Pharmacodynamic Assessment Based on Mutant Prevention Concentrations of Fluoroquinolones To Prevent the Emergence of Resistant Mutants of *Streptococcus pneumoniae*

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The objective of this study was to investigate the relationship between pharmacokinetic and pharmacodynamic parameters, on the basis of the mutant prevention concentration (MPC) concept, and the emergence of resistant mutants of *Streptococcus pneumoniae* to fluoroquinolone antibacterials. Some clinical isolates with various MIC and MPC values of moxifloxacin and levofloxacin were exposed under conditions simulating the time-concentration curves observed when moxifloxacin (400 or 80 mg, once a day) or levofloxacin (200 mg, twice a day) was orally administered by using an in vitro pharmacodynamic model. The decrease in susceptibility was evaluated by altering the population analysis profiles after moxifloxacin or levofloxacin treatment for 72 h. When the area under the concentration-time curve from 0 to 24 h (AUC0–24)/MPC and peak concentration (Cmax)/MPC were above 13.41 and 1.20, respectively, complete eradication occurred and no decrease in susceptibility was observed. On the other hand, when AUC0–24/MPC and Cmax/MPC were below 0.84 and 0.08, respectively, the susceptibility decreased. However, the time inside the mutant selective window and the time above the MPC did not show any correlation with the decrease in susceptibility. These results suggest that AUC0–24/MPC and Cmax/MPC are important parameters for predicting the emergence of resistant mutants and that higher values indicate greater effectiveness.

The increasing resistance of *Streptococcus pneumoniae* to fluoroquinolone antibiotics is an important clinical problem, although the frequency of the appearance of strains resistant to fluoroquinolones is lower than that of strains resistant to many β-lactam and macrolide antibiotics (11). The increased rate of appearance of fluoroquinolone-resistant *S. pneumoniae* strains has been reported in some regions (17, 29, 30, 35). For example, the rates of levofloxacin nonsusceptibility (MICs, ≥4 μg/ml) among *S. pneumoniae* strains were 13.3% in Hong Kong in 2000, 2.2% in Canada in 2002, 0 to 1.3% in European countries from 2001 to 2003, and 2.0% in Japan in 2002. It should be noted that the decrease in the susceptibility of *S. pneumoniae* to levofloxacin was suggested to be correlated with the increased use of levofloxacin at certain localities in the United States (4). The emergence of resistance in *S. pneumoniae* by the widespread use of fluoroquinolones is of great concern (32). Such resistance can mainly be attributed to chromosomal mutations in the fluoroquinolone resistance-determining regions (QRDRs) of parC and/or gyrA (18, 28, 33). ParC and GyrA are components of topoisomerase IV and DNA gyrase, respectively, which are the target proteins of fluoroquinolones. Amino acid substitutions at both ParC (Ser79Tyr, Ser79Phe, Asp83Gly, or Asp83Tyr) and GyrA (Ser81Tyr, Ser81Phe, or Glu85Lys) were reported to cause resistance (34).

To prevent the emergence of resistance, it is important to optimize the therapeutic administration strategy, as well as to predict the clinical efficacy. For fluoroquinolones, a higher dosage is more effective at eradicating the infecting organisms because the area under the concentration-time curve (AUC) from 0 to 24 h (AUC0–24)/MIC has been shown to be associated with bactericidal activities (3, 15). Nonclinical studies that have used an in vitro pharmacodynamic (PD) model or in vivo pneumococcal infection models have also yielded similar results (19, 21, 23). Some other nonclinical studies investigated the optimization of the therapeutic administration strategy for prevention of the emergence of resistant mutants by using an in vitro PD model. AUC0–24/MIC was reported to be the pharmacokinetic (PK)/PD parameter related to prevention of the emergence of resistant mutants, although only one fluoroquinolone-susceptible strain each of *S. pneumoniae* and *Staphylococcus aureus* was used in those studies (12, 13, 37). Some clinical isolates were reported to contain resistant subpopulations that were not detected by routine susceptibility testing, such as MIC determination (6). In such cases, the frequency of the appearance of resistant strains differed from that of standard strains. Thus, against strains with genetic backgrounds different from that of the wild-type strain, the PK/PD parameter required to prevent the emergence of resistance might not be the AUC/MIC.

