Vigilance - News

June 2011

In this issue:

I: Editorial

Drug safety – Overview and outlook

Dear Reader,

Swissmedic continually receives inquiries from professionals, patients, journalists or politicians about the safety of certain medicines. Most of the questions concern medicinal products that have been authorised in Switzerland. However, some of the inquiries are about medicinal products that are no longer authorised in this country or that have never been authorised but are nevertheless important for patient safety. We are not only asked about which adverse side effects have been reported to Swissmedic but also, for example, whether these are classified as serious or which segments of the population are affected. To respond to these inquiries we refer to the information in and statistical analyses of our database.

For 2010, Swissmedic compiled annual pharmacovigilance statistics in the following sectors:

- Human medicines
- Haemovigilance
- Vaccinovigilance
- Veterinary medicines

You will find a concise summary of these statistics in the next few pages.

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Two signals and the subsequent risk-minimising measures are also presented. These concern rosiglitazone and the combination prilocaine-lidocaine for topical application.

The annual EuroMeeting of the Drug Information Association (DIA) was held in Geneva from 28 to 30 March 2011. The DIA is a non-profit organisation of approximately 18,000 members from the pharmaceutical industry, medical technology sector and associated areas. We provide a few brief impressions from this conference.

During this conference, in conjunction with WHO, Swissmedic held a satellite symposium on the topic of cooperation between the two organisations. The collaboration between Swissmedic and WHO was highlighted in a presentation entitled “Overview of cooperation between Swissmedic and the WHO”. One important topic was the close collaboration between Swissmedic Pharmacovigilance and the Uppsala Monitoring Centre (UMC) in setting up and expanding the databases and international training courses. We have summarised the symposium topic “Counterfeit Medical Products: The way forward”, a presentation on counterfeit medicines.

We hope that this edition of the Vigilance Newsletter offers you an up-to-date overview of our work and we look forward to your feedback at vigilance@swissmedic.ch.

The Editors

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II: Flash: Signals relating to the safety of medicines from the Swiss database of the Vigilance Unit

Adverse drug reaction to prilocaine/lidocaine-based local anaesthetics: methaemoglobinaemia (MetHb)

Summary

The administration of large quantities of prilocaine/lidocaine-based local anaesthetics (Emla®) may lead to serious complications in patients, such as methaemoglobinaemia. It is essential that the non-medical personnel practising in beauty centres be informed of this issue to ensure that they use this type of product in accordance with the recommendations in the Compendium.

Clinical history and physiopathology

Absorption of prilocaine and lidocaine contained in certain local anaesthetics through the skin may cause local (cutaneous, ocular) reactions. Generally these will be minor but there may also be serious adverse events. These cases are rare, can occur in the form of an allergic reaction (e.g. urticaria, angio-oedema, bronchospasm, anaphylactic shock) regardless of the dose administered, or one of the following symptoms:

- central nervous system toxicity: stimulation or depression (drowsiness or even loss of consciousness)
- cardiovascular manifestations: bradycardia, hypotension or cardiovascular collapse
- and finally methaemoglobinaemia

as secondary symptom to an overdose. It is this latter point that we will briefly explain in the following.

Methaemoglobin (MetHb) is the oxidised form of haemoglobin, containing one molecule of Fe3+ instead of Fe2+, which gives the molecule a brownish colour. MetHb is not able to bind oxygen to the haem group and consequently causes functional anaemia. It is reduced by an enzymatic system comprising NADH-dependent cytochrome-b5 reductase. Normally, a small proportion (approx. 2%) of the haemoglobin in the erythrocytes is converted into methaemoglobin. If the level remains below 15%, patients show no symptoms. Above this level, there are signs of cyanosis, dizziness and headaches. A level higher than 40% causes more serious symptoms, with convulsions, drowsiness, or even coma. The condition becomes life-threatening when MetHb levels reach 70–80%.

No treatment is usually given as long as patients remain asymptomatic. Should symptoms appear, they are treated with intravenous methylene blue. Methylene blue acts as an electron acceptor and enables the NADPH to use accessory enzymes, reducing MetHb into oxyhaemoglobin. Oxygen therapy or in some cases even a blood transfusion may be necessary to correct poorly tolerated functional anaemia.

Methaemoglobinaemia may occur after administration of oxidising agents (such as sulfonamides, chloroquine but also local prilocaine- and lidocaine-based anaesthetics). Emla® used in the form of a cream or a patch is a local anaesthetic of this type. The Swiss Compendium of Pharmaceuticals states that in the event of an overdose "rare cases of clinically significant methaemoglobinaemia in children have been reported". The maximum permissible surface area for cutaneous application is clearly defined (between 10 and 200 cm^2 depending on the child's age).

It is not exceptional for this type of complication to occur in adults: one such case was recently reported in a 19-year-old adult hospitalised for cyanosis and dizziness that occurred a few hours after laser hair removal in a beauty centre, prior to which large quantities of cream had been applied to the areas to be treated (i.e. 30–40% of the body surface). The methaemoglobin level was 19.5%

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and the condition rapidly resolved with oxygen therapy alone.

Prior to this, three other cases had been reported in Switzerland following application of Emla® and two cases after administration of Xylonest® (injectable prilocaine). Three cases involved children (2 and 4 years old) and two cases involved adults. In all the cases where Emla® was administered, the quantity of cream applied exceeded the maximum prescribed dosage. The MetHb level varied between 15% and 22% and the outcome – when documented – was always favourable, either with oxygen therapy or with methylene blue infusion.

Internationally, a WHO database search revealed 21 cases of MetHb in children and six cases in adults, of which the majority was also caused by overdosing. The outcome was favourable in all patients.

Conclusions

The above-mentioned clinical case is an example for a potentially serious complication due to the overdose of local anaesthetics applied to intact skin in adults. Widely administered in the medical setting, their growing administration in beauty centres calls for the broad dissemination of precautions among non-medical staff for the use for these products. The Compendium's information for professionals has been adapted for adults to define a maximum application surface of 600 cm^2 i.e. 60 g.

References

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2. *Umbreit J., Methemoglobin - It's not just blue: A Concise Review. American Journal of Hematology 2007;82:134–44.*
3. *Swissmedic warnt vor Risiken bei unsachgemässer Anwendung topischer Lokalanästhetika (25.06.2010)*

Rosiglitazone (Avandia®, Avandamet®): Marketing authorisation suspended on 1 December, 2010

This article is a summary of the story of the second withdrawal from the market in most countries in 2010 which attracted worldwide attention. The first withdrawal concerned sibutramine (Reductil®),which was described in last year's Vigilance Newsletter No. 5.

Rosiglitazone was considered to be a blockbuster drug and was very broadly used worldwide. Under the brand name Avandia®, it was first authorised in Switzerland in September 1999 to treat type 2 diabetes, either as monotherapy or in combination with sulfonylureas or biguanides. There followed a large number of amendments to the marketing authorisation regarding efficacy and safety.

Warnings or precautions concerning heart failure were already mentioned in the package information in October 1999, and again in 2002 and 2008. Because of this problem, the initial dosage was adapted in 2006 and in 2007 NYHA classes III and IV heart failure, was included as a contraindication. In September 2007 a healthcare professional communication (HPC) on this issue was sent out to doctors and pharmacists.

Meanwhile, fluid retention and the related impairment of cardiac pump function were considered an established risk for the glitazone (or thiazolidinedione) substance class and did not play a decisive role in the present market withdrawal. Therefore, pioglitazone (Actos® and the combination preparation Competact®), the other glitazone on the market in Switzerland, is still authorised with the appropriate safety indications despite the known inherent risks for this substance class[1].

[1] *Editorial Update: Prior to the release of this edition, a formal investigation was opened for pioglitazone-containing products due to a suspected increase in the incidence of bladder cancer (see Chapter V).*

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Additional indications for officially authorised combinations with other antidiabetic drugs were approved in 2005 and 2006.

Due to a suspected increased risk of fractures in women, the package information was again adapted in March 2007 and another HPC was released.

Amendments to the package information to include cardiovascular risks (ischaemic episodes) were first issued in 2007 following analyses with a relatively low level of evidence. These amendments were announced in the above-mentioned HPC dated September 2007.

That same year a public debate arose after Nissen, Wolski et al (NEJM 2007;356:2457-71) published a meta-analysis of 42 controlled studies on rosiglitazone that showed an increased rate of heart attacks without an increase in overall mortality. Since then this topic has repeatedly been the subject of controversy in the specialised press and the general media with considerable political debate, especially in the USA.

More large-scale amendments to the package information, including the new contraindication "acute coronary syndrome" were announced in another HPC dated October 2008.

At the time, that concluded the possible options regarding restriction of the marketing authorisation and providing information to specialists and the general public. Up to that point, none of the world's major regulatory authorities, including the EMA (EU) and the FDA (USA), considered the overall risk-benefit ratio to be negative. Swissmedic also regarded the data available at the time as not sufficient to justify a withdrawal of the product from the market.

Two publications in June 2010 however, (Graham et al in JAMA, retrospective cohort study; Nissen et al. in Arch. int. Med., new meta-analysis) further strengthened the signal. On 9 July 2010 the EMA launched an inquiry intending to reanalyse the risk-benefit ratio. On 13 & 14 July 2010 the FDA conducted a public hearing in which the majority of the advisory panel voted for major restrictions on the use and dispensing of the product. Only a minority voted for the complete withdrawal from the market. On 29 July, 2010, Swissmedic opened a formal investigation.

On 23 September 2010, the decisions of the EMA and the FDA were published in a synchronised release, a first, indicating the great significance of the issue. In the EU, the EMA recommended the suspension of the marketing authorisation for all products containing the active substance rosiglitazone. In the USA, the FDA decided to leave these products on the market but under a stringent restricted access programme. The FDA had closely examined the many randomised controlled and epidemiological studies, including samples of the raw data from the RECORD study, which the marketing authorisation holder considered to be the most important exoneration. RECORD was a major randomised, controlled, open non-inferiority study over at least five years with the primary combined endpoint "cardiovascular death or cardiovascular hospitalisation". This study showed no increased cardiovascular risk but, besides having on principle a restricted representative value due to the open design and low event rate, it did reveal additional problems, which was why the FDA insisted on the complete examination and verification of the data by an independent committee.

