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Variations in the Occurrence of ESBL, CRE, and MDR Phenotypes among *Enterobacteriaceae* Isolates: Results from 20 Years of the SENTRY Antimicrobial Surveillance Program

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

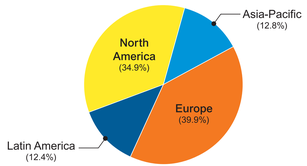
- Acquired resistance in *Enterobacteriaceae* species limits the antimicrobial therapeutic options for infections caused by these isolates and is a growing concern
- Among the numerous resistance mechanisms observed in *Enterobacteriaceae*, β-lactamases are especially worrisome due to the broad use and safety profile of β-lactam agents
- *Enterobacteriaceae* isolates producing extended-spectrum β-lactamases (ESBLs) and/or carbapenemases (CRE) are usually resistant to most or all β-lactam agents
  - These isolates often co-harbour resistance mechanisms to other antimicrobial classes that are carried on mobile genetic elements, which promote the dissemination of these resistance genes
- Multidrug resistance (MDR) that was once uncommon in *Enterobacteriaceae* isolates has now been reported with increasing frequency due to the accumulation of acquired resistance genes
- In this study, we analysed the trends of resistance phenotypes among 178,825 *Enterobacteriaceae* isolates collected in 199 hospitals from 42 countries over 20 years (1997–2016) of the SENTRY Antimicrobial Surveillance Program

Materials and Methods

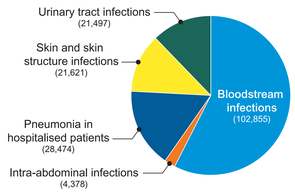
- A total of 178,825 *Enterobacteriaceae* isolates were collected (1/patient) during 1997–2016 in 199 medical centres from 42 countries (Figure 1A)
- Each participating centre was asked to collect consecutive bacterial isolates from bloodstream, skin and skin structure, pneumonia from hospitalised patients, urinary tract, and intra-abdominal tract (Figure 1B) specimens determined to be significant by local criteria as the reported probable cause of infection

Figure 1 Geographic and infection sources of the *Enterobacteriaceae* isolates analysed

A. Geographic sources of the *Enterobacteriaceae* isolates analysed



B. Infection sources of the *Enterobacteriaceae* isolates analysed



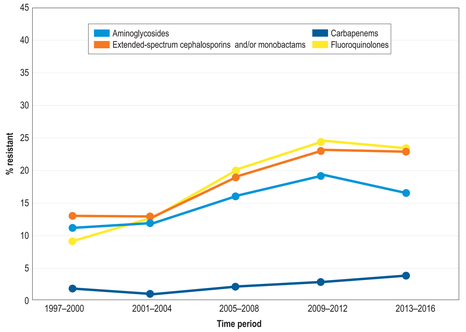
- Organisms were susceptibility tested by reference broth microdilution methods in a central laboratory according to the current Clinical and Laboratory Standards Institute (CLSI) documents
- Quality control (QC) was performed according to CLSI guidelines (M7, 2018), and all QC MIC results were within acceptable ranges as published in CLSI documents
- Categorical interpretations for antimicrobial agents were those found in CLSI criteria in M100 (2018), EUCAST breakpoint tables (version 7.1, January 2018), and/or United States Food and Drug Administration (US FDA) website
- The ESBL-phenotype was defined for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca,* and *Proteus mirabilis* as an MIC value ≥2 mg/L for ceftriaxone, ceftazidime, and/or aztreonam (CLSI, 2018)
- CRE was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 mg/L
  - *Proteus mirabilis* and indole-positive Proteeae were categorised as CRE if doripenem and/or meropenem MIC values were at ≥2 mg/L due to intrinsically elevated imipenem MIC values
- MDR *Enterobacteriaceae* was defined as any isolate nonsusceptible (CLSI criteria) to ≥1 agent in ≥3 of the following antimicrobial classes: broad-spectrum cephalosporins, carbapenems, broad-spectrum penicillin combined with a β-lactamase inhibitor, fluoroquinolones, aminoglycosides, glycylcyclines, and the polymyxins
- Resistance to fluoroquinolones (levofloxacin, ciprofloxacin, and moxifloxacin), aminoglycosides (amikacin, gentamicin, and tobramycin), cephalosporins/monobactams (cefepime, ceftazidime, ceftriaxone, aztreonam), carbapenems (doripenem, imipenem, and meropenem), and polymyxins (colistin and polymyxin B) was defined as resistance to any agent tested within the class
- Statistical analysis was performed by chi-square test to compare the 1997–2000 period to the 2013–2016 period using SAS 9.4

