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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Statistical signal detection for spontaneous reports

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Contents

1. Which disproportionality method to use?
2. Subgroups and stratification

3. Unmasking
4. Drug-drug interactions
5. Duplicate detection

Study Objectives

1. to evaluate the performance of different signal detection algorithms

2. to investigate the impact of stratified and subgroup analyses in routine first pass signal detection

Within several spontaneous databases of varying size and characteristics

Partners and Databases

- **Regulatory Authority**
- European Medicines Agency
- MHRA (UK)

- **Research**
- Uppsala Monitoring Centre

- **Pharma Industry**
- AstraZeneca
- Bayer*
- GlaxoSmithKline
- Roche*

* Participated in study #1 only on method comparison

Signal Detection Performance Indicators

Signal detection performance measured using two/three performance indicators:

These are calculated on the entire dataset and also as they evolve over time:

1) **Sensitivity (the true positive rate)**
   - Proportion of true ADRs that are correctly detected

2) **Precision (positive predictive value)**
   - Proportion of detected signals that correspond to a true ADR

3) **Time to detection for the true positives (median or average)**
   - How much time is gained by earlier signalling?

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Study Drugs & Reference Standard

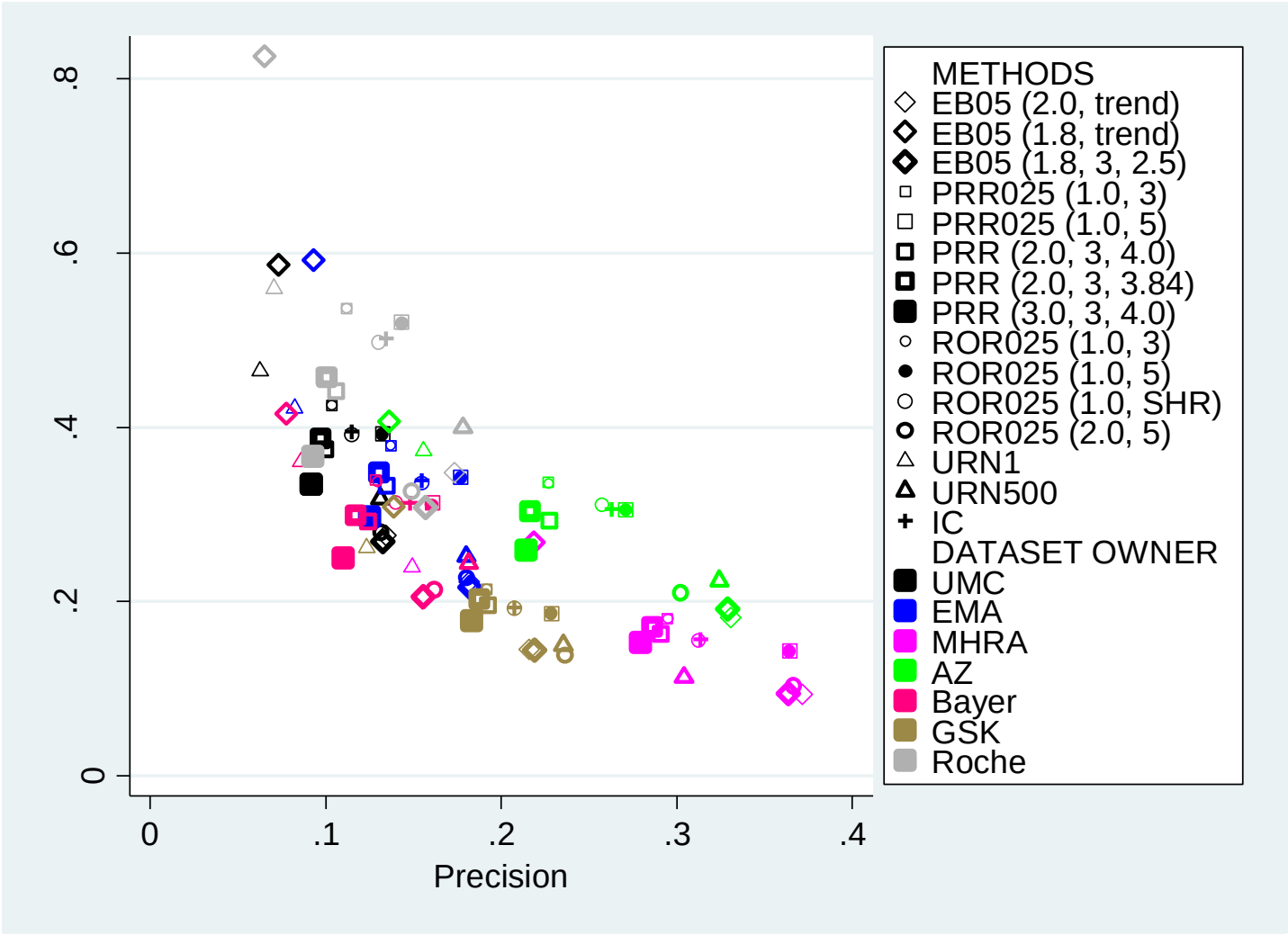
- 220 drugs were selected to represent a variety of therapeutic areas and patient populations

