# Global Evaluation of Gemifloxacin Activity Tested Against Community-Acquired Respiratory Tract Pathogens, *Haemophilus influenzae and Moraxella catarrhalis* (1999-2004)

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## ABSTRACT

**Objective**: Chronic lower respiratory tract disease and pneumonia are among the top ten leading causes of death in the United States. As resistance (R) to commonly used drug classes continues to increase, the newer generation fluoroquinolones (FQs) have provided an excellent therapeutic alternative for community-acquired respiratory tract infections (CARTI). The potency of gemifloxacin(GEMI) against *H. influenzae* and *M. catarrhalis* isolates was determined over a period of six years.

**Methods**: A total of 12,152 isolates of *H. influenzae* (9,411), *M. catarrhalis* (2,741) and other *Haemophilus* spp. (66; not presented) were collected during 1999-2004 from North America, Latin America and Europe. Reference CLSI/NCCLS test methods were utilized and MIC results were interpreted by current breakpoint criteria M100-S15(2005). Comparison agents included: ciprofloxacin (CIPRO), levofloxacin (LEVO), gatifloxacin (GATI), and moxifloxacin (MOXI).

**Results**: *H. influenzae* and *M. catarrhalis* susceptibilities (S) to GEMI have not changed over the last six years. GEMI had equal or greater potency when compared to other FQs. *H. influenzae* isolates tested showed >99.9% S to GEMI ($MIC_{90}$ from on-scale values, 0.004 mg/L). In 2003 and 2004, CIPRO, GATI, LEVO, and MOXI showed complete S among *H. influenzae* isolates, but some had higher MIC values indicating single-step QRDR mutations (MIC, >=0.12 mg/L). One *H. influenzae* isolate was R to all FQs tested (MIC values: GEMI 2, CIPRO >4, LEVO >4, GATI >4, MOXI >4 mg/L) and had multiple QRDR mutations. The number of beta-lactamase(BL)-negative/ampicillin-R isolates recovered in this study was only 7 or 0.1% overall. GEMI shows similarly high potency against *M. catarrhalis* with the highest observed MIC at 2 mg/L (1999-2002); >99.9% were at <=0.12 mg/L (see table for results):

| | $MIC_{50/100}$ in mg/L (%S) | | | | |
|---|---|---|---|---|---|
| Organism/year (no. tested) | GEMI | CIPRO | LEVO | GATI | MOXI |
| *H. influenzae* | | | | | |
| 1999-2002 (6213) | <=.008/2(>99) | <=.03/>4(>99) | <=.03/>4(>99) | <=.03/>4(>99) | <=.03/>4(>99) |
| 2003 (1854) | <=.002/.12(100) | <=.12/.5(100) | <=.03/.12(100) | <=.03/.12(100) | <=.03/.12(100) |
| 2004 (1344) | <=.016/.03(100) | <=.03/.25(100) | <=.03/.25(100) | <=.03/.12(100) | <=.03/.25(100) |
| BL-negative | | | | | |
| 1999-2002 (4841) | <=.008/2(>99) | <=.03/>4(>99) | <=.03/>4(>99) | <=.03/>4(>99) | <=.03/>4(>99) |
| 2003 (1423) | <=.002/.12(100) | <=.12/.5(100) | <=.03/.12(100) | <=.03/.12(100) | <=.03/.12(100) |
| 2004 (1037) | <=.016/.03(100) | <=.03/.25(100) | <=.03/.25(100) | <=.03/.12(100) | <=.03/.25(100) |
| BL-positive | | | | | |
| 1999-2002 (1286) | <=.008/.25(>99) | <=.03/.25(100) | <=.03/.25(100) | <=.03/.12(100) | <=.03/.25(100) |
| 2003 (402) | 0.004/.03(100) | <=.12/<=.12(100) | <=.03/.06(100) | <=.03/<=.03(100) | <=.03/.06(100) |
| 2004 (307) | <=.016/.03(100) | <=.03/.06(100) | <=.03/.06(100) | <=.03/<=.03(100) | <=.03/.25(100) |
| *M. catarrhalis* | | | | | |
| 1999 - 2002 (2473) | .008/2(NA) | <=.03/.5(NA) | <=.03/1(NA) | <=.03/.25(NA) | .06/.12(NA) |
| 2003 (268) | <=.12/<=.12(NA) | <=.03/<=.12(NA) | <=.03/.06(NA) | <=.03/.06(NA) | .06/.12(NA) |

