COMPARISON OF DATA-MINING METHODS FOR SIGNALS DETECTION ON A NATIONAL AND EUROPEAN SPONTANEOUS REPORTING DATABASES

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INTRODUCTION

Automated signal detection (ASD) is implemented in routine pharmacovigilance activities by the French and European Medicines Agencies respectively on the french national pharmacovigilance database (Base Nationale de Pharmacovigilance or BNPV) and on EudraVigilance (EV).

Besides having different databases in term of content and data size, the ASD methods applied on those databases are also different, which is to likely affect on signal detection performance.

The statistical algorithms used on the BNPV and EV are respectively the Bayesian GPS_{pH0} (a variant of the Gamma Poisson shrinker method) and the Reporting Odds Ratio (ROR), a frequentist approach.

On the BNPV, ASD is performed on all data, while on EV, it only considers serious adverse drug reactions (ADR) and drugs reported as "suspect" or "interacting".

OBJECTIVES

1. To compare the performance of ASD applied in the routine settings on BNPV and EV.
2. To assess the impact of various factors such as the statistical algorithm and data inclusion criteria (ADR seriousness, drug status) on the performance of ASD methods.

METHODS

Reference sets

- Reference set "1" was built from two validated international reference sets: the OMOP's and IMI PROTECT's. The inclusion criteria were {drug-ADR} combinations which ASD results in EV are available and substances marketed in France.
- Reference set "2" was defined from our first reference set after exclusion of all {drug-ADR} combinations with 4 counts or less on the BNPV and EV, in order to control the impact of under-reporting on ASD performances.

Data: extraction of data until December 2016 from BNPV and EV

- **BNPV:** 4 datasets were considered
  - All data (serious and non serious ADR)
  - Only serious ADR
  - Only drugs reported as "suspect" or "interacting"
  - Serious ADR and drugs reported as "suspect" or "interacting"
- **EV:** 1 dataset was considered
  - Serious ADR were drugs reported as "suspect" or "interacting"

Signal definition: with the GPS_{pH0} method, a signal was defined when the false discovery rate < 5%. With the ROR method, a signal was defined when the lower bound of confidence interval of the ROR > 1 and the number of reports ≥ 5.

Statistical analysis: the PhViD package was used on the R 3.4.0 program to apply the statistical algorithms of ASD on BNPV datasets. The indicators used to assess the performance of ASD methods were the sensitivity (Se), the specificity (Sp), the positive predictive value (PPV), the area under the receiver operating characteristics curve (AUC_{ROC}).

RESULTS

198 and 123 {drug-ADR} combinations were respectively included in the reference set "1" and "2".

Table 1: ASD performance on BNPV and EV applying routine settings and using reference set "1"

Study data	ASD method	Se (%)	Sp (%)	AUC_{ROC}	PPV (%)
BNPV	GPS_{pH0}	28.0	98.9	0.63	96.8
EV	ROR	57.0	97.8	0.77	96.8

In the routine settings, ie using reference set "1", the ASD on EV was twice as sensitive as on the BNPV (57.0% versus 28.0%) (Table 1). Sp and PPV were high in both case scenarios (above 97%). The AUC_{ROC} (0.77) was higher in EV due to the higher sensitivity of ASD performed on it. In current routine condition, the ASD on EV has a higher discriminating power than the one performed on the BNPV (AUC_{ROC} = 0.63).

Table 2: ASD performance on BNPV and EV in various settings and using reference set "2".

Study data	ASD method	Se (%)	Sp (%)	AUC_{ROC}	PPV (%)
BNPV	GPS_{pH0}	84.4	98.9	0.92	96.4
EV	ROR	90.6	97.8	0.94	93.5
BNPV[1]	ROR	28.1	100	0.64	100
BNPV serious ADR[2]	GPS_{pH0}	81.3	97.8	0.89	93.0
BNPV susp/interac[3]	GPS_{pH0}	90.6	98.9	0.95	97.0
BNPV susp/interac/ serious ADR[4]	GPS_{pH0}	84.3	98.9	0.92	96.4

1. Performance of ASD on the BNPV using the same statistical algorithm than the one of EV (ROR).
2. Performance of ASD on the BNPV applied on serious ADR only.
3. Performance of ASD on the BNPV applied on drugs reported as interacting or suspect only.
4. Performance of ASD on the BNPV applied on serious ADR and drugs reported as interacting or suspect.

