

Final summary of adverse drug reaction reports in Sweden with Pandemrix through October 2009 – mid April 2010

June 2, 2010

As of April 16, 2010 about 6.1 million adult doses of Pandemrix have been administered according to preliminary data from the county councils to the Swedish Institute for Infectious Disease Control (SMI). The Medical Products Agency (MPA) has received a total of 4380 adverse events reports (ADR) from Health Care Professionals and from consumers during the pandemic period. In view of the great number of vaccinated individuals in Sweden and the limited number of adverse drug reaction reports and their pattern, the conclusion is that the safety of the vaccine is satisfactory.

About 10 million adult doses of Pandemrix have been delivered to the public medical service until April 16, according to the manufacturer. To the same point of time, approximately 6.1 million doses of the vaccine have been administered according to the Swedish Institute for Infectious Disease Control (SMI). The data from SMI also indicates that about 700 000 doses have been used in children 6 months - 12 years of age. Preliminary data also indicates that about 421 000 children have received a second dose of the vaccine.

The MPA has from the time when vaccination was started in October 2009, continuously published summaries of adverse events reported with Pandemrix. The summaries have focused on reports relating to previously unknown or suspected serious side effects while known adverse and mild events have been reported only briefly. All individual reports from Health Care Professionals and Consumers respectively have been assessed individually at the time of receipt by the Regional Centres and by the MPA.

This final summary specifically addresses reports from Health Care Professionals on allergic reactions and neurological adverse events, musculoskeletal reactions and adverse reactions in children and in pregnant women, transplanted patients and fatal outcomes. Included is also a short summary regarding the reporting of adverse events on a European level as well as planned follow-up research studies. The reports received directly from Consumers are also briefly described and summarised.

The analysis is based on data from reports received from Health Care Professionals until April 16 2010 and from Consumers until February 4, 2010.

Reports from Health Care Professionals

About 2150 reports have been received from Health Care Professionals including a total of 3500 suspected ADRs. About 20% of the reports describe adverse events that have been classified as serious. The majority of the adverse events reported are expected and mild reactions such as injection site reactions and influenza like symptoms, e.g. fever, chills, fatigue, severe headache, pain in the body and malaise.

Interpreting adverse events reports

A report of an adverse event is often valid for a single individual but may comprise the description of more than one reaction. An assessment is made in order to evaluate the possible relationship of the reaction to the vaccination. Consideration is taken to the patient's medical history, concomitant drug therapy and the temporal relationship to the adverse event.

The degree of seriousness of the event is also evaluated. Serious adverse events are normally defined as being life threatening, leading to hospitalization or prolongation of hospitalization, to disability or miscarriage or a fatal outcome.

When the follow-up measures for Pandemrix, from a safety point of view, were intensified during the autumn the Health Care Professionals were encouraged to report all suspected adverse events with the exception of those described as common/very common in the summary of product characteristics.

Since the reporting is made already at the stage of suspicion the reporter does only have to acknowledge a time course, but not to consider whether there is a causal association.

A functioning system for reporting on adverse events is therefore a valuable complement to the knowledge of adverse events that were known at the time of approval of the vaccine and is of great importance for elucidation of the risk profile when the vaccine is being administered to a large population within a short timeframe.

The reporting pattern as a whole is consistent with what has been seen from the clinical trials, with the exception of certain allergic and neurological adverse events, which were observed only after the vaccination had started. Some of the observations have led to further investigations, and for some are results awaited from follow-up studies.

The cumulative number of adverse events reports received from October 12, 2009 until April 16, 2010 is over 2100 and constitutes parts per million of the number of administered doses (See figure 1.)

