EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 January 2010
EMA/39205/2010
Patient Health Protection

Seventh pandemic pharmacovigilance weekly update

This update has been prepared by the European Medicines Agency to provide a summary of the adverse drug reactions reported after the use of centrally authorised pandemic vaccines and antivirals. It also provides information on the evolution of the H1N1 pandemic, an estimate of how many doses of vaccines and antivirals have been distributed or administered in Europe, and other available information on the benefits and risks of the vaccines and antivirals. The centrally authorised pandemic medicines concerned by this update are the vaccines Celvapan, Focetria and Pandemrix and the antiviral Tamiflu.

This update includes reports of *suspected* reactions that were observed after the medicines were administered. This does not mean that these reactions were caused by the medicines. They could be a symptom of another illness or they could be associated with another product taken by the patient. Healthcare professionals are actively encouraged to report events occurring after vaccination.

It should be noted that, due to differences in the numbers of people receiving each vaccine, the number of reports shown for the three different vaccines cannot be used to compare the safety or the benefit-risk balance of the vaccines.

As a single patient may experience several reactions that will be included in a single report, the total number of reactions may not be equal to the total number of patients. In addition, as some patients have received two doses of the vaccines, the total number of doses administered is not necessarily equal to the total number of patients vaccinated.

Reports are collected on a continuous basis in EudraVigilance. EudraVigilance is a database and management system managed by the European Medicines Agency for the collection and evaluation of reports of suspected adverse drug reactions to medicinal products. It allows the transfer of reports from national regulatory agencies and marketing authorisation holders to the European Medicines Agency, and the early detection and monitoring of possible safety signals in relation to reported adverse reactions. This update includes reports received by EudraVigilance up to 10 January 2010. The graphs represent aggregated data related to the European Economic Area (EEA) only, and provide an overview of the reporting situation in the EEA. The updated safety information also considers worldwide cases from EudraVigilance.

A list of the most frequently reported suspected adverse reactions is presented for the organ systems with the largest number of reports.

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Key messages

As of 18 January 2010, in the EEA, at least 33.9 million people, including at least 258,000 pregnant women, had been vaccinated with one of the three centrally authorised vaccines (Celvapan, Focetria or Pandemrix). When the information available for the nationally authorised vaccines is included, the total rises to at least 38.3 million people. Some of these have received two doses of a vaccine, but the percentage varies across countries.

The vast majority of the adverse reactions that had been reported as of 10 January 2010 are considered to be non-serious.

After evaluation of the second periodic update safety reports submitted by the marketing authorisation holders for Celvapan, Focetria and Pandemrix, it was concluded that the benefit-risk balance of the pandemic vaccines and antivirals being used for the current H1N1 influenza pandemic continues to be positive. Additional data and reviews have been requested regarding selected suspected adverse reactions.

A review of reports of eye disorders was performed for the three centrally authorised vaccines and included 31 reports for Celvapan, 79 reports for Focetria and 190 reports for Pandemrix. For all vaccines, a large number of eye reactions were seen in the context of an allergic reaction or as part of a flu-like disease. The most common reactions were blurred vision and symptoms of eye irritation. The great majority of the reported reactions were considered non serious and there remains no evidence of any direct adverse effect affecting the eyes or the vision. Specific findings are discussed in the updated safety information for each vaccine.

For further information on the known adverse reactions included in the authorised product information for the centrally authorised pandemic vaccines (Celvapan, Focetria and Pandemrix) and the antiviral (Tamiflu), visit the Agency's pandemic influenza (H1N1) website.

For information regarding products authorised at a national level, please contact the relevant national competent authority (see regulatory bodies in the European Union for links).

Pandemic information

According to the European Centre for Disease Prevention and Control (ECDC)[1], as of 15 January 2010, a total of 2,271 deaths from pandemic influenza had been reported in Europe and the European Free Trade Association (EFTA) countries since April 2009. While most of the deaths to date have been in Western Europe, an increasing number of deaths are being reported from Central and Eastern Europe. The cumulative number of fatal pandemic (H1N1) cases reported worldwide has now passed 11,900. However, because of the lack of laboratory confirmation and under-reporting, among other factors, this is likely to be a gross underestimate of the true number of fatalities associated with the pandemic.

In its weekly influenza surveillance overview of 15 January 2010, the ECDC concluded that Poland reported high intensity of influenza-like illness (ILI) or acute respiratory infections (ARI). Six countries and the UK (Scotland) reported medium intensity of ILI/ARI, while all of the other countries reported low intensity. Eight countries reported an increasing ILI/ARI trend, while all remaining countries reported either stable or decreasing activity. While the proportion of influenza-positive sentinel samples continues to decline (19% positive), the 2009 pandemic influenza A(H1N1) virus still accounts for nearly all of the subtyped viruses in sentinel ILI/ARI and patients with severe acute respiratory infection (SARI). The number of SARI cases, measured by week of onset, continues to decline. Of the 181 reported SARI cases, 89 (49%) were known to have required intensive care unit admission.

[1] For the latest reports click here.

