Drug Saf 2010; 33 (10): 891-962
0114-5916/10/0010-0891/$49.95/0

INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

ABSTRACTS

10th ISoP Annual Meeting
'Pharmacovigilance in the Global Village'
Accra, Ghana
3–6 November 2010

Celebrating the 10th anniversary of ISoP, 2000–2010

INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

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1. Attitude, Perception and Barriers towards Adverse Drug Reaction Reporting Among Community Pharmacists in Malaysia

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Background: It is uniformly accepted that there is no drug that is absolutely safe. For this reason, most of the countries established their national pharmacovigilance systems to monitor the adverse drug reaction following the disaster of thalidomide in the 1960s.[1]

Within this context, the most common procedure to collect and analyze data about ADRs and identify signals is the spontaneous reporting system (SRS).[2] SRS depends on the voluntary reporting of suspected ADRs by health care professionals. Unfortunately, this system is associated with the phenomenon of under-reporting. Malaysia, like other countries, depends on the spontaneous reporting system for data collection on adverse drug reactions (ADRs). Within this context, the Malaysian community pharmacists (CPs) are seen as one of the important health care professionals in ADR reporting. However, underreporting of ADRs by CPs in Malaysia is common and the reasons behind this have not been truly explored.

Objectives: To investigate the awareness and attitude of community pharmacists in the northern states of Malaysia toward the adverse drug reaction reporting system and process in Malaysia.

Methods: In June 2008, a survey was conducted about the awareness and attitude of community pharmacists (N = 470) in 4 northern states of Malaysia (Perlis, Kedah, Pulau Pinang and Perak) using a validated self-administered questionnaire.

Results: From a total of 470 survey forms sent, only 116 pharmacists responded to the survey. (Response rate of 25.2%.) The total number of usable responses was 104 (24.7%).

The survey findings revealed that 75 pharmacists (74%) were not aware of the pharmacovigilance activates run by the drug regulatory authority in Malaysia.

Although 65 (61.5%) pharmacists in this survey emphasis the importance ADR reporting and 63 (62.4%) of them agreed that ADR reporting is an integral part for their professional duties, only 13 pharmacists (12.9%) claimed that they submitted ADR reports to the Malaysia adverse drug reaction advisory committee (MADRAC).

Several barriers identified, as preventing community pharmacists from reporting ADR included no previous knowledge of the reporting procedure (34.7%), unavailability of reporting forms (42.6%), ignorance of where the report should be sent (44.6%).

Conclusions: The results showed that although the community pharmacists in the northern states of Malaysia have a positive attitude toward pharmacovigilance system in the country, they have a poor knowledge. These results emphasized the urgent need for educational programs and establishing continuous efforts to promote ADRs reporting among community pharmacists.

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2. Drug-Drug Interactions: An Under-Estimated Problem

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Background: Drug-drug interactions are an increasing problem because of a growing number of new medications and the increasing life expectancy with the concomitant polypharmacy. DDI can be responsible for 15% of adverse drug reactions and can diminish the efficacy or increased the toxicity of the coadministered drugs. The objective of this work was to determine the prevalence of drug – drug interactions in rooms of Internal Medicine.

Material and Methods: The study was performed in two Internal Medicine rooms (''Dr Argerich Hospital'', Buenos Aires, Argentina and ''Dr Isidoro Iriarte'', Quilmes, Argentina). All medical prescriptions were evaluated for a period of six months. Interactions were classified as minor, moderate and majors. Chi square was performed for qualitative variables and Student t test and ANOVA for quantitative variables.

Results: 575 prescriptions were evaluated. 42.95% (CI 95%: 38.91, 47.00) were in females and 57.04% (CI 95%: 52.99, 61.08) in males. The average age was of 53.89 years (CI 95%: 52.36, 55.43). The average number of drugs per prescription was of 5.13 (CI 95%: 4.96, 5.30). The average number of interactions per prescriptions was 2.99 (CI 95% 2.71, 3.20): 0.26 (CI 95%: 0.20, 0.31) major, 1.96 (CI 95%: 1.75, 2.17) moderate and 0.76 (CI 95%: 0.68, 0.85) minor. In more than 60% prescription with three or more drugs an interaction was detected and in 100% of prescription with six drugs or more drugs. There was no significant association between sex or age and number of interactions. Significant association ($p < 0.00001$) was found between number of drugs and number of interactions. NSAIDs – heparin, NSAIDs – aspirin, and macrolides– statins were the most frequent major interactions found.

Conclusions: What we found is similar than information reported in international bibliography. The Average number of drugs was slightly lesser than other regional bibliography.[1,2] A great number of major interactions could be avoided to prevent potentially adverse drug reactions.

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3. Drug-Related Hospital Admissions

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Background: Hospital admissions due to Adverse Drug Reactions represents between 0.5 and 12% of all admissions according to international bibliography. We don't have certain information of our Country related to this topic. The aim of this study was to determine the true incidence of drug related admissions in a tertiary care hospital in Argentina.

Material and Methods: This study was performed within the pharmacovigilance system of the Argerich Hospital (a tertiary care hospital), from Buenos Aires, Argentina. The period included was from June 2008 to March 2010. Naranjo Score was applied to assess the causability of drug ADRs and all the probable and certain ADRs were included.

Results: We detected 121 drug related admissions that represented 0.6% of all hospital admissions. 50.41% (IC 95%: +/–8.90%) appeared in males and the average age was 58.96 years (IC 95%: +/–3.44%). The average number of drugs at the moment of admission was 3.89 drugs (IC 95%: +/–0.33). Immunosuppressive drugs were the mainly drugs involved with 20 cases (16.52%, IC 95%: +/-3.37%), NSAIDs and chemotherapeutics agents, 17 cases each (14.04%, IC 95%: +/–3.15%), cardiovascular and neuropsychiatric drugs 15 cases each (12.39%, IC 95%: +/–2.99%) and hematological drugs 14 cases (11.57%, IC 95%: +/–2.90). Upper

gastrointestinal bleeding and infectious complications because of immunosuppressive medications were the main causes of hospitalization.
Conclusions: Percentage of Drug Related admissions was lower than reported in other international bibliography.[1,2] As in other studies, anticoagulants are one of the main drugs involving hospitalization. Complications of Immunosuppressive treatment as a cause of hospital admissions were markedly higher then reported probably because our hospital has a very big transplant center.

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4. Decreasing the Consumption of ''Non-High Intrinsic Value'' Drugs

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Background: Drugs can be classified by the ''Intrinsic value'' according to the bibliography supporting their utility and security and divided into five groups: ''high value'', ''relative value'', ''low value'', ''no value'' or ''unacceptable value''; this four last groups can be included into ''non high intrinsic value'' drugs and the use should be avoided because of unacceptable risk benefit ratio.
Material and Methods: We have performed a pharmacoepidemiology study of population drug consumption of ''non high intrinsic value drugs'' between the periods of 2007, 2008 and 2009. This study was performed within the Federal Heath Program in Argentina. In this period this kind of drugs have been located out of the obligatory medical program and thus, with no economic coverage. The consumption was measured with Daily Definite Dose/1000 inhabitant/day. ANOVA test was applied to evaluate quantitative variables.
Results: The relative consumption of ''non high intrinsic value drugs'' has decreased in a significant way ($p < 0.001$) from near 9.8% of the total consumption in 2007 to less than 5% (4.76%) in 2009 and the trend is still going on. The drugs most consumed of this group were NSAIDs + vitamins, phlebotonics drugs and other drugs combinations in all periods. The consumption of this drugs occurred in patients with disability because we have a law that obligates to cover all the drugs that are prescript in this persons.
Conclusions: The consumption of this kind of drugs should be decreased because they provoke unnecessary costs and potential adverse drug reactions. We have applied certain policies that have reduced significantly the consumption of ''non high intrinsic value'' drugs.

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5. The PROTECT Project: an Innovative Public-Private Partnership for New Methodologies in Pharmacovigilance and Pharmacoepidemiology

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Background: Pharmacovigilance is in constant evolution. In Europe, the United-States and elsewhere, new regulations are being introduced to reinforce patient safety and risk management through earlier detection, evaluation and prevention of drug-related risks. These initiatives should be supported by methods ensuring the highest scientific standards. The Pharmacoepidemiological Research on Outcomes of Therapeutics by an European ConsorTium (PROTECT) project, with 17 public and 12 private partners, started in September 2009 to address limitations of current methods used in pharmacovigilance (PV) and pharmacoepidemiology (PE) and to significantly strengthen the benefit-risk monitoring of medicines.
Objective: To explain the methods being developed and tested for data collection, signal detection, signal evaluation through PE studies and benefit-risk integration and representation. One-year results are presented.
Methods and First Results: Feasibility and acceptability of early data collection on medication, lifestyle and risk factors directly from consumers via the internet and interactive voice response system are studied in 5600 pregnant women from 4 countries. Data linkage to other sources will be performed where possible.
A comprehensive set of signal detection (SD) recommendations applicable to different databases are developed based on extensive retrospective and prospective testing of existing and new methods for SD, creation of a structured database of known adverse drug reactions, and testing SD in electronic health records and clinical trials.
In order to explain discrepancies between PE studies of adverse drug events (AE), a framework for PE will characterise EU databases, test and compare analytical methods to control confounding and study 5 AEs in several databases to identify and further explore sources of variability (i.e. hip fracture and antidepressants, acute liver injury and antibiotics, myocardial infarction and antipsychotics, hormone replacement therapy and antiasthmatic drugs, suicide/depression and antiepileptics and cancer and calcium channel blockers). Best use of drug utilisation data in PE studies will be explored.
Methods of collating and integrating benefits and risks from various data sources and novel modelling approaches are tested to allow continuous modelling of the benefit-risk along the lifecycle of products and its graphical representation for use by patients, healthcare prescribers, regulatory agencies, and drug manufacturers.
Dissemination of methodologies will be enhanced by training and educational activities.
Conclusions: This comprehensive research programme in PV and PE is carried out thanks to the participation of academia, regulators, drug industry and other actors such as WHO-UMC and patients' organisations. It will contribute to the development of methodological standards in risk management. Collaborations with other research groups are welcomed.

6. Safety and Pharmacovigilance of ''Triomune®'' in HIV-1-Infected Adults in Mali

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Objective: The main objective was to evaluate the safety and pharmacovigilance of ''Triomune®'' in a hospital environment.
Methods: Our study concerned 68 patients infected by the HIV under antiretroviral treatment with ''Triomune®'' in infectious diseases service

of Point G hospital center. It was a prospective and observational study with a total duration of 12 months from January 1st to December 31st 2006. The patients were treated with the generic ''Triomune®''. Prior to initiation of treatment, the clinical history and biological parameters for each patient were collected including viral load, CD4 cells counts.[1]

Results: The majority of our patients consulted for Candidosis, fever of long duration, chronic cough and diarrhea. We reported that only 8.2% of patients had symptoms after 12 weeks of treatment. The Means, CD4 cells counts increased by 45 cells/mm^3 and the mean viral load of patients decreased by 470 807.83 copies/mL. After 12 weeks. 25.2% of our patients presented clinical side effects between them 17% were serious. The skin rash side effects represented 7.5% of the cases. They were made of rash and nettle rash. In 7.4% of cases, our patients had stopped their treatment because of dermatological side effects.[2,3] The peripheral neuropathies and myalgias represented 9.5% of the cases. The adherence to treatment was observed in 91.8% of the patients. At the end of the 12 weeks of our study, 2.9% of our patients died.[3]

Conclusions: This study suggests that ''Triomune®'' has its place as first-line treatment in Mali, we recommend monitoring of side effects of this drug on a larger sample.

Keywords: ''Triomune®'', Effectiveness, Safety, Antiretroviral therapy Mali.

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7. Assessment of Knowledge and Perceptions of Senior Pharmacy Students Towards Pharmacovigilance Activities in Malaysia

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Background: The role of community pharmacists in adverse drug reactions (ADRs) reporting is very crucial in improving patent safety. It was reported in many literatures that the low level of knowledge about pharmacovigilance activities and ADRs reporting among pharmacists is associated with a high rate of under reporting. Within this context, it is imperative that future pharmacy practitioners needed to be well educated about issues associated with ADR reporting in order to improve future reporting rate in Malaysia.

Aim: To assess the knowledge and evaluate the perception of the senior pharmacy student in five public universities in Malaysia towards the pharmacovigilance concept and ADRs reporting.

Methods: A cross-sectional survey study was conducted from December 1 to January 31st 2009, using a validated self administered questionnaire delivered to a sample of 510 final year pharmacy students who were enrolled full-time during the period of the study in a five Malaysian public universities. The questionnaire comprised of questions aimed at establishing the extent of the pharmacy student's knowledge about and their perception towards the Malaysian pharmacovigilance system. Descriptive and inferential statistics were undertaken using SPSS version16.0.

Results: A total of 421 students responded to the survey (response rate of 84.0%). Approximately 60% (n = 66.4) of the respondents were female. About 60% (n = 240) indicated that they had received courses on pharmacovigilance concept during their current pharmacy curriculum. The mean knowledge score of pharmacovigilance and ADRs reporting for final year pharmacy students was 6.91 ± 1.36. There was a significant difference in mean score of pharmacovigilance concept knowledge according to universities ($F = 5.89$; $p < 001$). The majority (n = 343, 82.3%) of the respondents felt it is necessary to confirm the causality relationship between the drug and the ADR. About 70% (n = 288) of the students believed the ADRs associated with herbal products should be reported. About 57.8% (n = 241) of the students believed that pharmacy student can perform ADRs reporting during their clerkship. The majority (363, 87.0%) of the respondents perceived that information on how to report ADR should be taught to senior pharmacy students.

Conclusions: The results of this study demonstrated that the majority of the final year pharmacy students in Malaysian public universities have insufficient knowledge about pharmacovigilance concept and adverse drug reactions reporting process.

8. Strontium Ranelate Utilisation from Prescription-Event Monitoring (PEM): Focus on 'Off Label' and Special Populations Use in Support of Risk Management

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Background: Strontium Ranelate is licensed in the UK for the treatment of postmenopausal osteoporosis (PMO) in women.

Objectives: To describe the utilisation characteristics of patients prescribed Strontium Ranelate, by analysing a completed PEM cohort, and to assess product use in relation to terms of license of marketing approval as defined in the summary of product characteristics (SmPC).

Methods: An observational cohort study using PEM. Exposure data were collected from dispensed prescriptions issued by general practitioners (GPs) October 2004-January 2008. Outcome data (event, patient demographic and clinical characteristics) were requested from GPs using a postal questionnaire, sent 12 months after patients' 1st prescription dates. Summary descriptive statistics were calculated. Menopause was defined by female age at 50+ years.

Results: The cohort consisted of 10 865 patients, of which 8.7% (n = 940) were reported to be male. Where specified, 2.4% of female patients (233/9909) were aged <50 years. One pregnancy occurred. Primary indications other than PMO were reported for 9.3% (946/10123) patients including 'prophylaxis' (n = 327) and 'osteopenia' (n = 156). Where specified, 2.5% (233/9255) patients had history of VTE and 1.0% (96/9252) patients were prescribed doses outside of the recommended starting dose (2 g/day).

Conclusions: Some GPs are prescribing this product outside the recommended terms of licence. Use in premenopausal women was reported. This study assumed natural menopause occurred aged 50+ years, though this doesn't apply for surgical menopause. The prevalence of patients with a history of VTE was common (this is a special warning and precaution for use) as were unusual dose regimens. Drug utilisation studies are important in describing populations that may not have been adequately studied in terms of risk in premarketing development

and these are important in the postmarketing risk management of medicines.

9. Analysis of Aripiprazole Utilisation from Prescription-Event Monitoring (PEM): Focus on Off-Label Use

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Background: Aripiprazole (Abilify®) is a novel atypical antipsychotic licensed for the treatment of Schizophrenia.

Objectives: To describe the utilisation characteristics of patients prescribed aripiprazole based on an analysis of a completed PEM cohort and to assess, where possible, if the product is being used outside terms of license of marketing approval.

Methods: An observational cohort study using PEM. Patients were identified from dispensed prescriptions that had been issued by general practitioners (GPs) between June 2004 and February 2006. Demographic and clinical data were requested from patients' GPs using a postal questionnaire, sent 6 months after patients' 1st prescription dates. Summary descriptive statistics were calculated and 'off label' use was defined according to the summary of product characteristics (SmPC) available at the time of study.

Results: The final cohort consisted of 4955 patients. Where specified, 2533 were female (51.5%), median age 41 years (IQR: 33–54 years). The licensed indication of Schizophrenia was reported for 2947 patients (59.5%). Other 'off label' indications were reported for 2090 patients (42.2%), including 'Dementia' (n = 70), 'Alzheimer's disease' (n = 17), 'Obsession/compulsive' (n = 56), 'Mental handicap' (n = 39), 'Aspergers syndrome' (n = 12), 'Tourettes syndrome' (n = 15) and 'Autism' (n = 6). Prescribing in Paediatric patients was common, with 120 patients under the age of 18 (2.4%) prescribed aripiprazole - six of these patients were under 10 years of age. There were 1651 patients (42.7% of patients who had dose specified; 1651/3871), who were prescribed aripiprazole outside of the normal recommended starting dose (15 mg/day).

Conclusions: This study has highlighted that some clinicians are prescribing this product outside the recommended terms of the licence. Drug utilisation studies are important in describing populations that may not have been adequately studied in terms of risk in pre-marketing development programmes.

10. Interim Results of a Modified Prescription-Event Monitoring Study on Ivabradine: Case Series of Utilisation in Patients <40 Years

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Background: Ivabradine is licensed for chronic stable angina. It reduces heart rate and myocardial oxygen demand. The utilisation of ivabradine in patients under forty years old is of interest, as angina incidence is expected to be low in this group.

Objective: To examine aspects of drug utilisation of ivabradine in primary care in England in patients aged under 40 years.

Methods: A subset analysis of interim data collected from a Modified PEM (M-PEM) observational cohort study. Since November 2005 patients have been identified from dispensed GP prescriptions. Demographic, drug utilisation and limited adverse event data (phosphenes or bradycardia) are being collected via questionnaires sent to GPs 6+ months after the patient's 1st identified prescription. Descriptive statistics summarise data to 1st interim data lock date (Oct 2008); percentages presented exclude missing values.

Results: Of 5441 questionnaires sent out, 1378 were returned, 277 were void. Interim cohort comprised 1101 patients: median age 68 years (IQR 59–76, Range 19–99) 58.8% male (n = 647). The most common indication was angina 84.9% (861/1014). Tachycardia was indication in 4.6% (47/1014).

Of the interim cohort, 3.6% (40/1101) patients were under 40 years old. In this subset: 27.5% (11/40) male; most common indication was tachycardia (51.4% (19/37); indication was angina in 13.5% (5/37); ivabradine was stopped in 32.4% (11/34); most common reason was DSRU dictionary LLT 'not effective' (36.4% [4/11]; all 4 had indication tachycardia - 2 on recommended dose). There were no reports of serious ADRs as reasons for stopping and no reports of deaths, phosphenes or bradycardia.

Conclusions: In this case series study of patients under the age of 40 treated with ivabradine, off label indication of tachycardia was common. There were no reports of known ADRs, serious ADRs or death associated with this. This study will continue to collect data on the utilisation of ivabradine.

11. Risk Assessment Study of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) & OTC Analgesics in South Korea

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Background & Aims: Recently, voluntary withdrawal of Vioxx (rofecoxib, a cyclo-oxygenase-2 selective inhibitor) from the U.S. & worldwide market and the halt of clinical trial involving NSAID - naproxen due to the increased risk of cardiovascular events (including heart attack and stroke) provoked safety concerns of NSAIDs and OTC (over-the-counter) drugs. So, the additional examination of risk/benefit balance for marketed NSAIDs overall was strongly needed.

Methods: Firstly, we searched for basic characteristics, mechanism of action, drug utilization data, and risk assessment results of NSAIDs, especially by WHO (World Health Organization) and regulatory agencies (US FDA, EMEA, UK MHRA, Japan PMDA, Australia TGA etc.). Secondly, we analyzed the pharmacy benefit claims of NSAIDs from 2007 to 2008 from Korea Health Insurance Review Agency (HIRA). Lastly, we performed the causal relationship assessment between NSAIDs and the serious adverse reactions. Descriptive statistics was derived and the chi-squared test was performed by SAS ver 9.1 (considered significant out $p < 0.05$).

Results: Currently, marketed single NSAIDs (1653 products) in Korea contain 53 active ingredients. We categorized NSAIDs into 5 classes based on chemical structure and selectivity to COX (cyclo-oxygenase) as followed : acetylsalicylic acid, para-aminophenol derivatives, non-selective COX inhibitors, COX-2 preferential inhibitors and COX-2 selective inhibitors. As the latest results of risk assessments by US FDA and EMEA, COX-2 selective inhibitors were found to be statistically

significant to the risk of cardiac disorder (myocardial infarction and stroke) and non-selective COX inhibitors were associated with gastrointestinal disorders and skin & subcutaneous tissue disorders in patients prescribed these medicines.

Conclusions: We concluded that the risk/benefit balance for NSAIDs remained favourable based on currently available information. Consumers are advised that all OTC pain medications including NSAIDs should be used in strict accordance with the label directions. Both prescribers and patients should continue to use NSAIDs at the lowest effective dose for the shortest possible duration to control symptoms. Considering above-mentioned information, we made ''Guidelines of NSAIDs Usage'' for practitioners/pharmacists and patients.

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12. Pilot Swine Flu Vaccination Active Surveillance Study: Design and Rationale

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Background: Following an expedited approval process UK marketing authorisations were granted for two H1N1 influenza A (swine flu) vaccines in October 2009.[1] There were calls for development of rapid data collection safety monitoring systems to facilitate evaluation of emerging safety issues.

Aim: To present the design and rationale of this novel post-marketing pilot active surveillance study.

Methods: A prospective observational cohort design. Voluntary enrolment was generated via posters/leaflets and a bespoke website; consent allowed monthly follow-up for one year and investigation of any serious adverse events requiring emergency treatment or resulting in hospitalization (primary outcome). Modern technology (email, text, web-based forms) streamlined this process to collect exposure, outcome and covariate data. Data on participation rates and cohort characteristics were summarised using descriptive statistics. Crude Odds Ratios (95% CI) were calculated to look at associations between patient characteristics and H1N1 vaccine uptake.

Results: The principal challenge is to expedite collection of data at low cost, which can then contribute to real-time evaluation of benefit: risk of the newly developed vaccine during and after the immunisation programme. Prior to study start (2/11/2009) study packs were sent out to all 1015 GP practices in Scotland. At close of recruitment (30/4/2010) valid cohort comprised 4055 patients. Where specified, the majority of participants submitted consented via GP vaccination sites (72.0%; 2825/3922), the remainder via hospital or postal route. Active surveillance involving patients as opposed to healthcare professionals along with outcome adjudication allows examination of aspects such as under-reporting and time to reporting of study outcomes as well as the potential for misclassification. The prospective nature facilitates scrutiny of temporal and other relationships. For those valid patients included in the study, the most frequently reported preferred method of subsequent contact to enable ongoing active surveillance was via email [51.5% (2090/4055)]. Patients were followed-up at monthly intervals after date of participation; the median number of follow-ups was 2 (range 0–6). Examination of the maximum number of possible follow-ups, by preferred route, revealed contact by phone as the most successful [58.4% (708/1212)].

Conclusions: This pilot study is complementary to other studies being conducted to monitor the use and safety of the swine flu vaccine, and offers the potential for near 'real-time' vaccine safety monitoring and alerts, with minimal additional workload for healthcare staff. Active surveillance programmes should be considered as additional pharmacovigilance tools.

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13. Pilot Swine Flu Vaccination Active Surveillance Study: Interim Results

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Background: The purpose of this academic pilot study based in Scotland was to examine the feasibility of using modern technology (email, text, web-based questionnaires) for monthly data capture of patient self-reports over 12 month period in order to conduct near 'real-time' post-marketing systematic active surveillance of eligible vaccinees following availability of H1N1 influenza A (swine flu) vaccine (October 2009).[1]

Aims: An interim analysis to examine weekly enrolment and utilisation characteristics of patients offered swine flu vaccination.

Methods: A prospective observational cohort study (start date 2/11/2009). Voluntary enrolment was generated via posters/ leaflets in vaccination centres and a bespoke website; consent allowed follow-up and investigation of serious adverse events requiring emergency treatment or resulting in hospitalization (primary outcome). Modern technology collected exposure, outcome and covariate data. Descriptive statistics and crude Odds Ratios (95% CI) are presented.

Results: Valid cohort at interim (4/2/2010) comprised 3280 patients; 91.7% (n = 3007) had swine flu vaccination, 80.8% (2350/2909) in GP surgeries. Of those vaccinated and where vaccine date specified (n = 2995) the mean time to vaccine uptake from start of vaccination programme (21/10/2009) was 56.7 days (SD 12.4). Of the 273 patients who decided not to have the H1N1 vaccination, 114 reasons were provided. Of these, frequent reasons cited included 'consider having it later' (12.1%, n = 33) and 'worried about side-effects' (7.7%, n = 21). Vaccinees were more likely to be: female (OR 1.6 [1.2, 2.0] 59.3% vs 48.3%); health professionals (OR 2.2 [1.4, 3.5]; 19.7% vs 10.0%), received another vaccination in 3 months prior (1.5 [1.2, 1.9]; 54.4% vs 44.3%); immunocompromised (OR 2.33 [1.1, 6.0]; 5.8% vs 2.6%) but less likely to have other medical conditions. Of 95 pregnant women 56.5% (n = 52) were vaccinated in the second trimester.

Conclusions: This pilot study demonstrates the viability of using modern technology to support patient self-reporting within an active

surveillance system. Uptake in clinical risk groups (in terms of vaccination and/or study awareness) requires further examination.

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14. Intentional Rechallenge: Experiment or Patient Benefit?

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Rechallenge is defined as the readministration of a medication suspected to be a possible cause of an adverse reaction, and which has been subsequently discontinued.[1] However, even continued dosing (without discontinuation of treatment), can be regarded as rechallenge.[2]

Despite the risk, rechallenge may be justifiable if the benefit still outweighs the risk. For example, studies have demonstrated that the benefit of continuing aspirin outweighs the risk of withdrawing it even in case of major gastrointestinal ulcer bleeding.[3] But, this is limited to high risk patients receiving aspirin for secondary prevention of cardio and cerebrovascular disease who have received appropriate peptic ulcer treatment. On the other hand, rechallenge with clozapine was harmful in case of clozapine induced neutropenia even with prophylaxis with granulocyte colony stimulating factors.[4]

This leads to the necessity of creating a structured algorithm evaluating the risk benefit ratio of suspected causative drug vs best available alternative treatment.[5]

The algorithm must take into consideration:

1. Risk of rechallenge despite serious reaction
2. Benefit of treatment
3. Risk of alternative treatment (or risk of disease progression in the absence of treatment)
4. Benefit of alternative treatment
5. Causality assessment (probability that the suspect drug was implicated)

This presentation aims to present the algorithm and conditions in which intentional rechallenge could be justified.

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15. Cohort Description of the Drug-Induced Arrhythmia Risk Evaluation (DARE) Study

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Background: Drug induced arrhythmia (DIA) is a major concern for patients, prescribers and the pharmaceutical industry.[1] Many are secondary to important drugs including class 1 and 3 antiarrhythmics, antipsychotics and antibiotics.[2] DARE, a national prospective case control study, has recruited cases of ventricular arrhythmia in England from 2003 to date.

Objectives: To systematically record and characterise incident cases of DIA.

Methods: Cases (Torsades de Pointe (tdP), ventricular fibrillation (VF), polymorphic and non polymorphic VT, severe and moderate QT prolongation with symptoms) were recruited throughout England by three regional research nurses. For each case, a comprehensive nurse-completed questionnaire provided demographic, lifestyle and medical data; ECG and hospital notes data were obtained for multivariate analysis. Controls were obtained from primary care in order for data analysis to be conducted using logistic regression.

Results: 112 cases (mean age 61.6, median 66 range 14–83, 62.9% female, 94.8% Caucasian) were recruited from 91 consultants with 313 controls (mean age 66.9, median 70 range 21–83, 53.9% female 99% Caucasian) from primary care. Cases comprised: tdP (n = 63, 56%), VF (n = 26, 23%), npVT (n = 25, 22%), and pVT (n = 18, 16%); 93 (84%) had severe QT prolongation, 12 (10%) moderate QT prolongation with symptoms and one (1%) had exacerbation of existing arrhythmia. Amiodarone alone was implicated in 23 (20%) cases (mean age 65.2, 64.1% female); other drugs included flecainide (n = 15, 17%), sotalol (n = 16, 19%), psychiatric drugs (n = 7, 8%), antibiotics (n = 4, 5%), drug combinations (including with antiarrhythmics) (n = 16, 19%) and other single drugs (n = 8, 9%).

Conclusions: DARE demonstrated that the most common drugs to cause DIA are antiarrhythmics with amiodarone being the main culprit in this study. Further analysis will be conducted to ascertain characteristics of patients at risk, particularly comorbidities, polypharmacy and inherited risk factors.

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16. Observational Assessment of Safety in Seroquel XL (OASIS) Study: Design and Rationale of a Non-Randomised Observational Safety Study

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Background: Prolonged-release quetiapine fumarate (SEROQUEL XL) and the immediate release (IR) formulation differ in duration of treatment, titration schedule and maximum dose.[1] OASIS is part of a risk management plan to examine safety during titration and at higher doses.

Objectives: To present OASIS design which monitors short-term (up to12 weeks) use and safety of quetiapine XL in the community care setting in England.

Methods: OASIS uses prospective, cohort event monitoring (CEM). From January 2010, 1500 patients (750 each formulation) will be recruited over 36 months: sample size based on detecting >2.5 fold increase in common events between sub-groups of patients defined by dose (>600 mg, ≤600 mg; ratio 1 : 2). For each reported event, Incidence Densities (IDs) (1st report per 1000 patient-months of treatment) will be calculated. ID differences (+ 95% CI) will be calculated for sub-sets of patients defined by dose (>600 mg) of quetiapine XL or quetiapine IR. ID differences (+ 95% CI) will also be calculated within the XL

cohort between low (≤600 mg) and high (>600 mg) dose. Signals generated will be investigated further using regression analysis and survival analysis techniques.

Results: In OASIS, randomisation is judged inappropriate for clinical reasons. Randomisation optimises isolation of treatment effects, but can compromise external validity and generalisability. The observational nature of OASIS enables examination of treatment in a heterogeneous population in actual practice. The comparison cohort exposed to quetiapine IR enables examination of risk between patients for whom the decision to initiate treatment with quetiapine has been based on clinical need.

Conclusions: CEM allows systematic collection of safety data on patients initiated on new treatments in health care settings not previously studied. OASIS addresses challenges inherent in designing post-authorisation safety studies where randomisation is not appropriate.

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17. Monitoring Compliance to the Thalidomide Pregnancy Prevention Program: Results from Portugal

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Background: Thalidomide was approved by the US FDA in 1998 for the treatment of ENL and subsequently for the treatment of multiple myeloma (MM). The latter indication was also approved in Europe in June 2008. Due to its teratogenicity, the commercialization of thalidomide has been conditional upon having a pregnancy prevention program (PPP) as part of the risk minimization plan. Since September 2008, a Thalidomide PPP has been in place in Portugal. The program has the following components:

(1) Educational materials for health care professionals (HCP) and patients.
(2) Documentation that patients have been counseled on teratogenicity risk.
(3) Prescription Authorization Form (PAF) that documents the patient's childbearing potential status, results of pregnancy tests (where applicable) and thalidomide indication. Celgene receives an anonymous copy of the PAF.

Objectives: To evaluate the role of the PAF in monitoring HCPs compliance with the PPP and estimating the percentage of female patients with childbearing potential treated with thalidomide, within the approved indication and off-label.

Methods: PAFs received in the period September 1st 2008 to April 9th 2010 were collected and relevant key data pertaining to the key elements of the PPP analyzed.

Results: We identified 4% of the hospitals to be non-compliant in returning the PAF, and this triggered an investigation to understand the possible reasons for non-compliance and institute corrective actions. Of the PAFs received, 77.2% showed that thalidomide was prescribed within the approved indication (MM), with 16.8% of the prescriptions representing off-label usage. Information on indication was lacking on 6% of the PAFs. Among the PAFs indicating MM as the indication for thalidomide prescription, females of childbearing potential represented 3.3%, with females not of childbearing potential and males accounting for 46.3% and 50.4% respectively. In the off-label indications the percentage of prescriptions for females of childbearing potential, females not of childbearing potential and males was 34.5%, 23.8% and 41.7% respectively. The compliance on the pregnancy tests was also verified. Of the 342 women with childbearing potential, 97% presented duly filled PAFs, which showed dates of the pregnancy test and the test results.

Conclusions: Most prescriptions for thalidomide in Portugal are for multiple myeloma, the approved indication. Overall, there are fewer females of childbearing potential within the approved indication. However, the percentage of females of childbearing potential is high within the off-label setting. The use of the PAF is an effective way of monitoring compliance to the pregnancy prevention program, and providing early opportunity to intervene in case of non-compliance.

18. Nocturnal Enuresis (Bed-Wetting) in Patients Taking Clozapine, Risperidone, Olanzapine and Quetiapine: A Comparative Cohort Study

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Background: Nocturnal enuresis (bed-wetting) has been reported in patients taking the atypical antipsychotic medicine clozapine,[1,2] but the incidence of this adverse effect has not been accurately established. The incidence of nocturnal enuresis in patients taking the atypical antipsychotic medicines risperidone, olanzapine and quetiapine is not known.

Study Aim: To compare the rate of nocturnal enuresis in clozapine patients with the rate of nocturnal enuresis in patients taking risperidone, olanzapine or quetiapine.

Study Design: Comparative cohort study using intensive methods of patient follow-up.

Setting: Dunedin, a main centre in the South Island of New Zealand, where psychiatric patients may be managed in a community and/or hospital setting.

Patients: Adult patients (age 15–64 years) with a Dunedin address, who were dispensed a prescription for clozapine, risperidone, olanzapine or quetiapine during a four month period (1 August to 30 November 2004).

Methods: The New Zealand Intensive Medicines Monitoring Programme (IMMP) uses Prescription/Cohort Event Monitoring methods.[3] For this study, cohorts of patients taking atypical antipsychotic medicines were established from prescription dispensing data sent directly to the IMMP from community and hospital pharmacies. Patients were followed up by specially designed questionnaires sent to doctors who asked patients directly about bedwetting.

Results: 606 patients were included in this study cohort: 327 (54%) men and 270 (46%) women. The age of patients ranged from 15 to 64 years with a mean age of 40 years. 642 questionnaires were sent for these patients and 508 (79%) valid responses were obtained. Nocturnal enuresis occurred in 20.7% (95% CI = 12.6, 31.1) patients taking clozapine, 9.6% (4.9–16.5) olanzapine, 6.7% (2.7–13.3) quetiapine and 6.2% (3.2–10.5) risperidone patients. Compared with clozapine patients, the risk of nocturnal enuresis was significantly lower in patients taking olanzapine (OR = 0.40, 0.17–0.92), quetiapine (OR = 0.27, 0.11–0.7) and risperidone (OR = 0.25, 0.11–0.55). Adjustment for age and sex and history of childhood enuresis did not significantly change these results.

Conclusions: Approximately one in five patients prescribed clozapine experience bedwetting. This is significantly higher than the rate of nocturnal enuresis in patients taking olanzapine, quetiapine and risperidone. Awareness of this common and unpleasant adverse effect should improve management of these patients.

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19. Assessment of the Effectiveness of the Thalidomide Celgene Pregnancy Prevention Programme (PPP) in the United Kingdom

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Thalidomide is contraindicated in women who are pregnant or women who could become pregnant unless all the conditions of the PPP are met. The conditions of the PPP must be fulfilled for all patients.

Celgene assesses the effectiveness of the PPP in order to ensure that all reasonable steps are being taken to reduce risk of pregnancy. Results are reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA).

As a condition of the Marketing Authorisation, and to ensure critical PPP actions are undertaken, a distribution control system has been implemented. Only pharmacies registered with Celgene are authorised to receive and dispense thalidomide. Further, the Chief Pharmacist agrees to implement and audit the use of a key step in the distribution control system, the Prescription Authorisation Form (PAF).

Celgene have agreed with the MHRA that pharmacies can fulfill their obligations in this respect by conducting a self-audit. The self-audit provides a retrospective review of the PAF by all registered pharmacies.

The self-audit process was initiated approximately 1 year post launch. However, the nature of the audit means that, because pharmacies registered at different times post-launch, the 1 year anniversary of pharmacy registration dates are staggered. Therefore, the pharmacy self-audit is a rolling process with anonymised, aggregate reports produced every 6-months. Here we provide an overview of the self-audit process and present results from audit reports received between 10th April 2009 and 9th April 2010. Amongst registered pharmacies, there is a high compliance with the PPP with evidence that the mandatory precautionary measures have been instigated.

Fifty-four percent of pharmacies registered for the PPP completed the pharmacy-self audit, with 96% of PAFs counter-signed by the prescriber and pharmacist. The prescriber confirmed that the patient had received the appropriate counselling, and had been on contraception for at least 4 weeks prior to the commencement of therapy, on 93% of PAFs for women of childbearing potential (WCBP). Confirmation of a negative pregnancy test prior to dispensing was provided on 90% of PAFs for WCBP.

Furthermore, the coverage represented by the current format of the pharmacy self-audit has been shown to be sufficient to provide a representative dataset, despite only a subset of PAFs being subject to audit. The audit process is constantly evolving with the results assessed to ensure that the self-audit approach and the PPP are applicable to the current treatment setting for thalidomide.

20. The Austrian Risk Minimisation Programme for Lenalidomide: Effectiveness Measurement Survey

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Background: In Austria, a risk minimization using a controlled distribution system and augmented by provision of additional educational materials to healthcare providers and patients has been implemented as a proactive tool to minimize possible in-utero exposure of lenalidomide, a thalidomide analogue. Risk minimization activities should be evaluated for effectiveness and potential improvement at different time points.

Objectives: To determine the effectiveness of interventions to improve compliance to the approved lenalidomide RMP in Austria. Additionally, compliance to the guidance in the SmPC concerning frequency of blood counts, venous thromboembolism prophylaxis, dose alteration due to renal insufficiency and the management of neutropenia or thrombocytopenia was assessed.

Methodology: A prospective, multi-centre survey was undertaken, involving interviews with selected healthcare professionals (HCPs) actively prescribing lenalidomide. A predefined standard questionnaire with leading questions was used. Further, the effectiveness of adverse reaction management by HCPS was determined. Data were descriptively analysed.

We included centers that cover approximately 75% of all patients treated with lenalidomide in the period 3rd July 2007 to 26th November 2008. The selected HCPs represented 15% of all potential prescribers in Austria.

Results: The survey enrolled 16 hospitals and a total of 28 HCPs were interviewed. The proportion of treated women of childbearing potential (WCBP) was lower than expected from global marketing experience (observed 0.55% vs expected 3–5%). The survey provided evidence suggesting that the PPP requirements in terms of pregnancy testing were being complied with. In total 59% of HCPs reported to adhere to the schedule for complete blood count monitoring as proposed in the SmPC. Ninety-two (92%) percent of HCPs prescribed thromboprophylaxis, demonstrating a high level of awareness on minimizing venous thromboembolism. 21% of HCPs had a patient who has experienced a neutropenia grade 4 and 38% of physicians a thrombocytopenia grade 3 or 4. A dose alteration due to an observed neutropenia was performed by 67% and due to a thrombocytopenia by 62% of HCPs.

