

Uppsala Reports 45

UPPSALA REPORTS April 2009

For everyone concerned with the issues of pharmacovigilance

Genetics and drug safety

Educating the media

Open access reviewed

Cohort Event Monitoring

ICSR reporting statistics



DIRECTOR'S MESSAGE



Ralph Edwards
Director
the Uppsala Monitoring
Centre

No one method can be relied upon for global signal detection, and I am often surprised that the UMC is regarded as only interested in individual case safety reports (ICSRs).

It is true that WHO had the first international database of ICSRs in 1968, and this was taken over operationally by the UMC a decade later through an Agreement between WHO and the Swedish Government. We, at about the same time as Stephen Evans in the UK, were the first to publish data-mining of ICSRs as an adjunct to clinical review.

In the past, however, I have worked with the world's first cohort event monitoring (CEM) system, and was instrumental in bringing the technique for use in the WHO Programme and UMC in collaboration with my colleague David Coulter. It is a natural tool for pharmacovigilance in public health programme roll-outs where there are cohorts of patients using new medicinal products.

Now, the UMC is the first group to introduce data-mining in longitudinal patient health care records. We have been doing this for over 5 years, and finding signals successfully¹. We use and promote each of these methods since they each have their strengths and weaknesses for signal detection and analysis.

Individual case safety reports have considerable value in bringing in the observations and intelligence of those who use medicines in their daily lives. They may contain information about medication errors, drug and food interactions, and other special risk situations that might not be captured any other way. They can also give, through verbatim descriptions of the adverse reaction, a subjective dimension to the impact of the adverse reaction on that individual patient: we should try to gain more of such insights. They bring the health professional and consumer reporters, and their concerns, directly into the process of regulating the medicines they use. Responses to their reports also allows for individual useful, educational feedback to them. The weaknesses are: biases, no denominator data and differential under-reporting.

Cohort event monitoring allows for a different capture of events which may or may not be medication related. As such, unusual clinical events may be found to have a relationship to medication, which might not be obvious to the users and reporters. These signals may be seen by the remote observer evaluating collated cases, quantified in a continuous known cohort of exposed individuals. Contemporaneous cohorts of other medications may provide some kind of control, but the lack of specially selected controls is a drawback in both determining causality and attributable risk. Coding strategies may obscure outcomes, as they may with ICSR.

Longitudinal health care records allow the comparison of cohorts of exposed patients with themselves as controls when they were not exposed (before treatment particularly) and against all or a selected control population taken from all other patients. Data-mining techniques can be used to follow exposed patients chronologically with comparison to any type of outcome (bad, good; laboratory finding, clinical event) and to signal disproportional relationships, compared with controls, quickly. Patterns of multiple data elements can also be valuable in the further analysis of a signal, and for determining special risk groups. The impact of coding strategies and multiple testing, which may increase the chance of spurious findings, is a subject of further work.

So, the UMC has pioneered work in data-mining in several, different, large sets of data to increase the richness of our knowledge, but we always acknowledge the necessity of clinical review and diagnostic insight, as well as more specific epidemiological testing as the tools for definitive testing of hypotheses, along the lines of the Bradford-Hill criteria². If you still think we just look at tens of thousands of ICSR per quarter think again and check our website too: www.who-umc.org !

1. Norén, G.N., Bate, A., Hopstadius, J., Star, K., and Edwards, I. R. Temporal pattern discovery for trends and transient effects: its application to patient records. in ACM SIGKDD international Conference on Knowledge Discovery and Data Mining. 2008. Las Vegas, Nevada, USA: KDD '08. ACM.
2. Bradford Hill, A., The environment and disease: association or causation? Proc R Soc Med, 1965. 85: p. 295-300.

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The Uppsala Monitoring Centre (*the* UMC) is the field-name of the WHO Collaborating Centre for International Drug Monitoring, responsible for the management of the WHO Programme for International Drug Monitoring.

An independent centre of scientific excellence, *the* UMC offers products and services, derived from the WHO database of Adverse Drug Reactions (ADRs) reported from member countries of the WHO Programme.

With an independent and global perspective on drug safety, *the* UMC provides resources for regulatory agencies, health professionals, researchers and the pharmaceutical industry.

The UMC's important worldwide work is financed solely by the organisation itself, without support from WHO, the Swedish Government, member countries of the WHO Programme or any grant-making body.



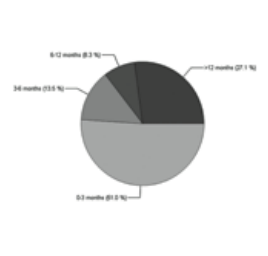
5 Rabat

The 2009 Annual Meeting of the WHO Programme for International Drug Monitoring will take place in Rabat, Morocco on 2-5 November 2009.



6 CEM in Africa

Cohort event monitoring is getting established – and a new tool is helping in Tanzania.



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A hundred Polish journalists increased their knowledge of pharmacovigilance with a visit to Uppsala last October.

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Kick-off for pharmacovigilance in Saudi Arabia

Sten Olsson

Saudi Arabia officially launched its national pharmacovigilance programme by organizing a symposium in the capital city Riyadh from 30-31 March 2009, under the theme 'Drug Safety, a Global Concern'. To emphasize pharmacovigilance as an international undertaking, the Saudi Food and Drug Authority (SFDA) had invited a number of international speakers, both from the Eastern Mediterranean Region and from Europe. Perspectives of the WHO Programme were presented by Sten Olsson from the UMC; the International Society of Pharmacovigilance (ISoP) was represented by its president Nicholas Moore. Barry Arnold, AstraZeneca, gave an industry view on pharmacovigilance and Saad Shakir from Drug Safety Research Unit, Southampton, UK presented thoughts of an experienced drug safety researcher. Experiences of well-established national pharmacovigilance centres in the region were given by Nida'a Bawarsh (Jordan), Sawsan Jaffar (Oman) and Rachida Souleymani-Bencheikh (Morocco). More than 600 healthcare professionals and industry representatives had registered for the symposium and there were many questions and active discussions after each presentation from the podium.



Sten Olsson presents a copy of the book *Drug Benefits and Risks from the UMC* to the new centre in Saudi Arabia, represented by Saleh Bawazeir (left) and Ghazi Saeed (middle).

Sound basis

After the creation of SFDA in 2004 the agency started building the basic structures and creating facilities for a national pharmacovigilance centre. Efforts were led by Saleh Bawazeir, deputy director of SFDA, and Ghazi Saeed, head of the pharmacovigilance centre. Regulations were put in place, guidelines were written, reporting forms were designed and tested and software for data management acquired. At the time of the official launch the Saudi pharmacovigilance centre had already joined the WHO International Drug Monitoring Programme as its 92nd member. The Saudi centre is inviting spontaneous reports on adverse reactions, quality problems, unexpected lack of efficacy and drug poisoning from all health

professionals, the pharmaceutical industry and from the general public. Reporting is in fact mandatory for hospitals, health organizations and for industry. The pharmacovigilance centre, with its 13 member staff, has produced various promotional materials and will embark on promotional campaigns and training courses in different parts of the country for stimulating reporting. It plans to appoint pharmacovigilance co-ordinators in all major hospitals and ensure that pharmacovigilance is incorporated in training curricula for health professionals.

Commitment

The commitment of the SFDA to its new pharmacovigilance programme is strong and visible. This provides hope for good results to come out of the efforts. It was suggested at the inauguration meeting that the Saudi centre could have a leadership role, together with the Gulf Collaboration Council (GCC), for the establishment of pharmacovigilance centres in other Gulf countries, where such centres are still not in operation.

Iraq

The Ministry of Health of Iraq have written to the UMC requesting membership of the WHO Programme. While awaiting compliance with reporting requirements, Iraq becomes an Associate member of the Programme.

Being a member of the Programme

The UMC recently produced and circulated a leaflet to all national centres setting out the current workings of the WHO Programme for International Drug Monitoring. Described are advantages of membership – things that countries are able to receive automatically from the UMC, such as access to VigiBase, early information about potential safety hazards, terminologies and software, guidelines and resources on pharmacovigilance practice, and access to the international network.

The leaflet also sets out what is expected from national centres, including reporting format compatibility and quality, frequent submission of ICSRs, the national drug formulary, good communication with the UMC, involvement in Vigimed and regularly sending at least one delegate to the National Centres Annual Meeting.

WHO Programme to Rabat

The 32nd Annual Meeting of countries participating in the WHO Programme for International Drug Monitoring will take place in Rabat, Morocco on 2-5 November 2009, hosted by the Moroccan Centre of Pharmacovigilance (Centre AntiPoison et de Pharmacovigilance du Maroc).

