were 1 mg/L by BMD and 2 mg/L by the Etest (Table 2). When the geometric mean MIC values were compared, they varied from 0.97 to 1.28 by BMD and 0.88 to 1.23 by the Etest.

The vancomycin MIC values showed fluctuation from year to year. This fluctuation was not statistically significant either by the BMD method ($P=0.225$) or the Etest ($P=0.136$). Although the vancomycin MIC values fluctuated from year to year, we could not detect vancomycin MIC creep with either method. These differences between the years could be due to the large variability among the number of isolates from each year. Similar to the vancomycin susceptibility trend, the daptomycin MIC values also showed fluctuation over time. This fluctuation was found to be statistically significant ($P=0.005$), but no MIC creep was detected between 1999 and 2009.

In conclusion, although MIC fluctuation was found in our institution over time, we did not detect a decrease in vancomycin and daptomycin susceptibility among MRSA blood isolates over an 11 year period, either by BMD or the Etest. It is important to monitor the trend in vancomycin and daptomycin MICs, as changes in vancomycin MICs for *S. aureus* can occur over time within specific institutions.

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Transparency declarations

None to declare.

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A Phase 2 study of the novel fluoroquinolone JNJ-Q2 in community-acquired bacterial pneumonia

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Sir,

JNJ-Q2 is a fifth-generation fluoroquinolone with *in vitro* coverage of community-acquired bacterial pneumonia (CABP) pathogens,

Table 1. Baseline pathogens and outcomes of primary and early response endpoints

	JNJ-Q2 ($n=16$)	Moxifloxacin ($n=16$)
Patients with respiratory pathogen at baseline	15 (93.8%)	13 (81.3%)
Identification of respiratory pathogens		
S. pneumoniae identified	14 (87.5%)	13 (81.3%)
S. pneumoniae by culture	3 (18.8%)	4 (25.0%)
S. pneumoniae by sputum PCR only	8 (50.0%)	7 (43.8%)
S. pneumoniae by sputum PCR with non-*S. pneumoniae*-positive culture[a]	3 (18.8%)	2 (12.5%)
non-*S. pneumoniae*-positive culture[b]	1 (6.3%)	0 (0%)
Clinical cure	14 (87.5%) 1.66 (0.23, 11.75)[c]	13 (81.3%)
Clinical failure	2 (12.5%)	3 (18.8%)
Early response at day 4[d]	9 (56.3%) 1.59 (0.27, 9.42)[c]	7 (43.8%)
30 Day all-cause mortality	0 (0%)	2 (12.5%)

[a]*Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Enterobacter cloacae*, *Serratia marcescens* and *S. aureus*.
[b]*Streptococcus mitis*.
[c]OR (95% CI).
[d]Early response at day 4: combination of (i) clinical stability, which was defined as temperature ≤37.8°C (100.0°F) taken orally, ≤38.2°C (100.8°F) taken tympanically or ≤38.4°C (101.1°F) taken rectally, heart rate ≤100 bpm, respiratory rate ≤24 breaths/min, systolic blood pressure (SBP) ≥90 mmHg, oxygen saturation ≥90% and confusion/disorientation absent—if any vital sign measurement at day 4 did not meet the criteria, the subject was not considered clinically stable, and if oxygen saturation was not tested at day 4 and the subject met the rest of the criteria, the subject was considered clinically stable; and (ii) symptom success, which was defined as none of the four signs and symptoms of community-acquired bacterial pneumonia (cough, dyspnoea or tachypnoea, chest pain and production of purulent sputum) worsening and at least one symptom improving.

atypical respiratory pathogens, multidrug-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*. This double-blind, randomized, non-inferiority, ethics-approved study was designed to enrol 120 hospitalized and consented CABP subjects at 60 sites. It was done in accordance with international guidelines and was based on the 2009 FDA CABP guidance,[1] with the following two exceptions: (i) one dose of a short-acting antibiotic within 4 h before randomization; and (ii) mandatory requirement for sputum production. Patients aged 18–85 years with a PORT score of ≥II and at least three CABP signs/symptoms were eligible for enrolment (cough, dyspnoea/tachypnoea, chest pain, fever/hypothermia or pulmonary consolidation). Sputum with a positive Gram's stain and a chest X-ray (CXR) showing infiltrates in at least lobar distribution were required for entry.

