Characterisation of databases (DBs) used for signal detection (SD): Results of a survey of IMI PROTECT work package (WP) 3 participants

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— ♦ — DISCLOSURE STATEMENT: SEE BOTTOM OF POSTER — ♦ — ACKNOWLEDGEMENT: ALEX ASIIMWE, previously of AstraZeneca[1],for help with electronic survey design, administration and data management — ♦ —

❶ Background

The work was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium; www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency (EMA).

Work-package 3 includes assessment of signal detection methods applied to databases of spontaneous adverse drug reactions. PROTECT Partners surveyed include 3 national regulatory agencies (AEMPS, DKMA, MHRA), 3 pharmaceutical companies (AZ, BSP, GSK), the EMA and the Uppsala Monitoring Centre (UMC)

❷ Objectives

To describe different spontaneous report databases with regard to size and content as context for future assessment of the relative performance of SD and duplicate detection methods in these databases

❸ Methods

Survey

Survey questions were developed collaboratively amongst WP3 participants during 2Q2010. The survey was divided into five domains as follows:

i. general information including types of therapeutic agent, coding dictionaries, use of metadata and signal and duplicate detection algorithms
ii. counts including seriousness, reporter type, country of origin, therapeutic agents and events
iii. data elements including presence of demographic data and drug details
iv. database coverage in terms of predominant drugs and events v. vaccine specific information

Data collection and compilation of responses

The survey was administered electronically using commercially available software (2ask, amundis communications Gmbh, Felix-Wankel Strasse 4, D-78467 Konstanz, Deutschland; http://www.2ask.net). The software allows for on-line completion of surveys with password protected access. The survey administrator was a WP3 participant and had sole ability to download survey data. Participants completed the survey between September 2010 and August 2011.

Responses were downloaded by the survey administrator into Microsoft Excel format. Tables were created within Excel for the purpose of summarising the responses and producing figures. The results presented below represent the status and use of the databases at the time the survey was carried out and may not reflect the status and use of the databases as it is today.

Table 1 – PROTECT Partners that participated in the Database Survey

Partner	Abbrevn.	Affiliation	Setting	Database name
Danish Health & Medicines Agency	DMKA[1]	National Competent Authority	National	n/a
Uppsala Monitoring Centre	UMC	International Drug Monitoring organisation	International	VigiBase
European Medicines Agency	EMA	European Competent Authority	International	Eudravigilance
Medicines and Healthcare products Regulatory Agency	MHRA	National Competent Authority (UK)	National	Sentinel
Agencia Espaniola de Medicamentos y Productos Sanitarios	AEMPS	National Competent Authority (Spain)	National	FEDRA
Bayer Healthcare Pharmaceuticals	BSP[2]	Pharmaceutical company	International	Argus
AstraZeneca	AZ	Pharmaceutical company	International	Sapphire
GlaxoSmithKline	GSK	Pharmaceutical company	International	Oceans

1. Since completing the survey, The Danish Medicines Agency and Danish National Board of Health merged under the name Danish Health and Medicines Authority. Throughout this poster, the former abbreviation is retained.
2. Since completing the survey, Bayer Schering Pharma AG (BSP) was renamed as Bayer Pharma AG. Throughout this poster, the former abbreviation is retained.

❹ Results

Table 2 – Signal algorithms & definitions of statistics of disproportionate reporting employed across survey participants' databases

Partner	Algorithm	How is a statistic of disproportionate reporting defined?
UMC	IC	IC025 >0
EMA	PRR	N >2 and lower end of 95%CI on PRR >1
MHRA	EBGM	EBGM ≥2.5, EB05 ≥1.8, N ≥3
AEMPS	IC, ROR	ROR: Lower limit 95% CI >1 and No. of ICSR ≥3 IC: Lower limit 95% CI >0 and No. of ICSR ≥3
BSP	PRR	PRR ≥2, Chi² ≥4, N ≥3
AZ	EBGM	EB05 ≥1.8, and/or +ve trend flag. A trend flag is +ve if either of the following are true: • An EB05 based on current data is >EB95 for the d-e pair 52 weeks ago • An 50% increase in EBGM score when current data are compared with the EBGM score 26 weeks ago
GSK	EBGM	EB05 >2 for non-serious unlisted adverse events; any event whose reporting rate has increased significantly compared to 6 months previously

Figure 1 – Summary graphic illustrating the general features of the 8 databases that participated in the survey

