Implementation of Signal Detection Methods in Pharmacovigilance — A Case for their Application to Safety Data from Developing Countries

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Abstract

Background: Pharmaceutical companies, regulatory agencies, or other government agencies conduct safety signal detection as one of the ways for mitigating the possible risks due to medical products. The safety signal is defined as information that arises from one or multiple sources (including observations or experiments), suggesting a new, potentially causal association, or a new aspect of a known association between an intervention like administration of a medicine and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. Definition of signal in this paper is restricted for pharmacovigilance to adverse events. Signal detection as a pharmacovigilance activity is highly recommended in the United States of America and it is mandatory in Europe. However, at the moment, the same cannot be said for any African country.

Findings: Traditional techniques for signal detection work well when the adverse drug reaction reports are few and manageable to enable manual review. The data mining algorithms for signal detection perform well with large and/or pooled drug safety monitoring reports. The methods discussed are proportional reporting ratio (PRR), the Report Odds Ratio (ROR), the Bayesian Confidence Propagation Neural Network (BCPNN) and the Multi-item Gamma Poisson Shrinker (MGPS). These sophisticated methods are routinely used in developed countries at the moment.

Conclusion: Data mining algorithms for signal detection need to be adopted in developing countries because the increased use of pharmaceutical products has led to exponential increase in safety reports and datasets.

ABBREVIATIONS

Council for International Organizations of Medical Sciences (CIOMS); Pharmacovigilance (PV); Signal Detection (SD); Adverse Drug Reaction (ADR); Proportional Reporting Ratio (PRR); Report Odds Ratio (ROR); Bayesian Confidence Propagation Neural Network (BCPNN); WHO Uppsala Monitoring Centre (WHO-UMC); Multi-item Gamma Poisson Shrinker (MGPS); Empirical Bayes Geometric Mean (EBGM); Food and Drug Administration (FDA); Information Component (IC); Adverse Event (AE)

INTRODUCTION

Collection of reports for suspected adverse drug reactions into very large databases and detection of signals are the cornerstones of pharmacovigilance (PV). The safety signal is defined as information that arises from one or multiple sources (including observations or experiments), suggesting a new, potentially causal association, or a new aspect of a known association between an intervention like administration of a medicine and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [1]. Definition of signal in this paper is restricted for pharmacovigilance to adverse events.

The use of data mining algorithms is essential in signal detection (SD) because of the large numbers of adverse drug reaction (ADR) reports. The application and validation of these methods have been mainly applied
in developed world. To-date, countries in developed countries have accumulated large volumes of ADR reports, and therefore the need to appropriately prioritize application of these SD approaches. These drug safety signals originate from statistical methods measuring disproportionality of reporting of drug-event pairs and are usually referred to as Signals of Disproportionate Reporting (SDR) [2].

This paper discusses analytical approaches of SD methods such as the frequentist approaches of proportional reporting ratio (PRR) [3] and the Report Odds Ratio (ROR) [4] used by European Medicines Agency EudraVigilance database [2], and the Netherlands Pharmacovigilance Foundation, Lareb [5] respectively. The Bayesian based approaches include Bayesian confidence propagation neural network (BCPNN) [6] applied on the WHO Uppsala Monitoring Centre (WHO-UMC) safety database [7], and the multi-item gamma Poisson shrinker (MGPS) [8] used on the Food and Drug Administration (FDA) safety database [9]. Though there are many methods that can be used in SD, these are the most commonly used ones [10]. African countries have not adopted any of such methods yet but depend on the WHO-UMC for SD services. Inadequate infrastructure and limited resources (both financial and human) pose challenges to implementing PV activities in developing countries but also increased vulnerability of local populations makes drug safety monitoring imperative [11]. The authors emphasise that establishing systems for PV in Africa is an initial step which should be followed by assessment of strengths and weaknesses, expansion of existing infrastructure and then standardizing methods of reporting, including approaches for defining events, determining severity, and assessing causal relationships will also be important [11].

