The activity of CEM-101, a fluoroketolide, was compared to those of 11 other antimicrobial agents using the reference broth microdilution method tested against 103 Neisseria meningitidis strains, including ciprofloxacin-nonsusceptible isolates with confirmed gyrA (T91I) mutations. Among the tested isolates, 79.6% were serogroup B or C and all isolates were susceptible to ceftriaxone, azithromycin, minocycline, and rifampin. However, penicillin-nonsusceptible strains were observed (15.5%) and susceptibility to trimethoprim-sulfamethoxazole was only 50.5%. CEM-101 was the most active macrolide-like compound (MIC₉₀ ≤0.015 μg/ml) compared with MIC₉₀ of telithromycin (MIC₉₀ 0.03 μg/ml), azithromycin and clarithromycin (MIC₉₀ 0.12 μg/ml), and erythromycin (MIC₉₀ 0.25 μg/ml). CEM-101 could provide a potent alternative for the prophylaxis of meningococcal disease. 

Currently, chemoprophylaxis is recommended for preventing the spread of bacterial meningitis caused by Neisseria meningitidis among nonimmune persons having contact with patients with active disease. In order to be an effective prophylactic agent, an appropriate antimicrobial agent must achieve concentrations in nasal secretions. Several antimicrobial classes have been traditionally recommended and utilized to achieve concentrations in nasal secretions. Several antimicrobial classes have been traditionally recommended and utilized for nasopharyngeal decolonization (3), including β-lactams, ansamycins (rifampin), fluoroquinolones, sulfonamides (also trimethoprim-sulfamethoxazole [TMP-SMX]), and macrolides. Unfortunately, resistance or reduced susceptibility has been documented among N. meningitidis isolates for all of these antimicrobial classes (9, 11, 13, 16–18, 20). A recent report documented the emergence of fluoroquinolone-resistant N. meningitidis in the United States, and the high rates of resistance to TMP-SMX in this species observed in some studies raise serious concern about the continued use of these agents either for decolonization or as prophylactic agents (4, 22). Among macrolide agents, only azithromycin has been included in the Clinical and Laboratory Standards Institute (CLSI) guidelines for providing susceptibility breakpoint criteria for prophylaxis of meningococcal case contacts and these criteria are not be utilized for therapy of patients with invasive meningococcal disease (7). Azithromycin was shown to have an eradication rate (ER) comparable to that of rifampin, with posttreatment ER at >91% for both drugs (12). The serious nature of disease caused by N. meningitidis and the evolution of resistance to currently used therapies for invasive infections and colonization suggest that the use of newer agents within other classes should be considered.

The ketolides are structurally similar to the macrolides among the macrolide-lincosamide-streptogramin (MLS₉₀) group. CEM-101 is a novel fluoroketolide agent being developed for parenteral and oral therapy targeted to treat moderate-to-severe community-acquired bacterial pneumonia and other indications. This antimicrobial agent has significant potency and activity against several bacterial species, including macrolide-resistant organisms (14). This study was initiated to provide comprehensive data on the activity of CEM-101, to facilitate development as a potential alternative chemoprophylaxis agent in the eradication of nasopharyngeal colonization of N. meningitidis, and to prevent transmission to nonimmune contacts. CEM-101 and comparison agents were tested against a global collection of N. meningitidis isolates, including those with reduced susceptibility to fluoroquinolones (22).

A total of 100 bacteremic N. meningitidis isolates from the SENTRY Antimicrobial Surveillance Program were collected from participating medical centers located in North America (58 isolates), Latin America (13 from three countries), Europe (31 from eight countries), and the Asia-Pacific region (1 isolate). Isolates were collected from patient bloodstream infections during 1997 to 2009 and were identified by at least three laboratories, including two reference laboratories (JMI Laboratories, North Liberty, IA, and the University of Iowa Hygienic Laboratory, Coralville, IA).

Four isolates from the SENTRY Program had elevated nalidixic acid MIC values of ≥8 μg/ml (data not shown), which can correlate with diminished susceptibility to fluoroquinolones according to the CLSI. These isolates were all recovered from European patients in Poland (one isolate), Switzerland (one isolate), and Sweden (two isolates, temporally related). However, all nalidixic acid-nonsusceptible strains had susceptible-level fluoroquinolone MIC results. Three additional isolates of ciprofloxacin-nonsusceptible meningococci from the United States (22) were provided by the Active Bacterial Core Surveillance (ABCS), a collaboration between the Centers for Disease Control and Prevention (Atlanta, GA) and several state health departments and universities participating in the Emerging Infections Program Network.

