 1 | 93.9 | 2 | 78.0 | 1 | 94.9 | 1 | 93.8 | 1 | 91.8 | 1 | 93.2 | 1 | 93.1 |
| Imipenem | 0.5 | 32.0 | 0.5 | 85.2 | 0.25 | 89.2 | 1 | 74.4 | — | — | 0.5 | 63.3 | 0.5 | 70.2 |
| Levofloxacin | 1 | 100 | 1 | 99.4 | 1 | 99.8 | 1 | 99.4 | 1 | 98.9 | 1 | 99.7 | 1 | 99.7 |
| Linezolid | 1 | 99.0 | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 | 1 | 100 | 1 | >99.9 |
| Meropenem | 1 | 56.2 | 1 | 47.3 | 0.5 | 83.4 | 1 | 75.4 | 1 | 73.2 | 1 | 70.7 | 1 | 75.5 |
| Minocycline | 8 | 78.6 | ≥16 | 38.2 | ≥16 | 66.7 | ≥16 | 69.1 | ≥16 | 57.7 | 8 | 77.5 | ≥16 | 69.2 |
| Penicillin | 4 | 14.3 | 4 | 37.0 | 2 | 65.6 | 2 | 47.2 | 4 | 43.4 | 4 | 49.7 | 4 | 53.9 |
| PIP-TAZ | 4 | NA | 8 | NA | 4 | NA | 4 | NA | 4 | NA | 4 | NA | 4 | NA |
| Tigecycline | 0.03 | 96.9 | 0.03 | 100 | 0.06 | 98.3 | 0.06 | 98.3 | 0.03 | 99.5 | 0.06 | 98.6 | 0.06 | 98.5 |
| Vancomycin | 0.5 | 100 | 0.5 | 100 | 0.5 | 100 | 0.5 | 100 | 0.5 | 100 | 0.5 | 100 | 0.5 | 100 |
| *Streptococcus agalactiae* | | | | | | | | | | | | | | |
| AMOX-CLAV | 0.12 | NA | 0.12 | NA | 0.12 | NA | 0.12 | NA | 0.12 | NA | 0.12 | NA | 0.12 | NA |
| Ampicillin | 0.12 | 100 | 0.25 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 |
| Ceftriaxone | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 |
| Imipenem | — | — | — | — | 0.25 | NA | — | — | — | — | 0.25 | NA | 0.25 | NA |
| Levofloxacin | 1 | 96.3 | 1 | 98.0 | 1 | 99.8 | 1 | 99.0 | 1 | 100 | 1 | 100 | 1 | 99.6 |
| Linezolid | 1 | 100 | 2 | 100 | 1 | 100 | 2 | 100 | 1 | 100 | 1 | 100 | 1 | 100 |
| Meropenem | ≤0.12 | 100 | ≤0.12 | 100 | ≤0.12 | 100 | ≤0.12 | 100 | ≤0.12 | 100 | ≤0.12 | 100 | ≤0.12 | 100 |
| Minocycline | ≥16 | 3.7 | ≥16 | 22.4 | ≥16 | 14.6 | ≥16 | 18.1 | ≥16 | 17.2 | ≥16 | 16.6 | ≥16 | 15.9 |
| Penicillin | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 | 0.12 | 100 |
| PIP-TAZ | ≤0.25 | NA | 0.5 | NA | 0.5 | NA | 0.5 | NA | 0.5 | NA | ≤0.25 | NA | 0.5 | NA |
| Tigecycline | 2 | 88.9 | 0.06 | 98.0 | 0.12 | 99.5 | 0.06 | 100 | 0.25 | 100 | 0.12 | 99.5 | 0.12 | 99.2 |
| Vancomycin | 0.5 | 100 | 1 | 100 | 0.5 | 100 | 0.5 | 100 | 1 | 100 | 0.5 | 100 | 0.5 | 100 |
| *Enterococcus faecalis* | | | | | | | | | | | | | | |
| AMOX-CLAV | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA |
| Ampicillin | 1 | 100 | 2 | 100 | 2 | 99.3 | 2 | 100 | 2 | 100 | 1 | 99.8 | 2 | 99.6 |
| Ceftriaxone | ≥128 | NA | ≥128 | NA | ≥128 | NA | ≥128 | NA | ≥128 | NA | ≥128 | NA | ≥128 | NA |
| Imipenem | — | — | — | — | 4 | NA | — | — | — | — | 4 | NA | 4 | NA |
| Levofloxacin | ≥64 | 48.4 | 32 | 77.3 | 4 | 88.9 | 32 | 81.7 | 32 | 86.2 | 2 | 92.4 | 16 | 87.4 |
| Linezolid | 2 | 100 | 2 | 97.7 | 2 | 100 | 2 | 100 | 2 | 100 | 2 | 99.8 | 2 | 99.8 |
| Meropenem | — | — | 16 | NA | 8 | NA | 8 | NA | 8 | NA | 8 | NA | 8 | NA |
| Minocycline | ≥16 | 32.3 | ≥16 | 40.9 | ≥16 | 34.6 | ≥16 | 30.0 | ≥16 | 34.5 | ≥16 | 34.0 | ≥16 | 33.8 |
| Penicillin | 4 | 100 | 4 | 100 | 4 | 99.3 | 4 | 98.9 | 4 | 100 | 4 | 99.8 | 4 | 99.5 |
| PIP-TAZ | 4 | NA | 8 | NA | 8 | NA | 8 | NA | 4 | NA | 4 | NA | 4 | NA |
| Tigecycline | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 100 | 0.25 | 99.0 | 0.25 | 99.6 |
| Vancomycin | 2 | 100 | 2 | 100 | 2 | 99.8 | 2 | 100 | 2 | 100 | 2 | 99.0 | 2 | 99.6 |
| *Enterococcus faecium* | | | | | | | | | | | | | | |
| AMOX-CLAV | — | — | ≥16 | NA | ≥16 | NA | ≥16 | NA | — | — | ≥16 | NA | ≥16 | NA |
| Ampicillin | — | — | ≥32 | 10.0 | ≥32 | 28.9 | ≥32 | 24.1 | — | — | ≥32 | 37.5 | ≥32 | 28.1 |

