Detecting Drug Safety Signals from Spontaneously Reported Adverse Drug Reaction Data

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The Yellow Card Scheme

- Spontaneous adverse drug reaction reporting scheme established in the UK in 1964 following the thalidomide tragedy
- Reports submitted voluntarily in confidence by healthcare professionals and patients
- Reports of suspicions – the submission of a report does not necessarily mean that the drug was responsible
The Yellow Card Scheme (cont.)

- Since 1964: > 620,000 UK spontaneous reports
- Currently ~ 25,000 reports received / year
- Reports entered onto MHRA ADR database
  - Drugs coded to in-house drugs dictionary
  - ADRs coded using MedDRA (Medical Dictionary for Regulatory Affairs)
  - Patient demographics, medical history etc.
- ~ 280,000 unique drug-ADR combinations
Signal detection at MHRA

• Drug safety ‘signal’ – drug-ADR combination that is a possible drug safety issue

  ➢ Generally observed number of reports more than expected

1. Disproportionality methods – expected derived from background rate across whole dataset

2. ‘Observed vs Expected’ methods – expected rate from background incidence rate in general population
Disproportionality Methods

Four Main Methods used for signal detection:

- Proportional Reporting Ratio (PRR)
- Reporting Odds Ratio (ROR)
- Multi-item Gamma Poisson Shrinker (MGPS)
- Bayesian Confidence Propagation Neural Network (BCPNN)

- All methods identify drug-ADR combinations that are disproportionately present in database
### Proportional Reporting Ratio (PRR)

<table>
<thead>
<tr>
<th></th>
<th>Drug of interest</th>
<th>All other drugs</th>
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<tbody>
<tr>
<td>Specific reaction</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>All other reactions</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

**PRR** = \( \frac{a}{a+c} \) / \( \frac{b}{b+d} \)

**Key concept:** is \( \frac{a}{a+c} > \frac{b}{b+d} \)?
**PRR Signal Selection Threshold**

- PRR used for signal detection at MHRA from 1997-2006

- Signal selection threshold defined by MHRA
  
  ➢ PRR ≥ 3
  ➢ $\chi^2$ value ≥ 4
  ➢ n ≥ 3

- In addition all fatal, paediatric, parent-child and ‘alert term’ reports are flagged as potential signals regardless of the PRR value
**Multi-item Gamma Poisson Shrinker (MGPS)**

- MGPS used for signal detection at MHRA from 2006
- Bayesian method of disproportionality testing
- Provides more reliable estimate of another method of disproportionality, the relative reporting ratio (RR)
- RR values are computed for every drug-ADR combination in database and then modelled through the MGPS process
### Relative Reporting Ratio (RR)

<table>
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<td>c</td>
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</tr>
</tbody>
</table>

\[
RR = \frac{a}{(a+b)(a+c)/(a+b+c+d)}
\]

Key concept: is \( a > (a+b)(a+c)/(a+b+c+d) \) ?
MGPS Model

• Empirical Bayesian approach assumes that:
  
  ➢ the observed RR values have arisen from a common “super population” of unknown true RR values
  
  ➢ the unknown values are distributed according to a mixture of two parameterised Gamma Poisson density functions
    ➢ provides a “prior” distribution

  ➢ Bayes rule is then used to compute a “posterior” distribution for RR

  ➢ Improved estimate of RR (Empirical Bayes Geometric Mean or EBGM) derived from geometric mean of posterior distribution
MGPS - Estimating the “prior” probability

Distribution of RR across all drug-ADR pairs in dataset

Count

RR

[Lincoln technologies / Phase Forward WebVDME 5.2 training material]
MGPS - Estimating the “prior” probability

- Distribution of RR modelled using a mixture of two gamma functions
MGPS – Estimate of RR using Bayes Rule

- Improved estimate of RR (Empirical Bayes Geometric Mean, EBGM)
**EBGM Signal Selection Threshold**

- Signal selection threshold defined by MHRA
  - EBGM $\geq 2.5$
  - EB05 $\geq 1.8$
  - $n \geq 3$

