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Antimicrobial Resistance Monitoring through the ATLAS Global Surveillance Program 2012-2018

IHMA
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

M. Hackel[1], S. Bouchillon[1], M. Dowzicky[2], D. Sahm[1]

[1]IHMA, Schaumburg IL, USA, [2]Pfizer Inc., Collegeville, PA, USA

Introduction

The ongoing problem of antibiotic resistance, including multidrug resistance is a global health issue. In order to determine the extent of the problem and to identify changes in the resistance patterns of global, regional and local pathogens, world-wide antibiotic surveillance programs are essential. The Antimicrobial Testing Leadership and Surveillance (ATLAS) program has provided reliable, global, regional and local *in vitro* susceptibility data, including mechanisms of resistance, since 2004. As it is important to monitor the emergence of new species and new resistance mechanisms over time, in this analysis we present a longitudinal analysis of resistance to commonly prescribed antimicrobials for isolates collected globally for ATLAS 2012-2018.

Methods

A total of 251,837 gram-negative and 132,363 gram-positive non-duplicate, clinical isolates were collected from multiple infection sources from 743 unique sites in 74 countries during 2012-2018 in the ATLAS program. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. Organism identification was confirmed by MALDI-TOF mass spectrometry, and susceptibility testing was performed by broth microdilution following CLSI guidelines at a central laboratory (IHMA, Schaumburg, IL, USA) [1]. Avibactam was tested at a fixed concentration of 4 µg/mL. MICs were interpreted using CLSI 2020 MIC breakpoint criteria [2]. FDA breakpoints were applied for tigecycline [3]. Quality control (QC) testing was performed on each day of testing using the appropriate ATCC control strains. Results were included in the analysis only when corresponding QC isolates tested were within the acceptable range according to CLSI guidelines [2].

Results

Overview of ATLAS Program

Targeted surveillance
Collection of a predefined number of selected bacterial pathogens

Global Geographic Focus
843 participating medical centers in 77 countries in Europe, Middle East, Africa, Asia/Pacific Rim, Latin America, North America

Organisms collected:
Gram-negative and Gram-positive aerobes and facultative anaerobes, e.g. select Enterobacterales, *P. aeruginosa*, *Acinetobacter* spp., *Haemophilus* spp., *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp., *Moraxella* spp.

Gram-negative and Gram-positive obligate anaerobes, e.g. *Bacteroides* spp., *Clostridium* spp.

Antimicrobial classes tested:
Cell wall/ cell envelope: β-lactams (penicillins, 3rd-5th generation cephalosporins, monobactams, carbapenems, β-lactam/β-lactamase inhibitor combinations); Glycopeptides; Polymyxins; Membrane depolarizers

Protein synthesis: Aminoglycosides; Tetracyclines; Macrolides; Lincosamides; Oxazolidinones

Nucleic acid synthesis: Fluoroquinolones; Antifolates

Total drugs/drug combinations tested: 27

Infection types:
Intraabdominal infections
Lower respiratory tract infections
Urinary tract infections
Bloodstream infections
Skin and skin structure infections

Community-acquired and hospital-acquired

Phenotypes
Isolates are collected regardless of antimicrobial susceptibility profile

ATLAS Surveillance program workflow

Non-duplicate causative pathogens are collected at participating medical centers

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The pathogens are shipped to the central laboratory (IHMA)

↓

Species identification is confirmed by MALDI-TOF spectrometry

↓

Antimicrobial susceptibility and quality control testing by broth microdilution (aerobes) or agar dilution (anaerobes) is performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines; MIC endpoints are determined manually (industry gold standard methodology)

↓

Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* isolates are screened for presence of known resistance mechanisms (e.g. presence or alteration in genes encoding β-lactamases and penicillin-binding proteins, porin profiling) by PCR and Sanger sequencing or by whole genome sequencing (WGS)

Fig 1. Distribution of organisms in the ATLAS surveillance study, 2012-2018

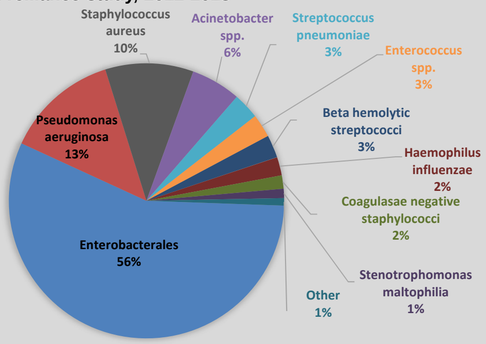


Fig 2. Distribution of Enterobacterales in the ATLAS surveillance study, 2012-2018

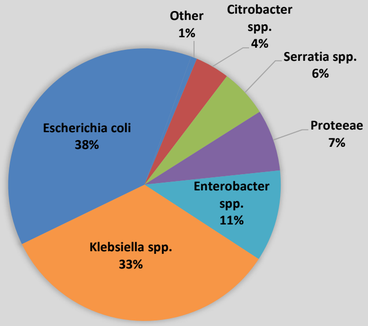


Table 1. Activity of commonly used drugs against Gram-negative and Gram-positive isolates from the ATLAS surveillance study, 2012-2018