On 30 September 2010 Swissmedic suspended the marketing authorisation as of 1 December 2010, then sent out a HPC to all doctors and pharmacists on 4 October 2010 and shortly afterwards made an announcement in the professional journals. The two-month transition period was granted in consultation with the diabetes societies in Switzerland to permit planning the change in treatment and to avoid any risks of a precipitated interruption of the treatment. Essentially the justification of this measure was the level of risk to the patient and adequate therapeutic alternatives, although a conclusive assessment with the highest possible level of evidence from clinical research was still not possible. However, owing to the amount of

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collected evidence and the consistency of the results of the various investigations, suspicions had exceeded the threshold for risk reduction measures.

The fundamental extent of the problem was debated a great deal in the major professional journals. This antidiabetic had been authorised in accordance with the customary criterion of proven, well controlled blood sugar levels measured by means of HbA1c, and had achieved high sales figures. It was not until later that the suspicion of an increased cardiovascular risk became stronger. Yet one of the main goals of diabetes treatment is precisely to prevent long-term consequences, such as the increased rate of cardiovascular disease, which is why this safety issue cannot be dissociated from the efficacy. Despite many practical problems it would therefore be best for the authorisation of antidiabetics to require in principle proof of efficacy with hard endpoints, such as cardiovascular events. The FDA guidelines from 2008 on the authorisation of Type-2 antidiabetics constitute a first step in this direction.

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III: Statistical review 2010

VIGILANCE OF HUMAN MEDICINES:
Descriptive statistics of adverse drug reactions (ADRs) in Switzerland

1. Reports of serious adverse drug reactions[1] according to system organ class (SOC)

During the period from January to December 2010 (datalock 28 February 2011), Swissmedic compiled 4,829 reports in its national ADR database, of which 3,103 presented at least one serious ADR. Serious is defined as: death, life-threatening, hospitalisation, permanent damage or disability, congenital anomalies, and medically significant ADRs.

This analysis did not take account of the ADR reports that are still being processed and ADR reports of vaccinations against "pandemic influenza (H1N1) 2009" which were collected in a separate database.

Each report contained an average of 3.6 ADRs (including non-serious ones).

Figure 1: Reports of serious adverse drug reactions per system organ class 2010

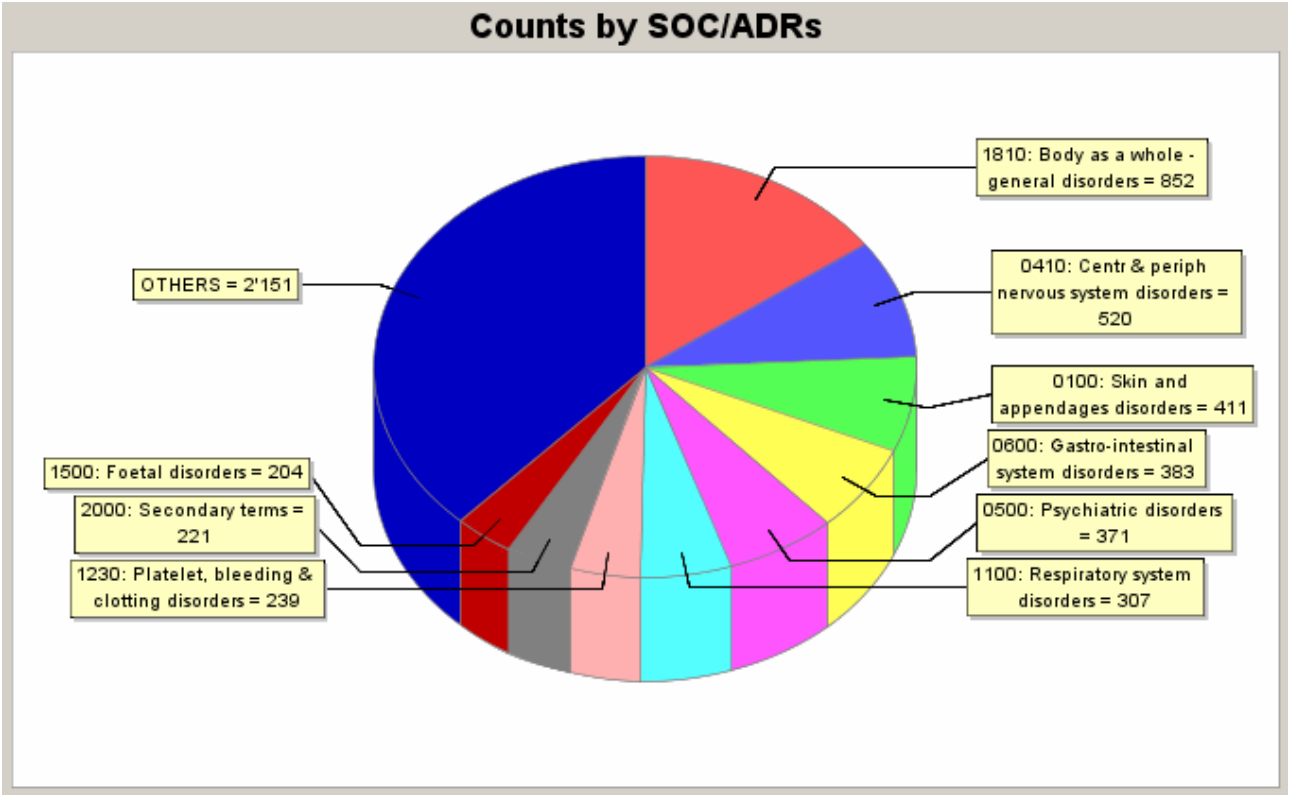

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Figure 1 indicates that the most common ADRs out of the 3,103 reports of serious ADRs were in the following system organ classes (SOC / WHO Adverse Reaction Terminology):

- Body as a whole – general disorders
- Central and peripheral nervous disorders
- Skin and appendages disorders
- Gastrointestinal system disorders
- Psychiatric disorders
- Respiratory system disorders
- Platelet, bleeding and clotting disorders
- Secondary terms
- Foetal disorders

All other serious ADRs were classified in the "Others" group and were not described in further detail.

Table 1: Distribution of ADR reports in 2010 according to seriousness and reporter (to Swissmedic

Sender Type	Death n (%)	Life Threatening n (%)	Hospitalization n (%)	Disabling n (%)	Congenital Anomaly n (%)	Medically Important n (%)	Total n (%) Reports
Total[a)]	***170 (5.5)***	***185 (6.0)***	***1236 (40.0)***	***113 (3.6)***	***7 (0.2)***	***1680 (54.0)***	***3103 (100)***
Direct report to Swissmedic by Health Professional	0	1 (0.05)	1 (0.05)	0	0	0	***2 (0.1)***
Pharmaceutical Company	94 (3.0)	51 (1.6)	341 (11.0)	45 (1.4)	2 (0.1)	903 (29.1)	***1347 (43.4)***
Regional PV Center	76 (2.5)	133 (4.3)	894 (29.0)	68 (2.2)	5 (0.2)	776 (25.0)	***1753 (56.5)***
No Data	0	0	0	0	0	1	***1 (0.05)***

[a)] ***Important:*** *It should be noted that a report may include more than one criterion for seriousness. Therefore the sum of the reports per criterion will not equal the total number of reports of 3,103 (100%).*

The distribution of the 3,103 reports of serious ADRs received by Swissmedic in 2010 is presented in **Table 1**: 56.5% of reports were from the regional PV centres and 43.4% were from pharmaceutical companies. 54% of reports contained medically significant ADRs; 6% were classified as life-threatening; 40% of cases resulted in hospitalisation; 3.6% led to permanent damage or disability; and 0.2% of cases were related to congenital anomalies. 5.5% (n=170) of all reports were of death, for which the following causes were quoted: 43.3% of cases were suspected to be related to the

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medicinal product; 41.0% that the medicinal product may have contributed to the fatal outcome; and 15.7% of cases that there was no relation to the medicinal product.

2. Reports of adverse drug reactions: labelling in the product information[2] and cases of interactions

34% of all ADR reports (n=1,050) mentioned at least one serious ADR that is not adequately mentioned in the relevant labelling. 156 cases (5%) were interactions with serious consequences for health.

Serious ADRs that are not or not sufficiently mentioned in the labelling can be critical and therefore shed light on a new drug risk and give rise to appropriate measures, such as the publication of healthcare professional communications, a revision of the Professional and Patient information in Switzerland or even a fundamental examination of the risk-benefit profile of the medicinal product in question. Even non-serious ADRs that are not mentioned in the labelling can result in measures being taken, in particular the updating of the Professional and Patient information.

3. Reports of serious adverse drug reactions according to sex and age

- Of the 3,103 serious ADR reports received in 2010, 53% (n=1638) concerned women and 38% (n=1191) men. In 9% (n=272) of cases the gender was not indicated.
- Almost three quarters (73%) of reports were adults/elderly, 3.5% concerned children/teenagers, and 2.5% were small children/neonates. In 21% of cases there was no indication of age.

