EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Sixth 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 3 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

In the EEA, at least 32.4 million people, including at least 220,000 pregnant women, have been vaccinated to date with one of the three centrally-authorised vaccines (Celvapan, Focetria or Pandemrix). When the information available for the nationally-authorised vaccines Panenza and Fluval P is included, the total rises to at least 36.4 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 have been reported 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. However, additional data and reviews were requested regarding selected suspected adverse reactions.

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 8 January 2010, a total of 2,078 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 10,000. 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 8 January 2010, the ECDC concluded that all countries that reported in the week 28 December 2009 to 3 January 2010 experienced low to medium influenza intensity and stable activity or a decreasing trend. While the proportion of influenza-positive sentinel samples continues to decline, the 2009 influenza A(H1N1) pandemic virus still accounts for nearly 100% of all subtyped viruses in sentinel and severe acute respiratory infection patients.

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

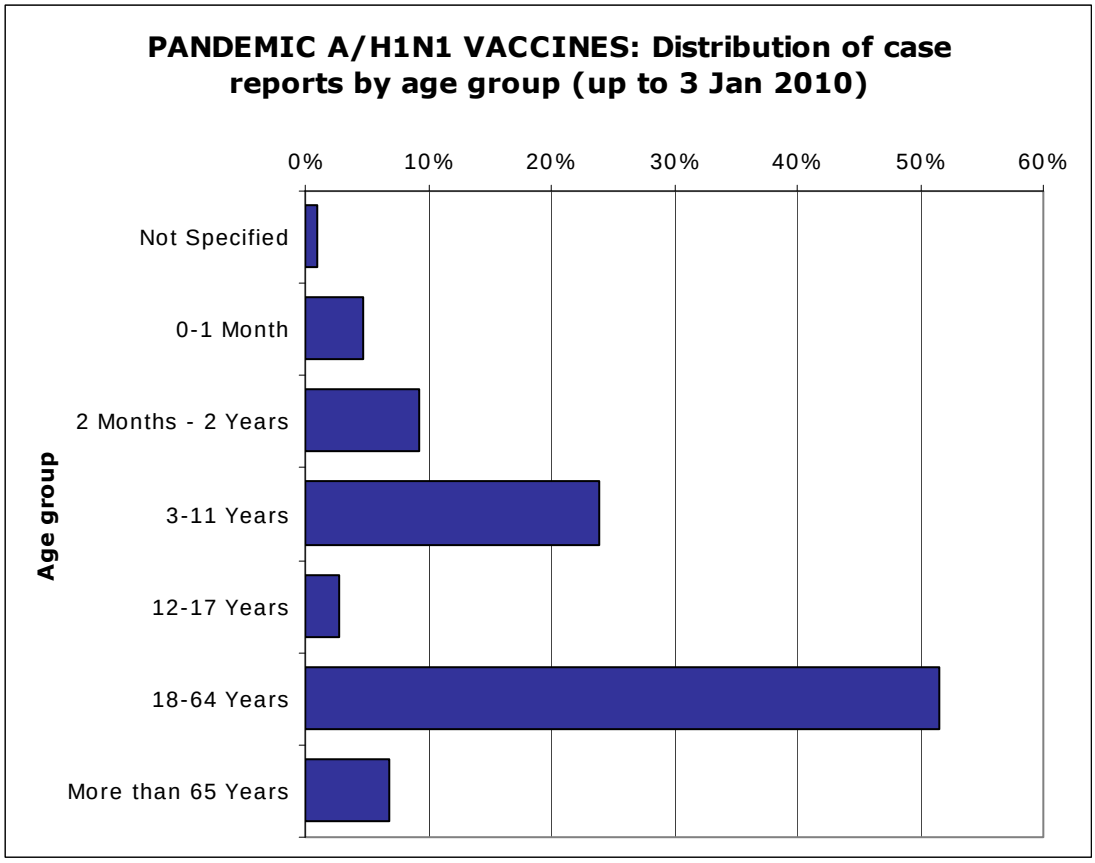
In its weekly update dated 8 January 2010, the World Health Organization states that, as of 3 January 2010, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 12799 deaths.