Using reference set "2", the Se on EV and BNPV increased considerably and rose to respectively to 90.6% and 84.4%. (Table 2). This lead to an increase of discrimination power of both methods (AUC_{ROC} respectively 0.94 and 0.92).

ASD on BNPV using the ROR method had low Se (28.0%) compared to the GPS_{pH0} method (84.4%).

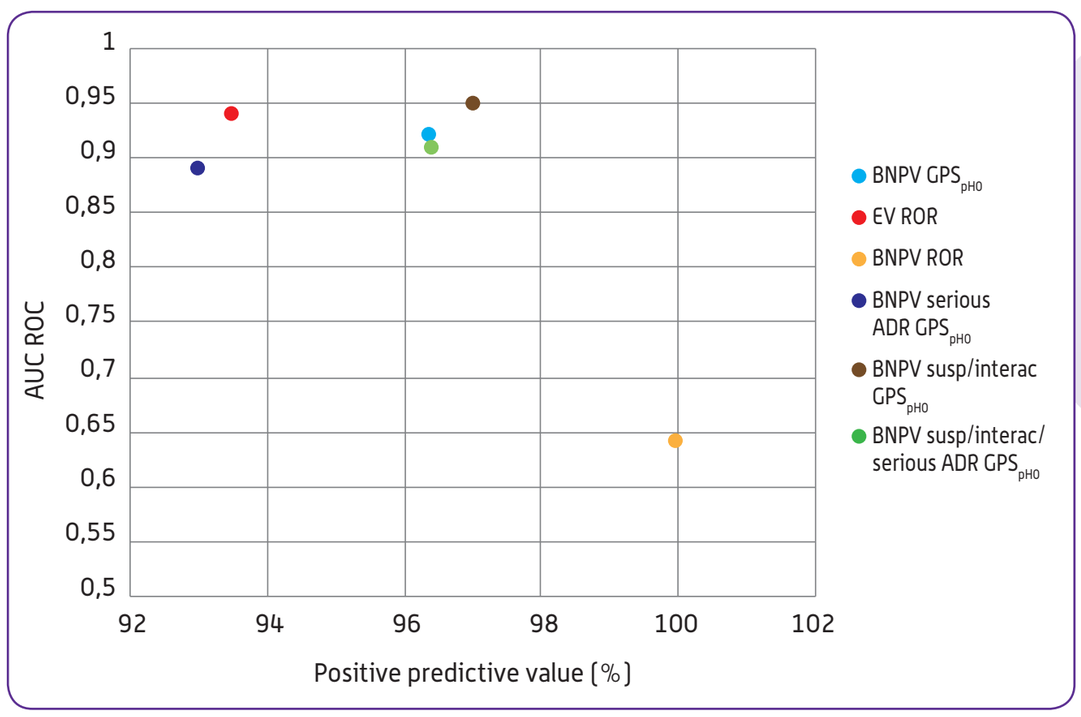
The Se of the ASD on BNPV applied on serious ADR only, showed a slight decrease (81.3%) compared to ASD on all BNPV data (84.4%).

ASD on the BNPV applied to drugs reported as "suspect" or"interacting" only was the most sensitive setting with the highest Se (90.6%) and the highest discriminating power (AUC_{ROC} = 0.95).

ASD on the BNPV applied on serious ADR and drugs reported as "suspect" or "interacting" was in fact a setting close to the ASD on EV. The Se was equivalent to the one observed on all BNPV data (84.4%) and higher than the one applied on serious ADR.

The previous results are presented in a scatter plot (Figure 1) to better illustrate the ASD performance in different scenarios.

Figure 1: ASD performance on BNPV and EV using reference set "2"



CONCLUSION

Under-reporting can have an important impact on ASD when performed on small databases, such as the BNPV. The ROR algorithm was not powerful on the BNPV. By considering non serious ADR reports and drugs reported as "suspect" or "interacting", ASD performance on the BNPV was enhanced at the level of EV performance. The inclusion of non serious ADR is crucial for ASD on small spontaneous reporting database such as the BNPV.

This study is:

a) scientifically relevant due to the importance of ASD in nowadays pharmacovigilance activities, in particular for public medicines agencies;

b) original and innovative as it allowed us to identify findings to optimize ASD on the national database (BNPV).

Conflicts of interest

No conflicts of interest to declare by authors.