1 *Source: Swissmedic pharmacovigilance database*
2 *N.B. "ADRs not listed in the labelling" also include insufficiently described ADRs*

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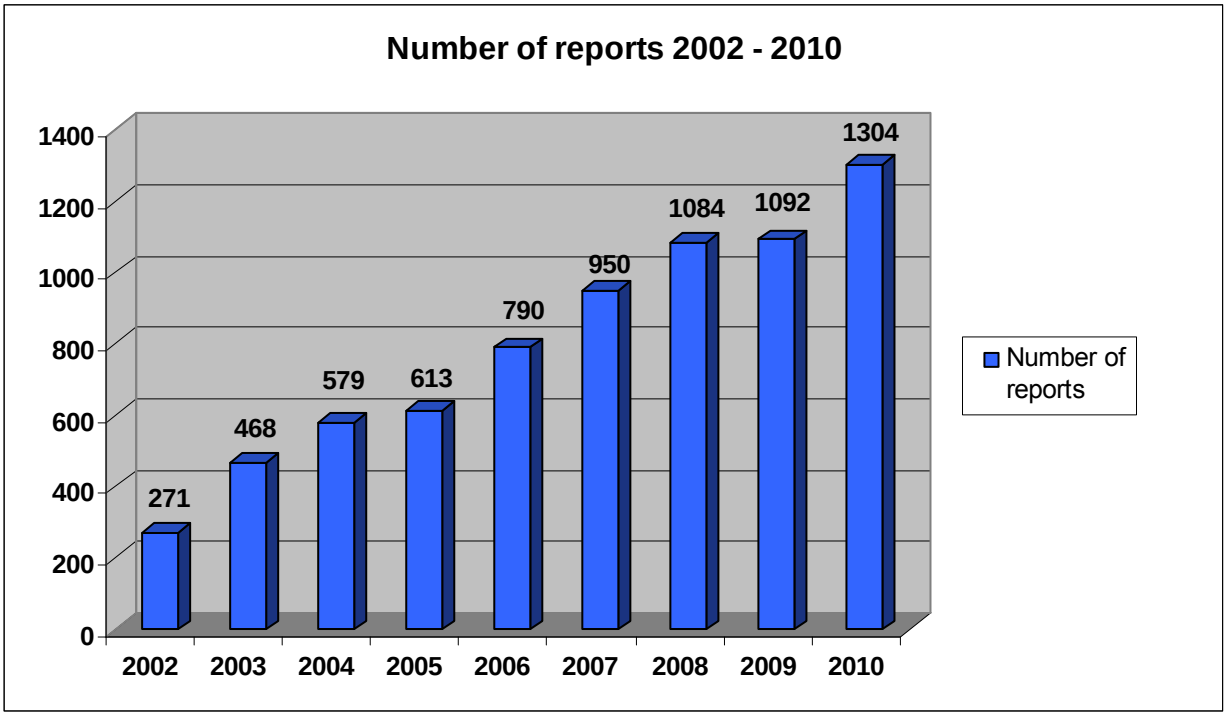
HAEMOVIGILANCE

Haemovigilance (HV) signifies collecting, reporting, analysing and evaluating suspected adverse transfusion events for the purpose of finding / determining measures to improve the quality and safety of blood transfusions. It is of particular importance to recognise potentially avoidable events.

The product risks have been largely reduced over the past few decades, so recently the risks of using blood components have come to the fore.

It is a prerequisite for identifying and reporting adverse transfusion events that the personnel administrating blood components have appropriate levels of knowledge and attentiveness. We notice in general that there is increasing awareness for the risks of transfusion in hospitals, which is reflected in the steady increase in the number of reports we receive.

Figure 1:



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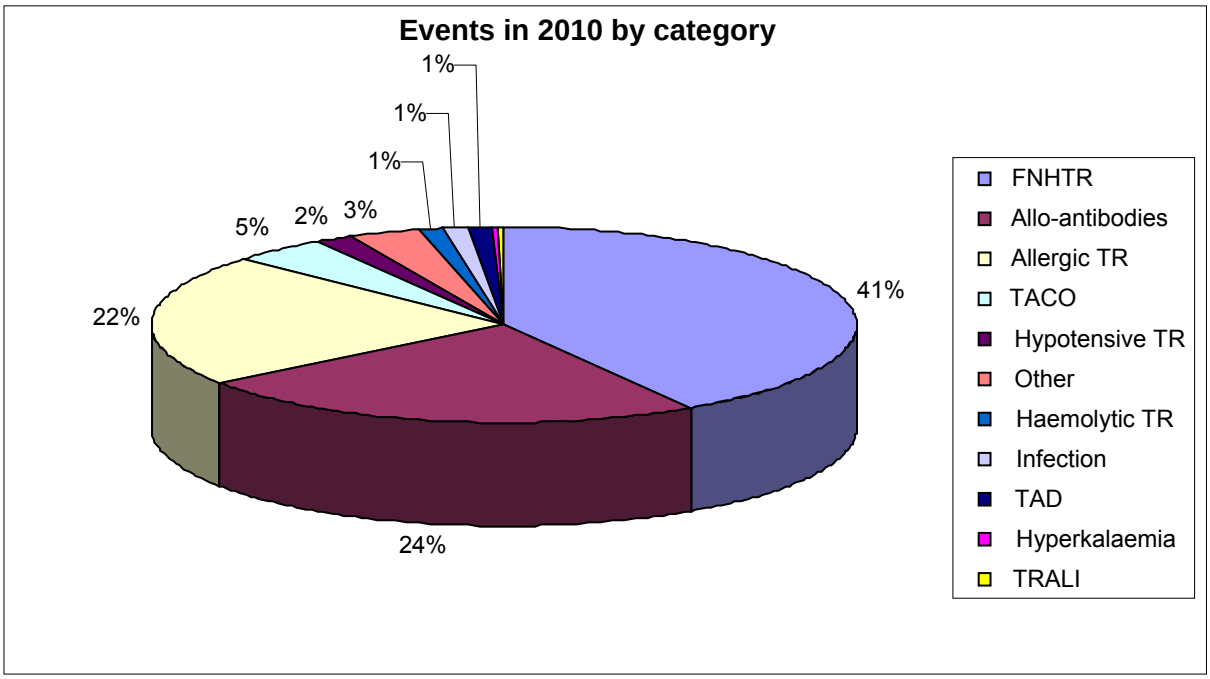
The overall reporting rate for Switzerland (number of reports per 1000 transfusions) was 3.25 in 2010, or approx. 1 per 300 transfusions. However, there is still considerable variation in the reporting frequency among the roughly 200 hospitals administrating transfusions.

Table 1: Number of transfusion reactions (TR) reported in 2010, by category and frequency

Category	Number of cases
Febrile non-haemolytic TR (FNHTR)	388
Alloantibody formation	222
Allergic TR	205
Transfusion-associated circulatory overload (TACO)	45
Hypotensive TR	15
Other	22
Haemolytic TR (HTR)	12
Infection	8
Transfusion-associated dyspnoea (TAD)	12
Hyperkalaemia	3
TRALI (transfusion-related acute lung injury)	3
No TR	3
Total of transfusion reactions	**938** (incl. 12 double reports)

Figure 2: Distribution of transfusion reactions reported in 2010 by percent



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As shown in **Table 1** and **Figure 2**, more than 85% of the reported transfusion reactions fall into the three main categories. All other incidents were observed relatively rarely and therefore require particular attention if they are to be reliably diagnosed.

In 63% of all transfusion reactions reported, the relation between the reaction and the transfusion was assessed as certain or probable (high imputability).

Severity of events in 2010

57% of the high imputability events reported were not serious and did not give rise to any long-term consequences. 38% were serious or resulted in permanent harm. 5% of the reports were life-threatening events. In 2010 there no fatal high imputability events were reported.

The reports of IBCT (incorrect blood component transfused) and NM (near miss) are listed separately from the transfusion reactions. In 2010 there were 41 IBCT (two of which were cancelled) and 337 NM events reported. This is a considerable increase in the number of reports in comparison with the previous year (34 IBCTs and 275 near misses in 2009).

The above-mentioned high imputability transfusion reactions and the number of blood components transfused each year in Switzerland enable us to calculate the current risks of a transfusion and to compare them for selected categories.

Selected transfusion risks

HIV	1:3'400,000 donations[1)]
HCV	1:3'200,000 donations[1)]
HBV	1:170'000 donations[1)]
Sepsis due to bacterial contamination of the blood component	1:11'000 platelet concentrates (PC) [2)]
IBCT	1:20'000 [3)] transfusions
Severe allergic TR	1:20'000 [3)] transfusions
TRALI	1:140'000 [4)] (2002–2007) 1:400'000 [5)] (2008–2010)
TACO	1:14'000 [3)] transfusions
Haemolytic TR	1: 80'000 [3)] transfusions

1) *National Centre of Reference for infections transmitted by blood and blood products, 2010*
2) *Swiss Haemovigilance data 2005–2010*
3) *Swiss Haemovigilance data 2010*
4) *Swiss Haemovigilance data 2002–2007*
5) *Swiss Haemovigilance data 2008–2010*

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Preventive measures

The following measures have so far been taken to increase transfusion safety in Switzerland (in chronological order):

TRALI

Since 1 January 2007 plasma for transfusion is collected exclusively from male donors (and from female donors who confirm that they have never been pregnant or who have tested negative for HLA and HNA antibodies). TRALI cases caused by these antibodies ("immune TRALI") can be prevented with these measures, hence a reduction in the risk of TRALI can be expected.

Hepatitis B transmission

Routine testing for viral infections transmitted by transfusions show that hepatitis B is the greatest risk, with a current incidence of approximately 1:170,000 blood donations. To reduce this risk, additional testing of all donations with nucleic acid amplification techniques (NAT) was introduced for hepatitis B in 2009 (detection limit of ≤ 25 IU/ml).

Bacterial contamination of PC

By mid-2011 the Intercept procedure for the inactivation of pathogens will be introduced for all PC produced in Switzerland. This will provide us with a reliable means to prevent clinically relevant bacterial contamination of PC in all patient groups.

In March–April 2011 another haemovigilance workshop was held with the main topic "Critical stages in the transfusion process". The workshop was attended by about 45 participants who made good use of the opportunity to exchange experiences.

On 8 and 9 September 2011 the annual congress **"Swisstransfusion 2011**", jointly organised by the SRC Blood Transfusion Service, the Swiss Blood Stem Cells Foundation, the Swiss Association of Transfusion Medicine and Swissmedic, will be held on the site of the University of Fribourg. Swissmedic will host the session on Haemovigilance, which is scheduled for the morning of Friday, 9 September 2011.