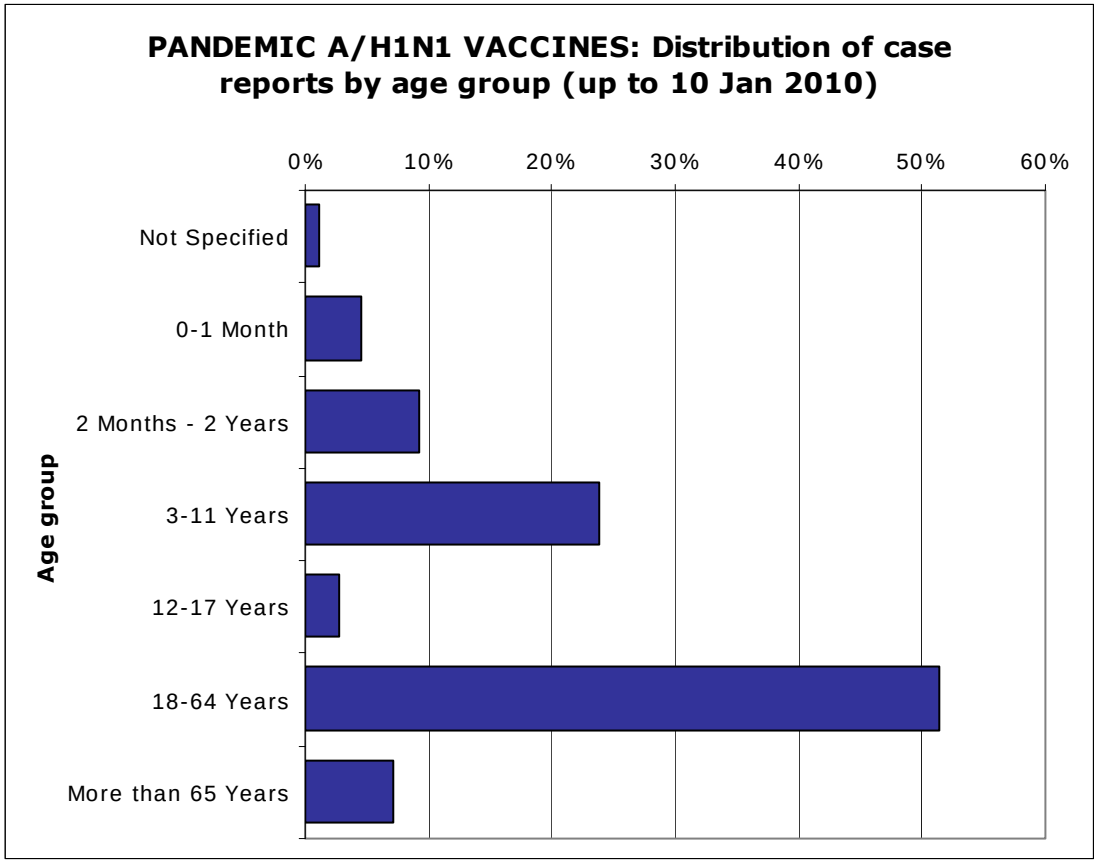
Detection of 2009 pandemic influenza A(H1N1) viruses that are resistant to oseltamivir remains sporadic. Of 1260 viruses reported, 34 (2.7%) were resistant.

See the ECDC pandemic website, its current risk assessment and its weekly executive update for additional information.

In its weekly update dated 15 January 2010, the World Health Organization states that, as of 10 January 2010, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 13,554 deaths.

Overview of centrally authorised vaccines

As of 10 January 2010, a total of 12,057 case reports had been received by EudraVigilance since the authorisation of the three centrally authorised vaccines. This represents an increase of 408 reports compared with the previous update, reflecting the increase in the number of people vaccinated. The graph below displays the age distribution of patients having experienced an adverse reaction reported to EudraVigilance. The percentages shown in the graph reflect the age distribution of the vaccinations, based on the available information on the age distribution of vaccinated people in a limited number of Member States, with the exception of the 0-1 month age group, as this group also includes reports of pregnancy outcomes.



Data available on 18 January 2010 from Member States and from the vaccine's marketing authorisation holders indicate that at least 112.1 million doses had been distributed and at least 33.9 million patients had been vaccinated with one of the three centrally authorised vaccines in the EEA. From the limited information received from seven EEA countries by 18 January 2010, at least 258,000 pregnant women had been vaccinated.

When the information available for the nationally authorised vaccines is included, at least 116 million doses have been distributed, with at least 38.3 million people (including at least 292,000 pregnant women) vaccinated in Europe.