Overview of centrally authorised vaccines

As of 3 January 2010, a total of 11,649 case reports had been received by EudraVigilance since the authorisation of the three centrally-authorised vaccines. This represents an increase of 523 reports compared with the previous update, reflecting the increase in the number of people vaccinated. The

[1] For the latest reports click here.

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 11 January 2010 from Member States and from the vaccine's marketing-authorisation holders indicate that at least 98.5 million doses had been distributed and at least 32.4 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 11 January 2010, at least 220,000 pregnant women had been vaccinated.

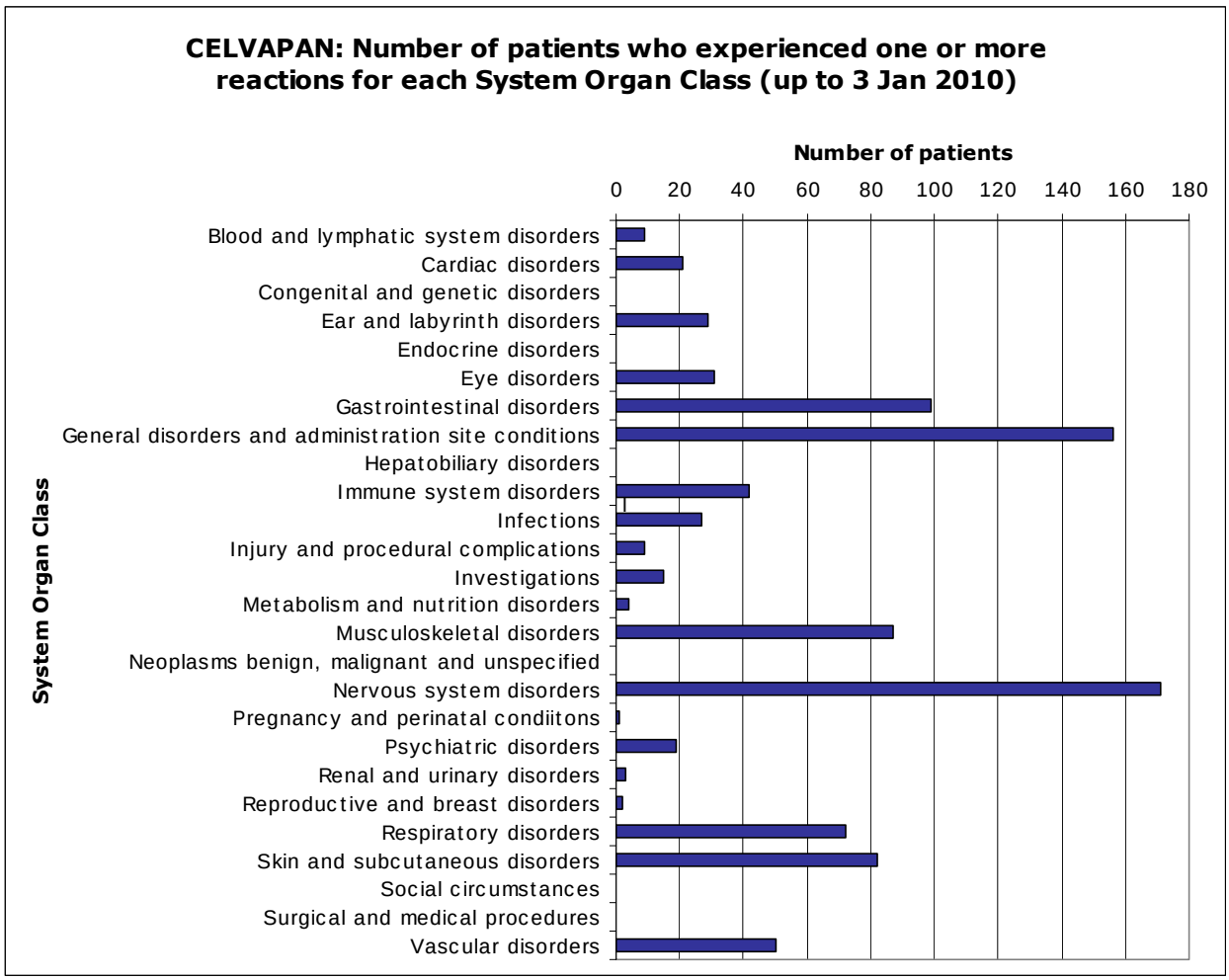
When the information available for the nationally authorised vaccines Panenza and Fluval P is included, at least 102.7 million doses have been distributed, with at least 36.4 million people (including at least 254,500 pregnant women) vaccinated in Europe.