Further information on this will be available on the Swissmedic website in due course under
http://www.swissmedic.ch/aktuell/00051/01249/index.html?lang=en
or under: http://www.swissmedic.ch/marktueberwachung/00159/00160/00438/index.html?lang=en
or on the Swisstransfusion website: www.swisstransfusion.ch .

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NEW: VACCINOVIGILANCE

Ten-year summary on reports of suspected adverse events following immunisation in Switzerland (2001–2010)

Background

Vaccine pharmacovigilance is an essential component of an immunisation programme to monitor and respond rapidly and appropriately to potential new vaccine safety concerns. Since 1988, the duty to report suspected adverse drug events is a requirement under Swiss law. Until June 2001, the Swiss Office of Public Health (SFOPH) and the National Drug Pharmacovigilance Centre (SANZ; "Schweizerische Arzneimittelnebenwirkungszentrale") shared responsibility for receiving spontaneously reported adverse events following immunisation (AEFI). Previous evaluations of surveillance years 1988–1990[1] and 1991–2001[2] have been published.

Following restructuring in 2001, the responsibility of AEFI surveillance was placed fully under the newly founded agency for therapeutic products, Swissmedic. Thus in Switzerland, the national regulatory authority is responsible for vaccine pharmacovigilance with independence from the national public health authority and immunisation recommendations or programmes.

An overview of the pharmacovigilance system in Switzerland, including the form to report a suspected adverse event to a regional pharmacovigilance centre, is available online at www.swissmedic.ch → Market Surveillance → Reporting undesirable side effects.

Summary

The ten years summary on AEFI reports from 2001 to 2010 includes data for *non-pandemic* influenza vaccines from the Swissmedic pharmacovigilance database. A separate evaluation on the surveillance of pandemic influenza vaccines was published in 2010[3]. Henceforth "all" vaccines in this report refers to all licensed vaccines in Switzerland other than the "pandemic influenza (H1N1) 2009" vaccines.

From 2001 to 13 December 2010 (year-end cut-off date), Swissmedic registered a total of 1,565 spontaneous reports with 4,615 AEFI, an average of 2.9 AEFIs per report. About 35 million doses of routinely administered vaccines were distributed in the time period 1991–2001[2] in the Swiss population and the estimate for 2001–2010 is expected to be even higher, considering the increase in the Swiss population and introduction and expansion of routine vaccination programmes.

Figure 1 indicates that the number of reports per year has generally increased until 2009.
In 2009, a total of 630 reports were received, 371 of which were for pandemic influenza vaccines, which was more than all reports for all other vaccines combined. In 2010, a total of 351 reports were received, with pandemic influenza vaccines again accounting for more reports received than all other vaccines together.

Figure 2 compares the number of reports for all vaccines for different age groups and gender received in two periods, 2001–2005 and 2006–2010. In general, the number of spontaneous reports of AEFI has increased across all age groups. In particular the number of AEFI reported in adoles-

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cents and adults have doubled in the later period, reflected by the introduction of routine immunisation against meningococcal meningitis and human papillomavirus (HPV) in adolescents. Increasing population size (increase of 7.3% in 10 years) may only partially explain the rise in the number of reports. Newly licensed vaccines and target population groups have expanded immunisation programmes and likely contributed, as well as an increased awareness by patients and health care providers to report a suspected adverse drug event. In the second period 2006–10, more reports concerned women than men in both adolescent and adult age groups, which is likely attributable to the first routine immunisation program which was gender selective. The HPV vaccine was licensed in Switzerland in 2007 and integrated within the Swiss routine vaccination program in 2008 for girls and young women (< 20 years old), and also offered up to the age of 26 years based on individual assessment.

Figure 3 indicates the number of AEFI reports by the vaccine subgroup and seriousness. The number of doses administered for each vaccine group is not available and thus the Figure does not indicate which vaccines would be associated with higher number of AEFI (per 100,000 doses). A report is coded serious when there is a death, required/prolonged hospitalisation, persistent or significant disability, life threatening or congenital abnormality. A report is coded “medically important” when it does not meet the serious criteria but is considered a significant medical event. All other reports were evaluated as non-serious (for example, expected or self-limited adverse events with good recovery). Of 1,565 spontaneous reports, 52.9% were non-serious, 25.2% were medically important and 21.9% had more serious consequences (e.g. hospitalisation).

Figure 4 is an overview of the 1,565 reports by System Organ Classes (SOC). The top five system organ classes reported for vaccines were: Body as a Whole, Central & Peripheral Nervous System, Application Site Disorders, Skin and Appendages, and Gastrointestinal. The adverse events under the group of “other” adverse effects are not specified further. **Table 1** indicates the top ten AEFIs that have been reported for all vaccines: fever, injection site reaction, headache, rash, nausea, muscle aches, vomiting, dizziness, joint pains, swelling. **Table 2** summarises the top ten AEFIs for the reports which were coded serious or medically important. The two tables have similar patterns except more neurological AEFIs were coded as serious or medically important.

Of 54 individuals with convulsions following different vaccines, 40 were fully recovered or recovering, 7 were not recovered, and 7 had unknown outcome at the time of the report. Many convulsions were associated with fever. Of 33 reports coded separately as “fever convulsions” in young children, 31 children fully recovered or recovering, 1 child was not recovered and in 1 child the outcome was unknown at the time of reporting, with further follow up not available.

Of 37 reports coded with paralysis or paresis, with an average of 1.4 AEFI per report. Eighteen individuals had facial paralysis, 14 had paresis, 4 with hemiparesis and 3 were reported as encephalitis. Of 37 individuals, 24 were fully recovered or recovering, 8 were not recovered, and 5 had unknown outcome at the time of reporting. The spontaneous reports coded as “serious” or “medically important” with neurological AEFIs were more commonly associated with tick-borne encephalitis and influenza vaccines. In the ten-year period (not shown in **Table 2**) there have been 9 reports of Guillain-Barré Syndrome reported spontaneously after several different vaccine products, most commonly after seasonal influenza vaccines (5 reports).

Figure 5 indicates the top three system organ classes per vaccine group. Exposures during or before pregnancy are coded under the System Organ Class “Foetal Disorders”. In **Figure 5** for rubella vaccines, the cases of “foetal disorder” were 2 drug exposures in pregnancy, 2 drug exposures before pregnancy and 1 elective abortion. No congenital abnormalities with rubella vaccine exposure were reported as an AEFI.

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There has been a total of 20 deaths reported between 2001–2010. Determining causality for a death event requires careful further assessment. A causal relationship with the vaccine cannot be established without a confirmed diagnosis and full investigations to identify other possible causes. A temporal relationship between a serious adverse event and vaccination can therefore be purely coincidental, as there is an expected rate of events that will naturally occur without a vaccine exposure. All death reports are investigated for as complete information as possible. Of 20 reports, only one was assessed as causally related to vaccination. A child who was given live attenuated BCG vaccine later developed BCG disseminated disease which was treated but proved fatal. The child had a suspected rare congenital immunodeficiency that was undiagnosed prior to vaccination. Three reports were assessed as "possibly" related, partly due to limited information available. A young child who had received the full vaccine series against *S. pneumonia* infection developed invasive streptococcal pneumonia disease. Unfortunately, information on the serotype of the invasive streptococcal bacterium was not available. It is not known if there was a mismatch with the serotypes in the vaccine, or a match and therefore an ineffective vaccination series. The second case was a teenage girl who had not completed her series of vaccinations against tick-borne encephalitis and was thus only partially immune at the time when she received a tick bite and developed fatal confirmed tick-borne encephalitis. The final case was of a 75-year old healthy gentleman with a minor heart condition who had a sudden death. Sixteen reports were assessed for causality as unlikely (four cases were of sudden infant death syndrome and twelve reports were explained by other medical causes such as known cancer, heart, lung or neurological diseases, aortic aneurysm, or suicide).

In the past decade, several vaccine safety signals have been investigated in Switzerland. The signals originated from the Swissmedic pharmacovigilance database and from international sources e.g. through communications with other regulatory authorities or the marketing authorisation holders. In pharmacovigilance terms, a signal is defined by Swissmedic as "a suspected new risk or relevant new aspect of a known risk that needs to be investigated further with regard to risk minimising actions". Prominent examples include a cluster of reports of facial paralysis associated with a nasally administered influenza vaccine product given in the 2000/1 season which led to the market withdrawal of the vaccine product; a case-control study conducted later provided strong epidemiological support for the link between this AEFI and the product.[4] In 2005, a hexavalent vaccine (against tetanus, diphtheria, polio, *Haemophilus influenzae*, pertussis, and Hepatitis B) was recalled due to decreased vaccine efficacy of the Hepatitis B component of the vaccine. Due to a considerable number of neurological AEFI associated with tick-borne encephalitis this problem has been closely reviewed and the labelling for these vaccine products in Switzerland was changed in 2009. Several instances include quality signals where a batch number was re-examined for a potential quality issue and relationship between a specific batch of vaccines and a series or increased number of AEFI reports.

Conclusions

Between 2001–2010, the total number of adverse events spontaneously reported for all (non-pandemic) vaccines was 1,565 reports, which is a very low spontaneous reporting rate considering that tens of millions of individuals received vaccines in the past decade in Switzerland. However, underreporting of AEFI remains an ongoing issue of a spontaneous reporting system. Swissmedic aims not only to improve awareness to raise the number of reports but also the quality of reports and completeness of the information. For instance efforts have been made to improve the batch number reporting for a suspected AEFI, to enable investigation of batch production issues and testing when appropriate. Since 2010, Swissmedic established meetings on a regular and as-needed basis to review current vaccine pharmacovigilance issues within its Human Medicines Expert Committee, Swissmedic's scientific and clinical expert advisory body for therapeutic products.