(Continued on following page)

**TABLE 2** (Continued)

| Species and antimicrobial agent | Africa | | Asia-Pacific Rim | | Europe | | Latin America | | Middle East | | North America | | Global | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S | $MIC_{90}$ | % S |
| Ceftriaxone | — | — | ≥128 | NA | ≥128 | NA | ≥128 | NA | — | — | ≥128 | NA | ≥128 | NA |
| Imipenem | — | — | — | — | — | — | — | — | — | — | ≥32 | NA | ≥32 | NA |
| Levofloxacin | — | — | ≥64 | 6.7 | ≥64 | 38.6 | ≥64 | 27.6 | — | — | ≥64 | 33.8 | ≥64 | 31.5 |
| Linezolid | — | — | 2 | 100 | 2 | 98.8 | 2 | 100 | — | — | 2 | 95.0 | 2 | 98.1 |
| Meropenem | — | — | ≥32 | NA | ≥32 | NA | ≥32 | NA | — | — | ≥32 | NA | ≥32 | NA |
| Minocycline | — | — | 8 | 70.0 | ≥16 | 61.4 | ≥16 | 56.9 | — | — | 8 | 76.3 | ≥16 | 66.7 |
| Penicillin | — | — | ≥16 | 10.0 | ≥16 | 25.3 | ≥16 | 20.7 | — | — | ≥16 | 35.0 | ≥16 | 25.1 |
| PIP-TAZ | — | — | ≥32 | NA | ≥32 | NA | ≥32 | NA | — | — | ≥32 | NA | ≥32 | NA |
| Tigecycline | — | — | 0.12 | 100 | 0.25 | 100 | 0.25 | 100 | — | — | 0.12 | 100 | 0.25 | 100 |
| Vancomycin | — | — | ≥64 | 83.3 | 4 | 90.4 | ≥64 | 53.4 | — | — | ≥64 | 57.5 | ≥64 | 71.9 |