Results

- *Enterobacteriaceae* displaying an ESBL-phenotype (n=24,313) increased worldwide from 10.3% to 24.0%
  - This increase was observed for all infection sources and geographic regions, except Asia-Pacific (Figure 2)
  - Isolates exhibiting an ESBL-phenotype were mainly *Escherichia coli* (47.5%) and *Klebsiella pneumoniae* (43.7%)
- A statistically significant increase of 2.3% (from 0.6% to 2.9%; p<0.05) was noted for CRE isolates over time
  - Similar trends were noted for all regions and infection sources, except urinary tract infections (Figure 2)
  - Carbapenem-resistant *Klebsiella pneumoniae* was the main driver for the CRE increase and comprised 71.1% of the CRE isolates
  - The 4 most common CRE species after *K. pneumoniae* were *Enterobacter cloacae* (9.0%), *Serratia marcescens* (5.4%), *Escherichia coli* (4.2%), and *E. aerogenes* (3.9%)
- MDR rates significantly increased from 7.3% to 15.3%, but similar trends were not observed in all regions or infection sources
  - A significant increase in MDR was noted in Europe, North and Latin America, but not Asia-Pacific, and in isolates from bloodstream and urinary tract infections (Figure 2)

Figure 3 Antimicrobial resistance trends for selected antimicrobial classes

A. Resistance trends of main antimicrobial classes



B. Selected resistance trends observed

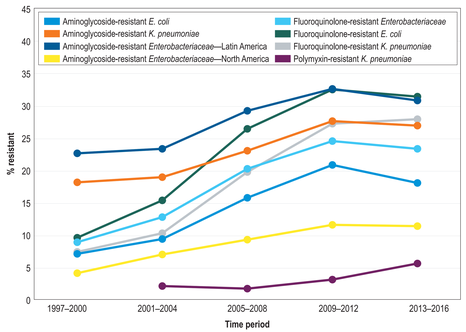
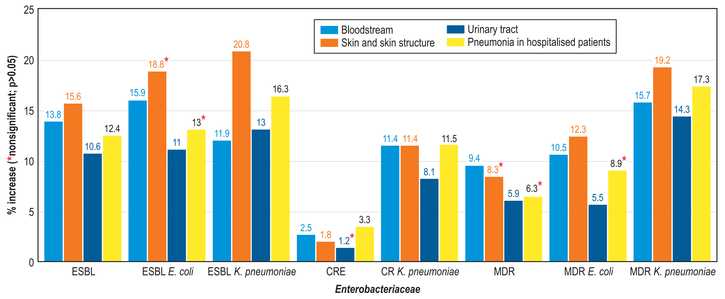
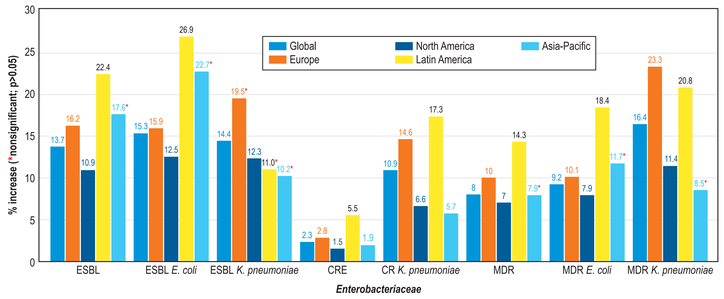


Figure 2 Selected antimicrobial resistance trends for all *Enterobacteriaceae*

A. Distribution of resistant phenotypes by infection source



B. Distribution of resistant phenotypes by region



- The most common MDR species were *K. pneumoniae* (35.2%), *E. coli* (30.2%), *E. cloacae* (9.7%), *P. mirabilis* (6.3%), and *S. marcescens* (5.3%), comprising 86.7% of the MDR isolates
  - A significant increase over time in MDR rates was noted for *K. pneumoniae* (16.4% increase) and *E. coli* (9.2% increase; Figure 2)
- Significant increases in resistance to specific antimicrobial classes were observed among the overall isolates and main species (Figure 3)
  - Aminoglycoside resistance increased in *E. coli* (7.0% to 18.0%) and *K. pneumoniae* (18.1% to 26.9%) globally and increased overall in North America (4.0% to 11.3%) and Latin America (22.6% to 30.8%) (Figure 3)
  - Fluoroquinolone resistance increased from 8.8% to 23.3% among the *Enterobacteriaceae* isolates, which was mainly due to *E. coli* (9.5% to 31.4%) and *K. pneumoniae* (7.3% to 27.9%) (Figure 3)
- A significant increase (p<0.0001) in polymyxin/colistin resistance rates was noted for *K. pneumoniae* from 2.0% in 2001–2004 (when this compound started being tested) to 5.5% in 2013–2016 (Figure 3)

Conclusions

- A significant overall increase in β-lactam resistance was observed in all geographic regions and infection types monitored during the 20 years of the SENTRY Program and included:
  - Resistance to cephalosporins (ESBL-phenotype) among *E. coli*, *Klebsiella* spp., and *P. mirabilis*
  - Carbapenem-resistance overall, but mainly among *K. pneumoniae*
- Resistance to other antimicrobial classes important for the treatment of infections caused by *Enterobacteriaceae* also increased
- A remarkable increase of MDR isolates was also noted, and these organisms greatly limit the options for the treatment of infections
- The SENTRY Program is the largest and longest-operating worldwide surveillance initiative, and its data highlight the emerging resistance issues that have been a great concern for the infectious diseases and clinical microbiology community for many years, reinforcing the importance of initiatives that address the threat of antimicrobial resistance

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