Recommendations for disproportionality analysis in small databases

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Background
Detecting signals of hitherto unknown adverse reactions is of paramount importance to the ongoing monitoring of the safety of marketed medicines. Disproportionality analysis is the most common quantitative approach to guide signal detection in collections of spontaneous reports. Yet, little is known about when disproportionality analysis can be expected to be robust. Such knowledge would be useful for countries and other organizations with newly set up pharmacovigilance systems, and for signal detection software users.

Objectives
To determine safe lower limits on the number of reports for performing disproportionality analysis in (i) general subsets of larger databases, and (ii) country-specific databases.

Conclusions
For disproportionality analysis in generically constructed subsets of databases of spontaneous reports, we recommend a lower subset size of about 3,000-5,000 reports. For disproportionality analysis in country-specific databases, we recommend at least 500 reports. However, while disproportionality analysis may produce robust results in very small databases, its utility is likely to be minor as few associations will be generated. Signal detection based on case-by-case assessment is likely to be more effective in such cases.

**Permutation**

This is an example of a permutation of a very small data set with four reports. The original report order is preserved with the adverse event of another, randomly selected report.

**Disproportionality analysis**

For both the original and the permuted version of each VigiBase subset, the number of drug-adverse event combinations highlighted by disproportionality analysis was identified. The IC is a shrinkage observed-to-expected ratio on log2 scale. Combinations were highlighted if IC025 > 0, i.e. if the lower endpoint of the 95% credibility interval of the IC exceeded zero.

**Spuriousness rate**

(number of highlighted combinations in permuted version) / (number of highlighted combinations in original version) = Spuriousness rate

This rate was computed for each VigiBase subset, excluding those with fewer than five highlighted combinations in the original version.