Resistance Surveillance Studies: Methods to Prevent Invalidation by Inter-Centre Variation

C2-2039

R. Reynolds[1], P. Lambert[2], P. Burton[2] and The BSAC Extended Working Parties on Resistance Surveillance[1]

[1]British Society for Antimicrobial Chemotherapy, Birmingham, B1 2JS [2]University of Leicester, Leicester, LE1 7RH

rreynolds@bsac.org.uk.

47th ICAAC, 17 - 20 Sept 2007, Chicago.

Background

Typical antibiotic resistance surveillance studies collect multiple isolates from a number of collecting centres. Traditional analysis for trend by e.g. χ^2 test for trend or logistic regression incorrectly ignores the variation in underlying resistance rates between centres. We investigated design and analysis methods to overcome this problem.

Method

5-year surveillance datasets were simulated 1000 times and analysed for trend by four variants of logistic regression:

- ignoring centre i.e.without adjustment
- with centre dummies ("fixed centre effect")
- with cluster-robust standard errors
- with random effects for centre

The percentage of datasets recording a trend significant at the 5% level is the power or, in the absence of real trend, type 1 error rate.

Simulation parameters

Baseline resistance rate:1, 5, 10, 25, 50%.

Odds ratio for trend: 1 or 1.149/year
(1 = no trend; 1.149 = odds double in 5 years)

Inter-centre variation: centre log-odds ratios normally distributed, with SD 0, 0.5 or 1.
Across a range of organism-agent combinations in the BSAC surveillance programmes1999 - 2006, the mean estimated inter-centre variation parameter was 0.4, and 95th centile 1.2.

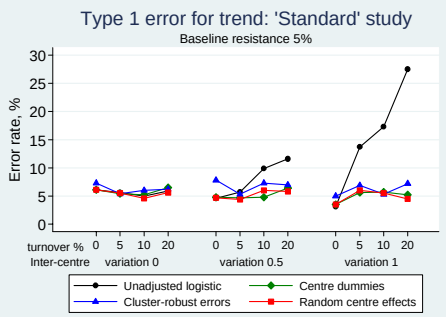
Centre turnover: 0, 5, 10, 20% (= annual probability of a centre being replaced).
Actual turnover in the BSAC surveillance programmes was 7% in respiratory (7 seasons) and 4% in bacteraemia (6 seasons); higher values seem plausible in other contexts.

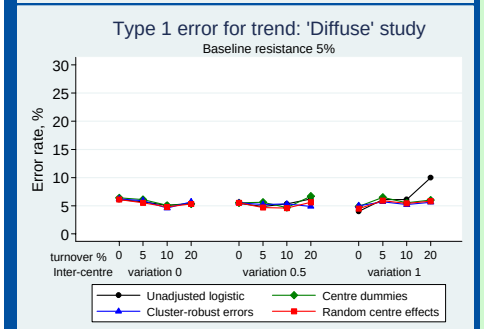
Study designs (both 1000 isolates/year total):
'standard': 20 centres, 50 isolates/centre/year
'diffuse': 100 centres, 10 isolates/centre/year

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

Type 1 error - false positive rate

When there is no trend, as below, the error rate (false detection of significant trend) should be 5%. Rates much above 5% indicate an invalid analysis method.





Results - error rate

Unadjusted logistic regression was invalid: it gave type 1 error rates well above 5% - up to 49% in the worst case (inter-centre variation 1, turnover 20%, baseline resistance 50%).

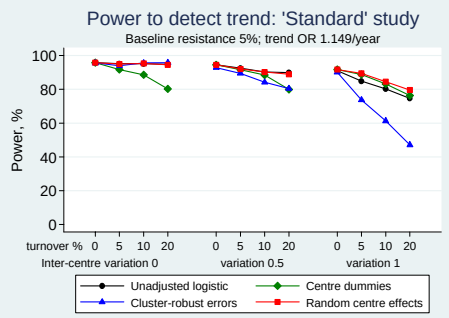
Both centre dummies and random effects methods reduced the error rate to near the design level of 5% (worst case 7%).

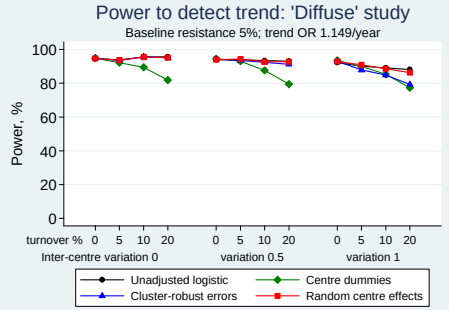
The centre dummies model was unreliable when centres lacked resistant isolates as isolates were dropped from analysis: 60-75% dropped in diffuse study at 1% resistance (R), and 8-36% at 5%R; 8-38% in standard study at 1%R, and up to 8% at 5%R.

The use of cluster-robust standard errors was a simple and fairly effective approach, with a worst-case error rate of 10%.

Compared to the standard design, the diffuse study had lower error rates for both the unadjusted analysis (worst case 16% *vs*. 49%) and the cluster-robust approach (worst case 7% *vs*. 10%).
This was expected as, with fewer isolates per centre, there is less clustering - more of the isolates are unconnected with each other.

Power - the ability to detect an effect





Results - power

The trend simulated here (OR 1.149/year) represents a doubling of odds of resistance in 5 years.

The random effects model generally had the highest power, and was the least affected by inter-centre variation and centre turnover, which reduced the power of other analyses.

The diffuse study had marginally higher power than the standard study with the same total size.

Power naturally depended on baseline resistance rate (e.g. 32-37% for 1%R, 80-96% for 5%R, 93-100% for 10%R, in the standard study with random effects analysis).

Conclusions

- Inter-centre variation combined with centre turnover invalidates the analysis of typical surveillance studies by unadjusted logistic regression.
- A more diffuse study design mitigates the problem at source.
- Random effects models are recommended to analyse these studies.

Further Research

- Test the robustness of the random effects model to forms of inter-centre variation other than the normal model simulated here.

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

Sponsors: The BSAC Resistance Surveillance Programmes, respiratory 1999 - 2006 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

Working Party Members (August 2007): A. MacGowan[1] (Chair), M. Allen[2], S. Barrière[3], D. Brown[4], K. Bush[5], R. Charters[6], N. Deaney[7], J. Dennison[8], R. Hope[9], D. Lewis[10], D. Livermore[9], M. Lockhat[11], L. Moore-Ramdin[12], R. Reynolds[1], C. Thomson[13], A. White[14].

[1]North Bristol NHS Trust ; [2]Novartis; [3]Theravance; [4]Addenbrookes Hospital, Cambridge; [5]Johnson&Johnson ; [6]Astellas; [7]Merck, Sharp & Dohme; [8]Pfizer; [9]Health Protection Agency, London; [10]HPA South West ; [11]AstraZeneca; [12]Wyeth; [13]IMS Health; [14]consultant

www.bsac.org.uk

E-mail: rreynolds@bsac.org.uk
Post: Dr. R. Reynolds, BSAC Resistance Surveillance Co-ordinator, Department of Medical Microbiology, Southmead Hospital, Bristol, BS10 5NB, England.