Conclusions: The survey results demonstrated a high awareness of the safety profile of lenalidomide and the strategies for minimizing specific risks. The high proportion of compliance to use of thromboprophylaxis could be considered to reflect the effectiveness of the information provided in the educational materials. This survey demonstrated effectiveness of the implemented Risk Minimisation Program for lenalidomide at a national level.

21. Patient Experiences with RevAid®, a Canadian Controlled Distribution Program for Lenalidomide

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Background: Lenalidomide is distributed in Canada through RevAid®., a controlled distribution risk management program requiring physician, pharmacist and patient registration.

To explore current perceptions and experiences with RevAid® and provide direction for possible enhancements, a market research study

was undertaken between February and March 2010 to understand from a patient perspective, among others, the process and experiences with the program on initial access/enrolment and on-going contact/monitoring.

Methods: A prospective telephone interview enrolled current lenalidomide patients (from a Canadian database) who had received a minimum of 3 or more cycles of treatment. Patients were invited to participate in the study and a toll-free telephone number to call the researchers provided. Once contacted, the researchers further screened patients for eligibility.

Results: 308 patients had received a minimum of 3 or more treatment cycles. Forty-two patients consented to participating in this study with 36 finally selected for interview. Of these, 32 received lenalidomide for multiple myeloma (MM) and 4 for myelodysplastic syndrome.

Time from program enrolment to receipt of first prescription ranged from within 1 week in 12 patients to 4 or more weeks in 5 patients. Thirty-three patients (92%) received a monthly prescription and 3 (8%) received lenalidomide every 2–3 months.

Twenty-two patients were dispensed treatment through a home delivery program compared to 14 picking up the drug at cancer clinics. Of the 22 patients receiving dispenses through the home delivery program, 3 indicated preference for picking up the medicines at their convenience from the pharmacies. Three patients picking up medicines from the pharmacy indicated a preference for home delivery.

On the on-going survey monitoring, 5 of the 36 patients questioned the relevance of the survey questions relating to sexual intercourse and childbearing potential.

Of the 36 patients interviewed, 31 recalled receiving educational materials (''sheet'' or ''pamphlet'') listing important adverse effects, including the risk of congenital malformations.

Thirty-three patients were satisfied with the program and the requirements necessary to receive and continue receiving lenalidomide.

Conclusions: The majority of patients received lenalidomide for MM. There was overall satisfaction with the RevAid® program. Furthermore, most patients found equal ease of access to the drug, although in a few cases there was a delay between enrolment into the program and initiation of first treatment. The Canadian Risk Management team will collect further feedback from health care practitioners and will analyze the results in an effort to streamline and enhance the administration of the program.

22. Safety of ''Triomune®'' in HIV-1-Infected Adults in Mali: A Preliminary Report on the Malian Antiretroviral Program

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Introduction: Adverse events during antiretroviral treatment (ART) are frequent and various.[1-3] Their diagnosis occur some difficulties in different orders according to the geographical context.

Aim: To identify the frequency with side effects of ''Triomune®''.

Methods: It was a prospective and observational study which lasted 24 months from 1 October 2006 to September 30, 2007.The patients were treated with the generic drug Triomune®. Prior to treatment initiation, demographic characteristics, clinical history and biological parameters including viral load and CD4 cell counts, were collected for each patient.[1] WHO's sides effects classification has been used to characterize the side effects.[4] Analysis of data has been done in the Software SPSS version 12.0.

Results: The age group of 27–36 years was 47.1% with a sex ratio of 1.68 for women. Candidiasis, fever during chronic cough or chronic diarrhea were the reasons for consultation. Clinical signs were reduced on the 1st and 3rd month, absent at 6 months follow-up. The average weight of patients increased from 55 kg to 60.7 kg in the third month and 66.3 kg at 6 months follow-up with a gain 11.3 kg. The viral load of patients from an average of 860 372 IU. At 6 months of treatment, it was undetectable (<50 copies/mL) in all patients. Patients had a CD4 count 127.5 cells/mm^3 at baseline against 324 cells/mm^3 after 6 months of treatment with a gain of 197 cells/mm^3. Adverse clinical type of peripheral neuropathy (10 cases), rash (4 cases), pruritus (2 cases), headache (2 cases), jaundice (one case). Side effects were skin rash generalized facts sometimes itchy. They were observed in 8.8% of patients after 6 months of follow-up. His greatest frequency, 3.9% was observed at 1 month follow-up requiring the cessation of treatment (WHO Stage 3). From 4th to 24th weeks of monitoring, the number of 51 patients has gradually decreased because of side effects (clinical or biological). The increase in transaminases and serum creatinine was observed at the initiation of treatment, respectively in 23.5% and 5.9% of cases. Regime change was found in 11.9% of patients because of side effects. Mortality was 11% during the study.

Conclusions: This study suggests that Triomune® has its place as a first-line HIV treatment in Mali. We recommend monitoring of its side effects on a larger patient population, particularly those due to D4T.

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23. Regional Differences in Reporting Patterns for Adverse Drug Reactions: A Retrospective Analysis of Reports from 2000 to 2009 in VigiBase

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Introduction: The World Health Organization (WHO) database for Adverse Drug Reactions (ADR), VigiBase, receives ADR reports from 96 WHO membership countries. VigiBase contains more than 5 million ADR reports and is a unique source for analysing ADR reporting patterns across countries. New information on regional ADR reporting patterns can help strengthen pharmacovigilance systems especially in low-resource settings, where funding for pharmacovigilance often is limited.

Aim: To characterize regional ADR reporting patterns on a worldwide basis over a period of one decade.

Methods: We analysed ADRs reports in VigiBase for which ADRs occurred between 2000–2009. ADR reporting patterns were analysed for different regions that we grouped by countries according to United Nations geographical regions.[1] The regions were Africa, Central America, Eastern Asia, Eastern Europe, North America, Oceania, South America, Western Asia, and Western Europe. Data were analysed with respect to distribution over time, reporting rates, ADR type (System Organ Class [SOC]), suspected medicines (level 1 of the Anatomical Therapeutic Chemical [ATC] Classification System, seriousness, and age and gender.

Results: We analysed 1 359 067 ADR reports corresponding to 3 013 074 ADRs. The majority of reports came from North America (473 482) and Western Europe (557 608). A large increase in ADR reports distribution was found for Africa and Central America from 2000–2009 compared to other regions. The lowest reporting rates (ADR reports/million inhabitants/year) were found for Eastern Asia (6) and Africa (8), while the highest rates were seen in Oceania (305) and North America (167). A significant difference (Chi-square = 22.0; $p < 0.01$) across regions was found for ATC group J: Antiinfectives for systemic use and especially in Africa it predominated with 21% of all reported ADRs. For ADR types significant differences was found across regions for skin and subcutaneous disorders (Chi-square = 47.91; $p < 0.01$) and infections and infestations (Chi-square = 22.16; $p < 0.01$). The distribution of serious (16%) and non-serious (84%) ADRs were found to be similar across regions. The most frequently reported patient age in ADR reports were 45–74 years old, while the age group 5–19 years old were the least frequently reported. For gender no significant differences were found across regions, where females accounted for 59% and males for 40% of all ADR reports.

Conclusions: This study has shown that regional differences exist for ADR reporting patterns with regards to the distribution of ADRs over time, reporting rates, suspected medicines, types of ADRs. This information can be helpful in strengthening current pharmacovigilance systems in various settings around the world.

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24. Influences of Socio-Economic Factors for Adverse Drug Reaction Reporting Patterns: A Retrospective Analysis of Reports from 2000–2009 in VigiBase

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Introduction: Establishment of national pharmacovigilance systems is essential, since presence of diseases, use of drugs, and trade with counterfeit and substandard drugs may vary across countries.[1-3] In 2007 less than 27% of developing countries were members of the World Health Organization (WHO) Programme for International Drug Monitoring compared to 96% for developed countries.[1] New information on the influence of socio-economic factors on Adverse Drug Reaction (ADR) reporting patterns can help strengthen pharmacovigilance systems especially in low-resource settings.

Aim: To examine the influence of economic status on ADR reporting patterns on a worldwide basis over a period of one decade.

Methods: We analysed ADR reports in the WHO-ADR database, VigiBase, for which the ADRs occurred between 2000 and 2009. ADR reporting patterns were analysed for income groups according to the World Bank definition for developing and developed countries.[4] The income groups were: high income, upper-middle income, lower-middle income, and low income. Data were analysed with respect to reporting rates, reporter type, suspected medicines (level 1 of the Anatomical Therapeutic Chemical [ATC] Classification System), ADR type (System Organ Class [SOC]), seriousness, and age and gender.

Results: We analysed 1 359 067 ADR reports corresponding to 3 013 074 ADRs. The majority of reports came from the high income group (1 160 208). An increasing reporting rate (ADR reports/million inhabitants/year) was found with increasing income: low income (3), lower-middle income (12), upper-middle income (27), and high income (130). The largest share of reports was submitted by physicians in all income groups (45–97%). Nevertheless, significant differences across income groups were found for all reporter types except one.

The distribution of total ADRs caused by ATC group J: Anti-infectives for systemic use differed significantly (Chi-square = 19.6; $p < 0.01$) among income groups and particularly in the low income group it predominated accounting for 31% of all reported ADRs. A significant difference was found for the ADR type skin and subcutaneous disorders across income groups and especially in the lower-middle income group it predominated (57%). The distribution of serious (16%) and non-serious (84%) ADRs were found to be similar across income groups. For neither age nor gender of the involved patients any significant differences was found in the ADR reporting patterns across income groups.

Conclusions: This study has illustrated that ADR reporting patterns vary across income groups with respect to reporting rates, reporter type, suspected medicines, and ADR type. Future studies should investigate the influence of other socio-economic factors on ADR reporting patterns.

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25. Suspected Adverse Drug Reactions in Children Following Immunization: Retrospective Analysis of Spontaneous Reports Over a Decade

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Background: Evidence is present that paediatric immunization prevents serious diseases, but the administration of these therapies to

Table I. Number of reported ADRs and serious ADRs (italic) for the Danish immunization programme by therapeutic groups and age groups (1998–2007)

Therapeutic groups	Age groups (y)						Total ADRs
	<2	2–3	4–6	7–11	12–13	14–17	
Immune sera and immunoglobulins (J06)							
Immunoglobulin	3 *(3)*	10 *(10)*	8 *(7)*	3 *(3)*	0	8 *(8)*	32 *(31)*
Vaccines (J07)							
MMR (measles, mumps, rubella)	692 *(243)*	44 *(15)*	8 *(2)*	40 *(19)*	49 *(16)*	5 *(5)*	838 *(300)*
Ditekipol/Act-hib	1348 *(339)*	18 *(3)*	256 *(27)*	0	0	17 *(5)*	1639 *(374)*
Gardasil (human papilloma virus)	0	0	0	0	1	10 *(7)*	11 *(7)*
Varilrix (varicella)	0	1 *(1)*	0	6 *(6)*	0	0	7 *(7)*
Influvac (influenza)	0	4 *(3)*	0	0	0	0	4 *(3)*
Meningovax (meningokok)	0	0	0	0	0	5 *(5)*	5 *(5)*
TicoVac (encephalitis)	0	0	0	0	0	1	1
Imovax (rabies)	4 *(4)*	0	0	0	0	0	4 *(4)*
Twinrix (hepatitis A and B)	0	3	4	0	0	9 *(9)*	16 *(9)*
Havrix (hepatitis A)	0	1	3	9 *(6)*	9 *(4)*	3	25 *(10)*
Engerix-B (hepatitis B)	14 *(12)*	2 *(2)*	9	0	0	0	25 *(14)*
Vivotif (Typhim Vi)	0	4 *(1)*	1	1	0	0	6 *(1)*
Japanese enchephalitis	0	3	1	0	0	1	5
Prevenar (pneumococpolysaccharides)	24 *(13)*	0	0	1 *(1)*	0	0	25 *(14)*
Total J06 and J07	2085 *(614)*	90 *(35)*	290 *(36)*	60 *(35)*	59 *(20)*	59 *(39)*	2643 *(779)*

healthy children also involves risks of adverse drug reactions (ADRs), some probably serious. The current evidence about ADRs from immunization therapy at population level is partly contradictory across countries, time periods and childhood immunization programmes.

Objective: To characterize suspected ADRs in children reported in Denmark over a decade.

Methods: We analyzed suspected ADRs reported for 0- to 17-year-olds reported to the Danish Medicines Agency from 1998 to 2007. The unit of analysis was one ADR. We analyzed data with respect to time, age of the children, category of ADRs and seriousness, reporting rate and suspected vaccines.

Results: A total of 2643 ADRs was reported, 30% of these were classified as serious. Two deaths were reported. Wide fluctuations in the number of ADRs reported annually were detected; however, the share of serious ADRs remained constant. Approximately 80% of ADRs were reported in children from 0 to 2 years of age. Forty-five percent of all reported ADRs were from the category "general disorders and administration site conditions", followed by the categories "skin and subcutaneous tissue disorders" (20% of total ADRs) and "nervous system disorders" (16% of total ADRs). The largest share of serious ADRs was from the category "nervous system disorders" (33% of serious ADRs). The reporting rate of serious ADRs was 11 per 100 000 vaccine doses for the Ditekipol/Act-Hib vaccine and 25 per 100 000 vaccine doses for the MMR vaccine. The most frequently reported serious ADRs were febrile convulsions, pyrexia and injection-site reactions.

Conclusions: In Denmark, a high number of suspected but not confirmed ADRs has reported in relation to child immunization. However, although not all ADRs are reported, the low number of serious ADRs supports the importance of immunization programmes. Data provide only a hint of the risk and not a complete picture, but the reported ADRs do not give rise to fear against immunization of children.

26. Signal Detection using Time to Event Analysis: Varenicline and Neuropsychiatric Events

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Background: Varenicline (Champix), a smoking cessation treatment, has previously been associated with neuropsychiatic events. Modelling the hazard function using time to event analyses has been proposed as a possible method for signal generation. The usefulness of using such models remains uncertain.

Objectives: To determine whether two parametric time to event models detected increasing or decreasing hazards over time for neuropsychiatic events in patients taking varenicline.

Methods: Data from a Modified Prescription-Event-Monitoring (M-PEM) study were used in this analysis. Patients were identified from dispensed prescriptions issued by primary care physicians Dec 2006 - Mar 2007. Data on exposure and events reported during first 3 months of treatment were collected from postal questionnaires. Neuropsychiatric events included were: depression, anxiety, aggression and suicidal ideation. The baseline hazard function was modelled using two parametric models (Weibull [W] and Gompertz [G]), which have a shape parameter [W = (p); G = (r)]. Evidence of a significantly increasing or decreasing hazard over time, was assumed when the 95% CI excludes the value one or zero respectively.

Results: The cohort comprised 12 159 patients. Numbers of included events reported and model shape parameters (+95% CI) are: depression [n = 94; p 1.15 (0.96, 1.37); r 0.0004 (–0.03, 0.04)]; anxiety (n = 99; p 1.27 (1.06, 1.52); r 0.009 (0.0005, 0.17)]; aggression [n = 7; p 1.28 (0.67, 2.48); r 0.004 (–0.03, 0.03)] and suicidal ideation [n = 8; p 1.00 (0.53, 1.86); r 0.01 (–0.017, 0.038)].

Conclusions: The hazard was estimated to be significantly increasing over time for anxiety (p = 0.009 and p = 0.038). None of the three other events were shown to have a statistically significantly increasing or decreasing hazard over time. The sensitivity of this signal detection method requires further evaluation.

27. Toxic Mercury Levels in Counterfeit Medicated Cosmetic in UAE and Potential of Toxicological Adverse Drug Reactions

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Background: Skin lightening (bleaching) cosmetic medications are widely used by women in UAE. They can be freely obtained without prescription in general sale stores and shops dealing in cosmetics e.g. beauty salons. The majority of these products are not licensed through Ministry of Health (MoH).

Methods: Assay of medicated Cosmetic products in national Drug quality control laboratory (QCL) of MoH, UAE from 2005 till July 2009, and identification of the counterfeit medicated cosmetics. Samples were collected via post marketing surveillance or have been referred by patients.

Results: Among 27 medicated cosmetics samples collected, total of 21 samples were counterfeits and adulterated, of which, 19 samples (70%, N = 19/27) were analyzed in QCL and found to contain high levels of mercury levels (90.5%, n = 19/21), two samples were containing undeclared Hydroquinone (10%, n = 2/20), one product contains corrosive Sodium chloride (Na Cl) and high PH level (5%, n = 1/20). 5 samples were submitted to QCL as patient complaint (23.8%, n = 5/21). Voluntary Adverse drug reaction (ADR) reporting were collected and analysed, 7 ADRs cases, 5 women (71.4%, n = 5/7) used three skin lighting creams preparation were reported ADR; reactions include; skin irritation and redness. Two women (28.5%, n = 2/7) reported burning sensation and went to see dermatologists.

Discussion: The potential ADR of these counterfeit products are very serious for example: exogenous ochronosis, impaired wound healing, wound dehiscence and fish odor syndrome, nephropathy.[1] Long term use of these compounds can cause dermatologic disorders such as dyschromia, exogenous ochronosis, acne, hypertrichosis, prominent striae, tinea corporis, pyoderma, erysipelas, scabies, and contact dermatitis and systemic complications such as hypertension, hypercorticism or surrenal deficiency, and mercurial nephropathy.[2,3] These products are not tightly controlled in the country as they are not registered in MoH and entered illegally. Analysis of products showed it contains more than permitted mercury levels (levels are higher than 1ppm). Mercury was added to enhance the bleaching effect. Since these products are used for long duration, on a large body surface area, and under hot humid conditions, percutaneous absorption is enhanced.[4]

Conclusions: In view of the health risks associated with skin exposure to higher levels of toxic mercury, patients with these complications can be common. Doctors should take a history of the use of cosmetics if patients have clinical or laboratory evidence of mercury exposure. Doctors should be aware that over-the-counter mercury-containing creams may raise the concentrations of mercury in the blood and urine to potentially toxic levels.[5]

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28. Attitudes of Hospital Doctors to Adverse Drug Reactions Monitoring in Khartoum State, Sudan (2009)

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Background: A pharmacovigilance department was established in Sudan in 2007 in order to monitor both safety and quality of registered medicines through a spontaneous reporting scheme. Unfortunately, since its inception, only 87 reports have been collected giving an overall reporting rate of less than 1% of the theoretical optimal.

Aim: To assess hospital doctors' attitudes and perception regarding the spontaneous reporting scheme and to study their suggestions to improve it.

Method: A self-administered questionnaire was distributed randomly among 250 physicians working in eight public hospitals in Sudan.

Results: The overall response rate was 60.8%. 78.9% of the respondents had ever suspected an ADR and only 33.3% had reported ADR before. The ADR with highest probability of being reported were severe reactions (85.5%), reactions to new marketed drug (72.4%) and unusual reactions (71.1%). Major justifications for not reporting were lack of awareness of the scheme (71.1%), unavailability of the reporting form (61.2%), absence of reporting guidelines (61.2%) and ignorance of how to report (52.6%). Awareness and training initiatives were suggested to improve reporting practice.

Conclusions: This study indicates some of the reasons why only a few doctors report an ADR. These reasons are believed to be potentially changeable through promotional and educational interventions.

29. Levonorgestrel/Ethinylestradiol (MINIDRIL®)-Induced Cytolytic Hepatitis

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We report a case of levonorgestrel/ethinylestradiol (MINIDRIL®)-induced cytolytic hepatitis confirmed with liver biopsy.

A 28-year-old female with no medical history, received contraceptive pill (levonorgestrel/ethinylestradiol) since January 2008 and isotretinoin for acne since July 2008. On 18-December-2008, laboratory tests performed before dermatological visit revealed elevated alanine aminotransferase (ALT) levels at 226 IU/L (7 times the normal level [N], normal levels <31 IU/L), aspartate aminotransferase (AST) levels at 93 IU/L (3N, normal levels <31 IU/L), and gamma glutamyl transpeptidase (GGT) at 37 IU/L (normal levels are 7–35 IU/L) and alkaline phosphatase (ALP) levels at 92 IU/L (normal levels are 35–120 IU/L). Total bilirubin (BT) (6 µmol/L, normal levels are 3–17 µmol/L) and prothrombin time (97%) and there was no peripheral blood eosinophilia. Transaminases elevation was related to isotretinoin and it was discontinued four days later. Another laboratory tests performed after isotretinoin discontinuation revealed persistence of transaminases elevation with progressive aggravation (table I).

Table I. Laboratory values (relates to abstract no. 29)

Dates	ALT (×N)	AST (×N)	GGT (×N)
18-12-08	7	3	1
02-01-09	11	3	1
09-02-09	15	6.6	<1
19-02-09	19.5	8	1
23-02-09	25	13	1.1
02-03-09	31	13	<1
06-03-09	**Contraceptive pill discontinuation**		
17-03-09	5.3	1.1	<1
11-04-09	<1	<1	<1

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **GGT** = gamma glutamyl transpeptidase.

Table I. Laboratory values (relates to abstract no. 30)

Dates	ALT (×N)	AST (×N)	GGT (×N)
02-Feb-09	3.5	2	<1
18-Feb-09	10.3	4.3	
23-Mar-09	14	7	<1
11-Apr-09	18	8	<1
06-May-09	17.3	10	<1
07-May-09	23	13.6	<1
	Contraceptive pill discontinuation		
11-May-09	21	12	<1
28-May-09	1.3	<1	<1

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **GGT** = gamma glutamyl transpeptidase.

On 02-March-2009, the patient was admitted in hospital, her temperature was 37.2°C, and her vital signs were stable. Her abdomen was soft without hepatosplenomegaly and she had no rash, no jaundice and no pruritus. She had no history of alcohol consumption, and there was no recent travel history. She had never received blood transfusions, and did not use intravenous drugs. The patient denied taking any other medications except contraceptive pill. She denied using any herbal and folk remedies. During her hospitalization, the monitoring of liver function showed severe aggravation of cytolysis (table I). Viral serologies for hepatitis including hepatitis A, B, C, D and E viruses, cytomegalovirus, Epstein-Barr virus, HIV and herpes simplex virus were all negative. Autoantibodies (antinuclear, antimitochondrial, anti-smooth muscle, anti-liver-kidney microsomal antibodies, and anti-soluble liver antibodies) were also negative. Alpha-one anti-trypsin, and ceruloplasmin were within normal limits. Hepatobiliary imaging with ultrasonography, Doppler, abdominal computed tomography scan was normal. An endoscopic retrograde cholangiopancreatogram was also normal. Because no causal factor for cytolytic hepatitis was found after the initial work-up, the responsibility of contraceptive pill was suspected and consequently, it was discontinued on 06-March-2009. The liver biopsy found focal necrosis in peri- and centro-lobular areas with ductular reaction compatible with drug hepatitis. There was no sign of underlying chronic liver disease. No evidence of tumoral or metabolic etiology. After pill discontinuation, hepatic abnormality rapidly decreased and became normal one month later (table I). According to the Naranjo probability scale, cytolytic hepatitis related to contraceptive pill was probable.

30. Levonorgestrel/Ethinylestradiol (ADEPAL®)-Induced Cytolytic Hepatitis

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Oral contraceptives (OC) frequently produce mild hepatocellular dysfunction. Three major categories of adverse hepatic effect have been linked to the use of OC: hepatic dysfunction, cholestatic jaundice, and benign hepatic tumors. We report a case of levonorgestrel/ethinylestradiol (ADEPAL®)-induced cytolytic hepatitis.

A 29-year-old female with no medical history, received contraceptive pill (ADEPAL®) since July 2008. On February 2, 2009, laboratory tests performed before gynecological visit revealed elevated alanine aminotransferase (ALT) levels at 111 IU/L [3.5 times the normal level (N), normal levels <31 IU/L], aspartate aminotransferase (AST) levels at 63 IU/L (2N, normal levels <31 IU/L). All the rest of hepatic parameters were within normal limits and there was no peripheral blood eosinophilia. A monitoring of liver function showed progressive aggravation of cytolysis (table I). On May 3, 2009, the patient was admitted in hospital, she had a good general condition, and physical examination was negative. She had no rash, no jaundice and no pruritus. She had no history of alcohol consumption, and there was no recent travel history. She had never received blood transfusions, and did not use intravenous drugs. The patient denied taking any other medications except contraceptive pill. She denied using any herbal and folk remedies. Viral serologies for hepatitis including hepatitis A, B, C, D and E viruses, cytomegalovirus, Epstein-Barr virus, HIV and herpes simplex virus were all negative. Autoantibodies (antinuclear, antimitochondrial, anti-smooth muscle, anti-liver-kidney microsomal antibodies, and anti-soluble liver antibodies) were also negative. Alpha-one anti-trypsin and ceruloplasmin were within normal limits. Hepatobiliary imaging (ultrasonography, Doppler, abdominal computed tomography scan and endoscopic retrograde cholangiopancreatogram) was normal. Because no causal factor for cytolytic hepatitis was found, the responsibility of contraceptive pill was suspected and consequently, it was discontinued on May 7, 2009. The liver biopsy displayed moderate necrosis in lobular and peri-portal areas with mixed cellular infiltrate in portal tracts includes lymphocytes and histiocytes and minim ductular reaction compatible with drug-hepatitis. There was no sign of underlying chronic liver disease. No evidence of immunological, tumoral and metabolic etiology. After contraceptive pill discontinuation, hepatic abnormality rapidly decreased and became normal three weeks later (table I). An objective causality assessment scale (RUCAM) suggested that contraceptive pill could "probably" be related to the patient's cytolytic hepatitis (score = 6).

31. Amiodarone-Induced Mild Acute Pancreatitis

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Only five cases of amiodarone-induced pancreatitis have been reported in international literature. We report the sixth case of acute pancreatitis during amiodarone therapy.

An 89-year old woman with a medical history of hypertension diabetes mellitus, chronic renal insufficiency, gout and cholecystectomy, received

Table I. Characteristics of literature cases of amiodarone-induced pancreatitis and the present case

Study (y)	Age/Sex	Serum lipase (normal value)	Serum amylase (normal value)	Dechallenge of amiodarone	Re-challenge of amiodarone	Causality relationship
Sastri SV et al. (1990)	67/M	38 (6–20)	64 (0–45)	No	No	Dubious
Munoz RAI et al. (1996)	67/M	546 (not applicable)	387 (70–220)	Yes	No	Possible
Bosch X et al. (1997)	46/F	946 (0–190)	1480 (17–115)	Yes	Yes	Certain
Famularo G et al. (2004)	80/M	548 (10–140)	732 (0–95)	Yes	No	Possible
Chen YY et al. (2007)	66/F	395 (0–30)	109 (0–220)	Yes	No	Possible
Present case (2010)	64/F	1736 (23–300)	Not available	Yes	No	Possible

the following drugs omeprazole, lercanidipine, furosemide, trimetazidine, and paracetamol as necessary. On 05-October-2009, she was hospitalized for acute pneumopathy with a favourable evolution under antibiotic therapy (piperacillin, tazobactam and amikacin). On 20 Octber 2009, the patient experienced episode of atrial fibrillation and she received amiodarone as an oral loading unspecified dose and then a maintenance dose of 200 mg per day. At this time, pancreatic (lipase: 48 IU/L, normal levels are 23–300 IU/L) and liver enzymes were again within the normal range. On 05-November-2009, the patient experienced moderate abdominal pain that radiated back and to her right flank. In clinical examination, the patient had a regular general condition, no fever (37.3°C). The abdomen was soft and depressible, with pain upon deep palpation. There were no abdominal masses and bowel sounds were present. The remainder of the examination was normal. Laboratory data showed moderate leucocytosis (11.1×10^9/L) with a normal differential count and serum lipase was 1736 IU/L, (6 times the normal level [N]) and 1980 IU/L, near 7N on 06-November-2009, but serum amylase was not performed. Lipid analysis (cholesterol, and triglyceride), calcium level, glycaemia, urine analysis, liver and renal functions were within normal range. Serologies of infectious agents were negative. Abdominal ultrasonography and abdominal computed tomography demonstrated no dilatation of intrahepatic ducts or common bile duct, no stones, no pancreatic enlargement or necrosis. A diagnosis of mild acute pancreatitis with a Ranson's score of 2 was made. There was no history of alcohol consumption or chronic diseases. The patient did not have any exposure to toxic chemicals or travel overseas. Because no causal factor for pancreatitis was found after the initial work-up, acute pancreatitis related to amiodarone was suspected. Amiodarone was discontinued 24 hours later when lipase reached 1980 IU/L. Intravenous fluids were administered and fasting advised. This leaded to a gradually decrease of pancreatic enzyme and abdominal pain. Five days after the antiarrhythmic treatment was stopped and the patient was going well, she suddenly died at the night. Physical and electrocardiogram examination was normal few hours before. A likely cardiac dysrhythmia was incriminated. According to the Naranjo probability scale, amiodarone-induced acute pancreatitis was possible.

32. Reversible Mixed-Type of Liver Injury Related to ANDROCUR® (Cyproterone Acetate) Therapy

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We report the case of a patient who developed a reversible mixed-type of liver injury related to Cyproterone acetate therapy for prostate cancer.

A 57-year-old male patient with a medical history of prostate cancer treated with CPA since February 2009, he was hospitalized on 12-Jun-2009 for mixed-type of liver injury. The biologic work up showed cholestasis and hepatic cytolysis with alanine aminotransferase (ALT) levels at 2340 IU/L (52 times the normal level [N], normal levels <45 IU/L), aspartate aminotransferase (AST) levels at 1435 IU/L (41N, normal levels <35 IU/L), and gamma glutamyl transpeptidase (GGT) at 385 IU/L (7N, normal levels <55 IU/L) and alkaline phosphatase (ALP) levels at 240 IU/L (2N, normal levels are 30–120 IU/L). Total bilirubin (BT) (171 μmol/L = 10N, normal levels are 5.1–17.1 μmol/L) and prothrombin time 55%.

He had a good general condition, clinical examination showed important jaundice but no hepatosplenomegaly and no neurologic symptoms. He had no history of alcohol consumption, and there was no recent travel history. He had never received blood transfusions, and did not use intravenous drugs. The patient denied taking any other medications except CPA. He denied using any herbal and folk remedies.

Viral serologies for hepatitis including hepatitis A, B, C, D and E viruses, cytomegalovirus, Epstein-Barr virus, HIV and herpes simplex virus were all negative. Autoantibodies (antinuclear, antimitochondrial, anti-smooth muscle, anti-liver-kidney microsomal antibodies, and anti-soluble liver antibodies) were also negative. Alpha-one anti-trypsin and ceruloplasmin were within normal limits. Hepatobiliary imaging (ultrasonography, Doppler, abdominal computed tomography scan and endoscopic exploration) was normal. Because no causal factor for mixed liver injury was found, the responsibility of CPA was suspected and consequently, it was discontinued on 17-Jun-2009. The patient was switched to ursodeoxycholic acid (DELURSAN) with corticotherapy. The liver biopsy showed hepatitis with severe necrotico-inflammatory lesion with moderate fibrosis. Mixed cellular infiltrate in portal tracts includes lymphocytes and histiocytes compatible with drug- hepatitis. There was no sign of underlying chronic liver disease. No evidence of immunological, tumoral and metabolic etiology. Mixed liver injury induced by Cyproterone acetate was retained. After CPA discontinuation, the patient improved quickly, the hepatic abnormality rapidly decreased and two months later was became nearly the normal levels with ALT (1.2 × ULN), ASAT (2 × ULN), PAL (1 × ULN), and total bilirubin 26 (1.2 × ULN) and became normal on 23-Sep-2009. An objective causality assessment scale (RUCAM) suggested that CPA could "probably" (score = 6) be related to the patient's mixed-type of liver injury.

33. The Association Between Statin Use and Systemic Lupus Erythematosus Using Spontaneous Reports

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Introduction: Several studies have shown that statins have anti-inflammatory and immunomodulatory properties which may influence

immune responses.[1,2] Therefore, statins may facilitate the development of autoimmunity and eventually resulting in autoimmune diseases. Several case reports of systemic lupus erythematosus (SLE) suggest that statins could trigger the development of this rare autoimmune disease.[3] However, data on the association between statin use and SLE are scarce.
Aim: To assess the association between statin use and the occurrence of SLE.
Methods: Based on spontaneous reports listed in the World Health Organisation (WHO) Adverse Drug Reactions Database (Vigibase), a case/non-case study was conducted. According to WHO adverse reaction terminology, cases were defined as reported ADRs of SLE reactions and verified by a test for the presence of lupus erythematosus cells and/or antinuclear antibodies. Non-cases were all other reports and were sampled by age, gender and time of reporting. Exposure of statins was classified according to the Anatomical Therapeutic Chemical (ATC) classification code system. Potential confounding factors, namely, use of corticosteroids, immunosuppressive and cardiovascular drugs, were determined. Multivariate logistic regression was used to calculate the reporting odds ratios (RORs) with 95% confidence intervals (CI).
Results: We identified 398 reports of SLE as cases and 27 092 reports as non-cases. Cases were more often users of statins (7.5%) compared to non-cases (2.7%). After adjustment for potential confounders, use of statins was associated with SLE (ROR 2.50; 95% CI 1.68, 3.73).
Conclusions: Using Vigibase, we found a possible association between statin use and SLE. Observational pharmacoepidemiological studies are needed to study and confirm this finding in more detail.

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34. Applying Data-Mining Techniques to Paediatric Data within the WHO-UMC Database; the Impact of Vaccines

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Background: Adverse drug reactions (ADRs) are collected in international databases like the Vigibase database of the WHO-UMC. These databases contain millions of ADRs including those in children.
In recent years, measures of disproportionality for detection of new safety-signals have been developed. Examples are the reporting odds ratio (ROR), the proportional reporting ratio (PRR) and the information component (IC). These methods have proven their value as a hypothesis generating tool. But to our knowledge, they have not been tested nor specifically applied to paediatric data.
Objectives: To compare three datamining methods in paediatric data, taking into account child specific conditions.
Methods: All spontaneous paediatric ICSRs received by the WHO-UMC between 2001 and 2006 were analysed.
For the drug exposure and adverse drug reactions of interest, we calculated the ROR, PRR and IC with 95% CI. All analyses were performed on a drug-ADR basis. The estimates were recalculated stratifying on age-categories and drug-classes.
Results: The WHO-UMC database comprised 218 840 paediatric ICSRs containing 812 415 records, of which 64% were vaccine related; this percentage is highest in the youngest children (86% 0–1y).
Exclusion of vaccine related records had a profound effect on the estimates of the ROR and PRR, while the IC remained more stable. As an example; for acetylsalicylic acid and Reyes syndrome the estimates (95% CI) changed as follows after excluding vaccines: ROR from 575 (339–978) to 208 (123–354), PRR from 563 (334–951) to 204 (121–344) and IC from 4.6 (4.0–5.2) to 4.4 (3.8–5.0). The effect of exclusion of vaccines was largest in the group with the highest proportion of vaccines.
Conclusions: The magnitude of the ROR and PRR were highly influenced by the proportion of vaccines within the database. The IC was more stable when vaccines were excluded from the analyses.
The performance of these methods shows that paediatric signal generation needs to be addressed carefully.

35. H1N1 Influenza Vaccine in Pregnant Women: French Pharmacovigilance Survey

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Pregnant women are at high risk for complications of A(H1N1) influenza (higher risk of hospitalization and mortality). For this reason, public health authorities have listed pregnant women as a priority group for vaccination. Several studies suggest that inactivated seasonal influenza vaccines are safe during pregnancy but there is no available data about effects of new A(H1N1) vaccines on pregnant women.
All spontaneous reports of Adverse Drug Reactions (ADRs) following A(H1N1) vaccination in pregnant women recorded by the 31 French Regional Pharmacovigilance centres in the National Pharmacovigilance database were investigated.
Between October 2009 (beginning of the vaccination campaign) and March 2010, 30 "serious" ADRs were notified to the French network of PharmacoVigilance: 13 intra-uterine deaths, 12 spontaneous abortions and 5 other cases. Intra-uterine deaths were diagnosed 7.9 ± 7.5 [1–23] days after vaccination. Mean gestational age of occurrence of intra uterine death was 28 ± 4 weeks of pregnancy. In 6/13 cases, risk factors were identified (umbilical cord striction, eclampsia, hydatiform mole, infections). Spontaneous abortions were reported for women at 11 ± 4 weeks of pregnancy. They occurred 17.2 ± 16 [1–56] days after vaccination. The 5 other cases were stillbirth, fetal tachycardia, uterine contractions/fetal arrhythmia, respiratory distress and anamnios/intra-uterine growth retardation. No causal relationship between immunization and in utero fetal death or spontaneous abortion was established.
This report summarizes the first French data about spontaneous notifications of ADRs following A(H1N1) vaccination in pregnant women. ADRs reporting systems are designed to detect signals of concern. Epidemiological studies will allow to quantify potential risk of A(H1N1) vaccines in pregnant women.

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36. Spontaneous Reports as a Source for Risk Assessment of Long Term Drug Use in Children

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Background: There is an urgent need for data on safety of drugs used in children. Especially knowledge on risks during long term use of drugs is sparse.

Objectives: Explore whether the WHO-UMC spontaneous reporting database is a valid tool to study adverse drug reactions (ADRs) in children being long term exposed to drugs.

Methods: From all spontaneous paediatric ADR reports received by the WHO-UMC until 2006 we selected ADRs occurring after long term use (≥6 months).

We focused on drugs known to be chronically used in children like antidiabetics, immunosuppresives and anti-epileptics.

Results: In 553 811 of the 812 415 ADR records (68%) information on duration of use of drugs was available; 15 668 records (3%) concerned use ≥6 months. In this group of records on long term use most frequently reported drugs were isotretinoin (10%), atomoxetine (6%), and paroxetine (4%).

Most reported drug-ADR combinations were depression (0.9%) and suicide attempt (0.5%) in isotretinoin and menstrual disorders in levonorgestrel users (0.4%).

37% (n = 284) of the reports received for antidiabetics concerned long term use. Most frequent long term ADRs were hyperglycaemia (9%), hypoglycaemia (9%) and ketosis (6%).

Long term use was present in 9% (n = 324) of the ADRs concerning immunosuppresives; methotrexate (30%) and etanercept (26%) were most frequently implicated. Most frequent combinations were malignant lymphoma in azathioprine (2%) or tacrolimus (2%), and thrombocytopenia in eternacept (2%).

15% (n = 1226) of the ADRs related to antiepileptics concerned long term use. Valproic acid was most frequently reported (37%). Most frequent reported combinations were visual field defects in vigabatrin users (3%) and pancreatitis in valproic acid (2%).

Conclusions: Information on duration is lacking in 32% of all reported ADRs, 3% of the available records concerned long term use.

Detection of ADRs associated with long term drug use is possible, however underreporting may be even more important compared to acute reactions.

37. Adverse Drug Reactions in Children Medical Inpatients in Mali: Prospective Observational Study

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Introduction: Adverse events during antiretroviral treatment (ART) are frequent and various.[1-3] Their diagnosis occur some difficulties in different orders according to the geographical context.

Aim: To describe the frequency, nature and preventability of community-acquired and hospital-acquired adverse drug reactions (ADRs) in Malian children.

