

UPPSALA REPORTS

— COVERING THE WORLD OF PHARMACOVIGILANCE —



Rapid access to safer drugs

Developing an Ebola vaccine • VigiBase: 2015 in hindsight

Global, regional, and national initiatives • Zika virus

National centres meeting 2015 • Vaccine safety



UMC staff
Group photo 1996



Sten Olsson
Editorial committee



Geoffrey Bowring
Editor

AN OLD FRIEND IN A NEW SUIT

DID YOU KNOW THAT this month exactly 20 years ago, the very first issue of Uppsala Reports was published? Back then it was a modest newsletter consisting of six pages. The magazine has certainly come a long way since then, nurtured over the years by dedicated writers and editors – some of those who put together the first edition of Uppsala Reports in 1996 have also had a hand in crafting the magazine you're holding in your hand today.

The magazine has undergone an intensive revamp over the past few months, and we're excited to welcome you to our new old Uppsala Reports – just in time for its 20th birthday!

As we've been putting together the 72nd issue of the magazine, we've also been busying ourselves behind the scenes, crafting something novel



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and different. Our communications team has been tinkering in their “creative garage” to build a magazine that would be unusual, surprising and original, but not entirely unfamiliar.

To this end we’ve made many changes; we’ve unfolded a new design language and brand identity to reflect the fact that Uppsala Reports is a global entity and covers the whole world of pharmacovigilance. You’ll find new ideas for columns, new writers, a new approach to creating headlines, new typefaces, new page designs, new ideas about the relationship between the printed and digital space, and, powering it all, a new spirit of inquiry that is both revolutionary and genuine.

Over the next few months, even more new pages and projects will roll out of the garage. But this will do as an introduction to our ambitions.

Uppsala Reports is your magazine – just like it’s always been – and we would love to hear what you think; please email us with comments and suggestions. If you’d like to join our ranks of contributing writers, please get in touch with one of our editors and share your story idea.

Warm regards, Paula Alvarado

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I S SCIENCE ABOUT finding the truth? No, it is not. It is about the quest for truth. Well, what's the difference, you may think. My view is that the difference is more profound than it first appears.

If we believe that science is about finding the truth, as in seeking and achieving the goal of establishing the truth once and for all, then it follows from this that there is such a thing as an undisputable truth – one that cannot be challenged.

We would then have a situation like that in the 1600s, when the Roman inquisition in its first trial of Galileo concluded that the theory of the planets, including the Earth circling the sun, which was first put forward by Copernicus, could only be supported as a possibility and not as an established fact. Then, when Galileo persisted in challenging the truth of the day maintaining that his evidence supported the hypothesis of a sun-centred solar system, he was found “vehemently suspect of heresy” and put under house arrest for the remainder of his life.

This to me has an eerie resemblance to the argument that you cannot put forward a signal of harm possibly caused by a medicine – unless the signal is an established fact.

If we, on the other hand, consider the truth as constantly evolving – not static – looking for truth is a process that does not finish. This applies to signals, too. Signal detection is a progression where we put forward new hypotheses based on available facts and arguments, and as new knowledge is generated we modify our accepted wisdom and change our behaviour.

The world I want to live in is firmly rooted in a fertile soil where curiosity, critical questioning and the search for truth are vital ingredients. The generation of new hypotheses is encouraged, and these are embraced for what they are: possibilities. Whilst we challenge those who come up with the hypotheses to show convincing supporting evidence, we also expect those who are not swayed to

present credible counter-arguments. Through this process of producing arguments and counter-arguments, progress is made, step by step.

Good science is characterised by the honest and transparent application of sound scientific methodology, together with an open and healthy debate as well as a recognition that the knowledge base will change as new evidence comes to the fore.

Good scientists recognise that there always will be some degree of uncertainty about existing knowledge; even established and credible ‘truths’ are no more than probabilities, albeit some much more likely than others.

I wish we would get away from the black-and-white thinking, as exemplified by the notion that just because something cannot be proven true it is automatically false. Not only is such thinking divisive, but it can also be dangerous. There is a risk that those who come up with hypotheses that go against today's truth will be met with silence, or even be silenced – when instead they should be met with critical, but open, minds.

Surely, it cannot be that those who do not want debate are devoid of arguments?

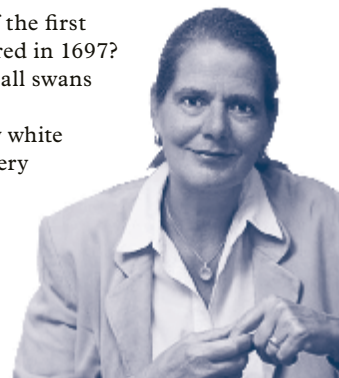
What would have happened if the first black swan had not been discovered in 1697? Would we still have thought that all swans are white?

And are the white swans really white – or are they varying shades of very light grey?

“The world I want to live in is firmly rooted in a fertile soil where curiosity, critical questioning and the search for truth are vital ingredients.”



Marie Lindquist, Director



UPPSALA REPORTS *Covering the world of pharmacovigilance*

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IN BRIEF

Recent events in the pharmacovigilance community.

Big data and signal detection at ISoP

*The International Society of Pharmacovigilance (ISoP) held its 15th annual meeting in Prague, Czech Republic, in late October last year. The theme for the meeting was **Cubism in Pharmacovigilance**, inspired by the Czech cubism movement in the early 1900s.*

TOPICS HIGHLIGHTED at the conference, which was hosted by the Charles University and the Czech Pharmaceutical Society, were risk management and benefit–risk in pharmacovigilance, new methodologies of signal detection and emerging sources of pharmacovigilance data, vaccines, herbals, as well as benefits and risks of medicines for women.

Among the keynote lectures were sessions on the future of pharmacovigilance, pharmacogenomics, patient safety, and the global perspective on big data by UMC’s director Dr Marie Lindquist.

A roundtable discussion by members of

the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency and a panel discussion on safety communication were also offered in the general meeting hall.

UMC was represented at the conference in a variety of ways. Dr Lindquist and former director Prof Ralph Edwards were active participants in several sessions, with many additional contributions from various UMC teams.

From the IT development department, the technology evangelist Magnus Wallberg gave a presentation at the pre-conference course on the topic of *Advanced data*

collection methods (social media, active surveillance, mobile technologies).

The communications team was present with an oral presentation by the communications expert Bruce Hugman.

UMC’s research department was well represented with Dr Rebecca Chandler, medical doctor, giving an oral presentation as well as submitting a poster on vaccines. Posters were also submitted by Dr Ola Caster, senior researcher, and Sara Hult, research pharmacist. Dr Caster was awarded first prize in the poster competition with his entry “vigiRank Improves Real-World Signal Detection Performance: Prospective Results from International Pharmacovigilance” – it’s the first time that a UMC poster has received this honour.



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CHICAGO

Clinical trial data and the challenge of setting standards from the start

The Clinical Data Interchange Standards Consortium (CDISC), a non-profit standards developing organisation, hosted its International Interchange meeting last November, where focus was on streamlining formats for data collection and harmonisation across system platforms.

The meeting was held at Fairmont Millennium Park in Chicago, US, and around 500 participants from all over the world attended – among them Uppsala Monitoring Centre’s technology evangelist Magnus Wallberg and software developer Mikael Nilsson.

CDISC is an organisation devoted to standards and harmonisation in clinical research. The CDISC standard is for clinical trial data and submissions what the E2B data transmission standard is for pharmacovigilance. The organisation’s pursuit for harmonisation and data sharing in clinical trials very much resembles what UMC strives for in pharmacovigilance.

In her opening remarks, CDISC’s



Mikael Nilsson and Magnus Wallberg at UMC’s booth at CDISC’s conference.

founder and president Rebecca Kush said, “When clinical data speaks the same language, research delivers. When data talks, a world of cures can be unlocked.”

A very big topic during the conference was the integration between electronic health record systems and the CDISC standards. This integration is crucial in order to streamline the collection of clinical trial data and avoid double data entries, and thereby minimize both the workload and the risk of

human errors. Standards from the start was the leading message at the conference.

Another major topic was Shared Health and Clinical Research Clinical Library – abbreviated SHARE – a web-based system provided by CDISC, which delivers all the standard terminologies and metadata defined by the CDISC standard. SHARE can theoretically be directly integrated in data collection tools to guarantee conformity with the CDISC standard.

WHODrug™ is very commonly used as the dictionary to code and transfer information about concomitant medications in clinical trials.



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www.cdisc.org/interchange

WASHINGTON DC

An Odyssey through oceans of health data

OHDSI’s first-ever symposium, held in Washington DC, US, in October 2015, focused on utilising a common data model that streamlines health data collection, and the process of generating evidence for healthcare research.

The founding members of Observational Health Data Sciences and Informatics (OHDSI, pronounced “Odyssey”) had a grand vision of creating a global network of data, collected from one billion patients, which could generate evidence about all aspects of healthcare.

Ambitious as it may sound, only a year after the start, data from 660 million patients are now put into a common data model (CDM), which makes it easier and more streamlined to generate evidence in healthcare research.

The OHDSI symposium was held for anyone interested in their work and the open source tools created within the community.

With OHDSI becoming a major international collaboration between industry, academia and research organisations, the turn-out was good with about 150 participants from all over the world.

The basic problem facing the research on longitudinal health records is that the data sources have different structures and use various terminologies to classify the data. To overcome this, the Observational Medical Outcomes Partnership (OMOP) CDM has been used and further developed. To populate the CDM, there must be transformation tools in place that are adjusted to each separate source.

Setting up the CDM is easy, since it is already defined and easy to generate. The big and complex task is to transform and map terminologies and codes from the source to the CDM. However, once completed, it gets really interesting when the open source tools are applied to the data.

On top of the CDM, the OHDSI community has built a number of tools in order to utilise these sources. Since all data is now accessible in the same format, any tool can be downloaded and applied to the local data (in CDM format) without any changes needed. In addition, all algorithms developed on top of the CDM can be very easily run on any local CDM.