**IMPLEMENTATION AND METHODS**

**Data source**

Two data mining algorithms were used to detect signals on safety data from a multi-centric phase IIIb/IV clinical study that was conducted between July 2007 and July 2009, in twelve sites located in seven African countries (Burkina Faso, Gabon, Nigeria, Rwanda, Uganda, Zambia, Mozambique) [12,13].

**Methods**

Practically, each submitted safety report may involve several suspected drugs and several observed events, leading to \( J \) (total number of) drugs and \( I \) (total number of) events mentioned at least once in a report. The association measures provided by the different SD data mining methods are calculated by collapsing the data into a 2 by 2 contingency table (see Table 1).

The SD process can be fully implemented using the open source statistical software R [14], accessible free of charge even in developing countries. A dedicated R package for pharmacovigilance signal detection called PhViD [15] containing data mining algorithms is easy to use once dataset containing both the drugs and adverse events are mapped and from chosen files.

**Findings**

The proportional reporting ratio (PRR) is based on the calculation of a relative risk and is defined as follows; for a given drug of interest, the proportion of reports with a pre-specified AE (or group of AEs) among all reports related to that drug is divided by the proportion of reports of that same AE(s) among all reports related to all other drugs in the database. The ratio of these two proportions is:

\[
PRR = \frac{a}{b} \cdot \frac{a+c}{b+d}
\]

The standard error of \( \ln(PRR) \) and confidence interval based on the standard epidemiology 2x2 table are calculated as,

\[
SE(\lnP) = \sqrt{\frac{1}{a} + \frac{1}{a+c} + \frac{1}{b} + \frac{1}{b+d}}
\]

\[
95\% CI = e^{\ln(P) \pm 1.96 \cdot SE(\ln(P))}
\]

Measures of statistical association are calculated using a chi-squared test with one degree of freedom. If the drug and condition are independent, the expected value of PRR should be 1; a PRR>1 indicates a greater than expected frequency of the report \( (ij) \) in the dataset. When the PRR is displayed with the chi-square statistics, a signal is reported if the PRR is greater or equal to 2, the chi-squared statistic is at least 4 and number of events is at least 3 [3]. Also when the PRR is displayed with its 95% confidence interval, a signal is generated if the lower bound of the 95% confidence interval greater or equal to one and the number of individual cases greater or equal to three [2].

This approach was used on the safety data reported on the UK Yellow Card database [16] and identified 487 signals [3] of which 17% were suspected signals which were investigated further, 13% due to the underlying disease and the rest were known ADRs. Among the suspected signals, 28% were reviewed in detail and in three cases the drug manufacturer was requested to change the products (drugs) information [3]. Recently, the PRR was applied on late phase clinical study pooled safety dataset of anti-malarial drugs from seven African countries [13] where applying PRR on 346 drug-event combinations generated seven suspected signals as shown in the sample R code in appendix 1.

The Reporting Odds Ratio (ROR) can be calculated basing on the two-way contingency in (Table 1) using the following formula;

\[
ROR = \frac{ad}{bc}
\]

Then calculate the standard error of \( \ln (ROR) \) and the 95% two-sided

<table>
<thead>
<tr>
<th>Table 1: Two by two table for the adverse drug-event pair.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reports with drug of interest, ( j )</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Reports with AE*of interest, ( i )</td>
</tr>
<tr>
<td>Reports of all other AEs in database</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*AE=Adverse Event

\( a = \) the number of reports involving the drug of interest \( j \) and adverse event of interest \( i \) combination; \( b = \) reports of adverse event of interest \( i \) observed with other drugs; \( c = \) reports of all other AEs with drug \( j \); \( d = \) reports of all other AEs with the other drugs; and \( a+b+c+d = \) the total number of reports in the dataset.
Bayesian confidence propagation neural network (BCPNN) method measures the association between a drug and an adverse event by the information component (IC) defined as the logarithm of the ratio of the observed rate of a specific drug-AE combination to the expected rate of AE under the null hypothesis of no association between the drug and the event. Thus, when a drug-AE combination is reported more often than expected relative to general reporting of the drugs and the AEs it results into positive values of IC. The crude estimate of IC, \( IC_0 \) without using a Bayesian framework is defined as:

\[
IC_0 = \log_2 \left( \frac{a}{(a + c)} \right) \left( \frac{(a + b)}{(a + b + c + d)} \right)
\]