Method: A 6 months prospective observational study of 36 children admitted to Wale ONG hospital in Segou. It was a prospective and observational study which lasted 6 months from 1st October 2009 to 31st March 2010. The patients were treated with the generic drug. Prior to treatment initiation, demographic characteristics, clinical history and biological parameters including CD4 cell counts, were collected for each patient. WHO's sides effects classification has been used to characterize the side effects.[4] Analysis of data has been done in the Software SPSS version 12.0.

Results: 36 children's HIV infected patients meet the criteria of Inclusion. After 24 weeks of treatment, we observed that 30.6% of children had at least one side effect during our study. The regimen has been most effective in our study is secondary (AZT/3TC/NVP) with 34.3%. Side effects that many were as varied and most observed were vomiting, diarrhea, respectively 63.6% and 54.5%. The side effects dominated by digestive disorders (83.4%). Adverse effects and toxicities were grade 1 and 2 with 63.6% of cases of vomiting of grade 2. We did not observe side effects of grade 3 or 4 during our study. The regimen of treatment was unchanged at 94.4% of children.

Conclusions: ADRs are an important, often preventable cause of hospitalizations and inpatient morbidity in Mali, particularly among children HIV- infected. We recommend a pharmacovigilance system for sustainable management of side effects in patients infected with HIV in Mali.

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38. Intensive Pharmacovigilance Monitoring for Influenza Vaccines and Antiviral Drugs Used During the Influenza A(H1N1)v Pandemic: The French Experience

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Introduction: In the context of the national mass immunization program against the pandemic (H1N1) 2009 virus and expected important use of antiviral drugs, safety of vaccines and antivirals was monitored by Afssaps in close collaboration with the national pharmacovigilance centre network.

Aim: To monitor, record and evaluate adverse drug reactions (ADRs) occurring after administration of pandemic influenza A(H1N1)v vaccines and antiviral drugs (oseltamivir, zanamivir) from October 2009 to 28 March 2010 for vaccines and to 26 April 2010 for antivirals.

Methods: In addition to the European risk management plan (RMP), Afssaps implemented a national RMP covering 3 key areas: proactive monitoring of ADRs and medication errors, regular updates on ADRs information on the Afssaps website, and the setting up of pharmacoepidemiological studies (pregnancy cohort, case-control study on Guillain-Barre syndrome). To achieve this, Afssaps developed specific reporting forms, offered the possibility to report ADRs through its website, mandated a specific group of clinicians to review cases of auto-immune complications and improved electronic exchanges with stakeholders.

Results: By the end of March, more than 5.7 million patients were vaccinated in France against influenza A(H1N1)v, mainly with Pandemrix® (4.1 M) and Panenza® (1.6 M). Overall, 4428 cases were received, including 3855 for Pandemrix® and 549 for Panenza®. Most ADRs were non-serious and expected. Only 5% of ADRs were serious for Pandemrix® and 16% for Panenza®, including neurological reactions (paraesthesias with Pandemrix® and febrile convulsions with Panenza®) and general reactions (influenzae reactions, fever). As a more specific ADR for Pandemrix®, this monitoring evidenced isolated cases of ascending paraesthesias (not suggestive of GBS) with a favourable but sometimes prolonged outcome.

For antivirals, more than 640 000 patients were treated by oral oseltamivir or inhaled zanamivir; 34 patients received intravenous zanamivir in the context of temporary authorisations for use. By the end of April, 210 reports were recorded for oseltamivir, 4 for inhaled zanamivir and 14 for intravenous zanamivir. Most frequently reported ADRs for oseltamivir were gastrointestinal, cutaneous, allergic or neuropsychiatric. The observed safety profiles were as expected.

Finally, a total of 22 bulletins (17 for vaccines) were published on the Afssaps website during the period under review.

Conclusions: Beside isolated and transient ascending paraesthesias, spontaneous ADRs reported in France for vaccines and antiviral drugs were in accordance with the expected safety profiles. However, further analyses, including pharmacoepidemiological studies are necessary to confirm these data.

39. Additional Safety Risk to Exceptionally Approved Drugs in the EU?

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Background: Sometimes serious adverse drug reactions (ADRs) are identified post approval, which need to be communicated through Direct Healthcare Professional Communications (DHPCs). Does this occur in particular when marketing authorisation (MA) is obtained under Exceptional Circumstances (EC) or as Conditional Approval (CA), when a drug is allowed to the market based on limited data?

Objectives: To assess whether licensing under EC or CA leads to more frequent and more rapid identification of serious safety issues resulting in a DHPC.

Methods: A retrospective cohort study was performed of DHPCs issued between '99 and '09 for new drugs in Europe. The determinant was EC/CA vs regular registration. Outcome variables were frequency and timing of a first DHPC. Chi square test was used to assess an association between registration procedure and number of drugs with ≥1 DHPC. The effect on time from MA to DHPC was assessed using Kaplan-Meyer (KM) survival analysis and Cox-regression to correct for possible confounders. Possible confounders evaluated were related to drug (ATC-2 level, first-in-class [y/n] and small molecule/biological), registration process (appeal [y/n], risk management plan [y/n], conditions imposed [y/n] and orphan [y/n]) and size of safety population in pre-registration clinical program (>1500 patients [y/n]).

Results: We identified 284 new drugs registered in the study period. Forty-seven (16.5%) received an MA under EC or CA of which seven (14.9%) received ≥1 DHPC. This was not different from the drugs that were regularly approved 33 (13.9%) with ≥1 DHPC (p = 0.861). The KM derived probability of acquiring a DHPC for regular and for EC/CA drugs during 3 years follow up is 10.0% (95% CI: 6%, 14%) and 7.0% (95% CI: 0%, 15%) and 11 years follow up is 22.0% (95% CI: 15%, 30%) and 26.1% (95% CI: 8%, 44%), respectively (Log-Rank p = 0.79). This difference remained not significant in the confounder-corrected Cox-regression model: hazard ratio 1.06 (95% CI: 0.44, 2.53)). Only the drug type (ATC-2 level) was identified as a confounder.

Conclusions: EC/CA registration does not increase the risk of a first DHPC after MA. The EC/CA procedure does not lead to more unforeseen safety problems despite these drugs had limited clinical development packages.

40. Impact of Regulatory Risk Communication in the Netherlands: 48 Time Series Analyses

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Introduction: Impact of Direct Healthcare Provider Communications (DHPCs) or 'Dear Doctor Letters' has shown contradictory results, in a limited number of drugs, mainly in the USA. A comprehensive review of their impact in the Netherlands is lacking.

Aim: To evaluate impact of DHPCs on drug use in ambulatory care in the Netherlands.

Methods: We evaluated impact of DHPCs (source: Dutch Medicines Evaluation Board) on new prescriptions in ambulatory care (new Rx = no previous drug use in 6 months) from Jan. '01 to Jan. '08 using interrupted time series analyses. Drugs with >10 Rx/month were retrieved from the Dutch Foundation for Pharmaceutical Statistics (SFK), comprising dispensing data of 90% (15 million) of the Dutch population. We developed appropriate autoregressive, integrated, moving average (ARIMA) models for each drug taking seasonal periodicities and underlying trends into account. We then explored impact of recommended action [adapt prescribing/monitor patient], repeated DHPCs [yes/no] and volume of drug use [low, medium and high (tertiles)] on the effect of DHPCs as determined in these ARIMA models using chi-square tests.

Results: In the study period 70 DHPCs were issued for 55 drugs. To date, we evaluated 61 DHPCs issued for 48 drugs. Forty-five (74%) DHPCs recommended to adapt prescribing and 18 (30%) were repeated DHPCs. Drug use ranged from 13 to 46 403 Rx/month, with tertiles for low, medium and high volume defined as <123, 124–948 and

>948 Rx/month respectively. Fourteen (22%) DHPCs for 13 drugs (cisapride, rosiglitazone, pioglitazone, desogestrel/ethinylestradiol, tamsulosin, lopinavir, atazanavir, anakinra, celecoxib, strontium ranelate, paroxetine, bupropion, venlafaxine) showed a change in use ($p < 0.05$). Recommended action or repeated DHPCs had no differential impact on effect of DHPCs. However, volume of use did; 3/21 (14%), 2/20 (10%) and 10/20 (50%) DHPCs for low, medium and high volume drugs were associated with a change in use ($p = 0.005$; $\chi^2 = 10.6$). We will extend the analyses to all identified DHPCs and drugs.

Conclusions: Our initial analyses show that approximately a quarter of DHPCs issued affected drug use. For now, mainly high volume drug use, but not repeated DHPCs or DHPCs restricting drug use appeared to affect this impact.

41. Participation of General Practices in a Swine Flu Vaccination Study

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Background: General practices often act as gateways as to whether their patients participate in research.[1,2] In an academic questionnaire study of the safety of swine flu vaccination, study materials were sent to 1015 general practices in Scotland in late 2009. Practices were asked to display posters, make study forms available to patients having vaccination and return completed forms in batches.

Objective: To determine levels of participation of practices and reasons why they took part or not.

Methods: We attempted to contact practice managers of a random 10% sample of the practices to ask whether they were participating in the study, who had made the decision and reasons for participation or not. Results are reported as numbers and/or percentages.

Results: 81 of the 102 (79%) practice managers could be contacted. 9 reported that their practice had not received the study information. Of the 72 who received it, 24 (33%) stated that their practice was participating in the study and 48 (66%) not participating. The decision whether to participate was made by: joint meeting 50%, general practitioners 29%, practice manager 18%, nurse 3%, unknown 8%. The most common reasons for participation were: 'no reason' 33%, 'interest in this particular study' 17%, 'easy to take part' 17% and 'swine flu important problem' 13%. The most common reasons for non-participation were: 'too busy' 69%, 'heard about the study too late' 11%, 'potential conflict between encouraging vaccination and a vaccine safety study' 6% and 'no reason' 6%.

Conclusions: Engagement of primary care is often key to the success of research. In this topical and simple questionnaire study requiring minimal staff input, only 1/3 of practices participated. Better understanding of how to engage primary care teams with research and how to make research easy to perform in the context of the heavy workload of primary care settings is required.

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42. Current Challenges in Drug Safety: A Perspective from the Pharmaceutical Industry

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Introduction: The regulations underpinning the pharmacovigilance (PV) activities of the pharmaceutical industry have had plenty of time to mature following their genesis in the wake of the thalidomide tragedy in the 60s. Nevertheless major challenges remain.

Challenges: (1). How to keep your drug on the market: In the last decade at least 15 drugs have been permanently withdrawn from the market due to safety concerns, e.g. Vioxx (rofecoxib), Baycol, Lipobay (cerivastatin),[1,2] and the pharmaceutical industry has consistently been in the top 10 on the list of the most crisis prone industries.[3] (2). Securing sufficient investment in PV can be an uphill battle: PV does not directly generate sales, and is often perceived by management to drain scarce resource. (3). High profile drug withdrawals have led to the introduction of more local regulations for industry to contend with often with little global coordination, e.g. Vol 9a EU-RMP v FDA REMS in the US. (4). Regulators are increasing their scrutiny of manufacturers: One PV system can be inspected by several local or regional inspectorates in the same year with little in the way of cross border coordination. (5). Increased scrutiny and risk averseness predicted to have negative consequences for patients unless tools and processes are developed to minimise false signals and consequent delayed or refused licenses.[4] (6). Single digit sales growth[5] compared to double digits a few years ago mean a greater quest for efficiency - for PV the question is not whether to offshore, but where and what processes to offshore.

Conclusions: PV has many challenges to contend with, several could be tackled through improving efficiencies by adopting a more global approach both with respect to the harmonisation of regulations and also with respect to adopting a more global approach in the creation of operating models, which in turn might free up much needed resource to improve tools for safety science.

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43. Vildagliptin: First Results of the French National Pharmacovigilance Enquiry

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Vildagliptin belongs to a new class of oral anti-diabetic drugs and is indicated in type 2 diabetes mellitus. It acts as a selective and reversible inhibitor of Dipeptidyl peptidase 4 (DPP-4), an enzyme which

inactivates the incretin hormones, glucagon-like peptide-1, and glucose-dependent insulinotropic polypeptide. It is used together with another antidiabetes medicine when the patient's diabetes is insufficiently controlled by this other medicine taken alone. It can be used with metformin, a thiazolidinedione or a sulphonylurea, but it is only used in combination with a sulphonylurea in patients for whom metformin is contraindicated or not tolerated.

Safety data were obtained from a total of 3784 patients exposed to vildagliptin in controlled trials of at least 12 weeks duration. Of these, 2264 patients received vildagliptin as monotherapy and 1520 patients received vildagliptin in combination with another medicinal product. The most common adverse drug reactions reported at a higher frequency compared to placebo were:

- in monotherapy: dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia
- in combination with metformin: tremor, headache, dizziness, fatigue and nausea
- in combination with pioglitazone : peripheral oedema, headache and asthenia
- in combination with sulphonylurea : tremor, weight gain, headache, dizziness, asthenia, constipation and nasopharyngitis.

The most important identified risks related to vildagliptine were transaminase elevation and angioedema. Furthermore, important potential risks exist such as hypoglycemia, skin lesions, cardiac conduction disturbances, gastrointestinal haemorrhage, neuropsychiatric events, infection and muscle events.

Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) have been marketed in France in August 2009. In addition to a European risk management plan (RMP), the French competent authority (Afssaps) set up a French national pharmacovigilance enquiry conducted by Paris-Henri Mondor Pharmacovigilance Centre, in collaboration with the qualified person responsible for pharmacovigilance of the marketing authorization holder. The aim of this enquiry is to perform a particular monitoring of vildagliptin safety profile in France after its commercialization. All reports of serious adverse reactions (SAR) suspected to be related to vildagliptin use in France are prospectively analyzed from August 2009.

This work will present the first results of the analysis of the reports of SAR notified from August 2009 to August 2010.

44. Adverse Drug Reactions of Biologicals: Evaluation of a New Classification System Using the WHO-ADR Database Vigibase

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Background: Biologicals have specific characteristics and carry specific drug hazards. Therefore, a new classification system for adverse drug reactions (ADRs) was proposed; type α (high cytokine and cytokine release syndrome), β (hypersensitivity), γ (immune (cytokine) imbalance syndrome), δ (cross-reactivity) or; ε (non-immunological side effects) ADRs.[1] Clustering of ADRs will be helpful for pharmacovigilance and risk management. However, this classification system has not been evaluated.

Objectives: To evaluate the proposed classification system for ADRs for biologicals using the WHO-ADR database VigiBase.

Methods: Data were obtained from the ADR database (VigiBase) maintained by the WHO Collaborating Centre for International Drug Monitoring. ADRs reported for cytokines, antibodies and fusion proteins (as specifically addressed by Pichler) approved between January 1995 and December 2008 included and classified according to the five categories. No type δ ADRs and only two type α ADRs, that were reported for a limited number of biologicals, could be selected. Therefore, these classes were not taken into account. For the selected ADRs Reporting Odds Ratios (RORs: reports for small molecules as reference) were calculated. Based on the RORs cluster analysis and pair-wise dissimilarities between pairs of ADRs were calculated (average pair-wise dissimilarity shown between brackets). A pair-wise dissimilarity of 0 means that the pair of ADRs are perfectly correlated whereas a dissimilarity of 2 means that the pair of ADRs are anti-correlated (NCSS 2007).

Results: Cluster analysis of 17 type β ADRs, 21 type γ ADRs, and 24 type ε ADRs resulted in seven clusters. **Cluster 1**: 2 β, and 22 ε ADRs (1.29); **cluster 2**: 1 β, and 13 γ ADRs (1.09); **cluster 3**: 2 β and 4 γ ADRs (0.94); **cluster 4**: 3 γ ADRs (0.76); **cluster 5**: 5 β ADRs (1.09); **cluster 6**: 2 β ADRs (0.81) and **cluster 7**: 4 β ADRs (0.59). The type β ADR injection site reaction and the type γ ADR psoriasis were not clustered in any cluster. Based on the calculated pair-wise dissimilarities, combinations of type β ADRs (1.18), γ ADRs (1.06), and β with γ ADRs (1.19) show more correlation compared to combinations of type β with ε (1.33) and γ with ε ADRs (1.34).

Conclusions: The proposed classification system seems to be valid for differentiation between the immunological β and γ ADRs and the non-immunological ε ADRs, which will be helpful during signal detection. However, differentiation is less clear between the immunological β and γ ADRs.

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45. What Information can Provide Pharmacovigilance in Non-Commercial Clinical Trials to Marketed Drug Safety Profile?

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Background: Clinical trials' and post-marketing pharmacovigilance share the same purpose but have different methodology and legislation. They are respectively based on reporting of serious adverse events from a selected population and on spontaneous reporting of adverse drug reactions from a general population.[1-3]

Aim: The aim of this study is to assess whether non-commercial clinical trials' pharmacovigilance could add information to classical post-marketing pharmacovigilance.

Methods: Post-marketing and clinical trials safety data were respectively extracted from the French Pharmacovigilance Database (FPD) and from the Assistance Publique - Hôpitaux de Paris clinical trials database, which is currently the first European non-commercial sponsor. All serious adverse reactions (SARs) to rituximab and sunitinib, recorded until 15th March 2009 from adult people, were analysed. These 2 drugs were selected because of their marketing date: one recent, with few post-marketing safety data, and one older, with a lot

of post-marketing safety data. Patient sex, age at time of reaction, type and distribution of SARs in the MedDRA® System Organ Class, outcome, seriousness, causality and expectedness assessment of SARs were mainly investigated.

Results: For rituximab, of the 114 reports included from the FPD, 25% have a high causality assessment with 9 SARs not listed on the summary product characteristics (SPC). Of the 20 reports included from the clinical trials database, 30% have a high causality assessment with 7 SARs not listed on the SPC. For Sunitinib, of the 71 reports included from the FPD, 38% have a high causality assessment with 12 SARs not listed in the SPC. Of the 20 reports included from the clinical trials database, 85% have a high causality assessment with 2 SARs not listed in the SPC.

Conclusions: Non-commercial clinical trials' data allowed completing drug safety profile, bringing information on non-listed SARs or about an organ class few described in the SPC. The next step would consist in extending this study to other drugs and define the greatest situation in which it would be useful to collect all the available information.

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46. Pharmacovigilance Survey on Pandemic Influenza (H1N1)v Vaccination of the Medical Staff Carried out by the Paris-Henri Mondor Pharmacovigilance Center

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Background: Like in most other European countries and in the United States, the French vaccination campaign against the (H1N1)v influenza was launched in priority in the healthcare establishments for medical staff. This campaign was associated with a reminder for the healthcare professionals regarding the reporting of adverse events potentially related to the vaccination. In this context, the Paris-Henri Mondor Pharmacovigilance Center has set up, in Mondor Hospital, a Pharmacovigilance survey on the vaccination against the (H1N1)v virus of the medical staff. This survey started on October 20, 2009 and ended on January 24, 2010.

Materials and Methods: To collect the adverse events potentially related to the vaccination, a questionnaire has been specifically drawn up and given to each vaccinated person. This questionnaire was to be filled in anonymously and returned to the Pharmacovigilance Center, at least one month after the vaccination, whether or not an adverse event had occurred.

Results: At the end of this campaign, 32% of the medical staff had been vaccinated, i.e. 3.5 time more than the general population. Among them, 21% had returned the questionnaire with, for 2/3rd of them the mention of one or more than one adverse event and for 1/3rd of them no adverse event.

The most important categories of the medical staff having returned the questionnaire are the physicians and nurses with respectively 29% and 25% of returned questionnaires.

The main adverse events reported, in decreasing order, were: pain at the injection point (86%) including skin red spots, oedema and indurations, fever (21%), headache and migraine (20%), myalgia (18%), shivering (16%) and arthralgia (10%). Most of them was not serious (99%) and their outcome was favourable within less than one week.

Three adverse events (1%) have necessitated a medical intervention, although without hospitalisation: a sudden adrenal insufficiency, paresthesia of the limbs and an abortion (which could spontaneously occur at the beginning of the pregnancy in one case out of 5). For these three cases, the relationship with the vaccination was not clearly established.

Discussion - Conclusions. These results are consistent with the national and European data regarding the acceptability of the vaccines against the influenza A (H1N1)v, with mainly local reactions at the injection point and flu syndromes. No Guillain-Barre syndrome was reported. No new event or event having led to a hospitalisation was reported.

47. Selective Serotonin Reuptake Inhibitors (SSRIs) and Sexual Disorders

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Introduction: Sexual dysfunction may be a symptom of major depression in both men and women. An effective treatment of depression can restore normal sexual desire. However some antidepressant, in particular selective serotonin-reuptake inhibitors (SSRIs) are currently thought to induce sexual disorders.

Aim: To investigate and compare the risk of sexual disorders associated with use of SSRIs in the French Pharmacovigilance Database.

Methods: All sexual adverse drug reactions (ADRs) reported to the French Pharmacovigilance Database until December 2009 where taken into account for this analysis in which SSRI were the suspect drug. Cases were defined as reports mentioning the preferred term '' decreased libido'', ''delayed orgasm'' or ''anorgasmia'', ''delayed ejaculation'', ''inability to ejaculate'', ''impotence reported''. The *odds ratio* (95% CI) was calculated by *Woolf*'s method. All other reports of the database were defined as non-case.

Results: A total of 98 spontaneous reports were identified. The sex ratio M/F was 6. The mean age was 45 years (range 24–80 years). SSRI was the only drug in 50 cases. 56/98 patients completely recovered. Sexual disorders are associated with the use of SSRIs antidepressant (OR: 4.47, 95% CI: 3.61, 5.53): milnacipran (OR: 11.72, 95% CI: 5.79, 23.72), fluvoxamine (OR: 6.91, 95% CI: 3.79, 12.58), paroxetine (OR: 5.54, 95% CI: 3.92, 7.83), venlafaxine (OR: 3.5, 95% CI: 1.93, 6.36), fluoxetine (OR: 3.46, 95% CI: 2.26, 5.29), citalopram (OR: 2.69, 95% CI: 1.28, 5.67) and sertraline (OR: 2.49, 95% CI: 1.03, 6.01). No sexual ADR was reported in the French Pharmacovigilance Database with escitalopram and duloxetine.

Conclusions: Most of the current antidepressants have significant side effects on sexual function. Published studies suggest that between 30% and 70% of SSRI-treated patients may experience some sexual dysfunctions.[1,2] More than 30% of patients treated for depression are estimated to be noncompliant with treatment. Minimization of antidepressant-induced sexual dysfunction could be an important factor to avoid unsuccessful treatment. Physicians who prescribe their patients an antidepressant therapy should advise them on the possible sexual side effects. There is a suggestion of difference between the SSRIs in their effect on sexual dysfunctions. The risk with milnacipram, fluvoxamine and paroxetine is superior to the risk of the therapeutic class.

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48. Vaccine Pharmacovigilance in Countries with Restricted Resources

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Introduction: In countries with restricted resources, high disease burden and limited access to primary health care, pharmacovigilance (PV) can pose considerable challenges. This is of particular concern for vaccine studies in which subjects are often infants.

Aim: To provide an overview of PV challenges encountered when implementing vaccine projects in resource-constrained countries as well as strategies and approaches to overcome them.

Observations: PV awareness and the ability to collect safety data are particularly limited in countries with restricted resources. Cultural perspectives specific to these countries may result in adverse reactions not being identified or considered reportable. Difficult access to basic communication media such as regular mail, telephone or internet further impedes the collection of safety information, and so does the lack of trained study personnel and of well documented medical records. In addition, illiteracy renders the written informed consent process and diary card completion challenging. Limited financial means can jeopardize compliance with the vaccination schedule. Finally, diversity in regulatory PV reporting guidelines and guidance among health authorities and healthcare providers complicates PV reporting systems.

Various approaches specific to resource-constrained countries have been developed and successfully implemented, including localized informed consent processes, appropriate fieldworker training with direct access to patients, electronic data capture as well as encrypted electronic regulatory case reporting.

Conclusions: Experience suggests that appropriate strategies designed to improve vaccine PV monitoring and reporting can help to overcome PV challenges in resource-constrained countries.

49. Orlistat 60 mg in France: First Results on Utilisation and Safety After One Year of Marketing

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Introduction: Orlistat 120 mg, an anti-obesity drug, is a potent and specific inhibitor of intestinal lipases and was first approved for marketing in the European Union (EU) as a prescription only product in 1998. Since May 2009, orlistat 60 mg (Alli®) is marketed without a medical prescription in France for weight loss in adults who are overweight with Body Mass Index (BMI) ≥28 kg/m^2 in conjunction with a diet. In addition to the European Risk Management Plan (RMP), a national RMP has been implemented by the French Health Human Agency. It includes prospective surveys to better characterise the French users with collection of demographic data and estimate the inappropriate use of Alli®, and intensive monitoring of adverse events.

Aim: To provide first results on utilisation and safety profile of orlistat 60 mg after one year of marketing in France.

Method: A survey of prospective orlistat purchasers was conducted in a sample of French pharmacies. Besides this, all spontaneous reports of ADRs with orlistat 60 mg, from healthcare professionals and the MAH, recorded in the French Pharmacovigilance database (FPD) from May 2009 were retrospectively analysed.

Results: The survey involved a representative sample of 348 pharmacies throughout France. 1177 questionnaires were completed by individuals who asked for Alli®, being dispensed or not. The average age of purchasers was 44 years, their average BMI was 30.8 kg/m^2 and 81% of subjects were female. Approximately 17% of misuse was observed.

The Pharmacovigilance database is containing a total of 166 spontaneous reports concerning 286 ADRs with orlistat 60 mg and more than 60% were reported directly by patients. The most frequent ADRs were: constipation (11%), lack of efficacy (10%), abdominal pain (7.5%), cutaneous eruption (8%) and rectal bleeding (3%). Both in the utilisation survey and from spontaneous reporting, 15.7% and 19.6% of patients who took orlistat had a BMI 28 kg/m^2, respectively.

Conclusions: At present, the safety profile of orlistat 60 mg is adequately reflected in the Summary of Product Characteristics except for rectal bleeding but it should be noted that most of the adverse events were not medically confirmed. In the first survey, off-label use was observed with no related identified risk. However a further study has started in April 2010 in order to estimate the off label use, one year after the launch, and to collect safety and usage data 3 months after the inclusion.

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50. Vaccine Safety Surveillance Using the MaxSPRT with a Delayed Start

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During the last few years, the Maximized Sequential Probability Ratio Test (MaxSPRT)[1] has been used by the CDC sponsored Vaccine Safety Datalink project for near real-time vaccine safety surveillance.[2-6] Using weekly data feeds of electronic health data from ten health insurance plans in the United States, surveillance has been or is being conducted for all recently approved vaccines, including e.g. Menactra for meningococcal disease, RotaTeq for rotavirus gastroenteritis, ProQuad for Measles-mumps, rubella and varicella; and MIV for H1N1. We first give a brief background on the MaxSPRT and illustrate its use within the Vaccine Safety Datalink. For all but one of the vaccines, we observed no increase in risk of any of the pre-specified adverse events.[2-5] An increased risk of febrile seizure after ProQuad MMRV was observed, leading to revised vaccination guidelines.[6]

In near real-time surveillance studies, there are several key design issues. For example, one can start the surveillance immediately after the first vaccine dose is given. Alternatively, the start may be delayed, either (A) until a fixed minimum number of vaccine doses have been given, or (B) until a fixed number of observed adverse events have been see. The critical values, statistical power and expected time to signal are obtained for the MaxSPRT under both of these scenarios and compared with the standard MaxSPRT without a delayed start. With option B, it is possible to reduce the expected time until a signal without any loss in overall statistical power. The same is not true for option A, which is not a recommended design, although it may be used if a delayed start is due to external logistical reasons not under the control of the investigators.

In conclusion, our research demonstrates the feasibility and usefulness of continuous sequential statistical methods for near real-time vaccine

safety surveillance. The standard MaxSPRT can be improved by not generating signals until there are a certain minimum number of observed adverse events.

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51. Success Factors for Registry Studies in Risk Management Programs

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Background: Registries (product- or disease registries) play an increasing important role in late phase development and risk management programs of medicinal compounds. These programs can be complicated in nature and management.

Objectives: This study was undertaken to investigate the success factors and limitations of registry studies with the objective to determine recommendations for successful registry studies for all involved parties.

Methods: A literature review was undertaken in Pub Med. More than 160 articles were identified on various published registry studies. Strengths and limitations were subtracted and translated in recommendations for successful registry studies.

Results: Registry studies are used for: Increase awareness and burden of disease or condition; highlight the deficiencies of current treatments; show the potential impact of products on disease prevalence, incidence, progression and outcomes; develop relationships with community-based physicians and cultivate support from key opinion leaders; obtain competitive intelligence; establish sponsor reputation as a therapeutic leader and/or commitment to franchise development; demonstrate commitment to product risk management strategy.

Registry designs can meet both clinical and marketing objectives; always let science lead; early planning and continuing flexibility are key; start planning registry outputs during the design phase and be creative; the best registries evolve over time.

Conclusions: Successful and less successful registries have been initiated. In order to be successful the following recommendations can be made:

Brand the registry; issue initial and ongoing press releases; establish a registry steering committee at inception; identify ongoing and ad hoc analyses; determine likely forums for results; build key relationships; promote the registry to Key Opinion Leaders; integrate other peri-approval activities like: Phase IIIB/IV studies; reimbursement strategy; Market research activities; incorporate a disease screening tool; host initial and ongoing investigator meetings, provide bench marketing reports.

52. Communication: Successful Weapon for Pharmacovigilance of Herbal Medicines

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Herbal medicines are promoted to the public as equally and less toxic than conventional drugs. However, some herbal medicines are known to have adverse effects. But the promotion of herbal medicines as natural safe alternatives neglects the possibility of these adverse effects. Patient information is similar to that for any over-the-counter medicine, with an additional requirement for a statement on labels and in advertisements that the indication is based on traditional use. This should concern the indication, strength, dosing recommendations, route of administration, herbal medicines preparation and other information on safe use particularly in risk patients: children, pregnant or lactating women and the elderly. The communication should concerns the interactions of herbal medicines and conventional drugs.

Several means of communication must be made to ensure good information: leaflets promoting proper use, things to know about evaluating medical resources on the internet, local language, and so on. Information should be disseminated using newsletter or bulletins, internet website, conferences, mass media, courses, and articles in professional journals and information should be also targeted messages for consumers in first intention.

The public should be fully informed about all medicines they take. Consideration also needs to be given to effective regulation of herbal medicines practitioners, so that they are identifiable in law, are governed by professional codes of practice and have agreed standards of training and competency.

The safety and quality of herbal medicine should be ensured through greater research, pharmacovigilance, greater regulatory control and good communication between regulators, practitioners, patients and the public which is necessary so that those who choose to take herbal medicines can do so with acceptable safety.

53. Integrating Pharmacovigilance in Revised National Tuberculosis Control Programme of India: A Pilot Study

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Background: Directly Observed Treatment Short Course (DOTS)/Revised National Tuberculosis Control Programme (RNTCP) of India is one of the largest Public Healthcare Programmes in the world.[1] About 3500 patients are initiated on Anti-Tuberculosis Therapy (ATT) every day at DOTS centres in India.[1] Safety information of DOTS in the local population is lacking and there is need to integrate pharmacovigilance in DOTS programme.[2,3]

Objectives: To develop DOTS centres as sentinel sites for monitoring of adverse drug reactions (ADRs) to ATT.

Methods: A prospective study was conducted at ten DOTS centres in Mysore city. DOTS centres attached to primary health centres, staffed with medical officer, pharmacist and TB health visitors were selected. Workshops for training on '**S**afety **M**onitoring of **A**nti-tubercula**r** **T**herapy (SMART)' were organized. Pre and post workshop assessments were conducted. A SMART trigger tool was developed similar to

Rozich JD et al.,[4] and implemented to assist the sites personnel in detecting ADRs to ATT. The sentinel sites personnel monitored the ADRs in patients receiving DOTS between September 2009 and February 2010. ADR reporting forms and patient information leaflets regarding adverse reactions to ATT were made available at all selected sites. Investigators visited the sites periodically to further train and assist the site personnel in detection and reporting of ADRs.

Results: Forty four healthcare professionals of DOTS/RNTCP centres were trained on ADR detection, reporting and medication safety counseling. Pre and post workshop assessments found 25% increase in the understanding of ADRs to ATT and 68% of the participants detected the ADRs to ATT in dummy TB patients using the trigger tool developed for the study. The participants of the programme opined that the project helped them to develop their skills in patient safety monitoring. The programme did not necessitate employing any extra human resource at the sites. Of the 274 patients treated with DOTS at the sentinel sites during the study period, 201 adverse reactions to ATT were detected /reported from 112 patients (prevalence 40.9%).

Conclusions: Extension of sentinel site approach in a phased manner to other DOTS/RNTCP centres will improve patient safety monitoring in large population. Our approach to safety monitoring of ATT may prove useful to integrate pharmacovigilance in public healthcare programmes in resource poor settings.

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54. Adverse Drug Reactions to Anti-Tuberculosis Therapy in a Public Healthcare Programme of India

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Background: The World Bank funded Revised National Tuberculosis Control Programme (RNTCP)/Directly Observed Treatment Short Course (DOTS) of India is one amongst the largest public healthcare programmes in the world.[1] Safety profiles of anti-TB medications in Indian population are lacking.[2]

Objectives: To determine the incidence rates, predictability, preventability, seriousness, severity and predictors for development of ADRs to ATT.

Methods: The prospective active surveillance study was conducted between September 2009 and February 2010 at ten selected DOTS/RNTCP centers in Mysore city. The DOTS/RNTCP centers personnel trained to monitor ADRs to ATT detected the ADRs in patients treated at DOTS/RNTCP centers using a trigger tool to detect common and very common ADRs to ATT. The observed ADRs were assessed for causality (Naranjo's algorithm and WHO ADR probability scale), severity (Modified Hartwig SC et al. scale[3]), seriousness (International Conference on Hormonization E2A criteria[4]), predictability (based on frequency of occurrence of ADRs and history of exposure) and preventability (modified Schumock and Thornton criteria[6]). ADRs were coded using World Health Organization Adverse Reaction Terminologies (WHO-ART).[6] Bivariate analysis and subsequent multivariate logistic regression was used to assess the predictors for development of ADRs to ATT.

Results: Out of the 274 patients included in the study, 112 patients experienced 201 ADRs to ATT (prevalence 40.9%). Majority of the ADRs were moderate in severity (66.7%), not serious (83.6%), predictable (78.1%) and were not preventable (67.1%). Highest incidence rate of ADRs was observed with gastrointestinal disorders due to rifampicin + isoniazid + pyrazinamide (2.65 per 1000 patient-days). Lowest incidence rate of ADRs was observed with vision disorders due to rifampicin + isoniazid + pyrazinamide + ethambutol (0.05 per 1000 patient-days). Bivariate analysis identified alcohol use with smoking (Odds Ratio (OR): 4.34, 95% Confidence Interval [CI]:1.49, 12.64, $p = 0.004$), treatment with category III of DOTS (OR: 1.77, CI: 0.97, 3.26, $p = 0.045$), co-morbidity with diabetes and hypertension (OR: 13.5, CI: 1.66, 109.69, $p = 0.003$) and other co-morbid conditions (OR: 10.08, CI: 1.19, 85.06, $p = 0.014$) as predictors of ADRs to ATT. Patients with diabetes and hypertension as co-morbidity (OR: 12.5, CI: 1.52, 90.91, $p = 0.018$), and alcohol use and smoking habit (OR: 2.94, CI: 1.04, 8.33, $p = 0.041$) were found as influential predicator for development of ADRs to ATT.

Conclusions: Very high (40.9%) prevalence of ADRs to DOTS was observed. There is a need to monitor ADRs at DOTS/ RNTCP centers.

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55. Free Text Extraction from Case Narratives to Highlight Suspected Drug Interaction

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Background: The WHO Global individual case safety reports (ICSR) Database, VigiBase, includes 5 million reports of suspected adverse drug reactions (ADRs) from 96 countries worldwide.[1] Some information is only available in free text case narratives. This information is currently underutilised in large-scale ADR surveillance.

Objective: To determine the extent to which text extraction from case narratives can improve ascertainment of suspected drug interaction on ICSRs.

Methods: Ascertainment of suspected drug interaction from case narratives was performed using free text extraction and matching against the word stems 'interact' and 'interakt'. Predefined text patterns were used to eliminate some references including negative interactions. The baseline consisted of extracting (1) all reports with two drugs classified as interacting by the reporter and (2) all reports that listed a MedDRA® term referring to suspected interaction.

Results: The baseline comparison highlighted 11 428 reports. Free text extraction from case narratives highlighted 3762 reports out of which 2062 were not included in the baseline comparison. Hence, free text extraction from case narratives increased the detection rate of reports with an underlying clinical suspicion of a drug interaction by 18%, compared to utilising only the structured information on these reports. A subset analysis disclosed approximately 3% of the free text matches as false positives. These referred either to the interaction between humans or a negative statement about drug interactions in other languages than English.

Conclusions: Explicit notes of clinical suspicion of drug interactions are rare, but might serve as effective markers of potential index cases related to suspected drug interaction. Even the very simple free text matching approach considered here increased the detection rate of suspected drug interaction in a meaningful way. An improved text matching approach that accounts for other linguistic differences, synonyms, words and characters without semantic meaning can be expected to improve performance even further.

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56. Reporting Patterns Indicative of Emerging Drug Interactions

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Background: Most efforts to implement systematic drug interaction surveillance in collections of Individual Case Safety Reports (ICSRs) have focused on disproportionality analysis. There has been little discussion of what detailed information on case reports could contribute to improved drug interaction surveillance.

Objective: To identify reporting patterns characteristic of emerging adverse drug interactions in the WHO Global ICSR Database, VigiBase.

Methods: A reference set of known adverse drug interactions and drug pairs not known to interact was constructed. The reference set was used to systematically study differences in reporting frequency of potential predictors; pharmacological information such as ATC information and metabolism through cytochrome P450, explicit remarks of suspected drug interactions by the reporter, clinical details such as dose and treatment overlap, and excessive co-reporting of two drugs and one adverse drug reaction (ADR) relative to an additive baseline model. Reports entered into VigiBase during the past 20 years were used in the analysis.

Results: The following reporting patterns are particularly strong predictors of emerging adverse drug interactions: suspicion of interactions as noted by the reporter in a case narrative, or in the assignment of the two drugs as interactive, or co-reporting of therapeutic response increased, or in terms of a MedDRA® term related to suspected drug interaction; and finally excessive co-reporting of the ADR together with the two drugs as measured by the Ω (Omega) measure of three-way disproportionality.

Conclusions: ICSRs carry valuable information predictive of emerging adverse drug interactions. Unlike previous studies, we go beyond the analysis of summary reporting rates and consider other reported information potentially predictive of adverse drug interactions. To our knowledge, this study is the first systematic analysis demonstrating the value of specific information reported on ICSRs in addition to disproportionality measures to recognise emerging adverse drug interactions.

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57. Monitoring Batch Related Safety of Vaccines During the Flu-Pandemic in the Netherlands

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Background: In the Netherlands, the vaccination campaign against Influenza A(H1N1) started in November 2009. The accelerated development and registration procedure of the vaccines Focetria and Pandemrix, used in this campaign, urged the need for a close monitoring of the safety. Since the vaccines were administered in a relatively short period of time, immediate action may have been warranted. Because safety issues could be batch related, a real time signal detection procedure had to be developed.