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www.ohdsi.org

CHENGDU

BOOSTING *pharmacovigilance* IN CHINA

More than 700 professionals from the pharma industry attended the 5th China Pharmacovigilance Conference in Chengdu, the capital of Sichuan province in south-western China, in October 2015.

The event, organised by the National Centre for ADR Monitoring (NCADRM) of the China Food and Drug Administration (CFDA), is the most important pharmacovigilance conference in the country.

Uppsala Monitoring Centre's director, Dr Marie Lindquist, was one of the invited speakers at the conference and presented data analysis and mining in VigiBase®, the WHO international database for adverse drug reactions.

During the course of the conference days, Dr Lindquist and the recently appointed director for NCADRM, Yang Wei, talked over areas of collaboration between their respective centres, with the latter saying that UMC has made a lot of contributions to NCADRM in the past years.

Dr Lindquist also met up with Wu Zheng, deputy director of CFDA, who spoke highly of UMC's contributions to China's ADR collecting and reporting system. In 2014, the CFDA co-organised the 37th WHO National Centres meeting in Tianjin, which Wu mentioned to the attendees at the conference in Chengdu.

One of the highlights of the conference was the CFDA's announcement that Chinese pharmaceutical companies will have to begin to actively monitor ADRs for their own medicines. It has previously been uncommon for domestic companies to have resources to carry out drug safety-related work, but this new directive means that pharma companies will start taking a major responsibility for drug safety issues. The expectation is that this mandatory requirement will significantly enhance pharmacovigilance in China and further improve safe use of medicines on the domestic market.



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UMC's Helena Sköld, Magnus Ekelo, and Elki Sollenbring at the WHO in Geneva, Switzerland.

GENEVA

WHO briefing highlights health initiatives and challenges

The WHO Technical Briefing Seminar (TBS) in Switzerland set out to provide an understanding of the Essential Medicines Programme and how the WHO supports countries in strengthening the pharmaceutical sector.

The seminar, which took place in Geneva in November 2015, drew experts from many different fields within regulatory authorities, WHO, industry, academia and NGOs.

The week began with an introduction of WHO's structure and how the member states give directives to WHO through resolutions in the World Health Assembly. The concept of universal health coverage was introduced, which highlights not only access to essential medicines but also their affordability. As the burden of disease shifts from mainly infectious diseases to non-communicable diseases, health systems also need to adapt accordingly and be constructed in a more sustainable way.

Many of the sessions on the agenda in 2015 had an Ebola angle. Even something as essential as which medicinal devices to use – not to mention how to use them – became life-saving knowledge that had to be developed and disseminated while the epidemic raged. Given that the team that deal specifically with devices at the WHO

headquarters consists of only a handful of people, they do astonishing work in a poorly regulated field with more than 10,000 types of devices.

Dr Lembit Rägo, head of Regulation of Medicines and Other Health Technologies at WHO, gave a presentation on regulations, norms and standards for medical products. Dr Rägo stated that we have now reached a stage where one national regulatory agency in a country might no longer be able to fulfil all tasks requested of such an agency, and cooperation is needed between countries.

During the TBS the participants were also introduced to a great publication resource – the EMP (Essential Medicines and Health Products) Information Portal, which contains more than 5,000 easily accessible publications from WHO and other organisations.



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EMP Information Portal

www.apps.who.int/medicinedocs

ACCRA

African drug safety in focus

The consultant group Pharmacovigilance Sans Frontières met in Ghana in November last year, to discuss present challenges and the future of drug safety on the African continent.

THE MEETING OF Pharmacovigilance Sans Frontières (PVSF: Pharmacovigilance Without Borders) was held at the offices of the Africa Collaborating Centre for Pharmacovigilance in Ghana's capital Accra.

Prof Alex Doodoo, director of the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, hosted the meeting together with his team. They had put together an agenda covering topics such as pharmacovigilance diplomacy, pharmacovigilance indicators, and the future of PVSF.

PVSF was set up by WHO nine years ago. The aim was to improve pharmacovigilance on the African continent by developing advanced drug safety capacities, aided by African experts with basic level training and personal experience of running pharmacovigilance programmes.

The PVSF group has been instrumental in achieving the expansion of African nations'

membership of the WHO Programme for International Drug Monitoring (PIDM). PVSF's deliberations have been focused on methodological development of public health programmes, issues of communication, expansion of the pharmacovigilance concept, regulatory capacity building, and fundraising for pharmacovigilance initiatives.

Representatives from Management Sciences for Health (MSH) have been part of the meetings over the last few years and more than ever this year. MSH supports pharmacovigilance efforts in selected African countries on behalf of USAID's programme Systems for Improved Access to Pharmaceuticals and Services (USAID-SIAPS). The hope is that by bringing the two support organisations PVSF and USAID-SIAPS together, a better coordination of activities may be achieved.

At the meeting, PVSF also discussed

what the group should focus on going forward. The primary need in most countries in Africa has so far been to establish a pharmacovigilance infrastructure and make health-care workers understand the importance of drug safety and ADR reporting. Now is the time to start building competence and capacity for analysis of the data collected. The continent has together more than 100,000 adverse drug reaction reports available in VigiBase®, the WHO international database for adverse drug reactions.

Another issue that PVSF may need to address is translating guidance material into all relevant African languages, as the lack of this has been identified as an obstacle to pharmacovigilance progress in some countries.

PVSF should also try to engage legislators to put regulations in place, a prerequisite for engaging marketing authorization holders and enabling authorities to make relevant decisions for the protection of the public.



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Above: Hasipha Tarpeh, Chief Registrar at Liberia Medicines and Health Products Regulatory Authority.

Left: UMC's director Marie Lindquist and Clive Ondari from the WHO leading a discussion.

An Ebola virus virion seen in a colorized transmission electron micrograph.

Andrea Marzi puts **Ebola under the microscope**

*Whether in the field in Liberia during a raging Ebola **outbreak** or back in the lab in Montana, virologist Andrea Marzi thinks the **reward** is worth the risk when it comes to finding viable **vaccines**.*

IN FIFTH GRADE in elementary school, Dr Andrea Marzi got hooked on biology. In tenth grade, she learned about viruses. “I was always fascinated by that they’re not considered to live because they can’t replicate themselves – they always need a host – but they can kill you in a matter of days. So although they don’t live, they can kill you pretty efficiently,” she said.

That fascination would take her through a MSc degree in biology and a PhD in virology in her native Bavaria, southern Germany. When she encountered the opportunity to do a postdoc, she decided to pursue a fellowship abroad rather than staying within the realm of academic institutes, and ended up at the Public Health Agency of Canada (PHAC) in Winnipeg.

“For me, it became obvious that I wanted to work with the real virus, and not just with a part of it,” she explained. That was something she could do at the agency’s Special Pathogens Program in the National Microbiology Lab.

When her supervisor there – Dr Heinz Feldmann, MD, an expert on high containment viruses and a consultant for WHO – was offered a position as chief of the Laboratory of Virology at the National Institutes of Health’s (NIH) Rocky Mountain Laboratories in Montana, US, Dr Marzi moved there too to finish her postdoc and later take a position as staff scientist.

With the move came also Dr Feldmann’s lab and some of his research projects – including the VSV-

vaccine platform that had been developed at PHAC; a few years later it would turn out to be sorely needed in the battle against the most severe Ebola outbreak to ever hit the African continent.

A NEW STRAIN OF THE EBOLA virus was identified in March 2014 as the cause of a viral outbreak that had started in rural Guinea at the end of the previous year. The strain, known as **EBOV-Makona**, caused what WHO has called “the largest and most complex Ebola outbreak since the Ebola virus was first discovered in 1976”.

By early 2016, the outbreak was considered to be largely under control, and in March it was confirmed that the three worst-hit countries – Guinea, Liberia and Sierra Leone – had managed to interrupt their original chains of Ebola virus transmission. WHO declared that the disease was no longer considered a Public Health Emergency of International Concern on 29 March, even though new clusters of infection have flared up in the three countries during the first quarter of the year.

The fatality rate of EBOV-Makona is around 50% and far lower than the approximately 90% rate of the 1976 outbreak, but the spread of the West African strain far exceeds previous occurrences of the virus. In the roughly two years since the disease broke out and up until 27 March 2016, WHO counted 28,646 confirmed, probable and suspected reported cases, and a death toll of 11,323. (All but 36 cases and 15 deaths occurred in Guinea, Sierra Leone or Liberia.)

By contrast, the death toll of all previous outbreaks combined – starting in 1976 and spanning 36 years – is estimated at about 1,590 people.

“In the beginning, people didn’t believe that it was actually Ebola virus, because it had never been found in West Africa; it was only known as a Central African disease or public health problem,” Dr Marzi said when explaining how the lower-fatality strain could have caused so much more damage than previous outbreaks.

“And [West Africa] is more densely populated than the areas where we generally see Ebola virus outbreaks in Central Africa. The people also trade a lot and travel a lot, so they cross the borders between Guinea, Liberia and Sierra Leone all the time... Plus the virus made its way into the capitals, and those are million-people strong cities.” ►

“In the beginning, people didn’t believe that it was actually Ebola virus, because it had never been found in West Africa; it was only known as a Central African disease”

EBOV-Makona

A new strain of Ebola virus isolated in Guinea in 2014, the genomic sequence of which is 97% identical to the original strain isolated in 1976. The fatality rate of Ebola Makona is around 50%.

Photo: NIAID



“In order to find vaccines and therapeutics against, we need to understand how they work, how they cause disease, and in the end how people die of them. Someone needs to do that work.”

◀ **Left:** Dr Marzi analyses Ebola test results from a hospital compound in Monrovia, Liberia.

Right: Dr Marzi, foreground, and Dr Dave Safronetz in a biosafety level 4 (BSL-4) research suite at Rocky Mountain Laboratories in 2008. ▶

Battling the disease once it was spreading proved challenging. “WHO was so overwhelmed with everything, it was unbelievable,” Dr Marzi said, continuing, “All the hospitals, everything closed. The entire health-care system shut down. There was nothing.” Subsequently, other ailments that could otherwise have been treated, such as malaria, also added to increasing death rates in the region.