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

Celvapan

As of 3 January 2010, a total of 363 reports had been received by EudraVigilance (an increase of seven 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 260,000 patients had 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, feeling hot, injection-site pain, influenza-like illness, chest discomfort;
  - 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: oropharyngeal pain, cough, dyspnoea;
  - Vascular disorders: pallor, flushing, hypotension;
  - Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
  - Eye disorders: vision blurred;
  - Ear and labyrinth disorders: vertigo.

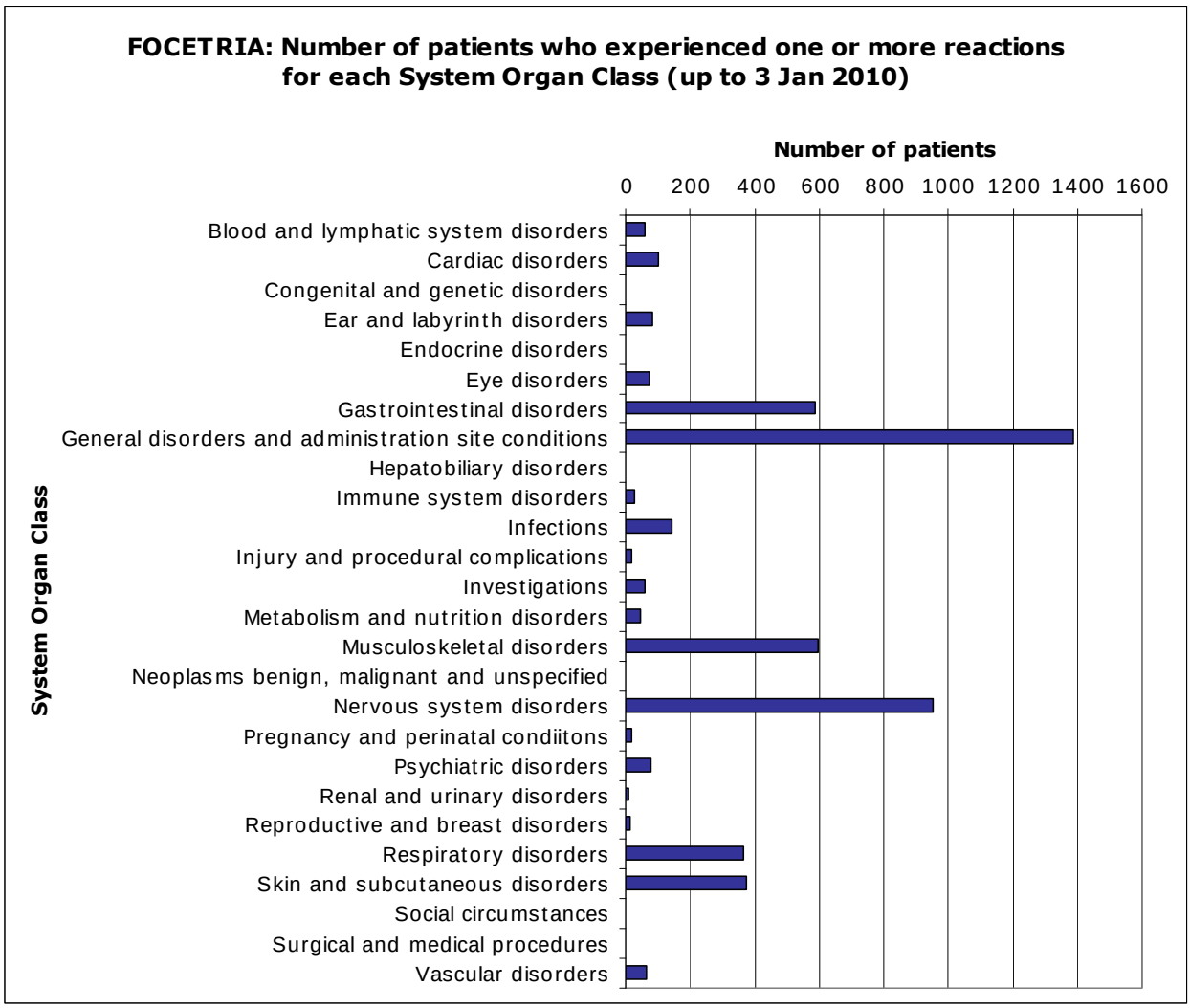
Updated safety information

- The most frequently suspected adverse reactions reported in children since authorisation included hypersensitivity, vomiting, syncope, pyrexia, dizziness, nausea, pallor, headache, rash, vision blurred, hyperhidrosis and cough.
- Since the last update, no fatal cases had been reported from the EEA in people vaccinated with Celvapan.
- The marketing authorisation holder submitted a periodic safety update report dated 23 December 2009. New safety concerns included convulsions, pain in extremity and influenza-like symptoms. These are being considered for addition to the Celvapan product information. After evaluation, the benefit-risk balance for the vaccine was considered to remain positive. Additional information is needed from the marketing authorisation holder regarding reported cases of anaphylaxis, anaphylactoid reactions and convulsions.

Focetria

As of 3 January 2010, a total 2,706 reports had been received by EudraVigilance (an increase of 65 reports since the previous update). Data available on 11 January 2010 from Member States and from the company[3] indicate that at least 30.7 million doses of Focetria had been distributed in the EEA, and at least 7.5 million patients had been vaccinated.

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



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, dysgeusia, somnolence, tremor, 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;
  - Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, dyspepsia;
  - Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, swelling face, rash generalised;

- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia;
- Infections: rhinitis, nasopharyngitis, pneumonia, pharyngitis, influenza, herpes zoster;
- Cardiac disorders: palpitations, tachycardia;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Psychiatric disorders: listless, insomnia.

