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Patient Health Protection

Eleventh pandemic pharmacovigilance weekly update

This report summarises the adverse drug reactions reported after the use of the centrally authorised pandemic vaccines Celvapan, Focetria and Pandemrix and the antiviral Tamiflu. 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.

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.

Due to different number of people receiving each vaccine, the number of reports 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 in EudraVigilance, a database and management system administered 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 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 7 February 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 7 February 2010, in the EEA, at least 36.3 million people, including at least 322,000 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 42.2 million people. Some of these have received two doses of a vaccine, but the percentage varies between countries.

The vast majority of the adverse reactions that had been reported as of 7 February 2010 are considered to be non-serious.

The benefit-risk balance of the pandemic vaccines and antivirals being used for the current H1N1 influenza pandemic continues to be positive.

A cumulative review of all cases related to pregnancy events reported to EudraVigilance in temporal association with Celvapan, Focetria, Pandemrix or vaccines without a brandname, has been performed for this update and is further discussed below. The available data do not indicate any association between the vaccines and the occurrence of abortion, intra-uterine death or stillbirth, or other pregnancy-related events.

A cumulative review of all cases of demyelinating disorders reported to EudraVigilance in temporal association with Celvapan, Focetria, Pandemrix has been performed for this update and is further discussed below. The issue of Guillain-Barré syndrome is being closely followed. There is currently no evidence that any of the vaccines could increase the risk of occurrence of Guillain-Barré syndrome. This issue will be re-assessed based on forthcoming data.

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

In its weekly influenza surveillance overview of 12 February 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that the 2009 influenza A(H1N1) pandemic is well past its peak in the EU/EEA countries and local low-to-medium intensity transmission was confined to eight countries, the majority of which in Eastern Europe. Elsewhere the intensity was low, but sporadic transmission of the pandemic virus was reported in the majority of countries.

There is currently no evidence of virus circulation due to other influenza A viruses, but there is some circulation of influenza B viruses. The number of reported cases of severe acute respiratory infections continued to decline.

The numbers of confirmed fatal cases announced by EU/EEA Member States on their official websites as due to the pandemic has reached 2,678 by 15 February 2010. Click here for the breakdown by country.

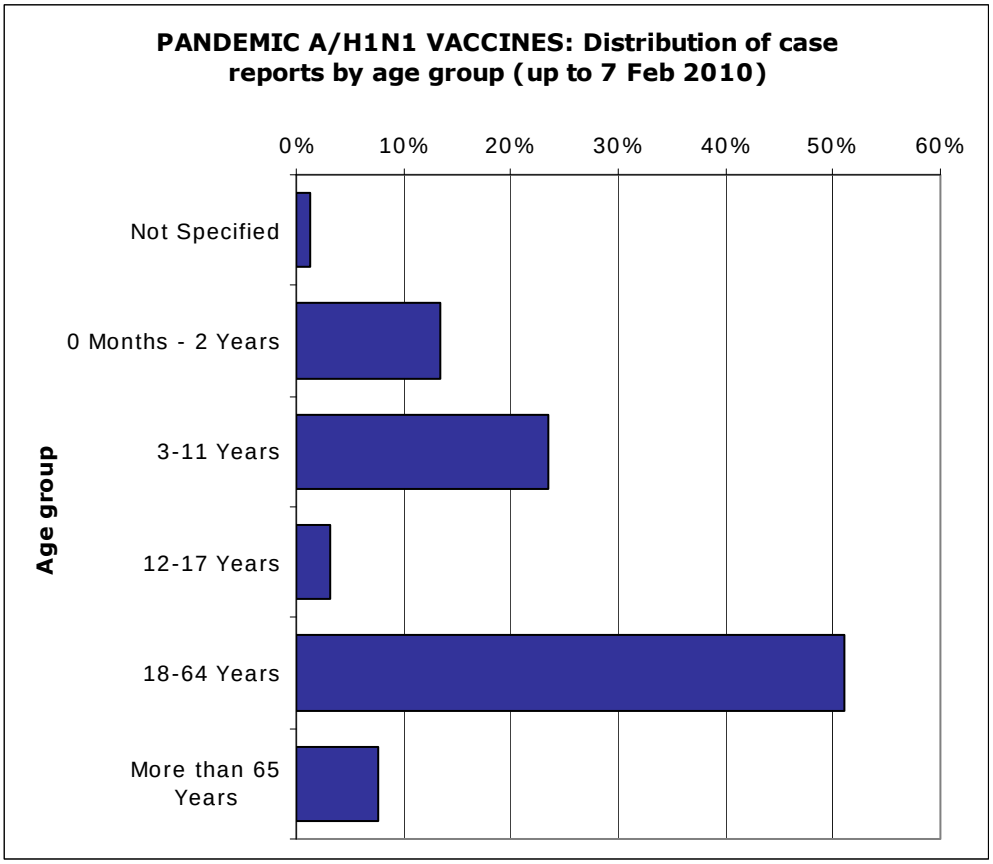
See the ECDC pandemic website, its current risk assessment and its weekly executive update for additional information.