**Conclusions**: GEMI continues to be a highly potent FQ when tested against the two most commonly isolated Gram-negative CARTI pathogens; *H. influenzae* and *M. catarrhalis*. This potency and spectrum was consistent across six years and three continents.

## INTRODUCTION

According to the World Health Organization Report (2004), lower respiratory infections are among the leading causes of death in the world. The bacteria that are common causes of community-acquired respiratory tract infections (CARTI) include *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*. *S. pneumoniae* has shown a wide variety of resistance rates to penicillin from very low in northern Europe to 70% in some Asian countries. A recent global study estimated the overall prevalence of penicillin resistance at 30% in *S. pneumoniae* isolates. The most common resistance mechanism for *H. influenzae* and *M. catarrhalis* remains to be the production of ß-lactamase. As an alternative class of agents, the newer generation fluoroquinolones (FQ) have provided an excellent therapeutic alternative for CARTI. Fluoroquinolone resistance levels have remained low worldwide among CARTI pathogens, particularly *H. influenzae* and *M. catarrhalis*. However, some areas such as Hong Kong have reported an increase in fluoroquinolone resistance in pneumococci. Institutional outbreaks of fluoroquinolone resistance have also occurred in the United States and other regions of the world.

Gemifloxacin is one of the newer potent fluoroquinolones with excellent activity against *S. pneumoniae, H. influenzae* and *M. catarrhalis*. This drug has a strong affinity for DNA gyrase and topoisomerase IV (dual action) which improves its activity against *H. influenzae* isolates with reduced susceptibility to fluoroquinolones. Gemifloxacin's success in killing most respiratory pathogens may also be due to the high concentration levels in the bronchial mucosa. Gemifloxacin possesses a good safety profile and single daily dosing should promote patient compliance. Gemifloxacin is a promising agent for the treatment of bacterial CARTI including isolates resistant to other fluoroquinolone regimens.

## MATERIALS AND METHODS

Specimen collections. A total of 12,152 isolates of *H. influenzae* (9,411) and *M. catarrhalis* (2,741) strains were collected and tested over a period of six years (1999 - 2004). Isolates were centrally processed at a reference laboratory (JMI Laboratories, North Liberty, IA). The isolates were collected from North America, Latin America and European hospitals for confirmation of identification and susceptibility testing.

Susceptibility testing. Antimicrobial susceptibility testing was performed using validated reference broth microdilution panels supplied by TREK Diagnostics (Cleveland, OH, USA) using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS). A bacterial suspension equal to a 0.5 McFarland Standard was prepared for each isolate, diluted 1/200 and inoculated using a Sensititre autoinoculator into 96-well panels targeting a final organism concentration of 5 x $10^5$ CFU/ml. After incubation in an ambient air environment at 35ºC for 20 - 24 hours, the minimum inhibitor concentration (MIC) for each antimicrobial agent was determined by visual inspection for growth and susceptibility was interpreted using CLSI/NCCLS breakpoint criteria (M100-S15, 2005), where available.

Isolates were tested against five fluoroquinolone drugs (gemifloxacin, ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin). Susceptibility quality control strains (*Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213 and *H. influenzae* ATCC 49247) were processed concurrently with the study isolates.

