Ribosomal Mutations Associated with Ketolide Resistance in *Haemophilus influenzae* found in the SENTRY Antimicrobial Surveillance Program

**Abstract**

**Objectives:** To determine the mechanisms of ketolide resistance in *H. influenzae* and to compare mic values of solithromycin to those of telithromycin and azithromycin.

**Methods:** In 2009, tested against all 1,198 *H. influenzae* isolates, solithromycin (MIC90, 2 mg/L) and azithromycin (MIC90, 2 mg/L) were two- to four-fold more active than telithromycin (MIC90, 4 mg/L). Telithromycin demonstrated greater potency than both azithromycin and telithromycin for many strains with the percentage inhibited at a MIC of 1 mg/L being 81.1, 66.2 and 52.8%, respectively (Table 1).

**Results**

Telithromycin is a ketolide antimicrobial agent and is a semi-synthetic derivative of erythromycin A. Ketolides bind to 23S at domain II, as well as domain V, and retain good activity against macrolide-resistant strains, hence ketolide resistance is rare. Ketolide resistance in *H. influenzae* is associated with mutations in L22 and 23S rRNA.

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**Materials and Methods**

**Bacterial strain collection:** During 2009, a total of 1,198 *H. influenzae* isolates were obtained from patients with community-acquired bacterial pneumonia in 24 countries, and were tested for susceptibility to ketolides by CLSI methods (M07-A8 and M100-S21) as part of the SENTRY Antimicrobial Surveillance Program (2009) and describe the activity of solithromycin against these strains.

**Susceptibility test methods:** All isolates were tested for susceptibility to telithromycin, solithromycin and comparators by reference broth microdilution methods using the CLSI recommendations (M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). Sensitivity testing of CLSI-recommended (M100-S21, 2011) quality control (QC) strains, including *H. influenzae* ATCC 49247. Categorical interpretation of comparator MIC values was performed according to CLSI recommendations (M100-S21, 2011) criteria, when available. Extended MIC results for azithromycin were performed by Etest (bioMerieux).

**Molecular test methods:** Telithromycin-resistant strains (MIC 24 mg/L) were screened for erm(A), erm(B), emm(C), emm(F) and mef(A/E) resistance genes by PCR, and for mutations in the 23S rRNA, L22 and L4 proteins by PCR and DNA sequencing.

**Introduction**

Macrolide resistance in *Haemophilus influenzae* is complex. Almost all *H. influenzae* possess an intrinsic efflux pump homologous to the aca/Ab efflux mechanism of *Escherichia coli* that lowers the activity of macrolide, lincosamide, streptogramin B and ketolide antimicrobial agents compared to strains that do not have this mechanism. For azithromycin, higher MIC values (and hence resistance), although rare, have resulted from mutations in the riboproteins L4 and L22 and/or 23S rRNA. Recently, macrolide resistance causing macrolide resistance causing acquisition of 23S rRNA methylase genes (erm(A), erm(B), emm(C), emm(F)) and/or macrolide efflux (mef(A/E)) have been described.

**Conclusions**

Telithromycin is a ketolide antimicrobial agent and is a semi-synthetic derivative of erythromycin A. Ketolides bind to 23S at domain II, as well as domain V, and retain good activity against macrolide-resistant strains, hence ketolide resistance is rare. Ketolide resistance in *H. influenzae* is associated with mutations in L22 and 23S rRNA.

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