Knowledge discovery in safety databases

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Statistical Issues in Medical Statistics 3rd Joint Workshop, 2008-04-24
“Where an existing body of data is relevant to a question of policy, those data are going to be used whether we like it or not. If statisticians refuse, others will attempt inference.”

David Finney

Presidential Address to the Royal Statistical Society, 1973
Presentation outline

• Adverse drug reaction surveillance
• WHO Programme for International Drug Monitoring
• Duplicate detection
• Drug-drug interactions
Adverse drug reaction (ADR) surveillance

- No drug is inherently safe
- The **full** safety profile of a new drug is never known at the time it is introduced to the general public
- Continued surveillance is in the interest of all parties
Motivation

• Pre-marketing randomised clinical trials...
  – ... focus on efficacy and not safety (too small to detect rare adverse drug reactions of importance)
  – ... exclude high risk patient groups (pregnant women, children, patients on co-medication, ...)
  – ... investigate the effects of drugs when used *as intended* (right dosage, in the right patients for the right reasons)

• Post-marketing surveillance...
  – Covers large populations
  – ... for extended periods of time
  – Is based on regular clinical practice
• Reports on **suspected** adverse drug reaction (ADR) incidents in real world clinical practice
  – Based on voluntary submission
  – Anecdotal in nature
  – Of varying quality
• **STILL** the most important source of information for **early** post-marketing discovery of previously unknown ADRs
Authentic ADR report

Courtesy of the Adverse Drug Reactions Unit at the Therapeutic Goods Administration of Australia
Report characteristics

- Free text
  - Later re-encoded in computerized format using standard terminologies by medically trained professionals
  - Useful information may be lost in the transition

- Sometimes hand-written
  - Misinterpretation may lead to erroneous information
  - Risk of missing data
Challenges

• ADR reports do not constitute a random sample
• Far from all suspected ADRs are reported
• Variations in reporting rates
  – Between old and new drugs
  – Between mild and severe ADRs
  – Due to attention in the press or in the scientific literature
• Considerable variation in quality between reports
More challenges

- One-sided information (only one cell in the contingency table)
  - No reliable information on how many patients have been exposed to a certain medicinal product
  - No controls

- Violated independence assumptions
  - Duplicate reports
  - Several reports from the same health professional
  - Reports from law firms
  - Reports created from information in the literature
Why important

- Large numbers of exposed patients
- International coverage
- Clinical judgment
- Great impact on public policy making
The WHO International Drug Monitoring Programme

- Initiated in the late 1960's in the wake of the thalidomide (neurosedyn) disaster
- Aim: to discover suspected adverse drug reactions (ADRs) earlier than is possible based on analysis of national collections of ADR reports
- Pool ADR reports from 84 member countries in one database
- Database maintained and analysed by the WHO Collaborating Centre for International Drug Monitoring in Uppsala (the Uppsala Monitoring Centre)
WHO programme member countries (2006)
Overall aims

• The early identification of suspected adverse drug reactions for further follow-up
• Generate new hypotheses ('signals') of previously unknown, possible adverse drug reactions
  – Ideally followed up by proper studies
  – Sometimes occasions the sole basis for direct action
  – Often the decision is to wait and see
Use of statistical methods

• Help direct resources for clinical review
  – 4 million reports in total
  – 200,000 new reports each year

• Assist clinical review work by highlighting:
  – possible confounders
  – stratum specific variation
  – reporting biases
  – related reports
Duplicate reports

• Unlinked reports referring to the same ADR incident
• In the WHO database, duplication may be due to:
  - Different sources (health professionals, national authorities, different companies) providing separate reports referring to the same incident
  - Mistakes in linking follow-up reports to the existing database record
  - Random errors such as type-os or unannounced changes to the authority report id field
Impact

• Inflates the number of reports on certain drug–ADR pairs
  – Around 5% of all reports expected to be duplicates
  – High profile cases tend to have much higher rates of duplication

• Report duplication
  – Misleads clinical review
  – Distorts summary statistics
Challenges

- Anyonymised reports
  - Patient age and gender, at best
  - Some reports carry very little information
- No perfectly reliable record fields
- Limited number of confirmed duplicates available to train flexible matching algorithm
Our approach
(Norén et al. 2005, 2007)

• Adapt and extend Copas & Hilton's hit-miss model (JRSS A, 1990)
  – Probability model for how errors on reports occur
  – New approach to handle numerical report fields
  – Approach to compensate for correlated report fields

• Strengths
  – Generic method applicable to a variety of data types
  – Sophisticated scoring of report pairs
  – Easy to see why a specific pair has been highlighted
  – Requires only limited amounts of training data
Hit-miss model

True value

X
Observed value on first report

Y
Observed value on second report

T

Miss

Blank

T

Hit

1-a-b

a

b

?
Example: Hit-miss scoring

<table>
<thead>
<tr>
<th>Date</th>
<th>Gender</th>
<th>Age</th>
<th>Country</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Tachycardia</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002-02-07</td>
<td>Female</td>
<td>60</td>
<td>Norway</td>
<td>Sertraline</td>
<td>Mirtazapine</td>
<td>Zopiclone</td>
<td>Tachycardia ventricular</td>
<td>+12.0</td>
</tr>
<tr>
<td>2002-02-07</td>
<td>Female</td>
<td>60</td>
<td>Norway</td>
<td>Sertraline</td>
<td>Mirtazapine</td>
<td>Zopiclone</td>
<td>Tachycardia ventricular</td>
<td>+6.1</td>
</tr>
</tbody>
</table>