[a] $MIC_{90}$s are expressed in milligrams per liter. Abbreviations and symbols: % S, % of isolates susceptible; AMOX-CLAV, amoxicillin-clavulanate; PIP-TAZ, piperacillin-tazobactam; NA, susceptibility breakpoint not available; —, *n* is <20, and therefore, $MIC_{90}$ and % S are not given.

**TABLE 3** Numbers of isolates tested by organism and region against imipenem and meropenem

| Species | Region | No. of isolates | | |
|---|---|---|---|---|
| | | | Tested with drug: | |
| | | Total | Imipenem | Meropenem |
| *S. aureus* | Africa | 100 | 32 | 68 |
| | Asia-Pacific Rim | 183 | 42 | 141 |
| | Europe | 1,384 | 218 | 1,166 |
| | Latin America | 465 | 57 | 408 |
| | Middle East | 136 | 17 | 119 |
| | North America | 1,346 | 488 | 858 |
| | Global | 3,614 | 854 | 2,760 |
| *S. pneumoniae* | Africa | 98 | 25 | 73 |
| | Asia-Pacific Rim | 173 | 27 | 146 |
| | Europe | 1,375 | 195 | 1,180 |
| | Latin America | 356 | 39 | 317 |
| | Middle East | 182 | 3 | 179 |
| | North America | 1,189 | 499 | 690 |
| | Global | 3,373 | 788 | 2,585 |
| *S. agalactiae* | Africa | 27 | 5 | 22 |
| | Asia-Pacific Rim | 49 | 3 | 46 |
| | Europe | 425 | 54 | 371 |
| | Latin America | 105 | 9 | 96 |
| | Middle East | 29 | 0 | 29 |
| | North America | 421 | 174 | 247 |
| | Global | 1,056 | 245 | 811 |
| *E. faecalis* | Africa | 31 | 13 | 18 |
| | Asia-Pacific Rim | 44 | 11 | 33 |
| | Europe | 407 | 70 | 337 |
| | Latin America | 180 | 18 | 162 |
| | Middle East | 29 | 1 | 28 |
| | North America | 421 | 152 | 269 |
| | Global | 1,112 | 265 | 847 |
| *E. faecium* | Africa | 3 | 1 | 2 |
| | Asia-Pacific Rim | 30 | 8 | 22 |
| | Europe | 83 | 10 | 73 |
| | Latin America | 58 | 1 | 57 |
| | Middle East | 13 | 1 | 12 |
| | North America | 80 | 28 | 52 |
| | Global | 267 | 49 | 218 |

(32.0% for all years), whereas Asia-Pacific Rim and European *S. pneumoniae* isolates were >85% susceptible. Penicillin susceptibility among *S. pneumoniae* isolates was low in all regions, ranging from 14.3% in Africa to 65.6% in Europe (Table 2). *S. pneumoniae* isolates with penicillin resistance were found in every region, constituting one-fifth of all *S. pneumoniae* isolates worldwide (see Table S1 in the supplemental material). Asia-Pacific Rim had the highest proportions of PRSP during TEST (41.6%). Europe recorded consistently low percentages of PRSP, with a total of 13.4% between 2004 and 2011.