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2. *Schumacher Z, Bourquin C, Heininger U. Surveillance for adverse events following immunization (AEFI) in Switzerland – 1991-2001. Vaccine;28(24):4059-64.*
3. *Swissmedic. Final Report: Analysis of the PaniFlow® database on suspected adverse events following "pandemic influenza (H1N1) 2009" vaccination in Switzerland, July 2010. http://www.swissmedic.ch/marktueberwachung/01315/index.html?lang=en.*
4. *Mutsch M, Zhou W, Rhodes P, Bopp M, Chen RT, Linder T, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med 2004;350(9):896-903.*

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Figure 1: Number of AEFI Reports per year in Switzerland, 2001–2010

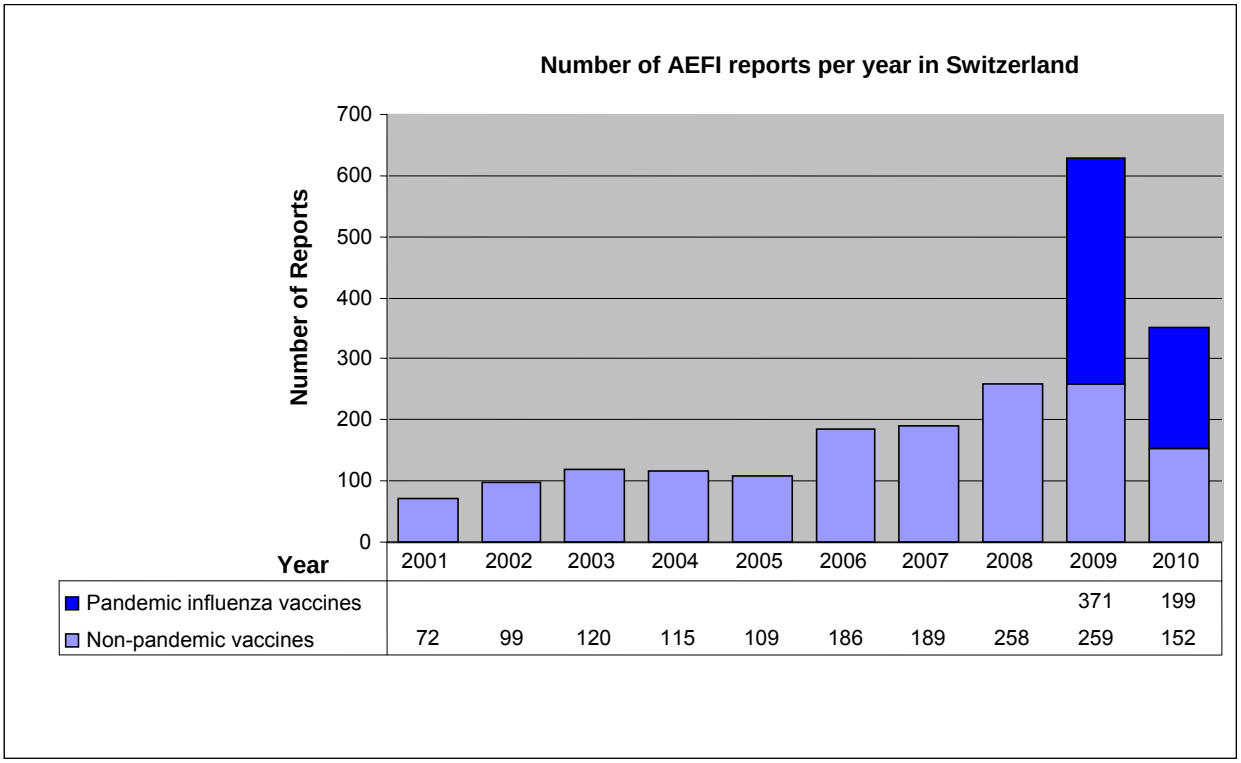

Figure 2: Number of AEFI Reports by age group and gender, 2001–2010

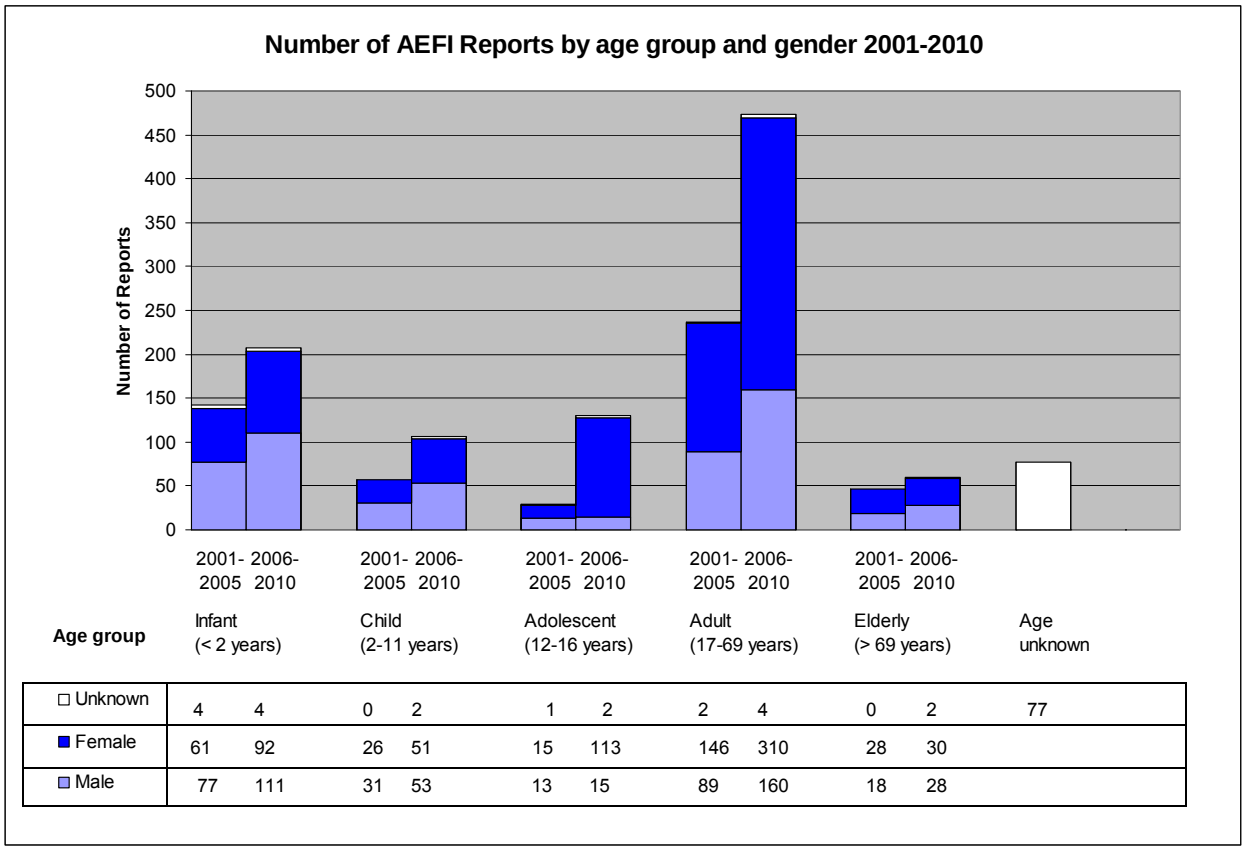

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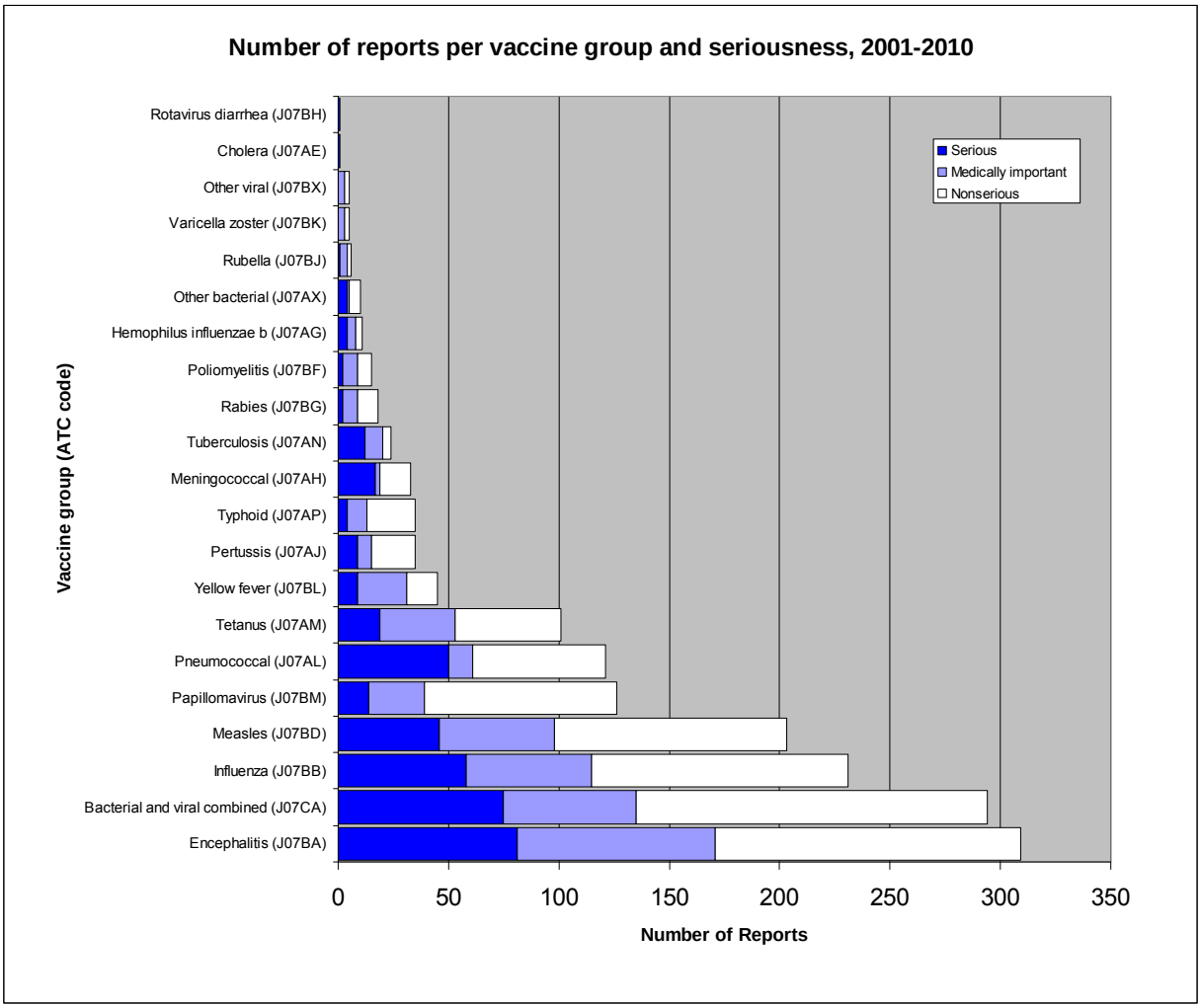
Figure 3: Number of AEFI Reports per vaccine group and seriousness, 2001–2010



The database is organised according to the WHO Anatomical Therapeutic Chemical (ATC) system for classification of therapeutic substances, with J07 as the vaccine subgroup. The ATC code J07BA for encephalitis vaccines includes both tick-borne encephalitis and Japanese encephalitis vaccines. J07CA “Bacterial and viral vaccines, combined” includes different combinations of multivalent vaccines against tetanus/diphtheria toxoid, *Haemophilus influenzae type b*, poliomyelitis vaccine, pertussis, and/or hepatitis B.