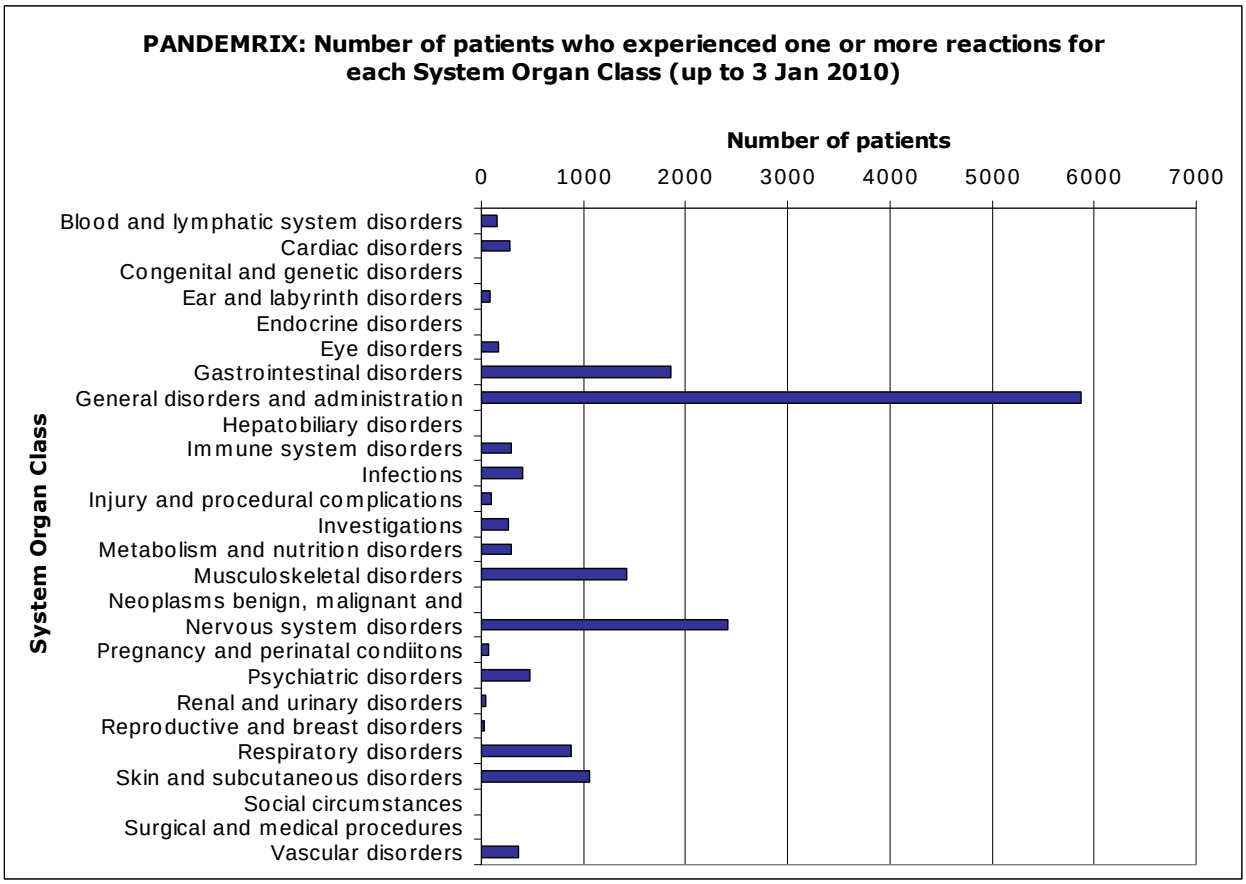
Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included pyrexia, hyperpyrexia, headache, vomiting, cough, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, influenza-like illness, fatigue, rash, dyspnoea and urticaria.
- Since the last update, no fatal cases had been reported from the EEA in people vaccinated with Focetria.
- The marketing authorisation holder submitted a periodic safety update report dated 8 December 2009. After evaluation, the marketing authorisation holder was requested to provide additional information on cases of eye disorders, muscular weakness, pregnancy outcomes, Guillain-Barré syndrome, neuritis, anaphylaxis, encephalitis, Bell's palsy, vaccination failure and potential interactions.
- From authorisation to 3 January 2010, four reports of thrombocytopenia were received. The cases occurred after 9 to 17 days following the vaccination and purpura also occurred in one of them. One case was considered more likely related to a concomitant medication (clopidogrel) and one case was considered unlikely to be related. This issue will be kept under close monitoring.

Pandemrix

As of 3 January 2010, a total of 8,580 reports had been received by EudraVigilance (an increase of 451 reports since the previous update). Data available on 11 January 2009 from Member States and from the company[4] indicate that at least 61.7 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 23.4 million patients had been vaccinated.

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



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;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, paraesthesia oral, swollen tongue, lip swelling, dry mouth, abdominal discomfort, hypoaesthesia oral;
  - 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, asthma, rhinorrhoea, wheezing, epistaxis, pharyngeal oedema, tachypnoea, throat tightness, bronchospasm;
  - 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: anaphylactic reaction, hypersensitivity, anaphylactic shock, anaphylactoid reaction;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction.