- True ADRs were those listed in the SPC section 4.8 or company core data sheets

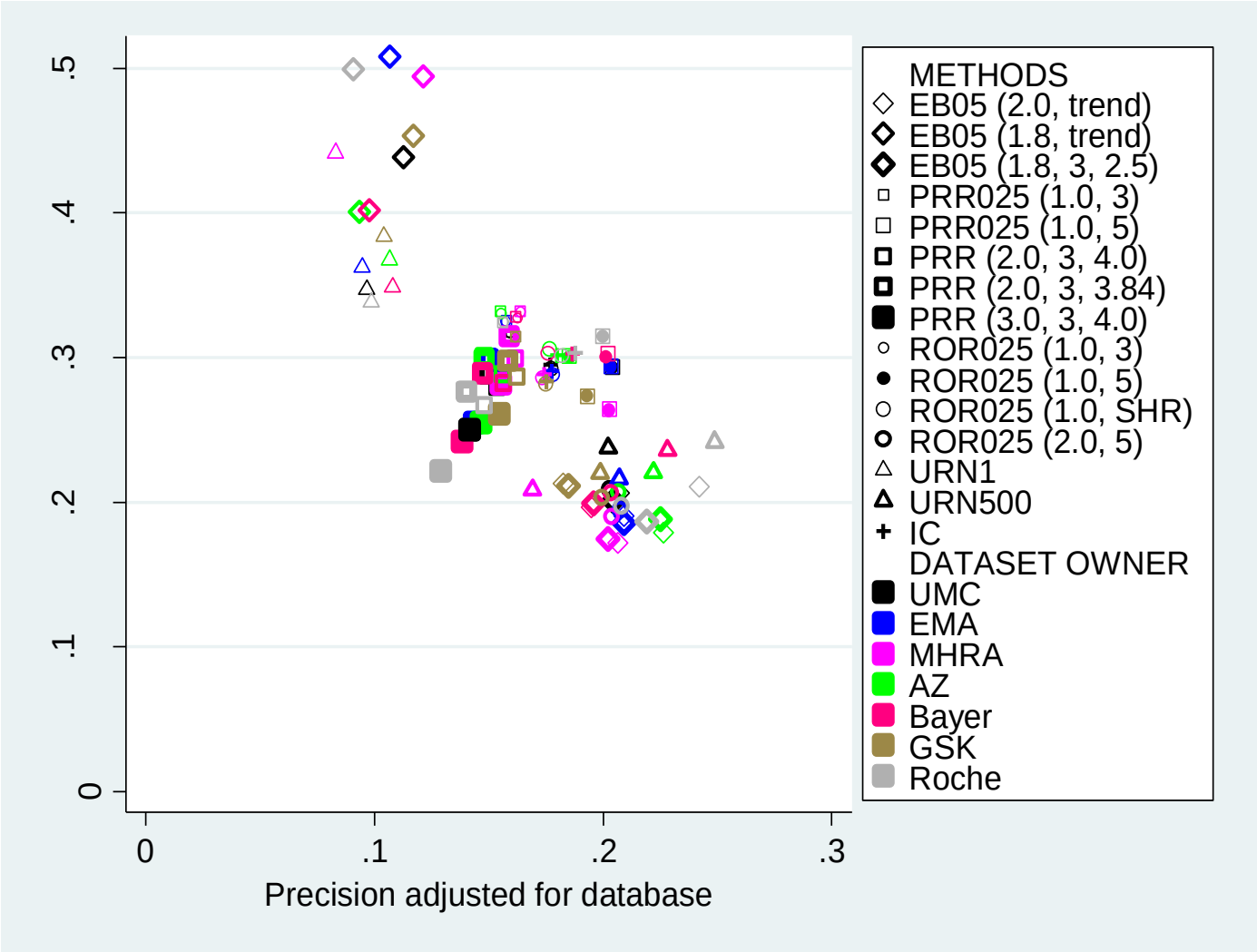
Study 1 – Which method to use?