*S. pneumoniae* had low susceptibility to azithromycin, clarithromycin, and erythromycin (see Table S4 in the supplemental material), such that the global susceptibility to each macrolide was approximately 60% during the collecting period. Clindamycin was least active against *S. pneumoniae* from Asia-Pacific Rim and Africa (54.4% and 65.5% susceptibility, respectively), but in all other regions, >75% of isolates were susceptible. Minocycline susceptibility decreased significantly in most geographical regions in this study (see Table S2). Susceptibility decreased significantly to eight antimicrobial agents on the TEST panel in the Asia-Pacific Rim region and to five agents in North America; tigecycline susceptibility increased significantly in Europe ($P < 0.0001$). Globally, *S. pneumoniae* susceptibility decreased significantly to ceftriaxone and minocycline ($P < 0.0001$ for both) but increased to imipenem ($P < 0.001$), meropenem ($P < 0.01$), and tigecycline ($P < 0.01$).

Source data were available for 3,362 *S. pneumoniae* isolates, the most common sources being HEENT (1,314/3,362) and respiratory (1,049/3,362) specimens (Table 4). Susceptibility to amoxicillin-clavulanate, meropenem, and penicillin was lowest among respiratory isolates. Clindamycin susceptibility was higher among CNS isolates than among isolates from other collection sources (see Table S5 in the supplemental material). Global macrolide susceptibility was slightly higher among isolates from patients aged 6 to 12 years than among isolates from those aged 1 to 5 years or 13 to 17 years (see Table S3b).

***Streptococcus agalactiae.*** Approximately 80% of all *S. agalactiae* isolates were submitted by European and North American centers (data not shown). These organisms were 96.3% to 100% susceptible, annually, to most antimicrobial agents (ampicillin, ceftriaxone, levofloxacin, linezolid, meropenem, penicillin, and vancomycin) (Table 2) in all regions. *S. agalactiae* isolates were

**TABLE 4** Antimicrobial susceptibility by collection source for Gram-positive isolates collected from pediatric patients as part of TEST 2004–2011[a]