Updated safety information

- The most frequently suspected adverse reactions reported in children since authorisation were pyrexia, hyperpyrexia, vomiting, injection-site pain, headache, diarrhoea, cough, fatigue, decreased appetite, rash, abdominal pain, malaise, nausea, listlessness, somnolence, injection-site erythema, injection site swelling, crying, influenza-like illness, myalgia, pallor and pain in extremity.
- Since the last update, six reports with a fatal outcome have been received from the EEA. These reports included three patients aged 27, 77 and 84 years old who had underlying cardiovascular and renal risk factors, a two-month-old child who died from H1N1 infection on the day of the vaccination and two poorly documented cases for which further information has been requested.
- The marketing authorisation holder submitted a periodic safety update report dated 21 December 2009. After evaluation, it was concluded that no new risks have been identified in any age group. The marketing authorisation holder was requested to provide additional information on cases of eye disorders, Herpes zoster, seizures in known epileptics, facial palsy and fatal outcomes.
- Since the last update, four new reports of Guillain-Barré syndrome (GBS) have been received, including one from outside the EEA. The diagnosis was confirmed in two cases, is pending in one case and is not documented in another one. Follow-up information has also been received for three cases presented in the fifth update and the diagnosis of GBS has now been confirmed. Cumulatively, a total of 18 cases of GBS and one case of Miller-Fischer syndrome (a variant of GBS) have been received up to date in relation to Pandemrix vaccination. The cases for which information about the delay of onset is