Recently, the mutant prevention concentration (MPC) concept has been used to evaluate the ability of each strain to acquire resistance. Briefly, the MPC is the concentration that inhibits the growth of first-step mutants and is experimentally defined as the MIC that prohibits the growth of mutants from a susceptible population of more than 1019 cells (10, 20). It was also reported that the MPC values combined with PK profiles...
could be used to optimize the dosing regimen to prevent the emergence of resistant mutants (1, 5, 8, 13, 32, 37). PK/PD parameters such as AUC_{0-24}/MPC, peak concentration (C_{\text{max}})/MPC, the time above the MPC (T > MPC), or the time inside the mutant selective window (T_{\text{MSW}}) were reported to be correlated with the emergence of resistance, but the definition has not yet been clearly established.

In this study, we investigated the relationship between the MPC-based PK/PD parameters and the emergence of resistance in S. pneumoniae to fluoroquinolones using an in vitro PD model.

**MATERIALS AND METHODS**

**Bacterial strains and susceptibility testing.** S. pneumoniae ATCC 49619 and three clinical isolates of S. pneumoniae obtained in Japan in 2002 were used in this study. MICs were determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute guidelines (7).

**Antimicrobial agents.** Moxifloxacin and levofloxacin were provided by Bayer AG (Germany) and Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan), respectively.

**Bacterial growth medium.** For all experiments, cation-adsorbed Muller-Hinton broth (CAMHB; Becton Dickinson, Sparks, MD) supplemented with 5% lysed horse blood (LHB; Nippon Biotest Laboratories Inc.) (CAMHB-LHB) was used. For determination of the number of viable cells, tryptic soy agar (TSA; Difco, Detroit, MI) to which 5% defibrinated horse blood (DHB; Japan Lamb) was added (TSA-DHB) was used.

**MPC determination.** MPCs were determined as described by Li et al. (20). Each strain was inoculated onto a Columbia agar plate supplemented with 5% DHB (Becton Dickinson) and incubated at 37°C in 5% CO₂. Bacterial cells were collected from these plates and transferred to 400 ml Todd-Hewitt broth (Difco), followed by incubation at 37°C for 8 h. Immediately after the bacterial suspension was cooled on ice, the bacterial cells were collected by centrifugation at 4°C. The cells were washed twice with broth medium and resuspended in a small amount of the broth to prepare a suspension containing 3 × 10⁹ to 1.5 × 10¹⁴ CFU/ml of bacterial cells. These suspensions were plated onto TSA containing 5% DHB and/or various concentrations of antibiotics. The MPC was determined to be the lowest antibacterial concentration that completely inhibited bacterial growth after incubation at 37°C in 5% CO₂ for 72 h.

**In vitro PD model.** The time-concentration curves of moxifloxacin or levofloxacin were simulated by using an in vitro model. The model was controlled minute by minute. Therefore, the time-concentration curves in this model were simulated by addition of the antibiotic solution to the bacterial cell suspension by addition of 4°C. The cells were washed twice with broth medium and resuspended in a small amount of the broth to prepare a suspension containing 3 × 10⁹ to 1.5 × 10¹⁴ CFU/ml of bacterial cells. These suspensions were plated onto TSA containing 5% DHB and/or various concentrations of antibiotics. The MPC was determined to be the lowest antibacterial concentration that completely inhibited bacterial growth after incubation at 37°C in 5% CO₂ for 72 h.

**RESULTS**

**Susceptibility and QRDR sequence.** The MICs, MPC values, and QRDR sequences for each strain are shown in Table 1. Among the four strains, the MIC values of three strains were two- to fourfold higher than the representative MICs. However, the MIC values of strain SR26137 were 32-fold higher than the representative MICs. This would be caused by the presence of the amino acid substitution of ParC (Ser79Phe).

**Alteration of amino acid sequences of the QRDRs.** Three independent colonies were randomly picked from the antibacterial agent-free plate, and the nucleotide sequences of the QRDRs were determined. Genomic DNA isolated from confluent bacterial growth on TSA-DHB was used as the template for PCR. The QRDRs were amplified by PCR with the primers previously described by Morrissey and George (24). Sequencing was carried out with an ABI PRISM BigDye Terminator kit (PE Applied Biosystems, Mississauga, Ontario, Canada) on an automated sequencer (model 310; Applied Biosystems). The amino acid sequences of the QRDRs of the strains were aligned with that of the standard strain (ATCC 49619) in order to identify amino acid substitutions.