Dr Marzi has first hand experience of the outbreak; she went to Liberia for a month at a time on two occasions in 2014, running Ebola diagnostics tests out of a field lab in the capital Monrovia in support of Doctors Without Borders and other organizations. “Nobody over there had any diagnostics tests for Ebola... So when WHO really got short-handed, they reached out to us and we put together a team and went there,” she said.

“It was really important to report back to the doctors quickly and tell them yes, this person has Ebola and this person doesn’t. When the patient comes in with clinical signs, everything presents pretty similarly – they’ll have a fever with Ebola, but also with malaria. You really want to minimize the time you keep those people together in the same tent of suspected [Ebola] cases.”

MORE IMPRESSIVE THAN HER FIELDWORK, however, is the work Dr Marzi carried out back in the lab in Montana, where they researched the vesicular stomatitis virus-based vaccine known as **VSV-EBOV**. Dr Marzi, herself focused on analysing the mechanisms of how and why the vaccine works, and her colleagues at Rocky Mountain Laboratories were able to show that their vaccine was successful in macaque monkeys. It was purchased by the pharmaceutical company Merck, and clinical trials started in Guinea in spring 2015.

“I think [the vaccine] is very promising because

it works quickly and it also works... against multiple different strains of Ebola virus, the old ones from 1976 and 1995, and the new one from the 2014-2015 outbreak,” Dr Marzi said. “Of course, we don’t know at this point how long the immunity will last. Do we need a booster vaccination and those kind of things?”

The success of phase 3 clinical trials with the VSV-EBOV vaccine in ring vaccinations in Guinea was shown in an interim analysis of the ongoing trial, published in *The Lancet* in July 2015.

The trial included 90 clusters of people – totalling 7,651 individuals – participating between April 1–July 20 2015, where a cluster consisted of an infected patient, the people they had been in contact with, and contacts of contacts. 48 of the clusters were given the trial vaccine immediately, while the other 42 clusters received it after 21 days. In the group who were immediately vaccinated, no cases of Ebola symptom onset occurred, while among the 3,528 people who received the delayed vaccination, 16 contracted the virus.

43 serious adverse events were reported in the interim analysis, and out of them one adverse case of febrile fever was judged to be caused by the vaccine. Further assessment of adverse reactions was still ongoing at the time the paper was published.

On July 24 2015, four days after the trial ended, Guinea’s national regulatory authority and various ethics committees approved the continuation of the clinical trial, with immediate ring vaccinations for all individuals in newly detected clusters.

WHETHER WE’LL SEE mass-vaccinations in at-risk communities in the future will be up to local authorities, Dr Marzi said. “Even if it’s not mass-vaccinations, at least vaccinate health care workers there, or military

VSV-EBOV

A recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebola virus. Also known as rVSV-EBOV, rVSV-ZEBOV or VSV-ZEBOV.



Photo: NIAID

personnel – people who would get called to outbreaks quickly... Maybe people from WHO, Doctors Without Borders, all those people who are first responders for outbreak situations,” she opined. “I think for those kinds of groups, vaccination is definitely a viable option and I think it would be very beneficial.”

That the VSV-EBOV vaccine takes effect so quickly – the preliminary results from the Guinea trials suggest 100% efficacy after 10 days – is also an important aspect, not least in terms of deployment. A fast-acting vaccine allows for a shorter waiting-period before emergency responders can be safely sent out into the field.

“I just hope that we get an Ebola vaccine [approved], because I don’t want an outbreak like this to happen again. It was bad enough,” Dr Marzi said.

“I also really, really hope that this entire scenario is setting a precedent.” She continued, “If an outbreak of this magnitude happens with something else, protocols could be in place and we can say: ok, it’s Lassa fever, it’s Marburg virus, it’s something like SARS – and we could move along quick and not have to wait for months or years in order to get those trials going.”

WHEN ASKED IF SHE’S EVER CONCERNED about the apparent safety risks that come with working daily with deadly viruses, both in the lab in Montana and in the field, Dr Marzi pragmatically replied, “In order to find vaccines and therapeutics against viruses, we need to understand how they work, how they cause disease, and in the end how people die of them.”

“Someone needs to do that work. It’s really rewarding when you get there, you identify a part of the virus that you can use as a vaccine or put into a vaccine platform, and then you do a few experiments and you see that it works,” she said and concluded, “That’s really rewarding, and it’s worth the risk.”



Photo: NIAID

Dr Andrea Marzi

Dr Andrea Marzi is one of the speakers at the up-coming Uppsala Forum on May 30-31 2016. Learn more about the conference on p. 31 or on www.who-umc.org/research



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Positive trends for VigiBase

12 MILLION REPORTS & COUNTING

In late 2015, the number of individual case safety reports (ICSRs) in VigiBase, the WHO international database for adverse drug reactions, passed 12 million – an increase of about 1.7 million reports during last year alone.

THERE ARE CURRENTLY 123 member countries of the WHO Programme for International Drug Monitoring (PIDM) who share their collected data on adverse drug reactions. To visualize the huge amount of data flowing into VigiBase®, imagine that you would review every single individual case safety report (ICSR) sent to the database last year, spending one minute on each case report. This would take 1.8 million minutes; about 30,000 hours. At that pace, a team of 10 persons working 8 hours per day, Monday to Sunday, would need a whole year to perform this task.

Although 76% of the ICSRs in 2015 originated from three countries, namely the United States, South Korea and China, there was an increased contribution from many other nations. Additionally, the share

of reports from low- and middle-income countries (LMICs) is steadily increasing, and has passed 1.2 million in total. During last year, the number of reports from LMICs increased by 30% – a clearly positive trend.

“The more data we can collect, the greater chance we have of getting more knowledge on rare events,” said Helena Sköld, Uppsala Monitoring Centre’s (UMC) product manager for VigiBase, with regard to the steep increase in ICSRs in 2015.

“It also increases the usefulness of the data for the member countries, as they can use VigiLyze™ to find global data on issues that may look like isolated incidents nationally,” Sköld continued.

Overall VigiBase report quality, as measured by the vigiGrade™ Completeness Score, is also slowly but steadily increasing.

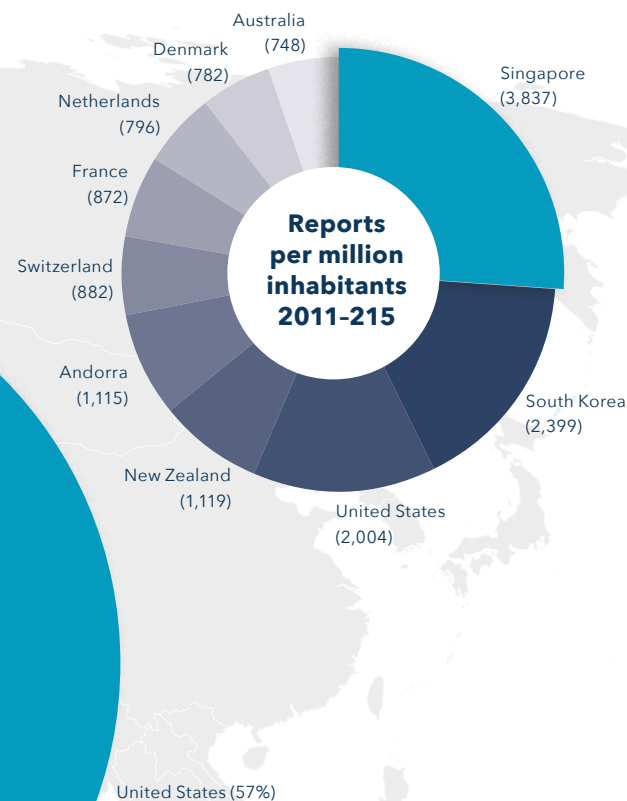
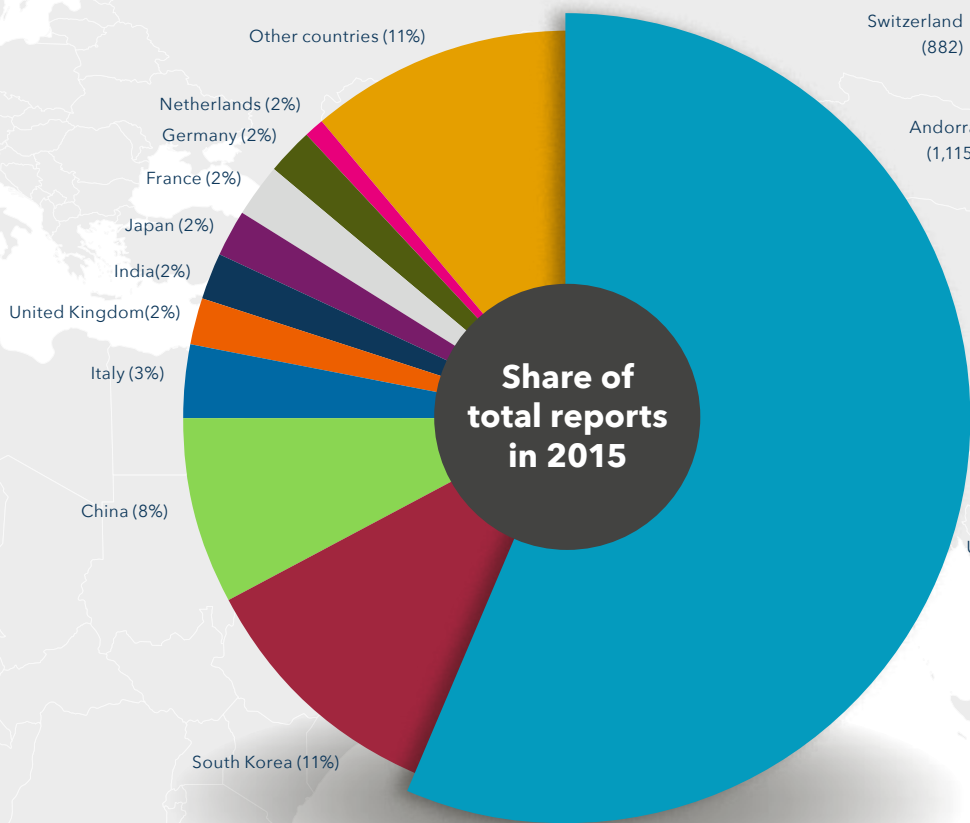
More and more countries use the completeness score report sent out regularly from UMC as a basis for activities such as improvement of the ADR reporting form, or discussion with their reporters about essential information to include in case reports.

