Comparison of BSAC agar dilution and NCCLS broth microdilution MIC methods for in vitro susceptibility testing of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis: the BSAC Respiratory Resistance Surveillance Programme

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Objective: The aim of this study was to establish the degree of comparability between the NCCLS broth microdilution and BSAC agar dilution MIC methods of antimicrobial susceptibility testing.

Methods: Six hundred and sixty-one clinical isolates of Streptococcus pneumoniae, 936 Haemophilus influenzae and 421 Moraxella catarrhalis, collected in the winter of 1999–2000 by 20 laboratories in the UK and Eire from patients with presumed community-acquired lower respiratory infections, were tested by the two methods. MIC agreement was defined as excellent (good) if results were within ±1 doubling dilution for ≥90% (≥80%) of isolates and within ±2 doubling dilutions for ≥95%. Isolates were categorized as susceptible, intermediate or resistant using the breakpoints appropriate to the testing method.

Results: MIC agreement was good or excellent in 27 of 36 organism–agent combinations. Agreement was less for M. catarrhalis than for other species, and lower in all three species for cefaclor and trimethoprim than for other antimicrobials. Discrepancies in categorization occurred only occasionally, and were generally explained by differences in breakpoints rather than in measured MICs. One exception was S. pneumoniae with penicillin. Despite excellent MIC agreement and identical breakpoints, 9% of these had minor discrepancies, mainly because 7% of isolates were found intermediate by the BSAC method but resistant by the NCCLS method.

Conclusion: There is generally very good agreement between the MICs obtained by the BSAC agar dilution and NCCLS broth microdilution methods in this population of isolates, comparable to the level of agreement achieved between different laboratories using a single method. Breakpoint differences contribute to most of the discrepancies in susceptibility categorization.

Keywords: methodology, antimicrobial susceptibility, respiratory pathogens

Introduction

There is an accepted need for surveillance of antimicrobial susceptibility of major bacterial pathogens, such as those causing community-acquired lower respiratory tract infection. The purpose of surveillance is to contribute towards overcoming resistance, both by providing early warning of emerging problems and by increasing understanding of the factors promoting resistance. MIC measurement is preferable to simple categorization of isolates as susceptible, intermediate or resistant, as gradual increases in MIC may indicate the development of new bacterial capabilities and precede the development of outright clinical resistance. There are several established methods of MIC measurement that are used in different studies and different countries. As resistance is a global issue, it is necessary to establish comparability between these methods in order to be able to compare results from different studies.

The BSAC Respiratory Resistance Surveillance Programme exists to provide long-term, large-scale surveillance of the major pathogens causing community-acquired lower respiratory tract infections in Great Britain and Ireland. This paper compares the
BSAC agar dilution method was used in the BSAC Surveillance Programme with the NCCLS broth microdilution method generally used in North America.

Methods

Isolates

The isolates used for comparison of the BSAC agar dilution and NCCLS broth microdilution MIC testing methods were collected by 20 clinical laboratories in the UK and Eire in the winter of 1999–2000. They were from lower respiratory sources of patients with presumed community-acquired infection, routinely referred for clinical testing. Isolates were sent to a central laboratory (GR Micro Ltd, London, UK) for re-identification and susceptibility testing. Details of collecting laboratories and storage have been described previously. Additional isolates of Moraxella catarrhalis, collected in the same way in 2000–2001, were used to assess the effect of inoculum size in the BSAC agar dilution MIC testing method.

Antimicrobial susceptibility testing

BSAC method. The method used has been described previously and was essentially the same as the most recently published version of the BSAC agar dilution MIC method, differing only in the inoculum size for M. catarrhalis. The inoculum used was 10^4 cfu. We also tested M. catarrhalis with ampicillin and co-amoxiclav using an inoculum of 10^6 cfu. Since the BSAC method now recommends the larger inoculum, we report here the results with 10^6 cfu for compatibility with future reports.

NCCLS method. MICs were measured by the NCCLS broth microdilution method using cation-adjusted Mueller–Hinton broth (Trek Diagnostic Systems, East Grinstead, UK) supplemented with 5% defibrinated lysed horse blood (TCS Biosciences, Buckingham, UK) for Streptococcus pneumoniae and M. catarrhalis, and unsupplemented Haemophilus Test Medium Broth (Becton Dickinson Microbiology Systems, Sparks, MD, USA) for H. influenzae. The inoculum size was 5 x 10^4 cfu and the volume per well was 100 µL. The trays (Trek Diagnostic Systems) were covered with an adhesive seal and incubated in air.