Bate et al incorporated a Bayesian framework and used the property under the null hypothesis of no association between drug \( j \) and adverse event \( i \):

\[
P(drugisj, eventis) = P(drugisj)P(eventis)
\]

Therefore,

\[
IC = \log_2 \left( \frac{P(eventis | drugisj)}{P(eventis)} \right) = \log_2 \left( \frac{P(drugisj, eventis)}{P(drugisj)P(eventis)} \right)
\]

Where:

\[
P(drug is j, event is i) = \text{probability that a specific drug-AE combination is listed on a case report}
\]

\[
P(drug is f) = \text{probability that a specific drug is listed on a case report}
\]

\[
P(event is f) = \text{probability that a specific AE is listed on a case report}
\]

Bate et al assumed that \( P(drug is j, event is i) \), \( P(drug is j) \) and \( P(event is f) \) each follow a beta-binomial distribution, and IC is estimated using posterior mean and variance from a fully Bayesian model specification. Unlike in the frequentist approach, in the Bayesian framework, population parameters like number of AE reports are assumed to have intrinsic probability distributions, reflecting the uncertainty in their parameter values [18]. A signal is generated if the lower limit of the 95% credible interval is greater than zero. The WHO safety Monitoring Centre, Uppsala [7] demonstrated the usefulness of BCPNN to detect signals of drug-specific and drug-class adverse drug reactions [19]. This showed the association of captopril and other angiotensin converting enzymes with cough, and the association with terfenadine and heart rate and rhythm disorders [19]. This method was also recently demonstrated on pooled safety data from a study in seven African countries [13] and the results are given by the R code in appendix 1.

The Multi-Item Gamma Poisson Shrinker (MGPS) developed by DuMouchel [9] aims at finding the ‘interestingly large’ cell counts in a large frequency table of drugs and events for possible further evaluation. This method computes the logarithm of the ratio of observed number of counts for the drug-AE combination over the expected number of events.

\[
\log_2 RR = \frac{a_0}{E_0}
\]

Where the expected number of events is

\[
E_0 = \sum (a_{ik} + b_{ik}) (a_{ik} + c_{ik})
\]

and, \( k \) = stratum such as age and/or gender (hence k 2x2 tables); and \( N_k \) = total number of reports in stratum \( k \).

This method assumes that the observed count for each drug-event combination \( a \) is drawn from a Poisson distribution with an unknown mean, \( \mu_a \). Also the ratio \( P_{drug} / E_{drug} \) is assumed to be drawn from a prior distribution. The empirical Bayes geometric mean (EBGM) which is an empirical Bayes estimate of the RR is obtained from the model. This is used to rank all cell counts and determine which cells have unusually large observed counts compared to the expected counts. The EBGM is also seen as a ‘shrinkage’ estimate of the true relative risk for a particular drug-event combination. The EBGM will be close to the crude RR if the observed or expected number of events of drug \( j \) is large, otherwise EBGM will be shrunk towards the null value of 1. If the lower 95% credible interval of the posterior distribution is greater than 2, then a signal is generated. This threshold is one possible choice of defining a signal. There is not, nor should there be, a single, fixed definition of a signal threshold when using MGPS; rather, it is important to consider the severity of the drug-event combination and the severity of the condition being treated [20]. This threshold ensures that a particular drug-AE combination is being reported at least twice as often as would be expected if there were no association between the drug and the AE. The US FDA used the MGPS to show that the signal scores (the adjusted ratio of observed to expected counts) increased for rhabdomyolysis with cerivastatin from 1998 until 2000, after voluntary withdrawal of this drug from the market [21].

**DISCUSSION AND CONCLUSION**

A high relative reporting rate does not necessarily indicate a high incidence of the event or suggest a causal relationship between the drug and the AE. Adjustment for covariates like age, sex and year of report through stratification is advantageous. Stratifying analyses by year of report specifically reduces the chance of detecting signals that might arise due to “trendiness” in the reporting of specific drugs and/or events. Signals detected with such quantitative method should always be medically assessed and this requires a multi-disciplinary composition of teams involved in generation and assessment of signals.