known occurred within 25 days after the vaccination. Considering that at least 23.4 million people have been vaccinated with Pandemrix and that the background incidence rate is about two cases per 100,000 persons and per year, the number of vaccinated patients expected to coincidently develop GBS within a delay of 25 days would be at least 32, which is higher than the observed number.
- Since authorisation, 15 reports of neuritis, two reports of polyneuritis, two reports of polyradiculoneuritis, 10 reports of peripheral neuropathy and two reports of polyneuropathy were received by EudraVigilance outside the context of a Guillain-Barré syndrome or of multiple sclerosis. The majority of cases occurred within two days after vaccination, but four occurred after seven, 11, 12 and 14 days. The age of patients varied widely (from 18 and 68 years), 16 were females and 15 were males. In the majority of cases, symptoms included loss of sensation, motor deficit, paraesthesia, hyper- or hypoaesthesia, myalgia, pain in the arm or Achilles' tendon reflex deficit. In the majority of cases, the outcome of the reaction is not yet known. In addition, reports were also received mentioning sensory loss or sensory disturbances (21 cases, with a concomitant motor deficit in five cases), neuralgia (14 cases), neuropathic pain (four cases) and peripheral paraesthesia (two cases). There are many causes to neuropathies, and the available information

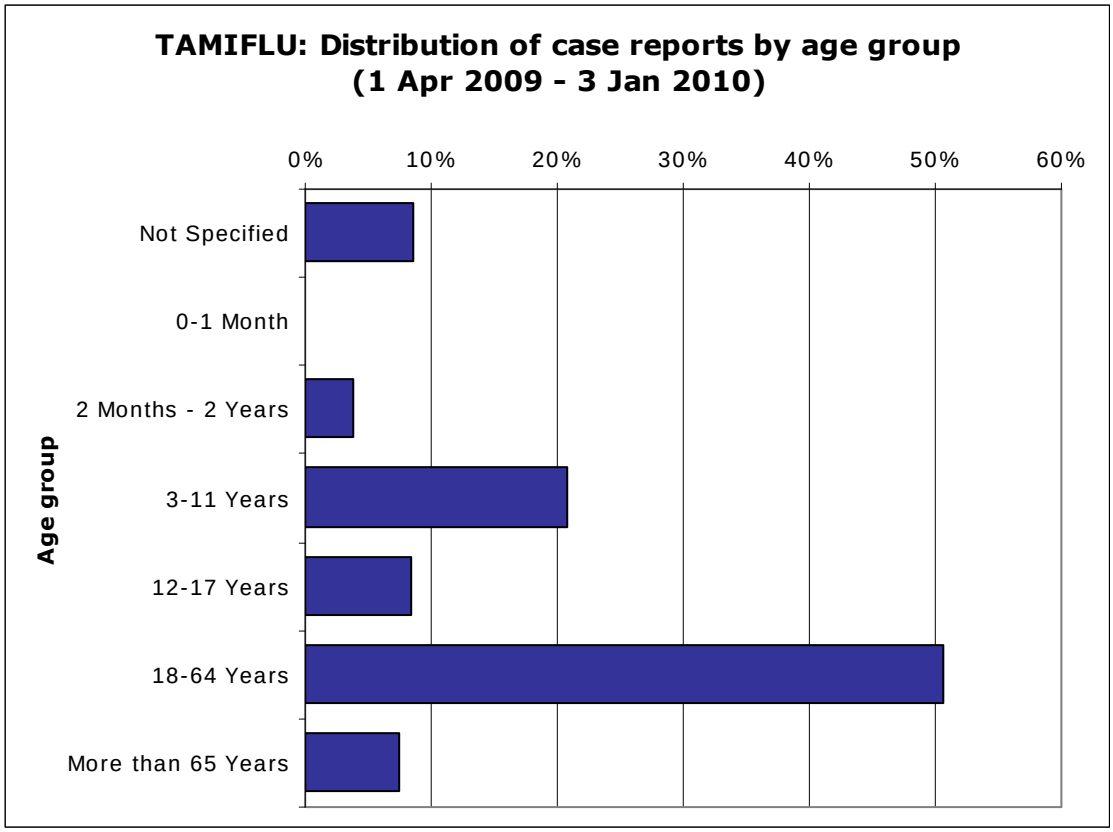
generally does not allow to identify an aetiology for the nerve disorder. Inflammatory neuropathies may be of immune origin and neuralgia and neuritis are mentioned in the product information of Pandemrix in connection to the interpandemic influenza vaccine. This issue will be further monitored.