In its weekly update dated 12 February 2010, the World Health Organization stated that, as of 7 February 2010, worldwide more than 212 countries and overseas territories or communities have

reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 15,292 deaths.

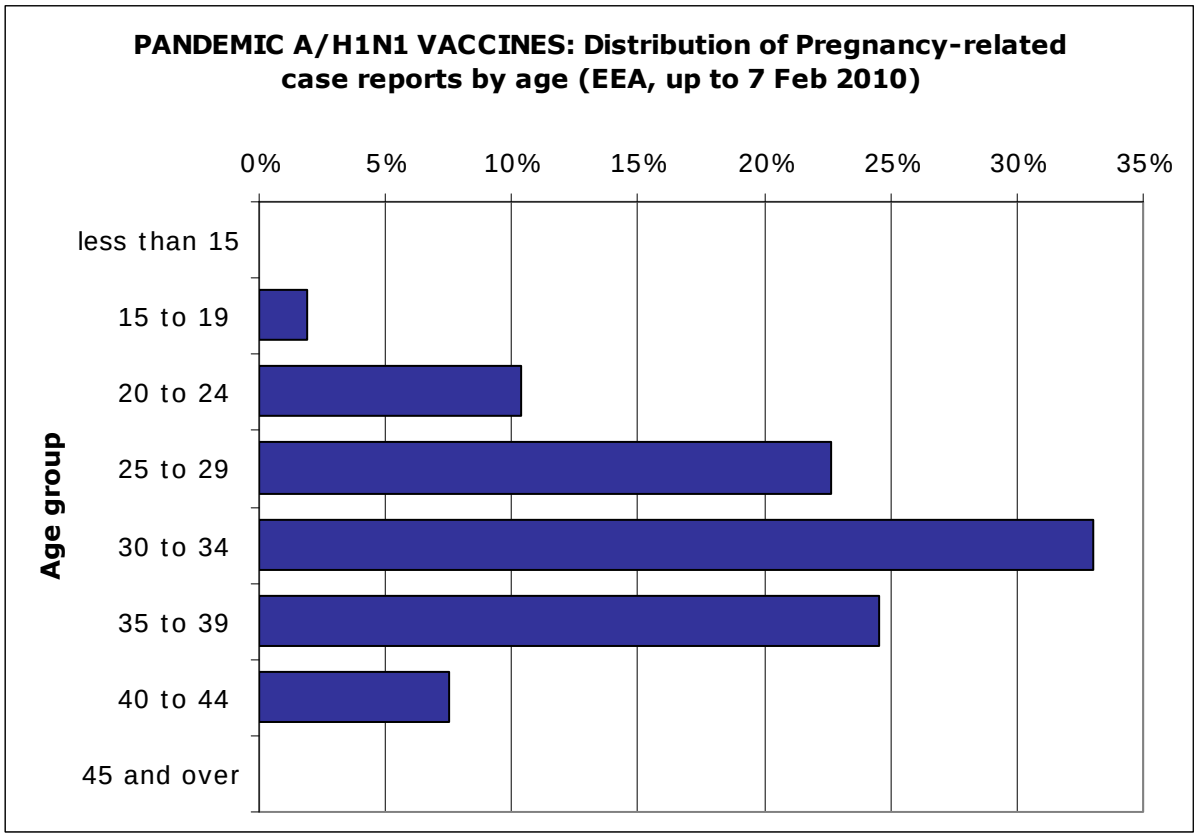
Overview of centrally authorised vaccines

As of 7 February 2010, a total of 13,130 case reports had been received by EudraVigilance since the authorisation of the three centrally authorised vaccines. This represents an increase of 215 reports compared with the previous update, reflecting the increase in the number of people vaccinated. The graph below displays the age distribution of all reports received by EudraVigilance.



Data available on 12 February 2010 from Member States and from the vaccine marketing authorisation holders indicate that at least 127.3 million doses had been distributed and at least 36.3 million patients had been vaccinated with one of the three vaccines in the EEA. From the limited information received from seven countries, at least 322,000 pregnant women had been vaccinated. When the information available for the nationally authorised vaccines is included, at least 131.5 million doses had been distributed, with at least 42.2 million people (including at least 361,000 pregnant women) vaccinated in Europe. These numbers are lower than in the 10th update due to corrected figures provided by two Member States.

