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# *In vitro* Evaluation of Delafloxacin Activity When Tested against Contemporary Community-Acquired Bacterial Respiratory Tract Infection Isolates (2014–2016): Results from the SENTRY Antimicrobial Surveillance Program


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## Amended Abstract


**Background**: Delafloxacin (DLX) is a broad-spectrum fluoroquinolone (FQ) antibacterial that has been approved by the Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. DLX is also in clinical trials for community-acquired bacterial pneumonia. In this study, *in vitro* susceptibility results for DLX and comparator agents were determined for clinical isolates from community-acquired respiratory tract infections (CA-RTI) collected in medical centers in the United States and Europe participating in the SENTRY surveillance program during 2014–2016.

**Methods**: A total of 3,093 isolates that included 1,673 *Streptococcus pneumoniae* (SPN), 805 *Haemophilus influenzae* (HI), and 555 *Moraxella catarrhalis* (MC) were collected during 2014–2016 and included only 1 isolate/patient/infection episode. Isolate identifications were confirmed at JMI Laboratories. Susceptibility testing was performed according to CLSI reference broth microdilution methodology, and results were interpreted per CLSI (2017) breakpoints. Other antibacterials tested included levofloxacin (LVX), penicillin (PEN), amoxicillin-clavulanate, ampicillin, azithromycin, ceftaroline, ceftriaxone, clarithromycin, clindamycin, erythromycin, meropenem, tetracycline, and trimethoprim-sulfamethoxazole. Beta-lactamase production for HI and MC was determined by the nitrocephin disk test.

**Results**: DLX demonstrated potent *in vitro* activity against SPN ($MIC_{50/90}$ 0.015/0.03 mg/L). Activity remained the same for penicillin-intermediate and -resistant isolates. For 23 LVX nonsusceptible SPN, the DLX $MIC_{50/90}$ were 0.12/0.25 mg/L with all isolates having DLX MIC values ≤1 mg/L. For HI, the DLX $MIC_{50/90}$ were ≤0.001/0.004 mg/L, and for MC the $MIC_{50/90}$ were 0.008/0.008 mg/L. DLX activity was unaffected by the presence of beta-lactamase for either HI or MC. Activity of DLX was similar for US and European isolates.

**Conclusions**: Delafloxacin demonstrated potent *in vitro* antibacterial activity against CA-RTI pathogens, including SPN, HI, and MC. These data support the continued study of DLX as a potential treatment for community-acquired pneumonia.


## Introduction

- Delafloxacin (DLX) is a broad-spectrum fluoroquinolone (FQ) antibacterial that received approval in 2017 from the US Food and Drug Administration to treat acute bacterial skin and skin structure infections (oral and intravenous formulations)
- Clinical treatment trials for community-acquired bacterial pneumonia are in progress; delafloxacin is not currently approved by the FDA for the treatment of CAP
- In this study, *in vitro* susceptibility test results for DLX and comparator agents were determined for clinical isolates from community-acquired respiratory tract infections (CA-RTI) collected in US and European medical centers participating in the SENTRY surveillance program during 2014–2016

## Materials and Methods

- A total of 3,093 isolates from community-acquired respiratory tract infections that included 1,673 *Streptococcus pneumoniae* (SPN), 805 *Haemophilus influenzae* (HI), and 555 *Moraxella catarrhalis* (MC) were collected during 2014–2016
  - Isolates were designated by the site as pathogens and were nonduplicate (1 per patient per infection episode)
- Species identification was performed at the participant medical centers and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using standard biochemical tests or matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker, Billerica, Massachusetts, USA), following the manufacturer's instructions
- Susceptibility testing was performed according to CLSI reference broth microdilution methodology, and results were interpreted per CLSI and EUCAST (2017) breakpoints
- Other antibacterials tested included levofloxacin (LVX), penicillin (PEN), amoxicillin-clavulanate, ampicillin, azithromycin, ceftaroline, ceftriaxone, clarithromycin, clindamycin, erythromycin, meropenem, tetracycline, and trimethoprim-sulfamethoxazole
- Beta-lactamase production for HI and MC was determined by the nitrocephin disk test

## Results

- For the 3 primary CA-RTI pathogens (SPN, HI, MC), the percent susceptible (%S) and $MIC_{50/90}$ values for DLX, LVX, and comparators are shown in Table 1
- DLX demonstrated extremely potent *in vitro* activity against SPN with an $MIC_{50/90}$ value of 0.015/0.03 mg/L
  - DLX activity was greater than LVX ($MIC_{50/90}$ was 1/1 mg/L)
  - MIC distributions of DLX and LVX tested against SPN from the US and Europe are shown in Figure 1
    - DLX activity was the same for isolates from the US or Europe