Disp. measure	Implementation
PRR	$PRR_{025} \geq 1$ & $n \geq 3$ $PRR_{025} \geq 1$ & $n \geq 5$ $PRR \geq 3$ & $\chi^2 \geq 4$ & $n \geq 3$ $PRR \geq 2$ & $\chi^2 \geq 4$ & $n \geq 3$ $PRR \geq 2$ & $p <= 0.05$ & $n \geq 3$
ROR	$ROR_{025} \geq 1$ & $n \geq 3$ $ROR_{025} \geq 1$ & $n \geq 5$ $ROR_{025} > 1$ with shrinkage $ROR_{025} > 2$ & $n \geq 5$
IC	$IC_{025} > 0$
EBGM	$EB05 \geq 1.8$ & $n \geq 3$ & $EBGM \geq 2.5$ $EB05 \geq 1.8$ **or** positive trend flag $EB05 > 2.0$ **or** positive trend flag
Urn	RR > 1 & unexpectedeness > 1 / 0.05 RR > 1 & unexpectedeness > 500 / 0.05

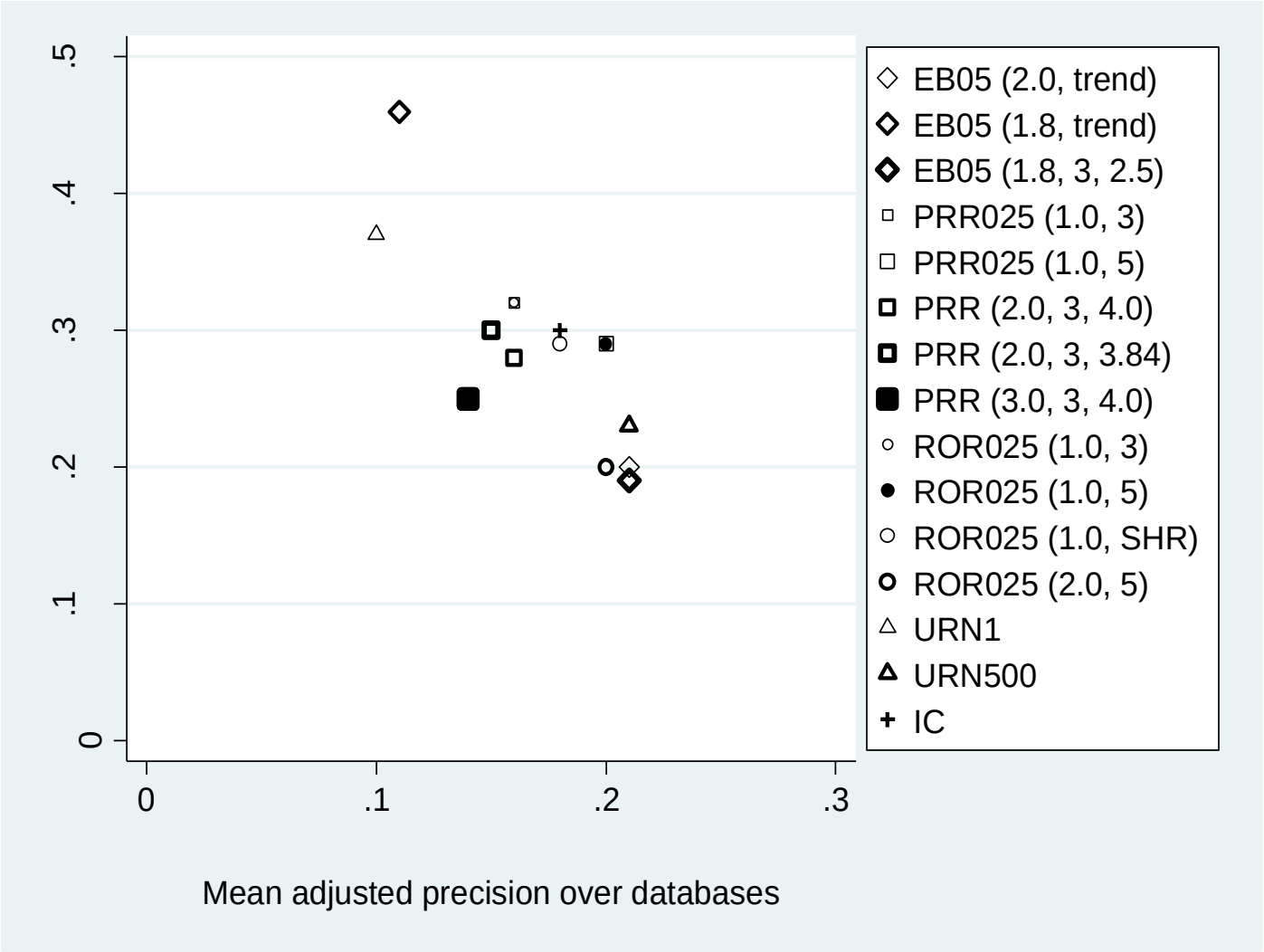
Study 1 - Precision and sensitivity for all measures across databases



