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Can Experimental Variation Give the Illusion of MIC Creep?

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BACKGROUND

We previously reported apparent upward creep in vancomycin MICs for MRSA tested in batches each year that was refuted when the same isolates were re-tested in a single week (JAC 2012; **67** 2912-18). Could variation in experimental factors over time explain the original results and similar reports?

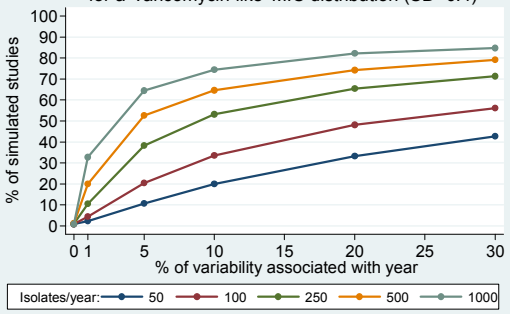
SIMULATION / MODELLING assumptions

- Studies lasted 5 years.
- 50 - 1000 isolates were collected each year, at times drawn from a uniform distribution.
- 'Underlying' MIC distributions were log-normal with standard deviation (SD) of 0.4 or 0.8 $\log_2$ units (doubling dilutions).
- MIC variance was made up of two log-normal components - between-year experimental variation at 0-30% of total, and within-year (between-isolate) variation at 70-100%.
- **There was no MIC creep in the model.**
- Underlying MICs were rounded up to give measured MICs on conventional $\log_2$ scale.
- Measured MICs were analysed for trend (creep) by linear regression against time.
- Each simulation was repeated 10,000 times.

RESULTS

Spuriously significant creep (p<0.01)

for a 'vancomycin-like' MIC distribution (SD=0.4)

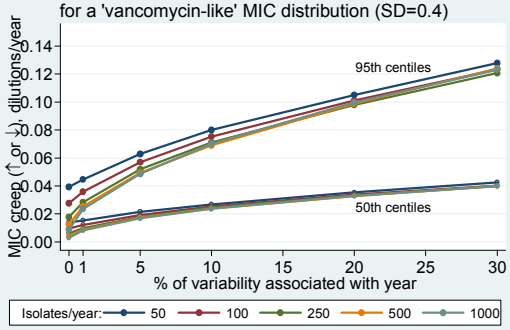


- Trends detected as significant at p<0.01 became common if any of the variation in MICs was associated with year, and more so with larger proportions of year-to-year variation.
- Spuriously significant trends were (counter-intuitively) more likely with larger sample sizes.
- Apparent trends were equally likely to be upwards or downwards.

N.B. No trend was built into any of these models, so only 1% of simulations should appear significant at p<0.01.

Speed of spurious creep - 50th & 95th centiles

for a 'vancomycin-like' MIC distribution (SD=0.4)



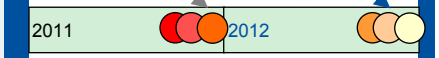
- The speed of the apparent creep increased with increasing year-to-year variation but was not greatly affected by sample size.
- The size of the induced trends is in line with previous reports of creep e.g. 0.078 doubling dilutions/year (JAC 2012; **67** 2912-18) is a plausible artefact (near or below the 95th centile) if year-to-year experimental variation is ≥10% of total.

Trends induced in wider MIC distributions (SD 0.8) were slightly steeper and more likely to appear (misleadingly) significant.

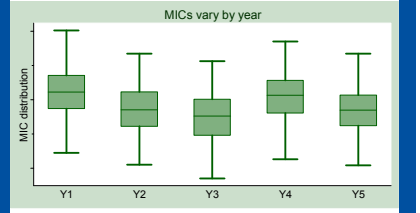
Why might experimental variation be linked with time of isolate collection?

In a central-laboratory study design...
isolates may be collected all year

but tested in a few batches over a short time each year



Experimental conditions for each year's batches are very similar (e.g. same lots of medium and potency of antibiotic powders), but slightly different from other years' conditions so ...



... the MICs vary from year to year more than expected from sampling variation. This can give the appearance of MIC creep.

IS THE MODEL REASONABLE? part 1

Log-normal underlying MICs, SD 0.4 - 0.8.

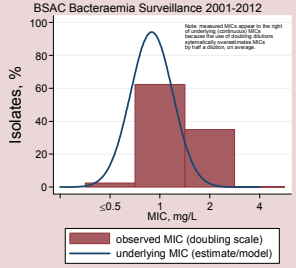
•A log-normal vancomycin MIC distribution for 4152 actual† *S. aureus* isolates fitted by interval regression‡ has SD=0.42 (graph; BSAC surveillance).

•This MIC model fits well, recreating the observed MIC distribution very accurately (table).

•The same method gives mean SD=0.8 for many 'wild-type distributions' (http://mic.eucast.org).

†BSAC surveillance. ‡Interval regression treats MICs correctly as being in the interval between tested concentrations.

Vancomycin MICs for 4152 *S. aureus*
BSAC Bacteraemia Surveillance 2001-2012



MIC Reconstruction

MIC mg/L	% of isolates	
	Real	Model
≤0.5	2.6	2.4
1	62.2	62.7
2	35.0	34.5
4	0.2	0.3

IS THE MODEL REASONABLE? part 2

Between-years variation 0-30% of total

•Re-testing 291 *S. aureus* with vancomycin in one week reduced estimated variation by 27% compared with the original MICs measured contemporaneously in 2001-07

•Accounting for year in the interval regression model for 4152 *S. aureus* from 12 years reduced estimated variation by 39%.

•Year-to-year experimental variation up to 30% of total is consistent with these observations.

CONCLUSIONS

- **Even low and very plausible levels of association between experimental variation and time of testing can often create a highly convincing illusion of MIC creep when none exists.**
- Reports of MIC creep should be treated with great caution unless the study was designed to eliminate confounding of this sort.

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Organism ID and Susceptibility Testing 2011 collection: A. Kidney, S. Mushtaq and staff at Quotient BioAnalytical Sciences, Fordham & Public Health England, London.

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Central Laboratories: **Public Health England, London; Quotient Bio Analytical Sciences, Fordham.** **Sponsors 2012:** Cempra, Cubist, Pfizer, Basilea (associate).
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BSAC The British Society for Antimicrobial Chemotherapy