

BACKGROUND

- Many programmes of antibiotic resistance surveillance rely on a panel of collecting centres to provide bacterial isolates.
- Since bacteria are infectious, it is predictable that isolates from one collecting centre will be related more closely to each other than to those from other centres i.e. there will be centre heterogeneity or inter-centre variation - contrary to the assumptions of many statistical analyses.
- Individual collecting centres may not contribute for the whole duration of a long-term study, creating the possibility of spurious trends produced by loss and replacement of centres.
- We used simulation to investigate the potential impact of inter-centre variation and centre turnover on the ability of a surveillance programme to detect trends in resistance.

METHODS

- Simulated datasets were designed to capture the main features of the BSAC Respiratory Resistance Surveillance Programme.
- Simulated data were created for a 5-year study with 20 centres collecting 50 isolates/year, uniformly distributed over the year.
- Turnover (the probability of a centre dropping out and being replaced at the end of each year) was 0, 5, 10 or 20%.
- Baseline probability of resistance was chosen to give 1, 5, 10, 25 or 50% mean resistance rate at the start of the study.
- Trends were either no trend (odds ratio 1) or doubling of odds over 5 years (odds ratio 2 per 5 years).
- Inter-centre variation was simulated by assigning to each centre a log odds ratio drawn from a Normal distribution with mean 0 and standard deviation 0, 0.5 or 1.
- The probability of resistance for each simulated isolate was calculated from the baseline probability, odds ratio for time and odds ratio for centre.
- For each combination of parameters, 1000 simulated datasets were analysed by logistic regression, with and without centre.
- P-values for trend were from likelihood ratio tests. Power (at 5% significance) is the percentage of analyses with $p \leq 0.05$.

Type 1 error / false positive

If an analysis produces a significant result when there is no real trend to find, this is a false positive or type 1 error. By choosing a significance level of 5%, we expect and accept a 5% error rate of this type. If the error rate is much higher, it shows that the analysis is invalid and will lead to mistaken conclusions in an unacceptably high proportion of cases.

Choice of simulation parameters

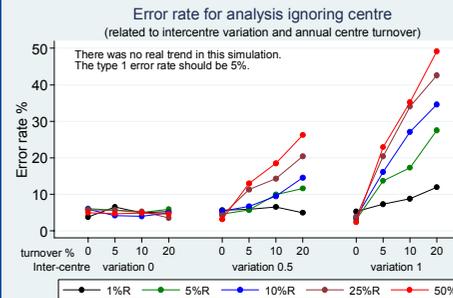
A variety of organism-resistance combinations from the BSAC Resistance Surveillance Programmes were analysed by logistic regression. The distribution of the estimated log-odds for centres was reasonably close to Normal in each case.

To match the observed variation in log-odds, an inter-centre variation parameter of between 0.1 and 1 needed to be included in simulations; values around 0.5 were typical. Annual centre turnover was 6% in the Respiratory Programme after six seasons and 4% in the Bacteraemia Programme after five. We believe that higher values are plausible in other studies.

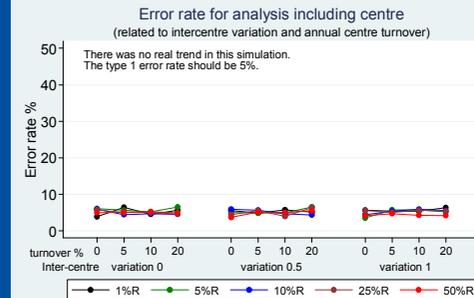
Simulation, analysis and graphs:
Stata version 9.2, StataCorp, 2005, College Station, TX.

RESULTS

See graphs and table.



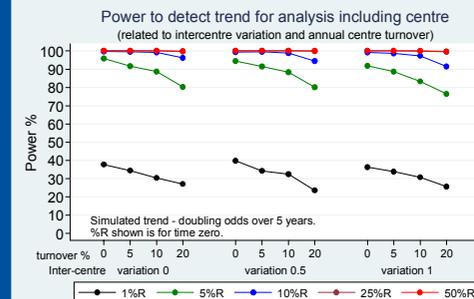
When centre was left out of the analysis, error rates rose well above 5% in the presence of inter-centre variation and centre turnover - as high as 50% in the worst case, and often between 10 and 20% even at moderate levels of turnover and inter-centre variation.



By including centre, false-positive rates were held at the design level of 5%. Power to detect doubling of odds over 5 years was usually above 80% for initial resistance rates $\geq 5\%$. High turnover reduced the power considerably but inter-centre variation had little impact.

Power to detect trend (5% resistance at baseline)

centre variation	centre turnover	NO TREND		DOUBLING in 5 years	
		ignore centre	WITH centre	ignore centre	WITH centre
0	0	6.1	6.1	95.8	95.8
	5	5.6	5.6	95.0	91.7
	10	5.0	5.2	95.1	88.7
	20	5.9	6.5	94.8	80.2
0.5	0	4.6	5.0	94.4	94.5
	5	5.7	4.8	92.4	91.5
	10	9.9	4.9	90.2	88.3
	20	11.6	6.5	89.8	80.1
1	0	3.1	3.5	91.0	91.8
	5	13.7	5.7	84.8	88.7
	10	17.3	5.7	80.2	83.2
	20	27.5	5.2	74.6	76.4



CONCLUSION

It is essential to account for inter-centre variation when analysing trends in resistance surveillance data to avoid unacceptably high error rates.

Central Laboratories: GR Micro Ltd, London; HPA, Centre for Infection, London.

Sponsors: The BSAC Resistance Surveillance Programmes, respiratory 1999 - 2005 and bacteraemia 2001-2005, were sponsored by:

Abbott, Aventis, Bayer, GeneSoft, GSK, Johnson & Johnson, MSD, Novartis, Pfizer, Theravance, and Wyeth, and supported by the BSAC

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