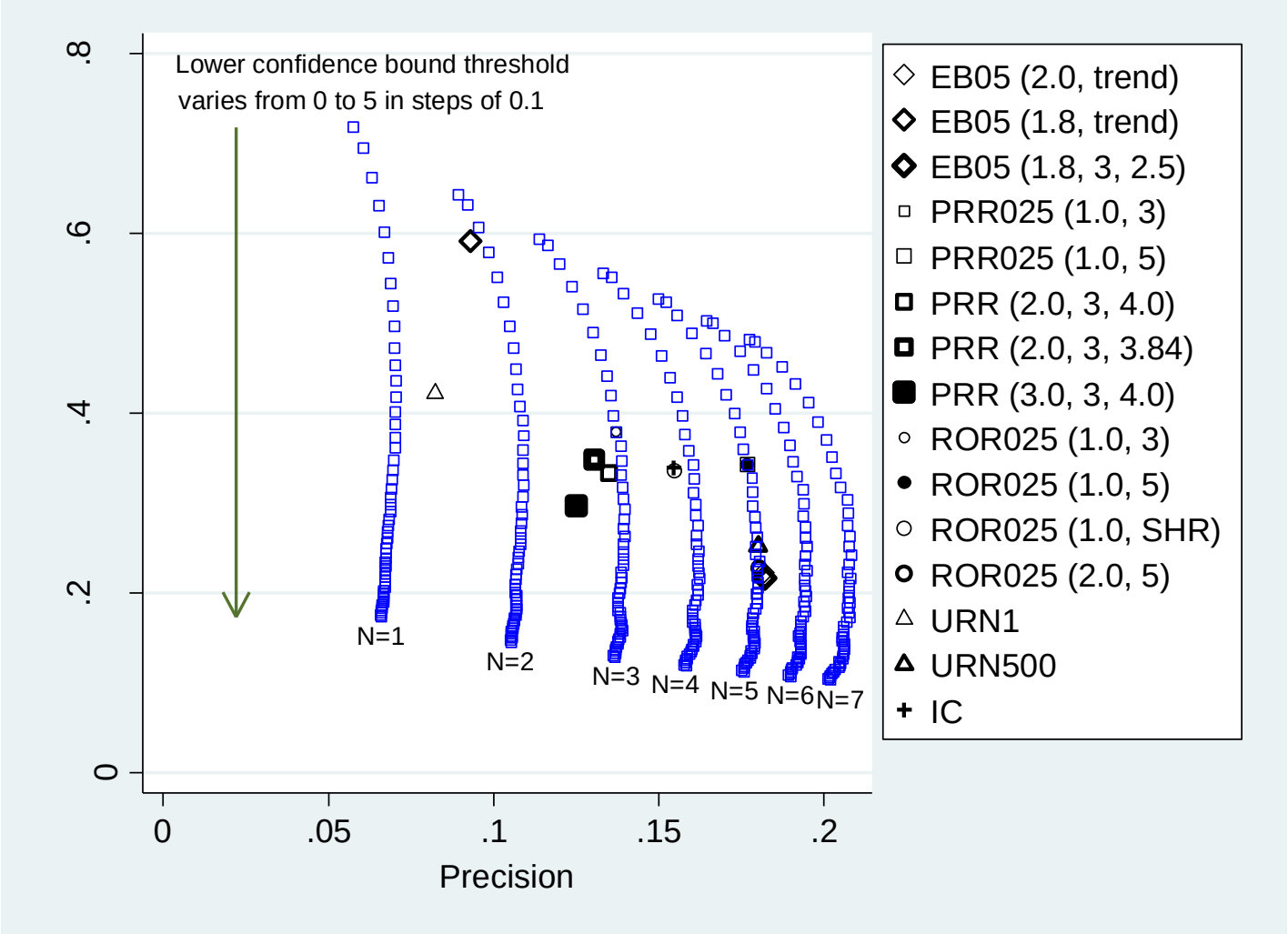
Study 1 - Performance of measures after database standardisation