An accessible venue

Morocco is just a step away from Europe across the straits of Gibraltar, but it is a world away in culture and landscape. This is due partly to its geographical position, sited at the crossroads where Africa shakes hands with Europe, and the Mediterranean merges with the Atlantic.

A mix of old and new

Rabat, with a population of 2 million, is the capital of the Kingdom of Morocco. Located at the mouth of the river Bou Regreg, the city is very much one for walking in, with historic sites including a medieval fortified royal town, although it also has much Art Deco and neo-Moorish architecture. Tourism and the presence of foreign missions in Morocco are important and the city also has a few official galleries and an archaeological museum. Rabat is nonetheless a modern city with wide boulevards, gardens, and light, white buildings. Although the city's position as a port has diminished there are important textile, food processing and construction industries.

In November temperatures are mild, ranging from around 21°C to 13°C, but with a chance of rain showers. The official language in Morocco is Arabic, although French is widely spoken in commerce and the professions.

What to expect at the meeting

Although the WHO meeting programme is still being drafted, there is likely to be a session on medication errors with a speaker from the International Medication Safety Network, a session on WHO pharmacovigilance strategy, as well as a VigiFlow user group meeting and the usual posters and Problems of Current Interest.



Rabat, the parliament.

See you there

We are hoping that as many WHO Programme countries as possible will be represented in Rabat next November and are looking forward to seeing old friends and new colleagues alike for an enjoyable and productive meeting.



The staff of the Moroccan national centre in Rabat. From right to left : Dr Houda Sefiani, Dr Nabiha Smiress, Dr Amina Tebaa, Dr Ismail Talibi, Dr Souad Skalli*, Dr Rachida Oueld Rkhiss, Dr Fatima Abadi, Dr Raja Benkirane*, Dr Rajae Benjelloun and Pr Rachida Soulaymani*
members of the local organizing committee.

Cohort Event Monitoring of ACTs in Africa: a field visit to Tanzania

Shanthi Pal, Quality and Safety of Medicines, WHO

Magnus Wallberg, WHO Collaborating Centre for International Drug Monitoring, UMC, Sweden

Malaria is one of the most severe public health problems worldwide and a leading cause of death and disease in many developing countries. About 80% of all malaria deaths occur in Africa south of the Sahara, and the great majority of them in children under five. Key among the factors contributing to the increasing malaria mortality and morbidity is the widespread resistance of *Plasmodium falciparum* to conventional anti-malarial drugs, such as chloroquine, sulfadoxine-pyrimethamine (SP) and amodiaquine. As a response to increasing levels of resistance to anti-malarial medicines, WHO is promoting the use of artemisinin combination therapies (ACTs) as a therapeutic tool to treat uncomplicated acute *falciparum* malaria.

WHO currently recommends the following combination therapies (in alphabetical order):

1. artemether/lumefantrine
2. artesunate plus amodiaquine (in areas where the cure rate of amodiaquine monotherapy is greater than 80%)
3. artesunate plus mefloquine (insufficient safety data to recommend its use in Africa)
4. artesunate plus sulfadoxine/pyrimethamine (in areas where the cure rate of sulfadoxine/pyrimethamine is greater than 80%)

ACTs are known to be effective, but their safety under large-scale operational use has not been fully assessed, particularly in pregnant women and children.



From left, Dr Alex Mwita (Manager Malaria Control Programme), Dr Magareth Ndomondo-Sigonda (Director General, TFDA), Dr Jean Baptiste Tapko (WR-Tanzania), Dr Shanthi Pal (WHO-Geneva), Dr Hiiti Sillio (Director, Medicines and Cosmetics-TFDA).

Active or passive surveillance?

It is important to carefully monitor the safety of ACTs. But what is the ideal way to do this, so that we can characterize the safety issues associated with ACTs in the least possible time? Spontaneous reporting is the most common form of pharmacovigilance, being the cheapest and the easiest to establish.



People arriving at Mnazi Mmoja Health Centre, one of the cohort monitoring centres.

But there are some inherent limitations to the usefulness of this passive surveillance method: spontaneous reporting is entirely dependent on the initiative and motivation of the potential reporters; there is gross under-reporting (only about 5% of adverse drug reactions are reported in developed countries), there are strong biases in reporting; reliable rates cannot be calculated and so risk cannot be measured and risk factors cannot be established with confidence. These problems can seriously affect our work in pharmacovigilance, particularly when seeking early and accurate information on potential risks with new medicines.

CEM and active surveillance

Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. WHO has been working to introduce the broad principles of cohort event monitoring (CEM), a prospective, observational method of recording adverse events associated with one or more medicines. Based on New Zealand's Intensive Medicines Monitoring Programme (IMMP), CEM is an

At a glance CemFlow

CemFlow is a web-based software designed to manage all data collection and analysis aspects of a Cohort Event Monitoring (CEM) programme. The software is based on the UMC's tool for the collection, reporting and analysis of ADR case reports – VigiFlow™ – which is used by many National Centres in the WHO Programme.

The CemFlow system has been designed to be simple and user friendly – but with flexibility to allow for simultaneous monitoring of different medicines as well as groups of medicines.

CemFlow is built to manage:

- ◆ Multiple CEM programmes simultaneously with easy administration
- ◆ Entry of all necessary CEM data in a 'CEM report'
- ◆ Simple registration and management of data entry users

CemFlow also provide:

- ◆ Compatibility with available paper questionnaires
- ◆ Search and analysis tools
- ◆ Built-in dictionaries and terminologies

CemFlow will be available on the web for countries that would like to carry out CEM programmes. The first version, built in collaboration between the UMC and the WHO, is already available but will be fine-tuned as the CEM pilots in Tanzania and Nigeria proceed.

For details about the Cohort Event Monitoring methodology, please read the WHO publication [A practical handbook on the pharmacovigilance of antimalarial medicines](#).

active surveillance method that is essentially an observation of a new medicine in the early post-marketing phase, but can also be used for older medicines.

CEM training

In June 2007, WHO organized a CEM training course for three African countries: Ghana, Nigeria and Tanzania. The countries will use CEM to collect comprehensive and near-complete data that will address the special needs of the malaria programme, including effects of malaria treatment in pregnancy, specific toxicities, safety in children. Advantages over spontaneous reporting will include the ability to produce rates, the ability to produce a near-complete profile of the adverse event and/or adverse reaction for the medicines of interest, and the possibility to identify signals at an early stage.

Field visit to Tanzania

Both Tanzania and Nigeria are now well on their way to implementing CEM for the safety monitoring of ACTs in selected health facilities in their countries. During a recent field visit to Dar es Salaam, WHO HQ Pharmacovigilance Technical Officer Shanthi Pal and UMC software architect Magnus Wallberg joined the Tanzania Food and Drugs Authority TFDA in the pilot phase of CEM implementation. Preliminary

feedback from three pilot sites

- a public health facility: Mnazi Mmoja Health Centre
- a private hospital: Tumaini Hospital
- a referral hospital: Muhimbili Hospital

was encouraging and useful in fine-tuning the CEM tools.

The UMC IT team is engaged in developing a data management tool CemFlow for CEM; this tool, when ready, will support the ongoing CEM initiatives in Tanzania and Nigeria.

In addition to providing important safety information, CEM of ACTs will provide an opportunity to test this method in Africa. TFDA is clearly well-placed to lead the current CEM efforts in eastern Africa. The agency is aiming to complete its ACT-CEM cohort by the end of the year.

Transparency of an ADR database: risk or benefit?

Kees van Grootheest Netherlands Pharmacovigilance Centre Lareb



Kees van Grootheest

Since 2004 all Dutch ADR reports have been accessible at the website of the Netherlands Pharmacovigilance Centre Lareb. Our opinion, in concordance with the policy of the Netherlands Medicines Evaluation Board, is that information about the safety of medicines should be transparent and publicly accessible.

Confidentiality about information regarding the safety of drugs suggests there is something to be hidden and is counter-productive to the much-needed confidence in pharmacotherapy. The only acceptable exception is the need for protection of the privacy of individual patients

and (to a lesser extent) reporters. Patent-related information could be an exception, but this matter is not relevant in a discussion about the openness of ADR databases.

Experiences in the Netherlands

Before Lareb decided on complete transparency and publish the Lareb ADR database on its website, the matter was extensively discussed internally, especially in the Scientific Advisory Board. All kinds of considerations were taken into account. The current experiences with some main points from the discussion, are:

Workload

Contrary to our expectations there was no increase in calls for information or other major disturbances in our normal routines.

Misuse

The fear of misuse by journalists or lawyers has been shown to be unfounded. Only on one occasion did a journalist phone us about a high number of fatal outcomes with a certain drug. This appeared to be an error in the way of showing the results, which suggested the fatal outcomes were related to the drug. The case involved was an example of confounding by indication and the patient's death was a consequence of the serious disease for which the drug was given. As a result, we adapted the way of presenting the outcome in order to prevent misinterpretation.