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**Bactericidal activity.** Simulated time-concentration curves for moxifloxacin and levofloxacin are shown in Fig. 1. This study used the unbound fractions of the time-concentration curves in serum that occurred with once-daily administration of 80 mg or 400 mg of moxifloxacin and twice-daily administration of 200 mg of levofloxacin.

**Decrease in susceptibility.** Alteration of the susceptibility after treatment with levofloxacin or moxifloxacin was examined by population analysis with strains SR26134 and SR26137.

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**TABLE 1. Susceptibility and QRDR sequence of the S. pneumoniae strains used in this study**

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (µg/ml)</th>
<th>MPC (µg/ml)</th>
<th>QRDR sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MXF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>LVX&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MXF</td>
</tr>
<tr>
<td>ATCC 49619</td>
<td>0.125</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>SR23958</td>
<td>0.125</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>SR26134</td>
<td>0.25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SR26137</td>
<td>0.25</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> MXF, moxifloxacin.
<sup>b</sup> LVX, levofloxacin.
<sup>c</sup> WT, wild type.
which were treated by twice-daily administration of 200 mg of levofloxacin (Fig. 3). In other cases, population analysis was not performed because no growth was observed even when the bacterial suspension was further incubated after 72 h of treatment. Population analysis indicated that the resistant subpopulations of strains SR26134 and SR26137 increased after treatment. In the case of strain SR26134, treatment with 4\,\mu g/ml levofloxacin caused the appearance of a resistant subpopulation with a twofold increase in the MIC (Table 2). However, substitutions in the GyrA and ParC QRDRs did not occur. In the case of strain SR26137, treatment with levofloxacin at 16\,\mu g/ml caused the appearance of a resistant subpopulation of levofloxacin and an eightfold increase in the MIC, which was speculated to be due to the alteration of Ser81 of GyrA to Phe. A high MPC against strain SR26137 was considered to lead to a significant decrease in susceptibility. These characteristics of strain SR26137 may have been due to the fact that this strain originally harbored ParC substitutions (Ser79Phe). Strain SR26137 acquired resistance to moxifloxacin even after levofloxacin treatment (Table 2), suggesting that cross-resistance between levofloxacin and moxifloxacin occurred. Nevertheless, SR26137 did not acquire resistance to moxifloxacin under conditions simulating time-concentration curves of 400 mg moxifloxacin.

In the case of levofloxacin treatment of strains SR26134 and SR26137, a decrease in susceptibility was observed, with AUC/MPC ratios of 0.84 to 6.70 and \(C_{\text{max}}/\text{MPC}\) ratios of 0.08 to 0.60. On the other hand, in the case of treatment with 400 mg of moxifloxacin, complete eradication occurred. Under these conditions, the AUC/MPC and \(C_{\text{max}}/\text{MPC}\) ratios were 2.47 to

![FIG. 1. Simulated time-concentration curves of moxifloxacin (A) and levofloxacin (B). (A) Bold and thin lines indicate the unbound concentrations of moxifloxacin in human serum when 400 mg and 80 mg were orally administered once a day, respectively. (B) The line indicates the unbound concentration of levofloxacin in human serum following the oral administration of 200 mg twice a day.](image1)

![FIG. 2. Activities against \(S.\,pneumoniae\) ATCC 49619 (open circles), SR23958 (open triangles), SR26134 (closed circles), and SR26137 (closed triangles) under conditions simulating the time-concentration curves of the unbound fraction which occurred with oral administration of 400 mg of moxifloxacin once a day (A) or 200 mg of levofloxacin twice a day (B).](image2)

![FIG. 3. Population analysis of \(S.\,pneumoniae\) SR26134 (A) and SR26137 (B) after levofloxacin (LVX) treatment. Open and closed circles, the populations before and after treatment, respectively.](image3)