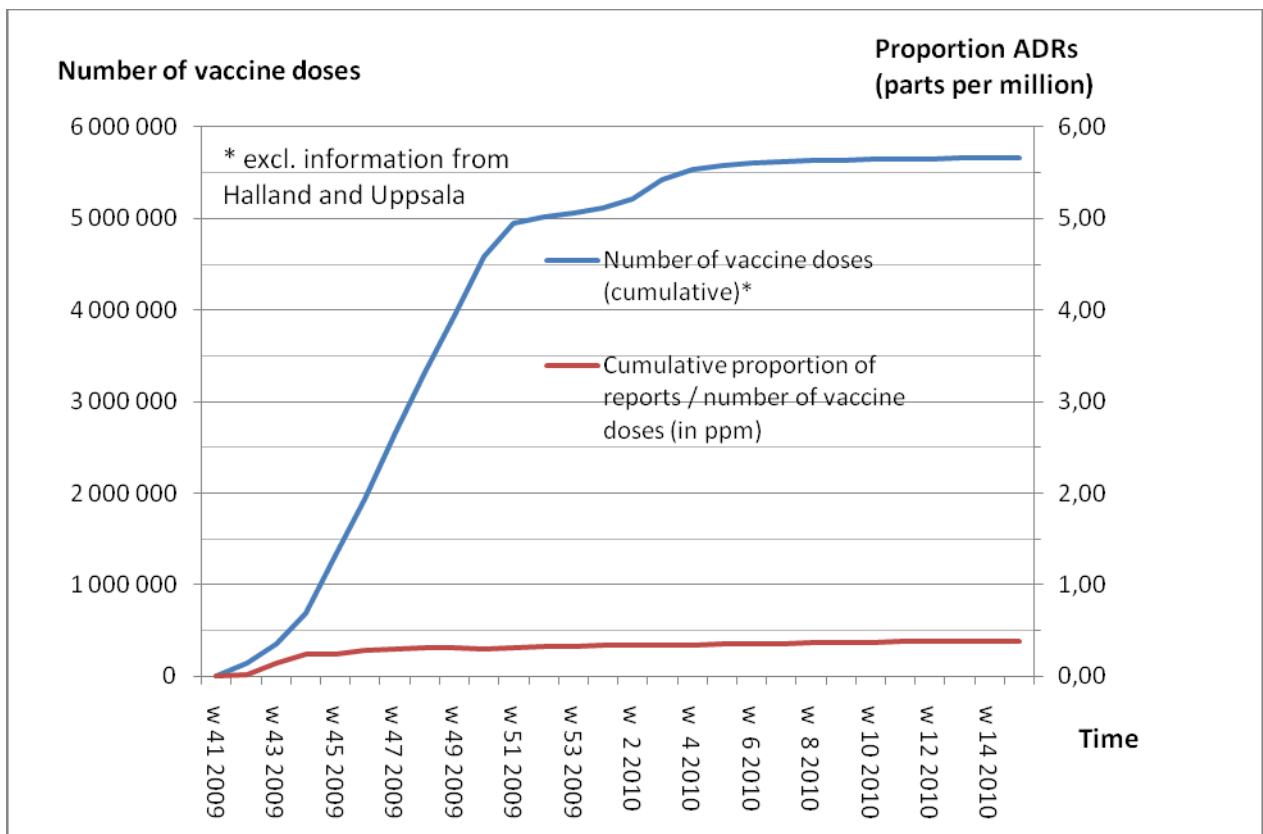


Figure 1. Proportion of the cumulative number of reports of adverse events from Health Care Professionals compared to the cumulative number of vaccine doses administered. The diagram shows the development during October 2009 – April 2010.

According to preliminary data from SMI the estimated number of adult doses of the vaccine administered (excl. Halland and Uppsala) increased the most until December 2009, more slowly until the end of January, where after fewer people have been vaccinated. The number of ADR reports' follow the pattern of the vaccination, although levelling somewhat later which can be explained by that the occurrence of an adverse event sometimes has a certain delay before being identified, reported and registered.

In figure 2 the most frequently reported suspected reactions are shown, grouped after System Organ Class (SOC). The numbers represent the frequency of suspected adverse reactions, irrespective of seriousness' or if there is a causal association between the reported event and the vaccination.