Privacy

At our website www.lareb.nl no date of birth is provided, but age only is given, in periods of five years and no feedback information to the reporter can be seen. The privacy aspects were checked by an

expert lawyer in this field to ensure compliance with legislation. We have never received any complaints regarding this.

Positive outcomes

In contrast to our concerns before implementing openness on our website, transparency resulted in some important positive side effects.

Impact on clinical practice

The final goal of all pharmacovigilance activities is to make the use of drugs safer. Besides retrieving new knowledge from daily drug use, we want to support the work of physicians and pharmacists in their daily practice. Many practitioners use the database in their medical and pharmaceutical work as a source of information.

The first articles have been published in papers such as the *Nederlands Tijdschrift voor Geneeskunde*, the main Dutch medical journal, and the *British Medical Journal*, in which information from our website is used and recognized.

International exchange of information

We were happy to discover that our web-based database is used by colleagues in many countries. They compare their reports and possible signals with reports and other information from the Netherlands, which is very encouraging for us.

Use in unexpected ways

Since our database is easily accessible, it is used by some others than those we had intended it for. The first new group of users was Lareb employees. It is an easy way to find information quickly, not only the reports, but also additional information such as publications, signals and so on. The database is also used by students in medicine, pharmacy and pharmacology - and many others, including patients and patient organizations.

Publications and research by others

If the Lareb ADR database is used by others for publications and scientific research, Lareb expects to be involved; this is mentioned in the caveat at the website. Although the information is public, we want to be recognized as the source. Lareb is often invited to participate in research and publications.

Conclusions

Making the Dutch medicines safety information available on the internet has, overall, been a constructive development. Transparency - not only the facts, but more: the attitude - is very much appreciated. Politicians, the general public and colleagues want us to be transparent. The Dutch experience has so far demonstrated that the side effects are positive; the benefit definitely outweighs the risk. It contributes to earning public confidence both in a well-established drug safety system and in the use of drugs itself.

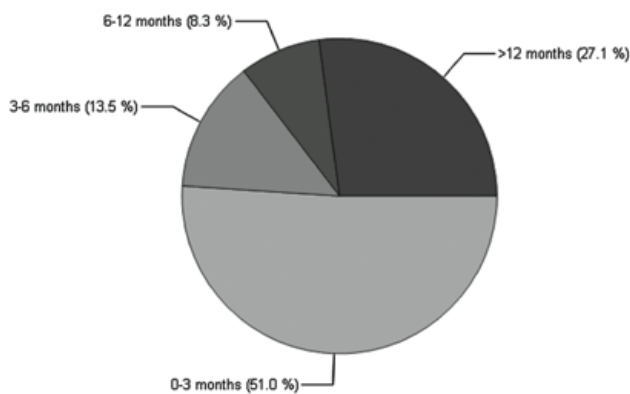
Database update

Helena Wilmar and Lovisa Sällstedt

Regular reporting

In February the UMC Reporting team sent out ICSR submission reminders to all official member countries which have not submitted case reports to the WHO global ICSR database according to the WHO requirements (at least every quarter). Out of the 94 WHO Programme member countries 24 were reminded in this manner. After two reminders six countries have submitted a new batch of ICSRs. In addition, 13 countries replied with reasons for not being able to submit ICSRs to the UMC as a result of the current situation at their National Centre (NC). Only 50% of our Programme members fulfilled the reporting requirements for the last quarter (see Figure 1 below).

Figure 1



Time elapsed since last submission (proportion of countries as percentage)

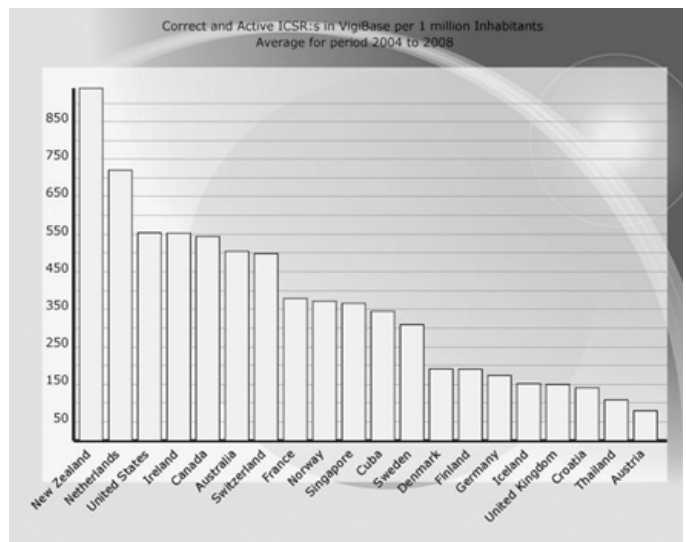
E2B format

The Reporting team is pleased to note that during the first quarter, three member countries have started to submit ICSRs in the E2B format instead of the old WHO format (INTDIS format). The countries to highlight are Bulgaria, Canada and United Kingdom. In addition, Egypt and Romania have recently started to use VigiFlow™ and we therefore anticipate these countries starting submission of ICSRs in the E2B format in the near future.

Currently 40 countries submit their ICSRs to VigiBase in the old WHO format, and 54 countries submit ICSRs in the E2B format. Of those countries reporting in the E2B format, 29 are using VigiFlow as their case management system.

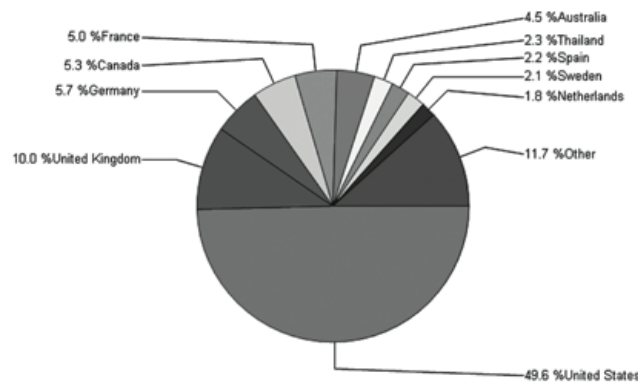
Due to the development of the new import process for ICSRs (see UR40), and therefore a pause in the insertion of cases into VigiBase, the frequently-requested population statistics have not been published in Uppsala Reports since 2006. We are now able to present some updated statistics on the reporting rates (Figure 2) as well as country distribution (Figure 3).

Figure 2



Reporting rates (per million inhabitants) to the UMC (January 2004 to December 2008). Top 20 countries are shown in this graph.

Figure 3



Country distribution of ICSRs in VigiBase as of March 2009 (total number of ICSRs = 4.6 million)

For more information about the WHO global individual case safety report (ICSR) database (Vigibase), see the pdf in the FAQ section of the UMC website, or the following paper: Lindquist M. Vigibase, the WHO Global ICSR Database System: Basic Facts. *Drug Information Journal*, 2008, 42:409-419.

EUDRAGENE

European collaboration to establish a case-control DNA collection for studying the genetic basis of adverse drug reactions

Co-ordinators: Dr Mariam Molokhia, Professor Paul McKeigue

London School of Hygiene and Tropical Medicine, University of London



We are currently undertaking a European study called EUDRAGENE (www.eudragene.org) to establish a freely-shared case-control collection of DNA samples as a

resource for studying genetic predictors of adverse drug reactions. Identifying genetic variants that influence susceptibility to adverse reactions will advance understanding of the molecular basis of these events and may also lead to the development of tests that can predict individual susceptibility to adverse reactions, with obvious benefits to human health.

Type B reactions

Type B adverse drug reactions (ADRs) are often serious, limit the usefulness of drugs that are otherwise effective, and increase the risks of drug development because they lead to withdrawal of drugs after the costs of bringing them to market have been incurred. Identifying genetic variants that influence susceptibility to ADRs has obvious practical and scientific value. Research in this area is hampered by the lack of a resource in which to study genetic determinants of susceptibility to Type B ADRs. As serious Type B ADRs are rare, case-control designs are the only feasible approach. A multicentre European collaboration has been necessary, as no single country will generate enough cases of any given ADR within a reasonable time.

Six centre collaboration

We are aiming to establish this freely-shared resource consisting of clinical data and DNA samples from at least 400 cases of each class of ADR, together with a control group. We are currently collecting cases from seven classes of ADR that are important and easily identified, throughout six European countries; in Italy, France, Netherlands, Spain, Sweden and the United Kingdom. These ADRs of interest are; drug induced liver injury, statin-induced myopathy and rhabdomyolysis, Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN), long QT syndrome, agranulocytosis, fluoroquinolone-induced tendon rupture, and mefloquine-induced neuropsychiatric reactions.