**TABLE 2. Alteration of MICs after antibiotics treatment.**

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antibiotic used</th>
<th>Dose</th>
<th>MIC ((\mu g/ml)) Before treatment</th>
<th>MIC ((\mu g/ml)) After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MXF</td>
<td>LVF</td>
</tr>
<tr>
<td>SR26134</td>
<td>MXF(^a)</td>
<td>80 mg q.d.(^c)</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>LVX(^b)</td>
<td>200 mg b.i.d.(^d)</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>SR26137</td>
<td>MXF</td>
<td>80 mg q.d.</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>LVX</td>
<td>200 mg b.i.d.</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) MXF, moxifloxacin.
\(^b\) LVX, levofloxacin.
\(^c\) q.d., once a day.
\(^d\) b.i.d., twice a day.
19.78 and 0.20 to 1.63, respectively, which were significantly higher than those obtained with levofloxacin treatment. Therefore, we tried to observe the potency of moxifloxacin and the concentration that caused the emergence of resistance by bringing the AUC/MIC and C\text{\textsubscript{max}}/MPC values of moxifloxacin close to those of levofloxacin, i.e., by treatment with 80 mg of moxifloxacin (AUC/MPC ratios of 0.49 to 3.96 and C\text{\textsubscript{max}}/MPC ratios of 0.04 to 0.33). As in the case of levofloxacin treatment, activity was observed against strains SR26134 and SR26137, but both strains began to grow again within 24 h (Fig. 4). In the case of strain SR26134, the subpopulation of resistant strains was not observed, although regrowth occurred after 72 h of treatment. In the case of strain SR26137, the frequency of the resistant subpopulation which grew in the presence of 0.25 or 0.5 \mu g/ml increased, but the concentration required to prevent colony formation did not change (Fig. 5). Furthermore, there was also no change in the MIC even after treatment, and the QORDR substitution did not occur (Table 2). Hence, under these conditions, moxifloxacin caused regrowth after 72 h of treatment, but the decrease in susceptibility was less significant than that after levofloxacin treatment.

**PD analysis.** From the results described above, the relationship between PK/PD parameters and the decrease in susceptibility was examined. The decrease in susceptibility was defined by alteration of the population analysis profiles after treatment. In the case of levofloxacin treatment, ATCC 49619 was completely eradicated, but strain SR26134 and strain SR26137 acquired decreased susceptibilities, even though they had the same AUC\text{\textsubscript{0–24}}/MIC (Table 3). In the case of treatment with 80 mg of moxifloxacin, strain SR26137 acquired decreased susceptibility but strain SR26134 did not (Table 3). These results suggest that AUC\text{\textsubscript{0–24}}/MIC and C\text{\textsubscript{max}}/MIC are not correlated with the decrease in susceptibility. It was interesting that the MPC values differed between these strains, even though they had the same MICs. This led us to evaluate the relationships with MPC-based PK/PD parameters, such as AUC\text{\textsubscript{0–24}}/MPC, C\text{\textsubscript{max}}/MPC, T\text{\textsubscript{MSW}}, and T > MPC. We found that T\text{\textsubscript{MSW}} and T > MPC did not seem to be correlated with the decreased susceptibility. For example, strain SR26137 acquired resistance when the T\text{\textsubscript{MSW}} was as little as 16.88% or 47.78% but not when T\text{\textsubscript{MSW}} was as great as 99.51%, and SR26134 and SR26137 did not acquire decreased susceptibility even when T > MPC was 0% (Table 3). On the other hand, the achievement of high AUC\text{\textsubscript{0–24}}/MPC and C\text{\textsubscript{max}}/MPC values was effective for the prevention of decreased susceptibility. Under all conditions in which AUC\text{\textsubscript{0–24}}/MPC values were $\geq 1.341$ and C\text{\textsubscript{max}}/MPC values were $\geq 1.20$, there was no decrease in the rate of susceptibility. However, under all conditions in which AUC\text{\textsubscript{0–24}}/MPC values were 0.84 and C\text{\textsubscript{max}}/MPC values were 0.08, the rates of susceptibility decreased. Under the conditions in which AUC\text{\textsubscript{0–24}}/MPC values were 2.47 to 6.70 and C\text{\textsubscript{max}}/MPC values were 0.20 to 0.60, a decrease in the rate of susceptibility was observed in some cases but not in others. These results suggest that AUC\text{\textsubscript{0–24}}/MPC and C\text{\textsubscript{max}}/MPC ratios are associated with the prevention of decreased susceptibility but that T\text{\textsubscript{MSW}} and T > MPC are not. Additional experiments are necessary to confirm these findings.