| Species and collection source | *n* | % susceptible to drug: AMOX-CLAV | Ampicillin | Ceftriaxone | Imipenem (*n*) | Levofloxacin | Linezolid | Meropenem (*n*) | Minocycline | Penicillin | PIP-TAZ | Tigecycline | Vancomycin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *S. aureus* | 3,614 | | | | | | | | | | | | |
| Bodily fluids | 599 | 70.1 | 10.7 | 67.6 | 94.8 (115) | 83.1 | 100 | 94.2 (484) | 97.8 | 8.8 | 77.8 | 100 | 100 |
| CVS | 583 | 82.2 | 12.7 | 79.6 | 92.7 (124) | 84.2 | 100 | 89.8 (459) | 98.6 | 11.1 | 84.2 | 100 | 100 |
| GU | 35 | 80.0 | 22.9 | 77.1 | — (10) | 74.3 | 100 | 80.0 (25) | 94.3 | 20.0 | 85.7 | 100 | 100 |
| HEENT | 521 | 87.3 | 14.4 | 85.4 | 98.3 (120) | 88.1 | 100 | 95.8 (401) | 98.1 | 12.9 | 91.7 | 100 | 100 |
| Instruments | 55 | 65.5 | 16.4 | 65.5 | — (9) | 63.6 | 100 | 73.9 (46) | 98.2 | 14.5 | 69.1 | 100 | 100 |
| Integument | 1,038 | 74.0 | 8.4 | 71.9 | 98.2 (275) | 85.1 | 100 | 94.2 (763) | 98.4 | 6.6 | 79.0 | 100 | 100 |
| Reproductive system | 28 | 82.1 | 10.7 | 85.7 | — (9) | 89.3 | 100 | — (19) | 100 | 7.1 | 92.9 | 100 | 100 |
| Respiratory system | 690 | 83.9 | 13.2 | 81.0 | 93.7 (175) | 82.3 | 100 | 89.7 (515) | 99.1 | 11.6 | 86.7 | 100 | 100 |
| *S. pneumoniae* | 3,362 | | | | | | | | | | | | |
| Bodily fluids | 214 | 91.1 | NA | 92.1 | 58.3 (36) | 99.5 | 100 | 79.2 (178) | 64.0 | 53.7 | NA | 98.6 | 100 |
| CNS | 25 | 100 | NA | 96.0 | — (7) | 100 | 100 | — (18) | 72.0 | 64.0 | NA | 96.0 | 100 |
| CVS | 664 | 91.6 | NA | 93.4 | 76.0 (146) | 99.5 | 100 | 80.3 (518) | 72.3 | 58.6 | NA | 99.1 | 100 |
| HEENT | 1,314 | 89.8 | NA | 93.6 | 72.8 (305) | 99.8 | 99.9 | 76.6 (1,009) | 68.9 | 55.2 | NA | 98.1 | 100 |
| Integument | 48 | 91.7 | NA | 93.8 | — (14) | 100 | 100 | 79.4 (34) | 66.7 | 58.3 | NA | 100 | 100 |
| Respiratory system | 1,049 | 85.0 | NA | 92.4 | 66.2 (272) | 99.5 | 100 | 69.1 (777) | 68.6 | 48.4 | NA | 98.6 | 100 |
| *S. agalactiae* | 1,056 | | | | | | | | | | | | |
| Bodily fluids | 86 | NA | 100 | 100 | NA | 100 | 100 | 100 (73) | 11.6 | 100 | NA | 98.8 | 100 |
| CVS | 349 | NA | 100 | 100 | NA | 99.4 | 100 | 100 (287) | 10.0 | 100 | NA | 99.1 | 100 |
| GI | 21 | NA | 100 | 100 | NA | 100 | 100 | — (19) | 19.0 | 100 | NA | 100 | 100 |
| GU | 158 | NA | 100 | 100 | NA | 100 | 100 | 100 (112) | 15.8 | 100 | NA | 98.7 | 100 |
| HEENT | 148 | NA | 100 | 100 | NA | 100 | 100 | 100 (110) | 27.7 | 100 | NA | 99.3 | 100 |
| Integument | 108 | NA | 100 | 100 | NA | 99.1 | 100 | 100 (70) | 25.0 | 100 | NA | 100 | 100 |
| Reproductive system | 110 | NA | 100 | 100 | NA | 99.1 | 100 | 100 (82) | 14.5 | 100 | NA | 99.1 | 100 |
| Respiratory system | 63 | NA | 100 | 100 | NA | 100 | 100 | 100 (48) | 14.3 | 100 | NA | 100 | 100 |
| *E. faecalis* | 1,112 | | | | | | | | | | | | |
| Bodily fluids | 124 | NA | 100 | NA | NA | 88.7 | 100 | NA | 38.7 | 100 | NA | 100 | 100 |
| CVS | 349 | NA | 99.7 | NA | NA | 89.1 | 100 | NA | 33.8 | 99.7 | NA | 99.4 | 99.4 |
| GU | 292 | NA | 99.7 | NA | NA | 87.7 | 99.7 | NA | 30.5 | 99.0 | NA | 99.3 | 99.7 |
| HEENT | 80 | NA | 98.8 | NA | NA | 86.3 | 100 | NA | 41.3 | 98.8 | NA | 100 | 98.8 |
| Instruments | 41 | NA | 100 | NA | NA | 85.4 | 100 | NA | 36.6 | 100 | NA | 100 | 100 |
| Integument | 131 | NA | 99.2 | NA | NA | 81.7 | 99.2 | NA | 33.6 | 99.2 | NA | 100 | 99.2 |
| Reproductive system | 24 | NA | 100 | NA | NA | 91.7 | 100 | NA | 20.8 | 100 | NA | 100 | 100 |
| Respiratory system | 45 | NA | 100 | NA | NA | 86.7 | 100 | NA | 35.6 | 100 | NA | 100 | 100 |
| *E. faecium* | 267 | | | | | | | | | | | | |
| Bodily fluids | 31 | NA | 32.3 | NA | NA | 29.0 | 100 | NA | 64.5 | 22.6 | NA | 100 | 67.7 |
| CVS | 107 | NA | 33.6 | NA | NA | 36.4 | 98.1 | NA | 66.4 | 30.8 | NA | 100 | 71.0 |
| GU | 51 | NA | 11.8 | NA | NA | 29.4 | 100 | NA | 64.7 | 13.7 | NA | 100 | 82.4 |
| Integument | 29 | NA | 27.6 | NA | NA | 27.6 | 96.6 | NA | 65.5 | 24.1 | NA | 100 | 65.5 |