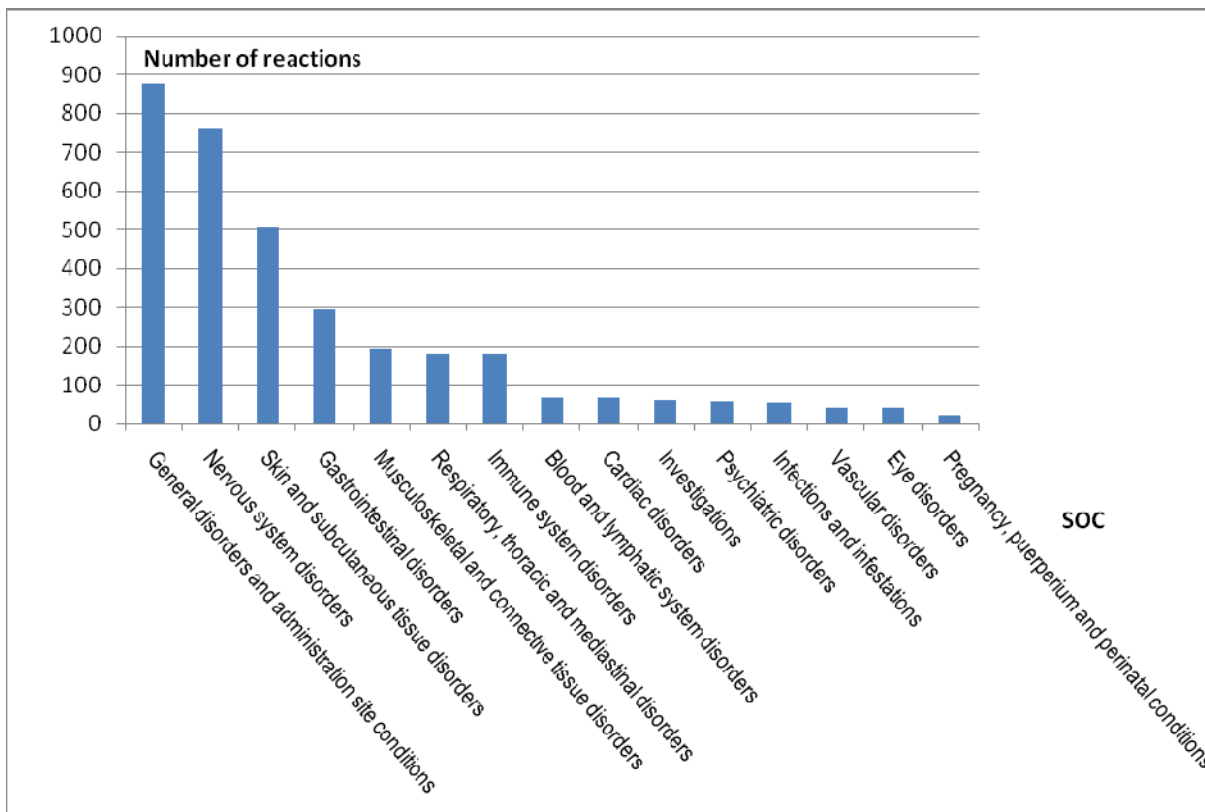


Figure 2. The most frequently reported suspected adverse reactions in each system organ class (n > 20) experienced by the patients.

In the reports received from Health Care Professionals, the most frequently reported suspected adverse reaction in each system organ class experienced by the patients were: general disorders and administration site conditions, nervous system disorders, skin and subcutaneous conditions , gastrointestinal disorders and musculoskeletal disorders.

Comments on certain types of reactions based on reports from Health Care Professionals

Allergic reactions

Various hypersensitivity reactions have been the most frequently reported suspected adverse events (distributed in several SOC's such as skin- , immune system- , gastrointestinal- and respiratory disorders). Allergic reactions which were not observed in clinical trials for the prototype vaccine have now been accounted for as adverse events for Pandemrix. This was also observed in the reporting from other countries in Europe. As a consequence additional information has been included in the product information (SmPC/PIL) for Pandemrix indicating that caution should be used when administered to persons with allergic disposition.

About one third of the reports (659/2150) received from Health Care Professionals involved allergic reactions, of which 163 reports were deemed as serious. The reactions occurred within short time after the vaccination. A total of 195 patients reported previously known allergy to substances, such as pollen, grass, drugs, egg, nuts, peanuts, fruit, fish or furred animals, etc. Sensitivity to egg was described in 46 reports, while 149 patients reacted against one or several other allergenic substances. Three reports on anaphylactic shock were received. One case had known egg allergy, one was allergic to various foods, including nuts, while the third case had no previous history of allergy.