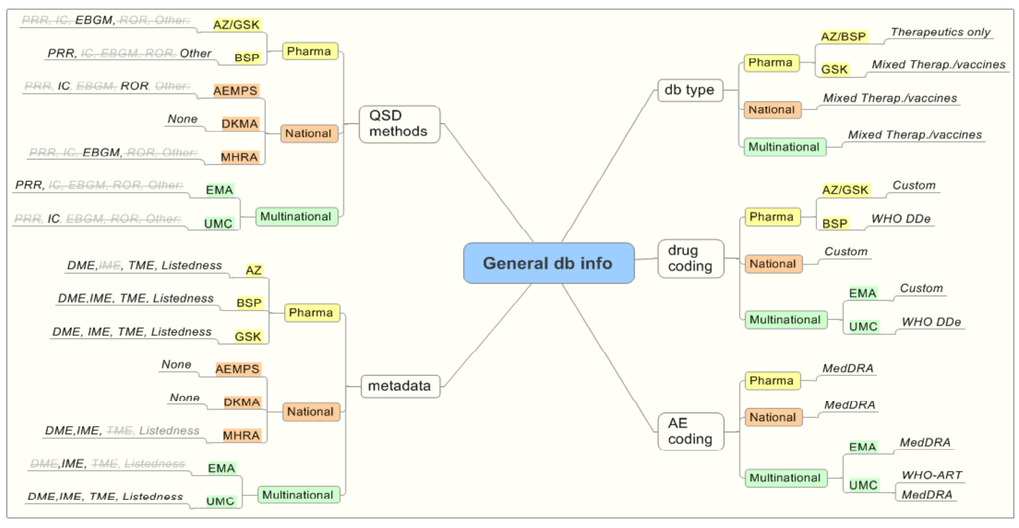
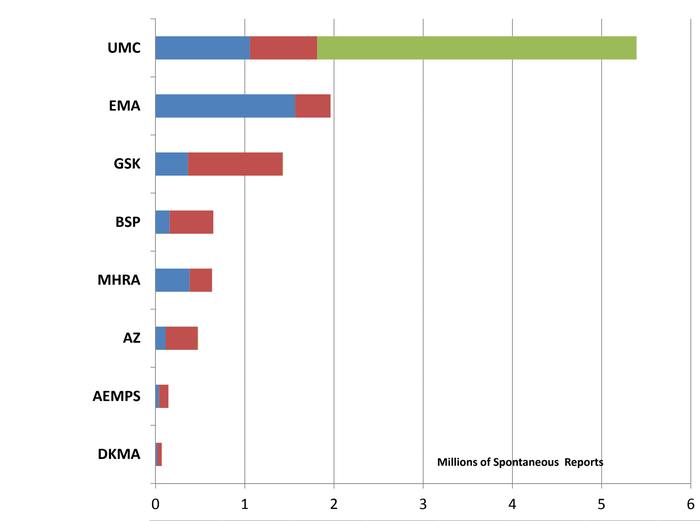


Figure 2 –Number of SPONTANEOUS reports broken down by Seriousness



	DKMA	AEMPS	AZ	MHRA	BSP	GSK	EMA	UMC
Total Serious	18,737	38,758	112,577	381,317	157,000	361,606	1,564,981	1,058,090
SPONTANEOUS Non-serious	50,398	104,951	359,045	251,431	490,000	1,061,856	396,127	752,842
SPONTANEOUS Unknown Seriousness	0	0	5,395	0	0	5,411	0	3,580,534

Figure 3 – SPONTANEOUS reports broken down by Reporter Type

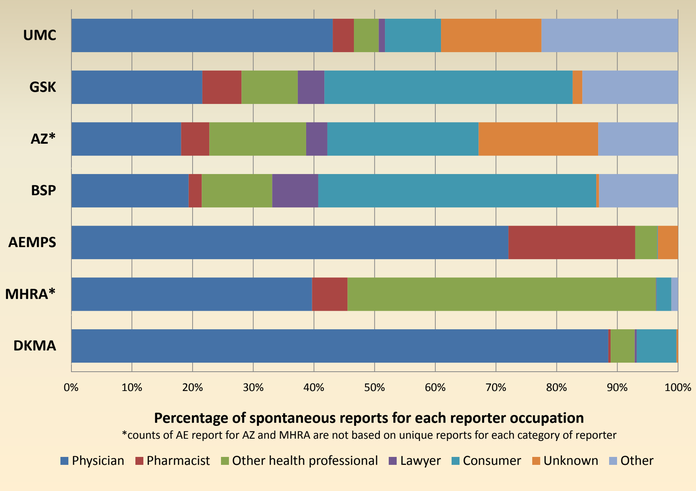


Figure 4 - Top 5 Countries of origin
percentage of case reports used for signal detection