## RESULTS

- Gemifloxacin has greater or equal potency compared to the other tested fluoroquinolones against *H. influenzae* and *M. catarrhalis* over the six year interval (Table 1).
- *H. influenzae* isolates tested > 99% susceptible to gemifloxacin, ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin with rare strains having a gemifloxacin MIC at > 0.12 mg/L (Table 1).
- The number of ß-lactamase-negative, ampicillin-resistant *H. influenzae* isolates in this study was seven, which only represents 0.1% overall. The overall ß-lactamase production rate in *H. influenzae* was 21.2% (Table 1).
- Gemifloxacin showed high potency against *M. catarrhalis* (Table 2). The vast majority of the gemifloxacin MIC results (> 99.9%) were ≤ 0.12 mg/L.
- Only one *H. influenzae* isolate exhibited resistance to all fluoroquinolones and had multiple QRDR mutations (Table 3).
- Gemifloxacin showed equal or greater potency compared to four other fluoroquinolones when tested against *H. influenzae* isolates that had reduced susceptibility to ciprofloxacin (MIC, ≥ 0.12 mg/L; Table 3). One *M. catarrhalis* isolate among three that demonstrated reduced inhibition by the new fluoroquinolones, had a gemifloxacin MIC at only 0.06 mg/L.

**Table 1.** Antimicrobial activity of gemifloxacin and comparison fluoroquinolones tested against *H. influenzae* (1999 - 2004).

| | 1999 - 2002 | | | | 2003 | | | | 2004 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MIC (mg/L) | | | | MIC (mg/L) | | | | MIC (mg/L) | | | |
| Organism/antimicrobial agent | 50% | 90% | Range | % susceptible[a] | 50% | 90% | Range | % susceptible[a] | 50% | 90% | Range | % susceptible[a] |
| *H. influenzae* | (6,213 strains) | | | | (1,854 strains) | | | | (1,344 strains) | | | |
| Gemifloxacin | ≤0.008 | ≤0.12 | ≤0.008-2 | >99.9 | ≤0.002 | 0.004 | ≤0.002-0.12 | 100.0 | ≤0.016 | ≤0.016 | ≤0.016-0.03 | 100.0 |
| Ciprofloxacin | ≤0.03 | ≤0.25 | ≤0.03->4 | >99.9 | ≤0.12 | ≤0.12 | ≤0.12-0.5 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 |
| Levofloxacin | ≤0.03 | ≤0.03 | ≤0.03->4 | >99.9 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 |
| Gatifloxacin | ≤0.03 | ≤0.03 | ≤0.03->4 | >99.9 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 |
| Moxifloxacin | ≤0.03 | ≤0.03 | ≤0.03->4 | >99.9 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 |
| ß-lactamase-negative | (4,841 strains) | | | | (1,423 strains) | | | | (1,037 strains) | | | |
| Gemifloxacin | ≤0.008 | ≤0.12 | ≤0.008-2 | >99.9 | ≤0.002 | 0.004 | ≤0.002-0.12 | 100.0 | ≤0.016 | ≤0.016 | ≤0.016-0.03 | 100.0 |
| Ciprofloxacin | ≤0.03 | ≤0.25 | ≤0.03->4 | >99.9 | ≤0.12 | ≤0.12 | ≤0.12-0.5 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 |
| Levofloxacin | ≤0.03 | ≤0.03 | ≤0.03->4 | >99.9 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 |
| Gatifloxacin | ≤0.03 | ≤0.03 | ≤0.03->4 | >99.9 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 |
| Moxifloxacin | ≤0.03 | ≤0.03 | ≤0.03->4 | >99.9 | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 |
| ß-lactamase-positive | (1,286 strains) | | | | (402 strains) | | | | (307 strains) | | | |
| Gemifloxacin | ≤0.008 | ≤0.12 | ≤0.008-0.25 | >99.9 | 0.004 | 0.008 | ≤0.002-0.03 | 100.0 | ≤0.016 | ≤0.016 | ≤0.016-0.03 | 100.0 |
| Ciprofloxacin | ≤0.03 | ≤0.25 | ≤0.03-0.25 | 100.0 | ≤0.12 | ≤0.12 | ≤0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.06 | 100.0 |
| Levofloxacin | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.06 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.06 | 100.0 |
| Gatifloxacin | ≤0.03 | ≤0.03 | ≤0.03-0.12 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03 | 100.0 |
| Moxifloxacin | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.06 | 100.0 | ≤0.03 | ≤0.03 | ≤0.03-0.25 | 100.0 |