[a] Abbreviations and symbols: CNS, central nervous system; CVS, cardiovascular system; GI, gastrointestinal; GU, genitourinary; HEENT, head, ears, eyes, nose, and throat; NA, susceptibility breakpoint not available; —, *n* is <20, and therefore, percent susceptible is not given.

>98% susceptible to tigecycline for all years in most regions, apart from in Africa, where total susceptibility was 88.9%. Minocycline was relatively inactive against *S. agalactiae* worldwide (15.9% global susceptibility over all years) (Table 2).

Source data were available for 1,056 isolates of *S. agalactiae*; one-third (349/1,056) of isolates were derived from CVS (Table 4). For European, North American, and global isolates, susceptibility to minocycline was lowest among patients aged 1 to 5 years (see Table S3a in the supplemental material).

***Enterococcus faecalis.*** Ampicillin, linezolid, penicillin, tigecycline, and vancomycin were highly active against *E. faecalis* isolates, with susceptibility of 97% to 100% in all regions (Table 2). Susceptibility of *E. faecalis* to levofloxacin was >77% in all regions except Africa, where it was dramatically lower (48.4%). The global susceptibility of *E. faecalis* to minocycline was low (33.8% during TEST). Global *E. faecalis* susceptibility to ampicillin, minocycline, and penicillin decreased significantly ($P < 0.01$, $P < 0.001$, and $P < 0.01$, respectively) during this study (see Table S2 in the supplemental material).

Source data were available for 1,112 *E. faecalis* isolates (Table 4), with CVS isolates being most common (349/1,112).

***Enterococcus faecium.*** Antimicrobial susceptibility of *E. faecium* in Africa or the Middle East could not be reported due to insufficient isolate numbers. In all other regions, *E. faecium* was 100% susceptible to tigecycline during the TEST study period (Table 2). Linezolid was also highly active against *E. faecium*, with 95% to 100% susceptibility reported regionally. Global susceptibility of *E. faecium* against the remaining TEST agents, in descending order, was as follows: vancomycin, 71.9%; minocycline, 66.7%; levofloxacin, 31.5%; ampicillin, 28.1%; and penicillin, 25.1%.

Acceptable sources included bodily fluid; central nervous system (CNS); cardiovascular system (CVS); gastrointestinal (GI) tract; genitourinary (GU) tract; head, ears, eyes, nose, and throat (HEENT); medical instruments; integument; lymph; and the muscular, reproductive, respiratory, or skeletal system. Over all TEST years, Latin American isolates had the highest resistance to vancomycin (41.4%), followed by North America (40%) (see Table S1 in the supplemental material). Only 9.6% of European *E. faecium* isolates were resistant to vancomycin. Linezolid susceptibility increased significantly ($P < 0.01$) globally while penicillin susceptibility decreased ($P < 0.01$) during this study (see Table S2).

Source data were available for 267 isolates of *E. faecium* (Table 4), the most common source being CVS (107/267). Ampicillin and penicillin susceptibility was notably lower among GU isolates. Globally, ampicillin, penicillin, and vancomycin susceptibility was higher among isolates from patients aged 1 to 5 years than among isolates from those aged 6 to 12 years and 13 to 17 years (see Table S3a in the supplemental material).