Only 6% of the reports that entered VigiBase in 2015 have a high completeness score of more than 0.9. This does not mean, however, that the other 94% cannot be used for qualitative signal detection.

For example, a detailed case narrative can provide crucial information for causality assessment, even if some of the structured data that contribute to a high completeness score are missing. Also, even poorly documented cases can become supportive evidence to a few well documented cases of the same drug–reaction combination. In the

Top 10 reporting countries

In 2015, the United States was the most active ADR reporter with 1,178,536 submissions sent to VigiBase, followed by China and South Korea. However, seen to the number of reports per million inhabitants in a country, Singapore was the most active reporter, followed by South Korea and the United States.



end, it is vital to share as much information as possible with all WHO PIDM members even if the completeness score is not always maximized.

IN ORDER TO reduce the lag time for reporting, a good practice is to share the initial version of a case, and complement with a follow-up report if new information is retrieved from the reporter later on.

Another way to speed up the process is to reduce the manual work needed for reporting to VigiBase, i.e. by creating more automated transmissions. In UMC's ICSR management system VigiFlow®, automated transmission is already in place and a country using it can choose to automatically send a copy of the case report to VigiBase as soon as it is finalized in the national centre.

For countries using other adverse drug reaction databases, and who are currently sending E2B files to VigiBase via e-mail or on CD, a solution for fully automated transmission is now also provided by UMC. The solution makes it possible to share ICSR data in an automated way using server-to-server transmission via an application programming interface (API). This can potentially save time and resources for the national centres.

“The VigiBase Import API can make a great difference to a major weak point in the WHO PIDM's data collection: lag time,” Sköld said. “With the API, it is possible to automate the transmission of reports to the global database with server-to-server communication, so that it is triggered for each individual case that is

received at the national centre. This can shorten lag time considerably and increases the chances to find issues that require fast evaluation,” she said.

A shortened lag time from initial reporting of an ADR until the case report is available in VigiBase will be useful to all WHO PIDM members in their daily work for improved patient safety.



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Global pharmacovigilance experts assemble in India for annual meeting

Delegates from 42 countries gathered in New Delhi for WHO's Annual Meeting of Representatives of National Pharmacovigilance Centres last November, to exchange information and discuss strategies for global patient safety.

FOR THE 38TH TIME since the WHO Programme for International Drug Monitoring (PIDM) commenced in 1968, representatives from national pharmacovigilance centres all over the world were invited to the programme's annual meeting on 4-6 November 2015.

"Integrating pharmacovigilance as an essential component of public health programmes is crucial for patient safety," WHO's Dr Lembit Rāgo said at the meeting, according to a press release from WHO's India office.

The meeting – which is commonly referred to as the national centres, or NC,



Photo: Organiser.



Photo: Organiser.

◀ **Left:** WHO's Dr Shanthi Pal (front), Indian union minister Jagat Prakash Nadda (far left) and others at the inauguration.

▲ **Above:** UMC's Sten Olsson, Helena Wilmar, Dr Pia Caduff and Anki Hagström in the audience at the meeting.

meeting – was held at the Grand New Delhi Hotel, and was hosted by the Indian Pharmacopoeia Commission (IPC) with support from the Ministry of Health and Family Welfare of India. The 42 countries represented constitute roughly a third of all WHO PIDM members; together they sent more than 150 delegates to attend the meeting, the WHO Country Office for India reported.

Dr Poonam Khetrapal Singh, regional director of WHO South-East Asia Region, was quoted by WHO India as saying, “The meeting is timely and expected to facilitate partnerships between WHO Member

States, collaborating centres of WHO, adverse drug reaction monitoring centres of the Pharmacovigilance Programme of India, industry and research institutions to showcase best practices of pharmacovigilance towards ensuring safety of medicines.”

THE OFFICIAL OPENING ceremony, containing several speeches on the importance of pharmacovigilance work, set the scene for the meeting. Amongst the distinguished speakers, the union minister of the Ministry of Health & Family Welfare Government of India, Jagat Prakash Nadda, was the highlight. During the inauguration, Minister Nadda announced that the Indian Pharmacopoeia Commission is working towards becoming the first WHO Collaborating Centre for medicines and vaccine safety in South-East Asia, and the country intends to become a regional watchdog for drug safety.

Dr Shanthi Pal, medicines safety group lead in the Safety & Vigilance Team at WHO Headquarters in Geneva, opened the first plenary session by reporting back on what progress had been made since the last annual meeting in China in 2014, based on the recommendations from that year's working groups.

In the plenary session *Supporting WHO and the countries in pharmacovigilance: new developments at the WHO Collaborating Centres*, the national centres had a chance to share their challenges and success

stories, which made this session a very interactive one.

Afternoon sessions were devoted to working groups on various themes, from setting up pregnancy registries, to collaborating with public health programmes and patient organizations. Other themes included revisions of the current *Minimum requirements for a functional pharmacovigilance System*, where the field of pharmacovigilance is heading, and what the benefits of quantitative benefit–risk assessments are. All these sessions had interactive discussions and produced new recommendations for the WHO Headquarters and the WHO Collaborating Centres to work on.

As always, national centres meeting is a great foundation for networking with global colleagues. The exchange and sharing of experiences and challenges in the pharmacovigilance area are crucial for current and future developments in the field.

The annual meeting 2016 will take place in Oman.



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Let's talk PV!

During the 2015 WHO national centres meeting in New Delhi, India, last year, Uppsala Monitoring Centre held its regular pre-meeting Let's talk PV! with discussions and dialogue around leading topics in pharmacovigilance.

LET'S TALK PV! began with an introduction and welcome address by the Indian Pharmacopoeia Commission (IPC) and UMC's head of Global Services, Anki Hagström. UMC's contagious enthusiasm helped to rouse the participants from the jet-lagged state that long hours of international travel had left them in.

The one-day programme was divided into 10 sessions, with extra time allotted for questions and answers. In addition to UMC speakers, several guest speakers from national pharmacovigilance centres were invited to share their experiences.

Highlights of the programme included talks on signal detection, the impact of communication, how we can develop drug safety in challenging scenarios, and sustainability of pharmacovigilance data management.

Ms Kim Su Jin from KIDS Korea, and FDA Philippines' representative Ms Lanette Lee A. Querubin spoke about national and international collaborations and how to exchange pharmacovigilance data between stakeholders. For instance, in the Philippines, integrating an eReporting function on their website where the patients can report to the national centre, linking to VigiFlow®, improved awareness and patient reporting.

The team from Lareb in the Netherlands introduced a case study on how to incorporate patient reporting and the significance of involving patients and their care givers in patient reporting, presented by Linda Härmark, head of Innovation and Projects. Another presentation by Eugène Van Puijenbroek, head of Science and Research, concerned quantitative and qualitative

signal detection – an area to be explored by many national centres with less expertise in that domain – gave an insight into bolstering their system to develop further. Lareb's director Dr Agnes Kant also held a talk on sharing patient safety information with different audiences.

MONITORING POTENTIALLY harmful medicines while maintaining confidence in the safe use of medicines in the healthcare system was dealt with in detail, in the session *Making PV work: developing patient safety in fragile public health care systems* by Dr Ambrose Isah from the Department of Medicine at the University of Benin/Teaching Hospital in Nigeria. Ensuring the sustainability of such systems was a concern raised by many of the participants.

The session on VigiAccess™, held by UMC's chief medical officer Dr Pia Caduff and product manager Helena Sköld, proved to be very beneficial because many in the audience had not used VigiAccess before. It is a new web based application that will allow anyone to access information on reported cases of adverse events held in VigiBase®.

Any effort, made by anyone, however well organized they may be, will only be complete with an effective communication strategy. That was the message that UMC's head of Global Communications, Paula Alvarado, and communications expert Bruce Hugman conveyed in their session where they discussed the master plan for how to best approach communication challenges.

The programme also included talks by other prominent pharmacovigilance professionals from across the globe, and offered participants the opportunity to share their challenges and achievements in pharmacovigilance. It was a day of learning, dialogue and discussions that engaged all 80 participants.

Ambrose Isah from the Department of Medicine at the University of Benin/Teaching Hospital in Nigeria.



Photo: UMC/Sten Olsson



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April 2016
Zika watch
In 2015-2016, Zika virus has spread steadily, with 33 countries and territories in the Americas now reporting autochthonous transmission.

33

COUNTRIES



0 VACCINES

Presently, there are no vaccines protecting against Zika.



PERSON-TO-PERSON

In the Americas, Argentina, Chile, and the United States have reported person-to-person transmission of the virus, probably through sexual transmission. France, Italy, and New Zealand have reported the same.



15 COMPANIES

Around 15 pharmaceutical companies have commenced work on a vaccine, according to WHO.

HARDEST-HIT

In Brazil, the hardest-hit country, 6,776 cases of microcephaly and/or central nervous system malformation have been reported. This compares to 2001-2014, when an annual average of 163 microcephaly cases were recorded nationwide.



18 MONTHS

It could take at least 18 months before any large-scale vaccine trials are possible, WHO estimated in February 2016.

MICROCEPHALY & GBS
 In the Americas, Brazil, Martinique, and Panama in 2013-2014 have reported cases of both microcephaly and Guillain-Barré syndrome (GBS). Colombia, Dominican Republic, El Salvador, Honduras, Suriname, Venezuela, French Guiana, Haiti, and Puerto Rico have only reported cases of GBS.