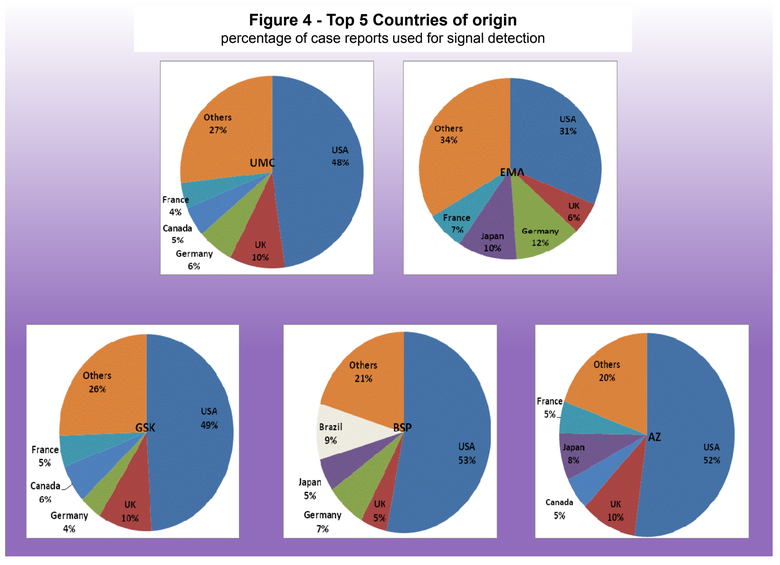


Table 3 – Presence of demographic data in partner databases (% of reports with a value recorded[1]) and time to onset data

	Receipt Date	Age/DoB	Gender	Ethnicity	Country of case	Subject ID	Time to onset[2]
DKMA	✓	✓(unk)	✓(100%)	×	✓(100%)	✓(unk)	×
UMC	✓	✓ (77%)	✓ (94%)	✓ (11%)	✓(100%)	✓ (>0%)	✓ (54%)
EMA	✓	✓(unk)	✓(unk)	×	✓(unk)	×	×
MHRA	✓	✓ (80%)	✓ (97%)	×	✓(100%)	✓ (57%)	✓ (5%)
AEMPS	✓	✓ (96%)	✓ (99%)	×	✓(100%)	×	✓ (59%)
BSP	✓	✓ (74%)	✓ (97%)	✓ (58%)	✓(100%)	✓ (83%)	✓ (37%)
AZ	✓	✓ (73%)	✓(92%)	✓ (26%)	✓(100%)	✓(41%)	✓ (37%)
GSK	✓	✓ (79%)	✓(86%)	✓ (10%)	✓(96%)	✓(59%)	✓(32%)

1. × - not recorded; value present in ≤ 5% of reports 2. First dose to event first occurrence

Table 4 – Number of drugs with >=10 reports in the database

	Number of drugs with >=10 reports
MHRA	1,814
AEMPS	1,955
GSK	2,146
AZ	2,931
EMA[1]	3,200
UMC	5,713

1. (Estimate, based only on reports including IMEs)