- Since authorisation, 12 cases of vasculitis or leukocytoclastic vasculitis have been received. Three reports contain limited information impeding evaluation, six reports mention vasculitis in association with an allergic reaction such as rash, urticaria or face oedema, one case was associated with an infection treated with antibiotics with a known association to vasculitis, one case was reported of vasculitis in the context of a cerebral infarction and carotid artery dissection and one case with a Marfan syndrome presented leukocytoclastic vasculitis one week after vaccination. There is therefore no strong indication at this stage that Pandemrix could cause vasculitis outside the context of an allergic reaction.
- In the 4th update, three cases of idiopathic thrombocytopenic purpura (ITP) and one case of autoimmune thrombocytopenia occurring in association with Pandemrix were discussed. Three additional cases of ITP had been received since the 4th update. Two cases lacked information and one case was associated with haematoma, purpura and gingival haemorrhage starting 10 days after the vaccination. No cause was identified for this case who recovered. Six additional cases of thrombocytopenia with a time to onset varying from three to 27 days were also received, five of them being associated with purpura (two cases), bruising (two cases) and petechiae (one case). Possible causes for thrombocytopenia were suspected in four cases. Cumulatively, a total of 21 cases of thrombocytopenia have been reported. Thrombocytopenia has been observed in patients vaccinated with other vaccines, and it is an adverse reaction mentioned in the product information for Pandemrix as observed with the interpandemic trivalent influenza vaccine. This issue will be further monitored.
- Since the last update, a report has been received concerning a 39-year old female patient who experienced two days after vaccination with Pandemrix necrotising oesophagitis and necrotising stomatitis in a context of severe erythema multiforme with involvement of several mucous membranes. The events were confirmed by skin biopsy. Other causes such as viral infections, inflammatory rheumatic diseases or other medications could be excluded to a large extent. The patient was recovering at the time of the report. A search for other cases of erythema multiforme, Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) was made in EudraVigilance. It identified two unconfirmed cases of SJS, one case of TEN for which a staphylococcal infection was also suspected as the causal agent and six cases of erythema multiforme, including one unconfirmed case and three cases where an infection and other medicines were other possible explanations. This issue will remain under close monitoring.
- Since the last update, one case of serum sickness following vaccination with Pandemrix has been received. It concerned a 42-year old male patient who experienced swelling of fingers, hands and feet seven days after the vaccination and erythema with synovitis of the knees two days later. Eleven days after the vaccination he experienced arthralgia of knees and hips. Serum sickness is a type of delayed allergic reaction where symptoms may appear up to two weeks after exposure and generally abate spontaneously. Every new case will be closely reviewed and followed.