ZIKA OUTBREAK. In May 2015, Brazil made the first report of locally transmitted infection of Zika virus in South America. The virus' geographical spread has increased steadily since last year, and to date 33 countries in the region have reported autochthonous (native) transmission of Zika within their borders. Autochthonous transmission has also been reported in 16 countries in the Western Pacific Region.

Symptoms of Zika infection commonly include fever, rash, joint pain, or conjunctivitis. However, an association between the virus and Guillain-Barré syndrome

(GBS), microcephaly and other central nervous system malformations is suspected in several countries. GBS is a syndrome where the patient's immune system attacks part of the peripheral nervous system. Severe cases can cause near-total paralysis. Microcephaly, a neonatal malformation, causes babies to be born with a small head or their head to stop growing after birth.

"The mounting evidence from observational, cohort and case-control studies indicates that Zika virus is highly likely to be a cause of microcephaly, GBS and other neurological disorders," WHO stated in a Zika situational report in March.

VACCINE DEVELOPMENT. Around 15 pharmaceutical companies have started working on a vaccine against the Zika virus, WHO reported in mid-February 2016. Two candidates are fairly advanced; a DNA vaccine from the US National Institutes of Health (NIH) and an inactivated product from Bharat Biotech in India. Vaccines are at least 18 months away from any large-scale trials, according to WHO estimates from February 2016.

Source: www.who.int/emergencies/zika-virus/en/

Training workshop one degree north of the equator

The Inter-Regional Pharmacovigilance Training Workshop – a collaboration between Singapore’s Health Sciences Authority, Uppsala Monitoring Centre, and WHO – drew over 50 participants to the heart of Asia in late September last year.



THE WHO-UMC-HSA Inter-Regional Pharmacovigilance Training Workshop, which took place in near-equatorial Singapore from 30 September–2 October 2015, is the three parties’ third collaboration on drug safety training since 2010.

The event attracted over 50 participants, including delegates from across ASEAN (Association of Southeast Asian Nations) and the Asia-Pacific region. Countries and territories represented amongst the attendees were Brunei, Cambodia, Fiji, Hong Kong, Indonesia, Laos, Malaysia, Myanmar, Philippines, Tuvalu, Thailand and Vietnam. Guest speakers also arrived from Japan, New Zealand, Pakistan, Sweden, and Switzerland.

Singapore joined the WHO Programme for International Drug Monitoring (PIDM) in 1993 and has benefited from the programme through knowledge-sharing across its international network, and by utilising UMC’s pharmacovigilance resources.

The aim of the inter-regional training collaboration was to conduct workshops that would build and strengthen drug safety capabilities around the Asia-Pacific region, while enhancing networking and working relationships among government regulators.

The agenda of the workshops that have taken place from 2010 to 2015 have covered the basics of pharmacovigilance, such as risk detection, assessment and communication, as well as advanced topics on pharmaco-epidemiology, data mining, and pharmaco-genomics.

The participants were given an overview

of the drug monitoring systems in different countries; Dr Yusuke Matsunaga, reviewer at Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) presented Japan’s system. The example of Singapore was introduced by Dr Dorothy Toh, HSA’s acting assistant group director of the Vigilance, Compliance and Enforcement Division and director of the Vigilance and Compliance Branch.

Dr Syed Khalid Bukhari, country advisor at the WHO, shared Pakistan’s experience with substandard and counterfeit medicines. From UMC, senior specialist Helena Wilmar spoke on the topics *Data exchange in a global PV environment* and *Quality of ICSRs, VigiGrade*, whilst Anna Hegerius, also senior specialist, touched on developing a positive ADR reporting culture and different ways of collecting ADR information.

ON THE SECOND DAY, Dr Ruth Savage, medical assessor and senior research fellow at the New Zealand Pharmacovigilance Centre, went back to basics and focused on the different aspects of safety signal detection through individual case safety report (ICSR) reviews, clinical diagnosis of adverse events, causality assessments and aggregated case reviews.

Assoc Prof Thoon Koh Cheng, head and senior consultant at the KK Women’s and Children’s Hospital, opened the third day by providing insights on active surveillance of adverse events following immunisation in Singapore. Dr Daisuke Tanaka, WHO’s technical officer, presented talks on the WHO PIDM, as well as on patient safety and medication errors.

This was followed by Paula Alvarado, UMC’s head of Global Communications, who conducted a lively lecture on the importance of effective risk communications. It was not all sit and listen, as the participants were also treated to a video from UMC’s Take&Tell campaign, a video and app that UMC uses to create awareness about reporting side effects. The training workshop ended on a successful note.

Participants felt energised and motivated to share their new knowledge in their own countries, as shown by the feedback given.

“Although I have no background in pharmacovigilance, it is a good knowledge that can be applied in my area to convey the importance of reporting to other colleagues in our department,” one participant from Brunei said in their feedback.

Another attendee from Fiji was very enthusiastic after the training, saying, “If other countries can set up their pharmacovigilance system, so can my country, and I have picked up many wonderful ways to start or revive the reporting system”.

HSA’s CEO, Dr Mimi Choong, also shared her thoughts: pharmacovigilance entails the application of science and utilisation of sophisticated technology. It is therefore crucial that regulators continue to keep abreast with this dynamic discipline through training and education.



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Photo by organizer.

Audience at the conference in Dubai.

UAE's recipe for success

As a hub for the regional pharma industry and with ambitions to be at the forefront of global healthcare, the United Arab Emirates has made pharmacovigilance a priority.

THE EMIRATES' 5TH National Pharmacovigilance Conference was held in sunny Dubai in mid-September 2015. The conference, organised under the patronage of the nation's Minister of Health, H.E. Abdul Rahman Al Owais, attracted over 200 health professionals from the UAE and neighbouring Gulf states. The agenda encompassed a wide range of topics, including regulatory, scientific and communication aspects of pharmacovigilance.

The Emirates became a full member of the WHO programme in 2013; although their centre is young they have come a long way in a short time. In the recently published book "Pharmaceutical Regulatory Environment: Challenges and Opportunities in the Gulf Region", representatives of six Gulf states were asked to list the requirements for a successful pharmacovigilance programme. The options 'well trained staff' and 'educational programmes' came out on top. A majority of the countries

recognized that the recipe for a successful drug safety programme also includes media interest and political support – both of which can be found in the Emirates.

The country's pharmacovigilance centre is based in the Drug Department within the Ministry of Health, with direct links to high levels in the ministry. Decision makers consider pharmacovigilance to be an important part of patient safety. The Ministry of Health fosters good relations with the mass media and is frequently contacted by them for information and clarifications. Accordingly, the 5th National Pharmacovigilance Conference was well covered in print, online and broadcast media in both English and Arabic.

The Emirates is also a hub for the pharmaceutical industry in the region. Both multinational firms and local market authorisation holders are located there in considerable numbers. Several initiatives are also aiming to put UAE at the forefront of healthcare worldwide. ►



Photo by organizer.

Alem Zekarias, Research Pharmacist at UMC, giving a presentation in Dubai.

Regional initiatives

Despite the good conditions for pharmacovigilance in the Emirates, under-reporting within the spontaneous reporting system is still a major concern. Conference President H.E. Dr Amin Hussein Al-Amiri recognised that pharmacists play a pivotal role in patient safety. They are the most common point of contact for patients and can have a substantial impact on adverse drug reaction reporting.

In fact, out of all the reports sent from the national centre to Uppsala Monitoring Centre between January-November 2015, only 8% come from pharmacists. A low number compared to the entire Gulf region, where more than 50% of individual case safety reports originate from pharmacists.



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R. K. Al-Essa, M. Al-Rubaie, S. Walker & S. Salek, *Pharmaceutical Regulatory Environment: Challenges and Opportunities in the Gulf Region*, Springer International Publishing Switzerland, 2015



Panel with Laila Mohammed Kazim, Head of Pharmacovigilance section of UAE Ministry of Health, and international colleagues.

Photo: Organiser.

Making coding work for you in WHODrug User Groups

Uppsala Monitoring Centre's WHODrug® User Group meetings drew more than 300 attendees last year, to events held in the United States, the United Kingdom, Japan and India.

Each year, UMC organises User Group meetings for WHODrug customers across the globe. The meetings include UMC updates, presentations, and interactive sessions, and are run by UMC staff from IT, WHODrug Content, Product Development, and Customer Relations departments.

In 2015, the theme for the gatherings was *Coding – Meeting the Demands of Internal and External Stakeholders*. Events took place in Washington DC and Cincinnati, US; London, UK; Tokyo, Japan; and for the first time a User Group meeting was held in India, in the city of Bengaluru.

Some of the highlights from the meetings included panel discussions and presentations by external speakers, and interactive sessions

between the WHODrug users. The interactive sessions are always appreciated and the audience has a lot of experience to share and exchange – some of the participants have been coding in WHODrug for the past 20 years and the accumulated know-how at the meetings can be quite substantial.

“Although I was over my head with the content, it was a very helpful meeting in



The expert panel in Cincinnati, US, in September 2015.

terms of making connections with other users, in particular the true coders,” one participant in London wrote in their course evaluation. They added, “I was able to get some of the basics and my burning questions answered. The UMC staff were all very friendly and helpful.”

In 2016, the team is organising meetings in Bengaluru, India, in February; in Hamburg, Germany, in April; in Philadelphia, US, in June; and in Tokyo, Japan, in November. In addition to these meetings, UMC will continue to present WHODrug at conferences and via webinars.



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Montenegro's ADR reporting goes digital

Spontaneous adverse drug reaction reports play a key role in obtaining information about drugs released on the Montenegrin market; a new digital application aims to make ADR reporting easier.

SPONTANEOUS REPORTING represents one of the most important sources of information for assessing the safety and quality of drugs that are on the market. In Montenegro, the Agency for Medicines and Medical Devices of Montenegro (CALIMS: Agencija za lijekove i medicinska sredstva Crne Gore) carries the legal responsibility to monitor the safety and to detect any change in the risk–benefit ratio of drugs that are marketed in the country.