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Figure 4: Number of AEFI Reports by System Organ Class in Switzerland, 2001–2010

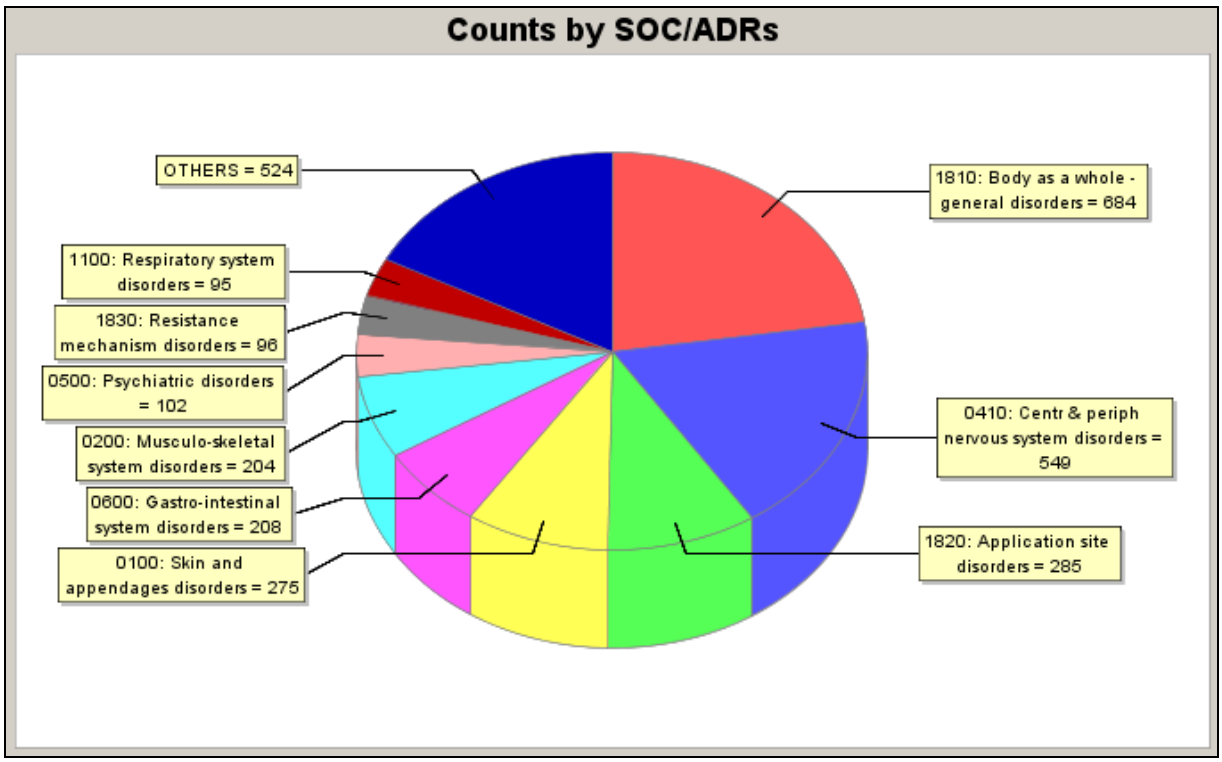

Figure 5: AEFI Reports by vaccine group and top 3 system organ classes, 2001–2010

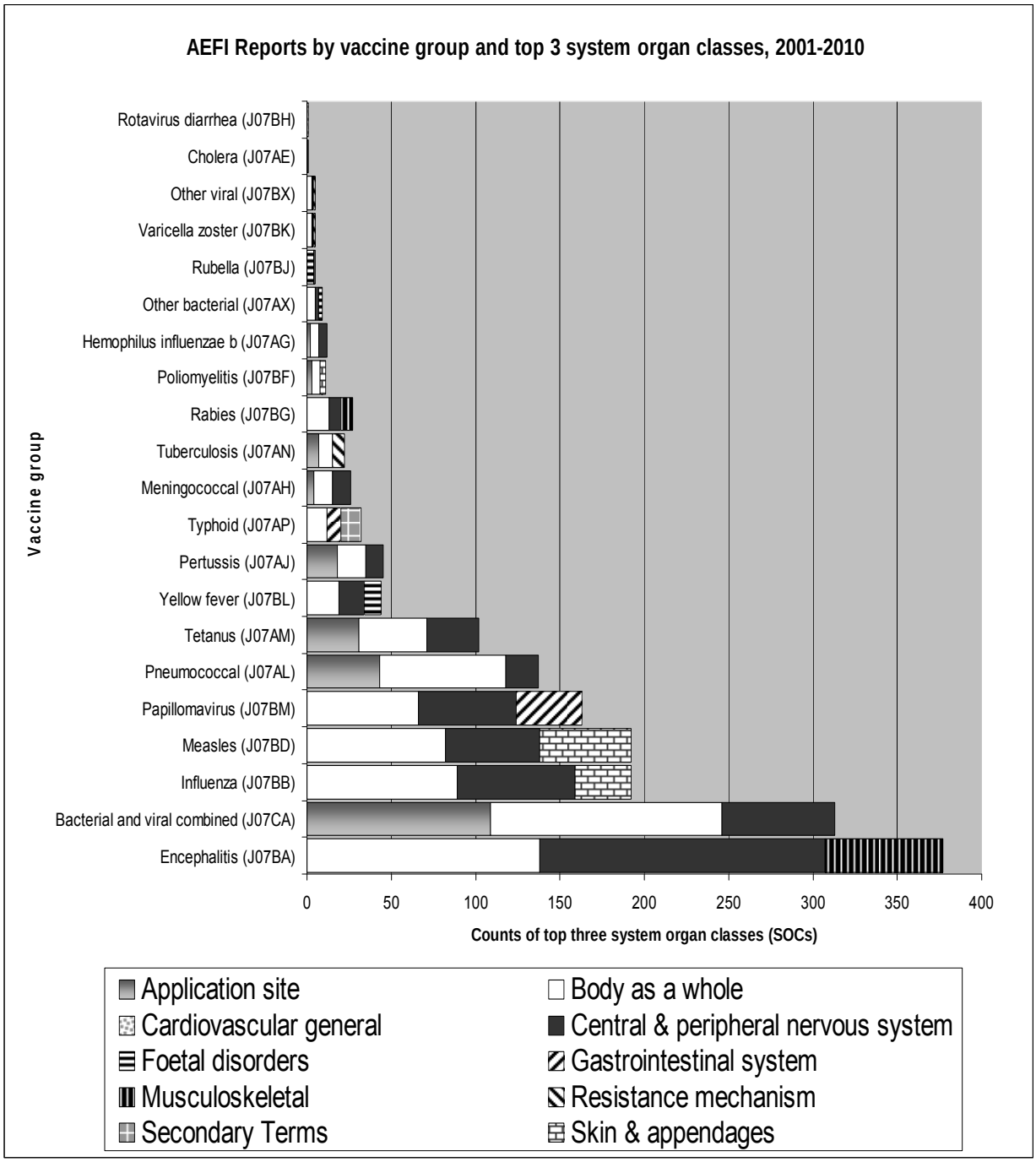

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Table 1: Overall top 10 AEFIs for all vaccine reports, 2001–2010

Adverse event	System Organ Class	Number of Reports
Fever	Body as a Whole	297
Injection site reaction	Application site disorder	261
Headache	Central & Peripheral Nervous System	163
Rash	Skin and Appendages	143
Nausea	Gastrointestinal System	102
Muscle aches (myalgia)	Musculoskeletal System	92
Vomiting	Gastrointestinal System	70
Dizziness	Body as a Whole	68
Joint pains (arthralgia)	Musculoskeletal System	62
Swelling (oedema)	Body as a Whole	63

Table 2: Top 10 AEFIs for reports coded “serious” or “medically important”, 2001–2010

Adverse event	System Organ Class	Number of Reports
Fever	Body as a Whole	129
Injection site reaction	Application site disorder	69
Headache	Central & Peripheral Nervous System	61
Rash	Skin and Appendages	55
Convulsions	Central & Peripheral Nervous System	54
Swelling (oedema)	Body as a Whole	63
Paralysis	Central & Peripheral Nervous System	37
Muscle aches (myalgia)	Musculoskeletal System	34
Fever convulsions	Central & Peripheral Nervous System	33
Drug exposure in pregnancy	Foetal disorders	29

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VIGILANCE OF VETERINARY MEDICINES

In 2010 the number of adverse effects reported rose considerably: in comparison to 2009 there were approx. 20% more, reaching a total of 160 reports. Over the two years 2009–2010 the increase has been therefore 48%. As in previous years, the reports were most commonly sent by the distributors or the manufacturers (83 reports, or 52% of the total). Reports were first and foremost describing events that were originally reported by practising veterinarians to the appropriate marketing authorisation holder. Under Articles 34 and 35 of the Ordinance on Medicinal Products, the marketing authorisation holders are obliged to forward these reports to Swissmedic within specific deadlines. We received 25% of reports (40) directly from practitioners, and the remaining 23% from animal owners (3%, 5 reports), other authorities (also 3%, 5 reports) or from the Swiss Toxicological Information Centre (STIC) in Zurich (17%, 27 reports).