Methods: When reporting an Adverse Event Following Immunisation (AEFI) on a dedicated web reporting form, the town/venue combination were the vaccination took place was asked for. Based on the distribution of the vaccines, an automatic pre-selection of the administered batch number was possible. In respect to batch related problems, different types of AEFIs were monitored for. Firstly, AEFIs related to reactogenicity, either injection site reactions or fever. In addition, AEFIs related to possible infections, indicative of a possible contamination of a batch, were monitored. Finally reports of lack of efficacy and serious AEFIs were analysed. The number of reports per batch was compared to all other reports received on influenza vaccines present in the Lareb database and expressed as a reporting odds ratio (ROR) with 95% confidence interval.[1] The analyses were carried out automatically and the resulting reports were forwarded by e-mail to an assessor.

Results: The batch number was retrieved in 812 (29.1%) reports where Focetria® had been used and in 3305 (69.6%) of the reports on Pandemrix®. In respect to the various types of AEFIs, no signals of possible batch related problems have been detected for both vaccines.

Discussion: A good collaboration with the institutions responsible for the distribution of the vaccines was needed to ensure reliable information about the batch numbers. Although a batch number wasn't always available, disproportionality analysis could be used to monitor for batch related safety issues. In the event two or more different batch numbers of a vaccine had been used in the same venue the option 'batch number unknown' could also be selected on the reporting forms. In this way, the risk for misclassification was reduced. In addition, possible misclassification is unlikely to have affected the height of the ROR since this misclassification would have been non-differential.[2]

Conclusions: Pre-selection of batch numbers, combined with a partially automated processing of reports, enabled an almost real time monitoring for batch related problems in case of a mass vaccination campaign.

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58. New Paradigms for the Outsourcing of Pharmacovigilance Operations

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Introduction: From the industry's perspective pharmacovigilance (PV) has 2 main strands: the collection and mandatory reporting to regulatory authorities of adverse events and the early detection of any signals of previously unknown adverse drug reactions. Put another way PV has an operational aspect and a more scientific aspect. The more 'operational' tasks such as data entry and adverse events coding are well placed for offshoring which can provide a cost effective means of meeting legislative requirements. This is a trend that is gaining in momentum. To date India has been the first choice for the offshoring of PV processes however this has not been without its challenges and latterly attention is turning to other destinations.[1,2]

Objective: To investigate whether Ghana could provide a viable offshore location for pharmacovigilance operations.

Methods: The following aspects were qualitatively assessed: Location; ease of accessibility & time difference from Europe, language, educational standards and expected salaries, IT infrastructure, labour laws, foreign investment incentives, global business index ranking, precedent as a site for offshoring in other industries, background in PV.

Results: Ghana is a stable democracy straight down the Greenwich meridian on Africa's west coast. There are daily flights to Ghana from Europe/US by major carriers, e.g. BA, Virgin Atlantic, United Airways, Delta. The official language is English, but many also speak French as Ghana is surrounded by Francophone countries. Availability of significant graduate (including medical) talent at substantially lower costs: A good graduate salary is at least 10× less than the European equivalent. IT infrastructure: broadband supplied at E1 level (European standard) by National provider: Vodafone, additionally there are 5 other broadband suppliers. Government offers significant incentives to foreign investors.[3] As an offshoring location, Ghana ranked at 15, ahead of UK and South Africa at 31 and 39 respectively,[1] and for ease of doing business at 92 ahead of India at 133.[2] The offshoring precedent was successfully set by Affiliate Computer Services, Business Process Outsourcing in 2000. Ghana's PV system is developing rapidly and she has been an official member of the WHO Programme for International Drug Monitoring since 2001.

Conclusions: With increasing technological advances, the availability of an highly educated, motivated and cost efficient workforce located in sub-Saharan Africa offers a viable alternative model for the outsourcing of global PV processes. It has the added advantage of minimal time difference with Europe, which will impact communication positively.

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59. Guillain-Barré Syndrome and A(H1N1)v2009 Vaccination: A French Case-Control Study

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Background: A possible association between pandemic A(H1N1) vaccines and Guillain-Barré Syndrome (GBS) following 1976 was suspected following vaccination episode.[1] Since 1976, this complication has been considered as an adverse effect of special interest (AESI) in A(H1N1) vaccines risk management plan.

In addition to the European risk management plan and the intensive monitoring of spontaneous reports to the French Pharmacovigilance regional centres, a case-control study (''Observatoire Guillain-Barré'') was set up in November 2009 in neurology and intensive care units of 7 French regions, covering about 22% of the entire population. The French Medicinal Products Agency has supported this study.

Objectives: To quantify the number of GBS occurring during pandemic influenza period (November 2009-June 2010) according to the suspected aetiology.

To compare exposure to vaccines and/or flu A(H1N1) virus in GBS patients and matched controls.

Methods: All GBS cases occurring during the pandemic period in participating units were included, and compared to 2 hospital controls matched on gender, age and date of hospitalization. For both cases and controls, we collected data on recent viral or bacterial infections, surgery, history of auto-immune disorders and drug exposure (including pandemic and seasonal flu vaccination) in a period of 2 months before the index date (date of onset of symptoms). Flu infection was confirmed by centralised serological diagnosis (Flu National Reference Centre) and exposure to pandemic flu vaccination was systematically checked in the French A(H1N1) vaccination database.

Results: Up to now, 37 cases of GBS were included among which 4 were vaccinated with A(H1N1) vaccine before the onset of symptoms. A recent gastro-intestinal infection was the most frequently observed event preceding the onset of symptoms (n = 10), followed by a presumed viral respiratory tract infection (n = 9). The study is currently on-going but full results will be available in November for the ISOP meeting.

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60. Investigation of Liver Toxicity of Chinese Herbal Medicine: Pilot Case-Control Study

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Introduction: Chinese herbal medicine (CHM) is widely used in the UK. There have been reports of liver toxicity that were considered possibly related to the use of CHM for a range of medical conditions including skin disease and pain relief. In these reports, No herbs that

are known to be liver toxic were used but these reports led to concerns about the safety of some frequently used herbs such as *Dictamnus dasycarpus* or *Paeonia* species.
Objective: To evaluate feasibility of using a case control study to assess potential toxicity of individual Chinese herbs, and obtain preliminary data on frequency of use of herbs in CHM.
Method: Herbal formulas used in 37 reports of liver toxicity possibly associated with use of CHM were identified. For each of these 'Patient' prescriptions, 3 'Control' prescriptions were obtained from patients matched on gender and reason for use who did not develop any abnormal liver function during TCM treatment. Odds ratios (OR) were calculated for the most frequently used herbs.
Results: The medicinal herbs that were used most frequently were *Glycyrrhiza* spp, *Rehmannia glutinosa* and *Paeonia* spp. The top twenty herbs in both Patient and Control groups were similar. Of 137 herbs used by the Patient group only 14 were used in more than 20% of formulas. Similarly of 166 herbs in the control group, only 11 were used in more than 20% of formulas. The only herb with a statistically significant increase in OR is used to treat hepatitis. There was no association (OR > 1) with herbs such as *Glycyrrhiza spp*, *Rehmannia glutinosa* or *Dictamnus dasycarpus*.
Discussion: Case control studies can be used for herbal investigations but there are specific difficulties and limitations of such studies when applied to CHM. As in Chinese medicine up to 20 herbs may be used in a formula, but only single or combinations of 2 herbs could be tested in this type of study. However it was possible to counteract the claim that some frequently used herbs cause liver toxicity as no association was found in this study. As hepatotoxicity may be the result of interactions between 2 or more herbs a larger more detailed study is needed.

61. The Contribution of Periodic Safety Reports (PSURs) To Safety Related Regulatory Actions of Biopharmaceuticals

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Introduction: A periodic safety update report (PSUR), composed by marketing authorization holders and submitted to regulatory authorities on predetermined time points, provides an update of the worldwide safety experience of a pharmaceutical. Information is lacking on how PSURs contribute to safety related regulatory actions.
Aim: The objective of the study is to analyze the contribution of PSUR evaluations to the initiation of safety related regulatory actions of biopharmaceuticals.
Methods: We performed a retrospective analysis of all safety related type II variations of biological products centrally approved in the European Union (since 1995) for which ≥1 safety-related Direct Healthcare Professional Communication (DHPC) was issued until December 2009. An evaluation of the role of PSUR assessments in the initiation of safety associated regulatory actions was performed through an analysis of European Public Assessment Reports and updates of the Summary of Product Characteristics (SPC). We compared "urgent" variations, defined as variations accompanied by the distribution of a DHPC, with "less urgent" variations, i.e. safety related SPC variations for which no DHPC was distributed. For each variation we determined if any reference was made to the contribution of PSUR evaluations. We determined the data source and nature of the safety issues included in the variations. Each variation could include ≥1 safety issue and ≥1 data source could contribute in a single variation.
Results: We identified 133 safety related type II variations for 15 biological products. Reference to PSUR evaluations was made in 2/24 (8.4%) of all urgent type II variations and 48/109 (44.0%) of the less urgent variations (x^2, $p < 0.01$). Data sources that contributed to the urgent variations were: 14 (58%) spontaneous reports, 9 (28%) clinical trials and 2 (8%) an analysis of pooled data. For the non-urgent variations, these were 53 (49%), 40 (37%) and 18 (17%) respectively. Overall, most of the variations concerned events from the System Organ Classes (SOCs) Infections and Infestations (32%), General Disorders and Administration Site Conditions (26%), Neoplasms (14%), Blood and Lymphatic System Disorders (14%) and Nervous System Disorders (14%). No differences in SOCs were observed between safety-related regulatory actions that did or did not result from PSUR assessments.
Conclusions: The contribution of PSUR evaluations was lower in urgent safety related regulatory actions when compared with less urgent safety issues. Despite the modest role of PSURs, spontaneous reports contributed to the majority of the urgent safety related regulatory actions.

62. Bile Salt Export Pump Inhibition Properties of Drugs not Associated with Disproportionate Reporting of Drug-Induced Jaundice in WHO-UMC VigiBase

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Background: One of the proposed mechanisms of drug-induced cholestasis involves inhibition of the bile salt export pump (BSEP). It has been suggested that molecular properties of drugs are related to BSEP inhibitory potential, and may be a useful predictor of drug-induced cholestasis to be applied in preclinical research. In this study, we identified drugs that have been associated with drug-induced jaundice in individual case safety reports (ICSR) from the WHO Global ICSR database, VigiBase, and related these to their BSEP inhibitory potential.
Methods: Using the online VigiMine tool, we selected all drugs with at least 100 reports of drug-induced jaundice from the WHO-UMC VigiBase, which contained 5 057 235 ADR reports at May 1, 2010. From this list of 53 drugs, we excluded 4 combination preparations and 1 vaccine. For the remaining 48 drugs we noted the information components (IC) for jaundice produced by VigiMine. Subsequently, we looked up the chemical structure and calculated the predicted inhibition of ABCB11-mediated taurocholate transport, a measure for BSEP inhibition, using the method proposed by Hirano et al.[1] We plotted the predicted BSEP inhibition against IC-values and fitted a linear regression line.
Results: The 3 drugs most strongly associated with jaundice were prajmalium (IC 6.07), halothane (IC 5.25) and fusidic acid (IC 4.81).

Predicted inhibition of ABCB11-mediated taurocholate transport varied between –20.64 for gemcitabine and 59.3 for rosiglitazone. For these 48 drugs predicted BSEP inhibition was not associated with the IC-value for reporting of jaundice (linear regression $R^2 = 0.016$). Of the top five drugs with highest predicted BSEP inhibition, four produced a signal for drug-induced jaundice (rosiglitazone $BSEP_{inh}$ 59.3 and IC_{025} 0.03; sulindac $BSEP_{inh}$ 54.4 and IC_{025} 2.14; ketoconazole $BSEP_{inh}$ 48.3 and IC_{025} 3.02; inidavir $BSEP_{inh}$ 43.3 and IC_{025} 1.62; ticlopidine $BSEP_{inh}$ 40.0 and IC_{025} 2.60).

Conclusions: Although some of the drugs had both high predicted BSEP scores and high IC values for jaundice, overall no linear association between predicted BSEP inhibition and disproportionate reporting of drug-induced jaundice in VigiBase was identified.

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63. Number of Spontaneous Reports of Guillain-Barré Syndrome after Flu A(H1N1) Vaccination versus Expected Number in France

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Background: In 1976, an increased incidence of Guillain-Barré Syndrome was observed in the United-States after a flu-vaccination, leading to an interruption of the vaccination campaign.[1] This is the basis for the surveillance of the risk of GBS associated with vaccination against flu A(H1N1). A total of 5.7 millions individuals have been vaccinated in France. The incidence of GBS has been stable in France in the last 5 years.

Objective: To compare the number of spontaneous reports of GBS following A(H1N1) flu vaccination with the number expected from background rates.

Methods: The expected number of GBS has been estimated under the hypothesis that vaccination does not modify the risk. This expected number is the sum of age-specific expected numbers (ASEN). Each ASEN is the product of the number of vaccinees per month in the age-group by the 2-months risk period and by the background incidence of GBS per age group (BIGAG). BIGAGs were estimated from the 2004–2008 French hospitalisation data base (PMSI).

Results: If the vaccination does not increase the risk of GBS and if the period of observation is limited to the two months after vaccination, 23 cases of GBS are expected. If no risk period is fixed, 42 cases of GBS are expected in the vaccinated population followed from vaccination till the end of March 2010.

Until the March 28 2010, 10 cases of GBS after A(H1N1) vaccination have been reported to the French pharmacovigilance system. The diagnosis of GBS was confirmed in all cases with Asbury criteria[2] (acute inflammatory demyelinating polyradiculoneuropathy with progressive bilateral and symmetric weakness of the limbs and a-reflexia) and validated by the French GBS expert group.[1] The onset of symptoms occurred 10 to 71 days after the last administration.

Conclusions: Only hospitalised GBS are collected in the PMSI. There may have inconsistency between codes registered by Health professionals. Unconfirmed cases may have been coded as GBS in some cases whereas in others only confirmed diagnoses have been registered.

The number of GBS observed after vaccination is much lower than the expected number. However, those figures do not take into account a potential under-reporting. To reach the expected number of 23 cases, one must assume an under-reporting rate of 61% which is unlikely, given the media coverage and the possibility given to patients to report themselves.

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64. Vaccine Surveillance in Italy: the Status of the Art, Critical Issues and Some Proposals

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Reporting every suspected adverse reaction to vaccines, including listed and not serious ones is mandatory in Italy. Routine Pharmacovigilance activities include monitoring of spontaneous reports and assessment of: (i) Periodic Safety Update Reports; (ii) Risk Management Plans; (iii) Post Authorization Safety Studies; (iv) other pharmacovigilance commitments. Pharmacovigilance activities alone are not sufficient to ensure adequate surveillance, especially in an emergency situations, without active involvement of all public health bodies. The recent pandemic has confirmed the need for full integration between activities of different stakeholders aiming to protect Italian public health.

Some critical issues emerged during each phase of the surveillance process:

1. *Data collection*: spontaneous reporting is an important source of information on safety and often the main source, but needs to be continually stimulated and facilitated. Cooperation between local pharmacovigilance and public health services should be strengthened to register subjects receiving vaccination and batch number. Stickers and other electronic tools could simplify this and establish links between patients and vaccine doses.

Exposure data: only during the recent H1N1 pandemic was it possible to collect real time aggregated data by region through specific electronic infrastructure. Collection of reliable exposure data based on vaccinated subjects should become a commitment for the National Vaccination Program (NVP).

Coverage data should be available in more quickly and included in the NVP.

2. *Signal detection*: Periodic and standardized activity conducted with experts at least at regional level should be set up. The main problem is that this is not perceived as a public health need and it would be necessary to have an operative group with expertise in Pharmacovigilance and in the vaccine field. Financial resources should be dedicated, roles and duties should be well defined.

3. *Signal Validation*: Collaboration with public health services is crucial both for diagnosis and to collect background incidence of AESIs.

4. *Signal confirmation and epidemiological studies*: Critical points are related to funding (it can not always be left to the Company) and to rapid availability of infrastructure and ethical committees, essential to promptly set up dedicated safety studies.
5. *Risk minimization and communication*: Implementation of risk minimization actions and communication requires active participation of all public health bodies.
Conclusions: Pharmacovigilance activities alone, without the involvement of public health protection services, cannot guarantee adequate vaccine surveillance. The need for formal integration should be reflected in the NVP and should receive the necessary attention, funding and human resources.

65. Strengthening the Spontaneous Reporting System for Influenza A/H1N1 Pandemic Vaccines: Was it Successful? Analyses in the EudraVigilance Database

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Background: Prior to the influenza A/H1N1 pandemic, the European Medicines Agency and the EU Pharmacovigilance Working Party recommended to regulatory authorities (RA) and vaccine manufacturers measures for strengthening the spontaneous reporting system to support early signal detection. Recommendations included a list of adverse events of special interests (AESIs) to be closely monitored, prompt reporting of fatal reactions, life-threatening reactions and AESIs to EudraVigilance (EV), as well as facilitation of notification of adverse drug reactions (ADRs) with minimal data elements by health care professionals and patients, preferably using a web-based system.
Objective: To assess the effectiveness of these recommendations based on an analysis of missing data and of delays for communicating ADRs to RA and transmitting them to EV.
Methods: We included all ADR reports received in the EV Post-Authorisation Module (EVPM), thus excluding data from clinical trials, from 1st October 2009 to 30 April 2010 for any of the three centrally-authorised H1N1 vaccines (Celvapan, Focetria and Pandemrix). We compared them to all ADR reports received in EVPM from 1st October 2008 to 30 September 2009 for any of the two centrally-authorised HPV vaccines (Cervarix and Gardasil/Silgard). We analysed missing data on patient identifiers (birthdate, age, sex), narrative, batch number and reaction start date. We calculated the time difference between initial receipt of an initial ADR by RA and the reaction start date, and the delay for RA to transmit reports to EudraVigilance.
Results: A total of 14 543 and 2703 reports were received for H1N1 and HPV vaccines. Missing data were respectively: sex: 1.1% and 1.3%; age: 1.5% and 5.8%; birthdate: 26.1% and 60.0%; narrative: 8.9% and 13.4%; reaction start date: 54.4% and 63.3%; batch number: 46.4% and 40.8%; seriousness: 0.2% and 0.1%. For H1N1 vaccines, the median delay from start of reaction to initial receipt by RA was 7 days and the median delay for transmission of reports to EVPM was 4 days. For HPV vaccines, these delays were respectively 31 and 11 days.
Conclusions: Quality and completeness of spontaneous ADR reports were higher for H1N1 vaccines during the pandemic than for HPV vaccines in a non-pandemic period. The most significant result is the shortening of delays for health care professionals to communicate ADRs to RA and for RA to transmit them to EV. The proportion of reports with information on batch number was not improved and needs to be further addressed by vaccine pharmacovigilance systems.

66. An Epidemiological/Statistical Approach to Determining Whether Lot-to-Lot Differences in Safety Information are Clinically & Statistically Significant

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Background: Adverse events associated with identical drugs from different lots could be representative of an issue with manufacturing, quality control, or the drug's inherent toxicity. Lot analysis is important in defining what issues may be responsible for the appearance of adverse events.
Objective: This poster describes a novel method of analyzing post-marketing safety data and lot data to determine whether significant differences between lots of the same product exist.
Methods: Using EBGM and Poisson p value tests, two statistical results are used to determine whether a significant difference in lot-to-lot identical drug exists. A final report using traditional pharmacovigilance methods and data mining techniques is produced to confirm or deny a lot difference between products.
Results: Analysis of data from different manufacturing sites showed a difference in the type of event based on MedDRA® SOC but no evidence of a statistical difference between products. Subset analysis revealed a trend in the type of patient receiving the product and the medical history of these patients.
Conclusions: Using EBGM and Poisson p value tests, we were able to objectively determine that there was no statistically significant safety difference between identical drugs from different lots from different manufacturing sites. No change in the product's benefit-risk profile was seen.

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67. Periodic Safety Update Reports (PSUR) and National Reports Assessment in Turkey

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Introduction: A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorisation.[1] National Reports are the safety reports about the drugs which are authorized/permitted only in Turkey. At these defined time points, Marketing Authorisation Holders are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new of changing information.[1] Our unit evaluates Periodic Safety Update Reports (PSURs)/National Reports in terms of authorization/permission renewals, marketing authorization/permission holder changes, and routine reports for brand new licensed products.
Aim: To identify how many reports have been received either authorization/permission renewal reports and authorization/permission holder changes or routine reports in 2009 and classify top 5 most evaluated active substance based on these reports.

Methods: We performed a study in the PSURs and National Reports Assessment Unit from March 2009 to December 2009. Complete data obtained about the drugs were entered into a database. The database was in excel format. All drugs were classified according to their active substances and listed top five of these substances which were most received in 2009. Additionally we counted all authorization/permission renewals, authorization/permission holder changes and routine reports which were received in 2009.

Results: The results showed that; electrolyte solutions reports (%35) were identified as the most received reports in 2009. Cough & cold medicines (%24), diclofenac (%17), estradiol (%15) and amoxicillin (%9) reports were the other substances that were ranked from 2nd to 5th respectively. The number of authorization/permission renewal reports and authorization/permission holder changes were counted 553 (%48.7) while the number of routine reports were 582 (%51.3).

Conclusions: This study is supposed to provide a foresight to PSURs and National Reports Assessment Unit in the future. These data will be used for the development of report assessment plans.

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68. Eu2P - European Programme in Pharmacovigilance and Pharmacoepidemiology

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Eu2P aims to improve the understanding of medicines-related risk by developing a European training and education platform in Pharmacovigilance and Pharmacoepidemiology for academia, industry and regulatory bodies. This challenge was embraced by seven Universities, the European and French Medicines Agencies and fifteen Pharmaceutical Companies who have put their strengths together in order to build the Eu2P consortium. This programme will offer courses in Pharmacovigilance and Pharmacoepidemiology with specialties in benefit assessment, regulatory aspects, risk quantification, public health and risk communication in order to deliver certificates recognised by Eu2P academia, industry and regulatory bodies and new postgraduate diplomas in the framework of the Bologna process. Initiated in September 2009, Eu2P is building up its education programme to offer first course deliveries in Autumn 2011. Eu2P targets specialists such as pharmacists, physicians, scientists and experienced professionals but also non specialists such as media-members, laypersons and patients especially for risk communication training. Eu2P users will build custom training programmes that can lead to short course certificates, a full master's or a PhD according to the options chosen. Emphasis will be put on hands-on training to maximise post-training employment opportunities. Eu2P courses will be delivered in English using a unique and innovative modular approach integrating face-to-face lectures, e-teaching (live videoconferences) and e-learning formats through the Eu2P e-learning platform. By the end of 2014, Eu2P training programmes should be self-sustaining through excellence, and its consortium should host and include new European and international partners.

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69. Appropriateness and Safety of Thalidomide: Implementation of RMP in Italy via the Cancer Drugs Register and the National Pharmacovigilance Network

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Background: The Italian Medicines Agency (AIFA) governs the correct place in therapy, use and risks of the innovative drugs through Post Marketing Drug Monitoring Registers that include complete Risk Management Plans. For the purposes of implementing and managing the plan provided for the prevention of risks associated with the use of thalidomide, the AIFA referred this product to systematic monitoring of requirements and processes trough a telematic register, published in a specific area of the AIFA Portal dedicated to the monitored drugs: http://monitoraggiofarmaci.agenziafarmaco.it. Moreover, the product is also included in the Monitoring Drugs List of the Adverse Drug Reactions (ADRs).

Methods: The Risk Management Plan (RMP) of thalidomide is then managed within the AIFA Cancer Drugs Register (RFOM). The RFOM acts as a management tool of the entire process of prescription, dispensing and analysis of consumption data of innovative cancer drugs; for these, AIFA has provided for the registration schedules of patients to control in real time the appropriateness of use. The schedules provided by the Registry include all the data required by the RMP with the classification of eligible patients in Man, potentially fertile Woman and potentially not fertile Woman. The monitoring started on April 27th 2009, which corresponds to the actual marketing date of the Thalidomide product in Italy.

Results: Only prescribers and pharmacies registered are able to prescribe and dispense the product. Patients must be advised of, agree to and comply with the requirements of the RMP. The unique characteristics of Th imposed to exclude the use in patients (males and females) potentially fertile and sexually active, without prevention of pregnancies at risk.

After the registration the complete flow of the treatment is traced via case forms, subsequently the safety data are collected in a telematic way in order to simplify the communications to the National Pharmacovigilance Network.

Conclusions: In addition to minimizing the potential risk for fetal harm associated with Th therapy, the RFOM-based RMP may provide a model for future cases in which a drug offers compelling benefits but poses potential risks unless its distribution is carefully controlled.

RFOM represents an important tool to promote not only the appropriateness of use, but also the healthcare providers spontaneously reporting: the main source of potential safety alarm generation after the marketing authorization.

70. Adverse Events and Adverse Drug Reactions in Hospital Observed by Nurses: Prospective Analysis of 4608 Patients

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Background: Adverse events (AE) are a relevant problem with major health consequences for both patients and health system in different

countries in the world. The international literature shows that 3–6% of hospital admissions are caused by adverse drug reactions (ADRs) and that the percentage of hospitalized patients with an ADR ranges between 6 and 15%.[1,2] The spontaneous reporting of ADRs is an important system for post-marketing safety surveillance worldwide. Nurses' ADR reports are increasing in Sweden,[3] Canada[4] and United Kingdom.[5] In Italy, in 2009, nurses' ADR reports represented only 4% of the total.

Aim: Assessing the ability of nurses to identify and report correctly ADRs; identification of the most frequent AE in relation to the characteristics of patients.

Methods: The project, lasting 6 months, started in February 2009 in three Verona Hospitals. The research was drawn as a practical training involving 174 nurses and 36 charge nurses from 41 different wards. These have been divided in six different groups depending on patients: Medicine, Surgery, Pediatrics, Geriatrics, Oncology and Other wards. For data collection it was created a monitoring form, where the nurses recorded for each patient: health condition, unexpected AE, administered drugs, and suspected ADRs. Nurses were also requested to send ADR reports to the Italian Pharmacovigilance System.

Results: Data were collected from 4608 patients. This sample was representative of the hospitalized patients during the study period (confidence level 99%, confidence interval 2%). Nurses identified AE in 2458 patients (53.3%) and observed 6647 different events, mostly psychiatric (800 cases), gastrointestinal, and cardiovascular. Female, elderly, and patients 0–1 years old, number of administered drugs, and poor health conditions were all risk factors for adverse events ($p < 0.01$). Nurses identified 160 patients with ADRs (3.5% of observed patients), while an *ad hoc* committee of experts identified a number of ADRs about seven times higher. Nurses sent 84 ADR reports to the Italian Pharmacovigilance System.

Conclusions: Nurses have shown a good observational skill for AE, but low ability to detect ADRs probably due to lack of pharmacological knowledge. For this reason a continuing education is essential. The project has incremented the spontaneous reporting of nurses.

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71. Adverse Drug Reactions in Italian Geriatric Wards

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Introduction: Adverse drug reactions (ADRs) are a common clinical problem. ADRs are considered to be among the leading causes of morbidity and mortality. In elderly patients about 16% of hospital admissions are due to ADRs,[1] and 19–23% of hospitalized experience ADRs, causing significant prolongation of hospital stay.[2,3] Older patients are particularly vulnerable to ADRs because of multiple-drug regimen and aged-associated changes in pharmacokinetics and pharmacodynamics.

Aims: To evaluate, in an elderly population, the incidence of ADR-related to hospital admission or occurred during hospitalisation, and to identify the drugs involved. To estimate the underreporting in the Verona Hospital.

Methods: The study, lasting six months, was conducted in three geriatric wards of Verona Hospital. For each patient, at the admission and during the hospitalization, physicians and nurses registered the ADRs and drugs responsible. Health staff was also requested to report ADRs to the Italian Pharmacovigilance System.

Results: The hospital admission of 114 patients (11% of 1023 studied inpatients) was caused by ADRs. The patients which experienced an ADR during the hospitalization were 256 (25%). The percentage of admissions due to ADRs is higher in women (12.1%) than men (10.1%), although the difference was not statistically significant (RR 1.19; CI 95% 0.84, 1.69). Also the incidence of ADRs during hospitalization is higher in women (27.1%) than in men (22.7%), close to statistical significance (RR 1.19; CI 95% 0.96, 1.47). The ADRs that most frequently led to hospitalization were the electrolyte alterations: hyponatremia was the most reported, followed by hypokalemia and hyperkalemia. During hospitalization the electrolyte abnormalities were also the most frequent ADRs, albeit with a different order: hypokalemia, followed by hyponatraemia and hyperkalemia. The drugs most involved in the development of ADRs causing hospitalization were diuretics, followed by antiplatelet agents and ACE inhibitors.

During hospitalization the drugs most involved in ADRs were, once again, diuretics, followed by anticoagulants and antibacterials.

During the six-month period of the study, the Pharmacovigilance System received 32 reports of ADRs coming from the geriatric wards (underreporting = 91.3%).

Conclusions: A significant incidence of ADRs leading to hospital admission or occurring during hospitalization was found among elderly people. Many of the implicated drugs in ADRs were old drugs. Our study showed that most of these ADRs are potentially preventable and that the vigilance by clinicians and nurses in detecting, diagnosing, and reporting ADRs is important for continued drug safety monitoring.

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72. Risk Management Plans in the Argentinian Regulatory Administration: Current Situation

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Introduction: In Argentina, an ANMAT regulatory Act of 2000 suggests to the MAH to send ADRs to the Pharmacovigilance Department (PhD). In 2008 an update of that Act was released, and included an item referred to Risk Management Plans (RMP). That article recommends to the MAH that all RMPs should be submitted to the PhD for approval.

Aim: To describe the current situation for risk management plans submission in Argentina.
Materials and Methods: The PhD receives and assesses the RMPs from the MAHs. A list of all RMPs is created. The rationale of this assessment are the ICH E2E guidelines and the Volume 9A of EMEA. An excel file is developed, and includes Name of the drug, MAH, date of approval, date of submission, consistency with recommendations according to guidelines, improvement requirements and outcome of this requirements.
Results: Since the 2008 update we received 31 RMPs from 12 different MAHs, 3 of them from a national MAH. All of them were consistent with the recommendations except the lenalidomide RMP that needed an improvement requirement that was fulfilled in a late submission. That RMP was the only one submitted prior to the launch.
Discussion: Almost all of the received RMPs were from drugs that were previously on the market. Only lenalidomide was sent before launch as a requirement due to the chemical similarities to thalidomide. Since the 2008 update wasn't mandatory the amount of RMPs submitted was small.
Conclusions: We believed a mandatory act must be implemented in order to achieve the ultimate goal that all drugs must have an RMP before launch. That act will be presented for discussion within this year.

73. Pharmacovigilance for Tuberculosis does not Feature Prominently in Grant Applications to the Global Fund to Fight AIDS, Tuberculosis and Malaria

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Introduction: The Global Fund to Fight AIDS, Tuberculosis and Malaria (GF) is a major provider of resources for tuberculosis (TB) control programs in low resource settings worldwide and 112 countries have now benefited from grants for TB. In 2002, the GF Board strongly recommended that recipients of its grants undertake pharmacovigilance (PV) and, if necessary, request financial support from the GF for this purpose. Adverse drug reactions to medications used against TB are known to be frequent, particularly in patients having HIV and those on regimens for drug resistant TB.[1-3]
Aim: To assess the PV component of recent proposals for TB control made in national applications to GF.
Methods: GF applications from grant recipients of Round 4 to Round 9, as well as their Procurement and Supply Chain Management plans if available, were searched for the presence and quality of a pharmacovigilance plan. A list of pre-tested terms was used in the search.
Results: The 117 countries receiving grants from the GF made a total of 431 proposals in Rounds 4 to 9. Of the 145 proposals for TB, 41 (28%) indicated that the country or public health programme had a PV system in place and indicated some of the activities they may be undertaking under the grant proposal. The proportion of proposals with a PV component for TB increased substantially between Round 4 (7%) to Round 9 (45%). The quality of proposals with PV varied widely. Of twelve countries with acceptable proposals for PV of anti-TB medicines, only seven are full members of the WHO programme for international drug monitoring. Twenty six countries made no mention at all of PV in their applications and PSM.
Conclusions: To date, countries applying for GF grants have not systematically included PV in their funding proposals. In those that did, there is yet no indication of whether the activity was implemented or about its effectiveness. In addition, the quality of the PV component of the proposals varied widely. It is recommended that all GF applications indicate what PV activities are being carried out in-country even if the country is not seeking support for monitoring the safety of drugs and even if the PV would be carried out by another agency. This is particularly important as countries scale up their treatment programmes for drug resistant TB.

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74. An Overview of International Reporting to WHO of Adverse Reactions to Anti-Tuberculosis Medication

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Introduction: Since 1968, the WHO International Drug Monitoring Programme has been collecting spontaneous individual case safety reports (ICSRs) on adverse reactions to medications from national pharmacovigilance centres worldwide.[1] This database, which now has over 5 million reports, represents a unique source of information on side effects to medicines used to treat diseases like tuberculosis (TB).
Aim: To describe patterns of spontaneous reporting of adverse drug reactions to anti-TB drugs.
Methods: A study of reports in the WHO ICSR database until 20 May 2010 was performed. ICSRs containing a "critical term"[2] were considered serious. This study included only reports linked to rifampicin, its derivatives isoniazid, ethambutol, pyrazinamide, thioacetazone, fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin), and injectable agents (amikacin, capreomycin, kanamycin, streptomycin). Reports where TB (confirmed or suspected) was not specified as an indication were excluded.
Results: There were 6904 ICSRs related to TB drugs from 75 countries. The number of reporting countries increased over time (see table I). Fluctuations in TB-drug related ICSRs occurred over time for certain drugs but their total number increased markedly in the last decade. In the 11 countries reporting a cumulative of >200 TB-drug related ICSRs, the proportion of ICSRs linked to TB-drugs out of the total ranged from 1% or less in high income countries to 11% in Viet Nam and 14% in Romania. The proportion of TB-drug related ICSRs with a critical term reported varied from 15% to 55% in these 11 countries (34% overall).
Conclusions: While the reporting of TB-drug related ICSRs increased and became more widespread, present figures do not reflect the real burden of adverse drug reactions in TB patients. Some fluxes in reporting, such as the drop in ICSRs attributed to thioacetazone and

Table I. International reports of ICSRs by associated anti-TB drug over time

Drug[a]	Up to 1980	1981–1990	1991–2000	2001–2010[b]
Rifampicin derivatives	482	615	766	1452
Isoniazid	321	557	761	1425
Ethambutol	245	205	221	644
Pyrazinamide	23	244	342	866
Thioacetazone	5	102	7	4
Fluoroquinolones		9	27	106
Injectable agents	294	221	57	413
Total ICSRs related to TB drugs	1245	1531	1347	2781
TB-drug ICSRs as % of all ICSRs	0.67%	0.23%	0.09%	0.10%
% of TB ICSRs with critical term	31%	32%	38%	33%
Countries reporting TB ICSRs	22	24	40	69

a Includes combinations of drugs, therefore sum of individual reports > column totals.

b Up to 20/05/2010.

streptomycin after the end of the 1980s, probably reflect the diminished use of these drugs in many countries. One third of reports are flagged as serious but this ratio varied markedly by countries more than by drug group, suggesting national differences in thresholds for reporting to WHO. The proportion of ICSRs attributed to anti-TB drugs also varies substantially between countries and reflects at least in part the frequency of TB and the intensity of TB drug use in a country. Efforts to increase spontaneous reporting by countries and improve its quality should continue so as to expand our understanding of ICSRs, including on long-term effects and risk factors for adverse reactions.

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75. Current Problems in Early Perception of Unexpected Hepatotoxicity

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Background: Hepatotoxicity is a main reason for the cessation of further drug development and for postapproval drug regulatory decisions. Usefulness of currently used scales for causality assessment in hepatotoxicity has not been fully explored.[1-3]

Objectives: The goal of this analysis was to compare the two most widely used scales in unexpected hepatotoxicity reported in Serbia, and to review their usefulness in signal detection.

Methods: We compared a nonspecific scale (NARANJO)[4] with a liver-specific one (CIOMS/RUCAM)[5] in 19 cases of unexpected hepatotoxicity reported in the period 2004–2009. Data of the cases were collected by a network of a medical specialist by using a structured reporting form. The agreement between causality assessments obtained with these two scales was analysed by *Kappa weighted* (K_w) statistical test.

Results: Of the 19 cases, 5 were with fatal outcome, 1 was life-threatening, 14 were with hospitalisation and 8 were jaundiced. There was no significant difference in gender distribution (52.63% males), mean age at onset was 47.58 years, and alcohol use was reported only in 1 patient. In 13 cases, the drug was an unknown cause of hepatotoxicity. In 10 of these cases, herbal medicines were implicated. In other 6 cases, hepatotoxicity was unexpected in terms of nature and seriousness. The agreement between these two scales was observed in 8 cases (42.11%, Kw of 0.28), with disagreement of one level in 11 (57.89%) cases. Disagreement of two levels between compared methods was not observed. Of the 13 cases in which the hepatotoxicity was scored as possible using the NARANJO scale, the agreement with the CIOMS/RUCAM scale was observed in 7 cases. However, of the 6 cases in which the hepatotoxicity was scored as probable using the NARANJO scale, the agreement with the CIOMS/RUCAM scale was observed only in 1 case. Causality score obtained with the CIOMS/RUCAM scale was lower in 11 of 19 cases of unexpected hepatotoxicity, in comparison with the NARANJO scale.

Discussion: The outcomes of the two methods were mainly influenced by differences in the values attached to the answers to the questions concerning previous information, concomitant drugs and alternative causes. At pharmacovigilance centers, the scale is more useful if it is not asked for "previous knowledge" and if it gives higher causality score, thus enabling early perception of unexpected serious reaction.[6]

Conclusions: This analysis reminded us of the need for the modification of the CIOMS/RUCAM method, which would contribute to better detection of unexpected hepatotoxicity.

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76. Skin Cancers Associated with Anti-TNF-α Treatments: A Signal Detection Analysis of the Italian Spontaneous Reporting Database

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Background: Tumour necrosis factor (TNF)-α plays a major role in the malignancy surveillance. An increased frequency of tumours has been

suggested for anti-TNF-α drugs, and the risk of neoplasms is currently labelled for infliximab, etanercept, and adalimumab. Malignant melanoma and basal cell carcinoma have been hypothesized as tumours associated with anti-TNF-α therapy.[1]

Aim: To investigate possible ''alarm signals'' of skin cancers associated with anti-TNF-α drugs.

Methods: The present analysis was performed on spontaneous reports of adverse drug reactions (ADR) received by the Italian Drug Agency (January 2000 - March 2010), integrated with ADR reports recorded by the Interregional Group of Pharmacovigilance (GIF) (1988–2006). Associations between drugs and skin cancers were assessed by means of ADR proportional reporting ratio (PRR), as a measure of disproportionality. Cases were defined as reports including at least one ADR codified with WHOART preferred term as ''malignant melanoma'' or ''basal cell carcinoma''. Non-cases comprised all remaining reports. Index reports included ADR associated with etanercept, infliximab or adalimumab while all ADR reports not involving index drugs were used as controls. PRR was calculated only for index drugs with at least 2 cases in the whole database.