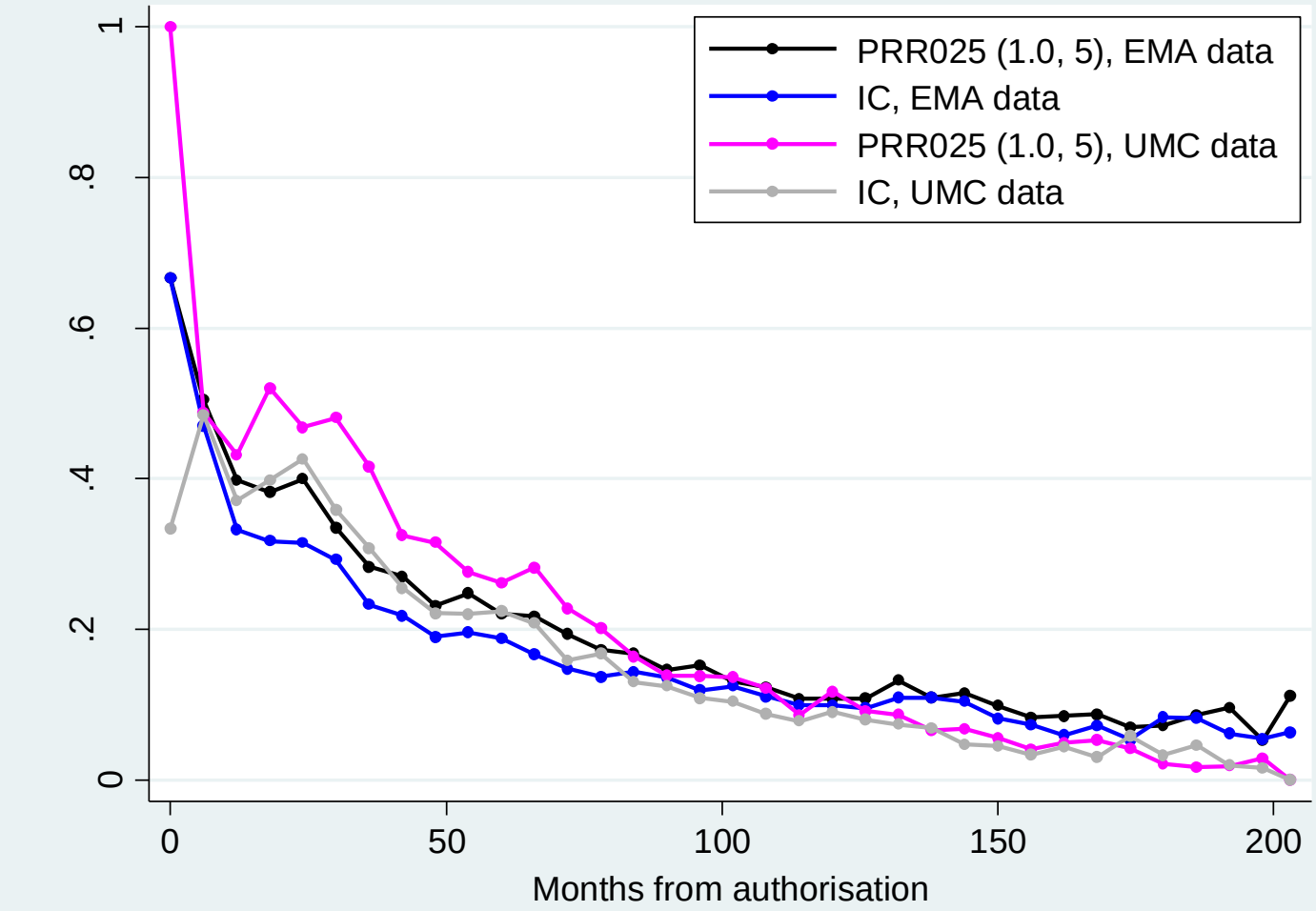
Study 1 - Mean precision and sensitivity over databases



Study 1 – Envelope of precision and sensitivity achievable with PRR



Study 1 - Change in precision over time



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Study 1 - Conclusions

- All disproportionality methods can achieve similar overall performance by choice of algorithm
- Choice of algorithm can provide very different levels of performance
- Relative performance of an algorithm in one database can be predicted from research in others
- Precision seems to decrease over time on the market

Candore G, Juhlin K, Manlik K, Thakrar B, Quarcoo N, Seabroke S, Wisniewski A, Slattery J. Comparison of statistical signal detection methods within and across databases. *Submitted.*

Study 2 – Subgroups & Stratification

Covariate	Strata
Age	0-23months, 2-11, 12-17, 18-35, 36-64, 65-74, 75+ years, unknown
Gender	Male, female, unknown
Time period	5-yearly
Vaccines/Drugs	Vaccines, non-vaccines
Event seriousness	Serious, non-serious
Reporter qualification	Consumer only, healthcare professional only, mixed
Report source	Spontaneous only
Country of origin	Individual country of origin
Region of origin	North America, Europe, Asia, Japan, Rest of the World