According to the Law on Medicines, healthcare professionals are obliged to report each suspected ADR to CALIMS, which receives reports directly from healthcare professionals or via representatives of drug manufacturers who hold marketing authorization.

Healthcare professionals in Montenegro could previously only report ADRs by filling in a hard copy of the reporting form. However, in 2013 the possibility to report digitally through the information system used at primary healthcare institutions and general hospitals was introduced.

After successfully entering the data into the digital application, the healthcare

professionals send the report directly to CALIMS by a simple click of a button. Compatibility between the healthcare information system and CALIMS's information system ensures that the report is automatically available to CALIMS's Pharmacovigilance Department, which is very important in cases when prompt regulatory action is needed.

AFTER THREE YEARS of experience and communication with users of the ADR reporting application, CALIMS improved and simplified the existing application and put it into operation in July 2015.

“Upgrading and improving the existing application is a result of intensive communication with our most valuable reporters – the users of the application,” said Maja Stanković, the head of CALIMS's Pharmacovigilance Department.

“It is important to emphasize that the upgrade of the digital reporting system correlates with the legal introduction of ADR reporting as an indicator of quality in healthcare services,” she said.

The application for ADR reporting


“We expect that an improved way of reporting ADRs is going to build a strong and robust pharmacovigilance system in Montenegro”


through the healthcare information system will also be made available to pharmacists in the public sector. The plan is to enable this kind of reporting in other institutions in the public healthcare system, primarily in the Clinical Center of Montenegro and in special hospitals.

This method of reporting is intended to become the dominant one, because it is simple, fast and efficient, and it should result in an increase in the number of ADR reports.

“We expect that an improved way of reporting ADRs is going to build a strong and robust pharmacovigilance system in Montenegro,” Stanković said.

One of CALIMS's goals in the next year is to intensify the collaboration and communication with experts at Uppsala Monitoring Centre, especially with respect to the possibility to transfer ADR reports received through its healthcare information system directly to VigiFlow® and then to VigiBase®.

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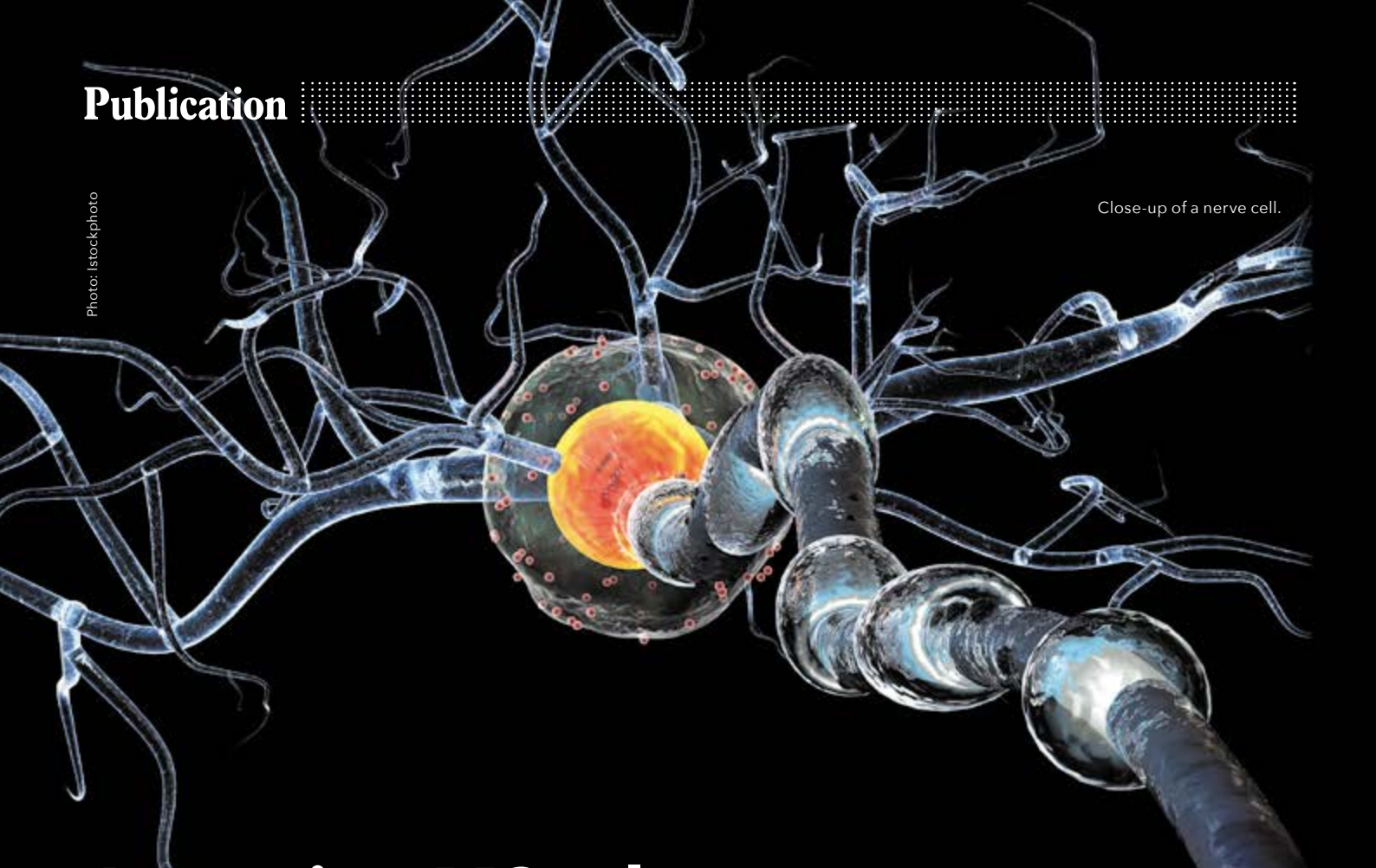
CALIMS's team in the Pharmacovigilance Department.



Photo: CALIMS.

Photo: iStockphoto

Close-up of a nerve cell.



Assessing MS relapse treatments with probabilistic decision analysis

In “Quantitative benefit–risk assessment of methylprednisolone in multiple sclerosis relapses”, Dr Ola Caster and Prof Ralph Edwards assess the most suitable medicine dosage in treating the condition, and apply a novel research method based on probabilistic decision analysis.

THE ONLY PHARMACOLOGICAL intervention with a demonstrated effect on multiple sclerosis (MS) relapses are glucocorticoids, with high-dose, short-term methylprednisolone being the recommended treatment.

However, the optimal dose of methylprednisolone in treating MS relapses is unknown, and it has been suggested that lower doses could be equally efficacious. In addition, glucocorticoids are associated with an array of adverse effects, many of which are determined by the dosage and the duration of the treatment; hence it would be desirable to investigate whether a lower dosage could strike an even better balance between benefits and risks.

Dr Caster, senior researcher, and senior advisor Prof Edwards at Uppsala

Monitoring Centre, set out to provide a quantitative benefit–risk assessment of methylprednisolone treatments for MS relapses, and determine if a high- or low-dose regimen, or no treatment at all, should be recommended.

Photo: UMC



Dr Ola Caster and Prof Ralph Edwards.

Their assessment is the first that considers both the effectiveness of the methylprednisolone treatment for this condition, as well as its risk for adverse reactions. Their conclusion, with regard to the treatment, is that with the currently available data, a high-dose, short-term regimen is indeed preferred over its low-dose alternative.

“Our results are reassuring with respect to current treatment recommendations and clinical practice,” the authors stated in the paper.

ALTHOUGH THE ISSUE of dosage is the primary research focus of the paper, it also has a secondary aim: to show how probabilistic decision analysis can be applied in order to combine information from

different sources in post-marketing benefit–risk assessment.

“The challenge here is that there are so many different kinds of data that must be taken into account,” Dr Caster explained. “So we’ve been working on finding a method, a rational framework that can include all the different types of data we want to use, including clinical trials, spontaneous reports, and so on. Then there’s the aspect of taking uncertainty into account, which is why we have used probabilistic decision analysis,” he said.

“We consider this to be a good model for how to work with pharmacovigilance. As it is now, very often you find the signal and then present it, and you stop there.”

Dr Caster and Prof Edward’s paper is based on a signal that they found and wanted to follow up on by putting it into the context of other side effects and the benefits of the treatment, something which often isn’t done within pharmacovigilance research. “Many people say that that’s what you should do, that’s the goal – but it’s just not practical to do so,” Dr Caster explained.

THEIR METHOD REQUIRES more research than the regular approach towards handling signals. “You need to learn more about the medication, what other side effects are relevant to the drug, and then you have to decide what to compare it to,” said Dr Caster, explaining that in their paper they compared different dosages of the same medicine, although in other studies it may be desirable to compare different medicines.

“That’s the first step, to identify what else to take into account, collect data on that and then structure and analyse everything together. So this method has a fair few extra steps, and it’s not something that you can really do for every signal. But if you’re sitting on a signal that seems extra important, this is one way you could proceed,” Dr Caster concluded.



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O. Caster & I. R. Edwards, ‘Quantitative benefit–risk assessment of methylprednisolone in multiple sclerosis relapses’, *BMC Neurology*, 2015

Achievements and challenges in global vaccine safety

At the 4th annual meeting of the Global Vaccine Safety Initiative (GVSI), organised in French Evian-les-Bains, stakeholders discussed current challenges and achievements in vaccine pharmacovigilance.

THE MEETING, which took place in October 2015, was attended by around 80 participants from pharmacovigilance and immunisation programmes in different countries, organisations that fund and support such programmes, WHO and its regional offices, and observers from vaccine manufacturers.

After introductory statements on the first day, Dr Alex Doodoo, chairman of the GVSI Strategic Priority Group (SPG), gave an overview of the GVSI structure, working processes and recent achievements. He mentioned, for example, the GVSI portfolio as the repository of prioritized projects in various stages of implementation. Brief reports from countries followed, and the subjects which were covered included: strengthening surveillance systems of adverse events following immunisation (AEFIs); responding to vaccine safety reports; managing vaccine safety crises; and managing mass psychogenic reactions and reactions related to immunisation anxiety.