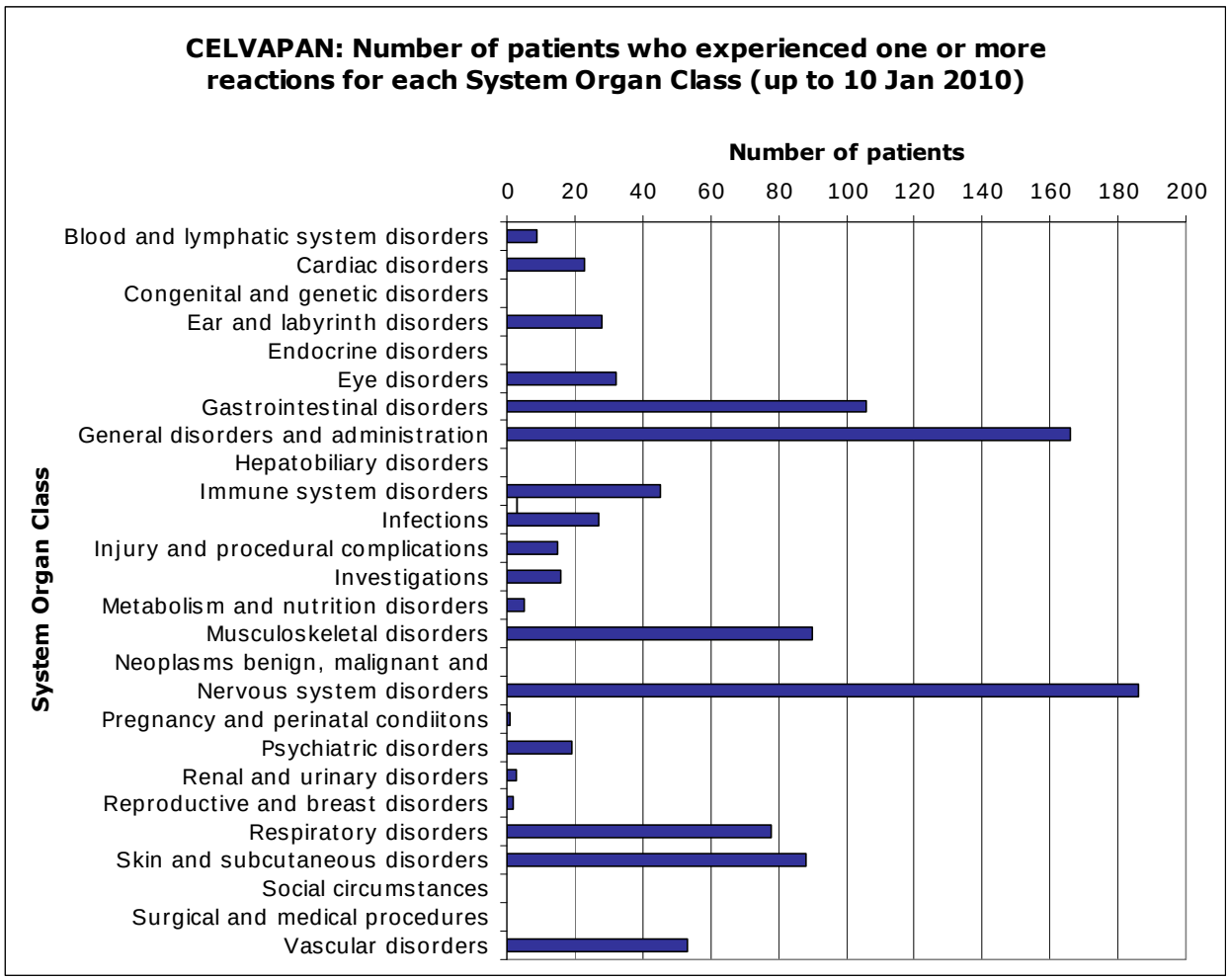
Since authorisation, nine cases labelled as medication error were received in EudraVigilance. Medication error reports have been reviewed to identify possible systematic errors that could be corrected. All cases involved Celvapan and Pandemrix. In six cases, the patient received one of the vaccines (generally Celvapan) for the first dose and the other vaccine for the second dose, but the interval between the two doses is not always documented. One patient received both vaccines on the same day, one patient had not remembered having already received an H1N1 vaccination and one report is not assessable. No adverse reactions were reported in association with these medication errors. The product information for both medicines states that the H1N1 vaccines are not interchangeable due to the lack of data about the consequences of using different vaccines for the two doses. The ability to trace the vaccines administered to each patient has also been stressed at the time of authorisation of the vaccines.

A list of specific topics discussed in previous updates is included in the Appendix.

Celvapan

As of 10 January 2010, a total of 393 reports had been received by EudraVigilance (an increase of 30 reports since the previous update). According to the information provided by the company[2] and Member States, a total of 6,006,000 doses had been distributed to EEA countries up to 29 December 2009. It is estimated that at least 480,000 patients have been vaccinated with Celvapan in the EEA.

[2] As stated by the marketing authorisation holder in the simplified periodic safety update report (S-PSUR) dated 23 December 2009.



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequent suspected adverse reactions in each system organ class (SOC) experienced by patients since the authorisation of the vaccine were:
  - Nervous-system disorders: headache, dizziness, syncope, paraesthesia, hypoaesthesia;
  - General disorders and administration-site conditions: pyrexia, chills, malaise, fatigue, asthenia, influenza-like illness, feeling hot, chest discomfort, injection-site pain;
  - Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, oral paraesthesia;
  - Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness;
  - Skin and subcutaneous conditions: hyperhidrosis, pruritus, urticaria, rash, erythema;
  - Respiratory disorders: cough, oropharyngeal pain, dyspnoea;
  - Vascular disorders: pallor, flushing, hypotension;
  - Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
  - Eye disorders: vision blurred;
  - Ear and labyrinth disorders: vertigo.