Data sources

In each participating country suspected cases are ascertained through physicians' reports of suspected ADRs to the national or regional pharmacovigilance agency. This has been supplemented where necessary with case ascertainment from existing registries of disorders such as blood dyscrasias, from databases of drug utilization and morbidity in primary care, and from hospital admission records.

Suspected cases are invited to take part via their physicians. Additional clinical data is obtained from questionnaires and medical records, before establishing whether each suspected case meets the case definition for that class of ADR. A blood sample is taken at the

local site and shipped to a laboratory at Erasmus Medical Centre in Rotterdam, for extraction of DNA for further studies.

Genome wide association studies of drug induced hepatotoxicity are currently underway with support from the Serious Adverse Events Consortium (collaboration of academia and industry) and Columbia University, New York as part of an international collaboration.



View of London School of Hygiene and Tropical Medicine

If you would like further information about the EUDRAGENE study please contact Mariam Molokhia: mariam.molokhia@lshtm.ac.uk or telephone +44 (0)20 7927 2633.

Seeking to predict serious ADRs

The Serious Adverse Event Consortium (SAEC) is a non-profit organization launched in 2007 comprising a dozen leading pharmaceutical companies, and academic institutions with scientific and strategic input from the US Food and Drug Administration (FDA). The academic collaborators include universities in Spain, the UK and USA and scientific consortia. The mission of the SAEC is to help identify and validate DNA-variants useful in predicting the risk of drug-related serious adverse events (SAEs). In addition to supporting original research of drug-related SAEs, it aims to:

- establish open-use research practices and standards
- encourage greater efficiency by pooling resources with public safety-driven goals
- enhance the public's understanding of how the industry, academia and government address drug-related adverse events in partnership.

Techniques drawn from the fields of pharmacogenetics and pharmacogenomics (PGx) will be used.

The SAEC collects SAE data already available from the participating pharmaceutical companies and academic institutions. These well-characterized databases of DNA from individuals who have experienced drug-related liver toxicity and Stevens-Johnson syndrome are then compared with control cases to identify genetic variants that may be associated with these SAEs.

The chair of International SAE Consortium, Ltd is Arthur L. Holden and its website is <http://www.saeconsortium.org/>.

New journal for developing countries

The Discipline of Social and Administrative Pharmacy at the School of Pharmaceutical Sciences, Universiti Sains Malaysia is leading the launch of a journal focusing on medicine use issues in developing countries. The aim is to promote rational use of medicines and sustainable health in developing countries and provide a strong platform for the researchers from the developing countries to publish their research findings.

Core areas of interest of the journal include:

- ◆ Research in generic medicines
- ◆ Drug utilization studies
- ◆ Pharmacovigilance
- ◆ Pharmaco-economics
- ◆ Issues related to counterfeit medicines
- ◆ Drug information
- ◆ Pharmaceutical policy and management
- ◆ Pharmaco-informatics

Contact

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<http://www.usm.my/dsap/journal/scope.html>

Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety (GACVS) was established by WHO in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance. Among topics discussed at its meeting on 17–18 December 2008 were the safety profiles of rotavirus and human papillomavirus vaccines.

Rotavirus vaccines

The Committee was presented with post-marketing information on the Rotateq and Rotarix vaccines from Australia, Latin America and the United States. Given the data presented, members were reassured that a risk of intussusception of the order of that which had been associated with Rotashield could be ruled out with confidence. The Committee also indicated, however, that the available post-marketing surveillance data were still too few to rule out, with confidence, a risk of substantially lower magnitude. The Committee emphasized the importance of continuing to accumulate post-marketing surveillance data on intussusception and other possible adverse effects and stressed the importance of setting up surveillance systems for such effects as the vaccines were introduced into an increasing number of developing countries.

Human papillomavirus (HPV) vaccines

The Committee reviewed the latest recommendations of the WHO Strategic Advisory Group of Experts on immunization on HPV vaccines as well as data related to their large-scale use and articles on early post-marketing surveillance. After careful methodological review of the evidence, GACVS concluded that none of the reports raised sufficient concern to change previous advice given by GACVS.

Given that many countries have only recently introduced HPV vaccines at the national level, and as plans exist to introduce the vaccines in many countries with varying capabilities for monitoring of adverse events following immunization, the Committee called for increased attention to building capacity for post-marketing surveillance in those countries where introduction is planned. The Committee also agreed to comprehensively review the post-marketing safety profile of HPV vaccines during 2009.

A full report may be downloaded from <http://www.who.int/wer/2009/wer8405.pdf>

Pharmacovigilance for ARVs pilot project

Improving patient safety, patient care and treatment outcomes for people living with HIV/AIDS treatment

Dr Micheline Diepart, Medical Officer, Department of HIV/AIDS, WHO

Readers may recall the WHO/UNAIDS '3 by 5' initiative, launched in 2003 to provide antiretroviral medicines for 3 million people suffering from AIDS by 2005. This target was only reached by end of 2007, but this was seen as a major success, considering the challenges and that most of the people on treatment are from resource-limited countries. This initiative has not yet been matched by the same effort to improve pharmacovigilance for antiretroviral medicines (ARVs) in low- and middle-income settings.

The background to monitoring

Today, close to 4 million people worldwide have access to antiretroviral medicines, and the new target is 'Universal access to treatment for all'. The effectiveness of treatment programmes, particularly in resource-limited countries, risks being compromised by problems related to toxicity, intolerance and drug-drug interactions. Adverse events linked to antiretroviral medicines used in AIDS infection, whether acute or chronic, mild or severe are relatively common, affecting both individual patients and public health. They not only reduce the treatment efficacy with increased morbidity and mortality, but also become a public health issue, as treatment programme effectiveness may be reduced through increased risk of emergence of secondary drug resistance. In spite of this, they remain only intermittently identified and scarcely systematically reported in low- and middle-income settings. New adverse events and toxicities are identified, and antiretroviral therapy became a chronic infectious disease, life-long treatment, with built-in toxicities. The availability of numerous new drugs and drug combinations makes it critical to systematically monitor adverse events linked to antiretroviral medicines.

The need for data

Antiretroviral medicines and other drug interactions are receiving increasing attention too. For instance, many patients receiving ART in low- and middle-income countries are also being treated for tuberculosis (TB) or malaria. Increasingly questions are raised concerning the acute and cumulative toxic effects, and impact on ARV efficacy resulting from drug regimes that combine treatment for HIV and TB. Limited data have been collected on co-administration of ARVs and second-line anti-TB treatment, and on artemisinin combination therapies for malaria. The influence of co-morbidity (especially hepatitis) and metabolic conditions on drug toxicity and drug-drug interactions also needs to be better understood.

Different setting, different approach

Moreover, what we know of adverse events and toxicities in antiretroviral drugs is provided by pharmacovigilance and cohort event monitoring data from developed countries. These data do not necessarily apply to the low- and middle-income settings, where the metabolic, nutritional, genetic background may differ. In these settings, through a public health approach, treatments are based on standard population-based HIVDR monitoring and surveillance,

focusing on increased adherence, with a limited number of prequalified medicines, generic products and simple recommendations for when to start, substitute or switch medicines due to toxicity.

WHO strategy

The WHO Department of Essential Medicines and Pharmaceutical Policies has published a document on pharmacovigilance for ARVs and organized country training in different parts of the world but there is a need for more effort in pharmacovigilance. A joint project, initiated by the HIV and EMP Departments, funded by the Bill and Melinda Gates Foundation will develop in four directions. Firstly, harmonizing norms and definitions, tools and methodologies for improving pharmacovigilance for ARVs as a preliminary step towards better management of available information. The UMC is fully and actively involved in the development of these tools and more specifically in developing *CemFlow*, an online tool for recording adverse events observed in a cohort of patients treated with one or more medicines. Secondly, a few countries have been selected and will be supported to field test and implement the tools developed. The objective is to propose a model that could later be adapted and adopted in other countries, if possible integrating active and passive surveillance methods, with training included. Thirdly, to meet the immediate needs for critical information on adverse events and toxicities in resource-limited settings and to better inform WHO and national guidelines, policies and strategies, key studies will be undertaken, based on a research agenda for the three years of the project. A project advisory group has been established and Dr Marie Lindquist, UMC, has accepted to be part of it. This Advisory Group will, over the lifespan of the project, help WHO define, plan and guide the project's scientific agenda, and more specifically, the targeted studies. A first meeting in March has defined the first year's research agenda. While focusing on low-income settings, it was agreed that the project will include and refer to the very significant existing and potential work undertaken by international cohort collaborators to rapidly bring some response to urgent questions regarding patient safety. Research protocols will be offered for competitive bidding.