ON THE SECOND day of the meeting, perspectives on the critical importance of safety communication were given. This session was followed by presentations on how to improve investigations of reported safety concerns. The WHO global surveillance and monitoring project for substandard and falsified medicinal products was also presented. Progress reports were then provided on the development of new vaccines to protect against Ebola, malaria and dengue fever.

The final session was devoted to perspectives from a variety of organizations including the Brighton Collaboration, Program for Appropriate Technology in Health (PATH), Agence de Médecine Préventive (AMP), Global Alliance for Vaccines and Immunization (GAVI), and the Bill & Melinda Gates Foundation.

Following the GVSI stakeholders meeting, the SPG had a one-day meeting to discuss development strategies. Alignment between GVSI and the GAVI strategic objectives for 2016–2020 were considered. A discussion

was also held on how GVSI can fully capitalize from the communication tools and approaches developed by the WHO European Region. Decisions were also made to refine the functions of the GVSI project portfolio to support project landscaping, fundraising and performance measurement.

IN CONNECTION WITH the stakeholders meeting, GVSI also issued its colourful and attractive 90-page annual report for 2013–2014. It provides an account of various projects and activities carried out with coordination and support of GVSI.

The report illustrates how GVSI projects have translated into capacity building and training activities in countries, and the development of practical tools that support specialists and health workers in communities, to better monitor and report experiences during the implementations of immunisation programmes. The report gives credible examples of important progress made in vaccine pharmacovigilance since the initiation of the GVSI mechanism.

It does not cover, however, the one area in which GVSI has failed to deliver expected results – the collection of AEFI data from national immunisation programmes is still inefficient. Sub-optimal choices have been made in the development of data management systems for AEFIs, leading to a failure in most instances to integrate fully with national pharmacovigilance databases and the WHO global database, VigiBase®.

The WHO database receives fewer AEFIs from national immunisation programmes today than before the GVSI mechanism started. Due to the lack of AEFI reports reaching the global database from immunisation programmes, the methodological advances made in identifying and analysing signals from individual case safety reports, including AEFIs, cannot be exploited.



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India moves ahead with signal detection

During four hectic days in early October 2015, a three-person delegation from Uppsala Monitoring Centre visited the Indian Pharmacopoeia Commission (IPC) to conduct a joint signal detection workshop in Ghaziabad.

PHARMACOVIGILANCE has considerable momentum in India, and it was the great pleasure of the UMC delegation to help push the world's second-largest population one step closer towards safer use of medicines.

With the level of pharmacovigilance rising all over the world – not least in India – there is increasing demand for education and training in the art and science of signal detection. With this background, a triumvirate of partners consisting of UMC, the pharmacovigilance unit of IPC headed by Dr Vivek Kalaiselvan, and Dr Parthasarathi Gurumurthy, dean of the College of Pharmacy at JSS University in Mysore, decided to try to apply the improved UMC signal detection process locally in India, with some alterations.

Joining the WHO Programme for International Drug Monitoring in 1998, pharmacovigilance in India has made enormous progress during the past few years. The quantity of reporting is steadily increasing, and its quality is high. Data analysis and signal detection is the next major milestone to aim for, and this too has progressed well over the last couple of years.

UMC's senior medical advisor, Dr Ruth Savage of the Centre for Adverse Reactions Monitoring in New Zealand, has been crucial in this process by travelling to IPC on several occasions to conduct training. Dr Savage joined UMC colleagues Lovisa Sandberg, research pharmacist, and Dr Ola Caster, senior researcher, on site to run the workshop at IPC.

The majority of the around 30 participants were IPC employees, complemented by a few people from India's central

drug authority Central Drugs Standard Control Organization (CDSCO), and the national signal review panel that consists of medical experts advising IPC on potential safety signals.

ALTHOUGH THEY WERE all very keen to learn from the experiences of UMC, an equally important objective of the workshop was for UMC to test the feasibility of visiting a national pharmacovigilance centre to perform a signal detection sprint. A third objective of the workshop was to see some fruitful results in terms of the actual signal detection work, i.e. to identify a number of drug-adverse drug reaction (ADR) combinations worthy of thorough in-depth assessment.

The workshop had a very practical set-up. Following an initial half-day of introduction that repeated the key aspects of a dense pre-study package, the participants spent most of the remaining time working practically in a manner similar to the signal detection sprints regularly conducted at UMC.

Drug-ADR combinations were picked from a

joint *vigiRank*[™]-ordered list, filtered to be of relevance in an Indian context. For each combination, the assessor checked whether the combination was already labelled; if it wasn't, the available *VigiBase*[®] data was reviewed to see whether further in-depth assessment was warranted. A total of 20 drug-ADR combinations were recommended for in-depth assessment, with an additional seven to keep under review.

The UMC delegates were there to support and oversee the process, with Dr Savage providing a final medical verdict to approve combinations to be recommended for in-depth assessment. The delegation also tried to apply the key components of UMC's agile approach to signal detection, such as small and mixed groups working together, daily scrum meetings, and a closing summing-up meeting.

All participants worked hard and the tangible outcomes of the workshop were impressive. Based on the feedback from the participants, they believed their newly-gained knowledge would be useful in their work, and the UMC delegation brought plenty of useful experiences back to Uppsala.



Ola Caster

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Modinagar in Ghaziabad.

50 years of pharmacovigilance in New Zealand

November 2015 marked the 50th anniversary of adverse reaction monitoring in New Zealand, highlighting the many ways in which pharmacovigilance has **advanced** in the country over the past decades.



Prof Fiona McQueen, Dr Michael Tatley, and Dr Ruth Savage

ON NOVEMBER 24 last year, Dr Michael Tatley, director of the New Zealand Pharmacovigilance Centre, presented the history of New Zealand’s Centre for Adverse Reactions Monitoring (CARM). He remarked that although New Zealand is a small country in the South Pacific, it was one of the ten founding members of the WHO Programme for International Drug Monitoring (PIDM) in 1968.

The celebration was joined by past directors Prof Ralph Edwards and Dr David Coulter, and Prof Fiona McQueen who represented the first director – her father – the late Prof E.G. McQueen. Also welcomed were Prof Sir David Skegg, former head of the Department of Preventive and Social Medicine at the University of Otago, Dunedin, where CARM is now based; and Emeritus Professor Tim Maling, former chair of the Medicines Adverse Reactions Committee. Medsafe,

the New Zealand medicines regulator, was also represented as CARM is contracted to them, working closely with its pharmacovigilance team to promote drug safety.

PROF MCQUEEN developed the pharmacovigilance centre in April 1965 with an emphasis on its independence, the need for an advisory committee, formal links with New Zealand’s Health Department, and good relationships with health professionals.

Prof McQueen also developed the poison and drug information centre, underpinned by a dedicated toxicology research unit. Brought together by Prof Edwards, these three operations became a single National Toxicology Group. Later, this was proposed by the WHO as a model for establishing an adverse reaction monitoring programme, noting the efficiencies and synergies with the other functions mentioned.

In his presentation, Dr Tatley recognised the health care professionals who have

diligently contributed. There are several features that appear to have contributed to New Zealand’s consistently high reporting rate and report quality. Its small population of 4.5 million has enabled a close collegial relationship with reporters, and each report has been given an individual response. The work has been done independently from the government, and confidentiality has been maintained. Also a contributing factor to the high reporting rate are the programmes that have run side by side with CARM.

DR TATLEY ALSO DESCRIBED the timeline of the history of CARM. In 1977, the internationally renowned Intensive Medicines Monitoring Programme (IMMP) was established, which worked closely with CARM and produced many signals over the next 36 years. In 2004, the Intensive Vaccines Monitoring Programme (IVMP) commenced and extracted real-time data from general practice electronic records for the first time.

In 2010, a Medication Error Reporting Pilot was undertaken by Dr Desiree Kunac, which led to the establishment of a programme in 2014. Dr Kunac is also lead investigator for a paediatric surveillance unit that has increased the reporting of paediatric ADRs. In 2013, psychoactive substances monitoring commenced.

In 2014, CARM obtained public health registrar training accreditation, so that practical training in pharmacovigilance can be a registrar option as one pathway to increasing the pharmacovigilance workforce.

CARM and the other programmes are now part of the New Zealand Pharmacovigilance Centre, which Dr Tatley described as “a centre of vigilance with a synergy of multiple related monitoring streams built on our expertise, infrastructure and credibility”.

Looking into the future, Dr Tatley saw three major influences for improvement: societal, with new data sources and increased patient reporting; technological, providing full integration with practice management systems and e-prescribing; and scientific, combining data sources for signal identification and validation.



Ruth Savage

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Photo: Organiser.



01. UMC's Helena Sköld and Anette Sahlin, WHO's Madhur Gupta, and friends in folk dress at the WHO's annual NC meeting in New Delhi, November 2015. **02.** Dr Frank May, Dr G. Parthasarathi, and Sten Olsson visiting his Holiness Jagadguru Sri Shivarathri Deshikendra Mahaswamiji, in Mysore, India, January 2016. **03.** UMC's Sten Olsson reading an article about the Asia Pacific Pharmacovigilance Training Course in a local Mysore newspaper in January 2016. **04.** A dedicated team at UMC found 20 signals over several days during an intense signal detection sprint. Pictured are Tomas Bergvall, Kristina Star, and Rebecca Chandler in March 2016.



Dr Lembit Rågo New Secretary- General of CIOMS

DR LEMBIT RÅGO has become the new Secretary-General of CIOMS (the Council for International Organizations of Medical Sciences) in Geneva. A member of the UMC Board for over ten years, he joined WHO Headquarters, Geneva in 1999, as Coordinator of the Quality Assurance and Safety, Medicines team, which included activities related to International Non-proprietary Names, quality assurance, pharmacovigilance, and regulatory support, supporting the prequalification of medicines and fighting falsified medicines. Since 2002, Dr Rågo has been the main organizer of WHO's biennial International Conference of Drug Regulatory Authorities (ICDRA), which gathers delegates from around 100 countries. He takes up his new role in April 2016.