Updated safety information

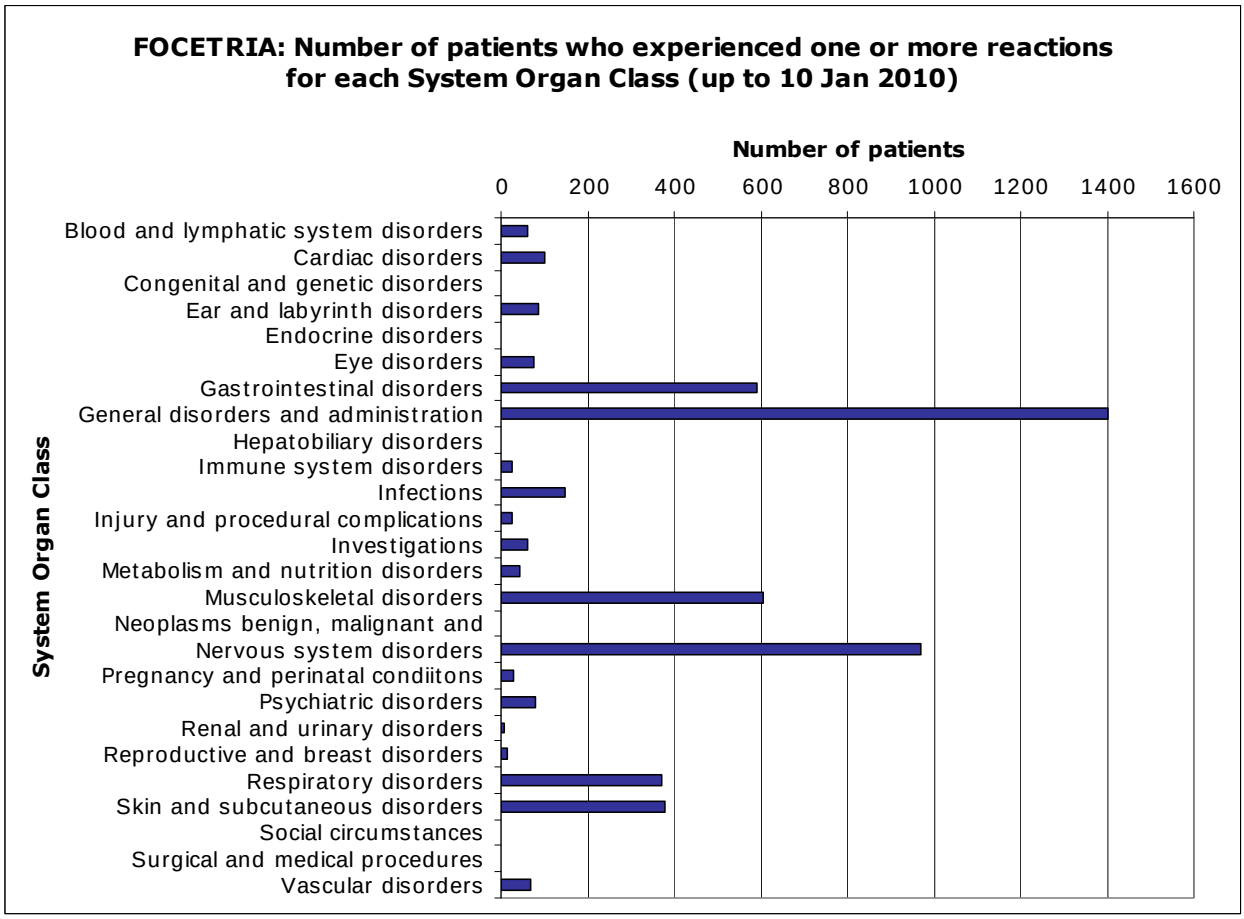
- The most frequently suspected adverse reactions reported in children since authorisation included hypersensitivity, vomiting, pyrexia, syncope, dizziness, pallor, nausea, headache, rash, cough, chills, hyperhidrosis, medication error and vision blurred.
- Since the last update, no fatal cases have been reported from the EEA in people vaccinated with Celvapan.
- A review of reports of eye disorders has been performed. A total of 31 distinct cases with patients' median age of 36.5 years have been received. The most frequently reported reaction has been blurred vision (ten cases). Other reported reactions included eye swelling or eye oedema and pain (two cases), conjunctivitis (two cases) and single reactions of eye rolling, eye stinging, mydriasis, photophobia, visual impairment and eye tiredness. One third of the patients had a medical history of asthma or allergies. In the majority of the reports, only limited information was available but the outcome of the event was reported as resolved. The eye disorders reported in vaccinated patients do not point to a common clinical presentation that would indicate an effect of Celvapan on the eye.

  Three moderately well documented reports concerned pregnant women. One case describes the occurrence of vasovagal reaction with spots before the eyes, which may be associated with the vaccination rather than the vaccine itself. Another case concerns a woman who had an allergy after previous vaccination and experienced eye swelling and hypersensitivity after the vaccination with Celvapan. The product information states that hypersensitivity reactions have been reported following Celvapan vaccination and caution is needed when administering the vaccine to persons with a known hypersensitivity. The third case describes blurred vision in a woman with hypertension not related to the vaccine. All the three patients recovered.

  One case described the occurrence of Amaurosis fugax (transient monocular visual loss) and visual loss in a 23-year-old male two days post vaccination. The case however contains limited information and no causality assessment can be made.
- Since authorisation, five cases have been received describing paresis (two cases), paralysis (one case), monoplegia (one case) and diplegia (one case). The report of paralysis concerned a patient who experienced vertigo, leg weakness and falls the day of the vaccination. No investigation was made regarding the cause of the symptoms and it is therefore not known if the term “paralysis” reflects a muscle weakness or the inability to move the legs due to a neurological disorder. Monoplegia was reported for a patient experiencing a transient but severe weakness of the leg in which the vaccine was administered. Paresis concerned a patient experiencing severe leg weakness with symptoms of an undefined illness who recovered after 10 days, which may indicate viral infection. Two poorly documented cases reported transient paresis in finger and arms and a transient muscular weakness and paralysis without further information (this case was coded as diplegia). No causal relationship with the vaccine was identified, but this issue will be kept under close monitoring.
- Since the last update, a report has been received concerning a 64 year-old male who experienced acute pancreatitis approximately seven days after each of his two doses of Celvapan. Although this recurrence could suggest a relation with the vaccine, the patient's medical history included a previous episode of acute pancreatitis less than two years earlier and some of the medications he was taking at the time of the vaccination may be associated with the occurrence of pancreatitis. There is therefore no evidence that the event was causally associated with Celvapan, but this issue will be closely monitored. Pancreatitis resolved each time with analgesics and diet.