In most cases which were deemed serious, the patients needed treatment with antihistamines, adrenaline and cortisone and in some cases also supervision in emergency room or were hospitalized. In all cases, the hypersensitivity reactions resolved completely within a short time.

The adverse events reported show that not only substances in the vaccine, such as egg cause hypersensitivity reactions, but also an overall allergic disposition seems to be of importance.

Table 1. Adverse reactions related to allergic reactions, reported by Health Care Professionals:

Reaction	Serious reactions	Non serious reactions	Total no of reported reactions
Anaphylactic reaction	44	6	50
Anaphylactic shock	3	0	3
Allergic reaction	36	85	121
Angiooedema	18	18	36
Oedema in mouth and throat	13	11	24
Lip swelling	2	12	14
Tounge oedema	3	3	6
Urticaria	18	144	162
Rash	4	70	74
Rash erythematous	4	20	24
Rash makulo popular	1	10	11
Dermatitis bullous	1	7	8
Erythema muliforme	0	7	7
Itching	2	79	81
Asthma	8	13	21
Status asthmaticus	1	0	1
Obstructive airways disorder	2	6	8
Dyspnea	1	5	6
Tachypnea	2	0	2
Total	163	494	659

Neurological reactions

A total of 769 neurological adverse events have been reported, of which 187 were classified as serious. The three most frequently reported neurological adverse events that have been reported throughout the observed time were dizziness, paresthesias and headache. As mentioned previously dizziness and paresthesias occurred predominantly in the context of allergic or vasovagal episodes. Paresthesias were also commonly reported together with symptoms suggestive of a local reaction at the injection site. Headaches commonly occurred with influenza like illness. Time to onset of symptoms was instantly to within minutes after vaccination; duration of symptoms was brief in the majority of cases. All of these events have been reported in clinical trials with the prototype vaccine and are labelled in the Summary of Product information (SmPC).

A total of 49 reports were received related to “sensory disturbances”, i.e. disturbances of smell, taste etc. or of sensing, of which only 6 reports were classified as serious. These were described as numbness, loss of sensation or burning sensation. Such disturbances were noted in arms, with extension to hand and fingers; legs and feet; and face. In several of the reports, there were associated “motor disturbances”, such as weakness and slurring of speech. Time to onset of symptoms ranged

from several hours to days after vaccination while duration of symptoms ranged from 1 day to several months after vaccination.

Seventeen cases of facial palsy or facial palsy like symptoms have been reported, of which 10 were classified as serious. Additionally, there were 3 reports on paresis of oculomotor nerves. Age range of those affected varied from 4 to 70 years of age. Time to onset ranged from 1 to 14 days while duration of symptoms ranged from several days to 4 weeks. Many of these cases have been evaluated by a health care provider, e.g. including lumbar puncture and a subset of those were treated with steroids. Taking all the reports received, the observed number of cases during the vaccination period is less than that expected compared to a period without vaccination.

There have been a total of 34 reports of convulsion, 25 of which were classified as serious. All but three cases involve subjects less than 19 years of age.

Five cases of stroke have been reported, including 3 events of cerebral infarction and 3 of cerebral haemorrhage. There is nothing to support a casual association between the vaccination and the reported cases of stroke.

There have been a total of 13 reports of Guillain-Barré syndrome (GBS). The age range of the patients varied between 5 to 82 years. All cases were assessed by neurologists and 12 of the 13 cases had documented diagnostic findings, either by CSF analysis or by electro neurography, consistent with GBS. Time to onset of symptoms ranged from 1 to 28 days, with approximately half occurring between 14 to 21 days. After assessment of the reports received, both from Sweden but also from other countries in Europe, the conclusion is that an association between the pandemic vaccines cannot be excluded. However, there is no reason to believe that the risk for GBS is any greater than associated with receipt of seasonal influenza vaccine.