A total of 130 cases have been received in EudraVigilance in the system organ class “pregnancy and perinatal conditions” for the H1N1 vaccines, including non-branded vaccines, since their authorisation. The graph below displays the age distribution of reports of pregnancy-related outcomes for Celvapan, Focetria and Pandemrix.



The pregnancy-related outcomes mentioned in the reports received for the three vaccines are listed below by decreasing order of frequency. When a report contained more than one event, the most serious one was selected.

Terms	Number of reports
Abortion*	57
Intra-uterine death	38
Stillbirth	11
Premature labour	6
Premature baby	5
Uterine contractions during pregnancy	3
Antepartum haemorrhage	2
Pre-eclampsia	2
Foetal hypokinesia	2
Complication of pregnancy	1
Ectopic pregnancy	1
Complication of delivery	1
Jaundice neonatal	1

* Abortion includes: abortion, abortion induced, abortion spontaneous.

There is a large variability in reported foetal mortality rates in European countries, partly due to differences in definitions. Foetal mortality rates range from 2.6 to 9.1 per 1000 of total births in the EEA (Europeristat 2004). Considering that the number of vaccinated pregnant women is a minimum of 322,000, the number of vaccinated pregnant women who would coincidently experience a foetal death would fall between 840 and 2,900. These figures should be taken into consideration when interpreting the total number of 49 reported cases of intra-uterine death or stillbirth. The number of reports of abortion is 57. The incidence of miscarriage among pregnancies has been estimated to be about 12–15% (17–22% when including early pregnancy losses). There is therefore no indication that the vaccines could increase the risk of abortion.

A cumulative overview of all reports of demyelinating disorders received up to 7 February 2010 in EudraVigilance from the EEA has been made for all pandemic vaccines. The number of reports is indicated below for each demyelinating disorder and each vaccine:

Number of reports	Celvapan	Focetria	Pandemrix
Total	3	20	66
Acute disseminated encephalomyelitis (ADEM)	0	1	1
ADEM+myelitis transverse	0	0	1
Demyelinating neuropathy	0	0	2
Encephalomyelitis	0	1	4
Guillain-Barré syndrome	2	13	34
Leukoencephalopathy	0	0	1
Miller-Fischer syndrome	0	1	1
Multiple sclerosis	0	0	4
Multiple sclerosis relapse or aggravated	0	2	9
Myelitis transverse	0	1	1
Optic neuritis	0	1	6
Trigeminal neuralgia	1	0	2

A total of 49 reports has been received for Guillain-Barré syndrome. The incidence rate of Guillain-Barré in Europe has been estimated to be between 1.1 and 1.8 per 100,000 persons and per year, which means that within a period of six weeks after the vaccination, a number of 49 to 80 cases would have been expected to occur naturally among the 36.3 million vaccinated patients. This issue is being closely followed, considering the certainty of the diagnosis of Guillain-Barré syndrome (as several cases have not been confirmed), the precision of the incidence rate and the accuracy of the statistics regarding the exposure (as the number of vaccinated people is probably an underestimation). Specific studies on Guillain-Barré syndrome have also been initiated in some Member Sates and results are awaited.