Focetria

As of 10 January 2010, a total 2,755 reports had been received by EudraVigilance (an increase of 49 reports since the previous update). Data available on 18 January 2010 from Member States and from the company[3] indicate that at least 38.7 million doses of Focetria had been distributed in the EEA, and at least 7.6 million patients had been vaccinated.



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequent suspected adverse reactions in each SOC experienced by patients since the authorisation of the vaccine were:
  - General disorders and administration-site conditions: pyrexia, fatigue, injection site pain, influenza-like illness, malaise, chills, injection-site erythema, hyperpyrexia, injection-site swelling, chest pain, injection-site pruritus, pain, asthenia, feeling cold, injection-site haematoma, feeling hot;
  - Nervous-system disorders: headache, dizziness, paraesthesia, tremor, dysgeusia, somnolence, syncope, hypoaesthesia, presyncope, convulsion, migraine;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, neck pain, muscular weakness, muscle spasms, musculoskeletal pain, back pain, sensation of heaviness, rheumatoid arthritis;

[3] As stated by the marketing-authorisation holder in the S-PSUR dated 8 December 2009.

- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Skin and subcutaneous conditions: rash, pruritus, erythema, urticaria, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, swelling face, rash generalised;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, pharyngitis, herpes zoster;
- Cardiac disorders: palpitations, tachycardia, atrial fibrillation, cyanosis;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Psychiatric disorders: listless, insomnia;
- Eye disorders: eyelid oedema, visual impairment; eye irritation, eye swelling.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included pyrexia, headache, hyperpyrexia, vomiting, cough, nausea, abdominal pain, injection-site pain, diarrhoea, myalgia, fatigue, influenza-like illness, rash, dyspnoea and malaise.
- Since the last update, two new cases of death have been received in EudraVigilance. They concerned a 65 year-old male with renal failure who died after experiencing chest pain two days after the vaccination, and a two-year old child who died from an unknown cause at an unknown time following the vaccination. Both cases are from outside the EEA.
- A review of 'eye disorders' at SOC level was performed. A total of 79 reports were retrieved, among which one third concerned non-serious cases with medical history of asthma or allergy. Excluding these cases, a total of 52 cases were reviewed. Seventeen of these cases were considered serious and 35 non-serious.

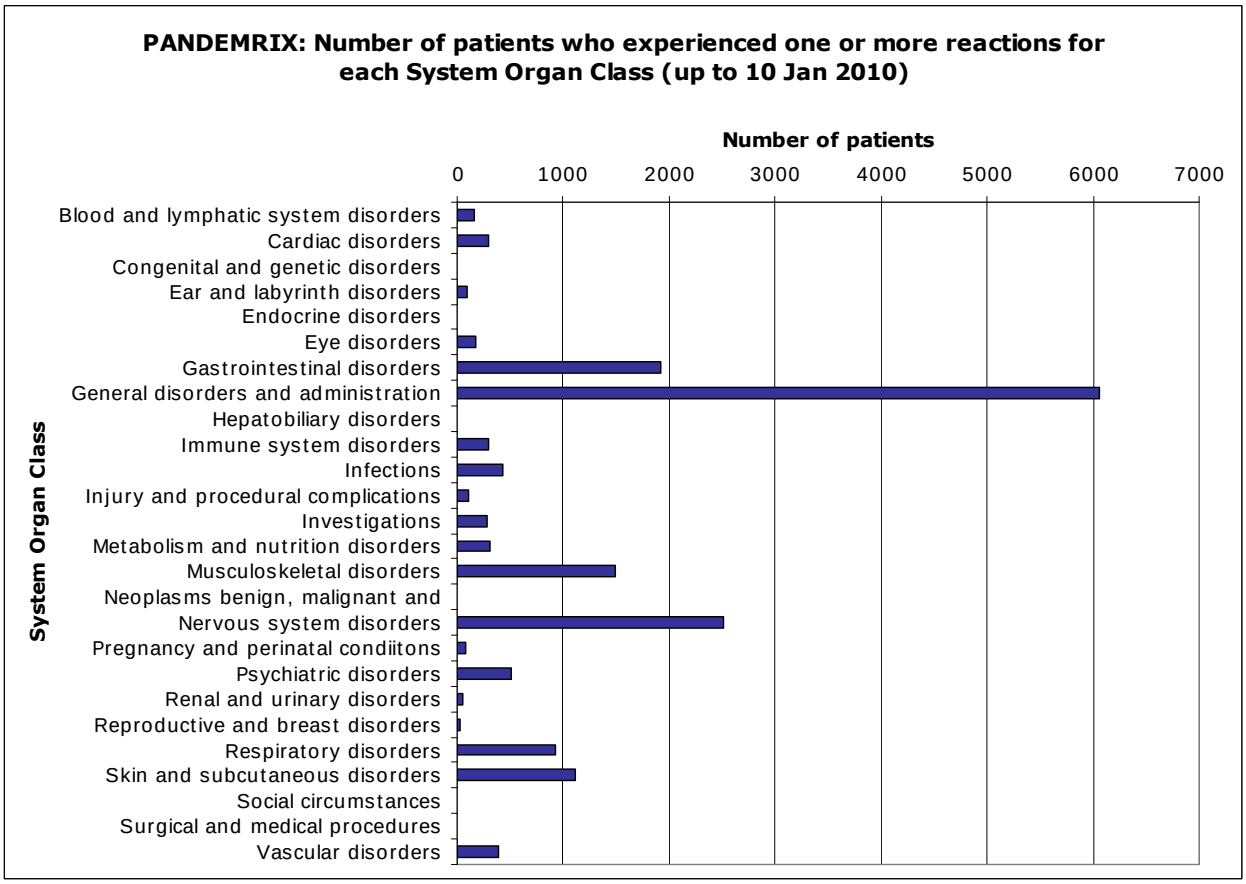
  Amongst the cases considered serious, four cases were reported with neurological reactions in children who were aged eight months, four years and five years and in one the age was not specified. In addition, five adult cases were reported with neurological symptoms. They included a blurred vision which developed into lateral neuritis, diplopia alone, diplopia and left unilateral oculomotor paresis accompanied by muscular weakness of the upper and lower limbs (a diagnosis of Tolosa-Hunt syndrome was made), diplopia with deficiency of the right seventh cranial nerve and weakness and hypoesthesia of the lower limbs (Guillain-Barré syndrome was ruled out), and a facial paresis with eyelid ptosis. The outcomes were reported as recovery in three cases, an unknown outcome at the time of reporting, and, for the patient with Tolosa-Hunt syndrome, an absence of recovery one month after the occurrence of the syndrome. This patient was suffering from underlying conditions such as chronic renal failure, diabetes mellitus and peritoneal dialysis at the time of vaccination. The remaining serious cases included occurrence of eyelid oedema (five cases), blurred vision (three cases), and photophobia (one case) with the majority of patients having recovered at the time of reporting.