Collaboration in prospect

The project team will ensure the appropriate co-ordination of the project activities and accurate reporting of data analysis and promote a wide sharing and dissemination of tools developed and data collected. This project attracts much interest within WHO and from partners, implementers in countries, researchers, academicians. As for most activities linked to pharmacovigilance, the expectation is that it will further strengthen the collaboration between the WHO, the project partners, and the UMC.

Uganda training assignment

Sten Olsson and Helena Wilmar

Set-up

Pharmacovigilance in Uganda began in 2004 with the establishment of the National Pharmacovigilance Centre (NPC) at the National Drug Authority (NDA). In June 2007 the NPC became a full member of the WHO Programme for International Drug Monitoring, and since then Regional Centres (RCs) have been created within seven referral hospitals. Around 300 individual case safety reports (ICSRs) have been received through spontaneous reporting since the start of the programme (VigiFlow™ software is used).



The practical VigiFlow training in Kampala

Activities

A training course took place in February with UMC participation, opened by Mr Apollo Muheirwe, NDA Chief Executive Officer. The course members were 32 professionals from the seven regional centres. As well as lectures, working groups discussed causality assessment and its application to case scenarios, and practical sessions took place on VigiSearch™ and VigiFlow. After the course, on 20 February, the NPC was formally inaugurated with speeches by Director General of the Ministry of Health, and the Chairman and the Chief Executive Officer of the NDA, recorded by the media.



*Back row: Mrs Helen Byomire Ndagije (Head of NPC), Mr Babiha Julius, Christine Naluswata, Ms Huldah Nassali, Mr Sten Olsson
Front row: Ms Angela Bonabana, Mrs Helena Wilmar, Ms Victoria Nambasa Bukonya and Dr Jeanne Muhindo*

Masaka

On 23 February 2009 Sten Olsson was taken by Helen Ndagije and Angela Bonabana of the NPC to the referral hospital in Masaka (one of the Regional Centres), 2½ hours by road south of the capital Kampala. Discussions focused on the wish of the hospital to develop further its pharmacovigilance activities, and the value the hospital management attach to quality of care. A visit was made to the HIV/AIDS clinic. While acknowledging the importance of the pharmacovigilance activity, the clinician in charge found it difficult to find time to report adverse reactions to ARV treatment (the clinic sees around 250 patients per day). At the health service of the District of Masaka, the responsible officer for the healthcare system was supportive of the pharmacovigilance system and wished to set an ambitious fixed monthly target of ICSRs coming from his district.

Conclusions

As a result of the course and site visits the UMC and NDC staff have assessed the current challenges to effective pharmacovigilance in Uganda. In spite of being relatively young, the Uganda pharmacovigilance programme has a good degree of institutional and structural stability and contains many of the key elements for achieving efficient monitoring of patient safety issues. Although infrastructure, resources and time for clinicians are – as in many countries – a key problem, there are certain steps that could be taken to build on the excellent foundations which Ugandan staff have made. These include legislation, better communications and further effort to involve public health programmes and professional medical and pharmaceutical councils.



Dr Sam Zaramba (Director General of the Ministry of Health), Dr Frank Mwesigye (Chairman, NDA) and Mr Apollo Muhairwe (Chief Executive Officer, NDA) at the launch of the national centre.

With further support on many levels the Ugandan system could move towards reliable outcomes in terms of drug safety signals and support for decision-making for the benefit of patient safety at all levels of the Uganda healthcare system.

Philippines pharmacist training

Cynthia Diza

The Philippines Bureau of Food and Drugs, in collaboration with the Bureau of Health Facilities of the Department of Health, conducted a basic pharmacovigilance training course from February 17-20, 2009 in the city of Davao, in the heart of the Philippines' exotic south, the south-eastern portion of Mindanao Island. The objective of the course was to strengthen pharmacists' clinical skills and competence in the recognition, prevention and management of adverse drug reactions.

The training was modelled on the WHO pharmacovigilance course held in Manila last September (see UR43 p7-8). The 28 participants, mostly pharmacists from government hospitals, participated actively in discussions after each lecture: the basics of pharmacovigilance, ADR reporting, causality assessment, ADR types and management, medication errors, drug interactions, food-drug interactions; literature sources and pharmacoepidemiological methods. A status report from the Philippines National Centre was also presented.

One issue which arose during the course and which influences how reporting is perceived by health workers is litigation. BFAD gave participants an assurance that all reports are treated with utmost confidentiality and it would be a rare case if information is divulged, and then only if there is a real threat to public safety.

The trainers comprised Dr Kenneth Hartigan-Go, Dr Suzette H Lazo, Dr Klara Tisocki (EU consultant for BFAD), Dr Douglas Ball, and Dr Cynthia Diza, the ADR Unit Co-ordinator.

At the end of the course, the participants had a planning workshop on what they intend to do to promote and strengthen pharmacovigilance in their hospitals and to develop and instill a 'safety and reporting culture' among health staff. The training course was rated well and there are plans to conduct three zonal training courses to cover all government hospitals nationwide this April, July and August.



Kenneth Hartigan-Go talking to participants in Davao

Singapore safety safari

Andrew Bate

In December I was an invited speaker at a major DIA meeting 'Safety is Global: Contemporary Pharmacovigilance and Medical Product Risk Management Strategies' in Singapore. It was an interesting meeting particularly with high-profile and influential presenters from Asia and elsewhere – such as Chan Cheng Leng and Wimon Suwanekesawong, Heads of the pharmacovigilance units at the Singaporean Health Sciences Authority and the Thailand Food and Drug Administration, respectively. John McEwen from Australia, Stephen A. Goldman from the USA and Elliott Brown from the UK also spoke. Registered delegates attended from throughout the Pan-Pacific region and gave the meeting an exciting international feel. It was particularly interesting to hear how pharmacovigilance varies – as it needs to – between different countries, while equally reinforcing many common global themes, such as the need for emphasis on effective communication.



Chan Cheng Leng and Andrew Bate (seated) with staff from the Singapore national centre.

I was also invited to present a lecture at the Singapore Health Sciences Authority (HSA) where I talked about signal detection in the context of the WHO Programme.

A social high point of the visit was the trip to the 'night safari', a unique Singapore experience where one wanders along paths with animals kept in enclosures at large. The sight and sound of hyenas howling as they contemplated me as a midnight feast will live long in the memory!

Certificate course in Maharashtra

Nilima Kshirsagar

A certificate course in pharmacovigilance was organized by Infectious Diseases Department (IDD) of Maharashtra University of Health Sciences (MUHS) in Mumbai on 21st and 22nd March 2009, in collaboration with University of Mumbai and Garware Institute of career education and development with financial assistance from Indian Council of Medical Research, New Delhi.



Participants exploring the Uppsala Monitoring Centre's VigiFlow software training for ADR assessment, with internet access provided to each course member.

Eminent speakers and experts discussed adverse drug reactions, methods used for assessment of adverse drug reactions, methods to prevent and minimize side effects, regulatory guidelines for different countries. A total 116 delegates participated in the course – from the faculty of medicine, industry, and postgraduate and graduate students of medicine and pharmacy.

The course involved not only lecture sessions but also practical hands-on training. The first day of the course consisted of lecture sessions which covered theoretical aspects of pharmacovigilance. On the second day every participant was provided independent computer access in the computer laboratory at Garware Institute, Mumbai University for entering adverse drug reaction data online via internet in the WHO database at Uppsala, Sweden.

A detailed analysis of the pre- and post-course assessment was undertaken to assess the impact of the course on the knowledge of the participants. Of the 112 delegates who answered both pre- and post-test, 96 delegates secured higher marks in the post-test than the pre-test.

Maharashtra University of Health Sciences is planning to conduct this course annually. Students following careers in clinical research and professionals with an industry background will greatly benefit from this certificate course. Such trained doctors and pharmacists will be helpful in enhancing safe use of medicines.

ISoP voyage to Reims

The International Society of Pharmacovigilance has announced the main topics for its 9th Annual Meeting, from 6 to 9 October 2009 in Reims, northern France.

Under the overall title 'From Pharmacovigilance to Risk Management' the conference will examine

- ◆ New data sources and methods for signal detection
- ◆ Improving the efficiency of pharmacovigilance systems
- ◆ Economic implications of drug development and pharmaco-economic implications of safety
- ◆ Organ specific toxicity
- ◆ Undesirable psychiatric and behavioural effects of medications
- ◆ Pharmacovigilance in clinical trials
- ◆ Pharmacovigilance challenges around the globe
- ◆ Regulatory initiatives with a global impact
- ◆ Pharmacovigilance for vaccines
- ◆ Ethical considerations
- ◆ Counterfeit medicines
- ◆ Implications of personalised medicine

There is also a communications workshop planned along with sessions on 'hot' topics.