- In addition all fatal, paediatric, parent-child and ‘alert term’ reports are flagged as potential signals regardless of the EBGM value

- Dataset stratification & subsetting:
  - UK & non-UK datasets kept separate
  - Vaccine & non-vaccine datasets kept separate
  - Stratification by age group, gender & time period
MGPS vs PRR or RR

- Greater stability with low counts compared with the PRR and RR methods
**Disproportionality Analyses**

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• No external data required e.g.</td>
<td>• Susceptible to reporting biases:</td>
</tr>
<tr>
<td>(background incidence, drug usage)</td>
<td>➢ masking of signals</td>
</tr>
<tr>
<td>• Data-mining methods i.e. no prior</td>
<td>- within drug suppression</td>
</tr>
<tr>
<td>hypothesis required</td>
<td>- ADR suppression</td>
</tr>
<tr>
<td>• Well suited for routine weekly data-</td>
<td>➢ false positive signals</td>
</tr>
<tr>
<td>mining for signals</td>
<td></td>
</tr>
</tbody>
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'Observed vs Expected’ Analyses

• Used at MHRA for vaccine safety surveillance since 2008
  ➢ HPV vaccine (vaccination programme started 09/2008)
  ➢ Pandemic vaccines (vaccination programme started 10/2009)

• Expected rate for ADR derived from background incidence rate in general population

• Require conditions of interest to be defined prior to implementation

• Require vaccine exposure information
**O/E analysis – 42 day risk period snapshot**

- Expected number of cases within 42 days post-vaccination calculated using number of vaccinated subjects and adjusted for varying follow-up times.

- Example of O/E analysis:
  - Exposure 4.2 million subjects
  - Background incidence rate of condition 1.8 / 100,000 per year
  - Expected number = 8.19
  - Observed number = 10
  - Rate ratio = 1.23 [0.59-2.26]
Maximised Sequential Probability Ratio Test (MaxSPRT)

• Sequential test method based on classic SPRT method developed by Wald in 1945

• Classic SPRT involves continuous / time-periodic testing of hypothesis that the relative risk (RR) is equal to 1 compared with alternative hypothesis
  ➢ Alternative hypothesis RR must be pre-specified as single alternative
  ➢ Poor choice of alternative RR may result in failure to support alternative hypothesis or delay in signalling

• MaxSPRT has composite alternative hypothesis of > 1

• p-values are adjusted for multiple testing
O/E MaxSPRT Results

Week

Log Likelihood Ratio

Critical value
10% events reported
25% events reported
50% events reported
75% events reported
100% events reported
O/E MaxSPRT Results

![Graph showing O/E MaxSPRT Results with log likelihood ratio against week. The graph includes critical values and different event reporting percentages.](image)
### Observed vs Expected Analyses

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<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
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<tbody>
<tr>
<td>• More robust method of signal detection than disproportionality analyses</td>
<td>• Requirement for accurate (preferably) age-stratified exposure data</td>
</tr>
<tr>
<td>• Reporting biases do not affect the ‘expected’ rate</td>
<td>• Not data-mining methods, can only be used for pre-defined conditions</td>
</tr>
<tr>
<td>• Adjustments for under-reporting of spontaneous ADRs can be made</td>
<td></td>
</tr>
<tr>
<td>• Well suited for vaccine safety surveillance following introduction of a new vaccination programme</td>
<td></td>
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</tbody>
</table>
Future Signal Detection at MHRA

- Ongoing research into optimising routine use of disproportionality analyses
  - Subsetting
  - Stratification
  - Masking
  - Signal thresholds

- Further implementation of ‘Observed vs Expected’ analyses for vaccine pharmacovigilance
References

**PRR**
- Evans SJW *et al.* Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf* 2001; **10**: 483-6

**MGPS**
- DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Stat* 1999; **53**: 177-90

**MaxSPRT**

- Lieu TA *et al.* Real-time vaccine safety surveillance for the early detection of adverse events. *Medical Care*. 2007; **45**(10):S89-95
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