  The cases considered non-serious included a decreased or abnormal vision (eight cases), eyelid oedema (five cases), eye pain (six cases), inflammation of the eyes (four cases), blurred vision (four cases), tearing eyes (three cases), and single reports of itching eyes, diplopia, eye disorder, dry eyes, and visual field defect or disturbance.

The review of the cases did not identify any common pattern of clinical presentations that would indicate a relationship with the vaccine outside the context of an allergic reaction.

Pandemrix

As of 10 January 2010, a total of 8,909 reports had been received by EudraVigilance (an increase of 329 reports since the previous update). Data available on 18 January 2009 from Member States and from the company[4] indicate that at least 67 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 24.4 million patients have been vaccinated.



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequent suspected adverse reactions in each SOC experienced by patients since the authorisation of the vaccine were:
  - General disorders and administration-site conditions: pyrexia, hyperpyrexia, injection-site pain, fatigue, influenza-like illness, malaise, chills, injection-site swelling, injection site erythema, pain, oedema peripheral, injection-site induration, asthenia, injection-site inflammation;
  - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, syncope, hypoaesthesia, crying, febrile convulsion, lethargy, convulsion, tremor, loss of consciousness, poor quality sleep;

[4] As stated by the marketing-authorisation holder in the S-PSUR dated 21 December 2009.

- Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, lip swelling, swollen tongue, dry mouth, abdominal discomfort, hypoaesthesia oral, lower abdominal pain;
- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, back pain, limb discomfort, musculoskeletal pain, neck pain, muscle spasms;
- Skin and subcutaneous conditions: rash, erythema, urticaria, hyperhidrosis, pruritus, rash generalised, angioedema, swelling face, cold sweat, rash erythematous, dermatitis allergic, rash macular;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, rhinorrhoea, asthma, wheezing, epistaxis, tachypnoea, pharyngeal oedema, throat tightness, bronchospasm, sneezing;
- Psychiatric disorders: listless, insomnia, tearfulness, sleep disorder, restlessness, nightmare;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, herpes zoster;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, hot flush, peripheral coldness;
- Metabolism and nutrition disorders: decreased appetite, oligodipsia;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction.