Figure 5 - Top 5 SOCs – Expressed as percentage of events for the top 5 SOCs

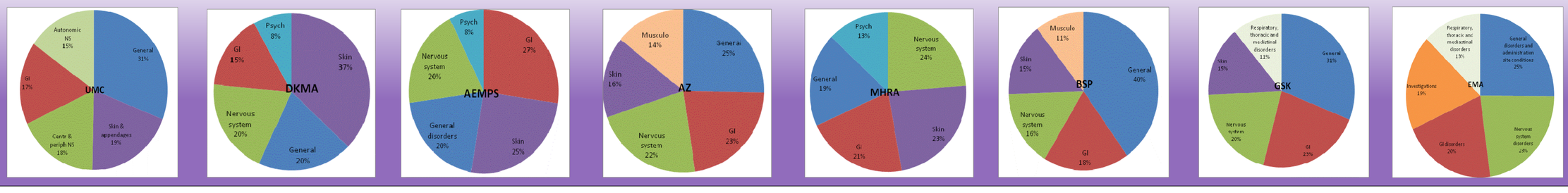
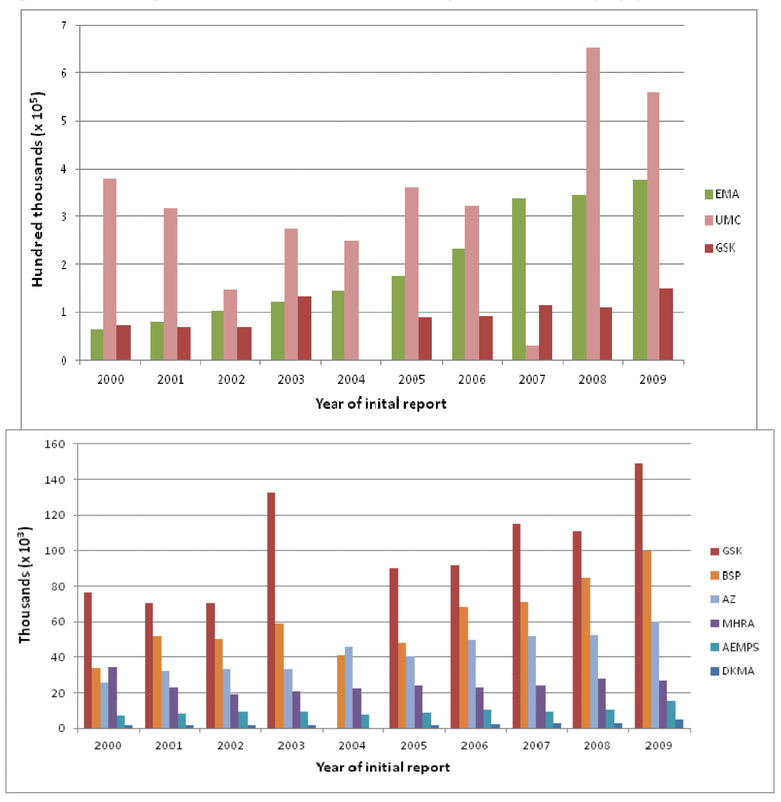


Figure 6 – Histogram of the number or reports (ALL REPORTS) by year 2000 - 2009



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Background: The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency (EMA). WP3 includes assessment of SD methods applied to DBs of spontaneous ADRs. Partners surveyed include 3 national regulatory agencies (RAs), 3 pharmaceutical companies (PCs), the EMA and the Uppsala Monitoring Centre (UMC).

Objectives: To describe different spontaneous report DBs with regard to size and content as context for future assessment of the relative performance of SD and duplicate detection methods in these DBs.

Methods: The survey, completed online, comprised 5 sections: i) general information including types of therapeutic agent, coding dictionaries, use of meta data and signal and duplicate detection algorithms; ii) counts including those based on seriousness, reporter type, country of origin, therapeutic agents and events; iii) data elements including presence of demographic data and drug details; iv) database coverage in terms of predominant drugs and events v) vaccine specific information. Data were summarised descriptively.

Results: Data from the 8 respondents were obtained between Sep 2010 and Aug 2011. DB size varies greatly (range 69,000–5,391,000 spontaneous reports). DBs are comparable in terms of: proportion of serious to non-serious reports; country of origin; predominant body systems to which events are coded; availability and completeness of certain data elements such as gender, age and country of case. There is little comparability in SD algorithms employed or use of meta-data (e.g. flags for targeted, designated or important medical events). Predominant drugs and drug-event pairs vary and appear to reflect historic parochial issues. Annual report numbers continue to rise in PC, EMA and UMC DBs. The pattern of reporters, particularly in PC DBs, has changed over time.

Conclusions: The heterogeneity of spontaneous DBs is likely to be an important consideration when assessing the performance of SD algorithms in future studies.

Summary & Conclusions

- Data from the 8 respondents were obtained between September 2010 and August 2011. Database size varies greatly (range 69,000 to 5,391,000 spontaneous reports)
- Databases are comparable in terms of: main countries of origin of reports; predominant body systems to which events are coded; availability and completeness of certain data elements such as gender, age and country of case
- Pharmaceutical company databases have higher proportions of non-serious adverse events and consumer reports than non-pharma databases
- There is little comparability in SD algorithms employed or use of meta-data (e.g. flags for targeted, designated or important medical events). Predominant drugs and drug-event pairs vary and appear to reflect historic parochial issues. Annual report numbers continue to rise in pharmaceutical company, EMA and UMC databases. The pattern of reporters, particularly in pharmaceutical company databases, has changed over time
- The heterogeneity of spontaneous databases is likely to be an important consideration when assessing the performance of signal detection algorithms in future studies to be carried out as part of PROTECT WP 3

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