Reims, the capital of the Champagne region, is a historic city 45 minutes from Paris by train famous its wine-growing. French monarchs were crowned in the cathedral, and its wealth of monuments has earned Reims the accolade of UNESCO World Heritage classification.

The chairman of the Local Organising Committee is Dr Thierry Trenque.

More education – more safety

Wojciech Kwilecki

The Association 'Journalists for Health', embracing around 100 leading Polish healthcare journalists, had the privilege of visiting the Uppsala Monitoring Centre during the seminar "Polka w Europie 2008".

The Association was founded in 2003 to promote science-based healthcare standards among journalists. It quickly became the biggest organisation of its kind in Poland – and probably in central Europe – with 90 active members and 32 associates. These make up a group of most of the professional healthcare press, radio and TV specialists in Poland. Prominent among the activities of the Association – conferences, seminars and workshops – is the annual professional cruise of 100 participants to Scandinavian countries, named 'Polka w Europie' ('Polish Women in Europe' – due to the Association's overwhelming female membership, where outnumbered men have to stay in the shadow).



Bruce Hugman addresses the large group of Polish journalists.

This unique cruise came about because a ferry is the only means of transport which allows lectures, conferences and presentations to take place while on the move. Over the 5-day 'Polka w Europie' seminar the participants, media from all around the country, politicians, doctors, pharmacists, industry representatives, have the opportunity to receive a huge dose of knowledge. Around 20 lectures (from 9am until 6pm, with a 2-hour break) touch the living healthcare experiences in nearby states across-the-sea: Sweden, Norway, Denmark, Finland, Estonia and Latvia. The perfect organization is thanks to a top-notch PR and event agency from Warsaw, which manages the herculean effort of handling around 100 participants at sea and abroad.

Once disembarked, the group follow a tight schedule, meeting their local counterparts, foreign officials, and prominent representatives of medicine and science. In 2008 the seminar's motto was 'Safety of drug usage – security for families', which is why the visit to Uppsala was of such importance.

The UMC is well-known among pharmacy-oriented journalists thanks to the Polish medicinal products and medical devices agency. The

agency held a series of conferences within the 'Safe Medicine' campaign from 2006-2008 covering the safety of antibacterial medicines usage, safe medicine – facts and myths, safety of painkillers, soporific and sedative medicines and much more. During the campaign the Uppsala Monitoring Centre was frequently mentioned; so the trip to Sweden without meeting UMC representatives would have been incomplete.

Taking a break from the WHO Programme meeting also being held that week, Bruce Hugman, the UMC Communications Consultant, gave us great insight into UMC statutory duties, the history of drug monitoring and many current issues. The interesting moment was when Mr Hugman raised the question: why Poland, one of the oldest WHO members having a population of 38 million, reported only 3,124 reports over 36 years, while Sweden, with 9 million inhabitants, reported about 100,000 reports? The answer is not straightforward. The Chairwoman of the Polish Pharmaceutical Chamber Mrs Irena Rej suggested that the duty of reporting was implemented only a few years ago. Moreover, the Polish reporting form might be seen as too complicated. It is very interesting that you regard the significant obstacles as mainly bureaucratic. If we want the drug monitoring system to function well, we need to keep the reporting simple, brief and elegant, declared Mr Hugman.

The meeting had a direct impact in the Polish media. *Dziennik Wielkopolski*, the main daily paper in Poznań, capital of western Poland, published an interview by Anna Nowak with Polish physicist Anna Jabłecka, where, challenged with the data discussed during the Uppsala meeting, the doctor widely referred to UMC experiences and indicated that the reporting system in Poland should improve.

In Gdansk the issues were covered by Jolanta Gromadzka-Andzelewicz twice: in main local daily *Dziennik Bałtycki* and the local online portal *naszeMiasto.pl*. The article referred to the withdrawal of particular drugs in Europe thanks to UMC's work. Mr Bruce Hugman was also quoted as a spokesman and UMC activities were briefly described.

The event was also covered in *Gazeta Farmaceutyczna* – Polish oldest monthly for pharmacists, by the author of the current article. I dedicated a large part of the "Polka w Europie" general report to describing Mr Hugman's lecture and also quoted the above-mentioned discussion with Mrs Irena Rej.

The Uppsala meeting was one of the most interesting of almost 20 various lectures held during the seminar and resulted in significant feedback. The growth of awareness among journalists is obvious and will result in many future publications.

The visit also had a personal touch. As the group was struck by some mysterious and nasty stomach illness (ferry sea-food cuisine suspected), the UMC crew provided our group with soothing mint lozenges. This sealed the memory of our Uppsala experience for the members of our Association.

Utrecht's Collaborating Centre for pharmacoepidemiology

Aukje Mantel and Hubert Leufkens

In 2008, the Division of Pharmacoepidemiology and Pharmacotherapy of the UIPS Institute for Drug Innovation, Utrecht University, in the Netherlands, was designated as a WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis. For several years the Division has been collaborating with the WHO Department of Essential Medicines and Pharmaceutical Policy on projects related to pharmaceutical policy and innovation. The Division was previously involved in the preparation of the Priority Medicines for Europe and the World report (2004), commissioned by the Dutch Presidency of the European Union, and the evaluation of the role of drugs for rare diseases on the WHO Model List of Essential Medicines. From 2006 and onward the Division has started, together with WHO

staff members (e.g. Dr Richard Laing and colleagues), to develop a platform for young, multidisciplinary researchers and policy analysts in order to build an innovative, independent and scholarly pharmaceutical policy community of fellows, PhD students and senior people in the field. As part of this, the model of 'professional PhDs' has been developed, in order to assist people who have daily responsibilities in various pharmaceutical roles to integrate their hands-on experience with scientific research.

The Collaborating Centre is aiming to translate its established record in pharmacoepidemiological research, and the expertise of the Division, into solving a number of public health questions. There are three important challenges in delivering medicines to the patients who need them. Firstly, there is a growing disconnection between the new knowledge and technologies that science creates and what is actually delivered to patients in the form of innovative and accessible medicines that are rationally used. Secondly, the suboptimal regulatory environment has been identified as a reason for the existence of therapeutic gaps and as a potentially important barrier to drug innovation. Thirdly, the apparent inequity in access to medicines is still the defining characteristic of the global pharmaceutical market place; hundreds of millions of people do not have access to essential medicines. This work on drug development, regulatory science and access to medicines has important overlaps with drug safety, an area where the division has close links with the UMC.

More information on the WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis and its activities may be obtained from the Centre's website (www.pharmaceuticalpolicy.nl) or the Divisional homepage (www.pharm.uu.nl/epithera).



Richard Laing, Hans Hogerzeil and Hubert Leufkens.

Advising WHO

Sten Olsson

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held its sixth meeting in Geneva from 4-6 March 2009. This committee provides advice to WHO and the WHO Collaborating Centre in Uppsala on pharmacovigilance policy and issues related to safety and effectiveness of medicines. The 6th annual meeting was chaired by Gerald Dal Pan from the FDA, USA. He guided the committee through a busy agenda including issues of scientific, strategic and technical importance. Several discussion items had been referred to ACSoMP by the annual meeting of national pharmacovigilance centres held in Uppsala in October 2008.

Indicators and database access

One such item was indicators for bench-marking and outcome assessment in pharmacovigilance. A sub-group was assigned to continue developing a set of practical indicators to be considered by member countries. After an initial discussion ACSoMP appointed another sub-group to develop suggestions for a long term strategy for the WHO pharmacovigilance programme. This group will submit its draft recommendations to the meeting of national centres in Rabat, November 2009. Also the issue of wider access to case information in Vigibase had been referred from a working group at the latest national centres' meeting. ACSoMP recommended WHO to further expand access according to defined criteria.

INSMPC

Four persons representing the International Network of Safe Medication Practice Centres (INSMPC), Michael Cohen, David Cousins, David U and Annemarie Hellebek, were invited for a discussion about the scope for wider collaboration between the global pharmacovigilance network and INSMPC. It was concluded that the two networks have many common concerns and aims and that it would be appropriate for INSMPC to be invited to the 2009 annual meeting of national pharmacovigilance centres.

Essential Medicines

ACSoMP had received a request from the WHO Expert Committee on the use of Essential Medicines for criteria to be employed when assessing the safety of medicines proposed for inclusion in the WHO Model List of Essential Medicines. Recommendations were provided on the basis of very thorough background work carried out by ACSoMP member Jürgen Beckman.

WHO programmes

Representatives of many of WHO's disease programmes were presenting updates on the progress of introduction of new pharmaceutical treatments and their safety monitoring in countries. Special attention was given to the fact that UMC now has a specialist, Jerry Labadie, devoted to safety follow-up of newly pre-qualified vaccines. He was on his first introductory visit to WHO headquarters during the ACSoMP meeting and attended some of the sessions.