Updated safety information

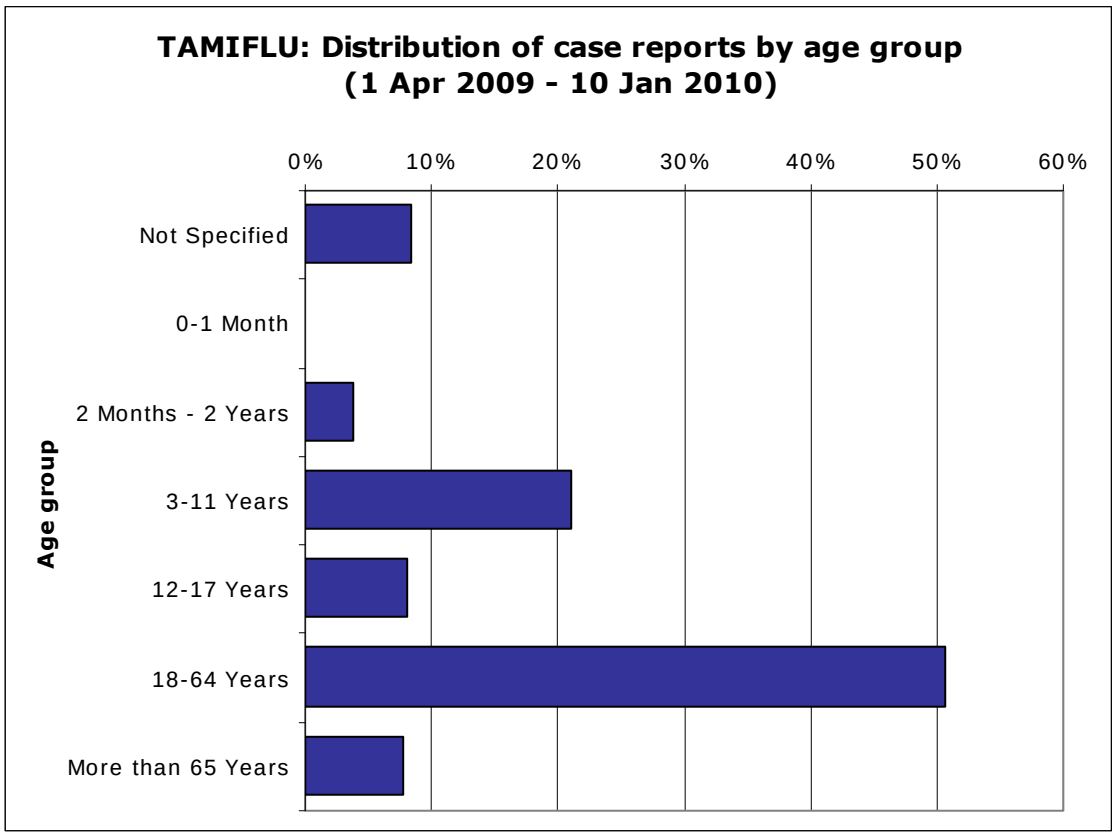
- Since the last update, five new fatal cases from the EEA have been received, including three reports describing patients aged 71 years, 91 years and 97 years with underlying risk factors such as hypertension and cardiac insufficiency, one poorly documented report of a sudden death, and one report concerning a 70 year-old patient who was reported to have died from an anaphylactic shock. However, preliminary investigation suggest that existing cardiac problems played an important role in the death. The result of the autopsy has been requested.
- The most frequently reported suspected adverse reactions in children since authorisation were pyrexia, hyperpyrexia, vomiting, injection-site pain, headache, diarrhoea, cough, fatigue, rash, decreased appetite, abdominal pain, nausea, malaise, listlessness, somnolence, injection-site erythema, injection site swelling, crying, influenza-like illness, dyspnoea, pallor and pain in extremity.
- Since authorisation, 31 reports of facial palsy (or Bell’s palsy) have been received in EudraVigilance, twenty of which were considered serious and 16 occurred in the first three days after vaccination. The available information indicates that the paresis associated with facial palsy resolved after a few days (completely in 10 cases and partially in three cases). According to literature data concerning the general population, Bell’s palsy occurs more frequently in adults than in younger individuals, and this age preference is reflected in the cases reported to EudraVigilance. Data from the United Kingdom report Bell's Pasly incidence as 12 per 100,000 persons and per year in patients below 17 years old and up to 45 per 100,000 persons and per year in older patients. Given the very large number of vaccinated patients, there remains no evidence that the vaccine is associated with facial palsy.

- A review of 'eye disorders' was performed and found 190 cases reported to EudraVigilance. The reactions reported varied very widely, expanding over the full range of eye signs and symptoms. In 124 of these cases, the reaction type was part of a broader clinical presentation that provided alternative explanation, such as an anaphylactic reaction, influenza-like illness or cold, or had a suitable alternative cause (such as cardiovascular accident or neurological event). The remaining 66 cases included 24 paediatric cases. The clinical presentation in the majority of these cases was related to an allergic reaction, a neurological event or an influenza-like disease and not to an adverse effect of the vaccine.
- Eight cases of photophobia have been received. They include two children and six adults aged from 28 to 51 years. Reports in children are seen in the context of influenza or a cold with vomiting and fever. Most of the reports in adults also include headache, fever or influenza-like disease. There is no reason to believe that the photophobia was directly induced by the vaccine.