Antiviral medicines

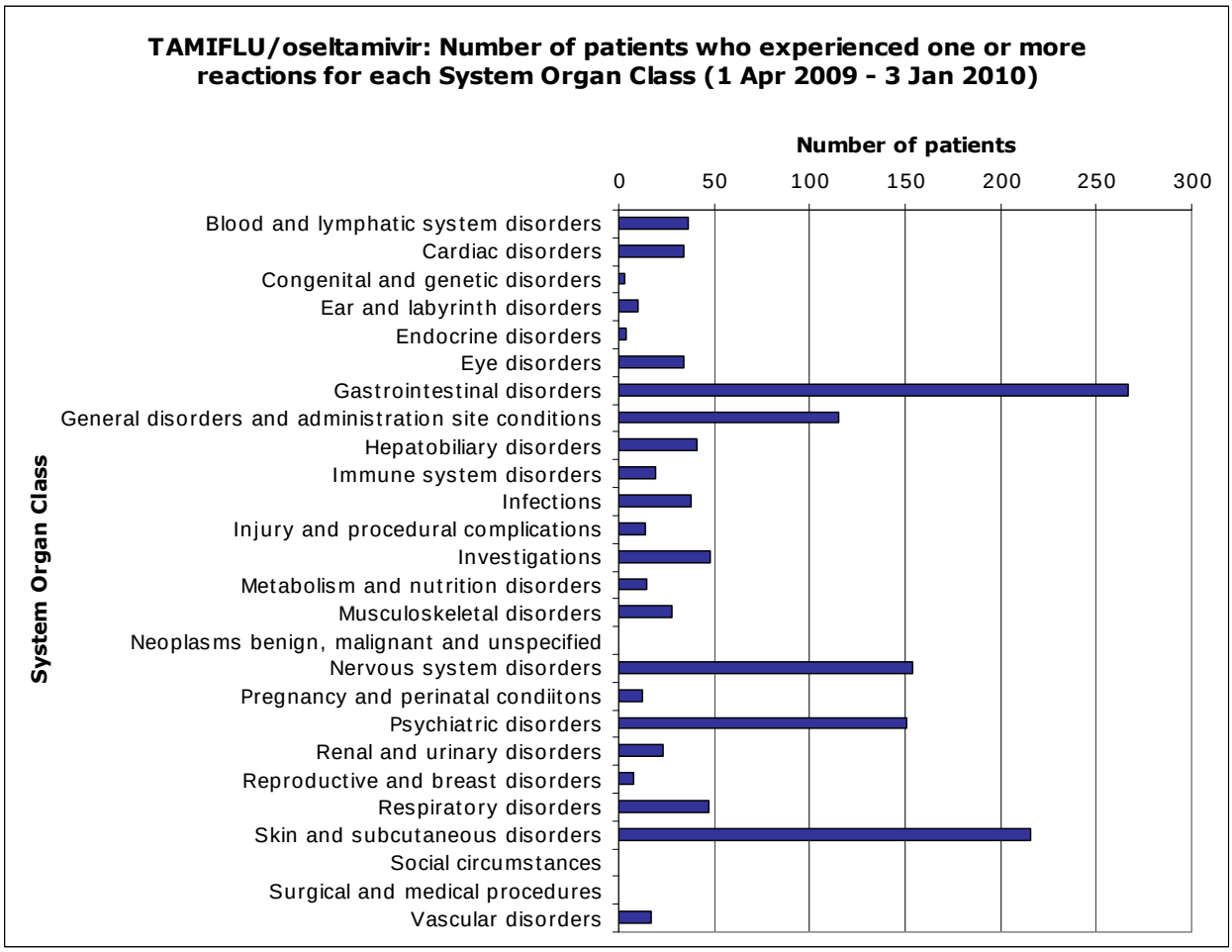
Tamiflu (oseltamivir)

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 oseltamivir is estimated to be 16,360,991 patients during the pandemic period of 1 May to 30 November 2009[5].

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



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, 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, fatigue, pyrexia, influenza-like illness, general physical health deterioration, condition aggravated, face oedema, pain;
  - Investigations: liver function test abnormal, international normalised ratio increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, prothrombin time prolonged;

  - Respiratory disorders: epistaxis, dyspnoea.

- Since the last update, 38 case reports worldwide have been received by the EudraVigilance system with a fatal outcome following oseltamivir use, including 11 fatal cases from the EEA. 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, e.g. due to underlying medical conditions.

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	Guillain-Barré syndrome Idiopathic thrombocytopenic purpura (ITP) Sudden hearing loss Seizures with fatal outcome.
5th Update	Guillain-Barré syndrome	Guillain-Barré syndrome Multiple sclerosis Cardiovascular accidents Leukocytoclastic vasculitis Encephalitis	Guillain-Barré syndrome Multiple sclerosis

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