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In vitro activity of tigecycline and comparators (2014–2016) among key WHO 'priority pathogens' and longitudinal assessment (2004–2016) of antimicrobial resistance: a report from the T.E.S.T. study

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ABSTRACT

We report contemporary (2014–2016) Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) global data on activity of tigecycline and comparators against WHO 'priority pathogens', and global trends (2004–2016) in antimicrobial resistance. MICs were determined using CLSI broth microdilution methodology. Antimicrobial resistance was determined using CLSI breakpoints (FDA breakpoints for tigecycline). Data are reported for Africa, Asia, Europe, North America and South America. From 2014–2016, Africa, Asia and South America reported highest resistance rates among *Acinetobacter baumannii*; North America lowest (all antimicrobials tested). The tigecycline MIC_{90} against *A. baumannii* was 2 mg/L in all regions except South America (1 mg/L). Among Enterobacteriaceae, meropenem resistance was low and tigecycline resistance was ≤1.3% in all regions (*Escherichia coli*, 0.0–0.3%; *Klebsiella pneumoniae* 0.0–1.3%; *Enterobacter* spp. 0.5–1.1%; *Serratia marcescens* 0.0–1.3%). Ceftriaxone resistance among *E. coli* ranged from 14.5% (North America) to 54.7% (Asia), and among *K. pneumoniae* from 9.1% (North America) to 54.0% (South America). North America reported highest rates of vancomycin-resistant *Enterococcus faecium* (64.6%); Europe lowest (17.7%). The tigecycline MIC_{90} against methicillin-resistant *Staphylococcus aureus* (MRSA) ranged from 0.12 mg/L (Africa and North America) to 0.5 mg/L (Asia). From 2004–2016, carbapenem resistance increased among *A. baumannii* (all regions), reaching 92.3% in Africa and 85.7% in South America (2016). Rates of ceftriaxone-resistant *E. coli* increased in all regions except Asia. Ceftriaxone resistance in *K. pneumoniae* increased in Europe. Rates of vancomycin-resistant *E. faecium* and MRSA were highest in North America and South America (and Asia for MRSA); lowest in Europe.

1. Introduction

The World Health Organization (WHO) recently published a list of antimicrobial-resistant 'priority pathogens' that pose a major threat to public health. The list aims to guide and promote research and development of new antimicrobials to help tackle global antimicrobial resistance [1]. The global increase in antimicrobial resistance is a major public-health crisis threatening healthcare delivery and patient safety [2]. Resistance to antimicrobials such as carbapenems is of particular concern as this leaves few treatment alternatives for patients with severe infections caused by resistant pathogens and may result in increased hospital admissions, prolonged length of hospital stay and increased mortality [2–6].

The WHO 'priority pathogens' are divided into three categories depending on their level of urgency in relation to their threat to human health and the need for research and development of novel antimicrobials. Priority 1 is labelled 'critical' and includes multidrug-resistant (MDR) Gram-negative bacteria that can cause severe infections and pose the greatest threat to the most vulnerable patients [1]. Priority 2 (high) and 3 (medium) contain some increasingly drug-resistant bacteria present mainly in the community.

The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is an ongoing global surveillance study that has monitored the in vitro activity of tigecycline and comparators against

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clinically important organisms since 2004. It has collected many isolates listed as WHO 'priority pathogens', including all priority 1 pathogens (carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and third-generation cephalosporin-resistant and carbapenem-resistant Enterobacteriaceae), two priority 2 pathogens [vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* (MRSA)] and two priority 3 pathogens (penicillin-non-susceptible *Streptococcus pneumoniae* and ampicillin-resistant *Haemophilus influenzae*). This report provides antimicrobial susceptibility data for pathogens collected between 2014–2016. Furthermore, we show the resistance rates for priority pathogens collected during the T.E.S.T. study over 13 years (2004–2016). Antimicrobial susceptibility data for isolates submitted between 2004–2013 have been published previously [7].

2. Methods

Between 2014–2016, five regions submitted isolates to T.E.S.T.: Africa (5 centres); Asia (21 centres); Europe (105 centres); North America (33 centres); and South America (15 centres). Between 2004–2016, the centre distribution was as follows: Africa (37); Asia (60); Europe (240); North America (236); and South America (69). Regions in this publication are grouped differently to previous T.E.S.T. publications. Not all centres submitted isolates during all study years. Asia (referred to as Asia-Pacific Rim in previous T.E.S.T. publications) did not participate from 2011–2013. Oceania did not participate from 2011–2016 and is not included in this analysis. Isolates were collected from all body sites from inpatients and outpatients with hospital- and community-acquired infections.

Detailed materials and methods for the T.E.S.T. study have been published previously (e.g. [8]), and uniform methodology was used by all study centres. The panel of antimicrobials used in the T.E.S.T. study included amoxicillin/clavulanic acid (AMC), ceftriaxone, levofloxacin, meropenem, minocycline and tigecycline. In addition, Gram-positive organisms were tested against linezolid, penicillin and vancomycin, and Gram-negative organisms against amikacin, ampicillin, cefepime, ceftazidime and piperacillin/tazobactam (TZP). *Streptococcus pneumoniae* isolates were also tested against azithromycin, clarithromycin, clindamycin and erythromycin. A switch from imipenem to meropenem occurred in 2006 owing to inadequate imipenem stability on testing panels. Minimum inhibitory concentrations (MICs) were determined at the respective study centres by applying Clinical and Laboratory Standards Institute (CLSI) guidelines for broth microdilution methodology [9] using Sensititre® plates (TREK Diagnostic Systems, East Grinstead, UK) or MicroScan® panels (Siemens, Sacramento, CA) [8]. Antimicrobial susceptibility was assessed using CLSI breakpoints [10], except for tigecycline for which US Food and Drug Administration (FDA) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used [11,12].