The internet

A technical issue of great importance for provision of health information but also for pharmacovigilance is the availability of broadband internet services in low-income countries. A presentation was given regarding Africa Health Infoway (www.who.int/africahealthinfoway), a strategic partnership with WHO involvement that aims at supplying 53 African countries with high-capacity telecommunications over five years. ACSoMP requested that VigiFlow be offered as a key service through this infrastructure.

UK patient reporting up

The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) has announced success both in its patient reporting as part of its long-standing Yellow Card scheme, as well as in the first year of a new on-line reporting form.

In the past year more than 2,500 Yellow Cards were submitted by patients or carers bringing the total number of patient reports to almost 9,000 (since February 2008 2,500 were received). During 2008, 89% of the patient Yellow Cards were from the patients themselves, 6% from a parent, and 5% from a carer. The Agency has also seen double the number of reports submitted on-line.

The main trends which have emerged from in the past year were a 17 per cent increase overall for all Yellow Card reports to 25,000; including an increase of 50 per cent of reporting from the public.

Boost for pharmacovigilance in Africa

Alex Dodoo

Pharmacovigilance in Africa has received what is potentially a huge boost with the imminent implementation of two projects that are geared to provide badly-needed financial and technical support. These are the INDEPTH Network Effectiveness and Safety Studies (INESS), funded by the Bill and Melinda Gates Foundation, and the Affordable Medicines for Malaria (AMFm) programme, funded by the Global Fund against AIDS, Tuberculosis and Malaria (The Global Fund).

INESS

The INESS platform, with funding of about US\$26 million, plans to examine the real-life safety and effectiveness of artemisinin-combination therapies (ACTs) deployed for the treatment of uncomplicated malaria in three African countries – Ghana, Tanzania and Mozambique. At a Protocol Development Workshop in Dar es Salaam, the INESS platform agreed to provide funding to strengthen the existing spontaneous reporting systems as well as support cohort event monitoring (CEM) studies in each of these countries. INESS has agreed to provide funding to recruit a dedicated local Safety Officer in each of the 9 Districts where the studies will take place and has also provided funds for the activities of dedicated local safety teams who will examine safety reports, carry out investigations and conduct causality assessment. INESS plans to innovate in the safety studies by utilizing PDAs (hand-held computers) to collect safety information and identifying patients for follow-up using a GPS system that shows where recent recipients of antimalarials live. The INESS project will be complimented by the setting-up of a large linked database to pick up safety signals. The pharmacovigilance aspects will be coordinated by Professor David Schellenberg of the London School of Hygiene and Tropical Medicine and Dr Alex Dodoo of the University of Ghana Medical School.

AMFm

Artemisinin-combination therapies (ACTs) are the most effective remedies for treating uncomplicated malaria. They involve the use of an artemisinin derivative and another antimalarial and this usually results in cure rates over 95% when appropriately taken. However, ACTs are expensive, a quality-assured ACT costing about US\$8 in the private sector, compared to US\$0.10 for the previously-used, but now parasite-resistant, chloroquine. The need to provide affordable good quality ACTs for malaria patients is a key global aim in a bid to eliminate and eventually eradicate malaria. The Global Fund and its partners therefore decided to create the AMFm to provide affordable ACTs to all who need them at a cost of about US\$0.10. These ACTs are intended to be widely available in all settings and the expectation is that they will be supplied as over-the-counter products, just like most medicines for the treatment of uncomplicated malaria.

Safety implications

The widespread availability of quality-assured and affordable ACTs raises several safety issues. These include safety when used without direct medical supervision, and safety when supplied by lower level health care personnel. A dynamic and relevant pharmacovigilance system has therefore been suggested as one of the key requirements for the AMFm programme and funding is being set aside for this. To prepare countries participating in the AMFm to present a harmonized

and robust pharmacovigilance proposal, the World Health Organization (GMP, QSM) and the Medicines for Malaria Venture organized a 3-day workshop from 6th-8th April in Geneva, Switzerland. The workshop was attended by pharmacovigilance experts from over eight countries including Ghana, Nigeria, Senegal, Mozambique, South Africa, Kenya and Madagascar. The United States Pharmacopoeia, the Uppsala Monitoring Centre (UMC), the WHO Regional Office for Africa and two pharmaceutical companies (Novartis, Sanofi) also took part.

Participants agreed that the specific objectives of any pharmacovigilance system would be to monitor the risk of ADRs associated with ACTs made available through the AMFm programme and supplied by the public and private sectors. This should be underpinned by a communication and feedback strategy based on the information generated through the pharmacovigilance system. Various approaches were agreed to achieve the pharmacovigilance aims, including:

1. traditional spontaneous reporting
2. strategies to stimulate spontaneous reporting particularly among private accredited retailers who are likely to dispense ACTs within the context of AMFm
3. active monitoring of a cohort of patients exposed to ACTs (cohort event monitoring)
4. development of a pregnancy register to document birth outcomes following exposure to ACTs whether inadvertent or deliberate.

Boost for safety

The INESS and AMFm programmes will surely provide large amounts of data on antimalarials in Africa and will provide benefits extending beyond safety monitoring of antimalarials alone. Both programmes intend to collaborate actively with the UMC and will utilize both VigiFlow and CEMFlow to manage any safety data collected. The activities being planned are being led and co-ordinated by the various national drug regulatory authorities to ensure that the findings of the various studies are utilized for decision making.

Pharmacovigilance in Africa has received a huge boost and it is hoped that the resources provided will provide stability and sustainability for safety monitoring in Africa.



Participants at the AMFm pharmacovigilance meeting in Geneva

Drugs and Bugs

Anna Celén and Bruce Hugman



A fabulous book for children about medicines became available in Sweden last November. It is a creative approach to the demanding task of informing children about medicines and disease. In Sweden there is no equivalent to the book, and it is a great contribution to a child's bookshelf as well as a useful tool for health professionals treating children. The target group for the book is 6–11 year olds which adds the bonus that parents and teachers will learn something as well while reading to their children. The book is written by Fredrik Brounéus, a pharmacist and author, employed at the Swedish Medical Products Agency which sponsored the publishing by Edition Andersson AB.

The 40-page book consists of the history of medicines from ancient Egypt until today, different ways of drug administration and the path of a drug through the body, including mechanism of action, metabolism and excretion. Other issues raised are reasons for illness and how the body can be protected from pathogens like virus, bacteria, fungus and parasites. It also deals with the immune system, fever and vaccines, and rounds off with drug development and the future. The attractive design of the book is due to rich and amusing illustrations by Nina Erixon-Lindroth, who has a PhD in clinical neuroscience.

The title is 'Piller och Baciller - en liten bok om läkemedel' – in English: 'Drugs and Bugs - a little book about medicines'. The book could also be adapted to different countries; the UMC communications consultant, Bruce Hugman, has met the author to discuss the possibility of an English version. Many of you will share the belief that education of children is among the measures needed to improve patient safety in the long-term. Fredrik Brouneus' book is a great example of what can be done in providing important, basic information about medicines and disease for children in an attractive and accessible way.

We are keen to hear from readers about similar well-produced publications around the world. Equally, if you have any thoughts about the needs of children in your country for this kind of information, do get in touch. We would like comments and advice about adapting content and illustrations for different cultures. Please contact Bruce Hugman (mail@brucehugman.net) or Geoffrey Bowring (geoffrey.bowring@who-umc.org) if you have any ideas.

Vision for healthcare communication

Healthcare Communication, by UMC's communications consultant, Bruce Hugman, is published this April by the Pharmaceutical Press, London.

It's a 300-page study of the knowledge and skills needed for every aspect of healthcare relationships and communications, with patients firmly leading the list of priorities. The book argues that only in relationships of truly reciprocal partnership with patients can healthcare achieve its potential for the safest and most effective therapy.

The book is primarily targeted at nurses, pharmacists and doctors in training and in practice, but it also addresses other medical professions and non-medical members of the whole team, including policy-makers, managers - and porters and cleaners, among many others. The book's vision is of a coherent, integrated system of healthcare in which effective communications play a central and crucial part in treatment of all kinds, in management of people and systems, and in all relationships and contact with patients and those close to them.