## DISCUSSION

Few studies have been performed examining the efficacy of tigecycline in children due to concerns about potential side effects. As a tetracycline derivative, tigecycline may cause the same adverse drug reactions as do the tetracyclines, including photosensitivity reactions and pancreatitis in children at any age and permanent tooth discoloration in children under 8 years of age (10, 11). Furthermore, the safety of tigecycline has not been established in pediatric patients, although one U.S. safety study has recently been published (12). In this study, patients of 8 to 11 years of age were administered tigecycline to treat a variety of infections at three doses (0.75, 1, or 1.25 mg/kg of body weight), and overall clinical cure rates at test-of-cure were 94%, 76%, and 75%, respectively, in the three dose groups. There were more indeterminate clinical cure assessments in the 1- and 1.25-mg/kg dose groups due to higher rates of protocol violations than in the 0.75-mg/kg group. Nausea was the most frequent adverse event experienced by patients (50% of all patients) but in only 18% of patients in the 0.75-mg/kg group compared to 65% in the 1.25-mg/kg group. Despite a lack of clinical study data, case reports have described the successful use of tigecycline to treat life-threatening, drug-resistant Gram-positive infections in children (13, 14).

In the current pediatric TEST study, Gram-positive pathogens from children of all age groups in all geographical regions were highly susceptible to tigecycline. The lowest global $MIC_{90}$ was noted for tigecycline in all study years (≤0.25 mg/liter). All organisms were similarly susceptible to linezolid in all regions. These findings reinforce the results of a recent TEST study of global Gram-positive isolates (2004 to 2009) by Dowzicky and Chmelařová, which included not only some of the data included in this work but also data for adult patients (15).

In the current study, the highest numbers of MRSA isolates were collected from North American children. A study of 25 U.S. children's hospitals between 1999 and 2008 saw a 10-fold increase in the incidence of infections caused by MRSA. In 2008, the number of MRSA infections in these U.S. pediatric hospitals had reached 58% of all *S. aureus* infections (16). In this pediatric TEST study, 51.1% of North American *S. aureus* isolates collected in 2008 were methicillin resistant, compared with 12.1% in Europe (data not shown). One reason for the higher rates of MRSA in North America could be the CA-MRSA strain known as USA300 (17). This strain originated in the United States and was first described in a pediatric setting in children from day care centers in the early 2000s (18). USA300 has undergone widespread dissemination within the United States, and only limited cases have been reported in European countries. A lower incidence of MRSA in Europe was also observed in the last global Gram-positive TEST study, which included part of this pediatric data set (15).

In the current TEST study, around 1 in 5 global pediatric isolates of *S. pneumoniae* were penicillin resistant. In 2008, the CLSI increased susceptibility breakpoints for parenteral penicillin against nonmeningeal isolates (19), and these revised breakpoints were applied to all samples in the current TEST study. The updated breakpoints were also used in the most recent global Gram-positive TEST study (15). This previous report showed a lower overall global proportion of PRSP (0.9%) than that in the present study (20.2%). Although the current data set had a longer surveillance period, it is likely that the pediatric focus of this analysis is the main reason for this difference. Children between 1 and 5 years old have higher carriage rates of *S. pneumoniae* in the nasopharynx than do adults (20), as well as the longest duration of carriage in one Swedish study (21). Thus, children are a major source of PRSP clones (20).

A Taiwanese 2000–2007 surveillance study, using the updated penicillin breakpoints, reported that 19.1% of nonmeningeal *S. pneumoniae* isolates were penicillin resistant in patients below the age of 10 years (22). The rate of penicillin resistance was significantly higher in isolates from these younger patients than in those from patients 60 to 80 years of age (13.2% susceptibility) ($P <$

0.001). In the present study, Asia-Pacific Rim had the highest overall percentage of PRSP isolates (41.6%); between 2007 and 2010, more than 50% of all *S. pneumoniae* isolates from Asia-Pacific Rim centers showed penicillin resistance (data not shown). Africa also recorded a high proportion of PRSP isolates (22.7% to 35.9%) between 2005 and 2007 (data not shown). The majority of African centers were located in South Africa, where high rates of penicillin resistance have been described previously (23).