Overview according to animal species and category of medicine

Table 1 shows the distribution of the reports we received according to animal species. This has remained stable over the past few years: the largest group is small animals, with dogs (88 reports) and cats (33 reports), followed by cattle or calves (27 reports) and pigs (5 reports). For all other species, fewer than five reports were submitted for the entire year. **Table 2** shows the distribution of reports sorted according to ATCvet categories. It corresponds largely to the distribution of the past few years: the most common reports were for reactions to the use of antiparasitics (48 reports, 30% of total) or antiinfectives (29 reports, 18% of total).

Overdose of chewable tablets

In 2010 non-steroidal anti-inflammatory drugs (ATCvet QM) were ranking third with 23 reports (14%). Many of these cases were reported by the STIC and describe an overdose in dogs and a few cats. All cases were recorded during telephone consultation and forwarded to Swissmedic within 15 days in accordance with a contractual agreement. At the time of the telephone call, most of the animals were symptom free and some had even already vomited the tablets. The overdoses must be understood in relation to various efforts by the manufacturers to improve the acceptance of the tablets in small animals. This was mainly achieved by the addition of flavourings. In addition to the term "aromatics" in the declaration, these tablets can be recognised by descriptions such as "chewable tablets", "flavour", or "yeast tablets". However, the addition of flavourings has improved acceptance so much that many dogs (and even some cats) associate the tablets with a reward and subsequently go looking for them. In addition, some anti-inflammatory preparations are available in large packs (e.g. 100 tablets) because they need to be administered over long periods for chronic conditions. If a dog manages to track down and open or bite through the packaging, or if the tablets are not in the package or blister, the animal may be able to swallow huge quantities of tablets: in the most extreme case in 2010, a 6 kg chihuahua ate 20 tablets with 100 mg carprofen each, corresponding to an overdose 83 times greater than the recommended dose of 4 mg/kg! The other overdoses varied between 5 and 80 times the recommended dosage. The outcome of the cases is only known in very few cases. The experience of the STIC shows that one-off overdoses, even when massive, are usually well tolerated. Treatment of such cases is symptomatic: if the tablets were taken recently and if the dog did not vomit, this can be induced with apomorphine. Activated charcoal can also be given and attention should also be paid to providing sufficient water and perhaps also correcting the acid-base balance. Misoprostol, a prostaglandin E2 analogue can be used to protect the stomach lining.

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Adverse effects from reconverted use

Reconversion in veterinary medicine means the use of a preparation for another species or for an indication other than that originally authorised. Fifteen reports of suspected adverse effects from reconverted use were submitted, including 11 cases of allergic reactions after intravenous administration of amoxicillin – clavulanic acid combinations in dogs reported by the Veterinary Hospital in Zurich. The preparations are intended for use in humans and were used because no comparable veterinary medicine is authorised for this application. The reactions described, such as urticaria, eyelid and facial oedema, tachypnoea and tachycardia, were associated with allergic manifestations. After a few such cases with an initial preparation, the veterinarians decided to change the treatment, but with no improvement as the second preparation (a generic without any excipients) was identical to the first. All reactions were therefore attributed to an allergic reaction to amoxicillin or clavulanic acid. Both of these active substances have the potential to cause these reactions. More recent publications describe hypersensibility reactions in the form of urticaria, anaphylaxis or maculopapular exanthema in humans associated with clavulanic acid[1]. However, no similar publications could be found for veterinary medicines and the precise incidence of such allergies in small animals is unknown.

Assessment of causality

In 16% of the reports it was possible to prove a ("probable") causal association between the application and the reaction, and in 33% of reports it was judged as "possible". The remaining reports either had too little information (41%) or else an association could be unequivocally refuted (10%).

Adverse effects of veterinary vaccines

In addition to the reports on veterinary medicinal products authorised by Swissmedic, 261 cases of adverse effects of veterinary vaccines were reported to the IVI (Institute for Viral Diseases & Immunoprophylaxis in Mittelhäusern, the competent authority for authorisations and surveillance of veterinary vaccines). As many as 179 of these reports were for reactions following administration of a vaccine for bluetongue disease in ruminants as part of a government campaign, while 82 other reactions occurring after administration of various other veterinary vaccines. At present no other analyses of these reports have been conducted.

[1] *Sanchez-Morillas et al.: Selective allergic reactions to clavulanic acid: a report of 9 cases, J Allergy Clin Immunol, 126: 177–179, 2010; José-Torres et al.: Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions, J Allergy Clin Immunol, 125: 502–505, 2010*

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Table 1: Reports in 2010 according to species

Species	Number	% Total
Dog	88	55 %
Cat	33	20 %
Horse / donkey	3	2 %
Cattle / calf	27	17 %
Sheep	1	1 %
Pig	5	3 %
Poultry	1	1 %
Pets, zoo animals	2	1 %
Total	**160**	**100 %**

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Table 2: Reports in 2010 sorted according to ATCvet category. The code QZ is fictitious and enables grouping of ADR reports in reconverted preparations (i.e. not used in the authorised species and/or indication)

Medicine group according to ATCvet	Number of reports (% of total)
QA: Gastrointestinal tract	10 (6%)
QB: Blood and haematopoietic organs	1 (1%)
QC: Cardiovascular system	3 (2%)
QD: Dermatologics	1 (1%)
QG: Urogenital system, sex hormones	3 (2%)
QH: Hormone preparations (except for sex hormones and insulin derivatives)	12 (7%)
QJ: Anti-infectives	29 (18%)
QL: Anti-neoplastic and immune-modulating preparations	4 (3%)
QM: Musculoskeletal system	23 (14%)
QN: Nervous system	5 (3%)
QP: Antiparasitics	48 (30%)
QR: Respiratory system	3 (2%)
QS: Sense organs	1 (1%)
QV: Miscellaneous	1 (1%)
"QZ": Off-label preparations	15 (9%)
ALP-registered products, animal-care products	1 (1%)
Total	**160 (100%)**

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IV: Conferences

D I A EuroMeeting of the Drug Information Association 28–30 March 2011 in Geneva

Conference small group on drug safety

Session 0808: Medicines for Pregnant and Lactating Women

- Session Chair: Viveca Odlind, PDCO, Adjunct Professor of Obstetrics and Gynaecology, University of Uppsala; Senior Expert, Medical Products Agency (MPA), Sweden: ***"Surveillance of use of medicines during pregnancy – The Swedish Medical Birth Register as an example"***

  The Medical Birth Register (MBR) comprises all children born in Sweden: ~ 100,000 per annum since 1973. Copies of all records are sent to the National Board of Health for analysis. Recording of the use of medicinal products during pregnancy started 1994. The current database comprises information on drug exposure in approx. 1.4 million neonates. Only exposure during the first trimester of pregnancy is available for analysis. 24% of all pregnant women reported using a medicinal product during the first trimester.

  Conclusion: The Swedish experience is positive with regard to exposure in early pregnancy, whereas adequate and reliable information on exposure during later parts of the pregnancy has proved more difficult to obtain via the MBR. In order to examine effects of drug exposure during late pregnancy, further studies are needed.

- Klaus Olejniczak, Preclinical Assessor, Director and Professor (retired), Germany: ***"Preclinical Aspects of Medicines During Pregnancy"***

  Reliable data – preferably prospective data – from more than 1,000 pregnancies with drug exposure are required to demonstrate that the increase of overall frequency of malformation is less than two-fold.

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Integration of human and animal data (risk)

Human data	Animal data Effects present	Animal data No effects
Demonstrated malformations	Proven risk in humans	Proven risk in humans
Suspected malformations	Strong suspicion of risk in humans	Risk is possible in humans
No or less than 300 outcomes and no increase	Risk is possible in humans, not confirmed	Malformative risk unlikely in humans, but low evidence
Between 300 and 1000 outcomes and no increase	Malformative risk unlikely in humans, but low evidence	Malformative risk unlikely in humans with moderate to substantial evidence
At least 1000 outcomes and no increase	Malformative risk unlikely in humans with strong evidence	Malformative risk unlikely in humans with strong evidence

- Eva Jirsova, M.D., Pharmacovigilance Unit, State Institute for Drug Control, Czech Republic: ***"Assessment of Safety of Medicines during Breastfeeding"***

  Nearly all drugs pass into breast milk.

  Principles for labelling: Reasons for the recommendations should be provided. Where discontinuation of breastfeeding is recommended, reasons should be provided.

Swissmedic commentary:

- Optimal use is probably not yet being made of the large amount of data in the Swedish Medical Birth Register (MBR). In future publications on the risk of taking medicinal products during pregnancy, attention should be paid to whether the authors have compared their results with the MBR.
- Experts argue for more comprehensible justifications for the specifications provided in the drug information. This refers to the restrictions/contraindications but also to any concessions regarding the intake of a drug during pregnancy or breastfeeding.
- Almost all active substances pass into the breast milk. The advantages of breastfeeding per se are generally considered secondary to the issue of drug safety, even from a legal point of view. The risks of lactation suppression by medication are generally not mentioned.
- Swissmedic supports the efforts for better greater transparency in the drug information by including explanations where relevant.

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Problems with counterfeit medicines

The continual increase in counterfeit therapeutic products worldwide was a topic at the annual DIA meeting in Geneva. According to reliable estimates as many as 700,000 people in developing countries have died in the past few years because of counterfeit malaria and tuberculosis medicinal products. Although there have only been a few recalls of therapeutically significant counterfeit medicinal products in Europe and so far no products have been discovered in Switzerland, it is still an issue here. The main problem in Switzerland is that private individuals import illegal medicinal products directly.