Musculoskeletal disorders

A total of 205 reactions have been reported within this group of adverse events. The majority (119) was reported as musculoskeletal and joint pain (arthralgia (52) and myalgia (67)). Twenty three reactions were assessed as serious. The few reports on rheumatoid arthritis do not indicate that the vaccination would trigger autoimmune rheumatic disease.

Rejection of transplanted organs

Two cases have been reported, one fatal outcome after rejection of a heart transplant in a 67 year old man and one case of rejection of a transplanted kidney in a 17 year old girl. In the first case the vaccination may have contributed by triggering the rejection which probably was caused by insufficient immunosuppressive treatment. In the second case it is not clear whether the rejection reaction was a spontaneous event or whether vaccination contributed to the outcome.

There are no other cases reported, neither in Sweden nor in other countries within Europe. These two Swedish reports, however, lead to the recommendation which emphasizes that an adequate immunosuppressive treatment should be verified before vaccination of organ transplanted patients.

Death cases reported

A total of 27 fatal cases have been reported from Health Care Professionals after vaccination with Pandemrix. After investigation of all the cases it was concluded that an association with vaccination cannot be excluded in four cases. This is based on information on the medical background, the course of the disease and the results from autopsies.

Two new cases where an association cannot be excluded have been reported since the previous summary, published in January 15, 2010.

One of the new cases involved a woman (90-years) with antihypertensive medication. She became ill with vomiting and diarrhoea. Her general condition declined during the following two weeks. The cause of death was general organ failure (heart, kidney liver).

The other case concerns a man (70-years) who had a sense of weakness in the legs and difficulties in standing a few days after vaccination. Investigations showed pronounced numbness and impaired sense of touch in the legs. The cause of death was pneumonia. The case resembled of GBS although the symptoms were not quite typical.

Lack of efficacy after vaccination

The reporting and assessments of suspected adverse events also include reports on lack of efficacy after vaccination, where the patient has become ill with influenza within a timeframe where protection from the vaccine is anticipated.

Fourteen reports have been received on lack of efficacy with Pandemrix, of which lack of efficacy could not be excluded in 10 cases. One vaccinated patient, who fell ill with influenza, had a concomitant rejection of a bone marrow transplant and died. The cause of death was, however, not considered to be influenza. Four adult individuals (43- 63 year of age) fell ill 5 days to 4 weeks after vaccination. Three of the patients had chronic underlying diseases and lack of efficacy of the vaccine was not considered likely in two of the cases. Two pregnant women fell ill 5 days and one month after vaccination, respectively. Information on the number of dosages received is missing but lack of efficacy is likely.

Five cases were children (4-13 years of age) and two of these had an underlying serious disease. The children fell ill 4-20 days after the vaccination and one child with asthma had influenza with very severe-respiratory distress and needed intensive care.

The time for incubation with influenza A(H1N1) is normally 3 days – but may vary (1-7 days). It is most likely that in those cases when a short time has elapsed between the vaccinations and illness the person has already been infected. In light of the large amount of vaccinated individuals and the large extent to which the influenza has been spread these few reports would indicate that the vaccine is effective. Since Pandemrix is a split inactivated vaccine and without any viral infectious activity it cannot cause H1N1 infection.

Adverse reactions reported in children

As of April 16, 2010 about 6.1 million adult doses of Pandemrix have been administered according to preliminary data from the county councils to SMI. The data from SMI indicates that about 700 000 doses have been used in children 6 months - 12 years of age. Preliminary data also indicates that about 421 000 children have received a second dose of the vaccine.

About one third of the reports received from Health Care Professionals involved children (0-17 years of age). In about one fifth of the reports concerning children (1-7 years of age) the reactions have been classified as serious, i.e. the same proportion as the reports for all ages.

The most frequently reported serious adverse events in children, reported from Health Care Professionals, were neurological reactions (82) (e.g. febrile convulsions and syncope), immunological reactions (28) (e.g. anaphylactic reaction/allergic reactions) or general symptoms (26) (e.g. fever and influenza like illness).

The most commonly reported reaction was febrile convulsion (17; of which 16 cases involved children below 2 years of age). The febrile convulsions occurred in close association with the vaccination (the same day or the day after) and all subjects have recovered within a short time. Other frequently reported neurological reactions for children are convulsions and petit mal epilepsy (26), mostly in children older than 3 years of age where the relation to vaccination may be difficult to judge. Isolated cases with other reactions have also been reported, i.e. GBS (2), abducens paresis (1) and weakness in limbs (1).