Results: According to selection criteria, 116 142 reports were included in the analysis. Anti-TNF-α were indicated as suspected drugs in ADR reports as follows: 561 reports for infliximab, 340 reports for etanercept, 193 reports for adalimumab. An overall number of 14 cases of malignant melanoma and 8 cases of basal cell carcinoma were identified in the database. Anti-TNF-α drugs were considered as suspected in 7 cases of malignant melanoma (infliximab: 1 case, PRR: NA; etanercept: 3 cases, PRR: 92.9 [95% CI: 25.8, 334.5]; adalimumab: 3 cases, PRR: 163.8 [45.3-591.7]) and 8 cases of basal cell carcinoma (infliximab: 1 case, PRR: NA; etanercept: 3 cases, PRR: 204.4 [95% CI: 48.7, 858.7]; adalimumab: 2 cases, PRR: 200.3 [95% CI: 40.2, 998.6]).

Conclusions: The estimation of PRR suggested a significant risk of reporting of malignant melanoma and basal cell carcinoma for etanercept and adalimumab. Although the present analysis is limited by the small number of reports and the elevated PRR values are due to the rarity of drug-associated skin cancer, our findings are in line with previous studies. Since the mechanisms underlying these ADRs likely depend on TNF-α blockade, it is reasonable to suggest skin cancers as rare class effects of anti-TNF-α treatments.

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77. Variations Across Drug Classes in Reported Time-to-Onset of Suspected Adverse Drug Reactions

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Background: The time from treatment start to onset of a suspected adverse drug reaction (ADR), hereby denoted time-to-onset (TTO), is fundamental to causality assessment.

Objectives: To study the extent to which reported TTO for a selection of ADRs in the WHO Global individual case safety report database, VigiBase, corresponds to information in the literature and is subject to variation by drug class.

Methods: Six commonly drug-induced ADRs were chosen using the MedDRA® terminology: agranulocytosis, angioedema, hepatitis, serum sickness, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Reported drugs were grouped using the WHO Drug Dictionary Enhanced and WHO Anatomical Therapeutic Chemical (ATC) classification (4th level). Only reports with one single suspected drug and complete treatment start and ADR onset dates were included. Box-plots were produced for the reported TTO of each ADR for the ten most frequently reported ATC groups.

Results: The reported TTO corresponded well to the literature for the six ADRs. Hepatitis exemplified the only substantial deviation with a shorter reported TTO than the chosen reference. Most drug classes displayed similar TTO for the respective ADRs, although some important variations were identified. Considerably longer TTO than for other drugs was found for agranulocytosis with clozapine, for angioedema with ACE-inhibitors, and for hepatitis with statins. Shorter TTO than for other drugs was observed for Stevens-Johnson syndrome and toxic epidermal necrolysis with antibiotics and non-steroidal anti-inflammatory drugs.

Conclusions: Aggregate information on TTO may be a useful reference in signal strengthening and refutation. Variations between drug classes can be influenced by treatment length, indicate different mechanisms or alternate explanations to the reported event, such as an association with the underlying disease. The possibility of a confirmation bias must also be considered, since events occurring with TTO suggestive of a causal association are more likely to be reported as suspected ADRs.

78. National Cohort Event Monitoring with Pandemic Influenza A/H1N1 Vaccines

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Introduction: From the start of Moroccan'campaign against pandemic influenza A /H1N1 in November 2009 to march 2010, The H1N1 vaccines in use in Morocco are Pandemrix and Arepanrix from GSK and Panenza from Sanofi Pasteur. 703 965 Subjects were immunized with pandemic H1N1 vaccines to 5 March 2010.

Aim: Moroccan Pharmacovigilance Centre (CNPV) has conducted a monitoring program strengthened including AEFI surveillance to evaluate the safety and efficacy of influenza A/H1N1 vaccine and to determine the frequency and the prevalence of occurrence of adverse reactions (AE) to influenza H1N1 vaccines in the immunized population selected.

Methods: it is a prospective cohort study included a sample of 1000 people vaccinated and monitored over a period of six months after immunization by pandemic influenza H1N1 vaccines. The study has been conducted at 10 immunization sites randomly selected.

Results: In the study, CNPV have received 771 reports of AE possibly related to vaccines administration, corresponding to a total of 882 adverse events, highly observed by Pandemrix and Arepanrix vaccines in 95% of cases. Frequently reported adverse events were local reactions with 39, 68% (350/882), general reactions 29, 47% (260 AEs) and neurological reactions with 18, 36% (162 AEs). Most of the AE (82.5%) were observed during the first 48h after immunization, 17% within two weeks after vaccination. no serious case was reported in the study. The high rate of notification has been identified in health care workers with a notification rate of 149 per 10 000 doses administered.

In the population with diabetes and chronic respiratory diseases, AEs were reported in 30.60% with a notification rate of 10 per 10 000 doses administered.

Conclusions: The analysis of all AEFI indicates that the vaccines used against pandemic influenza in Morocco have an excellent safety profile similar to that observed in clinical trials and in other countries.

79. Neurological Adverse Reactions Associated to Vaccination: Data from the Italian Spontaneous Reporting System

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Introduction: Serious neurological complications following vaccination raised fears and concerns about the safety of some vaccines. Studies have demonstrated the lack of association between autism, mumps, or multiple sclerosis and measles, rubella or hepatitis B vaccines respectively.[1,2] For other neurological events, such as Guillain-Barrè syndrome associated to influenza vaccination, contrasting data have been published.[3] On the other hand convulsions or hypothonic-hyporesponsive episodes are well known neurological events associated to vaccination.
Aim: To analyze the report with neurological adverse events associated to vaccines in the Italian Pharmacovigilance database.
Methods: Vaccines are coded with an Italian terminology that include ATC code. Reactions are coded with both WHO-ART and MedDRA® terminologies, but the first one has been used to group adverse reaction in this paper. Causality assessment of reports is made by the pharmacovigilance personnel using the WHO causality assessment method for AEFI. Neurological events have been defined as the event related to the WHO-ART System Organ Classes Central, Peripheral and Autonomic Nervous Systems (SOC codes 0410 and 0420).
Results: Vaccine spontaneous reporting rate in Italy in 2009 was 58.4 report per million inhabitant, with an increase of 77% compared to 2008. Up to March 31 2010 19 385 reports related to vaccines were present in the database; 3492 of these (18%) include at least one neurological reaction. Twenty-six percent of neurological reports were serious including 16 cases with fatal outcome. The most reported event was headache/migraine (1100 reports) followed by convulsions (including fever convulsions, 500 reports), hypotonia/hyporesponsiveness (395) and paraesthesia (305). Other serious reported reactions were ataxia (219), gait disturbance (204), neuritis (107), encephalopathy (95), and Guillain-Barrè syndrome (66). Vaccines most frequently associated with neurological events were hexavalent vaccine (571 reports with at least one neurological reaction, 14% of total reports associated to hexavalent vaccine), followed by pandemic H1N1 vaccine (437 reports, 33%), influenza vaccine (434, 22%), measles mumps and rubella vaccine (MMR) (421, 15%). Post vaccination neurological events are continuously monitored looking for potential signal. The last discussed issue is the increase of serious neurological events like ataxia associated to the combined vaccine MMRV (measles, mumps, rubella and varicella).
Conclusions: Neurological events are often temporally associated to vaccination. Some of these events can be serious and could raise serious concerns on the vaccine safety profile. A causality assessment evaluation together with the analysis of epidemiological data is necessary in the validation of potential signal.

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80. Importance of Spontaneous AEFI Reporting in Decision Making at National Level in the Routine Vaccination Programme for Maintaining Vaccine Safety

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Surveillance of vaccines safety on the territory of the Republic of Croatia is coordinated jointly by the Agency for Medicinal Products and Medical Devices (HALMED) and Croatian National Institute of Public Health (CNIPH). Therefore, in November 2006, a joint expert group for AEFIs has been established. In case of spontaneous reports of serious AEFIs, including suspected clustering of AEFIs, expert group makes a joined decision on further actions.
The importance of spontaneous AEFI reporting and joint surveillance of vaccines safety by HALMED and CINPH in decision making at national level in the routine vaccination programme for maintaining vaccine safety will be shown by the case of symptomatic horizontal transmission of the L-Zagreb mumps virus strain in Croatia:
The first case of *symptomatic horizontal transmission to adults after primovaccination of the child with Leningrad-Zagreb (L-Zagreb) mumps vaccine strain* was reported in the last quarter of 2005 and it referred to an adult patient (mother of the vaccinated child) developing unilateral parotitis and aseptic meningitis. At the beginning of 2008 four additional cases of symptomatic horizontal transmission were reported. After this clustering of horizontal transmission cases was detected, in February 2008, HALMED undertook risk minimisation activity that included risk communication on the new safety issue by carrying out safety variation to update vaccine's Summary of Product Characteristics and Patient Information Leaflet and by issuing Dear Doctor Letters. Short after the intervention, additional 26 cases of were spontaneously reported. Based on the number of spontaneous reports received, and their clinical relevance HALMED and CNIPH jointly decided to propose the replacement of the L-Zagreb strain with less immunogenic Jerry Lynn strain in the national vaccine mumps programme. This was implemented at the beginning of 2009. No new cases were reported since this intervention. All reports were collected through the national system of spontaneous reporting of AEFI and to our knowledge this is the world's largest number of cases of symptomatic and clinically relevant horizontal transmission of mumps virus strain after MRR vaccination. The system of spontaneous AEFI reports in which two main institutions interact has been proven critical for recognizing the safety issue and reacting on time to stop the shed of L-Zagreb mumps virus strain. The setting of shared responsibility over vaccine safety has proven to be both flexible and efficient, what was especially important in a highly delicate situation that posed potential threat to public health.

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81. Fast Detection of Adverse Drug Reactions of New Drugs by Community Pharmacists

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Introduction: Pharmacists have been recognised as having an important role in pharmacovigilance.[1] In that vein pharmacists in several countries are encouraged to submit spontaneous reports of suspected adverse drug reactions (ADR) to national health authorities. Likewise community pharmacists i.e. have participated in prescription event monitoring studies as intermediates.[2] The pro-active role of community pharmacists in pharmacovigilance based on face-to-face questioning of medicine users is yet a source for safety data and it has not developed into its' full potential. Being a profession increasingly engaged in customer centred care - i.e. detection, management and documentation of drug related problems – community pharmacists are in a unique position for detecting user experienced ADR. A feasibility study conducted in Denmark in 2009 revealed that the face-to-face questioning of medicine users about ADR in relation to drug dispensing constitutes a valid approach in detection of ADR.[3]
Objective: The study reports from an ongoing study of the newly launched anti-diabetic drug Victoza® and seeks to document ADR experienced by recurrent ordinary users through face-to-face questioning upon drug dispensing.
Methods: Pharmacy students undertaking regular internship at a community pharmacy – 8th semester - were approached as proxies for community pharmacists. On top of course work on patient centred drug management students attended a training seminar focusing on questioning medicine users in order to elucidate and achieve precise descriptions of experienced ADR. Recurrent users of Victoza® are asked about any experienced ADR. ADR are detected and reported through a semi-structured interview guide/algorithm.
Results: Within 2 months 14 students have approached 38 users of which 22 reported possible experienced ADR linked to Victoza®. 17 reports contain information on users initially experiencing nausea and generally reported to disappear within the first couple of weeks of treatment. Further diarrhoea, decreased appetite and dizziness have been reported.
Discussion: The collected ADR are all described in the summary product characteristics of Victoza®.[4] The results support the hypothesis that community pharmacists' may prove a valuable contribution in the process of signal generation of new drugs. Community pharmacy based pharmacovigilance is a low cost tool relying on existing skills among pharmacists. Due to the frequent contact with medicine users the approach has a wide range reaching possibly all users in the society. With educated pharmacists the approach may prove useful in all types of community pharmacy settings and may take the form as regular cohort studies or as part of intensive monitoring.

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82. Identifying the Incidence, Risk Factors and Mechanism of Rituximab induced Thrombocytopenia: A Cohort Study Using the Utrecht Patient Oriented Database

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Background: Drug-induced thrombocytopenia (DIT) is an increasingly common cause of isolated thrombocytopenia and is a known side effect of rituximab. Two mechanisms can cause DIT: (1) decreased platelet production via marrow suppression and (2) peripheral platelet clearance, usually by an immune mechanism. There is limited information on the incidence and risk factors for the development of thrombocytopenia with rituximab and although an immune-mediated mechanism is hypothesized further evaluation is needed.
Objectives: To estimate the incidence of rituximab induced thrombocytopenia, to identify risk factors and to evaluate the possible underlying mechanism.
Methods: Data was obtained from the Utrecht Patient Oriented Database (UPOD) in the University Medical Center Utrecht, the Netherlands. This cohort study included patients treated with rituximab between January 2005 and December 2009. Patients were included if they had a complete blood count 30 days before the start and 30 days after the end of the treatment episode. Thrombocytopenia was defined as a platelet count below 100 x 10^9 platelets/L. Potential risk factors for thrombocytopenia, including patients, disease and treatment characteristics, were compared between patients with and without thrombocytopenia using logistic regression. A high mean platelet volume (MPV) and platelet distribution width (PDW) are indicative for an immune-mediated mechanism, which were compared for patients with and without thrombocytopenia with a students t-test. Also the proportion of patients with an abnormally high MPV (>9.5 fL), was compared with a chi-square test (SPSS, version 16.0).
Results: Of the 235 patients treated with rituximab, 72 were eligible for inclusion. Eighteen patients developed thrombocytopenia resulting in an estimated incidence of 7.7%. Risk factors include use of rituximab in the oncology indication as compared to the auto-immune indication (OR: 0.16; 95% CI: 0.03, 0.75) and a haemoglobin level ≥12.5 g/dL before administration of rituximab (OR: 3.50; 95% CI: 1.09, 11.22).
Before start of treatment there was no difference in MPV between patients with and without thrombocytopenia (7.8 vs 7.7 fL). After treatment patients with thrombocytopenia had a significant higher MPV compared to patients not developing thrombocytopenia (10.0 vs 8.0; $p < 0.001$) and also the proportion of patients with an MPV >9.5 fL was higher (38.9% vs 9.3%; $p = 0.008$). No difference in PDW was found.
Conclusions: Patients treated with rituximab in the oncology setting and patients with a pre-treatment haemoglobin level above 12.5 g/dL were at an increased risk for thrombocytopenia. More frequent monitoring of their blood count is advised. Based on the MPV an immune-mediated mechanism seems highly likely.

83. Specific Characteristics of African Individual Case Safety Reports

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Background: Many of the new countries contributing with individual case safety reports (ICSR) to the WHO Global ICSR database,

VigiBase,[1] are African. There is so far no summarized information on the reports from this continent.

Objectives: To investigate characteristics of African reports in VigiBase in comparison to reports from the rest of the world.

Methods: VigiBase data up to 5th of February 2010 was included in the study. Duplicate reports were excluded using an automated duplication detection tool, according to previously described algorithms.[2] Only one report in a group of suspected duplicates (the one with the greatest amount of information) was kept in the analysis. Drugs were mapped and grouped using information in the WHO Drug Dictionary Enhanced. Adverse drug reactions (ADRs) were classified with the WHO adverse reaction terminology preferred terms. We compared the most frequently reported drugs and type of ADRs (including WHO-ART critical terms, which indicate that a serious event has occurred), age, sex, and primary reporter for African reports with all other reports in VigiBase.

Results: After excluding duplicates, a total of 4 925 984 reports were retrieved from VigiBase, of which 20 455 reports originated from 18 African countries. South African (n = 10 214), Tunisian (n = 4077), and Moroccan (n = 4054) reports represented 90% of all African reports. Among the African countries, these three had also been members of the drug monitoring programme the longest time. Antiretroviral medicines were most commonly reported for this continent compared with selective serotonin reuptake inhibitors reported for other VigiBase reports. The type of ADRs reported most often were pruritus, urticaria, and rash maculo-papular, compared with rash, nausea, and fever for other VigiBase reports. Most frequently reported critical terms for African reports were lactic acidosis, face oedema, and peripheral neuropathy, whilst death, thrombocytopenia, and face oedema were most often reported for the rest of the world. 61% of the African reports concerned women compared with 60% for other reports in VigiBase. 17% of the African reports were for children (0 to 17 years), compared with 13% in the rest of the world. A physician was the primary reporter for 85% of the African reports, whilst it was 43% for the other reports in VigiBase.

Conclusions: Data in VigiBase demonstrated that African reports have different characteristics than reports from other parts of the world with regard to the most frequently reported drugs and type of ADRs, age distribution, and primary reporter.

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84. Cutaneous Vasculitis Associated with Paracetamol, Codeine and Caffeine: A Case Report

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Vasculitis is a severe cutaneous reaction that is not known with use of analgesic drugs.

We reported here the case of a cutaneous vasculitis with the association of paracetamol, codeine and caffeine.

This case concerned a 39 year-old female who presented erythematous lesions associated with purpura on her lower limbs mainly on the left one. Since 3 months, she was treated by PRONTALGINE® constituted of paracetamol 400 mg, codeine 20 mg and caffeine 50 mg for fibromyalgia. Blood tests revealed negative antinuclear antibodies, normal hepatic and renal functions. The CRP level was normal.

The cutaneous biopsy showed a vasculitis for which the responsibility of the drug was evoked.

Two weeks after the drug discontinuation, a resolution of the lesions was observed.

Based on a MEDLINE search, we found rare cases of vasculitis after use of paracetamol and no case with codeine. Although this effect could be considered rare, clinicians should be aware of possible association between vasculitis and intake of paracetamol and/or codeine.

85. Regional Pharmacovigilance Centre and Green Channel Consultation Centre: a Synergy in the Monitoring of Vaccines in the Veneto Region

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Italian spontaneous reporting system collects reports associated to vaccines and to other drugs. Spontaneous reports are sent by the reporters to the Public Health Units (PHU) where data are inserted into the Italian pharmacovigilance database by a web-based software. Regional Pharmacovigilance Centres collaborate with the National Agency in signal detection analysis. Since 1988 the Regional Pharmacovigilance Centre of the Veneto region has been working to improve spontaneous reporting, analyzing periodically reports both by case-by-case analysis and data-mining tools.

At regional level, distribution and administration of vaccines and surveillance of adverse events is also responsibility of the Regional Public Health Authority.

In the Veneto Region, a Reference Centre for pre-vaccination consultancy and adverse event following immunization (AEFI) surveillance, named Green Channel, has been funded by the Regional Public Health Authority in 1993. The Centre, active at the Immunology Unit of the University Hospital in Verona, has the following tasks: (1) a specialized pre-vaccination consultancy for the PHUs, to evaluate the eligibility for vaccination of subjects with history of previous AEFI or contraindication; (2) a surveillance system for AEFIs reported in the Veneto region.

The Green Channel consultancy service is alerted on specific cases. Subjects with history of previous AEFI and/or potential contraindication to vaccination as potential risk factors are evaluated by clinical and/or accurate record's examination, an in-depth anamnesis, and *in vivo*/*in vitro* tests where necessary, to identify specific sensitizations; eventually, specialist consultation from other disciplines is performed. For each case, a conclusive report is sent to PHU, containing instructions for vaccination with standard procedure or precautions, or, in selected cases, for temporary suspension or exemption. In the period 1992–2009, 1425 subjects have been evaluated and 85% of them have been found eligible for vaccination with standard procedures or precautions.

The Veneto Regional Centre of Pharmacovigilance and the Green Channel have established an active and synergic collaboration in AEFI collection and analysis. The experience in signal detection and data mining combined with the clinical experience coming from the consultancy service and collaboration with PHU personnel results in a more effective monitoring of AEFI.

The spontaneous reporting rate for vaccines is very high in the Veneto region and most of the vaccine-related signals identified in Italy has been based on a first identification in this region.
The collaboration between the Regional Pharmacovigilance Centre and the Green Channel will be presented as a model to improve vaccinovigilance activities at national and international level.

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86. Drug-Induced Rhabdomyolysis: Reports from the Italian Database of Spontaneous Reporting of Adverse Drug Reactions

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Background: The association between statins and rhabdomyolysis is well documented and reported in several studies. There are also many evidences that the frequency of this adverse reaction is increased by concomitantly administered medications that inhibit statin metabolism; it is reported that approximately 50% of patients experiencing statin-induced rhabdomyolysis were receiving an interacting drug known to increase statin plasma concentrations.[1] However, recently case reports have been published suggesting a possible association between rhabdomyolysis and other drugs, such as laxatives,[2] atropine,[3] esomeprazole.[4]
Aim: To describe and discuss the spontaneous reports of drug-induced rhabdomyolysis in the Italian Pharmacovigilance database.
Methods: The database holds reports of suspected ADRs submitted since 1988. Every 6 months the database is analysed to filter out potential signals. Signal detection is done by qualitative case-by-case analysis and by using as quantitative methodology Proportional Reporting Rate (PRR).
Results: The Italian database actually holds 110 497 reports, 90.1% of them coming from physicians, 4.9% from pharmacists, 1.4% from nurses and only 0.3% from consumers. Rhabdomyolysis was reported in 416 reports with 119 different drugs. Seventy-one percent of reports have been associated to a statin or to a fibrate. The most involved statins were simvastatin (102 reports), atorvastatin (57), cerivastatin (43), pravastatin (22); the most involved fibrates were bezafibrate (22) and gemfibrozil (17). Among the other drugs the most reported were levofloxacin (9), haloperidol (8), cyclosporine (7) and olanzapine (6).
Rhabdomyolysis have been evaluated as a signal associated to paracetamol, colchicine, ceftriaxone, levofloxacin and lansoprazole.
In the Italian database we have 10 reports with rhabdomyolysis associated to macrolides (5 reports associated to chlarythromycin, 3 to azythromycin 1 to erythromycin and 1 to rokitamycin) drugs that do not report this reaction in their summary of product characteristics (SPC).
Moreover two cases of rhabdomyolysis after the administration of raltegravir has been reported; this reaction is not present in the SPC but recently some case reports described this possible association.[5]
Conclusions: Signal detection by qualitative case-by-case analysis could be an important instrument to identify possible new associations between drugs and adverse events. It is well known that rhabdomyolysis is a possible adverse event during statins or fibrates therapy, while it is rarely associated to other drugs.

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87. Linking Pharmacovigilance and Pharmacogenomics: Pharmacogenovigilance: An Idea whose Time has Come

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Introduction: Both pharmacogenomics and pharmacovigilance, in essence, aim to understand "heterogeneity" and population substructure in the distribution of drug efficacy and safety signals. Despite this undeniable conceptual and practical synergy, these two disciplines and their interest groups have not converged appreciably to date. In this regard, it is notable that the drugs that are frequently cited in ADR studies (59%) are reportedly metabolized by at least one enzyme with a genetically polymorphic variant allele known to be associated with altered drug metabolism.
Aim: To propose the new term "pharmacogenovigilance" defined as pharmacovigilance activities informed and guided by accompanying pharmacogenomic analysis to add a more mechanistic insight on ADR reports and contribute to causality assessments. In other words, pharmacogenovigilance would elevate the pharmacovigilance reporting to a more mechanistic context and could "raise the bar" for pharmacovigilance reporting standards, making them more scientific and mechanism oriented.
Methods: The Turkish Pharmacovigilance Center (TUFAM) aims to assess new pharmaceutical preparations for both effectiveness and safety prior to market authorization as well as during the postmarketing phase. For this purpose the study on ADRs reported to TUFAM with pharmacogenetic data have been searched.
Results: The spontaneous reports with mechanistic underpinning and firm pharmacogenetic causality assessment were very few and needs improvement. These reports will be discussed during the presentation.
Conclusions: National pharmacovigilance centers can develop methods for informing the health care professionals and patients about a possible pharmacogenomics involvement in the pathogenesis of a reported ADR, and facilitate access to high-throughput genomic analyses. It should be noted that pharmacogenovigilance could include not only ADRs but also analysis of drug resistance and therapeutic failures. Pharmacovigilance cannot afford to neglect the concept of pharmacogenomics.

88. The Knowledge and Attitude of the Undergraduate Students in the Faculty of Pharmacy Towards Pharmacovigilance

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Introduction: In July 2005, Turkish Ministry of Health adopted a more systematic approach to the safety of prescription medicines and

introduced new regulations for pharmacovigilance activities. In this matter, the Turkish Pharmacovigilance Center (TUFAM) aims to assess new pharmaceutical preparations for both effectiveness and safety prior to market authorization, as well as during the postmarketing phase. It's well known that education and training has positive effect on attitudes and knowledge of pharmacovigilance in health care professionals.

Aim: We have investigated the effectiveness of education on the knowledge of pharmacovigilance in the first, third and last grade pharmacy faculty students.

Methods: Ninety nine pharmacy students joined the survey. Thirty of them were first grade, thirty five were third grade and thirty four were last grade pharmacy students. The questionnaire had questions to test their knowledge about the existing national pharmacovigilance system in Turkey and its aim. The students were asked about their suggestions to reform the current pharmacovigilance system. During this face to face questionnaire, the students were also asked to name a drug that has been withdrawn from the market and the reason for removal.

Results: It was interesting to see that only 14% of the first grade students had an idea about the pharmacovigilance activities in Turkey. However they could not define it properly and believed such activities are carried only by pharmacists. 38% of the third grade students could identify TUFAM but their replies were towards drug resistance and therapeutic failures and they could not name a drug that has been withdrawn. All of the last year students had perfect knowledge of the system and had interesting suggestions to improve the current pharmacovigilance system.

Conclusions: These results show that the teaching of pharmacovigilance in pharmacy education should start in the first grade and continue till the last grade, so that the students can become familiar with the basic structure and learn responsibilities of the system before they graduate.

89. Cardiomyopathy and Fetal Exposure to Fluoxetine: A Case Report

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Mood and anxiety disorders such as depression, panic disorders and obsessive-compulsive disorders are common in women during their childbearing years. In the treatment of these disorders during pregnancy, selective Serotonin Reuptake Inhibitors (SSRIs) are the most frequently prescribed drugs.[1]

We report here the case of a woman treated with fluoxetine during pregnancy who underwent a medical abortion for a fetal cardiomyopathy.

Mrs R. was treated by 40 mg of fluoxetine by day. When she started a pregnancy, this treatment was continued. At 13 weeks of gestation, the echography showed an underdevelopment *in utero* and a congenital heart defect without tricuspid's permeability. Cytogenetic examinations after trophoblast biopsy allowed eliminating chromosome's abnormalities (chromosomes 13, 18, 21 and sex chromosomes). A medical abortion was made at 15 weeks of gestation. The feto-pathologic examination confirmed a fetal hypotrophy and showed hypoplasics right cavity and tricuspid valve. The left cavity was large with hyperplasic wall. There are also a ''small'' omphalocele and a single umbilical artery. Other examinations were normal.

Recently, a study showed a higher rate of cardiovascular defects after SSRIs exposure in the first trimester of pregnancy.[2] This rate was higher with fluoxetine than paroxetine. In the same time, the results of a study on mice indicated that prenatal fluoxetine exposure affects fetal development resulting in cardiomyopathy in a dose-dependent manner.[3] The cardiac abnormality was an increased left ventricular cavity and a decreased wall thickness.

The mechanism was probably linked to the 5HT2B receptor which is required for heart development.[4] The blockade of serotonin uptake by SSRIs inhibited proliferation of cardiac cells.

Hypotrophy of the Mrs R's fetus could be explained by vascular anomaly (single umbilical artery), it's not sufficient to explain the cardiopathy which could be linked to high doses of fluoxetine.

Important doses of fluoxetine (>20 mg/day) during pregnancy should certainly made after taking the benefit/risk ratio into account.

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90. Emergency Contraception: An ''Acceptable'' Solution?

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For one year, between the 06/21/2009 to the 06/21/2010, ten inefficacity reports of emergency contraception with levonorgestrel were declared to the Regional Center of Pharmacovigilance of the Poitiers's CHU. All this cases led to an elective abortion. The middle-age of the women was 29.4 years (19 to 40 years old).

It's known that evolutive pregnancy is possible after emergency contraception. The effectiveness of levonorgestrel up to 72h is based on the result of a trial undertaken by WHO in which levonorgestrel prevented 95% of expected pregnancy when taken within 24h of sexual intercourse.[1] Nevertheless levonorgestrel seems to prevent fewer pregnancies than reported by WHO in line with recent reports suggesting that the efficacy of levonorgestrel might be lower than expected.[2]

Results of a meta-analysis (1625 women) and a study including 1696 women showed a rate of pregnancy respectively of 2.6 and 2.3%.[3]

As it is known firstly that the majority of these pregnancies led to an elective abortion, secondly that levonorgestrel remains a drug with possible adverse events, is it reasonable to accept about 2 and 3% of pregnancies? Can we envisage a misuse of levonorgestrel, a drug easily accessible? Can we also envisage an emergency contraception becoming a simple contraceptive method?

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91. Thromboembolic Events or Stroke Related to Intravitreal Injections of Ranibizumab: A Signal from Italian Pharmacovigilance System

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Background: Ranibizumab is indicated for the treatment of neovascular age-related macular degeneration (AMD). Several pre-marketing clinical trials have demonstrated that intravitreal anti-VEGF (human vascular endothelial growth factor) therapies generally are well tolerated. However, within these trials, there is some circumstantial evidence that links systemic VEGF inhibition to systemic adverse events, particularly systemic thromboembolic events and stroke.[1]

The Summary of Product Characteristics of ranibizumab states that there is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors and that a low incidence rate of these events was observed in the ranibizumab clinical trials without major differences between the treatment groups.

Aim: To investigate the association between intravitreal administration of ranibizumab and systemic ADRs.

Methods: We performed an analysis on the Italian Pharmacovigilance database of spontaneous reports of adverse drug reactions (ADRs). We selected all the reports of suspected ADR attributed to ranibizumab. Furthermore, we make a comparison with data collected in Eudravigilance system.

Results: Up to 15 June 2010, the database holds only eight reports of ADRs associated with the use of ranibizumab, six of which regarding systemic events. These included: ischemic stroke (3 cases), intestinal infarction (1), myocardial infarction (1), hypertensive episode (1). No fatal cases were reported. In the three cases of stroke, one of which presumably preceded by an hypertensive episode, the patients developed the event after 1–3 months of ranibizumab treatment. Two patients had a history of prior stroke. In the case of bowel infarction, the event due to mesenteric artery thrombosis appeared at the third administration of the drug. In the Eudravigilance database we found 114 reports of stroke or thromboembolic events related to ranizumab. The mostly frequent reported events were: myocardial infarction (68 case), cerebral infarction (23), and stroke (17, of which 7 haemorrhagic and 3 ischaemic).

Conclusions: Since all of the intravitreal anti-VEGF agents have been associated with detectable levels in the systemic circulation, there is a scientific rationale for the occurrence of systemic ADRs. Further research is needed to verify if stroke or thromboembolic events related to intravitreal ranibizumab use are ADRs or coincidental events due to other predisposing factors of patients. If the signal will be confirmed, the use of ranibizumab might be contraindicated in patients with previous history of stroke.

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92. Public Perceptions of Increased Post-Authorization Vigilance Towards Pharmaceutical Sector Sustainability

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There has been a notable observed trend towards the strengthening of pharmacovigilance systems for medicines as part of *ex-post* regulation leading to enhanced post-authorization vigilance (Hodges, 2005). For the pharmaceutical industry, the opportunities for economic sustainability are evident. Particularly, the potential for switching from reliance solely on costly pre-authorisation testing of medicines towards postponing completing development post-authorisation as part of lifecycle product management should yield considerable savings by allowing revenues on a marketed product (Hodges, 2008). However, to enable this model requires reinforced post-authorisation pharmacovigilance. While the benefits of this change for the industry may be apparent, several technical and ethical challenges are simultaneously realized. In particular, two questions arise: firstly, how much do we know about the lay value-based implications associated with earlier drug approvals, such as trust in the regulatory system, so that the public will not feel more vulnerable to the occurrence of adverse drug reactions than prior to such a shift in policy? Secondly, how should we hypothesize the social contract desired by patients in regards to the logistics of increased pharmacovigilance, primarily in regards to whom or what would be held accountable for any related adverse outcomes ? We can start answering both these questions by drawing upon existing empirical evidence from similar past case studies in the field of risk perception (Slovic, 1993; Lofstedt, 2005) and by extrapolating from ongoing risk perception research on public attitudes towards the pharmaceutical industry and its regulators in relation to the role of trust in chronic prescription drug-taking. Pooling of such evidence will allow for predictions on how the public might receive earlier approvals through the use of an evidence-based perspective (Chakraborty, 2010).

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93. Electronic Health Record Pharmacovigilance Signal Extraction: A Semi-Automated Method for Reduction of Confounding Applied to Detection of Rhabdomyolysis

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Background: Post-market pharmacovigilance has traditionally relied on spontaneous reporting databases to ensure pharmaceutical safety. Inherent limitations in this method, such as: underreporting, biased reporting rates, incomplete patient information, and indeterminate population exposure,[1] generates obscurity that may be addressed through complementary data sources such as electronic health records (EHR). A major limitation to the utilization of EHR data is the need for expert manual review of cases to distinguish between adverse reactions to drugs and confounding due to treatment indication.

A European Union Adverse Drug Reaction Project (EU-ADR) study identified 23 key serious adverse events important to monitor in EHR databases for pharmacovigilance signal detection.[2] We chose to focus on one of those adverse events, rhabdomyolysis, a relatively common clinical syndrome characterized by acute necrosis of muscle fibers. Rhabdomyolysis may result from myopathy inducing medications or various disease states. Published chart review indicates medications cause 6.9–11% of cases.[3,4]

Aim: To develop a semi-automated method to remove confounding from EHR pharmacovigilance signal extraction. The long-term goal of our work is to apply this method of signal processing to detect the 23 key serious adverse events.

Methods: Our study analyzed EHR data from NewYork Presbyterian Hospital from the years 2004–2008. We included all patients with a serum Creatine Kinase >5 times normal. We wanted to explore if confounding could be removed automatically using Natural Language Processing (MedLEE)[5] and a filter build with expert-knowledge and standardized terms. To test the accuracy of our method, it was compared to a manual review of 150 records.

Results: Compared to the gold standard manual review, our method had a sensitivity of 96.7% and a specificity of 81.4%. There were 687 patients with an elevated CK and a discharge summary. The filtering method was able to remove 522 discharge summaries where the elevated CK could clearly be attributed to a medical condition/disease. A 2 x 2 contingency table analysis of the drugs remaining after removal of confounding revealed several medications known to cause an elevated CK or rhabdomyolysis, including valproic acid, tenofovir, statins, and haloperidol.

Conclusions: As the gold standard of manual chart review is a time intensive process, the semi-automated method, including time required for expert filter development, resulted in a considerable time savings, per 1 hour investment in development there is at least a 20 hour savings in required manual review. Our semi-automated method to remove confounding may be beneficial to others involved in EHR signal processing.

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94. Pharmacoepidemiological Study of Antiretrovirals in Lagos University Teaching Hospital Idi-Araba, SouthWest Nigeria

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Introduction: The introduction of highly active antiretroviral therapy (HAART), a treatment paradigm using three or more antiretroviral drugs in combination, has led to significant declines in HIV-associated morbidity and mortality.[1] In many settings however, despite the effectiveness of antiretroviral drugs in reducing viral load to

undetectable plasma levels, a lot of deaths and morbidity still occur in HIV infected persons. Adverse reactions to antiretrovirals in HIV patients cause medication non-adherence leading to treatment failure.[2]

Aim: The objective of this study was to determine the prescribing pattern, adherence levels and incidence of Adverse Drug Reactions (ADRs) in the PEPFAR Clinic of Lagos University Teaching Hospital (LUTH) Nigeria.

Methods: PEPFAR HIV clinic at LUTH is one of the PEPFAR approved centres for the HIV relief program serving about 8000 registered HIV infected patients.

In this retrospective study all combinations of antiretroviral drugs prescribed to 390 ambulatory patients in the clinic between January 2005 and June 2009 were assessed.

The percentage of each combination prescribed was then calculated and the most frequently prescribed combination of antiretroviral drug was determined.

Adherence in this clinic was measured as a ratio of the number of days of patient attendance.

The incidence of ADRs was also investigated with the aid of drug toxicity forms.

Results: The most commonly used antiretroviral drug combination was found to be a combination of zidovudine, lamivudine and nevirapine (44.39%) followed by a combination of stavudine, lamivudine and nevirapine (19.6%) Five percent of the total number of HIV patients studied had poor adherence with most developing therapeutic failure. The most commonly reported ADR was cough (13.3%) followed by fever (8.75%), skin rashes (8.01%) and body aches (7.02%).

Conclusions: Drug adherence to antiretroviral drugs is essential for good therapeutic outcome in the treatment of HIV infection. Recording of ADRs needs to be improved upon.

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95. Report of Three-Month Survey of Nimusulide Use in Thailand

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Introduction: Following suspension of the national marketing authorization in Finland and Spain due to concerns regarding hepatotoxicity, the Committee for Medicinal Products for Human Use (CHMP) concluded that the benefit/risk profile of nimesulide for systemic use remained positive. The CHMP released a risk management plan for nimesulide use in the EU limiting the maximum daily dose to 100 mg. twice a day for as short a duration as possible, limiting use to the treatment of acute pain, osteoarthritis and dysmenorrheal, contra-indicating use in patients with hepatic disorders and including warnings relating to the risk of serious hepatic reactions. The CPMP Opinion was endorsed by the European Commission in April 2004 and the product information was subsequently amended in line with the legally binding European Commission Decision.

In Thailand, some risk management for nimesulide use was initiated in 2009, including limiting the maximum daily dose, performing risk communication via Dear Healthcare Professionals Letter to reduce risk. Following these restrictions, prescribing information from prescribers and amounts of nimesulide use in hospitals are to be reviewed. Additionally, developing efficient and effective measurement could be evaluated for a nimesulide risk management plan.

Objective: Reviewing hospital prescribing information and nimesulide use after restriction measurements during July- September 2009.

Methods: Data was sourced from hospital information using a survey questionnaire, descriptive analysis was used to analyze the results. The survey was conducted by Health Product Vigilance Centre, Food and Drug Administration, Ministry of Public Health, Thailand. Between July and September 2009, the survey evaluated restriction measurement, amount of nimesulide use, type of hospitals, type of reporters and related information among hospitals nationwide. 421 reports from 1000 public and private hospitals in this three-month survey were evaluated.

Results: The principal results were found that drug use evaluation was the most restriction reported from hospitals (96%), followed by restricted use and restricted dosage regimen in hospitals. Mostly, government hospitals reported the questionnaires (68.40%) when compared with private hospitals (21.40%). The most dosage form used was tablet (59.4%). Pharmacists were the most reporters to the survey (93.10%), followed by physicians (3.80%).

Conclusions: Results from the survey were briefly concluded that some measurements from FDA could effect drug use in hospitals. Even this results have been initiated after some restriction decision. Further evaluation after this survey will be useful for other recommendations or initiate risk management module for manage risk/benefit for Thai FDA in nimesulide use.

Note: The findings and conclusions in these reports are those of the author(s) and do not necessarily represent the views of the Thai FDA.