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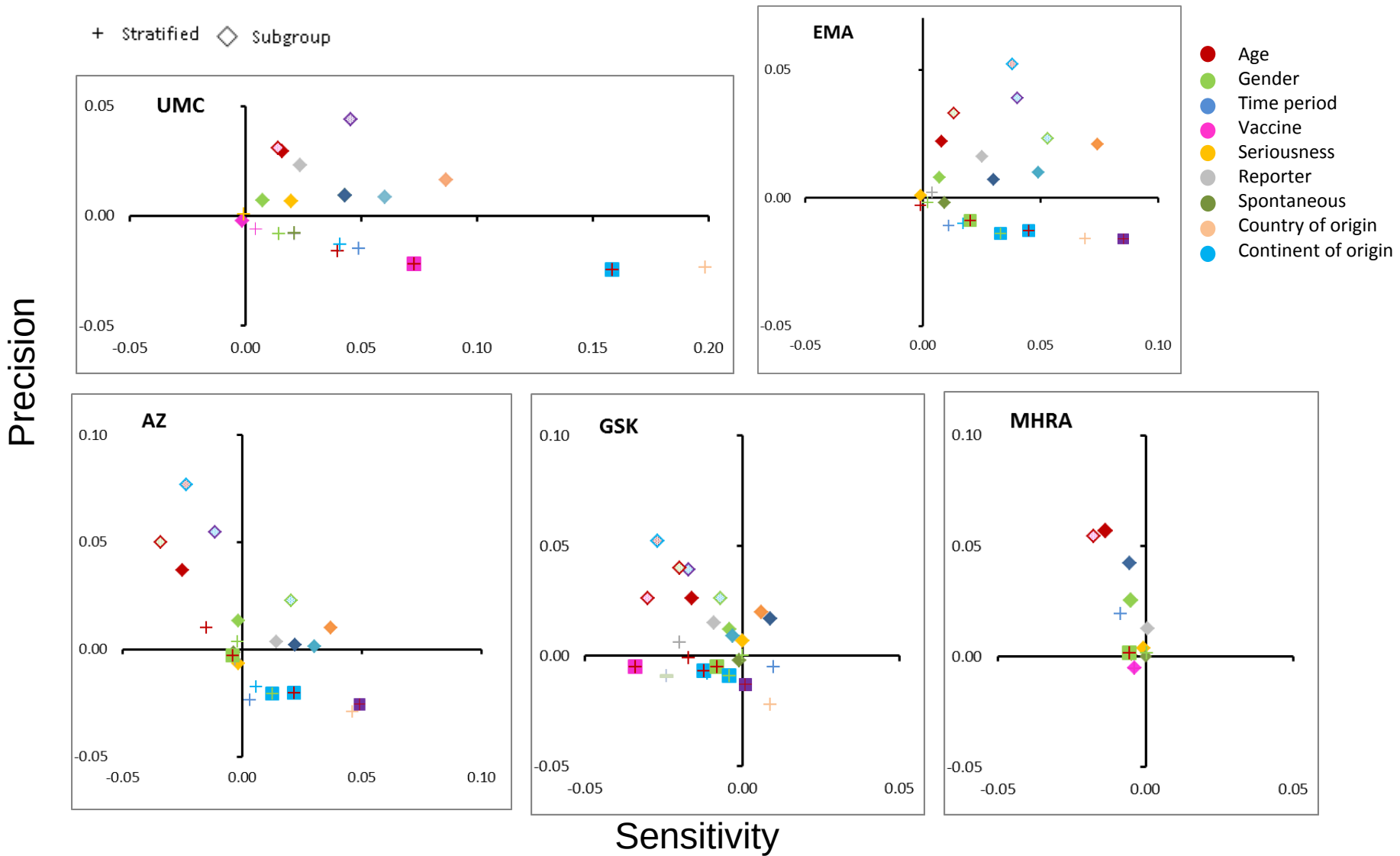
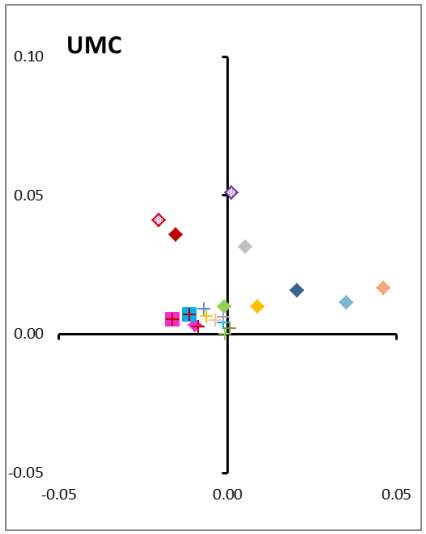
Study 2 - Methods

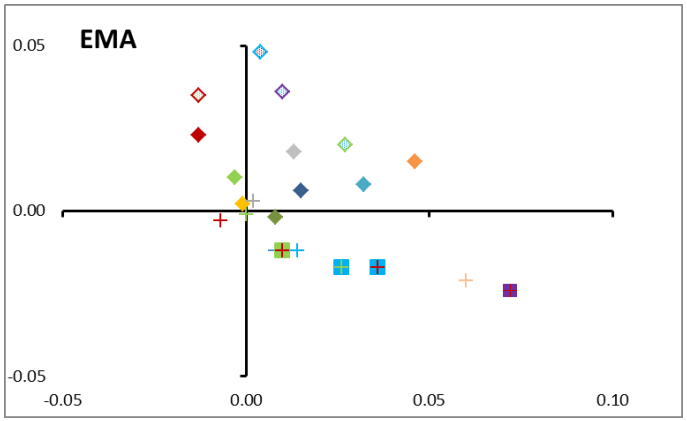
- Stratified analyses conducted using Mantel-Haenszel approach to obtain a single adjusted value
- Subgroup analyses calculated disproportionality statistics within individual strata separately
- Stratified/subgroup results compared to crude unadjusted results
- Disproportionality statistics:
  - $ROR_{025} \geq 1$ & $n \geq 3$
  - $IC_{025} > 0$
  - EBGM >=2.5, EB05 >=1.8 and n>=3