The most commonly reported immunological reactions have been anaphylactic/allergic reactions. Individual reports on arthritis/rheumatoid arthritis and idiopathic thrombocytopenia have also been reported.

The majority of the adverse events reported for children were known and solicited

Adverse reactions in pregnant women

As of April 16, 2010 preliminary data from SMI more than 30 000 pregnant women are estimated to have been vaccinated with Pandemrix. A total of about 50 reports of suspected adverse events in relation to vaccination of pregnant women have been received from Health Care Professionals. The comprehensive overview demonstrates that the pattern of adverse events in pregnant women is the same as previously and no new or unexpected events were observed.

A-total of 31 women experienced miscarriages according to 16 reports from Health Care Professionals and 15 reports from Consumers in temporal association with the vaccination with Pandemrix, 23 cases in the first trimester of the pregnancy and 8 in the second. In addition, 7 women reported intrauterine foetal deaths (from gestational age week 24). In two women the intrauterine foetal death occurred in the gestational week 24, in two women in week 28 and 33 respectively and for three women at full time pregnancy. In three cases the follow up investigation indicates that the vaccine is not associated with the foetal deaths, for the other four cases a causal association has not been established.

The evaluation of the specific reports does not give reason to conclude that the vaccine has caused the miscarriages. The assessment of the individual cases of intrauterine foetal deaths, in 6 cases through autopsy, has not supported any causality (that the vaccine should have been the cause) of the foetal deaths.

Although these reports do not include all actual cases after vaccination, due to known underreporting of adverse events, the number probably is considerably lower than what would be expected from statistics regarding miscarriages or intrauterine foetal deaths. Miscarriages may occur in 10-15% of all early verified pregnancies and intrauterine foetal deaths occurred at a size of 3 cases per 1000 new born babies in 2007.

In Europe as a whole at least 220 000 pregnant women have been vaccinated with pandemic vaccines, of which a great number with the same vaccine (Pandemrix) as used in Sweden. A summary and an assessment of all known reports of miscarriage or intrauterine foetal death within the EU have not given any cause to suspect that pandemic vaccination would increase such a risk.

In conclusion, a large number of pregnant women have been vaccinated in Sweden at different stages of the pregnancy. The proportionally low number of reports and with no defined risk profile this would indicate that the vaccination with Pandemrix does not increase the risk for miscarriage or intrauterine foetal death. Similar conclusions have been drawn from reports in other European countries for Pandemrix and other pandemic vaccines.

Experience from other countries in Europe

The European Medicines Agency (EMA) has continuously published summaries on suspected adverse events for Pandemrix in Europe. In view of the estimated number of vaccinated individuals, 30.1 million people, the conclusion is that the reports do not give evidence that new, previously unknown adverse events have occurred, with the exception of allergic reactions. The risk/benefit balance therefore remains positive.

An expert group at EMA have evaluated and assessed some possible signals of adverse events. One important issue has been the rare condition of GBS. The conclusion was that a somewhat increased risk after pandemic vaccination cannot be excluded but there is no reason to believe that the risk for GBS is greater than compared to vaccination with seasonal influenza vaccine. Research studies are ongoing to evaluate if there is an associated risk and in that case how big the increase in risk is.

Research studies in Sweden

There are two follow-up studies on going in Sweden including 1.6 million vaccinated individuals in order to measure, in a more controlled way the occurrence of serious adverse events which have led to contact with medical care. This will be studied both as a whole and in some subgroups such as vaccinated pregnant women, children, and patients with immunological disease or organ transplanted patients etc. The preliminary results from these studies will be available some time in autumn 2010. The results will enable us to further evaluate the safety of the pandemic vaccine Pandemrix.

Experience from Consumer reporting

The possibility for consumers to report suspected adverse events to MPA was initiated in June 2008. During the first year until the mass vaccination with Pandemrix only a few reports were received, they could be counted in hundreds. As of the beginning of February 2010 more than 2000 reports were received from consumers, via the electronic service on the MPA's website, including a total of more than 7200 suspected adverse reactions of Pandemrix.