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96. Bulging Fontanelle Following Vaccination

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Background: The WHO Programme for International Drug Monitoring coordinates the collection of spontaneous adverse reaction reports to medicines from 99 member countries. These reports are entered into a global database, VigiBase, which is managed by the Uppsala Monitoring Centre (UMC). Staff at UMC perform periodic analysis of VigiBase data to look for previously unrecognized adverse effects of medicines. Routine screening of VigiBase highlighted an association between Pneumococcal vaccine and Intracranial Hypertension (IH). Since 1985, UMC has received 175 reports of IH associated with vaccination. This review concerns a subset of these reports, specifically those which refer to 'fontanelle bulging'.

Causes of IH include head injury, cerebral infarction, intracranial bleed, brain tumour, meningitis, acute liver failure, and congenital malformations which result in blockage of the normal CSF drainage mechanism. Signs and symptoms include drowsiness, headache, and vomiting.[1,2] In infants, intracranial hypertension is manifest by bulging of the fontanelles; the large anterior fontanelle is usually not closed until between 12–24 months of age.[3]

Aim: Analyse reports in VigiBase of an association between vaccines and subsequent development of fontanelle bulging.
Method: Clinical review of all reports of intracranial hypertension (specifically those which refer to 'fontanelle bulging') possibly attributable to vaccines (ATC group J07).
Results: There are 28 reports of bulging fontanelle associated with vaccine administration in VigiBase, as of June 21st 2010. The reports come from 12 countries. Gender is specified in all but one report (15 females, 12 males): age at onset varies between 0 days and 12 months (median 4 months). Concomitant medication is reported in three reports (palivizumab in one report, sodium fluoride in one report, and ferric hydroxide polymaltose complex, colecalciferol, folic acid and ascorbic acid in the third).
The vast majority of the reports contain more than one suspected vaccine; the most frequently reported vaccines are pneumococcal vaccine (16 reports) and diphtheria/Haemophilus influenzae b/Tetanus/Polio/Hepatitis B/Pertussis (8 reports).
Discussion: The reports in VigiBase are consistent with the condition "transient bulging fontanelle" described by Freedman et al.[4] This rare condition resolves spontaneously without sequel, but nevertheless requires neurological investigation. The condition is not listed in the labeling of any of the vaccines reviewed. Even if further studies verify this association, it is important to remember, that the benefits of vaccination outweigh the possible risks of this adverse drug reaction.

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97. Pharmacovigilance Program for India for Assuring Drug Safety

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Introduction: With the rapidly growing pharmaceutical industry in India and the absence of an effective Adverse Drug Reaction monitoring system in place, there is a dire need to have a well designed, robust Pharmacovigilance program for India.
Aim: To develop a Pharmacovigilance program for India.
According to the Economic Survey, 2009–10, of the Government of India, the Indian pharmaceutical industry has grown from a turnover of Rs 15 billion in 1980 to about Rs 1006 billion in FY2010 (September 2009). Globally, India now ranks third in terms of volume of production with 10% of global share and 14th by value.[1] India is now being recognized as the 'Global pharmacy of Generic Drugs' with the distinction of providing quality drugs at an affordable cost along with being known as a rapidly emerging hub of Global Clinical trials & Drug Discovery & Development.
The presence of so many products in the market throws up the challenges of monitoring Adverse Drug Reactions (ADRs) in a large population base. With a population of over 1.2 billion people with vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines and varied socioeconomic status there is a requirement of a standardized and robust pharmacovigilance & drug safety monitoring program.
The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi is initiating a nation-wide Pharmacovigilance Program for protecting the health of the patients by assuring drug safety. The program shall be coordinated by the Department of Pharmacology at AIIMS as a National Coordinating Centre (NCC).
The long term objective is to establish a Centre of Excellence for which the PvPI National Coordinating Centre will collaborate with the WHO Collaborating Centre - Uppsala Monitoring Centre (UMC) based in Sweden. The Vigiflow software provided by WHO-Uppsala Monitoring Centre will be utilized as the safety database, where all data originating from India will be maintained in a secure and confidential manner.
Conclusions: The program will ensure that ADR monitoring is done for the drugs approved in India and the risks with any of these drugs are identified and communicated to the relevant stakeholders.

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98. A Signal from the Italian Pharmacovigilance Database: Levodopa/Carbidopa and Polyneuropathy

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Background: Motor fluctuations (MF) are a common problem following the long-term treatment of Parkinson's disease (PD). The short serum half-life of oral levodopa/carbidopa and its variable absorption, are known to be important factors in the development of MFs. Continuous infusion of levodopa/carbidopa into the small intestine of PD patients results in a marked reduction of MFs by reducing plasmatic levodopa variability. During Duodopa infusion side effects are relatively uncommon and are similar to oral dopaminergic therapy.[1] Mild somnolence, confusion and hallucinations are the most common side effects reported. Some reports described the occurrence of Guillain-Barré syndrome (GBS) or polyneuropathy following Duodopa treatment.[2,3]
Methods: We performed an analysis of spontaneous reports collected through the Italian Pharmacovigilance Database (IPD). We selected all cases of critical illness neuropathy associated with Duodopa. The analysis have shown a possible association between critical illness neuropathy and Duodopa assessed by means of adverse drug reaction proportional reporting ratio (PRR), as a measure of disproportionality.
Results: The IPD collected differential diagnoses like neuropathy (2 cases), polyneuropathy (3 cases), GBS (2 cases), all occurring in patients treated with Duodopa. Neuropathy occurred in a 74-year-old man and in a 57-year-old woman following Duodopa treatment. In both cases, electromyography confirmed the diagnosis. The first patient experienced, there was a gradual clinical improvement of neurological function, whereas the second one failed to improve after cessation of the agents. We report three cases of polyneuropathy, a 62-year-old

man, a 76-year-old woman and a 83-year-old woman. The first patient received a diagnosis of chronic inflammatory demyelinating polyneuropathy, the second one a chronic axonal polyneuropathy, and third one a subacute sensitive-motor polyneuropathy. In the first two cases, neurologic improvement was detected following Duodopa reduction, whereas the last one improved following interruption. To note that a 62-year-old man was treated with simvastatin which can induce mild peripheral neuropathy as described in the summary product characteristics. GBS was reported in a 69-year-old man and in a 79-year-old woman, respectively, following treatment with Duodopa. For the first patient, clinical and electrophysiological features supported the diagnosis, and he improved following the interruption of the Duodopa therapy. No data are available for the second patient.

Conclusions: In the IPD, the estimation of PRR suggested a significant risk of reporting of Duodopa infusion and critical illness neuropathy. Moreover, as only limited cases related to neuropathy events and Duodopa[2,3] further studies will be important for assessing this emerging safety issue.

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99. Gastrointestinal Haemorrhages with Use of Clopidogrel: About 12 New Cases Since January 2010 in Poitiers University Hospital

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Increasing use of antiplatelet therapies such as clopidogrel is associated with increasing gastrointestinal (GI) complications such as ulceration and GI bleeding. Since January 2010, among 611 patients treated by clopidogrel and admitted at emergency department, we reported 12 GI haemorrhages leading to hospitalization in intensive care. Clopidogrel could be suspected in all cases.

Patients were 76 years old on average. There were 10 men and 2 women.

The evolution was favourable for 11 patients, one patient died.

Indication of clopidogrel was off label use for 3 patients (stroke).

Eight patients received acetylsalicylic acid and clopidogrel co-therapy.

Six patients presented risk factors for which they were treated by a proton pump inhibitor.

The duration of treatment by clopidogrel before the onset of the haemorrhage was 5 years on average, only one patient was treated for 15 days.

Among these 12 cases, clinicians did not see the necessity of continuing clopidogrel for 4 patients, clopidogrel was continued for 5 others and in 3 cases, the information was not done.

In conclusion, prolonged duration of treatment is the common point of theses cases. A reevaluation of this treatment by the medical practitioner should be made. Studies of efficacy of clopidogrel did not exceed one year whatever the indication.

In a second time, we can wonder if the B/R balance of clopidogrel could be jeopardised especially in the patients at risk of GI bleeding.

100. Reporting of Psychiatric Adverse Events in Randomised Clinical Trials

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Introduction: Bupropion, varenicline and rimonabant have all been associated with psychiatric adverse events (AEs) in preregistration trials. The number of spontaneous reported psychiatric AEs was higher than expected post-registration. This may be due to limited inclusion of patients with psychiatric history in the RCTs while in daily practice such patients may be at higher risk for developing psychiatric AEs.

Aim: To assess whether patients with a psychiatric history were included in RCTs (pre- and postregistration) of bupropion, varenicline and rimonabant, and how this influences the reported absolute and relative incidence estimates of psychiatric AEs.

Methods: Descriptive study including full clinical study reports for bupropion, varenicline and rimonabant that were obtained from the Dutch Medicines Evaluation Board. In addition to general information on these studies, information was extracted on in- and exclusion criteria for psychiatric comorbidities, and incidence of reported (total and psychiatric) AEs. Descriptive statistics were applied and relative risks were calculated.

Results: We identified 27 studies for bupropion, rimonabant and varenicline, including on average 677 participants (range 52–3045). For 23 studies (85.2%) psychiatric disease was an exclusion criterion; in 3 (11.1%) patients with psychiatric disease could be included. In one study, in- and exclusion criteria were not mentioned. The RR for overall AEs reported for the active substance versus the trial comparator was the same for trials in- or excluding psychiatric disease (1.08 [95% CI 1.02, 1.14] vs 1.09 [95% CI 1.06, 1.11]). The RR of psychiatric AEs was the same (1.6 [95% CI 1.3, 1.8] vs 1.4 [95% CI 1.3, 1.5]) for trials in- or excluding patients with psychiatric disease as well. However, the absolute incidence of psychiatric AEs was twice as high for trials including vs. not including patients with psychiatric history (66.4% vs 30.6%, $p=0.021$). No difference was found in absolute incidence of overall AEs.

Conclusions: Although the relative incidence of psychiatric AEs was comparable for trials in- and excluding patients with psychiatric disease, the absolute incidence of psychiatric AEs was twice as high for trials including vs. not including patients with a psychiatric history. Patients with a higher baseline risk for psychiatric disease might be more vulnerable for psychiatric AEs. This influences the benefit-risk balance both on an individual and population level.

101. Management of Medication Error Reports Associated with the Use of Medicinal Products at the French Health Products Safety Agency

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Introduction: In the framework of the objectives set by the Public Health Act aimed at reducing drug-related adverse events (enacted in 2004), the French Health Products Safety Agency has set up in 2005 a dedicated unit to collect and manage, in a single location, reports of medication errors or potential errors related to the packaging, labelling or names of medicinal products, and coordinate the follow up of those likely to present a risk to Public Health.

Methods: The "Medication errors' Guichet" enables healthcare professionals to report directly medication errors or near misses; reports collected from the Regional Pharmacovigilance Centres are also taken into account. A mailbox and a reporting form facilitate the reporting of such errors. All reports of medication errors sent to the Afssaps are stored in a specific database.

Results: Since its creation until the end of 2009, 2207 reports have been registered. Most of them were the consequence of a confusion between vials of solutions for injection, lack or misinformation (labelling, package leaflet, provision of the Summary Product Characteristics, etc.), inadequacy of the packaging, or confusions between medicinal products names.

58% of the reports (1272) consisted in a patent error and were due to the administration of a wrong medicine, a wrong dose or route of administration or an inappropriate schedule. Among the patent errors, 694 resulted in an adverse effect (31% of reports).

Each issue considered to be directly related to the medicinal product could lead to risk minimization measures such as changes to Summary Product Characteristics or packaging, communication to healthcare professionals and patients, batch recall… When the error is linked to a medical practice or related to a dysfunction in the medication management chain, the reports were shared with the relevant Health institutions (French National Authority for Health, Direction of Hospitalization and medical care's Organisation…).

In addition, the French Health Products Safety Agency has initiated some action plans with the objectives of harmonizing the vials' labelling and providing recommendations to encourage the development of unit dose packaging. A reflection concerning minimisation measures to distinguish plastic single-dose vials containing different liquid forms (medicines, cosmetics, medical devices…) is also ongoing.

Conclusions: After almost 5 years of existence, the evaluation of these activities shows the importance of such centralised system as well as the increasing involvement and awareness of healthcare professionals in the prevention of medication errors.

102. DPP-4 Inhibitors and the Occurrence of Infections

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Introduction: Dipeptidyl peptidase-4 (DPP-4) inhibitors are a recently introduced class of antidiabetic drugs. They inactivate incretin hormones, but also exert many other effects throughout the body, including on the immune system. Therefore, there are concerns about the safety of DPP-4 inhibitors regarding the occurrence of infections.

Aim: To evaluate the baseline risk of infections for patients initiating DPP-4 inhibitors and to assess the impact of these medicines on the number of infection-episodes.

Methods: All incident users of an antidiabetic drug in the period 1998–2008 were identified in the PHARMO Record Linkage System. This database contains pharmacy dispensing data from a representative sample of the Dutch population. We calculated the cumulative incidence of treatment episodes for antibiotics for each patient in the three months before and after start of antidiabetic medication (multiple starts allowed for 1 patient). To assess differences in treatment episodes for infections before and after the start of an antidiabetic a chi-square test was used.

Results: A total of 156 344 patients were identified who started either with a biguanide (n = 73 335), SU-derivate (n = 44 831), TZD (n = 12 853), DPP-4 inhibitor (n = 382) or insulin therapy (n = 24 943). In the three months before start of a DPP-4 inhibitor, the cumulative incidence of an infection episode was 9.4%. For all other medication, this cumulative incidence was higher (biguanides 14.6%, SU-derivates 16.6%, TZDs 13.8% and insulin 16.6%). In the three months after start, the incidence was significantly lower as compared to before start for biguanides (12.1%), SU-derivates (12.8%), TZDs (12.4%) and insulins (15.0%), while the cumulative incidence of infection episodes was higher for patients initiating a DPP-4 inhibitor (14.9%).

Conclusions: The results of this study, in combination with the biologic plausibility may suggest a potential relation between DPP-4 inhibitors and infections. Further research is needed to evaluate the clinical and regulatory consequences of this finding.

103. Is it Possible to Modelize the Consensual Experts' Judgement?

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Introduction: The consensual experts' judgment is considered as the reference to assess the causal relationship between a drug and the occurrence of an adverse event. Recently has been developed a causality assessment method, which predicts the probability of drug responsibility from the evaluation of 7 assessment criteria statistically weighted by a consensual experts' judgment.[1] To convert the evaluation of the criteria in probability, the logistic function has been used as a mathematic function to modelize the experts' judgment.

Aim: To measure the ability of the Logistic Method (LM) to modelize the consensual experts' judgment.

Methods: A sample of 50 randomly pairs of drug-event from the pharmacovigilance database of Bordeaux was evaluated by a group of 3 experts on a visual analogical scale until reaching consensus. In parallel, the pharmacovigilance team of Bordeaux assessed the same pairs with the LM. The Spearman correlation coefficient was used to measure the degree of likelihood between the probabilities obtained with the experts' judgment and the LM. Sensitivity, specificity, positive and negative predictive values were calculated without the pairs for which the experts have a neutral judgment (i.e., probabilities between 0.45–0.55). The probabilities ≥0.50 with the LM were considered in favour of drug responsibility and those <0.50 in defavour.

Results: The distribution of probabilities obtained with the LM is similar to those of the experts' judgment but brought forward the right (median probability with the LM 0.73 vs 0.58 with the experts). A statistically significant correlation was found between the LM and the consensual experts' judgment (Spearman coefficient: 0.38, p = 0.006) but the strength of the association between both methods is mediocre. The LM with a high sensitivity (se = 0.96) and good predictive values (positive predictive value at 0.73 and negative predictive value at 0.83) tends to well classify and identify the cases judged positive by the experts. On the other hand, when the drug responsibility is low, the results obtained with the LM tend to differ from those of experts' judgment (sp = 0.42).

Conclusions: The modelization of the consensual experts' judgment by the LM is overall satisfactory except for the low probabilities of drug

responsibility. The LM is accurate with the experts' judgement for the high probability of drug responsibility, which is essential for a causality assessment method to identify the adverse drug reactions. As the LM overestimates the drug responsibility, a new weighting will be sooner performed on a new set of observations.

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104. Update of the French Causality Assessment Method: Results of the Validation Phase

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Introduction: An updated version of the French Causality Assessment Method (FCAM) has been developed aiming at improving the discrimination and the reproducibility of the current method mandatory in France. The main changes are related to chronological and semiological criteria (more accurate definitions, new quotations), to the intrinsic imputability criterion (with a broader range of scores), to the bibliographical score (with a new level for the expected adverse drug reactions), to the introduction of an informativeness score (for assessing the level of information of each case).

Aim: To assess the validity of this updated version of the FCAM.

Method: A sample of 30 randomly pairs of drug-adverse reaction from the French pharmacovigilance database was evaluated by a group of 3 experts on a visual analogical scale until reaching consensus. Concomitantly, another group constituted of 2 pharmacovigilance teams, from a pharmacovigilance centre and a pharmaceutical industry department, assessed separately the same pairs firstly with the current method and, one month later, with the updated method. To test the inter and intra-observer reproducibility, a third group set up of 2 senior and 2 junior observers, each of one from a pharmacovigilance centre and from industry, assessed the pairs by using the updated method with a time interval of one month. A weighted Kappa coefficient was used to measure the concordance between the two causality assessment methods.

Results: The agreement of the current FCAM to the consensual experts' judgment was moderate for both pharmacovigilance centre (Kappa 0.33) and pharmaceutical industry (Kappa 0.41). In the same way, by using the updated method, the agreement was better for both pharmacovigilance centre (Kappa 0.58) and pharmaceutical industry (Kappa 0.52). The intra-observer reproducibility was high with a Kappa, respectively, of 0.91 and 0.65 for the senior and the junior of the pharmacovigilance centre and, of 0.61 and 0.86 for the senior and the junior of the pharmaceutical industry. The inter-observer reproducibility between juniors (Kappa at 0.53 and 0.51) was clearly better than those of seniors (Kappa at 0.34 and 0.37). The main source of discrepancy between juniors and seniors concerned semiological assessment.

Conclusions: This updated method has a better agreement with the consensual experts' judgement than the current method. The intra- and inter-observer reproducibility obtained with the updated method is overall satisfactory. These results suggest that the updated method brings a real improvement and this argues for its use in routine practice.

105. Diagnosing and Assessing Allergic Drug Reactions: Case Evaluation of Maculopapular Exanthema with a Antiretroviral Three-Drug Treatment Plus Levofloxacin

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Background: Allergic skin reactions are a frequent problem in medical practice. Medical history doesn't often provide elements to identify causal drug and to confirm allergic mechanism; diagnosis is specially difficult in patients with multi-drug regime. In-vivo tests, when possible, are useful tools to evaluate hypersensitivity reactions and to identify causal drug, after having assessed the pathophysiological way.

Case report: A 40 year-old woman, HIV positive, high CD4 count, was prescribed nevirapine, lamivudine and didanosine because of her willingness to get pregnant. Seven days later, she presented pneumonia; levofloxacin 500 mg bid was prescribed. She presented severe itching, exanthema in lower limbs, abdomen and thorax, fever and epigastric pain after the second dose of levofloxacin. She was then hospitalized because of the reaction's severity. In spite of the seemingly temporal association with levofloxacin, nevirapine was suspected as causal drug because of its higher frequency of skin reactions. Antiretrovirals were discontinued, but not levofloxacin. She was treated with corticosteroids and antihistamines, the exanthema healed. Pneumonia was solved.

Methods: prick tests and intradermal tests with 20 minutes reading are useful for IgE-mediated reactions (type I, immediate); and patch tests and late reading intradermal tests are useful for type IV T-cells mediated reactions.[1] In this case, intradermal tests weren't performed because suspected drugs aren't available as parenteral form. For patch tests, tablets of each suspected drug were powdered and 30% solutions in water or Petrolatum (Vaseline and water) were patched with cura test. Patch tests were also performed in one healthy control patient.

Results: Specific type IV skin patch tests were performed for nevirapine, didanosine and lamivudine. Due to patient's improvement under levofloxacin treatment, this patch test wasn't performed. Patch test was positive to nevirapine and negative for lamivudine and didanosine. This result confirmed nevirapine type IV allergic reaction.

Discussion: Type I reactions characteristics are urticarian rash usually flaring within 24 hours, itching, angioedema, whizzing and hypotension. The allergic reaction was diagnosed as type IV because of exanthema's characteristic: maculopapular, progressive, persistent, itching, and with general symptoms (i.e. fever, gastric pain, general discomfort, enantema). High CD4 count allows type IV reaction presentation, which aren't possible with low CD4 count.

Conclusions: Diagnostic protocols for allergy to drugs, although not completely standardized, should be systematically used in order to identify and prevent allergic reactions. Confirmatory tests for allergic reactions to drugs are useful in order to identify causal drug and to exclude it from further treatments.

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106. An Important Component of Turkish Pharmacovigilance System: Pharmacovigilance Contact Points

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Introduction: In July 2005, Turkish Ministry of Health introduced new regulations for pharmacovigilance activities and in accordance with the relevant regulations of the Turkish Pharmacovigilance Center (TUFAM), hospital administrations appointed physicians or pharmacists as pharmacovigilance contact points.

Aim: The aim of this study was to evaluate the legal framework of the ''pharmacovigilance contact points'' which takes place in the pharmacovigilance system since 2005. For this purpose the benefits of its implementation, duties of the contact points, the applied standard operating procedures, the distribution of the contact points with respect to their provinces, profession distribution, the hospitals of practice and their role in reporting adverse effects have been assessed.

Method: The contact information and profession of the pharmacovigilance contact points appointed by the relevant hospitals have been notified by TUFAM and recorded in a database. Those responsible contact points have been studied according to their provinces, professional groups and hospital groups.

Results: As of June 2010, there are 329 contact points working at 317 hospitals according to TUFAM records. In parallel with population distribution most of them are located in capital cities such as İstanbul (35.26%), Ankara (11.25%) and İzmir (2.28%). 60.88% of the appointed contact points are at private hospitals, 17.35% at training and research hospitals and 16.72% are in university hospitals. 4.56% of adverse effects that reached to TUFAM between 2008–2009 were reported by pharmacovigilance contact points. This ratio seems to increase each year.

Conclusions: Contact point has been provided to health care professionals to consult for adverse effect reporting and the main target of this procedure was to provide more active communication between health care professionals and TUFAM. However, the fact that contact points work full time in the hospitals with a busy schedule and the fact that they are not paid extra for their services as contact points provide the major drawback of the system. Low ratio of the adverse effect reports from contact points should not be considered as an indicator of the operability of the system as a whole. Also, the other characteristics will be discussed in our presentation. Finally, the system is improved in order to work more efficiently.

107. Cohort Event Monitoring: A WHO Strategy to Complement Spontaneous Reporting Systems

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Introduction: For over forty years the WHO programme for International Drug Monitoring has promoted spontaneous reporting as the main method for collecting data on adverse drug reactions (ADRs). Globally this method continues to be popular in being the easiest and the cheapest to run, and in detecting previously unrecognized and rare signals of adverse reactions. But reliable rates cannot be calculated, nor is it possible to measure risk. With the current efforts to improve access to new medicines for priority diseases (e.g. ACTs) whose ADRs are not yet fully characterized, there is a need to complement spontaneous reporting with pharmacovigilance (PV) methods that can measure risk and rates of ADRs in a robust fashion, within a short period of time.

Aim: To present current strategies in WHO to develop and promote a model of active surveillance that addresses current needs in public health programmes, and lends itself to systems and structures within countries in resource limited settings (RLS).

Method: WHO disease programmes were consulted on current needs and priorities for pharmacovigilance (PV) in RLS. PV of medicines used in malaria and HIV was flagged as a topic of highest priority requiring immediate attention and methodological solution. The WHO Advisory Committee on Safety of Medicinal products (ACSoMP) was consulted to define the strategic elements of an active surveillance method that would best address current PV needs of HIV and malaria treatment programmes. New Zealand's Intensive Medicines Monitoring method was considered a good model and was adapted for the Cohort Event Monitoring (CEM) of medicines in RLS.

Results: Two practical handbooks have been published, describing the principles of CEM of patients treated with antimalarial and ARV medicines. Reporting tools have been developed for collecting baseline information and post treatment events. An Adverse Events dictionary has been developed for coding the events and a data management tool, CemFlow, to record and manage data from CEM. 11 countries were trained in the CEM of antimalarials (n = 3) and ARVs (n = 8). Lessons from pilot efforts have been useful in fine tuning tools and methodology.

Conclusions: Two countries are implementing CEM of antimalarials. There is growing interest in CEM, in countries in RLS that are currently deploying ACTs. But the method is resource intensive and should be used only when monitoring new medicines, for a limited length of time. It should be seen as a complement to spontaneous reporting.

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108. Monitoring the Safety of the Influenza A H1N1 Vaccine: An Observational Cohort Study

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Background: When the vaccines against the Influenza A H1N1 virus became available after an accelerated registration process, questions about their safety arose leading to public unrest. Careful monitoring of the Adverse Events Following Immunization, AEFIs, was needed. In addition to its spontaneous reporting system, Lareb set up a cohort study in order to quantify and identify AEFIs related to Focetria®.

Method: In the Netherlands it was decided that persons above 60 and persons with a medical indication should be vaccinated by their GP. Eligible patients were identified when receiving the first pandemic vaccine. They were given a flyer with information about the study and instructions on how to sign up for the study online. After online

registration, patients received a questionnaire via e-mail within a week after registration. The second questionnaire was sent three weeks later and the third questionnaire three months after the first questionnaire. Questions were asked about personal characteristics, the immunization and AEFIs. Injections site reactions and labeled reactions were actively asked for, other AEFIs could be reported as free text.

Results: 3569 participants filled in the first questionnaire; the subsequent questionnaires were filled in by 3395 and 3162 patients. 50.1% were female, the average age was 58.4 years (SD 14.8). The main indication was age above 60, followed by pulmonary and cardiovascular disease. 1311 (36.7%) patients reported an AEFI. In total 2305 injection site reactions were reported. The reactions usually occurs on the day of immunization and persists for 3 days. 2198 labeled AEFIs were reported. The median latency is one day, median duration is 2 days for the events related to the first immunization and 3 days for the second. The AEFIs reported as free text did not reveal any new signals.

Discussion: This study is limited to patients vaccinated in general practice and may not be applicable on other populations. However, we have shown that it is possible to monitor the safety of the influenza vaccine with a web-based intensive monitoring system. If the future, this methodology can be used to monitor real life use and AEFIs of vaccines and if necessary interim analysis can be performed quickly.

Conclusions: In our study the incidence of AEFIs was 36.7%. The AEFIs had a short latency, a short duration and were in most cases self limiting. There were no reports of unexpected serious reactions and there were no signals of new AEFIs identified.

109. Pattern of Adverse Drug Reactions Reported by Nepal Regional Pharmacovigilance Centers

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Introduction: Adverse Drug Reactions (ADRs) are related with a significant morbidity and mortality.[1,2] There are limited information available about the ADRs in the developing countries. Socioeconomic status, disease entities, medical education programs and the availability of pharmaceutical products may have significant effects on the incidence and pattern of ADRs.[3,4] Nepal has started ADR monitoring during the year 2004 in the country. In July 2006, Nepal became World Health Organization (WHO) program member for International Drug Monitoring. Department of Drug Administration (DDA), a national drug regulatory authority, acts as the National Pharmacovigilance Center for ADR monitoring. At present there are four Regional Pharmacovigilance Centers operating in the country. The ADRs reported to the Regional Pharmacovigilance Centers by spontaneous reporting system are reported to the National Pharmacovigilance Center. All the Regional Pharmacovigilance Centers are tertiary care teaching hospitals.

Aim: To identify the pattern of ADRs reported by Regional Pharmacovigilance Centers in Nepal.

Methods: We performed a retrospective observational study of the ADRs reported to the DDA of Nepal by four Regional Pharmacovigilance Centers, based on spontaneous reporting system, from January 2006 to December 2009. The reported cases of ADRs by the Regional Pharmacovigilance Centers were analyzed and evaluated to find out most ADR causing drugs and organ system involved.

Results: There were total 304 cases of ADRs reported during the year 2006 to 2009 by four Regional Pharmacovigilance Centers. Phenytoin was reported as the highest ADR producing drug (4.3%) followed by carbamazepine (3.9%) and amoxicillin (3.6%). In terms of organ system involved, skin was found to be most affected organ system (55.6%) followed by gastrointestinal (16.8%) and central nervous (9.9%) systems. There were 2 cases (0.7%) of ADRs associated with complementary and alternative medicine (CAM) products reported.

Conclusions: This study has identified the most ADR producing drugs as well as the most organ system affected based on the reported ADRs by Regional Pharmacovigilance Centers in Nepal. As the pharmacovigilance activates in Nepal is in infancy, appropriate measures are necessary to increase the number and quality of ADR reports.

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110. Bisphosphonate-Associated Psychiatric Adverse Events: A Signal from the Italian Pharmacovigilance Database

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Background: Oral and intravenous bisphosphonates (alendronate, risedronate, pamidronate, ibandronate and zoledronate), used in oncology and for the treatment of osteoporosis, have been associated with different types of adverse reactions (ADRs) as oesophageal ulcer, influenza-like illness, hypocalcaemia, musculoskeletal pain, osteonecrosis of the jaw and ocular events. The frequency of these reactions is variable, in relation to the different single bisphosphonates, type of use, route of administration, dosage and duration of therapy. In literature no case of psychiatric disorders related to bisphosphonates is reported. The summary of product characteristics of pamidronate and zoledronate lists some psychiatric disorders as anxiety and sleep disturbances, all reported among uncommon events. No psychiatric adverse events are mentioned for the other bisphosphonates.[1]

Aim: To describe and discuss the spontaneous reports of psychiatric disorders associated to bisphosphonates in the Italian Pharmacovigilance Database.

Methods: The database holds reports of suspected ADRs submitted since 1988. Within spontaneous reporting system in Italy the database is analysed twice in a year to filter out potential signals. Signal detection is done by qualitative case-by-case analysis and by using quantitative methodology like Proportional Reporting Ratio (PRR).

Results: The database actually holds 110 497 reports, 90.1% of them coming from physicians, 4.9% from pharmacists, 1.4% from nurses and 0.3% from consumers. In 1260 reports a bisphosphonate is reported among the suspected drugs. Among these reports, 29 (2.3%) referred at least one psychiatric disorders. Twenty six patients were women, age

ranged from 29 to 89 years and in 4 reports other drugs acting on Central Nervous System were present.
The highest number of reports were related to alendronate (13 cases out of 310 alendronate reports), followed by clodronate (4 out of 113) and ibandronate (4 out of 69).
Most frequently reported bisphosphonates-related psychiatric ADRs included agitation, drowsiness, confusion, anorexia and depression. Serious reactions included one case of acute psychosis with aggressive reactions, one case of paranoid reactions and two cases of hallucination.
Conclusions: Data from Italian Pharmacovigilance Database suggest an association between bisphosphonates and psychiatric ADRs. Psychiatric reactions are generally underreported, since often it is difficult to identify the role of a drug in the causality assessment evaluation. Therefore more data are necessary to strengthen this signal.

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111. A Signal in the Italian Pharmacovigilance Database: Aceclofenac and Hepatitis

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During the signal analysis carried by the Italian Medicine Agency (AIFA) together with the regional centers of pharmacovigilance a signal of acute hepatitis and aceclofenac was detected. In particular, in the Italian Pharmacovigilance database (RNF) 5 cases of hepatitis are recorded (all serious), They are three women and two men aged 31 to 71 years (respectively 31, 40, 51, 71 and 71 years old). In 3 cases data of laboratory tests are present: in one case there was a massive cell necrosis at liver biopsy and the patient was transplanted. In the other two cases the ALT values were respectively 20 and 30 times higher than normal values.
The outcome of the reaction, out of the case of liver transplantation (who recovered), in two cases there was an improvement whereas in the others the condition did not changed at the time of the report was written. As concomitant drugs in the transplant case adalimumab was detected (his summary of product characteristics (SPC) do not mention an hepatotoxic effect), in one case no drugs taken together were reported, in one other case the patient underwent a prulifloxacin cycle of therapy (known as hepatotoxic); two patients took other drugs not known as hepatotoxic (Lisinopril + HCTZ, simethicone, lansoprazole, oxerutine). The duration of therapy with aceclofenac was 4 years for the transplant case, in one case a week, in another two days, while in two cases patients took the drug occasionally and no more information were available.
In Italy the SPCs of products containing aceclofenac (Gladio, Airtal, Kafenac) mention the possibility of hepatitis even asymptomatic. In Micromedex hepatotoxicity of aceclofenac is not cited.
A survey carried in Pub Med with the words ''Aceclofenac and liver injury'' produced 6 results: out of six, five articles were present in Spanish journals.[1]
The hepatotoxicity is a well known class effect of NSAIDs with different levels of risk. We believe it would be useful to better inform healthcare professionals about the possibility of hepatitis induced by aceclofenac.

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112. Cartography of Adverse Drug Reactions in Hospital Wards

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Our study aims at revealing the distribution of adverse drug reactions (ADRs) in hospital wards and the details about implicated drugs in order to have a better view of the impact and severity of the ADRs in hospital. The European Georges Pompidou Hospital is a teaching hospital with a total annual activity of 20 744 admissions in 2008 and no paediatric and obstetric wards. ADRs were reported spontaneously to the pharmacovigilance regional centre, by professional healthcare, prospectively during 2008. Description of the ADRs, patient characteristics, outcome, details about the drug were collected and analysed. Drug consumption in each ward was obtained from the pharmacy software. Medications were expressed as active ingredient and regrouped into 31 therapeutic classes. For each ward, we calculated a notification rate expressed as the number of cases involving a therapeutic class divided by the consumption of this class.
In 2008, 191 cases of ADRs were reported spontaneously by 20 wards (17 medical and 3 surgical) involving 182 patients with a median age of 63 years; 103 (56.6%) were male with a median age of 61 years and 79 (43.4%) were female, median age of 65 years. The 191 cases accounted for 306 ADRs, thus an average of 1.6 effect per case. The majority was serious (141, 73.8%); 77 out of the 141 serious cases occurred during hospitalization while 64 directly caused admission to hospital accounting for 0.3% of total admissions to hospital. 19% of the recorded ADRs were preventable. Top 3 system organs affected by *serious reactions* were: haematological system (20.4%), cardiovascular system (12.0%) and nervous system (10.2%) while nearly half of the system organs affected by non serious reactions (49.2%) were skin and appendages. Patients suffered from serious ADRs were older than those with non serious ADRs (62.0 years, 56.6 years respectively). Top 4 wards (internal medicine, pneumology, ICU and immunology) together caused nearly half of all the ADRs. 138 drugs were suspected in ADRs. The average number of suspected medicine taken was 1.55 drugs per patient. The therapeutic classes most frequently implicated were: anticoagulant (17.8%), antiviral (14.1%), antibacterial (13.4%) and antineoplastic agents (10.1%).
This is the first study of observational ADR's cartography of a French university hospital. Internal medicine was found to report the most ADRs; haematological system and skin were the 2 most affected class organs; anticoagulant and antibacterial agents were the major causes of ADRs in nearly half of the wards (see table I on following page).

113. Means of Evaluating the Effectiveness of Risk Minimization Interventions: A Literature Review

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Introduction: Since the introduction of guidelines on therapeutic risk management, a significant increase in the number of risk minimization/mitigation interventions has been observed.[1,2] Despite the fact that Risk Management Plans are required to incorporate an evaluation

Table I (relates to abstract no. 112 on previous page).

	No. of ADRs (%)	System organ affected (%)	Drug group (no. of cases caused)	Notification rate ($\times 10^{-4}$)
Internal medicine	45 (14.7)	GI (20.0),	Anticoagulant (6),	6.1
		Haematological system (13.3),	NSAID (3),	6.7
		Respiratory system (11.1)	Antibacterial agents (3)	1.2
Pneumology	35 (11.4)	Haematological system (28.6),	Antibacterial agents (7),	3.7
		Liver and biliary system (17.1),	Anticoagulant (5)	7.1
		Respiratory system (14.3)		
ICU	35 (11.4)	Renal and urinary system (17.1),	Antibacterial agents (4),	1.1
		Haematological system (14.3),	Neuroleptic agents (4)	37.0
		Cardiovascular system (14.3)	Anticoagulant (4)	2.8
Immunology	34 (11.1)	Cardiovascular system (20.6),	Antiviral agents (18),	26.8
		Renal and urinary system (20.6),	NSAID (2),	25.6
		Skin and appendages (20.6)	Antibacterial agents (2)	1.3
Oncology	24 (7.8)	Skin and appendages (50.0),	Antineoplastic agents (8),	7.5
		Cardiovascular system (16.7),	Antiemetic agents (2)	1.6
		Haematological system (8.3)		
Radiology	21 (6.9)	Skin and appendages (33.3),	Diagnostic agents (9)	
		Liver and biliary system (17.1),		
		Respiratory system (14.3)		
Anesthesiology	21 (6.9)	GI (14.3),	Antibacterial agents (6),	1.2
		Nervous system (9.5),	Anticoagulant (4)	46.2
		Cardiovascular system (9.5)		
Cardiology	16 (5.2)	Haematological system (31.3),	Anticoagulant (4)	1.3
		Cardiovascular system (25.0),	Gastric acid secretion inhibitor (2),	8.1
		Renal and urinary system (12.5)	Antihypertensive agents (2)	0.5
Nephrology	15 (4.9)	Skin and appendages (26.7),	Immunosuppressant agents (3),	5.5
		Cardiovascular system (13.3),	Anticoagulant (2)	3.0
		Renal and urinary system (13.3)		
Emergency	12 (3.9)	Nervous system (50.0),	Neuroleptic agents (2),	11.9
		Renal and urinary system (16.7),	Anticoagulant (2)	4.9
		GI (16.7)		
Geriatrics	10 (3.3)	Haematological system (40.0),	Antibacterial agents (5),	1.0
		Nervous system (30.0),	Antineoplastic agents (2)	63.7
		Skin and appendages (20.0)		
H.G.E	9 (2.9)	Skin and appendages (33.3),	Antineoplastic agents (3)	6.5
		Nervous system (22.2),		
		Cardiovascular system (11.1)		
Medicine vascular	8 (2.6)	Liver and biliary system (37.5),	Anticoagulant (3),	4.3
		Skin and appendages (25.0),	Antihypertensive agents (2)	1.6
		Haematological system (12.5)		
Others	8 (2.6)	Haematological system (25.0), Investigations (25.0), Cardiovascular system (12.5)	Platelet aggregation Inhibitor (2)	11.0
Cardiac surgery	8 (2.6)	Haematological system (40.0),	Anticoagulant (5),	2.5
		Cardiovascular system (20.0),	Antibacterial agents (2)	1.1
		Renal and urinary system (20.0)		
Other surgery	5 (1.6)	Haematological system (40.0),	Anticoagulant (2),	0.8
		Cardiovascular system (20.0),	Antibacterial agents (1)	0.6
		GI (20.0)		
Total	306 (100)			

of the effectiveness of these interventions, the methods used for these evaluations are not well known.

Objective: To search the literature concerning methods of evaluation of effectiveness of risk minimization interventions in order to identify any methodological gaps.

Methods: A methodological search of the EMBASE and MEDLINE journal databases was performed using the following key words related to risk minimization interventions: ''Drug Safety'' AND ''Dear Doctor Letters'', ''Drug Safety'' AND ''Black Box Warnings'', etc. Specific inclusion and exclusion criteria concerning effectiveness evaluations were applied to each article obtained from this search. Only articles involving the use of medications, in addition to a risk minimization intervention incorporating an assessment, were retained. Cost-effectiveness evaluations or studies concerning natural products were excluded. The data extracted from the articles were: type of intervention, target population, country, year of publication, objectives of the study, and methods used to evaluate the effectiveness of the risk minimization intervention.