UMC on social media

- www.linkedin.com/company/Uppsala-Monitoring-Centre
- www.facebook.com/UppsalaMonitoringCentre
- www.twitter.com/UMCGlobalSafety
- www.youtube.com/c/UppsalaMonitoringCentre

Join the conversation that UMC and its associates engage in on social media. Even our WHO Programme Expert Sten Olsson has a Twitter account – follow him: @stenolssonPV





Photo: Göran Ekeberg

19 years with Mats

MATS PERSSON, Uppsala Monitoring Centre's head of Global Sales and Customer Relations, retired in September 2015 after 19 years at UMC, and will be greatly missed by his colleagues and the people he worked with.

Mats gained a management degree in international/industrial marketing, before beginning his career working in various sales and marketing positions in the Swedish pharmaceutical industry. In the decade before he joined UMC in 1996, he held a position at the Swedish Association

of the Pharmaceutical Industry, selling statistical services.

Mats was responsible for UMC's sales and during his time with UMC, he helped secure the financial basis of the centre by greatly expanding the number of WHODrug Dictionary customers, thus enabling the UMC to consolidate and expand its work. Through the years, Mats has been one of the cornerstones in developing UMC's strong network of connections through numerous exhibitions and business meetings around the world.

With his strong and charismatic appearance, he became known as the "Big Swede", always with a big smile and effort to help out in all business matters. UMC will now continue to foster and care for the long-term relationships that Mats initiated with our commercial customers around the world over many years.

We wish Mats and his wife the best of luck in their next chapter in life, enjoying Portugal – their new country of residence!



IN MEMORIAM



**Professor
Chelbi Belkahia**
(1944-2015)

TUNISIA, AND THE WORLD of pharmacovigilance, has lost a steadfast supporter, Professor Chelbi Belkahia. After studies in Tunis, Paris, and Lyon he held successive posts at the Faculty of Medicine in Tunis, finally as Dean from 1993-99. He set up a pharmacovigilance unit in Tunis in 1977 and the Tunisian National Centre in 1983.

An active participant in the meetings of the WHO Programme for International Drug Monitoring, hosting the one in Tunis in 2000, he was also a keen supporter of the International Society of Pharmacovigilance. He welcomed its first annual meeting to Carthage, Tunisia in 2001, which was held in the difficult circumstances very shortly after the 9/11 catastrophe. His reassuring optimism and his stature amongst his ISoP colleagues overcame considerable doubts about the wisdom of holding the meeting as planned. In the event there was a good attendance at the meeting that kick-started the continuing commitment of ISoP to be truly global. Later he became a Vice-President and Honorary Member of ISoP.

His colleagues will miss his energy, bustling presence and his good humour.



**Dr Juhana
Idänpään-Heikkilä**
(1937-2015)

WE ARE SAD to report the death last October of Dr Juhana Idänpään-Heikkilä. A medical doctor, trained in Helsinki, he worked in clinical settings before becoming Chief Medical Officer at the medicines control agency in Finland for most of the 1970s and 80s.

Dr Idänpään-Heikkilä was the Director of the Division of Drug Management and Policies at WHO in Geneva from 1990-1999, and Secretary-General of the Council for International Organizations of Medical Sciences (CIOMS) from 2000-2006.

Dr Juhana Idänpään-Heikkilä will be greatly missed.



**Dr Andrew
Herxheimer**
(1925-2016)

MY FRIEND, Andrew, has died peacefully at 90 after a most fulfilled life. I met him first in the 1970s at a meeting and we talked about the responsibilities of clinical pharmacologists to ensure that medical students could use medicines competently. He has spent his professional life not only doing that but also as a driving force to ensure that patients' voices and needs are heeded by all those who should be concerned that only the best and safest therapy is adequate.

'Driving force' is a common cliché and Andrew was particular about the use of words (often using them forcefully and as part of wonderfully witty comments): but Andrew was just that. He would go it alone and take on major agencies – the pharmaceutical industry, regulators, institutions – if he thought they were failing to do their best for patient care. Equally he was tireless in supporting people and organisations that had the same aims – the Cochrane Foundation, WHO, Health Action International, ISoP, the International Society of Drug Bulletins, and UMC – and he mostly worked alone with those organisations in the sense that he didn't just follow their ways: he was critical as well as supportive. Needless to say he was an instigator of new enterprises, being the founder of "Healthtalk Online" and the "Drug and Therapeutics Bulletin".

We will miss him greatly, Ralph Edwards.

Pharmacovigilance's role in rapid access to safer drugs

The need to develop and rapidly deploy new treatments pushes the boundaries of traditional pharmacovigilance and demands new thinking and practice. How can pharmacovigilance contribute to the safety of new drugs when rapid access is of paramount importance?

Uppsala Monitoring Centre's 4th biennial research conference "Pharmacovigilance's role in rapid access to safer drugs" provides an international forum to discuss the challenge of balancing the need for rapid access to new drugs with the need to avoid exposing patients to unnecessary risks.

30 - 31 May Uppsala, Sweden

Dr Marie Lindquist

Agile pharmacovigilance, is that possible?

Dr Andrea Marzi

The conceptualisation of an effective and safe Ebola vaccine in the midst of a pandemic

Wiltshire Johnson

Deployment of pharmacovigilance during mass drug administration in Sierra Leone

Dr Noel Southall

Drug repurposing: Benefits and risks in using existing medicines in new indications

Dr Ralph Edwards & Dr Alex Doodoo

When the heat is on: A debate on real time, real life drug surveillance

Dr Gerald Dal Pan

Assessing the impact of pharmacovigilance: Predictors and correlates

François Houyez

Patients? Pharmacovigilants!

Dr Dyfrig Hughes

Uncertainty and examples of reimbursement issues with accelerated release of drugs

Dr Alex John London

Ethical and methodological considerations for pharmacovigilance with accelerated release of medicines

Ingela Larsson

Sharing the burden: How can marketing authorization holders support infrastructures needed with accelerated release of medicines

Andreas Palmberg

Accelerated release of HIV medicines: The challenges of a manufacturer



Pharmacovigilance Meetings 2016

25-27 April 2016

Mid-Year Training Course

Manila, Philippines • International Society of Pharmacovigilance (ISoP)
www.isoponline.org

28-29 April 2016

5th Global Pharmacovigilance Summit

Dubai, UAE • OMICS International
www.globalpharmacovigilance.pharmaceuticalconferences.com

9-20 May 2016

10^{ème} Cours Francophone de Pharmacovigilance

Rabat, Morocco • Centre Anti Poison et de Pharmacovigilance du Maroc
www.capm.ma

16-27 May 2016

18th International Pharmacovigilance Training Course

Uppsala, Sweden • Uppsala Monitoring Centre
www.who-umc.org

24-25 May 2016

Pharmacovigilance Europe 2016

London, UK • Graviton Events
www.gravitonevents.org

30-31 May 2016

Uppsala Forum 2016: Pharmacovigilance's role in rapid access to safer drugs

Uppsala, Sweden • Uppsala Monitoring Centre
www.who-umc.org

2-3 June 2016

Risk Assessment of Drugs During Pregnancy and Lactation

Berlin, Germany • ISoP & ENTIS
www.isoponline.org

6-24 June 2016

7th Pharmacovigilance Fellowship

Accra, Ghana • WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance
www.who-pvafrika.org

8-9 June 2016

Global Regulatory Pharmacovigilance Environment

London, UK • Drug Safety Research Unit
www.dsru.org

14-15 June 2016

Pharmacovigilance 2016: Ensuring Drug Safety, Ensuring Life

London, UK • Recconnect
www.reconnect.com

20-22 June 2016

Pharmacovigilance

London, UK • Management Forum Ltd
www.management-forum.co.uk

22-24 June 2016

Medical Aspects of Adverse Drug Reactions

Southampton, UK • Drug Safety Research Unit
www.dsru.org

26-30 June 2016

DIA 2016: 52nd Annual Meeting

Philadelphia, USA • Drug Information Association (DIA)
www.diaglobal.org

4-8 July 2016

Pharmacoepidemiology & Drug Safety

Utrecht, Netherlands • WHO Collaborating Centre for Pharmaceutical Policy and Regulation
www.utrechtsummerschool.nl

11-15 July 2016

Pharmaceutical Policy Analysis

Utrecht, Netherlands • WHO Collaborating Centre for Pharmaceutical Policy and Regulation
www.utrechtsummerschool.nl

18-22 July 2016

Pharmacoeconomics

Utrecht, Netherlands • WHO Collaborating Centre for Pharmaceutical Policy and Regulation
www.utrechtsummerschool.nl

15-17 August 2016

Pragmatic Approaches to Drug Safety Across the Premarketing and Postmarketing Continuum

Boston, USA • Drug Information Association (DIA)
www.diaglobal.org

25-28 August 2016

32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management

Dublin, Ireland • International Society for Pharmacoepidemiology (ISPE)
www.pharmacoepi.org

28 August-1 September 2016

76th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2016

Buenos Aires, Argentina • International Pharmaceutical Federation (FIP)
www.fip.org

5-16 September 2016

2nd Vaccine Pharmacovigilance Fellowship

Accra, Ghana • WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance
www.who-pvafrika.org

7-8 September 2016

Back to Basics in Pharmacovigilance

Fareham, UK • Drug Safety Research Unit
www.dsru.org

7-9 September 2016

ISoP-UMC pharmacovigilance training course

Lima, Peru • ISoP & UMC
www.isoponline.org

28-29 September 2016

Pharmacovigilance Planning and Risk Management

Fareham, UK • Drug Safety Research Unit
www.dsru.org

28-30 September 2016

Advanced Pharmacovigilance

London, UK • Management Forum Ltd
www.management-forum.co.uk

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