Swiss patients increasingly order products of questionable quality on the internet. Based on campaigns conducted in the past few years by Swissmedic in collaboration with the Swiss customs authorities, we estimate that at least 50,000 illegal shipments are ordered by private individuals in Switzerland each year. This does not include roughly 50,000 imports of small quantities[1]. These illegal medicinal products include erectile stimulants, hormonal muscle-building products and weight-loss products but also prescription-only medicines, such as painkillers, contraceptives, and sleeping pills. In addition there are the so-called natural, purely herbal products or food supplements that often contain non-declared prescription-only ingredients.

The analysis of confiscated drugs in the Swissmedic laboratories confirms that the quality of the drugs ordered on the internet is usually insufficient and more than the half are of critically bad quality. Often they are counterfeit products. Counterfeit products are medicines that intentionally feature false information on the composition of the product or its origin. They often contain no active ingredient, the wrong active ingredient or the active agent in doses lower or higher than claimed. They were not manufactured under controlled conditions and were not tested in clinical trials.

Analysis of many so-called natural slimming products in our laboratory have shown that these often contain high doses of the active ingredient sibutramine or other prescription-only substances without the according declaration. This issue also came to light in an investigation carried out in Germany. The review of 17 cases of hospitalisation on account of adverse drug reactions (ADR) reported to the toxicology centres in Göttingen and Freiburg between 2005 and 2008 revealed that the capsules allegedly containing purely herbal ingredients actually all contained double the maximum daily dose of sibutramine[2].

The marketing authorisations for medicinal products containing sibutramine were suspended in Switzerland and the EU last year on the grounds of cardiovascular risks.

Swissmedic also regularly receives information on counterfeit products that have been discovered due to the occurrence of serious side-effects through the international network for combatting pharmaceutical crime. In view of the relatively large quantities of medicinal products purchased by private individuals over the internet, it is important for doctors also to consider imported products as the possible cause when consulted by patients for adverse drug reactions or unexpected inci-

[1] *Importing medicines by private individuals is possible under the Therapeutic Products Act and therefore legal for their own therapeutic use and for the duration of one month. This regulation was originally conceived for the benefit of incoming tourists but is increasingly being used by Swiss residents to purchase prescription only medicines from abroad over the internet. However, the import of large quantities of drugs or of narcotics without the appropriate prescription is illegal.*

[2] *Müller, Dieter; Weinmann, Wolfgang; Hermanns-Clausen, Maren (2009): Chinese slimming capsules containing sibutramine sold over the Internet: a case series. – Deutsches Ärzteblatt international; Vol. 106, No. 13, p. 218-22 (http://goedoc.uni-goettingen.de/goescholar/handle/1/5791)*

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dents. Suspected cases should be reported to Swissmedic without fail even if the cause of an ADR is an unauthorised or illegally imported drug.

Summary of presentation

Session 0306: Causality assessment of a medicinal product: how can the performance of current instruments be improved? (L. Abenhaim)

At the present time there is no ideal method in determining imputability for adverse drug reactions. Research using current electronic databases (such as VigiFlow managed by the UMC) does not enable surveillance in real time. Furthermore, the prospective databases set up to collect clinical data in real time are not appropriate when the adverse events are rare and when there is a long delay between the time the medicine is taken and the onset of the illness. Finally, it is important to take account of environmental factors, the fact that reporting by the patients themselves may be misleading (omission of important information and other biases) and that the medical prescriptions do not take account of the patient's compliance or the possible use of over-the-counter products.

For this reason, the London School of Hygiene & Tropical Medicine in England, the INSERM in France, and McGill University in Canada developed an innovative solution since 2008: the Pharmacoepidemiologic General Research eXtension (PGRx), which would make it possible to systematically apply case-control study methodology.

Its purpose is:

- surveillance: systematic collection of adverse event incidents
- evaluation of relative risk: comparison with selected controls from the reference panels
- risk-benefit analysis: positive and negative events estimated compared with the same reference panel

The results thereby facilitate the drafting of Risk Management Plans to enable rapid responses to safety alerts and the establishment of risk-benefit management plans.

In practice, PGRx continually maintains an updated database for 14 diseases of which nine were autoimmune diseases (multiple sclerosis, Guillain-Barré syndrome, Type I diabetes, Graves' disease, autoimmune thyroiditis, rheumatoid arthritis, lupus erythematosus, myositis, idiopathic thrombocytopenic purpura), and myocardial infarction, torsades de pointe, acute liver injury, suicide attempt and depression. A network of specialised centres in France, Britain and Canada have prospectively collected incident cases with patients aged from 14 to 79 years who presented with the abovementioned diseases. Appropriate epidemiological case definitions were developed by experts. Control patients were collected from general medical practice at the same time and independently, from which matched controls could be selected for comparison with the cases. Cases and controls were investigated with a detailed standardised questionnaire, from which about 300 medicinal products and vaccines and suspected or known risk factors for these illnesses can be considered. Details of the medical history and prescriptions from both cases and the controls are collected from the treating physician. So far a pool of several thousand potential controls has been collected in general medical practice who agreed to answer the detailed questionnaire.

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The results are interesting. For example, we were presented with the results of an investigation into an association between the H1N1 vaccine and Guillain-Barré syndrome (the results enabled a causal association to be rapidly excluded). In the second presentation, the results of an epidemiological analysis of breast cancer in women with diabetes indicated how the influence of environmental factors (BMI, period with an elevated BMI, gestational diabetes, and biological markers) could be reduced.

PGRx is therefore a very useful database for research in certain rare diseases and for monitoring medicinal products and vaccines.

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V: Information on the safety of medicines – published on the Swissmedic website

Abschlussbericht Celtura Schwangerschaftsregister *
28.06.2011

Nimesulid und schwerwiegende Leberschädigungen - Swissmedic erinnert an die korrekte Anwendung *
24.06.2011

HPC - Erhöhte Inzidenz von Blasenkarzinomen unter der Einnahme von Pioglitazon-haltigen Arzneimitteln (Actos®, Competact®) *
20.06.2011

Sistierung der Zulassung von pioglitazonhaltigen Produkten (Actos®, Competact®) in Frankreich per 11. Juli 2011 *
10.06.2011

Heilmittelfälschungen bekämpfen: Bundesrat verabschiedet neues Übereinkommen des Europarates *
10.06.2011

HPC Caninsulin ad us. vet. – Kontamination der Herstellungsanlage *
09.06.2011

Alarming analysis results: Dangerous slimming products available from the Internet: new figures
06.06.2011

Examples of supposedly herbal yet partly also dangerous slimming products
05.06.2011

HPC - 52089 Permax (Pergolid) : Verzicht auf Zulassung zum 30. September 2011 *
30.05.2011

HPC - Topiramat (Topamax®): Erhöhtes Risiko von Lippen-Kiefer-Gaumenspalten bei Exposition während der Schwangerschaft - Aktualisierung der Arzneimittelinformation: Kontraindikationen, Warnhinweise und Vorsichtsmassnahmen, Schwangerschaft/Stillzeit *
24.05.2011

HPC – Efient® (Prasugrel) – Überempfindlichkeitsreaktionen einschliesslich Angioödem – Aktualisierung der Arzneimittelinformation (Warnhinweise und Vorsichtsmassnahmen, Unerwünschte Wirkungen) *
11.05.2011

Übersetzung des Kodex der Mitglieder der Swissmedic Medicines Expert Committees auf Französisch *
09.05.2011

HPC Anzemet® (Dolasetron) – Rückzug der Tabletten zu 200 mg am 15. Mai 2011 wegen dosisabhängiger QT-Verlängerung und Risiko von Herzrhythmusstörungen *
29.04.2011

HPC Zerit® (Stavudin): Einschränkung der Indikation und Erweiterung der Warnhinweise *
29.04.2011

Update on pandemic influenza (H1N1) 2009 vaccine (Pandemrix®) and narcolepsy
20.04.2011

Lasix 250mg Ausfällungen mit dem Hilfsstoff (Furosemidum) *
15.04.2011

VIVAGLOBIN® (subkutanes Immunglobulin-Präparat) und Risiko von Thromboembolien *
05.04.2011

Impfstoffe Prevenar® und ActHIB® dürfen in Japan wieder eingesetzt werden *
04.04.2011

Nachtrag 7.1 der Europäischen Pharmakopöe in Kraft *
01.04.2011

Ketoprofen-Gel (Fastum® Gel) und Photoallergie *
31.03.2011

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Thromboembolische Ereignisse unter VIVAGLOBIN®, einem subcutan applizierten Immunglobulin - Health Professional Communication durch die FDA *
18.03.2011

Rotarix® update zu Intussusception – Daten aus australischer Interimsanalyse *
15.03.2011

Anti-HIV Wirkstoff Abacavir – neue Meta-Analyse zeigt kein erhöhtes Risiko für Myokardinfarkt *
11.03.2011

Impfstoffe Prevenar® und ActHIB®: zeitweilige Sistierung in Japan *
07.03.2011

Die europäische Arzneimittelagentur und Swissmedic verlängern Vereinbarung zum Informationsaustausch*
14.02.2011

A further increase to imports of illegal medicinal products
04.02.2011

Stellungnahme der Swissmedic zu Medienberichten betreffend die französische Heilmittelbehörde Afssaps im Zusammenhang mit dem Arzneimittel Mediator (Mediaxal) *
27.01.2011

Current information on the use of Avastin® to treat breast cancer
17.12.2010

Please find the complete list at the following web address:
http://www.swissmedic.ch/aktuell/00003/index.html?lang=en

*** *in German and/or French only***

Report of a suspected adverse drug reaction (ADR)

► The ADR reporting form can be filled in electronically:

MU101_20_001d_FO Meldung einer vermuteten unerwünschten Arzneimittelwirkung (UAW) [in German]
MU101_20_001f_FO Annonce d'effets indésirables suspectés d'un médicament (EI) [in French]

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We want to thank all colleagues for their contribution to the realisation of this Vigilance-Newsletter.

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