a. Susceptibility rates are based upon CLSI (NCCLS) recommendations (M100-S15).

**Table 2.** Antimicrobial activity of gemifloxacin and comparison fluoroquinolones tested against *M. catarrhalis* (1999 - 2003).

| | 1999 - 2002 | | | | 2003 | | | |
|---|---|---|---|---|---|---|---|---|
| | MIC (mg/L) | | | | MIC (mg/L) | | | |
| Organism/antimicrobial agent | 50% | 90% | Range | % susceptible | 50% | 90% | Range | % susceptible |
| *M. catarrhalis* | (2,473 strains) | | | | (268 strains) | | | |
| Gemifloxacin | ≤0.008 | ≤0.12 | ≤0.008-2 | NA | ≤0.12 | ≤0.12 | ≤0.12 | NA |
| Ciprofloxacin | ≤0.03 | 0.06 | ≤0.03-0.5 | NA | ≤0.12 | ≤0.12 | ≤0.12 | NA |
| Levofloxacin | ≤0.03 | 0.06 | ≤0.03-1 | NA | ≤0.03 | ≤0.03 | ≤0.03-0.06 | NA |
| Gatifloxacin | ≤0.03 | ≤0.03 | ≤0.03-0.25 | NA | ≤0.03 | ≤0.03 | ≤0.03-0.06 | NA |
| Moxifloxacin | 0.06 | 0.06 | ≤0.03-0.12 | NA | 0.06 | 0.06 | ≤0.03-0.12 | NA |

**Table 3.** *H. influenzae* with reduced susceptibility to ciprofloxacin (MIC, ≥ 0.12 mg/L).

| | | Antimicrobial agent | | | | |
|---|---|---|---|---|---|---|
| Bank # | Year | Ciprofloxacin | Gemifloxacin | Gatifloxacin | Levofloxacin | Moxifloxacin |
| *H. influenzae* | | | | | | |
| 148399 | 2001 | 0.12 | 0.016 | 0.06 | 0.12 | 0.25 |
| 143957 | 2001 | 0.25 | 0.12 | 0.12 | 0.25 | 0.25 |
| 152686 | 2001 | 0.25 | 0.016 | 0.12 | 0.12 | 0.06 |
| 226151 | 2002 | >4 | 2 | >4 | >4 | >4 |
| 1846 | 2004 | 0.12 | 0.03 | 0.12 | 0.25 | 0.12 |
| 266 | 2004 | 0.25 | 0.03 | 0.12 | 0.25 | 0.12 |
| *M. catarrhalis* | | | | | | |
| 3132 | 1999 | 0.5 | -[a] | 0.5 | 1 | -[a] |
| 3276 | 1999 | 0.5 | 0.06 | 0.25 | 1 | -[a] |
| 3108 | 1999 | 0.5 | -[a] | 0.5 | 1 | -[a] |

a. Not tested.

## CONCLUSIONS

- Over the last six years, gemifloxacin has consistently demonstrated the highest potency among fluoroquinolones against *H. influenzae* and very low MIC values for *M. catarrhalis*.
- Resistance rates remained extremely low for all fluoroquinolones tested for the Gram-negative pathogens associated with CARTI.
- Continued monitoring of fluoroquinolone susceptibility should be performed against the common causes of CARTI, as the use of this drug class escalates in the future.

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