Table 3.1 A basic skeleton framework of activities and tasks relevant to every encounter between HCP and patient (continued)

Key questions	Key issues	Key attitudes, knowledge and skills	Key areas for effective one-to-one technical knowledge, skills and expertise	Key areas for effective communication skills	Commentary
5. What further tests or procedures (if any) are necessary to reach diagnosis?	Identifying and communicating next steps. If any, it is key to patient's reaction, setting timeline and making plans.	Explanation and reassurance, joint planning, managing patient's reaction and feelings.	✓	✓	Patient may be disappointed or compromised if diagnosis may be complex or unusual about tests or procedures; may have practical problems about more appointments.
6. What is the patient's reaction to the diagnosis or lack of diagnosis?	Accurate understanding of the meaning of the diagnosis or lack of diagnosis for the patient and their life.	Empathy, listening, observation, questioning.	✓	✓	Whether verbal, degree, degree, anger, or many other emotions, the reaction must be acknowledged and dealt with. The slow, painstaking process of complex diagnoses may need time.
7. What resources do I have?					

10 The basic framework for working with patients

Part A Getting started

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2 Signposts for the journey through this book

ADR reports on children

Catrine Pansegrau Hauge

As a 4th year pharmacy student at the University of Bergen in Norway, I am finishing my degree by writing a thesis on ADR reports on children in Norway. The thesis was prompted by the new EU regulation on medicinal products in paediatrics which has increased the focus on pharmacovigilance of drugs used by children. I have extracted all ADR reports for a 10-year period on children from the Norwegian ADR database (NADR). Based on the analysis of the data one expects to be able to detect an effect of regulatory changes and of a national campaign in 2009 focusing on ADRs in children. My inclusion criteria were:

- Patients ≤ 17 years
- ADRs caused by one or more drug(s), not by in utero exposure or through breast-feeding
- One or more suspected drug(s) or drug related product(s), except vaccines.

The thesis is carried out at RELIS in Bergen, a regional drug information and pharmacovigilance centre (one of five regional centres in Norway). RELIS registers all ADR reports from its region into NADR, in addition to assessing them and giving each reporter individual feedback. The centre also helps with questions concerning drugs and ADRs, interactions, and offers lectures.



Catrine Pansegrau Hauge

I felt a visit to the UMC would be quite helpful in my writing, and a programme was arranged to provide me with basic information on the function of the UMC and the services it offers. My visit included presentations of the WHO Programme, VigiBase and WHO-ART. I also got a demonstration on how to use VigiMine, which to me is an extraordinary program. It was an interesting and informative day which has helped me to

better understand how extensive the field of pharmacovigilance is and the degree to which the UMC contributes in making drugs safer.

My visit at the UMC will without a doubt help me in writing my thesis and I am very thankful for the chance to come, especially to Anna Celén for making the day possible.

Welcome back David

We were pleased to see David Coulter again in March. He continues to provide expert advice and input for several areas of UMC work, especially terminology for Cohort Event Monitoring and the CemFlow system being developed.

Among the topics on the crowded contents pages you'll find:

- What is effective communication?
- Why do we communicate?
- Vision and communication at the heart of healthcare
- Core concepts and skills (caring, helping, empathy, listening, questioning, explaining and lots more)
- Communication and cultural diversity
- Angry and aggressive patients; mental disorders
- The whole team and the whole patient
- When time and resources are limited
- Informed consent
- Sex and sexuality
- Dying and death
- Effective written and spoken communications
- Media relations, managing meetings and teaching

And, especially for readers of Uppsala Reports, there are chapters on patient safety and risk communication, with references to pharmacovigilance and the WHO Programme.

The text is enhanced with amusing illustrations and a large number of provocative and illuminating quotations from familiar and obscure personalities.

The author runs a blog and a forum to involve readers in the discussion and development of best practice and to share experiences and ideas.

The book is available from the Pharmaceutical Press (www.pharmpress.com), Amazon and major booksellers at £29.95. The author's blog and forum are at www.BruceHugman.com.

Book received

The *Guide to Vigilance and Adverse Event Reporting*, 2nd Edition 2008–09. Published by Washington Information Source Co, the massive book is a compilation of the latest regulations, guidance documents and compliance manuals from the US FDA, the European Union and ICH. www.fdainfo.com.

Welcome to Sara



Sara Bergh has recently joined the UMC, working as a Sales Assistant. This involves ensuring our commercial customers – particularly of the WHO Drug Dictionary – have their transactions administered in an efficient and timely manner.

Sara is originally from Säffle in the west of Sweden. She came to work at the UMC having studied international marketing and sales at Folkuniversitetet in Uppsala.

Outside of work she is interested in sport: "In 1997 I moved to Uppsala to play volleyball in Sweden's highest league. After 6 years I now play in the second league for Tierp Volley, more for fun, where I am also the team captain."

Drug Safety bulletins and the UMC

At present at the UMC we have an incomplete view of the existence and coverage of bulletins issued by national pharmacovigilance centres. In UR42 we requested information from national pharmacovigilance centres and academic departments about newsletters in both print and digital format, and have managed to fill some gaps. Many thanks to those centres who responded to our appeal!

It is recommended that centres produce ADR newsletters and bulletins as a good way of sharing important information. Newsletters however vary greatly in frequency and content and the groups at which they are aimed. Some regulatory authorities and pharmacovigilance centres maintain websites at which you can subscribe to updates.

The UMC is keen to see examples of good practice – in each region, in different languages and from national (or regional) centres on different scales. We circulate and store recent issues for reference and for educational purposes. We believe there may also be a possibility of future co-ordination with those responsible as editors of pharmacovigilance bulletins.

Member countries are encouraged to provide the UMC with information about their medicine safety newsletters where available. If the UMC is not already receiving your newsletter, do send us a copy – whether printed (to our post address), distributed by e-mail and/or downloadable from your website (to info@who-umc.org).

WHO-ART–MedDRA bridge updated

A bridge between WHO-ART and MedDRA was developed in 2007 for those who want to continue using WHO-ART and at the same time need to be able to report ICSRs to organizations in MedDRA coded format.

The file mapping WHO-ART terms to corresponding MedDRA terms is updated annually and the latest version mapping terms from the first version of WHO-ART 2009 (2009.01) to MedDRA 12.0 has now been released.

The bridge consists of all WHO-ART Preferred terms, not Included terms, with a link to the nearest MedDRA term, which may be a Low level term or a Preferred term. The bridge is available free of charge to all WHO-ART and MedDRA customers.

COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
13-14 May 2009	Compliance in pharmacovigilance and the role of the EU QPPV	London, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
13-15 May 2009	Practical Guide for Pharmacovigilance: Clinical Trials and Post Marketing	London, UK	DIA European Branch Office Tel: +41 61 225 51 51; Fax: +41 61 225 51 52 E-mail: diaeurope@diaeurope.org
18 May 2009	An essential guide to pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 730071 Fax: +44 (0)1483 730008 www.management-forum.co.uk
1-3 June 2009	18th Annual Scientific Congress ARCS; Education in Practice	Sydney, Australia	ARCS Australia Ltd Tel: +61 (02) 8905 0829 E-mail: asc@arcs.com.au ; www.arcs.com.au
3-4 June 2009	Periodic Safety Update Reports (PSURs)	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
4-5 June 2009	IX Jornadas de Farmacovigilancia, 25th Anniversary of the Spanish Pharmacovigilance System	Oviedo, Spain	Spanish Medicines Agency in collaboration with Regional Health Authority of Asturias www.farmacovigilancia2009.es
15-17 June 2009	Pharmacovigilance: A Basic Training Course for those working on drug safety monitoring in the EU, USA and Japan	London, UK	Management Forum Ltd Tel: +44 (0)1483 730071 Fax: +44 (0)1483 730008 www.management-forum.co.uk
24-25 June 2009	5th Biennial Signal Detection meeting (Pre-Conference tutorial: 23 June 2009)	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
8-10 July 2009	Medical Aspects of Adverse Drug Reactions	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
12-15 July 2009	9th Congress of the EACPT	Edinburgh, Scotland	European Association for Clinical Pharmacology and Therapeutics (EACPT) www.eacpt2009.org/
15-16 July 2009	Introduction to pharmacoepidemiology	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
4-8 August 2009	10th Commonwealth Pharmacists Association Conference	Accra, Ghana	CPA Accra 2009: E-mail: info@psgh.org www.psg.org/cpa
16-19 August 2009	25th Anniversary International Conference on Pharmacoepidemiology & Therapeutic Risk Management	Providence, Rhode Island, USA	ISPE www.pharmacoepi.org/meetings/25thconf/index.cfm E-mail: ISPE@paimgmt.com
9-10 September 2009	Back to basics in pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
23-24 September 2009	Critical appraisal of medical and scientific papers	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
6-9 October 2009	Annual Meeting of the International Society of Pharmacovigilance (ISoP)	Reims, France	ISoP www.isoponline.org/upcoming-meeting.html
12-16 October 2009	Excellence in Pharmacovigilance: Clinical Trials and Post Marketing	Berlin, Germany	DIA Europe Tel. +41 61 225 51 51 diaeurope@diaeurope.org

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