Services for signal detection are still not adequately integrated into the drug safety monitoring systems and policies in most developing countries. Meanwhile, developed countries have used automated methods to generate signals which are routinely applied by regulatory authorities. Databases from authorities such as US FDA Adverse event...
In recent past, the use of various data sources other than the spontaneous reporting systems have gained traction in pharmacovigilance activities. This is especially true for the sub Saharan region where initiatives like health outcomes surveillance systems are being set up and many late phase multi-centric and multi-country clinical trials are taking place. Such studies target the most common diseases like malaria, HIV/AIDS, and tuberculosis. Consequently, large drug safety datasets have been generated which makes it possible to apply statistical data mining approaches in drug safety surveillance in addition to the existing and used by pharmacovigilance professionals. This practice however, needs to be adopted by the same professionals and regulatory bodies in developing countries.

Signal detection processes are weak in most sub Saharan countries due to lack of technical competence and capacity to carry out SD, poor infrastructure, poor quality of data from healthcare workers and lack of priority setting within the medicine regulatory authorities and public health programs where pharmacovigilance is not emphasized enough.

African countries through the national regulatory authorities have accumulated a considerable number of adverse drug reaction reports at national PV centre’s which are stored in the VigiBase hosted by WHO-UMC. It is therefore possible for countries to proactively start applying the described methods to locally generate signals for PV purposes. This will translate into timely decision making in case of a confirmed signal for a given drug-event pair as opposed to waiting for communication from WHO-UMC. Countries in Africa suffer from major health problems like high levels of child mortality [22], requiring a well-functioning PV system.

ACKNOWLEDGEMENTS

We would like to thank the leadership of Four Artemesinin Based Combination (4ABC) study team who kindly provided the safety database for this analysis. The ‘4 ABC study’ was funded by the EDCTP.

APPENDIX 1: R CODE TO GENERATE SIGNALS (COMMENTS IN GREY).

We use a pooled safety dataset for a study evaluating 4 antimalarial drugs in seven African countries [12, 13] as an illustration. Commands and output are in courier font.

```
Start R, and load the PhViD package containing the PV data mining:
Library (PhViD)

Load a dataset containing drug (trt) and event (pt) variables and then create a 2x2 table.
newvar<-rep(length(trt))
aggdata<-aggregate(newvar,by=list(trt,pt),FUN=sum,na.rm=TRUE)

Create a data frame
signalat<-data.frame(aggdata)

Use as:PhViD a function that converts a data.frame into an object that can be used in the signal detection method functions.

signalat<-as.PhViD(signalat, MARGINTHRES = 1)

BCPNN (signaldat, RR0 =, MIN.n11 = DECISION = 3, DECISION.THRES = 0.05, RANKSTAT = 2, MC = TRUE, NB.MC = 10000)
```

**SIGNALS GENERATED**

<table>
<thead>
<tr>
<th>AQAS Anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL Eye discharge</td>
</tr>
<tr>
<td>AQAS White blood cell count decreased</td>
</tr>
<tr>
<td>DHAPQ Diarrhoeahaemorrhagic</td>
</tr>
<tr>
<td>AL Malaria</td>
</tr>
<tr>
<td>AQAS Bronchopneumonia</td>
</tr>
<tr>
<td>AQAS Alanine aminotransferase increased</td>
</tr>
<tr>
<td>AL Pyrexia</td>
</tr>
<tr>
<td>AQAS Neutrophil count increased</td>
</tr>
</tbody>
</table>

Drugs are: AL = Artemether-Lumefantrine; ASAQ = Artesunate-Amodiaquine; DHAPQ =Dihydroartemisinin- Piperaquine

**PRR – Proportional reporting ratios (PRRs) for signal generation**

(Evans et al)

PRR (signaldat, RR0 = MIN.n11 = DECISION =3, DECISION.THRES = 0.05, RANKSTAT = 2)

**SIGNALS GENERATED**

<table>
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<td>AQAS Neutrophil count increased</td>
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</table>

REFERENCES

7. Lindquist M. Vigibase, the WHO Global ICSR Database System: Basic