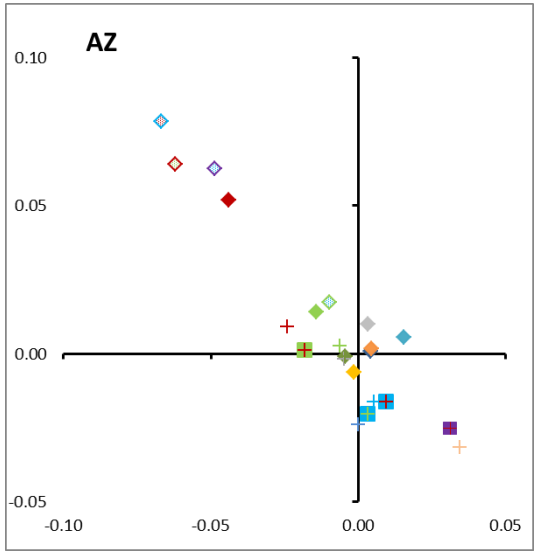
Study 2 - Precision and sensitivity for stratified & subgroup analyses (ROR)

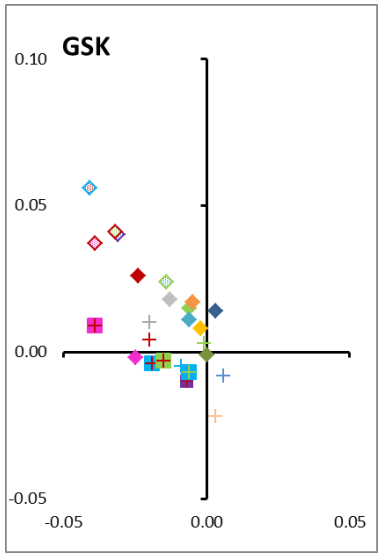


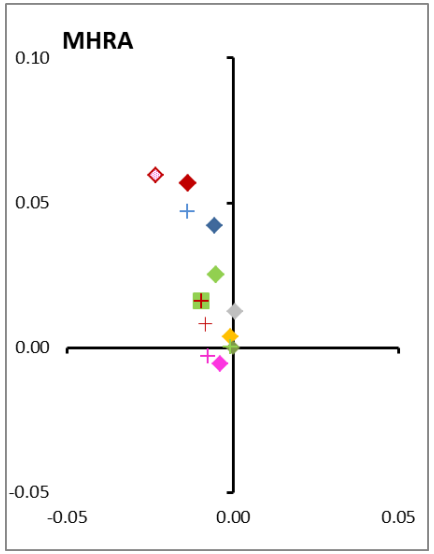
Study 2 - Precision and sensitivity for stratified & subgroup analyses (Bayesian)