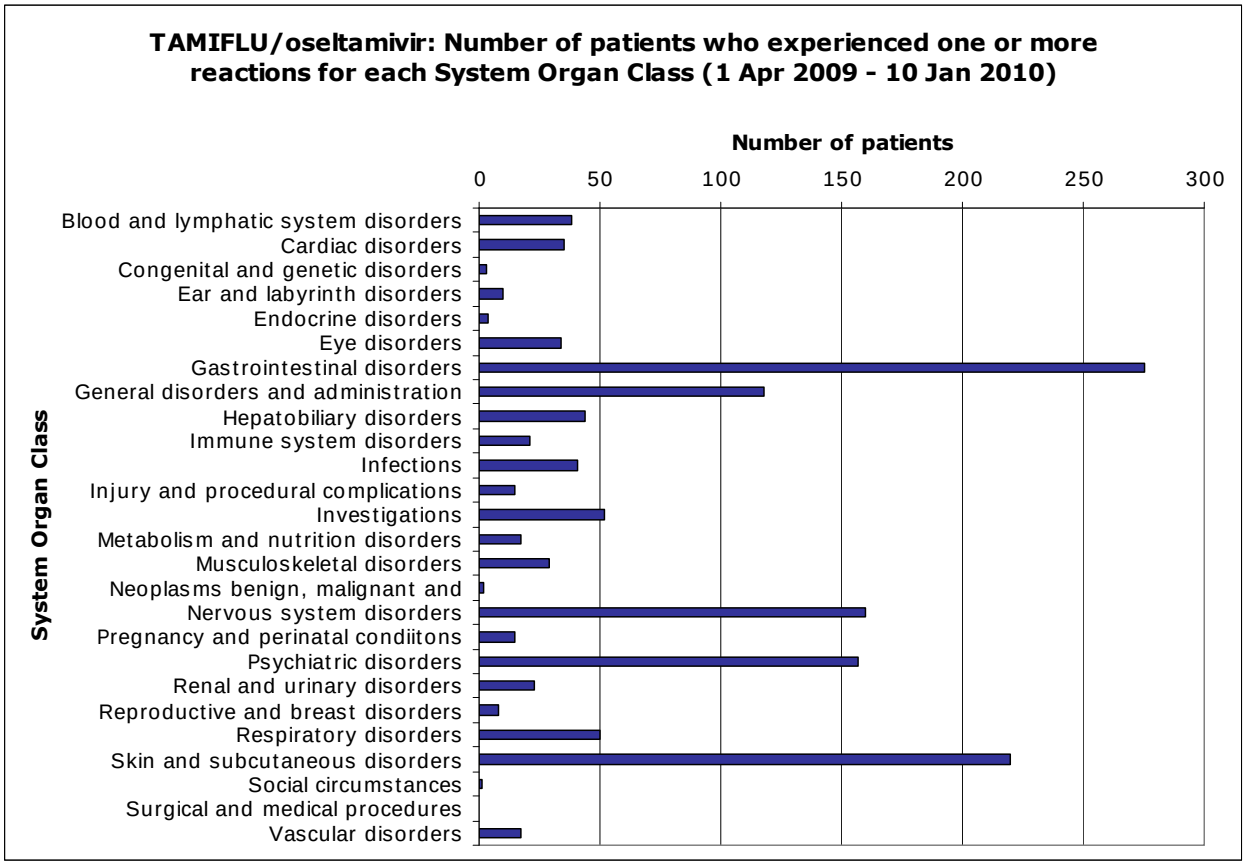
Antiviral medicines

Tamiflu (oseltamivir)

From 1 April to 3 January 2010, a total of 904 reports worldwide were received by EudraVigilance (an increase of 69 reports since the previous update). The graph below displays the age distribution of patients having experienced an adverse reaction reported to EudraVigilance.



According to information received from the marketing authorisation holder dated 23 December 2009, exposure to Tamiflu is estimated to be 16,360,991 patients during the pandemic period of 1 May to 30 November 2009[5].



Distribution of adverse reactions by system organ class

- The adverse reaction reports received from the EEA are consistent with the safety profile described in the product information. The most frequently reported suspected adverse reactions experienced by patients in each SOC were as follows:
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, mouth ulceration, lip swelling, swollen tongue, haematemesis;
  - Skin and subcutaneous conditions: rash, rash generalised, urticaria, swelling face, Stevens-Johnson syndrome, rash erythematous, pruritus, erythema, rash pruritic, rash macular;
  - Nervous-system disorders: headache, convulsion, paraesthesia, dizziness, tremor, cardiovascular accident, syncope, nystagmus;
  - Psychiatric disorders: hallucination, confusional state, nightmare, insomnia, anxiety, delirium, hallucination visual, disorientation, agitation, panic attack, abnormal behaviour;
  - General disorders and administration-site conditions: malaise, death, chest pain, oedema peripheral, drug interaction, pyrexia, drug interaction, fatigue, influenza-like illness, general physical health deterioration, condition aggravated, face oedema, pain;

[5] As stated by the marketing-authorisation holder in the pandemic safety report dated 23 December 2009.

  - Investigations: liver function test abnormal, international normalised ratio increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, prothrombin time prolonged;
  - Respiratory disorders: epistaxis, dyspnoea.

- Since the last update, three case reports worldwide have been received by EudraVigilance with a fatal outcome following oseltamivir use, including one fatal case from the EEA. Two cases of death were related to pneumonia and influenza. One case of death was due to hepatic failure which occurred two weeks after starting Tamiflu. Concomitant treatments included caspofungin, meropenem, erythromycin, paracetamol, clarithromycin, fluconazole. The primary cause of hepatic failure was reported to be due to prolonged severe hypoxia. For these fatal cases, a causal association with the treatment has not been established. It should be noted that healthcare professionals are actively encouraged to report events occurring after the administration of Tamiflu. Such events may be coincidental and could have occurred in absence of therapy, maybe due to underlying medical conditions.
- The most frequently suspected adverse reactions reported in children since the beginning of the Pandemic in April 2009 were vomiting, rash, hallucination, confusional state, nightmare, epistasis, headache and convulsion.

Appendix

Specific topics discussed for H1N1 vaccines in previous updates

	Celvapan	Focetria	Pandemrix
1st Update		Cerebral haemorrhage	Fever, local reaction and drowsiness following 2nd dose in children 6-35 months old Pregnancy-related events Anaphylactic reactions in children Guillain-Barré syndrome Heart transplant rejection
2nd Update	Paraesthesia Anaphylaxis, angioedema, hypersensitivity	Pregnancy-related events Guillain-Barré syndrome	Anaphylactic shock Pregnancy-related events Transplant rejection
3rd Update	Circulatory collapse	Anaphylactic shock Acute Disseminated Encephalomyelitis (ADEM) Encephalitis	Transplant rejection Injection site necrosis Guillain-Barré syndrome Paralysis and paresis Cerebral infarction
4th Update	Guillain-Barré syndrome Eye disorders	Guillain-Barré syndrome Facial palsy Intra-uterine death	Guillain-Barré syndrome Idiopathic thrombocytopenic purpura (ITP) Sudden hearing loss Seizures with fatal outcome Delayed hypersensitivity reaction type IV
5th Update	Guillain-Barré syndrome	Guillain-Barré syndrome Multiple sclerosis Cardiovascular accidents Leukocytoclastic vasculitis Encephalitis	Guillain-Barré syndrome Multiple sclerosis
6th Update		Thrombocytopenia	Guillain-Barré syndrome Peripheral neuropathy Vasculitis Idiopathic thrombocytopenic purpura (ITP) Necrotising pharyngitis and necrotising stomatitis Serum sickness

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