Results: Among the 2103 articles identified using the key words, only 52 (2.5%) met inclusion criteria. The most frequent evaluation methods observed were: Acceptability surveys of the interventions conducted among Health Care Professionals or patients (n = 15), time series analyses (n = 25), and cohort studies comparing the incidence of adverse events within a group exposed to the intervention versus those within an unexposed group (n = 10). Less frequent methods such as randomised studies (n = 2) were also observed. The methods were more often geared towards general practitioners and specialists, than to patients or other Health Care Professionals.

Conclusions: The regulations on therapeutic risk management did not lead to an important increase in the analyses of effectiveness of risk minimization interventions nor an improvement of the methods already in use. This constitutes an important methodological gap within risk management plans.

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114. Can Serious Drug-Related Hyponatraemia be Avoided? Changing Patterns in Spontaneous Reports of Medicine-Related Hyponatraemia Lead to New Prescribing Advice

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Background: Reports of hyponatraemia (plasma sodium <135 mmol/L) to the Centre for Adverse Reactions Monitoring (CARM) have been continually increasing since they first appeared in 1979. In some cases hyponatraemia has been severe (<120 mmol/L) with serious consequences.

Aim and Method: Emerging suspect medicines and changing patterns of prescribing that might lead to hyponatraemia were sought through a review of reports over the last three decades. Evidence for emerging suspects was evaluated. Reports of hyponatraemia received between January 2007 and February 2009 were assessed in more detail for causality, medicines implicated and other contributory factors.

Results: The review, over three decades, indicated a marked increase in the range of suspect medicines within the last ten years. Most recently, the emergence of proton pump inhibitors, sodium valproate and angiotensin converting enzyme inhibitors (without diuretics) have emerged as suspects with supporting evidence and characterization from the WHO adverse drug reactions database, Vigibase, and publications. The use of multiple hyponatraemic agents by individual patients also increased. In the more detailed review, twenty-four of 28 reports of hyponatraemia received between January 2007 and February 2009 were considered at least possibly related to medicine use. As expected selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) (11) and diuretics (4) were the most frequently reported suspects. Combinations of potentially hyponatraemic medicines were used by 11 (40%) patients. The reports indicated patterns of use of multiple agents that can lead to a profound and symptomatic fall in plasma sodium. It was concluded that current prescribing advice for hyponatraemic medicines was no longer adequate and new advice was issued to prescribers. This included the need to evaluate plasma sodium before as well as after starting a hyponatraemic medicine, particularly if the patient is already taking such a medicine. Evaluation of the necessity for co-prescription of multiple potentially hyponatraemic medicines for each patients was also recommended.

Conclusions: The review of reports of hyponatraemia in the CARM database revealed emerging new suspects and increasing use of a combination of hyponatraemic medicines. It was concluded that current prescribing advice for monitoring plasma sodium in patients taking potentially hyponatraemic medicines was no longer adequate. This was amended and will be described.

115. A Medication Error by Calcium Ampule Led to an ADR

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A medication error led to an ADR and the drug causing this error was calcium ampule. It occurred in one governmental hospital (where in all Iraqi governmental hospitals calcium gluconate ampule is the type of calcium ampule most widely used), when run out of this medicine the hospital was supplied from a governmental store by ca- chloride (not gluconate) ampule and the store did not notice the hospital about this change of calcium salt type.

We suggest the following causes of this medication error: calcium chloride is 3 times more potent than ca- gluconate and may be added to that extravasation and inappropriate size of canula.

This is a category F error (according to NCC MERR): an error occurred that cause harm and led to increased hospitalization period to 5 patients (3 babies and 2 teenagers), causing severe skin damage and necrosis; babies were more affected. This case was soon reported to our center by clinical pharmacists working in that hospital and we took the following measures:

1. circulate this case to all Iraqi hospitals (including the photos) and ask them for feed back about action taken by them concerning educating the staff through pharmacy and therapeutic committees;
2. letter of thanks to the clinical pharmacist that report this case to us;

3. circulate the differences between these two substances to all health directorate, showing that Ca chloride is 3 times for potent than calcium gluconate.

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116. Formal Symbolic Methods for Signal Detection and More Complex Associations in Pharmacovigilance

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The huge and increasing size of spontaneous reporting systems (SRS) precludes case-by-case human analysis. Data mining algorithms (DMAs) mainly uses disproportionality measures to automatically extract signals, i.e. potentially relevant adverse drug reactions for further investigations by experts in pharmacovigilance. Despite very efficient implementations, these measures reached some limitations: potential signals are numerous, statistical measures hide some interesting signals from the expert's point of view but raise some uninteresting, experts needs more qualitative information in order to explain associations, they need to relate signals with more complex associations and, finally, drugs-adverse effects mining should take into account some knowledge of the domain. We show that a symbolic classification method such as Formal Concept Analysis (FCA) reaches these goals providing (i) a synthetic view of the database (ii) a search space for candidate signals (iii) an environment to navigate among results and all possible associations.

FCA builds a lattice from a formal context where objects are cases and attributes are Drugs ($d_1 \ldots d_n$), Adverse Effects (AE) ($e_1 \ldots e_m$), and Demographic attributes such as gender (M,F) and age bracket (<18,…,>60) of the patient. FCA extracts all itemsets which are secondly associated with current statistical measures. FCA defines a partial order on itemsets so that signals can be related to drug-drug interactions, to syndromes or drug protocols. For each association, an special interface presents a part of the lattice which enable the expert to relate, for example, a drug interaction with its related signals and to add commentaries.

Experiments were conducted on a subset of the French national SRS database. This subset contains 3.249 cases, 976 drugs, 573 AE, and demographic attributes such as gender and age, divided in 3 brackets (<18, 18–60, >60). The resulting lattice contains 13.178 concepts, among which 6.788 contains at least 3 cases in the extent. The 2.812 candidate signals in the lattice concepts led to 565 potential signals (following MHRA criteria) and the 836 candidate interaction-concepts to 102 potential interactions.

Blind evaluation involved two experts who were asked to evaluate signals and drug interactions using our interface which proved to be helpful for providing a qualitative analysis. We also defined about 20 different types of agreement and disagreement situations between experts and PRR values that we ranked according to their frequencies. These first results based on an extract of the French database are very encouraging and should be applied to the national database.

117. Sweet Syndrome after the Intake of Azathioprine

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Introduction: Sweet syndrome (SS), also known as acute febrile neutrophilic dermatosis, was recognized to occur in association with malignancy or auto-immune disease, including inflammatory bowel disease. Drug induced SS is less common. The drugs typically implicated in SS inducing are the granulocyte colony stimulating factor and retinoid acids. We report a case of SS induced by azathioprine with positive rechallenge.

Case report: BH, a 55 year-old man diabetic under insulin therapy since 2001, with a history of Crohn's disease since 2008 treated occasionally by corticosteroids and antibiotic therapy. On the 17th of April he was given azathioprine (150 mg/day). Thirteen days later, he developed fever (39°C), joint aches and vomiting. Three days later, a pustular eruption appeared on the face, the earlobe than on the limbs. He was given antibiotic therapy (amoxicillin + clavulanic acid) without any improvement. The azathioprine was stopped on the 5th of May, and two days later, the eruption started to improve, the joint aches and the fever resolved. Biopsy specimens and tissue culture were taken from the pustular lesions. On the 10th of May all the eruption disappeared. The tissue culture results were negative for infection. The laboratory data showed a high level of white blood cells with neutrophilic predominance and elevated C-reactive protein level. All other laboratory parameters were within the normal range. Azathioprine was reintroduced on the 12th of May, at the dose of 50 mg × 3/day. The patient took one tablet of azathioprine (50 mg) at midday and one tablet at 4 pm. A few hours after the second intake, the same eruption started again on the earlobe and on the limbs. The azathioprine was permanently discontinued.

Discussion: The responsibility of azathioprine was retained in front of the compatible delay of onset of the symptoms (13 days), the resolution of the symptoms after the drug withdrawal, and the recurrence of symptoms with drug rechallenge. The diagnosis of SS was suspected in front of abrupt onset of painful erythematous plaques or nodules, pyrexia and the elimination of the other etiology such as chickenpox or DRESS syndrome due to azathioprine. Biopsy was defective. In literature few cases of azathioprine induced SS were published. The symptoms occurred within one to two weeks after the onset of azathioprine, which is true in our case.

118. Fixed Drug Eruption Related to H_1 Anti-Histamines

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Introduction: H_1 anti-histamines are usually used in allergic disorders. Some side-effects have been reported with these drugs such as gastrointestinal disorders, weight gain, and allergic reactions. Fixed drug eruption (FDE) has been rarely associated with H_1 anti-histamines.

We report two cases of FDE related to H_1anti-histamines, and notified to the National Pharmacovigilance Centre of Tunis. Score imputation was performed according to the French method of imputability.[1]

Cases Reports

Case 1: A 58-year-old man takes occasionally paracetamol without any problem. In 2004, he was given Fervex® (paracetamol, ascorbic acid, pheniramine) for a flu syndrome. Four days after, he developed

an erythematous, pruritic lesion on the outside area of the penis with burning sensation. FDE was diagnosed. The lesion resolved in 7 days into a hyperpigmented sequela. The patient reported two other episodes of burning sensation after automedication with Fervex®. In January 2009, the patient took paracetamol and ascorbic acid for a flu syndrome without reactivation of the lesion. The intrinsic score of pheniramine was established as I4 or very likely.

Case 2: A 64-year-old man takes Mestinon® for myasthenia, metformin for diabetes, and inhaled corticosteroids for asthma. Since 2006, the patient has presented twice, three macular and erythematous lesions on the back and the bottom after the intake of loratadine. On the 24 April, he inadvertently received loratadine. On the 25, he described the reactivation of old lesion with the occurrence of new ones. FDE was diagnosed and the role of loratadine retained. The intrinsic score of loratadine was I4 or very likely.

Discussion: The role of the H_1 anti-histamines was retained in those cases, in front of the following chronologic criteria:

- The onset of the lesion compatible with the medication role
- The progressive good evolution after the drop of the drug (H_1 anti-histamines) suggesting the role of this drug
- The reoccurrence of the lesions at the same site after the readministration of the drug (H_1 anti-histamines),
- The absence of reactivation of the lesions after the intake of the others drugs.

In literature, FDE was associated with H_1 anti-histamines in few cases. We found 7 cases with dimenhydrate, 2 cases with hydroxyzine, 2 cases with loratadine, and six cases with cetirizine.

Even though, H_1 anti-histamines are anti-allergic drugs they can be source of hypersensitivity reactions.

119. Panniculitis at the Site of Subcutaneous Interferon Beta Injections in a Patient with Multiple Sclerosis

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Introduction: Subcutaneous Interferon-β (IFN-β) injections used for the treatment of multiple sclerosis (MS) can cause inflammatory skin reactions at the injection site. Panniculitis is a severe and exceptional local skin reaction. We report a case of a panniculitis at the site of subcutaneous interferon beta injections in a patient with multiple sclerosis.

Case report: A 30-year-old woman, with multiple sclerosis was prescribed since 2004 interferon β-1a (Rebif®) 44 μg, twice a week. Subcutaneous injections were usually done, at the same site, in the abdomen. In April 2010, 6 years after therapy onset, she presented plaques, ulceration, erythema, pain and induration at the site of injection. Histological analysis confirmed the diagnosis of panniculitis. Investigations for common etiologies of panniculitis were excluded: no signs were found for lupus erythematosus, scleroderma or dermatomyositis. Bacterial or other infectious agents were also excluded. The patient stopped using Rebif® and was treated by local care and systemic antibiotherapy. The cutaneous lesion healed in about 1 month.

Discussion: The responsibility of interferon-beta injections were retained in the genesis of the panniculitis because of favourable evolution after drug withdrawal, the negative investigations for other etiologies and the suggestive location of the event (at the site of injection). Local skin reactions to subcutaneous injections of interferon beta-1 a in MS are common. Severe skin reactions with are rare. Panniculitis is the most severe local skin reaction described with interferon. Although it is a rare complication. Fourteen cases of panniculitis due to interferon beta-1b have been reported in literature by Ball et al, Yoshiyuki et al Heinzerling et al.[1] The mechanism of panniculitis induced by interferon is unknown.

In literature some factors are associated with this severe reaction such as, poor injection technique, inadequate skin cleansing and repeated use of the same site.

Our patient repeated the injection at the same site.

Conclusions: Panniculitis is a rare and severe local cutaneous adverse effect of subcutaneous interferon beta injections.

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120. Lichenoid Drug Eruption Induced by Irbesartan-Hydrochlorothiazide Combination

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Introduction: CoAprovel® is a drug that contains two active substances, irbesartan a selective angiotensin II receptor antagonist and hydrochlorothiazide a diuretic drug of the thiazide class. The most common cutaneous side effects with CoAprovel® are rashes. Lichenoid drug eruption is exceptionally reported with this drug. We reported a case of lichenoid drug eruption induced by Co-Aprovel®.

This case was notified to the National Centre of Pharmacovigilance of Tunis and evaluated according to the French method of imputability.

Case report: A 59 year-old Mediterranean woman without personal or family history of atopy or other allergic diseases, had been treated with acebutolol (Sectral®) 400 mg/day for hypertension. She had started irbesartan + hydrochlorothiazide (Co-Aprovel®) 300 mg + 12.5 mg/day on December 2009. One month later, she presented a skin eruption composed of purplish papules that began on the arms and spread within few weeks to abdomen, armpit, folds of the groin, lower limb and oral mucosa. The clinical aspect was suggestive of lichenoid eruption. Histologic examination of the skin lesions showed hyperorthokeratosis, vacuolar degeneration of the basal cell layer, and band-like upper dermal infiltrate of melanophage, which disturbed the interface between epidermis and dermis. This cutaneous biopsy confirmed the diagnosis of lichenoid eruption. The patient was treated with a topical corticosteroid without resolution of these lesions.

Co-Aprovel® was switched to amlodipine. Two months later an improvement was noted.

Discussion: The role of Co-Aprovel® was retained with possible imputation score or I_2 in front of: a suggestive delay (1 month after the beginning of this treatment), the regression of the eruption within a short time after drug withdrawal.

The role of acebutolol was eliminated because of improvement of skin eruption in spite of its continuation.

In literature, there is only few cases of lichenoid drug eruption induced either by the combination irbesartan-hydrochlorothiazide (1 case), irbesartan (3 cases), or hydrochlorothiazide (15 cases).

Conclusion: This observation illustrates a rare association between lichenoid drug eruption and irbesartan+ hydrochlorothiazide combination.

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121. A Review of Risk Minimization Interventions - 2000 to 2009

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Introduction: Due to the publication of regulatory guidelines on therapeutic risk management, an increasing number of risk minimization/mitigation interventions have been executed. However, the traits of these interventions and the methods used to evaluate their effectiveness remain insufficiently explored.

Aim: To review risk minimization interventions in pharmacovigilance implemented over the past 10 years, and to assess whether the publication of regulatory guidelines on risk management in 2005 led to changes in the number and the types of interventions.

Methods: MEDLINE and EMBASE databases were searched using key words related to topics such as: ''Pharmacovigilance'' AND ''Medication guide'', ''Pharmacovigilance'' AND ''Black Box Warning'' and others. Resulting articles were scanned manually and the following inclusion/exclusion criteria were applied: Published from 2000 to 2009 inclusive; involving drug products; use in humans; involving risk minimisation interventions, or tools used to increase the reporting of adverse events. Natural healthcare products, devices, diagnostic chemicals, pregnancy registries without follow-up, medication errors, and products not used as therapy for illness, were not retained. For each article, the following characteristics were extracted: nature of the intervention, target population, therapeutic area, adverse event(s) of special interest, country, year of publication, and presence of effectiveness assessment.

Results: 169 sources met the inclusion criteria, or were obtained from snowballing. Removal of duplicate interventions resulted in 121 unique interventions. Only 49.6% included an assessment of effectiveness. The most frequent interventions were: education materials (32.2%), black-box warnings (18.2%), therapeutic drug monitoring (9.1%), education programs (7.4%) and restricted distribution (6.6%). Most interventions involved drugs of the nervous system (33.1%), followed by drugs of the alimentary tract and metabolism (14.0%) and thirdly blood and blood forming organs (9.1%). Interventions including effectiveness measures from 2000 to 2004 were 27 in number, those without were 29. From 2005 to 2009, interventions with effectiveness measures were 28 while those without were 37.

Conclusions: Interventions specific to drugs, therapeutic areas or populations are rare. More such specific analyses need to be conducted and published in order to better understand their effectiveness with individual products, and therapeutic areas. The low proportion of interventions possessing an effectiveness assessment constitutes an important gap in the risk management process.

122. Bronchiolitis Obliterans with Organizing Pneumonia (BOOP) Associated with Interferon: Successful Rechallenge

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Introduction: Severe respiratory adverse reactions to interferon are uncommon and only rare case-reports of interferon associated bronchiolitis obliterans with organizing pneumonia (BOOP) are available in the literature.

Case report: We report the case of a 58 year old male patient treated chronically by acetyl salicylic acid and losartan for arterial hypertension. He was started on pegylated Interferon alpha 2a (IFN) and ribavirine (RBV) for chronic hepatitis C. After 4 weeks of treatment he complained of rapidly progressive respiratory symptoms with dry cough, dyspnea, associated with fever, asthenia and syncope. Clinical examination found pulmonary crackles. Lung computed tomography revealed bilateral pulmonary infiltrates, ground glass opacities, reticular opacities with pleural and peri-broncho-vascular thickening. Bronchoscopy and further investigations did not reveal any viral or infectious etiology.

A BOOP associated with the IFN therapy was then suspected. The suspension of the IFN and RBV treatment (10 weeks after starting the therapy), while losartan and aspirin remained unchanged, was followed by a complete recovery of the symptoms and a resolution of the radiographic infiltrates within 2 weeks. Two weeks later losartan was also stopped and the IFN and RBV therapy was restarted in association with beclomethasone without recurrence of the symptoms.

Discussion: In the present case the suggestive onset time after starting the treatment and the rapid relief of the symptoms after withdrawal of the IFN and RBV therapy strongly suggest a close relationship between IFN and the pulmonary disease. Imputability score according to Begaud et al. was I2B3. The absence of recurrence of the symptoms after rechallenge with IFN and RBV is not against this diagnosis. Several factors are discussed in order to understand this negative rechallenge. The immunomodulatory role of losartan should also be considered.

Conclusions: To our best knowledge, this is the first case of IFN associated BOOP where a rechallenge was performed. This successful reintroduction of the IFN therapy needs to be confirmed by further clinical studies.

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123. Propofol: Recreational Drug?

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Background: Propofol is a short-acting, intravenous agent used extensively in anaesthesia and intensive care medicine to provide dose-dependent sedation and hypnosis. It is characterized by a short onset, a short duration of action, low toxicity, ability to control sedation, and ease of administration. Because of its pharmacokinetic features, propofol seems not to be the substance of choice for drug abuse. However, reports about sexual disinhibition, about pleasant and euphorics feelings during recovery from propofol anesthesia and sedation since the beginning of its use in clinical practice shed some light on the abuse potential of this drug.

Methods: We reviewed all spontaneous reports of Adverse Drugs Reactions with propofol in the French Pharmacovigilance database up to 31 may 2010 with the following MedDRA® terms: ''hallucinations'', ''hearing hallucinations'', ''somatic hallucinations'', ''visual hallucinations'', ''sensory hallucinations'', ''anomaly concerning dreams'' and ''excessive dreams''.

We did a literature review up to 31 may 2010 using PubMed, Medline.

Results: Three case were reported in the French Pharmacovigilance database: one serious and two non-serious. The hallucinations and dreams were described as pleasant with frequent ''sexual connotation'', ''uninhibited behaviour''.

Forty-five articles were relevant to the topic.[1] Dreaming is commonly reported after anesthesia or sedation and the reported prevalence of such episode ranges between 5 and 36%. The incidence is reported to be greater in patients receiving ketamine-based, opioid-based and propofol-based anaesthesia.[2]

Seven lethal cases were reported. A suicide and a homicide are suspected in two cases. Five reports of self-administration for recreational purposes were described, essentially in health professionals.

Discussion – Conclusions: An association between propofol anaesthesia and the occurring of hallucinations and dreams following anaesthesia is rarely reported in the French Pharmacovigilance database. Propofol induce hallucinations, most of them described as pleasant with frequent sexual connotation, and sexual disinhibition.[3] These effects can partly explain propofol abuse as recreational drug by medical staff. We consider that the international medicines agencies must regulate propofol as a controlled substance.

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124. Local Reaction to Nadroparin Calcium Followed by Generalized Hypersensitivity

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Introduction: Skin reactions to Low Molecular Weight Heparins (LMWH) are rare and usually localized. Habitually two types of local skin reactions can occur: erythematous skin lesions, or skin necrosis. We report a case of local hypersensitivity which became generalized eruption in a patient under LMWH treatment.

Case report: A 53-year-old obese menopaused woman (BMI = 31,22) was treated by oral anti-coagulant therapy for valvular replacement. She received in 1978 and in 1992, subcutaneous anticoagulant therapy and developed indurations at the site of injections. In October 2009, she was hospitalized for teeth extraction and received a nadroparin calcium (Fraxiparina®:LMWH). Few minutes after each injection, she developed a cutaneous lesion at and around the point of Fraxiparina® injection .This lesions persisted despite changing the site (forearm and abdomen). The lesion was erythematous, well circumscribed, very pruriginous, and measured between 0.5 cm and 2 cm. In the second week of hospitalization she presented a generalized erythema immediately after subcutaneous injection of Fraxiparina®. Intravenous heparin replaced Fraxiparina® treatment without any problem. Generalized erythema resolved in four days and the local lesions in approximately one month.

Three months later, Fraxiparina® was readministrated inadvertently, and the patient developed immediately the same local reactions.

Discussion: In the literature, skin eruptions to LMWH are usually localized at the site of injection and occasionally may become generalized. The mechanism involved is a delayed hypersensitivity reaction. Delay of these reactions varies from 24 hours to 21 days. It can be shorter in presensitized-patients. In our observation, the patient was probably presensitized in 1972 and 1992. She had developed immediately a local reaction which secondary generalized. This type of event has been rarely reported with LMWH. Among the 18 cases of localized skin eruption related to LMWH reported by Wutschert, only 3 cases became generalized.[1]

In literature, female sex, obese patients and postmenopausal women or pregnancy were more associated with LMWH hypersensitivity reaction.

Conclusions: Local skin reaction to LMWH can be secondary generalized reaction.

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125. Immediate Hypersensitivity Reaction Induced by Pyrazinamide

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Introduction: Pyrazinamide is a major antituberculosis drug. It is generally used in combination with other drugs such as isoniazid and rifampicin in the treatment of Mycobacterium tuberculosis. Hepatoxicity is the most serious adverse effect. Immediate hypersensitivity reactions have been exceptionally reported. We report three cases of immediate hypersensitivity reactions to pyrazinamide and confirmed by a positive reintroduction. These cases were notified to the National Centre of Pharmacovigilance of Tunis and evaluated according to the French method of imputability.[1]

Case reports:

Case 1: A 44-year-old man had started, for urinary tuberculosis, pyrazinamide (2000 mg/day), isoniazid (300 mg/day), rifampicin (600 mg/day), and streptomycin (1000 mg/day). Within 90 minutes, he developed generalized erythema. The treatment was stopped and the skin eruption disappeared within 24 hours.

Case 2: A 54-year-old woman had started, for ganglionic tuberculosis, pyrazinamide (1750 mg/day), isoniazid (500 mg/day), rifampicin

(900 mg/day), and ethambutol (1200 mg/day). Within 90 minutes she developed an itchy rash. All drugs were stopped and the skin eruption disappeared in few hours.

Case 3: A 48-year-old deaf woman had a history of Sjogren's syndrome. She had started, for active lung tuberculosis, pyrazinamide (1750 mg/day), isoniazid (250 mg/day), rifampicin (600 mg/day), and ethambutol (800 mg/day). Within 15 minutes she developed an itchy rash. All drugs were stopped and the skin eruption evolved well within 24 hours under symptomatic treatment.

For the three cases, patients are without prior antituberculous treatment, and the skin eruption appeared at initiation of antituberculosis therapy. A sequential challenge was performed. After administration of pyrazinamide, all patients developed an identical skin rash within few minutes. Challenge with isoniazid, rifampicin (case 1,2,3), streptomycin (case 1) and ethambutol (case 2,3) was well tolerated in all patients.

Discussion: The role of pyrazinamide was retained with likely imputation score or I_3 in front of[1]: a suggestive delay (90 minutes in two cases and 15 minutes in one case), a regression of the reaction within a short time after drug withdrawal, a positive challenge. In literature, hypersensitivity reactions to antituberculosis drugs usually appear within 3–7 weeks after initiation of treatment.[2] Hypersensitivity reactions occurring within few minutes after pyrazinamide initiation are exceptionally reported. Pyrazinamide can be tolerated after reintroduction at a lower dose followed by a stepwise dose increment.

Conclusion: Pyrazinamide should be suspected if an immediate skin rash develops at initiation of antituberculosis chemotherapy.

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126. Positive Challenge Tests with Placebo in Patients with History of Reactions to Multiple Drugs

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Background: History of allergic reactions to multiple drugs can hinder the physician's decision to prescribe due to patient's anxiety. There are concerns about the nature of factors that trigger allergic reactions (drug molecule or endogenous substances) when patients have history of adverse reactions to drugs of different groups. Challenging patients with placebo has been suggested as a way to rule out a psychoneuroimmunological mechanism for such adverse drug reactions. If placebo-test is negative, psychological factors are less likely to cause the reaction.

Method: challenging placebo single-blind tests were performed, by oral or parenteral (intradermal or subcutaneous) administration of placebo, with progressive increasing volume of saline solution. A patient's relative's informed consent is needed. Starch was used in oral-placebo, and saline solution in parenteral placebo-tests. If patient experience adverse symptoms or signs, the single-blind is opened immediately. If adverse reaction doesn't improve, specific treatment is administered (parenteral antihistamines and corticosteroids, up to adrenaline).

Case reports:

a. A 37 year-old woman, with history of allergic reaction to diclofenac, paracetamol and amoxicillin, was challenged with parenteral placebo-test; she presented generalized itching, dyspnea and anxiety 4 hours after the test. The patient was derived to hospital ward and given dexametasone 8 mg + difenhidramine IV.

b. A 46 year-old woman, with history to anaphylactic shock after xylocaine and carticaine, itching after ciprofloxacine and ibuprofen, and positive *in vitro* tests (specific Ig-E) to carticaine, prilocaine, cefalexina, azythromycine and lincomicine. She was first challenged with a parenteral xilocaine prick-test and after intradermal test, with negative effect. She presented later an allergic-like reaction after a paracetamol tablet, she was then challenged with an oral placebo tablet: she presented erythema, rash, severe itching between shoulder blades. She had to be administered IM dexametasone and difenhidramine, and symptoms solved/disappeared 15 minutes later.

c. A 17 year-old woman, with history to penicillin (at 1st year of life), dipirone and erythromycin in the last year. She was challenged with placebo oral compounds. 30 minutes later, the patient experienced itching in legs and arms, symptoms improved spontaneously.

Discussion: Mast cells receptors can react to multiple substances, both endogenous and exogenous. Placebo is used in order to compare both efficacy and adverse events, because psychological factors can influence clinical responses.

Conclusions: In patients with history of seeming allergic reactions to multiple drugs, challenging placebo-tests can produce an allergic-like reaction, suggesting an anaphylactoid reaction, non Ig-E mediated.

127. Pityriasis Rosea-Like Eruption Due to Flurbiprofen

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Introduction: Flurbiprofen is a non-steroidal anti-inflammatory drug, used in musculoskeletal and joint disorders and in mild to moderate pain including dysmenorrhoea and migraine. It has generally few reported cutaneous side-effects such as dermatitis herpetiform and cutaneous vasculitis. Pityriasis rosea-like eruption had not been reported with this drug.

We reported one case of pityriasis rosea-like eruption in a patient receiving flurbiprofen. This case was notified to the National Centre of Pharmacovigilance of Tunisia and validated by the French Method of imputation.

Case report: A 26-year-old woman, in good health with no family history of psoriasis, had received on April 3rd 2010 flurbiprofen (Antadys®) 100 mg daily for dysmenorrhoea. She developed two days later itching skin eruptions with no fever.

Dermatologic examination revealed erythematous, sharply bordered, oval and finely scaling (collarette) lesions along skin cleavages, located on the face, trunk, back, arms and thighs. The lesions were 3–25 mm in diameter and symmetrically distributed. The first visible lesion of pityriasis rosea (herald patch) had not been detected. The diagnosis of pityriasis rosea-like eruption was suspected.

Systemic physical examination and biological tests were all normal. Flurbiprofen was discontinued and the lesions were successfully treated with levocetirizine 5 mg/day and topical corticosteroid (fluticasone propionate) cream for 2 weeks. One month later, patch

tests with flurbiprofen 1% and 10% in petrolatum on the back were negative.

Discussion: The responsibility of flurbiprofen was retained, with possible imputation score or I2, in front of: a compatible delay of two days, clearance of the lesions after drug withdrawal, absence of another cause explaining the occurrence of this event. In fact, the patient gave no history to suggest an intercurrent infection, no previous rashes nor a familiar history of psoriasis and she was taking no other medication when the skin eruption developed.

Pityriasis rosea-like eruption had not been reported with flurbiprofen or other non-steroidal anti-inflammatory drugs.

Many drugs can cause pityriasis rosea-like eruption such as bismuth compounds, gold compounds, captopril, omeprazole, isotretinoin, terbinafine, and benfluorex.[2]

The pathophysiology of these cutaneous reactions is unclear.

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128. Palmar-Plantar Erythrodysesthesia Induced by Tetrazepam

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Introduction: Palmar-plantar erythrodysesthesia (PPE) or hand–foot syndrome (HFS) is a syndrome characterized by erythema and dysesthesia located in palms of the hands and plants of feet. It was described first with cytotoxic chemotherapy agents. It has never been reported with tetrazepam. We report the first case of hand foot syndrome induced by tetrazepam with positive rechallenge.

Case report: A 30-year-old woman, with no medical history, was treated in 1998 for genital infection with doxycycline and for cervical spondylosis with nonsteroidal anti-inflammatory drugs (NSAIDs), and tetrazepam. Four days after the onset of this treatment, she presented erythema and dysesthesia in the palms, fingers and soles of feet, which progressed to desquamation after stopping the drugs.

The patient has later taken NSAIDs without recurrence of the symptoms. She has not taken tetrazepam until December 2009. For recurrence of cervical arthritis, she was prescribed: dexamethasone and tetrazepam. Five days after the beginning of this treatment, she presented the same symptoms as in 1998. After stopping the drugs, desquamation occurred. The case was notified to the Centre National of Pharmacovigilance.

Discussion: The responsibility of tetrazepam was retained in the genesis of this PPE with an intrinsic score of I3 (likely) according to the French method of imputation[1] mainly because of the positive rechallenge. PPE was first reported in 1974 by Zuehlke in a patient who developed a syndrome of "erythematous eruption on the palms and soles" while receiving mitotane. During the 1980s, there were several short reports describing a similar syndrome with antimetabolites as well as chemotherapeutic antibiotics. PPE is emerging as a common, dose-dependent toxicity of many newer chemotherapy drugs. However, the exact mechanism is still unknown. There is no reported case of PPE with tetrazepam or other benzodiazepines after a Medline and Scopus research using the terms of Hand-Foot syndrome, palmar-plantar erythrodysthesia, acral erythema, tetrazepam and benzodiazepine.

Conclusions: This observation reported the first case of PPE induced by tetrazepam.

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129. Drug Interactions: Retrospective Analysis of the ADRs Reported to the Pharmacovigilance Department of ANMAT from January 2007 to May 2010

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Introduction: A pharmacological interaction is defined as the modification of the effect of a drug by the concomitant use of another. Drug interactions are considered part of pharmacovigilance as ADRs or lack of efficacy.[1] According to different published series, drug interactions are responsible of up to 15% of all ADRs.[2] Several studies have been conducted to assess the importance and economic consequences of drug –drug interactions. However, such work has not been previously undertaken in Argentina.

Aim: To analyze and describe the pharmacological interactions as cause of notifications of ADRs received in our department.

Methods: We performed a retrospective observational study of the Drug–Drug Interactions reported to ANMAT for the period from January 2007 to May 2010. All drugs were classified using the Anatomical Therapeutic Chemical classification code system, and subsequently entered into a database. After that a list of reports of drug-drug interactions will be shown as an example of clinically relevant and of different mechanisms.

Results: The results showed that among all the reported ADRs (n = 18 241), during the time of the study, only 0.21% of the ADRs referred to drug–drug interactions (n = 38). Reports selected for description were the use of ergotamine in HIV positive patients, Clopidogrel and proton pump inhibitors, decrease of absorption of itraconazole due to concomitant treatment with ranitidine, increase of seizures due to enzymatic induction of different drugs, ventricular arrhythmia and simultaneous use of amiodarone and levofloxacin. And lack of efficacy of tamoxifen with the use of fluoxetine.

Conclusions: Drug interactions increase morbidity and mortality and may lead to hospital admission. In primary healthcare, 9–70% of patients are reported to be exposed to drugs with the risk of a drug interaction, with 1–23% of these interactions being of major relevance.[5] Despite some limitation, this type of study reveals that a spontaneous reporting database can be a resource for detecting adverse drug reactions from the concomitant use of interacting drugs. The frequency of drug interactions in our database is clearly inferior in comparison to published data, reason why we should work together with the Peripherals effectors in order to increase the frequency of reports.

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130. Anti-TNF Paradoxical Reactions: Generalized Papulopustular Exanthema with Etanercept and Palmoplantar Pustular Eruption with Adalimumab in a Woman with Psoriatic Arthritis

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Background: Biological anti-TNF agents have shown to be effective in some autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, Crohn disease, ankylosing spondylitis and psoriasis. However, cases of psoriasis after anti-TNF-a agents' exposure have been published, and a study from a RSRBR[1] shows an increased rate of new onset psoriasis in patients treated with anti-TNF-a biological agents. This seems to support the causal role of anti-TNF agents in the presentation of psoriasis as paradoxical adverse reaction.
Case report: A 60-year-old woman, with 18-month psoriatic arthritis was prescribed to receive adalimumab 40 mg every other week in combination with methotrexate 10 mg weekly due to failure of treatment with two previous disease-modifying antirheumatic drugs. She had been previously treated with methotrexate 10 mg weekly and later leflunomide 20 mg was added to methotrexate, but leflunomide had to be discontinued due to massive hair loss. After the second dose of adalimumab she presented a palmoplantar pustular eruption (June 2009). Adalimumab was then discontinued. Three months later, etanercept 50 mg every week was prescribed (first dose, October 4th 2009) due to disease activity. She told her rheumatologist she had to stop etanercept treatment due to generalized pustular exanthema, affecting lower limbs, up to inguinal and genital zone. After having stopped etanercept therapy, exanthema healed. Five months after etanercept discontinuation by the patient's decision (no medical consultation at that time), she consulted again for worsening of arthritis' symptoms.
Discussion: this report provides an interest case of recurrence of the paradoxical adverse event after exposure to a second anti-TNF agent; however its value is limited because of the lack of neither direct medical observation nor experimental findings, i.e. confirmatory biopsy. Case reports in literature mention adalimumab as the anti-TNF preceding most of the cases of psoriasis or psoriasis-like reactions. Another case of pustular psoriasis after etanercept treatment, with recurrence after adalimumab therapy, was published.[2]
Conclusions: This case reports the recurrence of psoriasis-like skin lesions after re-exposure to a second anti-TNF agent. Thorough study of cases can help identify factors that could predict paradoxical adverse reactions.

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131. Profile of Adverse Events Following Immunization with Human Papillomavirus and Hepatitis B Vaccines in Females 9 to 26 years in Canada

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Background: Human Papillomavirus (HPV) and Hepatitis B virus (HBV) are sexually transmitted infections for which vaccines are available in Canada. HPV and HBV vaccines are part of publicly funded immunization programs in Canada. While Hepatitis B vaccines have been used in Canada for over a decade, an HPV vaccine has only been available since July, 2006 for females aged 9 to 26 years. The Public Health Agency of Canada conducts several post-marketing surveillance activities to ensure continued safety of marketed vaccines.
Objective: To present a profile of reports of adverse events following immunization (AEFI) with HPV and HBV vaccines received by the Public Health Agency of Canada (PHAC). To compare AEFI reports of the recently marketed HPV vaccine to that of HBV vaccines.
Methods: AEFI reports for HBV vaccine (HB)[Recombivax™ and Engerix™] and HPV vaccine (Gardasil) received at PHAC with date of vaccine administration between July 1st, 2006 and May 31st, 2010 were extracted from the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS). Only AEFI reports from females between the ages of 9 and 26 years were included. Adverse Event (AE) Terms were listed and grouped using MedDRA® (Medical Dictionary for Regulatory Activities) terminology. A serious adverse event (SAE) is one that resulted in hospitalization, prolongation of hospitalization, death, permanent disability, and/or was life threatening. Analyses were conducted using *SAS® EG*.
Results: In total, 969 AEFI reports for Gardasil™ and HB were received. There were 634 reports received for Gardasil™, 263 for HB, and an additional 72 reports for recipients of both. AEFI reports for HB were slightly younger than those reports for Gardasil™. For Gardasil™, 3.5% of reports were serious as opposed to 1% for HB ($p = 0.1853$). Injection site reaction, pyrexia, rash, urticaria, hypersensitivity were the most commonly reported terms in AEFI reports for both Gardasil™ and HB (range 10–13% of reports). For both vaccines the most common System Organ Classes (SOC) affected were: General disorders and administration site conditions (approximately 50% of reports for both vaccines), Skin and subcutaneous tissue disorders (40% for Gardasil, 50% for HB-V), Gastrointestinal disorders (29% vs 15%) and Nervous system disorders (35% vs 18%). For serious reports, the profile is also similar between the two types of vaccine.
Conclusions: Gardasil and Hepatitis B vaccines are considered safe vaccines to use in Canada. The AEFI profile of Gardasil is very similar to that of Hepatitis B vaccines which have been used in Canada for over a decade.

132. Assessing Safety Signals in Large Observational Databases Using Heckman's Model

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Introduction: Once an adverse event signal has been detected by disproportionality analysis, there are very few analytical tools available to test the possible relationship between an adverse event and a drug. In observational studies, comparisons are not protected by randomisation. Thus, they present with problems of selection bias, false association and inappropriate design. Comparisons between a given drug and all other drugs of the same class are confounded by the very reasons

physicians prescribe those drugs to a given patient. The true (causal) effect of a signal can only be evaluated if the effects of confounding are removed. Although several analytical methods (e.g. multivariable (adjusted) analyses or propensity scores) can help to account for observed or potential confounders, unobserved confounding is unlikely to be corrected for by any of the above-mentioned standard techniques. One potential method for accounting for unknown confounders is the use of the sample selection (Heckman) models.

Aim: To describe the basic concepts of Sample Selection Models (SSM) and apply methodology to real life and simulated data sets.

