A novel high-throughput lab-on-chip test for rapid phenotypic antibiotic susceptibility testing directly from positive blood cultures

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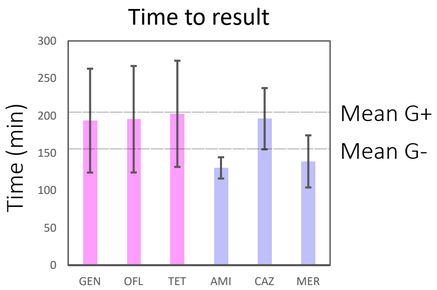
1 There is a need for rapid AST methods

Classical antibiotic susceptibility tests such as broth microdilution (BMD) are reliable and accurate, but often too slow in severe infections such as sepsis. As the prevalence of multidrug-resistant bacteria increases, rapid diagnostics are needed to avoid treatment failure from inappropriate empirical antibiotic therapy.

Previously, we have described a phenotypic antibiotic susceptibility test providing results from positive blood cultures within 2-4 hours, using label-free time-lapse microscopy of bacterial microcolonies. The aim of this study was to design and evaluate a high-throughput AST system based on 3D-printed microfluidics, capable of measuring 8 samples simultaneously.

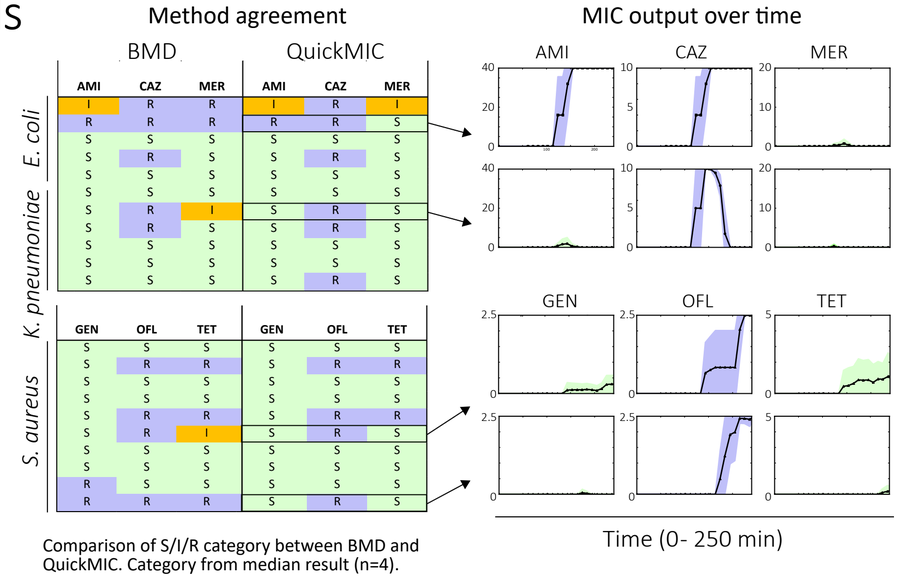
2 QuickMIC: Rapid AST results in 2-3 h

The MIC results were within 1 log2 difference from reference BMD results in 24 of 33 tests (G-) and 19 of 30 tests (G+). Times-to-result for all isolates were on average between 2-3 hours, while maintaining good categorical agreement compared to BMD. Essential agreement was acceptable except for gentamicin.



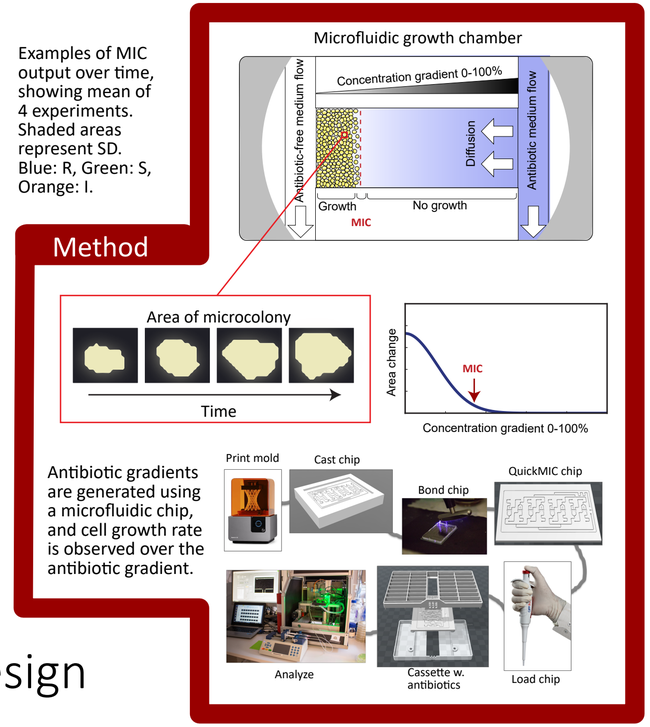
3 We conclude:

The presented method has the potential to provide very rapid antibiotic susceptibility results directly from positive blood cultures, which would be of high clinical importance. Challanges remain for phenotypic rapid AST, especially regarding carbapenem resistance, due to late expression of carbapenemases.



Comparison of S/I/R category between BMD and QuickMIC. Category from median result (n=4).

Examples of MIC output over time, showing mean of 4 experiments. Shaded areas represent SD. Blue: R, Green: S, Orange: I.



Categorical and essential agreement (%)

	AMI	CAZ	MER	GEN	OFL	TET
EA	100	63.6	72.7	18.2	100	72.7
CA	100	90.9	72.7	81.8	100	81.8

4 Study design

We tested 21 clinical isolates of *E. coli, K. pneumoniae* and *S. aureus* from the EUCAST Development Laboratory, Växjö, Sweden. The isolates were tested against a Gram positive or Gram negative panel of 3 drugs per type (G-: amikacin, ceftazidime, meropenem; G+: gentamicin, ofloxacin, tetracycline). Automatic cell and microcolony growth tracking was performed using a cluster analysis algorithm on images from an automated darkfield microscope (1.8x magnification). Cells in the image were identified and MIC readout was performed by tracking the growth rates of individual microcolonies. Reference BMD MIC were acquired from EDL for comparison. QuickMIC data was right censored to nearest 2-log for comparison of essential agreement.

Acknowledgements:
The authors wishes to thank Vinnova, Uppsala Antibiotic Center and the European Union's Horizon 2010 research and innovation program (grant agreement No. 642866) for funding this research.

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