Carbapenem resistance was defined as resistance to imipenem or meropenem. Multidrug resistance in *P. aeruginosa* was defined as resistance to three or more classes of antimicrobials among aminoglycosides (amikacin), β-lactams (cefepime, ceftazidime, TZP), carbapenems (imipenem, meropenem) and fluoroquinolones (levofloxacin). Methicillin resistance in *S. aureus* and extended-spectrum β-lactamase (ESBL) production among *Escherichia coli* and *Klebsiella pneumoniae* were determined at the central laboratory [International Health Management Associates, Inc. (IHMA), Schaumburg, IL] following CLSI guidelines [10].

The rates of resistant phenotypes between 2014–2016 were compared between regions using Fisher's exact test. A *P*-value of <0.01 was considered statistically significant.

3. Results

A total of 51 756 isolates were collected between 2014–2016; 300 187 isolates were collected between 2004–2016. Pooled data for 2014–2016 and 2004–2016 show the majority of isolates were collected from Europe [62.3% ($n=32\,256$) and 48.4% ($n=145\,270$), respectively] and North America [20.6% ($n=10\,649$] and 32.6% ($n=97\,947$)], followed by South America [7.4% ($n=3821$) and 9.7% ($n=29\,083$)], Asia [7.2% ($n=3739$) and 5.0% ($n=15\,130$)] and Africa [2.5% ($n=1291$) and 4.2% ($n=12\,757$)].

3.1. WHO priority 1 organisms (priority: critical)

3.1.1. Acinetobacter baumannii

A total of 2720 *A. baumannii* isolates were submitted between 2014–2016 (Table 1). Resistance rates among isolates of *A. baumannii* to all antimicrobials in the T.E.S.T. panel were generally higher for isolates submitted from Africa, Asia and South America. In all regions, the lowest rate of resistance was to minocycline (ranging from 3.3% in North America to 16.3% in Africa), and MIC_{90} values for tigecycline were 1–2 mg/L.

Between 2014–2016, the global carbapenem resistance rate among *A. baumannii* isolates was 65.8% (1791/2720). Regionally, the rate of carbapenem-resistant *A. baumannii* in North America (45.8%; 178/389) was significantly lower compared with each of the other regions [Europe 62.8% (1017/1620), South America 81.2% (238/293), Asia 85.0% (267/314) and Africa 87.5% (91/104); $P < 0.0001$ for each comparison) (Table 1; Supplementary Table S1). Over the 13-year period (2004–2016), changes in carbapenem resistance rates were seen (Fig. 1). Rates increased in Africa from 21.4% (12/56) in 2005 to 92.3% (36/39) in 2016, and in South America from 64.8% (35/54) in 2004 to 85.7% (78/91) in 2016. Resistance rates in Asia increased from 32.0% (24/75) in 2004 to 83.3% (90/108) in 2016. In contrast, the rate of carbapenem-resistant *A. baumannii* isolates from Europe and North America increased initially [2004 to 2014, 20.6% (77/373) to 67.8% (501/739) and 12.5% (100/802) to 53.0% (96/181), respectively], then in 2016 resistance was 55.8% (174/312) in Europe and 23.7% (14/59) in North America.

3.1.2. Pseudomonas aeruginosa

Between 2014–2016, 6508 *P. aeruginosa* isolates were submitted (Table 1). Irrespective of region, isolates of *P. aeruginosa* showed high rates of resistance to levofloxacin and meropenem; South America reported the highest rates (31.3% and 35.8%, respectively) compared with other regions. The lowest rate of resistance was to amikacin (ranging from 1.1% in North America to 14.0% in South America). MIC_{90} values for tigecycline were 16 mg/L in all regions.

Between 2014–2016, 9.6% (623/6508) of *P. aeruginosa* isolates were MDR and 23.0% (1496/6508) were carbapenem-resistant. The carbapenem resistance rate among *P. aeruginosa* isolates was significantly higher in South America (35.8%; 202/565) compared with each of the other regions [Asia 24.8% (111/447), $P < 0.001$; Europe 23.1% (924/4002), $P < 0.0001$; Africa 21.6% (33/153), $P < 0.001$; North America 16.9% (226/1341), $P < 0.0001$) (Table 1; Supplementary Table S1). Over the 13-year period (2004–2016), all countries showed year-on-year variability with no clear trends in rates of carbapenem-resistant or MDR *P. aeruginosa* (Fig. 2).

3.1.3. Enterobacteriaceae

3.1.3.1. Escherichia coli. A total of 8484 *E. coli* isolates were submitted between 2014–2016; the isolates showed highest rates of resistance to cefepime, ceftriaxone and levofloxacin (Table 1). By region, North America and Europe reported lower rates of resistance to cefepime (9.6% and 14.2%, respectively) and levofloxacin (30.6% and

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