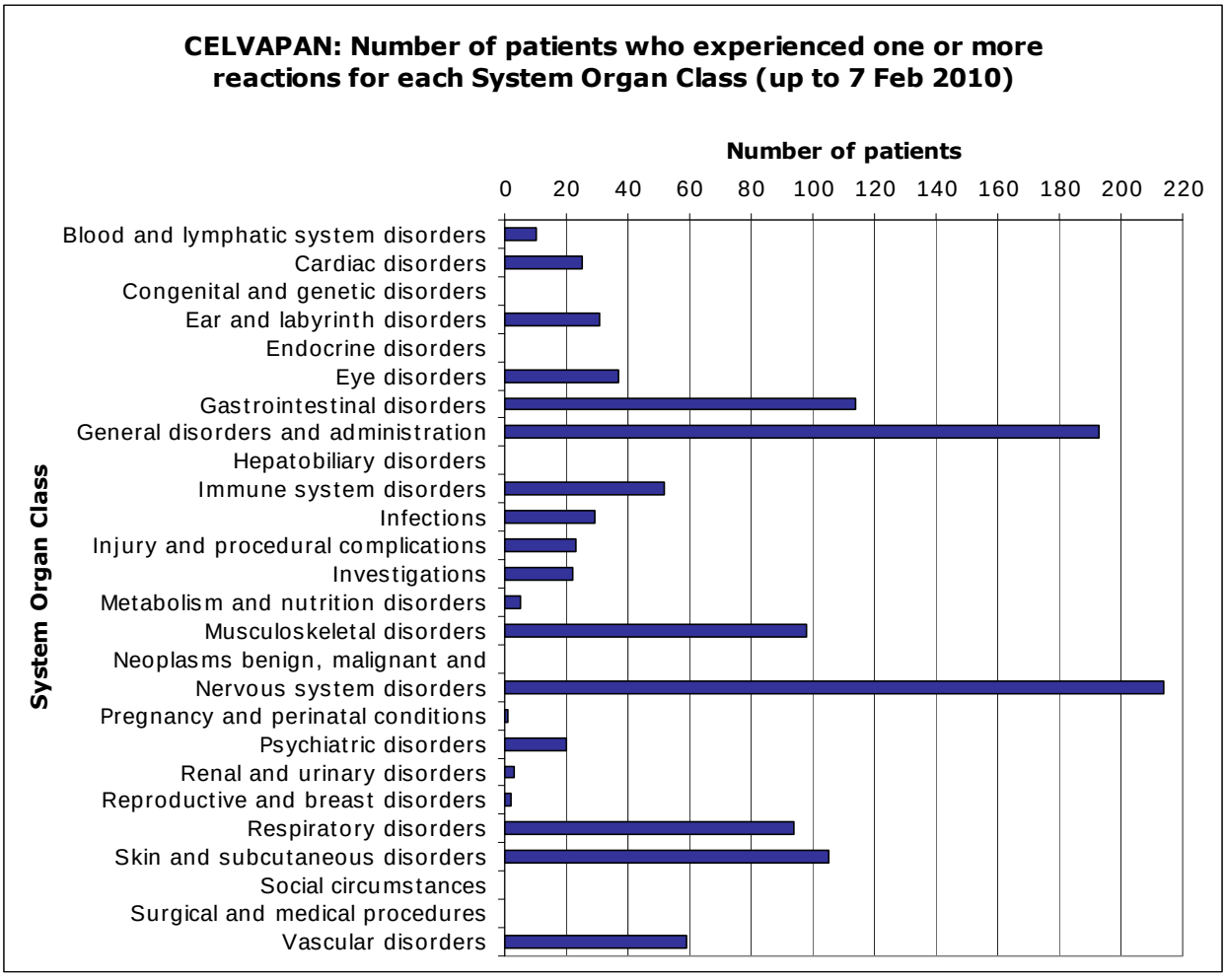
Four new cases of multiple sclerosis and nine cases of multiple sclerosis relapse or aggravation have been reported. The incidence of new-onset multiple sclerosis varies by age, gender and country, and the number of cases reported up to now in vaccinated patients is much lower than the expected

number of cases that would occur naturally. Multiple sclerosis relapses are often unpredictable. Viral infections such as common cold, influenza, or gastroenteritis are known to increase the risk of relapse, but there is no evidence that vaccination may be a trigger. There is no indication that the vaccines may increase the risk of multiple sclerosis or the risk of multiple sclerosis relapse or aggravation.

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

Celvapan

As of 7 February 2010, a total of 457 reports had been received by EudraVigilance (an increase of eight reports since the previous update). According to the information provided by the company[1] and Member States, at least 7.5 million doses had been distributed to EEA countries up to 11 January 2010. It is estimated that at least 571,000 patients have been vaccinated with Celvapan in the EEA.



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequently reported suspected adverse reactions in each system organ class (SOC) experienced by patients since the authorisation of the vaccine were:

[1] As stated by the marketing authorisation holder in the periodic safety update report dated 22 January 2010.