Organism (n)	% Susceptible							
Gram negative	**CZA**	**CT**	**TGC**	**AMK**	**FEP**	**LVX**	**MEM**	**TZP**
Enterobacterales (185,287)	98.9	89.6	96.1	97.4	79.0	71.3	96.3	84.9
CRE (5,976)	71.7	2.6	91.7	62.7	3.3	9.4	0	3.0
ESBL+ (31,505)	96.4	67.7	94.8	90.5	27.8	31.8	87.8	55.0
Pseudomonas aeruginosa (44,346)	91.7	90.3	na	91.7	77.9	62.4	72.2	74.4
Acinetobacter spp. (19,640)	na	na	na*	61.2	47.7	48.9	51.2	47.1
Gram positive	**CPT**	**LNZ**	**TGC**	**AMP**	**ERY**	**LVX**	**VAN**	
Enterococcus spp. (22,861)	na	99.0	98.2	67.7	12.0	49.5	87.6	
S. aureus, MSSA (45,227)	>99.9	>99.9	99.7	na	75.6	92.0	100.0	
S. aureus, MRSA (46,471)	89.2	>99.9	98.8	na	31.0	32.6	>99.9	

CRE, carbapenem-resistant Enterobacterales (MEM [meropenem] MIC >2 µg/mL; ESBL+, extended-spectrum β-lactamase positive; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus;* na, no breakpoint; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; TGC, tigecycline; AMK, amikacin; FEP, cefepime; LVX, levofloxacin; TZP, piperacillin-tazobactam; CPT, ceftaroline; LNZ, linezolid; AMP, ampicillin; ERY, erythromycin; VAN, vancomycin
*MIC_{90} = 2 µg/mL

Figure 3. Countries participating in the ATLAS study in green

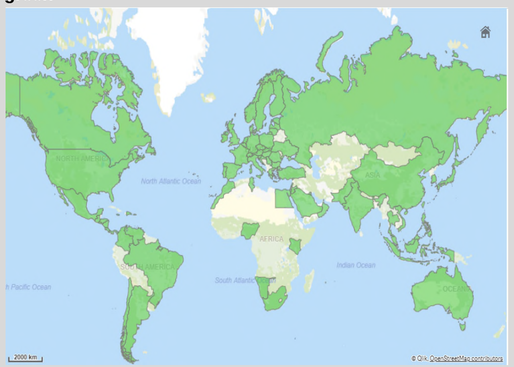
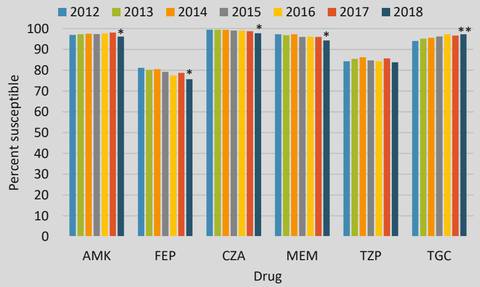


Figure 4. Percentage of susceptibility among Enterobacterales over seven years from the ATLAS surveillance study



AMK, amikacin; FEP, cefepime; CZA, ceftazidime-avibactam; MEM, meropenem; TZP, piperacillin-tazobactam; TGC, tigecycline
Percent susceptible based on CLSI 2020 breakpoints; * statistically significant decrease in susceptibility between 2012 and 2018 based on Chi-square with Yates' correction (p<0.0001); ** statistically significant increase in susceptibility between 2012 and 2018 based on Chi-square with Yates' correction (p<0.0001)

Results Summary

- The proportion of Enterobacterales isolates resistant to commonly used antimicrobials has fluctuated over the seven years compared in this analysis, with significant increases in resistance for amikacin (3.0% to 3.8%), cefepime (18.9% to 24.4%), ceftazidime-avibactam (0.5% to 2.2%), and meropenem (2.7% to 5.7%), and a significant decrease in resistance to tigecycline (5.9% to 2.7%) between 2012-2018 (Chi-square with Yates' correction, p<0.0001) (Figure 4).
- Piperacillin-tazobactam showed no significant change in resistance over seven years of study.

Conclusions

This longitudinal analysis of seven years of global surveillance confirms rising rates of antimicrobial resistance to commonly used antibiotics. Continued monitoring is essential to understand the scope of this global public health issue, and to aid in the development of new strategies and treatments for these key pathogens.

References

1. Clinical Laboratory Standards Institute (CLSI), 2018. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eleventh Edition. CLSI document M07-A11. Pennsylvania 19087-1898 USA.
2. Clinical and Laboratory Standards Institute (CLSI), 2020. Performance Standards for Antimicrobial Susceptibility Testing – Thirtieth Informational Supplement. CLSI Document M100S, Pennsylvania 19087-1898 USA.
3. Tygacil®, 2016. Tigecycline FDA prescribing information. Pfizer, Inc., Collegeville, PA.

Disclosures

This study was sponsored by Pfizer. AstraZeneca's rights to ceftazidime-avibactam and ceftaroline fosamil, which were acquired by Pfizer in December 2016. IHMA received financial support from Pfizer in connection with the study and the development of this poster. MH, SB and DS are employees of IHMA. MD is an employee of Pfizer.