Subjects were stratified by PORT score (II/III versus IV/V) and age (<50 versus ≥50). Sputum was processed locally and sent for PCR detection of *S. pneumoniae* (PrimerDesign®) to PPD GCL (Highland Heights, KY, USA); pathogens were forwarded to JMI Laboratories (North Liberty, IA, USA) for confirmation of identification and susceptibility testing. Patients were randomized 1:1 to receive JNJ-Q2 (150 mg intravenously twice daily followed by 250 mg orally twice daily) or moxifloxacin (400 mg once daily, both intravenously and orally).

Thirty of 60 centres were US based; 16/60 enrolled at least one patient. Over 12 months, 896 patients were screened and 32 randomized; 12 were from North America and the remaining 20 from Eastern Europe or Latin America. The study was terminated early, secondary to slow enrolment.

Pathogens were identified in 28/32 (87.5%) patients either by routine culture (13/32) or PCR detection of *S. pneumoniae* (15/32). *S. pneumoniae* was identified in 27/32 subjects; several subjects with *S. pneumoniae* also grew another pathogen at baseline. The MICs for *S. pneumoniae* were ≤0.004–0.015 mg/L for JNJ-Q2 and 0.06–0.25 mg/L for moxifloxacin.

Nine of 16 JNJ-Q2 subjects met criteria for early response at day 4 compared with 7/16 moxifloxacin subjects. The small number of subjects was insufficient to show non-inferiority for clinical test of cure, the historical CABP endpoint, however. The cure rates were comparable and reflected historical rates (see Table 1).

Three subjects in the moxifloxacin group were clinical failures: two did not survive to 30 days and the third required additional antibiotics. Two subjects were clinical failures in the JNJ-Q2 group: one who did not meet the pneumonia criteria was withdrawn, while the other survived after respiratory failure requiring mechanical ventilation. Adverse events were comparable; however, nausea and vomiting were seen in the moxifloxacin group, but not in the JNJ-Q2 group.

The slow enrolment observed in this study was mainly due to prior antibiotic use, requirements in CXR, sputum production, Gram's stain and emphasis on severe patients. FDA guidance discourages prior antibiotic use in CABP studies, based on heightened regulatory concern about the potential of antibiotic use to confound the validity of non-inferiority trials.[2] Prior antibiotic use excluded the largest number of subjects in our study: 220/864 (25.5%).

In addition, 147/864 patients (17%) could not be enrolled because of the absence of lobar infiltrate on CXR and/or sputum production with a positive Gram's stain. Historically, CABP studies have not mandated a lobar infiltrate or sputum production. Importantly, up to 40% of patients with CABP cannot produce good quality sputum;[3,4] new techniques (e.g. nasopharyngeal PCR) need to be evaluated for these patients.[5,6]

CABP enrolment in US studies is becoming more difficult. The recent ceftaroline programme of CABP[7] did not require sputum production or lobar infiltrate and excluded patients with PORT scores

of V. Although it recruited >1200 patients in 24 months at 303 centres, only 2% of their population came from the USA.[7]

Respiratory pathogen recovery rate was unusually high. Sputum PCR testing remains an experimental tool[8] and requires that clinicians distinguish between colonization and infection. In our study, each patient with *S. pneumoniae* PCR-positive sputum had $\geq 5.3 \times 10^4$ copies per mL, exceeding the rate recommended by Yang *et al*.[9]

Compared with historical pathogen identification rates (generally <50%),[4,7] our recovery was encouraging.[1] Johansson *et al*.,[10] using multiple recovery techniques, including PCR, yielded recovery rates of only 38% for *S. pneumoniae*, 48.9% for common CABP pathogens and 62.5% when including atypical organisms and mycobacterial species. In comparison, the Phase 3 CABP ceftaroline studies recovered respiratory pathogens in 26% of their patients.[7] We attribute our high rate of bacterial pathogen recovery to the strict criteria for CXR, sputum production and positive Gram's stain, as well as the PCR techniques.

Our data, limited by small sample size, provide qualitative information that JNJ-Q2 warrants further study. While the combination of standard pneumonic symptoms, lobar infiltrates, sputum production with positive Gram's stain and no prior antibiotics is strongly predictive for respiratory pathogen recovery, it is at the expense of reasonable recruitment timelines.

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