Reference strains and antimicrobial agents

The reference strains (for both methods) and suppliers of antimicrobial agents were as described previously for the BSAC method.

Trek Diagnostic Systems supplied freeze-dried microdilution plates containing antimicrobial agents.

Repeatability of the BSAC method

In a preliminary study, 20 isolates each of S. pneumoniae, H. influenzae and M. catarrhalis, chosen to represent a wide range of MICs, were tested at the central laboratory, GR Micro, and two independent laboratories. At GR Micro and one other laboratory the measurements were repeated, giving 40 data points per drug for assessment of within-laboratory repeatability (33 in the case of H. influenzae due to seven culture failures in one run at one laboratory). Between-laboratory repeatability was assessed by comparing GR Micro run 1 with laboratory A run 1, and GR Micro run 2 with laboratory B, again with 40 data points per drug. The drugs tested were amoxicillin, cefaclor, cefuroxime, cefotaxime, erythromycin, ciprofloxacin, tetracycline and trimethoprim for all species, plus penicillin and clindamycin for S. pneumoniae, ampicillin and co-amoxiclav for H. influenzae, and ampicillin and co-amoxiclav at both 10^6 and 10^8 cfu per spot for M. catarrhalis.

Testing for effect of inoculum size on MIC measured by the BSAC method in M. catarrhalis

In the 1999–2000 season, M. catarrhalis isolates were tested against ampicillin and co-amoxiclav using inocula of both 10^4 and 10^6 cfu per spot, allowing direct comparison of these two variants of the BSAC method with the NCCLS method. Inocula of both 10^4 and 10^6 cfu per spot were used for all β-lactam antibiotics tested against 424 isolates of M. catarrhalis collected in the same way in the 2000–2001 season.

Comparison of MICs

For each isolate tested with each agent, the doubling dilution difference (or tube difference) in the MIC was calculated as: log2(MIC by NCCLS method) – log2(MIC by BSAC method). Thus, an MIC tube difference of one tube indicates that the NCCLS MIC was 1 doubling dilution higher, that is, double the BSAC MIC; a tube difference of –2 tubes indicates that the NCCLS MIC was 2 doubling dilutions lower, that is, one-quarter of the BSAC MIC.

Occasionally, particularly with the NCCLS method, where the testing range was predetermined, exact MIC results were not available and MICs at the ends of the range could only be interpreted as ‘greater than’ or ‘less than or equal to’. In these cases, MICs for the two methods were censored at the same level, and in the ‘greater than’ case were reported as ‘greater than or equal to’ the next highest concentration in the series. For comparison between methods, the censored results were then treated as equal to the lowest or highest reported values. For example, if an isolate grew at the highest tested concentration of 16 mg/L in the NCCLS method, it required an MIC ≥ 16 mg/L: this was reported as ≥32 mg/L and treated for purposes of calculation as =32 mg/L. If the MIC for the same isolate by the BSAC method was 128 mg/L, the recorded doubling dilution difference in MICs would be zero tubes (because the BSAC result would also be truncated to difference in MICs would be zero tubes (because the BSAC result would also be truncated to 16 mg/L). If the MIC measured by the BSAC method was 8 mg/L, the difference would be 2 tubes (log2=32–log2=8). The censorship levels used are shown in Tables 1–3.

The percentage of isolates with MICs measured by the two methods agreeing to within ±1 and ±2 doubling dilutions was calculated for each species–agent combination. Agreement between the methods was considered excellent if the MICs were within ±1 doubling dilution for ≥90% of isolates and within ±2 doubling dilutions for ≥95%. Agreement was good if ≥80% of the MICs were within ±1 doubling dilution and ≥95% within ±2 doubling dilutions. Agreement was poor if <80% of MICs were within ±1 doubling dilution or <95% within ±2 doubling dilutions.

Comparison of susceptibility

Isolates were categorized as susceptible, intermediate or resistant to each agent twice, once using the NCCLS MIC with NCCLS breakpoints and again using the BSAC MIC with BSAC breakpoints. Discrepancies between the categorizations were considered minor when an isolate found intermediate by one method was found susceptible or resistant by the other, and major when an isolate found susceptible by one method was found resistant by the other.