Compensation for correlation between sertraline, mirtazapine and tachycardia

\[ +12.0 ± 0 -0.2 +7.2 +6.1 +8.7 -2.3 +8.1 -1.4 +38.2 \]
Results I

- Evaluation based on 1559 reports from Norway 2003
- 12 out of 19 labelled duplicates properly identified (the remaining 7 contained very little information)
- One previously unknown duplicate was identified:

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Patient gender</th>
<th>Country</th>
<th>Drug substances</th>
<th>ADRs</th>
<th>Onset date</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>F</td>
<td>NOR</td>
<td>6 matched</td>
<td>Vesicular rash; Sting</td>
<td>2004-04-30</td>
<td>?</td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>NOR</td>
<td>6 matched + 1 unmatched</td>
<td>Rash</td>
<td>2004-04-20</td>
<td>?</td>
</tr>
</tbody>
</table>
Results II

- One national centre agreed to evaluate their over 300 suspected duplicates that we had identified in the WHO database
  - 145 confirmed duplicates (including 75 previously unknown)
  - 83 yet unconfirmed but still suspected duplicates
- Even though the centre carry out their own duplicate detection based on additional information such as birth dates and patient initials, >150 previously unknown duplicates were discovered
Related non-duplicates

- Not all high scoring record pairs are duplicates
- The hit-miss model compares two hypotheses:
  - The two records relate to the same suspected ADR event
  - The two records are entirely unrelated
- Many record pairs fall between these two extremes:
  - Different reports for the same patient
  - Different reports from the same health professional
  - Reports related to the same vaccine batch
  - Mis-labelled reports from clinical trials or active surveillance programs
Future work

- Screening for groups of related case reports (e.g. submitted by the same individual)
- Highlighting data quality problems (e.g. mislabelled reports)
- Assistance in merging data sets / searching for additional case reports in other data sets
Drug-drug interaction

• Interaction between drug substances may yield excessive risks of certain ADRs when different drugs are taken in combination
  – Two drugs may compete for the same biologic receptor
  – One drug may inhibit an enzyme that metabolizes the other and thus induce an accidental over-dose

• Identification of a drug–drug interaction may allow
  – High risk combinations of drugs to be avoided in the future
  – A drug that would otherwise be withdrawn to remain on the market with warnings concerning co-medication
Drug-drug interaction surveillance

• Motivation
  – Patients on concomitant medication often excluded from clinical trials
  – Broad coverage of spontaneous reports increases chance of discovering interactions between drugs that are rarely co-administered

• Challenge:
  – What constitutes a reporting rate indicative of suspected drug–drug interaction?
Quantitative methods

• There have been attempts to develop methods for drug-drug interaction surveillance based on:
  – Logistic regression
  – Log-linear models

• ... with limited success
  – None appear to be in routine use
  – There are examples for which the proposed methods produce unreasonable results
Cerivastatin – gemfibrozil – rhabdomyolysis

- A well established drug–drug interaction
- Concomitant use with gemfibrozil was contraindicated for cerivastatin even as it was introduced on the market
- Later, cerivastatin was withdrawn on account of the large number of reports on rhabdomyolysis
Relative reporting rates in the WHO database

- Proportion of reports listing rhabdomyolysis:

  - Neither cerivastatin nor gemfibrozil listed: 0.1%
  - Cerivastatin but not gemfibrozil listed: 25%
  - Gemfibrozil but not cerivastatin listed: 4%
  - Cerivastatin and gemfibrozil both listed: 76%
Logistic regression analysis

- The third order log-odds ratio between cerivastatin, gemfibrozil and rhabdomyolysis is negative.
- ... because of high relative reporting rates of rhabdomyolysis for each drug on its own
  - that are essentially multiplied to produce a very high expected relative reporting rate under co-prescription in the logistic baseline model.
Our approach to drug–drug interaction surveillance

- A baseline model for the expected risk of the ADR under co-prescription of two drugs
  - Based on **additive** attributable risk for each drug
    \[
    P(A|D_1, D_2) \approx \alpha_0 + \alpha_1 + \alpha_2
    \]

- Translated to an expected relative reporting rate in the database

- Highlight suspected drug-drug interaction based on
  - log observed-to-expected ratio, $\Omega$
  - With variance stabilising (shrinkage) transform
Example revisited

• Quick recap:
  – Established drug-drug interaction
  – Massive reporting
  – Not highlighted with logistic regression

• $\Omega$ equal to +1.47 with lower 95% credibility interval limit +1.30
  – Nearly 3 times as many reports as expected under the additive baseline model
  – Indicative of suspected drug-drug interaction – as desired!
Theoretical arguments for baseline model with additive risk

(Rothman et al. 1980)

• Public health perspective
  – Indicates whether the **disease burden** in the population depends on to what extent the two drugs are co-prescribed

• Individual decision-making perspective
  – Indicates whether the **absolute** attributable risk from one drug depends on whether the other drug is taken at the same time
Summary

• The aim of collecting and analysing ADR surveillance data is to improve patient safety
• There is a range of important statistical challenges
• ... and statisticians make important contributions
  – Developing methods
  – Providing a theoretical basis for existing methods
  – Participating actively in day to day data analysis
References


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