A pediatric study in Peru found that 8.1% of nonmeningeal *S. pneumoniae* isolates were penicillin resistant according to the new CLSI breakpoints for penicillin (24). Though this Latin American study was carried out in only one country, the trend of fewer PRSP isolates in Latin America than in Asia-Pacific Rim matched the observations of the current study (18.5% versus 41.6%, respectively). Worldwide, the rates of macrolide resistance appear to have increased alongside rates of penicillin resistance (20). While regional decreases in susceptibility have been noted in Asia-Pacific Rim and North America, this pediatric TEST study revealed no statistically significant global decreases in *S. pneumoniae* susceptibility to penicillin or any of the macrolides between 2004 and 2011. Also noteworthy here was the statistically significant increase in the global susceptibility of *S. pneumoniae* to tigecycline over the study period.

*S. agalactiae* is a clinically relevant pathogen to pediatric diseases, as described above. This report demonstrated that *S. agalactiae* isolates from children were >98% susceptible to tigecycline in all geographical regions In this study, the global $MIC_{90}$ of tigecycline against *S. agalactiae* (0.12 mg/liter) was similar to that of several other antimicrobials on the TEST panel (amoxicillin-clavulanate, ampicillin, ceftriaxone, imipenem, meropenem, and penicillin). An earlier TEST study (2004 to 2007), which included some of the isolates used in the current study, also published a global $MIC_{90}$ of 0.12 mg/liter for tigecycline against *S. agalactiae*, suggesting that the efficacy of tigecycline against *S. agalactiae* has not changed in recent years (25).

Penicillin susceptibility was high against *S. agalactiae* in this pediatric study (100% global susceptibility over all TEST years). Penicillin is usually the preferred treatment for *S. agalactiae* infections, as these organisms maintain sensitivity to this antimicrobial worldwide (2, 26). This is in contrast with *S. aureus*, *S. pneumoniae*, and *E. faecium*, all of which had a lower global susceptibility to penicillin than did the other TEST agents, as has been previously reported (25). The low susceptibility to penicillin in these pathogens is linked with the inappropriate use of antibiotics over the last few decades (27). These TEST data, however, show a statistically significant increase in the susceptibility of pediatric *S. aureus* isolates to penicillin but a significant decrease in the susceptibility of *E. faecalis* and *E. faecium*. Penicillin resistance is more common in *E. faecium* than in *E. faecalis* due to the overproduction of PBP-5 (28).

Data comparisons in this study were sometimes complicated by low numbers of specific organisms globally or incomplete isolate submission in some geographical regions in one or more years. Thus, the pooled global figures for antimicrobial susceptibilities or percentages of drug-resistant organisms may not reflect these regions. Conversely, there may have been inconsistencies in the sites from which isolates were collected from one year to the next, affecting the overall data from that geographical region.

This TEST report is one of the few studies to examine isolates collected from pediatric patients. Susceptibility of the key resistance phenotypes (PRSP, MRSA, and VR *E. faecium*) to the TEST agents was not assessed overall nor by collection source or patient age in the present study. Considering the high prevalence of antimicrobial resistance in the general population, it might be useful to ascertain whether drug-resistant organisms in children were equally susceptible to tigecycline, or indeed any of the TEST panel drugs, in future studies. The transmission of pathogens from children to adults is a major cause of pneumococcal infections (20), and children were one of the first major groups to be at risk of contracting CA-MRSA infections (18). Therefore, it is important that the activities of antimicrobials against pathogens in children are monitored worldwide.

## ACKNOWLEDGMENTS

We thank the many TEST investigators and laboratories for their participation in this study, as well as the staff at IHMA for their coordination of TEST.

TEST is funded by Pfizer Inc. Michael J. Dowzicky is an employee of Pfizer Inc.

Neera Hobson (Micron Research Ltd., Chatteris, United Kingdom) provided editorial assistance, which was funded by Pfizer Inc. Micron Research Ltd. also provided data management services which were funded by Pfizer Inc.

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