Most of the consumer reports, about one third, concern adults (18-65 years of age). The majority of the other reports concern children and adolescents up to 18 years of age.

Less than 100 reports have been sent from elderly people (>65 years). Women dominate in consumer reporting, consistent with the pattern for reporting of suspected adverse events in common.

About one fourth of the rapporteurs indicate that the adverse reaction has lead to contact with Health Care Professionals and an equal proportion indicates that the adverse events have required some kind of treatment. At the time for their report of an adverse event of Pandemrix more than 50% have indicated that symptoms still remain.

The most frequent reactions reported from consumers are influenza like symptoms, such as fever, headache musculoskeletal and joint disorders, cough, fatigue, chills, nausea, vomiting, diarrhoea, malaise or abdominal pain. These symptoms have been reported by around 1500 individuals. Apart

from that about 330 individuals have reported on influenza like illness, e.g. fever in combination with some of the above mentioned influenza like symptoms.

Local reactions at the injection site of vaccination i.e. pain, swelling and rash are also frequently reported for about 350 cases, whereas what is understood as more severe pain in the vaccinated arm have been reported by almost 400 consumers.

In figure 3 the most frequently reported adverse events from consumers are shown.

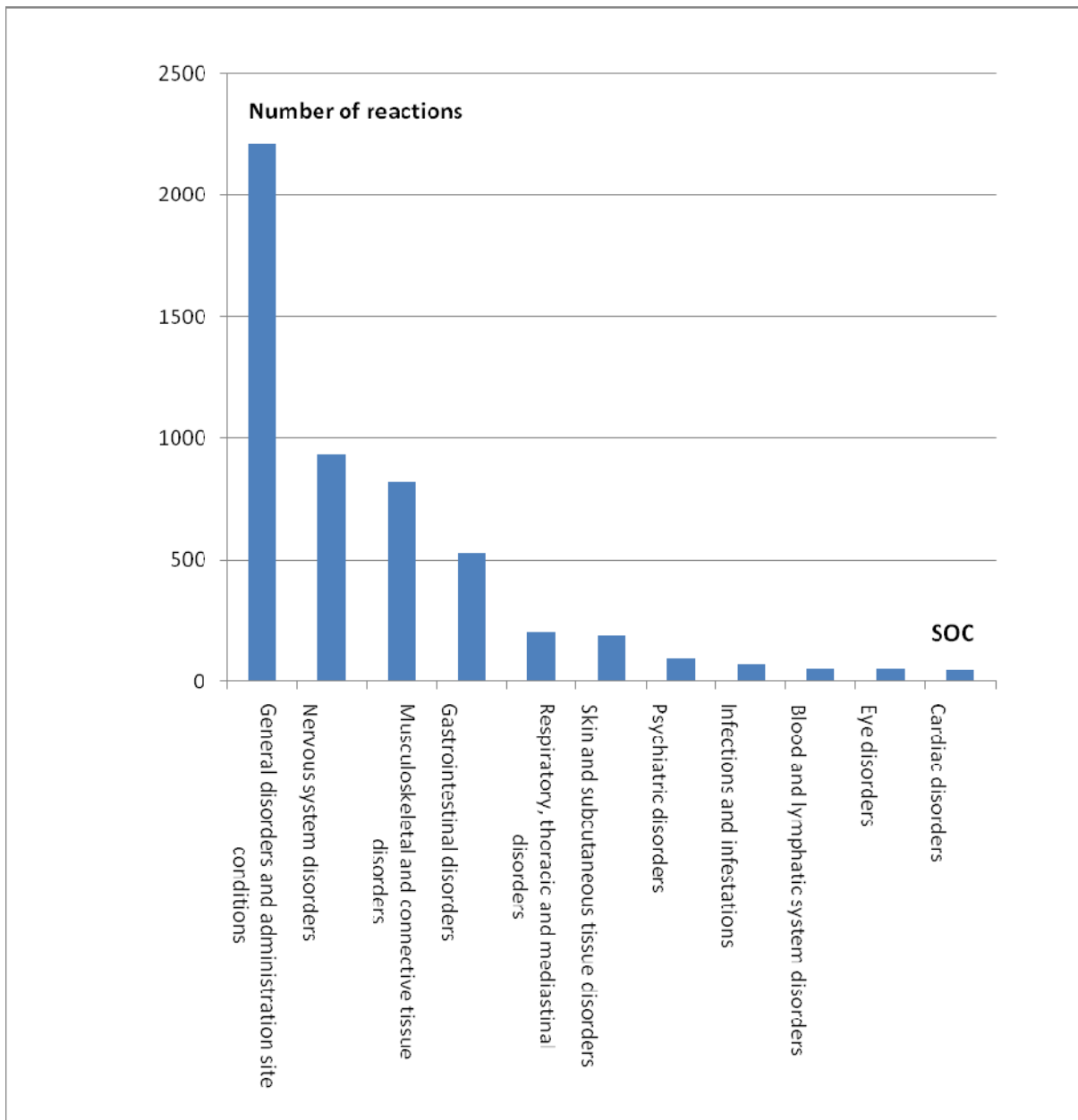


Figure 3. The most frequently reported suspected adverse reactions in each SOC (n > 20) reported by Consumers during October 2009 –beginning of February 2010.

A majority of the suspected adverse events have been reported by both Health Care Professionals and Consumers. Thus, the consumer reports have contributed to the conclusions summarised for each area of focus as presented above for reports from Health Care Professionals.

The brief description in the consumer reports do not always allow that *allergic reactions* are distinguished from other adverse events, but 14 reports on hypersensitivity reactions of which one is an anaphylactic shock have been reported. 41 individuals describe that they have had hives and 13 reports that they have had asthma like symptoms in association with the vaccination.

Commonly reported *neurological adverse events* after vaccination with Pandemrix, and of which a majority have been transient, apart from headache also report on dizziness (196), loss of sensation or sensory disturbances (147) (most often in the vaccinated arm but also in other extremities), change in taste (22), migraine (21), facial palsy (6) and convulsions (9) (of which a few were febrile convulsions).