**DISCUSSION**

In clinical practice, the resistance of *S. pneumoniae* to levofloxacin and the failure of levofloxacin treatment have been reported (9). *S. pneumoniae* develops resistance as a result of the acquisition of a *gyrA* and/or a *parC* mutation during treatment with levofloxacin. Recently, there has been interest in the optimization of clinical regimens to prevent the formation of resistant mutants. The purpose of this study was to investigate the association between MPC-based PK/PD parameters and the emergence of resistant mutants of *S. pneumoniae*. The results of this study suggest that AUC\text{\textsubscript{0–24}}/MPC and C\text{\textsubscript{max}}/MPC are associated with the emergence of resistance in *S. pneumoniae*, with higher values being more effective for the prevention of resistance. On the other hand, Allen et al. reported that AUC\text{\textsubscript{0–24}}/MPC, C\text{\textsubscript{max}}/MPC, T > MPC, and T\text{\textsubscript{MSW}} are correlated with a reduction in viable cell numbers but that none of these parameters were associated with the emergence of resistance (1). It was also reported that increasing levofloxacin concentrations in order to exceed the MPC was effective for the prevention of mutant selection, suggesting that higher AUC\text{\textsubscript{0–24}}/MPC and C\text{\textsubscript{max}}/MPC values are more effective, just
as we had concluded. Although, TMSW was not associated with resistance in our study, Firsov et al. suggested that resistant mutants of *S. aureus* were selectively enriched when antibacterial concentrations fell inside the mutant selective window (13). Zinner et al. also reported that no selection of resistance among *S. pneumoniae* strains was seen with shorter TMSW's (37). However, each of those two studies used only one fluoroquinolone-susceptible strain. In the present study, we used four strains with various MICs and MPCs to enable a more reliable PK/PD analysis of a means for the prevention of the emergence of resistant mutants. We found that AUC0–24/MIC and Cmax/MPC were associated with the emergence of resistance in *S. pneumoniae*. Other studies have also reported that time-dependent parameters (TMSW and T > MPC) do not correlate with the appearance of resistance in *Escherichia coli* or *S. aureus* (2, 27). However, those results were not sufficient to establish a conclusion, and more experiments with a larger number of test strains and various time-concentration curves are needed to clarify the relationship between the MPC-based PK/PD parameters and the emergence of resistant strains.

The PK/PD parameter which is correlated with bacterial killing has been shown to be AUC/MIC. The bacteria were shown to be eradicated by levofloxacin when the AUC/MIC was about 25 or greater (7a, 19, 21, 23), but the parC mutants were reported not to be eradicated under the same conditions (14). In the present study, it was surprising that once-daily administration of 80 mg moxifloxacin showed good bactericidal activity even against strain SR26137, which possesses a parC mutation, because that the AUC/MIC was about 16 under those conditions (Fig. 4; Table 3). These results show that the established breakpoint is sufficient for the eradication of parC mutants, such as the wild-type strain. Experiments with a large number of parC mutants are required for the PK/PD analysis of the effectiveness of fluoroquinolones against the resistant parC mutants.

In this study, the decrease in susceptibility was defined as an alteration of the population analysis profile. The presence of resistant mutants is clear when regrowth, an elevation of the MIC, and an alteration of the QRDR sequence appear simultaneously. However, in this study, these phenomena did not occur simultaneously. To investigate the contribution of active efflux to the decrease in susceptibility, the MICs after treatment with antibacterials were determined in the presence of reserpine, but changes in the MICs did not occur in the presence of reserpine (data not shown). We cannot explain why the susceptibility decreased, even though the presence of a QRDR mutation and efflux mutation were not confirmed. In particular, treatment with 80 mg moxifloxacin caused the regrowth of strain SR26134 but not alterations by population analysis or of the MICs and QRDR sequences. Although the absence of resistant mutants could not be completely excluded because of the further incubation of the bacterial suspension after moxifloxacin treatment, the same results were observed in duplicate experiments. The reason for the regrowth of strain SR26134 may have been the reversible adaptation to fluoroquinolone resistance, such as the induction of gene expression rather than selection of the resistant mutant. MacGowan et al. also reported that little eradication of *S. pneumoniae* and no emergence of resistance occurred simultaneously in an in vitro PD model (22). While these findings are very interesting, the mechanisms of this adaptation have yet to be reported. On the other hand, levofloxacin treatment, under which the AUC0–24/MPC value was higher than that with treatment with 80 mg moxifloxacin, caused a significant decrease in the susceptibility of strain SR26134 even when the bacterial suspension was further incubated after 72 h of treatment. Furthermore, in the case of SR26137, the decrease in susceptibility that resulted from moxifloxacin treatment was less significant than that which resulted from levofloxacin treatment. These results might indicate a decrease in susceptibility by treatment with both levofloxacin and 80 mg moxifloxacin. However, moxifloxacin may have been the cause of the mutation, but at a lower rate. There may be differences between moxifloxacin and levofloxacin regarding their properties for the selection of resistant mutants. Allen et al. suggested that moxifloxacin was superior to levofloxacin in decreasing susceptibility when the two fluoroquinolones were normalized with regard to their respective AUC/MPC values (1). In order to clarify the interesting issue of whether the PK/PD characteristics for the prevention of the emergence of resistance are different between levofloxacin and moxifloxcin, additional experiments to be performed in the future are being planned.