Methods: We describe a case study on the application of SSM approach to evaluate the effects of drug therapies in rheumatoid arthritis patients. This case study presents empirical comparisons of methods such as Inverse Probability of Treatment Weight (IPTW), Propensity Score Adjusted Regression (PSAR) and Standard Logistic Regression (SLR). Further, the performance of the SSM method is evaluated using simulated data under a number of practical scenarios.

Results: Analysis of simulated data suggests that SSM are successful at reducing the impact of bias from a single unknown confounder. In the particular case of drug therapy in patients, SSM yielded similar conclusions regarding treatment effects compared to SLR, PSAR and IPTW, but with the added benefit of indicating presence of unmeasured confounders. In observational research, assessing the sensitivity of the study conclusion for likely unmeasured confounders is essential and, we believe the use of SSM could be a good option.

Conclusions: Sample selection models can offer an attractive way of reducing the impact unmeasured confounding and provides a useful addition to the statistical toolkit available to epidemiologists.

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133. Household Survey of Drug Use in a Nigerian Community

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The study was carried out to evaluate knowledge of drug use and drug seeking pattern in a Nigerian community. The survey was interviewer based. The responses were analysed using percentages. Pearson Chi-square was used for assess relationships between sex and compliance to medication; qualification and knowledge of drugs; and weekly income and source of drugs.

About 62% of the population were not aware that antibiotics were prescription only medicine. There was no significant dependence of educational level on knowledge about drugs ($p = 0.135$). Likewise, 62% of the respondents source their drugs from chemists. This finding was not affected by weekly income ($p = 0.059$). Fifty one percent of the respondents stated that they finish their doses. Women adhered more to their medications compared to men ($p = 0.314$). Drugs mostly found at home are anti-infectives (30%) followed by vitamins (19%).

The general knowledge about drugs was low irrespective of the educational level. Respondents mostly sourced their drugs from chemist shop. Drug use/seeking pattern noticed in the household survey could lead to improper medication use since their are no opportunities of patient education.

134. Do Human Factors Play a Role in Pharmacovigilance Systems?

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The world in which we live is becoming increasingly more complex, but this fact is constantly underestimated when we construct systems to deal with high-risk processes such as pharmacovigilance systems (PVS). Humans have a very limited ability to function well in complex systems because we process information in a linear manner. Yet we influence these complex systems by making crucial decisions all the time. The impact of this is unreliable performance, which creates unpredictable outcomes.

The pharmaceutical industry has had its fair share of safety issues over the years, e.g. withdrawal of over 10 drugs in the last decade for safety reasons, the Tegenero debacle. As expected regulators have responded by implementing new regulations around clinical trials in volunteers,[1] risk management processes,[2,3] the implementation of the PVS inspection programmes[4] etc.

Human performance is a large contributor to system breakdown and should be a major concern in PVS. As illustrated above we tend to deal with these issues by developing Standard Operating Procedures, quality systems, elaborate regulations and compliance assurance processes. These are all necessary components in high reliable organisations, but without considering human limitations safety will at best be continually challenged and at worst remain a distant aspiration.

Aviation, another highly complex arena, has long traditions in the embedding of human factors within its systems with excellent results; it is probably one of the safest industries today. Even though the pharmaceutical industry is very different from aviation there are clear parallels when it comes to safety issues. This talk will highlight some of the major areas in human factors and provide some insights in to how human performance issues can limit or even contribute to bad events within pharmacovigilance.

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135. ADVISE – Adverse Drug Reactions in Children International Surveillance and Evaluation: A Comparison Study

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Introduction: Safety of paediatric pharmacotherapy is of major concern. A recent Meta-Analysis indicated that the incidence of adverse

drug reactions (ADRs) in hospitalized patients is about 9.5% (95% CI, 6.81%, 12.26%).[1] Varying methods in determining ADRs are a major reason for the differences in reported ADR incidence. Systematic observations are essential to further define and consequently improve the safety of medicines used in children. The aim of this study was to investigate the incidence and characteristics of adverse drug reactions in hospitalised children in different European and non-European countries.
Method: A prospective multicentre cohort study was conducted in paediatric hospitals in Germany, UK, Hong Kong, Malaysia and Australia. Data were collected over a three month period using a web-based data entry tool. ADRs were identified by intensive chart review and evaluated by a team of experts using standardised algorithms.[2,3] Multivariate logistic regression was used to identify risk factors.
Results: A total of 1280 patients relating to 1322 admissions were included [Australia n = 146 (149), Germany n = 376 (407), UK n = 313 (321), Malaysia n = 302 (302), Hong Kong n = 143 (143)]. The mean age was 4.37 years (SD ± 5.03, range 0–18 years) and 55.4% of the children were male. Patients received a total of 5367 drugs (mean 4.09 ± 4.06) and stayed in hospital on average 6.55 days (SD ± 8.73). The main classes of prescriptions in all three countries were antibacterials for systemic use (25.25%), analgesics (16.83%) and drugs for obstructive airway diseases (8.79%). A total of 380 ADRs were identified in 212 patients. Using WHO ADR classification, gastrointestinal-system disorders (n = 183) were most common, followed by metabolic and nutritional disorders (n = 47) and heart rate and rhythm disorders (n = 41). The overall ADR incidence was 16.6%, 95% CI 14.6, 18.7, varying significantly between the three countries ($p < 0.01$). Using logistic regression modeling the age, gender and length of hospital stay did not have a significant association with the incidence of ADRs whereas the number of drugs and underlying diseases are to be seen as major risk for the development of an ADR.
Conclusions: This large-scale study provides a comprehensive overview on ADRs in hospitalized children in different countries and confirms that more than every tenths child in hospital experiences an ADR. Although varying incidences among countries may be explained by different prescribing patterns more detailed information about the nature of ADRs and associated risk factors in different paediatric populations is still needed.

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136. Is Statin-Induced Rhabdomyolysis Avoidable? An Example of Preventability Assessment from the New Zealand Pharmacovigilance Centre

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Background: Rhabdomyolysis is a rare, dose-related and frequently fatal adverse effect of statins that has been increasingly reported as the use of statins has increased in New Zealand. A number of patient and prescribing characteristics can increase the risk.
Aim: To assess whether each report of rhabdomyolysis attributed to a statin included data that suggested the reaction was preventable and, if so, the patient characteristics, co-morbidities or prescribing patterns that were implicated.
Method: All reports in the CARM database of rhabdomyolysis considered attributable to statin use were assessed using preventability assessment criteria and a confidence score for strength of evidence of preventability.
Results: Thirty three reports of rhabdomyolysis associated with statin use were entered into the CARM database between 1998 and March 2010. Nine were fatal (27%). Simvastatin was implicated in 29 reports. Interacting medicines were prescribed for 23 patients, four for acute serious infection. Nine of these "probably" and 14 "possibly" contributed to rhabdomyolysis. Delayed diagnosis affected seven patients and severe rhabdomyolysis was "probably" preventable for this reason in four. Assessment of preventability became more complex when considering co-morbidities and appropriateness of prescribing for primary prevention. Patients for whom statin prescribing was probably inappropriate were those with co-morbidities that indicated seriously reduced remaining life expectancy. Use of statins in the elderly for primary prevention of cardiovascular disease is based on limited evidence and, especially in high doses, may have been inappropriate. The results concerning interactions highlighted the need for prescribers to be able to easily access information about clinically important drug interactions with commonly prescribed medicines. This type of information is now being developed in New Zealand to overcome the problem of comprehensive and detailed information that does not emphasise the interactions of greatest clinical importance.
Conclusions: Preventability assessment in this case series illustrates the need for readily accessible reminders about clinically important drug interactions and these are being developed. It also illustrates the need for education to aid early diagnosis of myopathy before rhabdomyolysis develops. Inappropriate prescribing of statins may have also contributed to preventability but this is more contentious. There is a need to consider the value of statin use towards the end of life and, for primary prevention, in the elderly.

137. Patient Reporting of Drug Adverse Effects

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Mounting evidence suggests that patient reports of drug adverse effects complement physician reports, augmenting both number and character of adverse effects reported. We present evidence from survey data from subjects with perceived adverse effects to a common drug class, statins (HMG-CoA reductase inhibitors). According to patients surveyed, physicians commonly dismissed the possibility of a connection of symptoms to drug; these cases would be missed through physician reporting.[1] According to other sources, physicians commonly fail to report adverse effects even when recognized, so that expanding the reporting corpus through patient reports may augment the "signal". Our own evidence concurs with external evidence showing that patients' and physicians' focus with respect to adverse effects overlaps but is nonidentical, with physicians' focus more prominently on laboratory abnormalities; and patient reports more commonly including domains for which simple tests are not widely available. Our findings and others'

suggest that patient reports of adverse effects are relatively reliable in attribution, and commonly presage more authoritative identification and validation of adverse effects.[2] Together, evidence suggests that greater attention to patient reports may accelerate recognition, and more authoritative study designs for confirmation of hitherto unrecognized adverse effects of drugs.

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138. H1N1 Vaccine Adverse Event Monitoring at the Korle-Bu Teaching Hospital: An Outcome of Mass Staff Immunisation Program

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Introduction: The new swine-origin influenza virus A(H1N1) is a zoonotic disease which originated in Mexico in March 2009.[1] Due to its propagated source of infection among humans coupled with the lack of partial immunity, transmission was high. Within months, it was present in almost all the WHO regions. As a result of this, the WHO declared a pandemic alert (level 6) on the 11th June, 2009.[1] 2.3 million doses of A(H1N1) 2009 influenza vaccines arrived in Ghana on the 15th May, 2010[2] for immunization of Ghanaians (with a population of about 23 million). This resulted in prioritization and health workers were among the first priority[3] for early vaccination. This study examined the incidence of adverse events that occurred following a mass immunization with the Pandemrix vaccine.

Method: Trained community health nurses from the Ghana Health Service were used fro the immunization program. Five vaccination centers were set up and all workers of the Korle-Bu Teaching Hospital (KBTH) were eligible for vaccination. Those who have had the infection previously and have been treated were excluded because they will have developed partial immunity. Injection was given intramuscularly o the deltoid muscle (shoulder) of the left arm (the choice of Ghana for standardisation). Vaccine adverse event forms designed with the vacinee in mind were distributed to all those who were immunized and they were advised to fill these and return them to specific places or call designated staff members of the Public Health Unit of the KBTH for assistance in the event of any possibility of adverse events. Vaccination was done over a period of one week (14th-18th June, 2010). The Pandemrix vaccine was used.

Results: In all 5870 people were vaccinated. There were 140 reports of vaccine adverse events. The nine most occurring events are as shown in table I. Vacinees reported multiple reactions. 21 people complained of two events, 31 complained of three events and 24 complained of four events. Furthermore, 19 vacinees had five events, 18 complained of six events, 7 people complained of seven events and a maximum of 8 events were reported by 3 recipients. A total of three patients were admitted within one week of vaccination, however, there were no reported fatalities.

Discussion: Most of the adverse effects reported were those classified as very common.[4] There were a few common adverse events like swollen glands, shivering, increased sweating. Uncommon reports included cases of people feeling sick, dizziness and sleepiness.

Table I. Distribution of the first nine most occurring adverse events

No.	Adverse event	No. of reports (n = 140)	Percentage reported
1	Headache	98	70.0
2	Weakness	90	64.3
3	Muscle/joint aches	84	60.0
4	Low fever	70	50.0
5	Pain at injection site	64	45.7
6	Dizziness	48	34.3
7	Nausea	30	21.4
8	Behaviour change	9	6.4
9	Hoarseness	8	5.7

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139. Patient Reporting of Drug Adverse Effects

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Introduction: Mounting evidence suggests that patient reports of drug adverse effects complement physician reports, augmenting both number and character of adverse effects reported.

Aim: To assess patients' descriptions of physicians' responses when they are told about a possible adverse drug reaction.

Methods: 1. Survey of patients taking a statin who had reported an ADR were asked about the drug, dose, character of ADR, time course of onset, dechallenge, rechallenge, effect on quality of life, and interactions with their physician relating to the perceived ADR. 2. Literature review.

Results: Of 650 patients surveyed 87% had spoken to their physician about the possible ADR (Golomb et al. 2007).[1] Most commonly the patient initiated this conversation. More physicians denied than confirmed the connection of the symptoms with the drug, even when these had been reported in the literature and the patient's story supported ADR causality.

Conclusions: Many cases would be missed through physician reporting. Other sources confirm that physicians commonly fail to report adverse effects even when recognized, so that expanding the reporting corpus through patient reports may augment the "signal". Much evidence indicates that patients' and physicians' focus with respect to adverse effects overlaps but differs: physicians focus more prominently on laboratory abnormalities, patient report more commonly in domains for which simple tests are not widely available. Our findings and others' suggest that patient reports of adverse effects are relatively reliable in attribution, and commonly presage recognition of adverse effects arising from other sources. Together, evidence suggests that greater attention to patient reports may accelerate recognition, and more

authoritative study designs for confirmation of hitherto unrecognized adverse effects of drugs.

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140. Report of Potential Signals from Thaivigibase During Year 2007–2008

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Introduction: A signal in pharmacovigilance is more than just a statistical association. It consists of a hypothesis together with data and arguments in favor and against the hypothesis. These relate to numbers of cases, statistics, clinical medicine, pharmacology and epidemiology, and may also refer to findings with an experimental character. The large database of voluntary adverse event reports of Thailand Health Product Vigilance Center has been more accumulated every year. Develop signal tool or initiate the signal detection program to detect safety signal from Thaivigibase can provide critical evidence about known and unknown events associated with single or combination drug treatments. From year 2007, Health Product Vigilance Center chose the method to determine the association of suspected drug and the adverse drug reactions (ADR) by the tool (a program tool for detect signal) that using concept of data mining approach and case-control principle in epidemiologic design to detect signal from drug-adverse drug reactions (ADR). Report of number of signals and validated signals from the program were studied and evaluated for good detecting of potential signals promptly.

Objective: The objective of this study is to report performance of the signal detection program from Thaivigibase during year 2007–2008. The 2-year large database of voluntary adverse event reports of Thailand is the data resource for the study.

Methods: Unit of analysis is retrospective adverse reaction reports from Thaivigibase (National adverse drug reactions database) during year 2007–2008. Criteria for drug-ADR with potential signal and evaluate/assess drug-ADR with potential signal as designed by signal detection program were set. Routinely running the program every 6 month was performed automatically. Reporting odd ratio with 95% confidence interval (case-control principle in epidemiologic design) is statistical method to detect signal. Signal review panel assessed the important drug-unknown ADRs.

Results: The principal results were 1571 drug- ADR reports. 765 of which were fatal outcome. 219 of them had sufficient data for further evaluated. 165 of 219 reports were drug-ADR related to fatal outcome which were labeled/known drug-adverse drug reactions like Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) from antiepileptic drug group, anti-gout preparations and hepatitis from anti-tuberculosis drug group. 2 events from Effavirenz and 8 events from GPOvir (stavudine + lamivudine + nevirapine) were found to be related to fatal outcome, mostly they were labeled/known ADR like SJS and TEN. One acute renal failure report from herbal product (Houttuynia cordata Thunb, family of Saururaceae) was found in chronic renal failure patient. It is the first report in Thaivigibase to intensive monitored onwards. Risk mitigation from Thai signal detection program was done by distribute acknowledge among healthcare professional.

Conclusions: Although no potential signal was found from Thaivigibase, fatal outcome adverse drug reactions were leaded to further evaluate and continuously intensive monitor. Early signal detection would assist healthcare professionals to do risk evaluation and mitigation plan promptly. Additionally, we realized that there was the other method to measure ADR risk which would be evaluated.

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141. Time to Reform 'Spontaneous Reporting'

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During the 'pharmacotherapeutic revolution', midway through the last century, a series of unexpected and serious adverse drug reactions have lead to the understanding that there is a need for continuous monitoring of the safety of medicines after their introduction. Around 1970 in countries in different parts of the world national pharmacovigilance centres were introduced, using the technology and focusing on the concerns of that time. Since then advances in medical diagnosis and treatment and in computing and medical-pharmaceutical administration, together with changes in organisation and financing, have changed the landscape of healthcare in many respects. Unprecedented possibilities have become available for comprehensively studying the benefit and harm of medicines. While also pharmacovigilance has developed and changed enormously, it is up till today to a large extent still based on the 'spontaneous reporting' principle of 50 years ago. A succession of safety issues has emphasised the continuing need for alertness and improvement, the more so since the recent 'biopharmaceuticals' are again revolutionising pharmacotherapy. In recent years many proposals for improvement have been made and attempts been initiated, but evidence as to the timeliness and effectiveness of the new requirements and novel methods is still limited. A critical follow-up of their performance, ethics and costs is necessary. In addition to these developments, there is an urgent need for a careful reconsideration of the current and future roles of 'spontaneous reporting', and of its organisation and governance, in order to ensure that data of the best possible quality be collected and used to their best advantage, also paying due attention to the differences between various parts of the world.

142. Antiretroviral Drugs Induced Adverse Events in Retro-Positive Adults at Korle Bu Teaching Hospital

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Introduction: Most data on adverse drug reactions (ADRs) in patients on highly active antiretroviral therapy (HAART) come from clinical trials of specific antiretroviral agents. The prevalence of ADRs and their impact on quality of life are largely unknown outside of such trials. The safety profile of antiretrovirals (ARVs) in Ghanaians is not well established and documented. Adverse reactions to drugs are major reasons for patients defaulting during treatment.[1-5] Knowledge of the incidence prevalence of various adverse reactions and their management is therefore essential to effective ART programme.

Study objective: The objective is to study the adverse events in adult patients receiving antiretroviral therapy at Korle Bu Teaching Hospital, Ghana.

Method: Data was collected both prospectively through interviews with all adult retro-positive patients on ARV drugs at Korle Bu Teaching Hospital and retrospectively from patient records.

Findings: A total of 430 respondents were recruited, among which 318 (74%) experienced adverse events. In all 34 individual adverse events was reported by the respondents. A total of 1989 adverse events were reported by the 318 respondents with gastrointestinal effects accounting for 616 (31%), neurologic effects 555 (27.9%), immunologic & dermatological effects 206 (10.4%), haematological effects 43 (2.2%), metabolic effects 11 (0.6%), sexual effects 3 (0.2%) and others 619 (31.1%). Of the 318 respondents, 91% started experiencing adverse events within the first four weeks after initiation of ARVs and adverse events stopped within four months in 70% of the respondents.

Out of the 318 patients with adverse events, 198 (61.6%) continued their ARVs medications after, counselling, 78 (25%) respondents were given medication(s) to treat the presenting events and 41 (13%) had some of their ARVs withdrawn.

The outcome of the adverse events and action taken were, 243 (76%) of the respondents recovered without change of ARVs medication, 36 (11.5%) had some of their ARVs medications substitution/changed and in 38 (12%) of the respondents, events were still on-going but at a lesser extent.

Conclusions: Adverse drug events among the respondents on antiretroviral therapy were substantial. Most reactions were light to moderate. Majority of the adverse events were within the first four weeks after initiation of ARVs, and these adverse events stopped within four months. Syndromic management of presenting signs and symptoms, and substitution of one or more drugs were identified as the main interventions used for the management of adverse reactions to ARV in the study population.

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143. Survey of Awareness, Views and Experiences of Health Professionals of Tamale Teaching Hospital Regarding Adverse Drug Reactions in Patient Care

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Introduction: A spontaneous reporting system for adverse drug reactions (ADR) was introduced at Tamale Teaching Hospital, Ghana in 2005. Reporting of incidents of clinically important ADRs has generally been poor though there is anecdotal evidence of their occurrence. The impact of unawareness of issues concerning ADRs on the poor reporting attitude has not been investigated.

Aim: To explore awareness, views and experiences of health professionals of the hospital regarding ADRs in patient care and solicit suggestions to improve their knowledge and reporting of incidents.

Methods: A 25-item questionnaire was developed which focused on awareness with regards to the following: World Health Organisation (WHO) definition of an ADR; types A and B classifications, key predisposing factors to ADRs; pharmacovigilance; the National Spontaneous Reporting System (NSRS) and attitude of reporting. All doctors (n = 18), pharmacists (n = 8), medical assistants (n = 6), pharmacy technicians (n = 10) and 50% of nurses (n = 95) of the hospital at post during the period of the survey were sampled by quota that reflected the proportions of rank and gender. After piloting and adjustment, the final questionnaire was distributed to eligible participants and collected within two weeks with follow up of non-respondents.

Results: Eighty-six valid questionnaires out of 90 retrieved were anonymously analysed by SPSS 13.0. The response rate was 65.7%. Twenty-four percent understood an ADR to mean any undesirable effect of a drug. Awareness of WHO definition of an ADR was about 50% and of types A and B classifications 22%. Awareness of age and co-morbidity as patient predisposing factors was better compared to sex, race and genetic variability. Fifty percent and 35.1% respectively of respondents perceived antimalarials and antibacterials as drug classes that are commonly responsible for clinically important ADRs among patients in the hospital.

Frequency of clinically important ADRs in the hospital was estimated to be less than 1% by most respondents. Awareness of the term pharmacovigilance among respondents was 53%.

Awareness of the NSRS was poor (23%) with only 30% of those aware ever reporting an incident. Ninety-six percent fear increasing personal liability if they report ADRs and 95% felt really serious ADRs had been documented by the time a drug is marketed.

Conclusions: Awareness of ADRs, pharmacovigilance and the NSRS among health professionals of Tamale Teaching Hospital is poor and need improvement through training to guarantee the safety of pharmacotherapy in patient care in the hospital.

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144. Safety, Affordability and Adherence to Artemisinin: Combination Therapy in Ghana

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Introduction: Increasing resistance of the malaria parasite to chloroquine, Sulphadoxine-Pyrimethamine and other monotherapy led the WHO to recommend the use of artemisinin-based combination therapy (ACT) as first line medicines for treating uncomplicated falciparium malaria across the world. To date, several malaria-endemic countries have changed their national malaria policies and are deploying ACTs as first line treatment for malaria. Although the value of ACT is widely acknowledged and accepted, high costs and safety issues are still major barriers to their use.

Objective: To assess the level of adherence to artesunate-amodiaquine, the recommended ACT in Ghana. Safety perceptions of patients as well as their ability to purchase the combination were also explored.
Method: This was a cross sectional using mainly quantitative methods in the "Kpone-On-Sea" community, Tema in the Greater Accra Region of Ghana. Respondents included both male and female of all age groups who have had malaria in the six months prior to the study. Using both stratified and systemic sampling a total of 150 people were interviewed from that community. The data collection took 12 weeks, from beginning of April to the ending of June.
Results: Over 80% of respondents perceived the causes of malaria to be due to mosquitoes and unhygienic surroundings. Only 62 (42%) of respondents claim they have heard of the new ACT (Artesunate-Amodiaquine) and out of that number only 29 (47%) of them had actually used the drug . Seven (24.1%) out of the 29 users of artesunate-amodiaquine claimed they suffered one form of adverse effect or other. When told of the cost of ACTs, 137 (91.3%) of respondents found the medicine too expensive and unaffordable.
Conclusions: At the time of the study, there was poor knowledge among the sampled population on the change in national policy to ACTs. Nearly a quarter of the small number of users of amodiaquine-artesunate suffered ADRs. ACTs were deemed unaffordable by the population.
Recommendations: The roll of any new treatment policy for malaria should be accompanied by detailed education at the community level to ensure smooth implementation. Advocacy and behavioral change communication should be the main communication strategy employed. Real-life safety studies should also accompany drug deployment to retain confidence of the local population in the drugs and to ensure that any safety signals are quickly identified and dealt with.

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145. State of Direct Patient Reporting of ADRs in 14 European Countries

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Introduction: The European Union is in the process of amending its rules for pharmacovigilance to require all Member States to accept direct reports of suspected adverse drug reactions from citizens.
Aim: To find out how far and by what methods patients/consumers were reporting suspected ADRs in 14 European countries, how such schemes had developed, and how such reports were being dealt with.
Methods: Interviews by telephone, email or in person were conducted in the second half of 2009 with members of drug regulatory agencies and relevant non-governmental organisations in these countries.
Results: In half of the countries the regulatory agency accepts reports from citizens, in the others they do not, but this is gradually changing. Those that accept them value them; the ways in which the reports are analysed and used varies. Most countries segregate these reports from those sent by professionals, but combine them for analysis. In most countries experience with patients' reports is still small; different approaches are being tried to help people to report and to increase the number and quality of their reports. Most agencies acknowledge receipt of reports, but few are followed up. Whether reports are accepted via the internet, on paper or by telephone, varies between countries. Patients' preferences for these routes differ, so it seems that all will be needed.
Conclusions: Most countries accepting reports have found that they add valuable and often detailed information that complement reports from professionals. They use more direct language and give more detail than reports from professionals and often describe not only what happened but also the effect on the person's life and carers. They can also contribute to the earlier recognition of signals. Many citizens gladly contribute their report to help improve drug safety.

146. Barriers and Promoters to Adherence to ART in Ghana: A Hospital Based Case-Control Study

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Introduction: The introduction of Anti-retroviral therapy (ART) in the management of HIV/AIDS has seen dramatic improvement in the quality of life of the patients. Adherence to ART is an essential determinant of the outcomes of management of HIV/AIDS but safety is often cited as a barrier to adherence.
Aim: The study was undertaken to determine factors that promotes or constrain adherence to ART.
Methods: A case-control study at the Ridge Hospital conducted between May to August 2009 with a total of 224 respondents of which there was 122 each of cases and controls. Adherence levels to ART was the criteria for Case definitions. Respondents were purposively sampled after both a pill count and self-reporting were undertaken. A case is a PLWHA on ART at the Ridge Hospital who is 18 years and above, on therapy for 3 months or longer, had missed at least 20% of the doses of ART since their last refill of medication. A control is a PLWHA on ART at the Ridge Hospital who is 18 years and above, on therapy for 3 months or longer, has missed at most 5% of the doses of ART since their last refill of medication. Risk factors studied were grouped into patient factors, client–provider relationship, knowledge and perception of treatment and medication factors.
Results: Logistic regression analysis at 95% CI showed that the risk factors Knowledge of Adherence to ART, OR-5.247 (1.487–18.518), Missed pills, OR-8.220 (3.548–19.046) and Ability to pay for medication, OR-0.454 (0.208–0.992) were significantly associated with adherence to ART. The binary analysis showed that Quality of care by doctors (OR-0.32) pharmacists (OR-0.5) laboratory technicians (OR-0.42) and counselors (OR-0.46) were identified as promoters to adherence. Other risk factors Pill burden (OR-2.98) Concerns about disclosure (OR-2.36) and side effects (OR-2.36) were identified as barriers to adherence. Curiously, both education and occupational status were not significantly associated with adherence.
Conclusions: The study identified Quality of care by health care provider and Ability to pay for medication as promoters and Pills burden as a barrier to adherence.

147. Elevating our Thinking – A Need for a Holistic Approach to Pharmacovigilance Training

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Pharmacovigilance is not just a set of transactions, not just a matter of processing safety data and not just confined to one department within an organisation. It is increasingly a more proactive activity.

Over recent years, there has been an increase in public awareness of safety issues and the need to improve patient safety. The recognition of Pharmacovigilance has grown as stakeholders (regulatory agencies; pharmaceutical companies; Pharmacovigilance consultants; contractors and service providers) seek to ensure that emerging safety information is reported and appropriate action is taken to safeguard public health.

In addition, all companies face challenges in today's climate; demands of reduced budgets and restricted headcount go hand-in-hand with a high-pressure working environment and companies are forced to find more streamlined and innovative ways of working.

In the face of this reality, robust quality awareness and effective training is critical as safety specialists carry out their day to day tasks. The damaging negative impacts of "getting it wrong" are all too real following several drug safety crises resulting in a drop in confidence in the way safety of medicines is handled.

Stakeholders need to ensure that a holistic approach to training and quality is provided to our safety specialists - the gatekeepers of all safety information. We need to humanise the process, start at the beginning and explain why key events such as the thalidomide disaster in the 1960s resulted in the need to regulate pharmacovigilance. Each side effect report processed tells a story of what happened to a patient at a point in time. What is the life cycle of this report? How did this adverse event start and where will it end? One needs to understand who our key partners are and why we collaborate. Finally we need to link this back to how we process this data into our daily workflow systems. Through this approach, the safety specialist can bring the case/adverse event back to life, sharpen their focus and elevate their thinking, ensuring that case quality is the highest priority.

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148. The Role of Spontaneous Reporting in the Identification of Substandard Medicines: The Case with Diazepam Injection

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Introduction: Spontaneous reporting is the major pharmacovigilance reporting system in Ghana. The National Pharmacovigilance Centre rely on healthcare professionals to identify and report any suspected adverse drug reaction, therapeutic failure, suspected counterfeit and poor packaging or labelling voluntarily to the Centre.

The major weakness of this system is under-reporting; the National Database currently has up to 850 spontaneous reports received from healthcare professionals. Although, the number of reports in the database is limited a number of regulatory decisions had been taken by the National Regulatory Authority based on the limited reports received, key amongst these the withdrawal of certain batches of Diazepam Injection from circulation 2008 and 2009.

Diazepam is a long acting benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnestic properties. Diazepam also possesses dependence liability and may produce withdrawal symptoms; this is particularly common in patients with history of alcohol or drug abuse and in those with marked personality disorders. Peak blood levels are reached within 15 minutes after IV administration and are of the same magnitude as after oral administration. The dose by IV injection is 10–20 mg at a rate of 0.5 mL (2.5 mg) per 30 seconds.

Methodology: Normal spontaneous reporting, quality control laboratory analysis as per the British Pharmacopeia specification for Diazepam injection and regulatory action.

Results and Discussions: In January 2008 to November 2008, the Ghana National Pharmacovigilance Centre received nine reports of suspected therapeutic failure to five different batches of Diazepam 10 mg injection from two different manufacturers. The doses administered ranged between 10 mg to 50 mg with minimal or no therapeutic effect. Quality control laboratory analysis of the suspected batches indicated that all suspected batches did not conform to the specifications of the British Pharmacopoeia with respect to assay, the values ranged between 5.6%–88.2% (normal value 90–110%). The affected batches have since been withdrawn from the market and the importers sanctioned.

Six out of the nine patients developed cough, the association between cough and the product has not been previously established, the National Centre has not identify the possible cause of the cough with the suspected product.

This issue highlights the importance of spontaneous reporting to quickly identify substandard products from circulation and prevents patients from being affected by the negative consequences of these products.

Conclusions: Spontaneous reporting is useful in the identification of substandard products.

149. Challenges Involved in the Safety Assessment of Herbal Medicines in a Developing Country

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In Ghana, as in most African countries, it is estimated that more than 90% of the population has used herbal medicine at a point in their life to help meet some of the primary health care needs.

The use of herbal remedies is common because of cost and availability. It is also believed that these products do not have adverse effects associated with conventional medicines.

Out of the 607 adverse drug reaction reports received between 2005 to December 2009 by the National pharmacovigilance Centre in Ghana, 14 (2.30%) were associated with herbal products. Most (64.30%) of these reactions were serious with two deaths.

The challenges involved in the assessment of reports received by the National Centre for Pharmacovigilance were:

1. Reporters do not indicate the name of the product because most patients cannot remember the name of the suspected product since they do not consider these as 'drugs'.
2. Patients find it difficult to disclose the source of the product due to spirituality associated with the practice of herbal medicine and fear that the supplier of the medicine might harm them spiritually were they to indicate his or her identity.

3. Products are that are dispensed by herbalists to patients are not properly labelled, these products contain different concoctions or herbs mixed together.
4. Lack of inadequate laboratory infrastructure and equipment to characterize and identify the products submitted. Also, monographs for most tropical plant species are not available.

Conclusions: The need to strengthen pharmacovigilance system of herbal medicines is important and National Centres would need the continuous leadership of WHO in developing norms and standards for herbal medicine pharmacovigilance. The absence of laboratory infrastructure in resource constrained environments poses a formidable barrier which needs to be overcome if product identity is to be established beyond doubt.

150. Vitamin K3-Associated Serious Adverse Events in Ghana – How a Functional Pharmacovigilance System Helped Identify an Unregistered Product

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Introduction: Vitamin K is routinely used in Ghana for the prevention of bleeding in neonates and given at birth to all newborns. In Ghana, the registered variant is vitamin K1 (phytomenadione), a fat soluble analogue of vitamin K. Vitamin K3 (menadione) is a synthetic water soluble analogue of Vitamin K which is not licensed for use in Ghana due to the association of the following side effects with its usage: haemolytic anaemia, hyperbilirubinaemia, and kernicterus. Vitamin K3 is also associated with haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD).

Methodology: Normal spontaneous reporting and regulatory action.

Results and Discussions: In April 2010 the Ghana National Pharmacovigilance Centre received four reports of bleeding and severe jaundice after Vitamin K3 injection was given for the prevention of hemorrhagic disease in neonates. In- house assessment of the relationship of the medicine to the reactions suggested strong likelihood for the role of Vitamin K3 in the reported reactions which included severe jaundice, yellow discoloration of the eyes and skin and profuse bleeding at injection site an hour after injection. The products involved had no marketing authorization from the national drug regulatory authority and have since been removed from the market with further regulatory action been taken against the distributors.

This issue highlights the importance of pharmacovigilance to quickly detect and prevent important drug-related problems in society including unearthing the presence of unregistered products some of which may be associated with serious safety problems.

Conclusions: Four reported cases of vitamin K3 associated adverse reactions led to the identification of unregistered vitamin K3 in Ghana and withdrawal of the product from the local market.

151. Is Artesunate-Amodiaquine Associated with More Adverse Drug Events Compared with the Other Anti-Malarial Therapies?

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Introduction: In 2005, the Ghana Ministry of Health changed the policy on the first-line therapy of malaria to artesunate-amodiaquine (ART-AQ). However, several reports of adverse drug events (ADE) received by the then National Centre for Pharmacovigilance coupled with high negative media coverage led to withdrawal of specific brands of ART-AQ. This study looked at the "real-life" safety profile of ART-AQ compared with other anti-malarials on the Ghanaian market.

Objectives: To document the safety experience of antimalarials by patients in selected health facilities in Accra, Ghana.

Methods: Cohort event monitoring in which patients attending 24 health facilities were recruited after informed consent and followed up 7–10 days later by phone calls or home visit to document safety issues.

Results/Discussion: A total number of 2084 patients were followed up in the study. The ART-AQ was prescribed to 42.1% (n = 877) of the cohort. Other artemisinin based combination therapy (other ACT) was administered to 14.9% (310) of the cohort, artemisinin based monotherapy 34.6% (721) and non-artemisinin based monotherapy 8.4% (176). Patients administered ART-AQ had a higher risk of experiencing an ADE compared with the other therapy types. The risk of experiencing an ADE with ART-AQ was 1.49 fold higher compared with other ACT (OR 1.49 [CI 1.12, 2.00]), 1.35 fold higher compared with artemisinin based monotherapy (OR 1.35 [CI 1.09, 1.66]), and 2.2 fold higher compared with the non-artemisinin based monotherapy (OR 2.22 [CI 1.47, 3.33]).

Among the 877 patients administered ART-AQ, a total of 115 (13.1%) reported general weakness, (5.7%) dizziness, 26 (3.0%) headache, 25 (2.9%) patients vomiting, 24 (2.7%) anorexia, 22 (2.5%) pruritus and 20 (2.3%) pyrexia. Also, patients administered ART-AQ had a 1.69 fold higher risk of experiencing general weakness compared with other ACT (adjusted OR 1.69 [CI 1.02, 2.86]), 2.17 fold higher risk compared with artemisinin monotherapy (adjusted OR 2.17 [CI 1.49, 3.13]) and 5.26 fold higher risk compared with non-artemisinin monotherapy (adjusted OR 5.26 [CI 1.92, 14.29. The total number of drugs administered (anti-malarial plus concomitant medication) had no association with the presence or absence of an ADE ($p > 0.05$) and this relationship was spread across the various therapy types.

Conclusions: ART-AQ appears to be associated with a higher risk of ADE than other antimalarials.

152. Are the INDEPTH Demographic Surveillance Sites the Answer to Regular Collection of Rigorous Medicine Safety Data in Resource-Constrained Settings?

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Spontaneous reporting, the mainstay of national pharmacovigilance systems is associated with well-known limitations including under-reporting.[1] It has been estimated that even in well-resourced settings only about 3% of adverse reactions are reported.[2] The situation in resource-limited settings is worse.

Demography surveillance sites (DSS) are local populations under long term longitudinal surveillance for vital events and other characteristics. They help provide vital data on health characteristics in developing countries and have been regular sources of reliable information on population and healthcare characteristics and the impact of health interventions in these settings.[3] The regular collection of health information from these relatively stable populations makes DSS attractive for the evaluation of the safety of medicines.

INDEPTH – the International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries

(INDEPTH) is a global network of DSS sites in low- and middle-income countries. INDEPTH has 38 health and demographic surveillance system (HDSS) members in 19 countries with 26 sites in Africa, 11 in Asia and 1 in Oceania. INDEPTH has been involved in several types of research stretching from infectious diseases[4] to healthcare financing.[5]

The long experience of INDEPTH sites in testing globally-acknowledged health interventions provides a unique opportunity for the real-life evaluation of the safety of medicines. These sites offer the ability to perform short and long term studies of medicines in real-life settings.

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153. INESS – a New Platform for Evaluating Anti-Malarial Drug Safety and Effectiveness in Africa

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The INDEPTH Effectiveness and Safety Studies of Anti-malarial Drugs in Africa (INESS) is a new platform for the conduct of phase IV studies on anti-malarials. The goal of INESS is to provide national, regional and international health decision makers with independent and objective evidence on the safety and effectiveness of new anti-malarial drugs as a basis for malaria treatment policy in Africa. The specific objectives are to develop and maintain a Phase IV effectiveness and safety studies platform in Africa; assess the effectiveness and safety of new malaria treatments – and the factors that determine effectiveness and safety – in real life settings in Africa; and finally to undertake comprehensive pharmacovigilance in the context of African health systems. The INESS platform operates in demographic surveillance sites (DSS) in Ghana and Tanzania with studies in Burkina Faso and Mozambique due to begin. Overall, the INESS platform would be carrying out longitudinal safety assessment of anti-malarials in over 2 million Africans in 8 dispersed administrative districts in 4 countries. Under INESS, safety information on anti-malarials would be collected in two ways: (1): strengthening the existing spontaneous reporting system in the DSS in consultation with national health authorities and drug regulatory authorities and (2): cohort event monitoring (active follow-up) of specified brands of anti-malarials and also anytime a new antimalarial combination is deployed in the DSS. Since the INESS DSS sites are under continuous surveillance, a large linked database would be constructed and used to identify potential drug safety issues including pregnancy exposures and outcomes. The INESS sites would concurrently be examining the efficacy of specified anti-malarials, access to medicines, health provider compliance, patient adherence, acceptability, cost and cost effectiveness. The safety data collected would therefore be evaluated within the context of the existing health system providing a unique background against which any safety issue can be discussed and evaluated.

INESS offers an intriguing possibility of obtaining hitherto difficult-to-obtain n in drug safety research in resource-limited countries including assisting in obtaining background data on disease prevalence, prevalence of relevant clinical events, background rates of infant and maternal mortality against which any drug-associated problems may be measured. Data from INESS would be regularly and continuously published giving all players in drug safety – industry, governments, health professionals, international organizations – important safety information on anti-malarials in a timely manner.

INESS is fully funded by the Bill and Melinda Gates Foundation