**Table 1 Susceptibilities of *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* from community-acquired respiratory tract infections tested against delafloxacin and comparators**

| Organism / antibiotic | $MIC_{50}$ (mg/L) | $MIC_{90}$ (mg/L) | CLSI[a] %S | CLSI[a] %R | EUCAST[a] %S | EUCAST[a] %R |
|---|---|---|---|---|---|---|
| *Haemophilus influenzae* (n=805) | | | | | | |
| Delafloxacin | ≤0.001 | 0.004 | N/A | | N/A | |
| Levofloxacin | ≤0.015 | 0.03 | 99.9 | | 98.3 | 1.7 |
| Amoxicillin-clavulanic acid | 0.5 | 2 | 99.6 | 0.4 | 95.0 | 5.0 |
| Ampicillin | 0.5 | >8 | 68.3 | 26.3 | 68.3 | 31.7[h] |
| Azithromycin | 0.5 | 1 | 99.0 | | 1.1 | 1.0 |
| Ceftaroline | 0.008 | 0.03 | 99.9 | | 95.4 | 4.6 |
| Ceftriaxone | ≤0.015 | ≤0.015 | 100.0 | | 99.6 | 0.4 |
| Clarithromycin | 8 | 8 | 91.2 | 1.7 | 0.7 | * |
| Meropenem | 0.06 | 0.12 | 99.9 | | 99.4<br>100.0 | 0.0[d]<br>0.0[e] |
| Tetracycline | 0.5 | 0.5 | 99.3 | 0.7 | 98.9 | 0.7 |
| Trimethoprim-sulfamethoxazole | 0.12 | >4 | 64.8 | 31.8 | 64.8 | 33.8 |
| *Moraxella catarrhalis* (n=555) | | | | | | |
| Delafloxacin | 0.008 | 0.008 | N/A | | N/A | |
| Levofloxacin | 0.03 | 0.06 | 100.0 | | 100.0 | 0.0 |
| Amoxicillin-clavulanic acid | 0.12 | 0.25 | 100.0 | 0.0 | 100.0 | 0.0 |
| Azithromycin | 0.015 | 0.03 | 99.8 | | 99.8 | 0.2 |
| Ceftaroline | 0.06 | 0.25 | | | | |
| Ceftriaxone | 0.25 | 0.5 | 100.0 | | 99.6 | 0.0 |
| Clarithromycin | ≤0.12 | 0.25 | 99.8 | | 99.4 | 0.2 |
| Meropenem | ≤0.015 | ≤0.015 | | | 100.0 | 0.0 |
| Penicillin | >4 | >4 | | | | |
| Tetracycline | 0.25 | 0.5 | 100.0 | 0.0 | 100.0 | 0.0 |
| Trimethoprim-sulfamethoxazole | 0.12 | 0.25 | 97.8 | 0.0 | 97.8 | 0.5 |
| *Streptococcus pneumoniae* (n=1,673) | | | | | | |
| Delafloxacin | 0.015 | 0.03 | N/A | | N/A | |
| Levofloxacin | 1 | 1 | 98.6 | 1.1 | 98.6 | 1.4 |
| Amoxicillin-clavulanic acid | ≤1 | 2 | 94.9 | 2.6 | | |
| Ceftaroline | ≤0.015 | 0.12 | 99.9 | * | 99.7 | 0.3 |
| Ceftriaxone | ≤0.06 | 1 | 88.2<br>97.1 | 2.9[g]<br>0.6[e] | 88.2 | 0.6 |
| Clindamycin | ≤0.25 | >1 | 84.2 | 15.3 | 84.7 | 15.3 |
| Erythromycin | ≤0.12 | >2 | 62.9 | 36.6 | 62.9 | 36.6 |
| Meropenem | ≤0.015 | 0.5 | 84.8 | 5.6 | 84.8<br>100.0 | 0.0[d]<br>0.0[e] |
| Penicillin | ≤0.06 | 2 | 66.2<br>66.2<br>96.2 | 10.5[f]<br>33.8[g]<br>0.1[h] | 66.2<br>66.2 | 33.8[g]<br>3.8[e] |
| Tetracycline | ≤0.5 | >4 | 77.9 | 21.7 | 77.9 | 21.7 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | >4 | 72.2 | 17.5 | 77.9 | 17.5 |

[a] Criteria as published by CLSI [2017] and EUCAST [2017]
[b] β-lactamase test positive reported as resistant for penicillins without inhibitors
[c] Dilution range did not extend high enough to determine between I and R so only susceptible percentage is displayed
[d] Using meningitis breakpoints
[e] Using nonmeningitis breakpoints
[f] Using oral breakpoints
[g] Using parenteral, meningitis breakpoints
[h] Using parenteral, nonmeningitis breakpoints