### Table 3. Relationships between MPC-based parameters and resistance evaluation of *S. pneumoniae*

<table>
<thead>
<tr>
<th>Antibiotic (dose [mg])</th>
<th>Strain</th>
<th>AUC0–24/MIC</th>
<th>Cmax/MIC</th>
<th>AUC0–24/MPC</th>
<th>Cmax/MPC</th>
<th>TMSW (%)</th>
<th>T &gt; MPC (%)</th>
<th>Change in susceptibility</th>
</tr>
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<tbody>
<tr>
<td>MXF (400)</td>
<td>ATCC 49619</td>
<td>158.24</td>
<td>13.05</td>
<td>39.56</td>
<td>3.26</td>
<td>21.81</td>
<td>77.78</td>
<td>None</td>
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<tr>
<td></td>
<td>SR23958</td>
<td>158.24</td>
<td>13.05</td>
<td>39.56</td>
<td>3.26</td>
<td>21.81</td>
<td>77.78</td>
<td>None</td>
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<tr>
<td></td>
<td>SR26134</td>
<td>79.12</td>
<td>6.53</td>
<td>19.78</td>
<td>1.63</td>
<td>69.58</td>
<td>30.14</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>SR26137</td>
<td>79.12</td>
<td>6.53</td>
<td>2.47</td>
<td>0.20</td>
<td>99.51</td>
<td>0.00</td>
<td>None</td>
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<tr>
<td>MXF (80)</td>
<td>SR26134</td>
<td>15.82</td>
<td>1.31</td>
<td>3.96</td>
<td>0.33</td>
<td>16.88</td>
<td>0.00</td>
<td>None</td>
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<tr>
<td></td>
<td>SR26137</td>
<td>15.82</td>
<td>1.31</td>
<td>0.49</td>
<td>0.04</td>
<td>16.88</td>
<td>0.00</td>
<td>Decrease</td>
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<tr>
<td>LVX&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ATCC 49619</td>
<td>26.81</td>
<td>2.40</td>
<td>13.41</td>
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<td>39.86</td>
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<td>4.81</td>
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<td>1.20</td>
<td>87.22</td>
<td>7.92</td>
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<tr>
<td></td>
<td>SR26134</td>
<td>26.81</td>
<td>2.40</td>
<td>6.70</td>
<td>0.60</td>
<td>47.78</td>
<td>0.00</td>
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</tr>
<tr>
<td></td>
<td>SR26137</td>
<td>26.81</td>
<td>2.40</td>
<td>0.84</td>
<td>0.08</td>
<td>47.78</td>
<td>0.00</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

<sup>a</sup> TMSW was calculated as the percentage of the first 24 h.<br><sup>b</sup> T > MPC was calculated as the percentage of the first 24 h.<br><sup>c</sup> MXF, moxifloxacin.<br><sup>d</sup> LVX, levofloxacin.
In conclusion, this study demonstrated that AUC\textsubscript{\text{50-70}}/MPC and C\textsubscript{max}/MPC are the PK/PD parameters which correlated with the emergence of resistance in S. pneumonia but that T\textsubscript{50-70} and T > MPC are not and that higher AUC\textsubscript{50-70}/MPC and C\textsubscript{max}/MPC values are effective at preventing the emergence of resistance.

REFERENCES


