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Unsuitability of MIC_{50}, MIC_{90} for comparison of antibiotic potency

R. Reynolds for The BSAC Extended Working Parties on Resistance Surveillance

British Society for Antimicrobial Chemotherapy, Birmingham, B1 2JS

rreynolds@bsac.org.uk
Dept Medical Microbiology
Southmead Hospital
Bristol, BS10 5NB, UK

Background

Antibiotic potency is commonly ranked by comparison of MIC_{50} or MIC_{90}. The reliability of this simple method was investigated by simulation for unimodal distributions; it is plainly unsuitable when there are distinct resistant subpopulations.

Method

MICs for 20, 50, 100 or 500 isolates were simulated and analysed on a $\log_2$ scale, i.e. measured in doubling dilutions. 'Underlying' continuous MICs showed intrinsic variation between isolates (normal, SD 0.3*) and experimental variation (normal, SD 0.3, 0.4 or 0.6*). MIC distributions had their peak exactly at, or at various levels between, exact doubling dilution MIC values. The intrinsic MIC difference between drugs A and B was fixed at 0, 0.25, 0.5, 1 or 2 dilutions. 'Measured' MICs were rounded up to conventional values for analysis.

MICs of A and B were compared by MIC_{50}, MIC_{90}, Wilcoxon matched-pairs signed-rank test, and descriptively by summarising paired MIC differences.

The percentage of 1000 replicates showing a difference (significant at the 5% level for a formal test) is the power or, in the absence of real difference, type 1 error rate.

*based on data from EUCAST & BSAC Resistance Surveillance Project.

Results

Comparison of MIC_{50} often gave high error rates in the absence of real differences, and had very erratic (often poor) detection of small differences, depending on the precise position of MIC peaks relative to exact doubling dilutions. MIC_{90} was no better.

The Wilcoxon matched-pairs signed-rank test was reliable, had higher power, and was unaffected by exact peak positions.

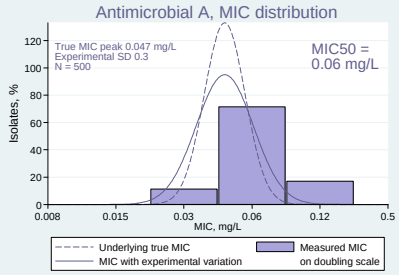
Summaries of paired MIC differences could estimate the size of fractional MIC differences accurately, unlike MIC_{50} and MIC_{90}.

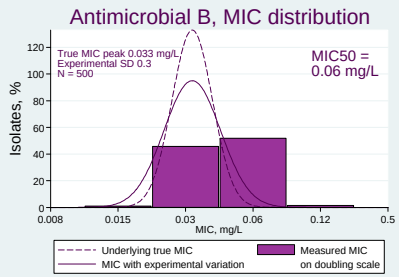
All methods could detect larger differences (1 or 2 dilutions) but only the paired comparison could estimate their size reliably.

Conclusion

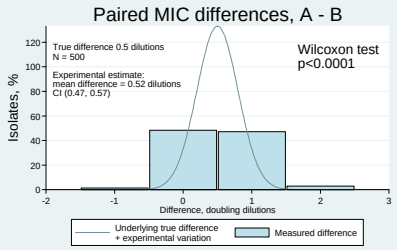
- Simple comparison of MIC_{50} or MIC_{90} is a seriously flawed method for the comparison of antibiotic potency.
- The Wilcoxon signed-ranks test is safer and more powerful.
- Description of paired MIC differences is more informative.

Example



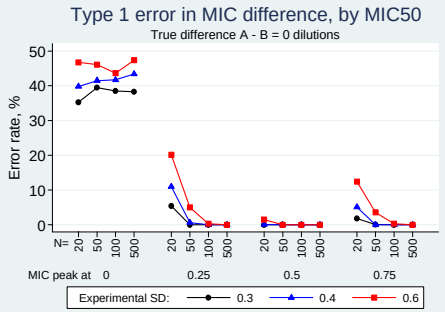


MIC_{50} comparison failed to detect a 0.5 dilution (1.4-fold) difference between MICs of A and B, despite large sample.

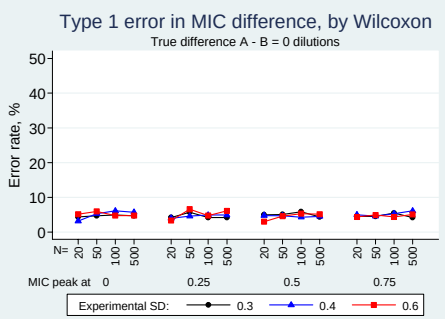


Paired MICs identified the difference and estimated its size correctly.

Type 1 error (false positive) rate



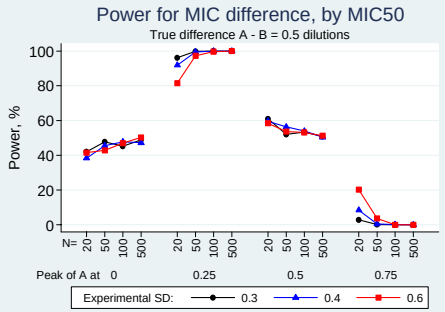
Simple MIC_{50} comparisons could produce extremely high false positive error rates, and these persisted even with very large sample sizes if the peaks of the MIC distributions were close to an exact MIC on the conventional doubling dilution scale.



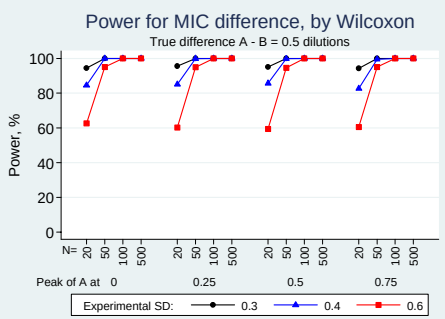
The Wilcoxon matched-pairs signed-rank test gave a type 1 error rate close to the design level of 5% in all circumstances.

Position of MIC peak is shown on doubling dilution scale: 0 is exactly at a conventional doubling MIC, 0.5 is halfway between conventional MIC levels.

Power - ability to detect a difference



MIC_{50} performed very erratically. A true difference of 0.5 dilutions was essentially undetectable if the MIC peaks of both drugs were in the same doubling dilution band (e.g. 0.25 & 0.75 $\log_2$ units from an exact MIC), however large the sample size.



The power of the paired analysis increased with increasing sample size and decreasing experimental variation, as expected. A difference of 0.5 dilutions could be reliably detected with 50 isolates (power >94%), regardless of exact MIC peak positions.

Simulation, analysis and graphs: Stata version 9.2, StataCorp, 2005-07, College Station, TX.

Working Party Members (March 2008): A.P. MacGowan[1] (Chair), M. Allen[2], D.F.J. Brown[3], K. Bush[4], R. Charters[5], J. Copeland[6], N. Deaney[7], J. Dennison[8], D. Felmingham[9], R. Hope[10], D. Lewis[11], D.M. Livermore[10], M. Lockhat[12], C. Longshaw[13], K. Maher[9], I. Morrissey[9] R. Reynolds[1], C. Thomson[14], A. White[15]

[1]North Bristol NHS Trust; [2]Novartis; [3]Addenbrookes Hospital, Cambridge; [4]Johnson&Johnson; [5]Astellas; [6]Theravance; [7]Merck, Sharp & Dohme; [8]Pfizer; [9]Quotient BioResearch Ltd., Microbiology, London; [10]HPA Centre for Infections, London; [11]HPA South West; [12]AstraZeneca ;[13]Wyeth; [14]IMS Health; [15]Consultant.

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