Results

Repeatability of the BSAC method within and between laboratories

Within laboratories, and averaging over all antibiotics tested, 91% (98%), 92% (99%) and 92% (99%) of S. pneumoniae, H. influenzae and M. catarrhalis MICs, respectively, were repeated to within ±1 (±2) doubling dilutions. Repeatability between laboratories was lower, with 87% (97%), 80% (94%) and 71% (88%) of S. pneumoniae,
**Comparison of BSAC and NCCLS MIC methods**

*H. influenzae* and *M. catarrhalis* MICs, respectively, repeatable to within ±1 (±2) doubling dilutions. The reduction in repeatability was most marked for *M. catarrhalis*.

Thus the definitions of ‘excellent’ and ‘good’ agreement used in the comparison between NCCLS and BSAC methods were exacting standards. Excellent agreement between methods corresponded approximately to the level of agreement seen with one method within one laboratory. Good agreement roughly corresponded to (or, in the case of *M. catarrhalis*, exceeded) the level of agreement seen with one method between laboratories.

**Effect of *M. catarrhalis* inoculum size on MIC measured by the BSAC method**

In 424 *M. catarrhalis* isolates tested with β-lactams by the BSAC method, larger inocula (10<sup>6</sup> cfu) resulted in higher MICs than did smaller inocula (10<sup>4</sup> cfu). The mean differences in MIC between these inocula were 3.52, 3.41 and 2.75 doubling dilutions for amoxicillin, ampicillin and cefaclor, respectively, with the difference greater for β-lactamase-positive isolates (2.92–3.74) than for β-lactamase-negative isolates (0.65–1.19). The mean differences were 0.86, 0.84 and 0.84 doubling dilutions for co-amoxiclav, cefuroxime and cefotaxime, respectively, with little distinction between β-lactamase-positive and -negative isolates.

Correspondingly, in the comparison between NCCLS and BSAC methods, BSAC amoxicillin MICs obtained with the smaller inoculum of *M. catarrhalis* were, on average, 2.02 doubling dilutions lower than NCCLS MICs, whereas with the larger inoculum they were 0.93 dilutions higher. The percentage of isolates with BSAC and NCCLS amoxicillin MICs agreeing to within ±1 (±2) doubling dilutions increased from 39% (66%) with 10<sup>4</sup> cfu to 73% (92%) with 10<sup>6</sup> cfu. For co-amoxiclav, a change in inoculum size had little effect: the larger inoculum only changed the mean MIC doubling dilutions difference from +0.19 to −0.35 tubes, and the agreement within ±1 (±2) dilutions from 98% (100%) to 93% (98%).

**Comparison of MICs measured by NCCLS and BSAC methods**

Three-quarters of the organism–agent combinations (27/36) showed good or excellent MIC agreement (Tables 1–3). The exceptions were: *S. pneumoniae* with cefaclor, cefuroxime and trimethoprim; *H. influenzae* with cefaclor and trimethoprim; and *M. catarrhalis* with ampicillin, amoxicillin, erythromycin and tetracycline. Of these, *S. pneumoniae*/trimethoprim, *S. pneumoniae*/cefuroxime and *M. catarrhalis*/ampicillin approached good agreement, with ≥70% of isolates within ±1 and ≥90% within ±2 doubling dilutions.

**Comparison of susceptibility categorization by NCCLS and BSAC methods**

Categorization of isolates as susceptible, intermediate or resistant was compared for the 19 organism–agent combinations for which breakpoints had been defined by both methods: 10 combinations with *S. pneumoniae* and nine with *H. influenzae* (Tables 1 and 2). In 17 of these, NCCLS defined an intermediate category while BSAC only defined susceptible and resistant categories. Fourteen combinations had <2% major discrepancies and <5% minor discrepancies. Two (*S. pneumoniae* with penicillin and cefaclor) had <2% major discrepancies but >5% minor discrepancies (9% and 7%, respectively). Three combinations (*H. influenzae* with co-amoxiclav, cefaclor and cefuroxime) had >2% major discrepancies (8%, 96% and 18%, respectively).

**Discussion**

A necessary precursor to comparing two different methods is to assess the repeatability of a single method. We found that the BSAC MIC method was highly repeatable within a single laboratory, 91–92% of tests being repeated to within ±1 doubling dilutions and 98–99% to within ±2 doubling dilutions. As expected, between-laboratory repeatability was somewhat lower, although 80–87%.
Ciprofloxacin

Cefuroxime

E, excellent; G, good; P, poor; S, susceptible; R, resistant.