Antimicrobial agents tested included CEM-101, telithromycin, azithromycin, clarithromycin, erythromycin, penicillin,
TABLE 1. Comparison of the in vitro activities of CEM-101 and selected antimicrobial agents tested against N. meningitidis (103 strains)

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (µg/ml)</th>
<th>50%</th>
<th>90%</th>
<th>Range</th>
<th>% susceptible % resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEM-101</td>
<td>≤0.015</td>
<td>≤0.015</td>
<td>≤0.015-0.06</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>≤0.015</td>
<td>0.03</td>
<td>≤0.015-0.12</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.06</td>
<td>0.12</td>
<td>≤0.015-0.25</td>
<td>97.1/1.9</td>
<td>97.1/1.9</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.03</td>
<td>0.12</td>
<td>≤0.015-0.25</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.12</td>
<td>0.25</td>
<td>0.03-0.5</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.03</td>
<td>0.12</td>
<td>≤0.015-0.25</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤0.015</td>
<td>≤0.015</td>
<td>≤0.015</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤0.008</td>
<td>≤0.008</td>
<td>≤0.008-0.25</td>
<td>97.1/1.9</td>
<td>97.1/1.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤0.008</td>
<td>≤0.008</td>
<td>≤0.008-0.25</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0.12</td>
<td>0.25</td>
<td>≤0.015-0.25</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.015</td>
<td>0.03</td>
<td>≤0.015-0.12</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>0.12</td>
<td>2</td>
<td>≤0.06-4</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
</tbody>
</table>

a Criteria as published by the CLSI (7). The susceptible breakpoints were as follows: azithromycin, ≤2 µg/ml; penicillin, ≤0.06 µg/ml; ceftriaxone, ≤0.12 µg/ml; ciprofloxacin, ≤0.03 µg/ml; levofloxacin, ≤0.03 µg/ml; minocycline, ≤2 µg/ml; rifampin, ≤0.5 µg/ml; and TMP-SMX, ≤0.12/2.4 µg/ml. --, no interpretative criteria are available.

ceftriaxone, ciprofloxacin, levofloxacin, minocycline, rifampin, and TMP-SMX. CLSI reference broth microdilution (6) methodology was performed using cation-adjusted Mueller-Hinton broth panels supplemented with 2.5 to 5% lysed horse blood as well as recommended safety precautions described by the CLSI (7). Direct colony suspensions from a 20- to 24-h growth from a chocolate agar plate were used to obtain a 0.5 McFarland standard inoculum. Plates were incubated at 35°C in 5% CO₂ for 20 to 24 h. Quality control (QC) was performed during each testing event using Streptococcus pneumoniae ATCC 49619 (7). QC strains Escherichia coli ATCC 25922 and Staphylococcus aureus ATCC 29213 were used to control MIC ranges for ceftriaxone and levofloxacin. All MIC values were within specified QC ranges (7).

Isolates were tested for serogroup identification by the University of Iowa Hygienic Laboratory using four antisera which included CEM-101 was the most active compound, with an MIC₀ of ≤0.15 µg/ml (telithromycin MIC₀, 0.03 µg/ml; azithromycin and clarithromycin MIC₀, 0.12 µg/ml; erythromycin MIC₀, 0.25 µg/ml).

Current guidelines for control of community-acquired outbreaks of N. meningitidis via widespread vaccination programs have not been widely adopted in most countries and rely primarily on antimicrobial prophylaxis to reduce the risk to close
contacts with the index patient (3, 21). The high rate of resistance to TMP-SMX and the reduced percentage of penicillin susceptibility among N. meningitidis isolates observed in this study are concerning. Adding to this concern is the emergence of fluoroquinolone resistance in this pathogen. Isolated occurrences of fluoroquinolone-resistant N. meningitidis isolates have been documented since 1992 in several countries, including Greece (first case), Argentina, Australia, France, Hong Kong, India, Italy (imported case), Spain, and the United Kingdom (1, 2, 5, 8, 10, 13, 15, 19). However, this resistance phenotype was only recently documented in the United States (2007 to 2008), isolated from cases in the upper midwestern states and California (22). The isolate from a patient in California may have been acquired by horizontal gene transfer from N. lactamica, a common commensal species (22). The authors reporting these fluoroquinolone-resistant isolates also performed a carriage survey and documented a positivity rate of 7.5% for N. meningitidis carriers among close contacts and a convenience sample of the local population (22). The emergence and potential spread of fluoroquinolone-resistant N. meningitidis are a serious public health problem, as this class of agents is currently recommended for contact prophylaxis. In contrast, all isolates were susceptible to azithromycin using the current CLSI breakpoint used for defining susceptibility (7).

These in vitro observations that CEM-101 had greater potency than other related MLSβ class agents, including telithromycin (≈2-fold), azithromycin and clarithromycin (≈8-fold), and erythromycin (≈16-fold), suggest that this new fluoro-8-ketolide could be an advantageous alternative for the prophylaxis of meningococcal case contacts, including fluoroquinolone-, TMP-SMX-, and penicillin-nonsusceptible clinical strains.

We thank all of the participants in the Emerging Infections Program for sharing the three fluoroquinolone-nonsusceptible strains, with special thanks to the Minnesota Department of Health, St. Paul, MN, the Alameda County Public Health Department. We also appreciate the efforts of G. D. Gerken from the University of Iowa Hygienic Laboratory for providing serotyping information and L. N. Woosley and L. M. Deshpande for susceptibility and molecular testing support.

REFERENCES