About Facialis pares

Facial palsy is a unilateral weakness/paralysis of facial muscles. It can be caused by damage to the facial nerve or an injury of the brain. The cause of peripheral facial palsy, Bell's palsy, is in most cases unknown but may be caused by certain infections, e.g. Borrelia, varicella-zoster virus or herpes simplex virus. It also occurs in women during pregnancy. Most of the cases resolve within a few months without residual symptoms. In Sweden 50 individuals per week are diagnosed with facial palsy.

Joint-ant muscle disorder is as already mentioned one of the most frequently reported adverse events. A few reports on *lack of efficacy* have been received, e.g. onsets of influenza but without clear information on whether the influenza illness has been verified or not. Fifteen cases of miscarriages have been reported. One consumer report was received on *organ transplant rejection* also reported from the Health Care Professionals. The two *deaths* that had been reported by consumers had also been reported from Health Care Professionals.

In conclusion, the consumer reporting of adverse events reflects the already known risk profile of Pandemrix. Individual reports on suspected adverse events, which were not known for Pandemrix, have been received. An assessment of causality between the adverse event and vaccination is not always possible. Further systematic processing of the consumer reports is ongoing.

Summary

In view of the great number of vaccinated individuals in Sweden during the pandemic period and the assessment of the reported suspected adverse events the conclusion is that vaccination with Pandemrix is reassuringly safe. Now when the mass vaccination has ceased, it is important to follow up the experiences by means of research studies.

In Sweden as well as in other European countries studies are initiated to analyse the occurrence of adverse events which has led to contact with health care professionals, especially the rare and serious reactions, both totally and in subgroups of vaccinated individuals, as well as studies of the effectiveness of the vaccine to protect against influenza.

Acronyms

ADR	Adverse Drug Reaction
GBS	Guillain-Barré Syndrome
EMA	European Medicines Agency
MPA	Medical Products Agency

PIL	Patient Information Leaflet
SMI	Swedish Institute for Infectious Disease Control
SmPC	Summary of Product Characteristics
SOC	System Organ Class