Trimethoprim

Levofloxacin

Erythromycin

Ampicillin

Amoxicillin

Co-amoxiclav (2:1)

Ampicillin

Amoxicillin

M. catarrhalis

The remaining case of poor agreement was for tetracycline in NCCLS and BSAC methods, respectively) on 124 varied isolates (although 100% agreed within 1 doubling dilution). A previous study by Koeth et al. using the NCCLS microdilution procedure and comparing Mueller–Hinton with IsoSensitest broth (used in the NCCLS and BSAC methods, respectively) on 124 varied isolates also found close agreement in the measured MICs.

The level of agreement seen between percentages of isolates found susceptible, intermediate and resistant by the two methods was also generally high: 14 of 19 evaluable organism–agent combinations had <2% major errors and <5% minor errors in classification. Differences in breakpoints largely explained the major discrepancies seen for H. influenzae with co-amoxiclav, cefaclor and cefuroxime. The NCCLS breakpoints for these agents were 2–4 doubling dilutions higher than the BSAC breakpoints, causing many isolates found resistant by the BSAC method to appear susceptible by NCCLS criteria. The 7–9% minor discrepancies seen for S. pneumoniae with cefaclor and penicillin could not be explained by breakpoint differences. With cefaclor, an average MIC difference of +1.2 doubling dilutions and a low breakpoint close to the mode MIC combined to give 5% of isolates being found susceptible by the BSAC method but intermediate by the NCCLS. For penicillin, MIC agreement was extremely close for susceptible isolates of S. pneumoniae, but in non-susceptible isolates the BSAC MIC was typically 1 or 2 dilutions lower than the NCCLS MIC. As the mode NCCLS MIC for non-susceptible isolates coincided with the upper breakpoint, 7% of isolates were found resistant by the NCCLS method but intermediate by BSAC. This high level of agreement is again similar to that seen in the earlier comparison between Mueller–Hinton and IsoSensitest broths, in which there was 98–99% categorical agreement.

Percentage susceptibility is a useful summary measure and will, no doubt, continue to be used as such in reports of surveillance studies. It is therefore reassuring that two major methods of measuring susceptibility in an important group of pathogens have been shown to give a large measure of agreement. Nonetheless, it is important to recognize the three particular weaknesses of susceptibility categorization when surveillance results are to be compared between periods or countries. The first is that differences in the breakpoints applied by different organizations or at different times can lead to artefactual differences in percentage susceptibility, as shown here for several antimicrobials with H. influenzae. The second is that, where breakpoints

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Table 2. Comparison of MICs and susceptibility categorizations by NCCLS and BSAC methods for 936 H. influenzae isolates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC comparison</th>
<th>Category comparison</th>
<th>Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean tubes difference</td>
<td>% agree ≤1 tube</td>
<td>% agree ≤2 tubes</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>-0.32</td>
<td>93.7</td>
<td>99.4</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>-0.44</td>
<td>91.8</td>
<td>97.9</td>
</tr>
<tr>
<td>Co-amoxiclav (2:1)</td>
<td>-0.49</td>
<td>95.7</td>
<td>99.9</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>-1.27</td>
<td>57.6</td>
<td>93.3</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>-0.19</td>
<td>95.4</td>
<td>99.5</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>-0.35</td>
<td>95.4</td>
<td>99.1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>-0.04</td>
<td>96.4</td>
<td>99.8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>-0.64</td>
<td>82.9</td>
<td>99.8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>-0.42</td>
<td>97.6</td>
<td>99.6</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>-0.51</td>
<td>95.7</td>
<td>99.9</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.20</td>
<td>98.3</td>
<td>99.8</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>-1.19</td>
<td>63.9</td>
<td>93.8</td>
</tr>
</tbody>
</table>

E, excellent; G, good; P, poor; S, susceptible; R, resistant.

*Mean difference in log2 MICs, MICs, NCCLS – BSAC.

% Agree ≤1 (≤2) tube(s) = % of MICs by the two methods within ≤1 (≤2) doubling dilutions of each other.

*In the absence of a high breakpoint, all non-susceptible isolates are classified as intermediate.

(94–97%) of S. pneumoniae and H. influenzae still gave results agreeing to within ±1 (±2) dilutions. M. catarrhalis gave the lowest between-laboratory repeatability, probably because in this species the MIC of β-lactams is sensitive to inoculum size, precise control of which is hindered by the species’ tendency to aggregate.