- DLX activity against drug-resistant SPN is shown in Figure 2
  - DLX activity was unaffected by penicillin resistance (DLX $MIC_{50/90}$ 0.015/0.03 mg/L)
  - For 23 LVX-resistant SPN, the DLX $MIC_{50/90}$ values were 0.12/0.25 mg/L with all isolates having DLX MIC values ≤1 mg/L
- MIC distributions for DLX and LVX against HI and MC are shown in Figure 3
  - For HI, the DLX $MIC_{50/90}$ values were ≤0.001/0.004 mg/L, and for MC the $MIC_{50/90}$ values were 0.008/0.008 mg/L
  - The LVX $MIC_{50/90}$ values for HI were ≤0.015/0.03 mg/L, and for MC the $MIC_{50/90}$ values were 0.03/0.06 mg/L

**Figure 1 MIC distribution of delafloxacin and levofloxacin tested against 1,673 *S. pneumoniae* isolates from North America (n=930) and Europe (n=743)**

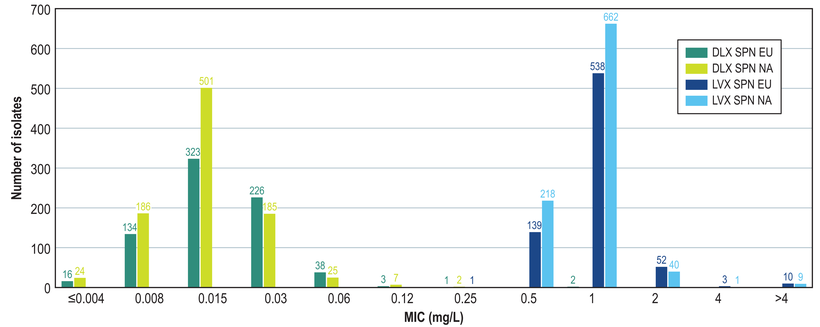



**Figure 2 MIC distribution of delafloxacin tested against 175 penicillin- (PEN-R) and 23 levofloxacin-resistant (LVX-R) *S. pneumoniae***

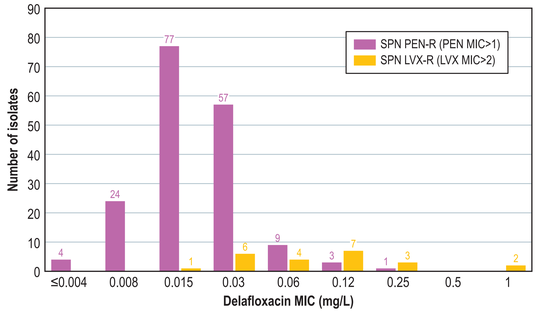
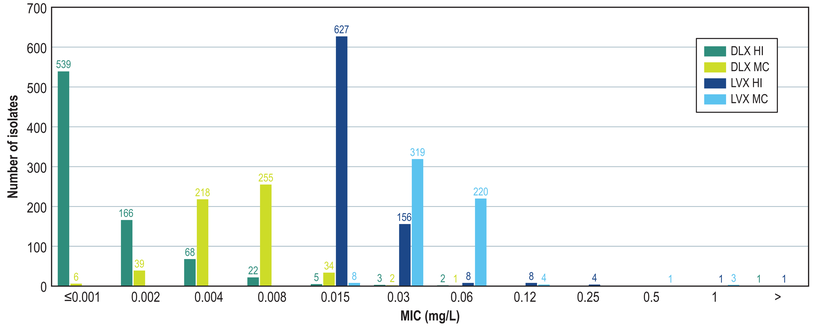



**Figure 3 MIC distribution of delafloxacin and levofloxacin for 805 *H. influenzae* and 555 *M. catarrhalis* isolates**




## Conclusions

- DLX demonstrated potent *in vitro* antibacterial activity against the 3 main CA-RTI pathogens: SPN, HI, and MC
- Against SPN, DLX had the lowest $MIC_{90}$ of the agents tested
  - DLX activity was unaffected by PEN resistance
  - No difference in activity observed between US and EU isolates
  - Against LVX-R SPN, DLX was very active with all isolates having an MIC ≤1 mg/L
- For HI and MC, DLX had the lowest $MIC_{90}$ value of the agents tested
  - All isolates had a DLX MIC ≤0.06 mg/L
  - DLX was more potent than LVX
  - FQ-resistant isolates of HI and MC were rare: 0 MC and 1 HI LVX-R
- These data support the continued study of DLX as a potential treatment for community-acquired pneumonia

## Acknowledgements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## References


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