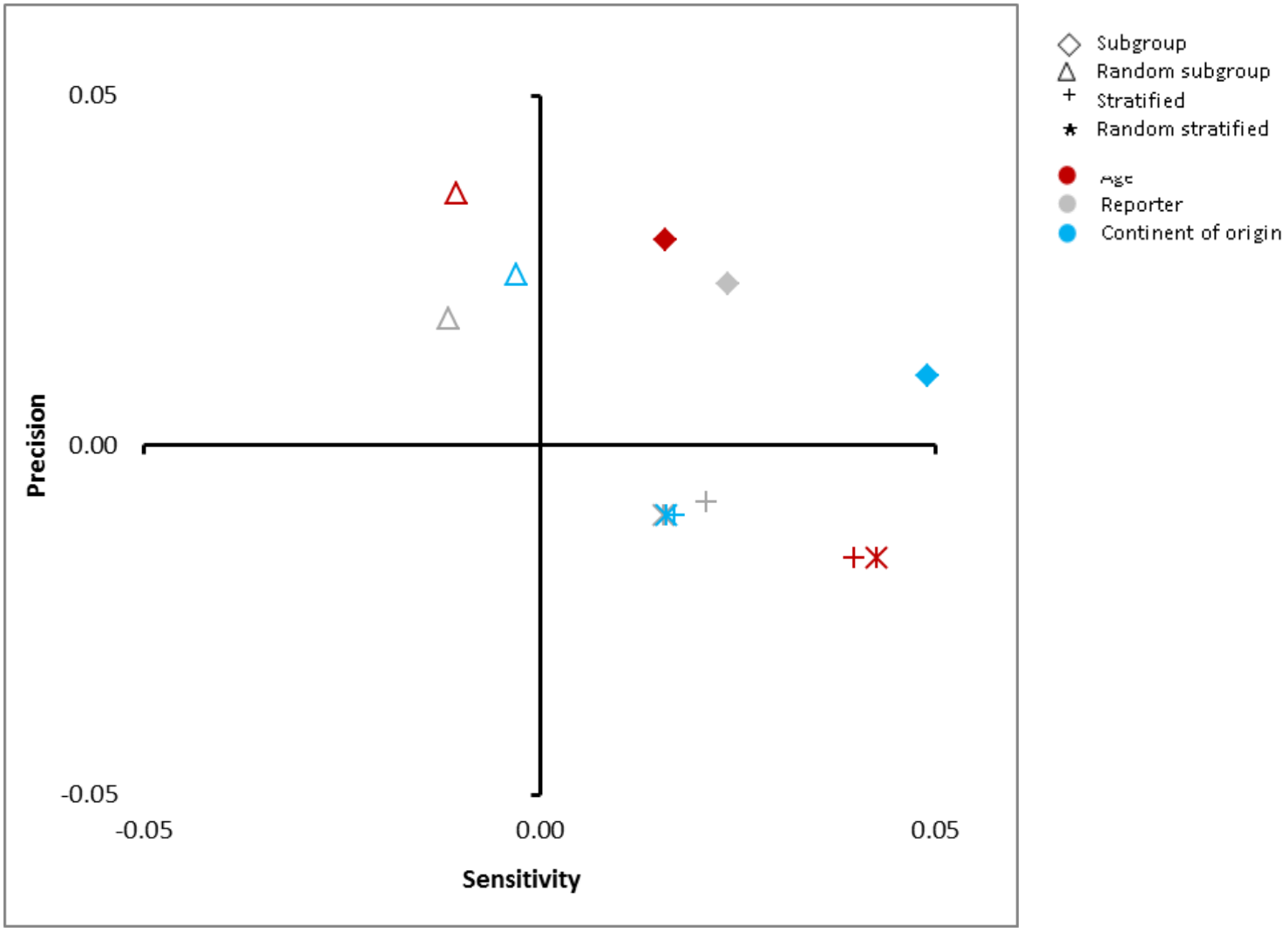




Precision

Sensitivity

Study 2 - Precision and sensitivity for stratified, subgroup & random strata



Study 2 - Conclusions

- Subgroup analyses consistently performed better than stratified analyses
- Subgroup analyses are beneficial in large, international databases. Smaller databases may need to consider a likely tradeoff between sensitivity and precision
- Choice of variables for subgroup analyses will likely vary between different datasets

Seabroke S, Candore G, Juhlin K, Norén GN, Quarcoo N, Tregunno P, Wisniewski A, Slattery J. The use of stratification and subgroup analyses in statistical signal detection. *In Preparation.*

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Influence of Masking on Disproportionality

- Developed masking ratio to quantify masking effect of given product
- Assessed extent and impact of masking in Eudravigilance and Pfizer spontaneous database

- ➢ Prevalence of important masking quite rare (0.003% DECs)
- ➢ Important masking mainly concerns rarely reported events

1. Maignen F, Hauben M, Hung E, Holle LV, Dogne JM. A conceptual approach to the masking effect of measures of disproportionality. *Pharmacoepidemiol Drug Saf.* 2014 Feb; 23(2):208-17

2. Maignen F, Hauben M, Hung E, Holle LV, Dogne JM. Assessing the extent and impact of the masking effect of disproportionality analyses on two spontaneous reporting systems databases. *Pharmacoepidemiol Drug Saf.* 2014 Feb; 23(2):195-207

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Drug-Drug Interaction Detection

- Objective: Compare sensitivity & specificity of 4 different measures to detect drug-drug interactions

- Reference set:
  - established DDIs & D-E pairs with no known association
  - emerging DDIs from Stockley's interaction alerts 2007-2009 & D-E pairs not included in same reference

- WHO Vigibase used for analysis

Drug-Drug Interaction Detection

Baseline	*Established* interactions		*Emerging* interactions	
	Sensitivity	Specificity	Sensitivity	Specificity
Additive	**0,39**	0,86	**0,08**	0,97
Multiplicative	**0,24**	0,86	**0,02**	0,97

- Conclusion: Statistical interaction measures with additive baseline models should be preferred over multiplicative models for detecting drug-drug interactions in spontaneous data

Soeria-Atmadja D, Juhlin K, Thakrar B, Norén GN. *Pharmacoepidemiol Drug Saf.* 2014 Feb; 23(S1):294-295

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Duplicate Detection

- Objective: compare probabilistic record matching algorithm (VigiMatch) with rule-based approaches
- MHRA, DHMA & AEMPS participated
- Initial evaluation: suspected VigiMatch duplicates 2000-2010 were assessed by respective national centre
- Second evaluation: direct comparison between VigiMatch & MHRA rule-based algorithm

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Duplicate Detection

- Initial evaluation showed VigiMatch to return few false positives in all 3 national centres

- Direct comparison:

Evaluation	Rule-based screening	vigiMatch™
Unrelated	**56**	**0**
Not duplicates, but otherwise related	14	12
Likely duplicates, not yet confirmed	0	1
Confirmed duplicates	**30**	**87**
Total	100	100

Duplicate Detection

- Conclusion: Probablistic record matching should be considered as an alternative to rule-based methods for duplicate detection in spontaneous data

Tregunno P, Bech Fink D, Fernandez-Fernandez C, Lazaro-Bengoa, Norén GN. Performance of probabilistic method to detect duplicate individual case safety reports. *Drug Safety.* 2014; 37(4):249-258