Our results comparing inocula of 106 with 104 cfu of M. catarrhalis in the BSAC method confirmed that the larger inocula resulted in greater MICs of β-lactamase-labile antimicrobials, and it is clear that 106 cfu, as now recommended, is the more appropriate test inoculum. Not only did the smaller inoculum give poor agreement with the NCCLS method, but among β-lactamase-positive isolates tested in this way, ~40% were incorrectly categorized as susceptible to amoxicillin and ampicillin. This error rate was reduced to ~1% with the larger inoculum.

The level of agreement seen between the MICs measured by the BSAC agar dilution and NCCLS broth microdilution methods was very good in general, and comparable to the level of agreement achieved between different laboratories using a single method. Of the six organisms–agent combinations that fell markedly short of good agreement, four were combinations that also showed only moderate between-laboratory repeatability by the BSAC method (cefaclor in S. pneumoniae and H. influenzae, trimethoprim in H. influenzae, and erythromycin in M. catarrhalis). The poor agreement for M. catarrhalis with amoxicillin can be attributed to the use of the superseded 105 cfu inoculum in the BSAC method: it can be expected to improve with the increased inoculum size in the revised BSAC method.2,3 The remaining case of poor agreement was for tetracycline in M. catarrhalis, for which only 53% agreed within ±1 doubling dilution (although 100% agreed within ±2 doubling dilutions). A previous study by Koeth et al. using the NCCLS microdilution procedure and comparing Mueller–Hinton with IsoSensitest broth (used in the NCCLS and BSAC methods, respectively) on 124 varied isolates also found close agreement in the measured MICs.
Comparison of BSAC and NCCLS MIC methods

Table 3. Comparison of MICs by NCCLS and BSAC methods for 421 M. catarrhalis isolates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>mean tubes difference</th>
<th>% agree ± 1 tube</th>
<th>% agree ± 2 tubes</th>
<th>qualitative</th>
<th>censorship levels (≤, ≥)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>-0.93</td>
<td>73.4</td>
<td>91.7</td>
<td>P</td>
<td>0.06, 16</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1.81</td>
<td>42.5</td>
<td>72.9</td>
<td>P</td>
<td>0.06, 32</td>
</tr>
<tr>
<td>Co-amoxiclav  (2:1)*</td>
<td>-0.35</td>
<td>93.1</td>
<td>98.3</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>0.57</td>
<td>83.4</td>
<td>97.9</td>
<td>G</td>
<td>-</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.95</td>
<td>84.8</td>
<td>99.5</td>
<td>G</td>
<td>-</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.45</td>
<td>95.7</td>
<td>98.6</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1.49</td>
<td>46.1</td>
<td>98.8</td>
<td>P</td>
<td>0.03, -</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>-0.25</td>
<td>99.8</td>
<td>100.0</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>-0.10</td>
<td>98.8</td>
<td>100.0</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>-0.27</td>
<td>99.8</td>
<td>99.8</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>-1.42</td>
<td>53.4</td>
<td>99.8</td>
<td>P</td>
<td>-</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>0.44</td>
<td>90.0</td>
<td>98.8</td>
<td>E</td>
<td>-</td>
</tr>
</tbody>
</table>

E, excellent; G, good; P, poor; S, susceptible.

*Mean difference in log₂ MICs, NCCLS – BSAC.

†% Agree ±1 (±2) tube(s) = % of MICs by the two methods within ±1 (±2) doubling dilutions of each other.

Inoculum for BSAC method 10⁴ cfu except ampicillin and co-amoxiclav (10⁶ cfu).

are near peaks in MIC frequency, minor methodological differences (which may equally well exist within or between methods) have an exaggerated impact on percentage susceptibility: this was seen here for S. pneumoniae with penicillin at the breakpoint between intermediate susceptibility and resistance. Thirdly, and conversely, where breakpoints are remote from the mode MIC, the percentage categorized as susceptible is insensitive to gradual MIC changes in the population. Therefore, it is important to report MICs as well as categorical susceptibility data for surveillance purposes. This study has shown a large degree of concordance between MIC results obtained by the BSAC agar dilution and NCCLS broth microdilution methods, supporting cautious comparisons between surveys using the two methods.

Information from the BSAC Respiratory Resistance Surveillance Programme is available to investigators through the BSAC website at www.bsac.org.uk. The isolates can also be made available for further study.

Acknowledgements

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Grow Aerobically—Fifth Edition: Approved Standard M7-A5. NCCLS, Wayne, PA, USA.