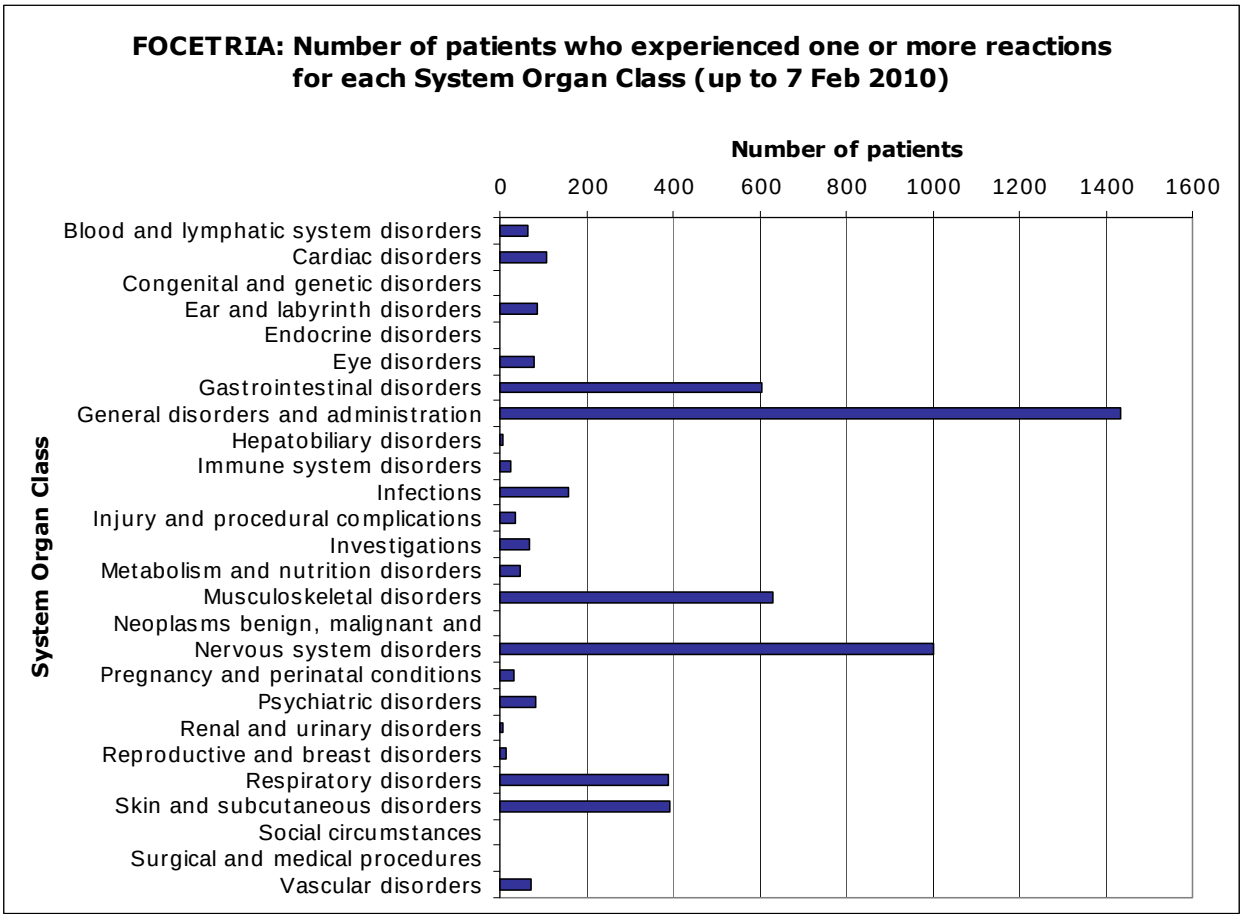
- Nervous-system disorders: headache, dizziness, syncope, paraesthesia, hypoaesthesia, lethargy;
- General disorders and administration-site conditions: pyrexia, malaise, fatigue, chills, asthenia, influenza-like illness, feeling hot, injection-site pain, chest discomfort;
- Gastrointestinal disorders: 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: 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;
- Infections: rhinitis;
- Cardiac disorders: tachycardia, palpitations;
- Investigations: body temperature increased;
- Psychiatric disorders: sleep disorders;
- Injury and procedural complications: medication error.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included hypersensitivity, syncope, vomiting, pyrexia, dizziness, pallor, medication error, nausea, headache, rash, cough, urticaria, vision blurred, chills, hyperhidrosis and malaise.
- Since the last update, no fatal cases have been reported in people vaccinated with Celvapan.

Focetria

As of 7 February 2010, a total of 2,875 reports had been received by EudraVigilance (an increase of 24 reports since the previous update). Data available on 5 February 2010 from Member States and from the company[2] indicated that at least 34.9 million doses of Focetria had been distributed in the EEA, and at least 6.5 million patients had been vaccinated (these figures are lower than those reported in previous updates due to corrections provided by some Member States).



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequently reported 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, injection-site induration, chest pain, asthenia, pain, injection-site pruritus, feeling cold, injection-site haematoma, feeling hot, injection-site warmth, oedema peripheral;
  - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, tremor, syncope, dysgeusia, hypoaesthesia, presyncope, convulsion, Guillain-Barré syndrome, migraine;

[2] As stated by the marketing authorisation holder in the periodic safety update report dated 6 January 2010.

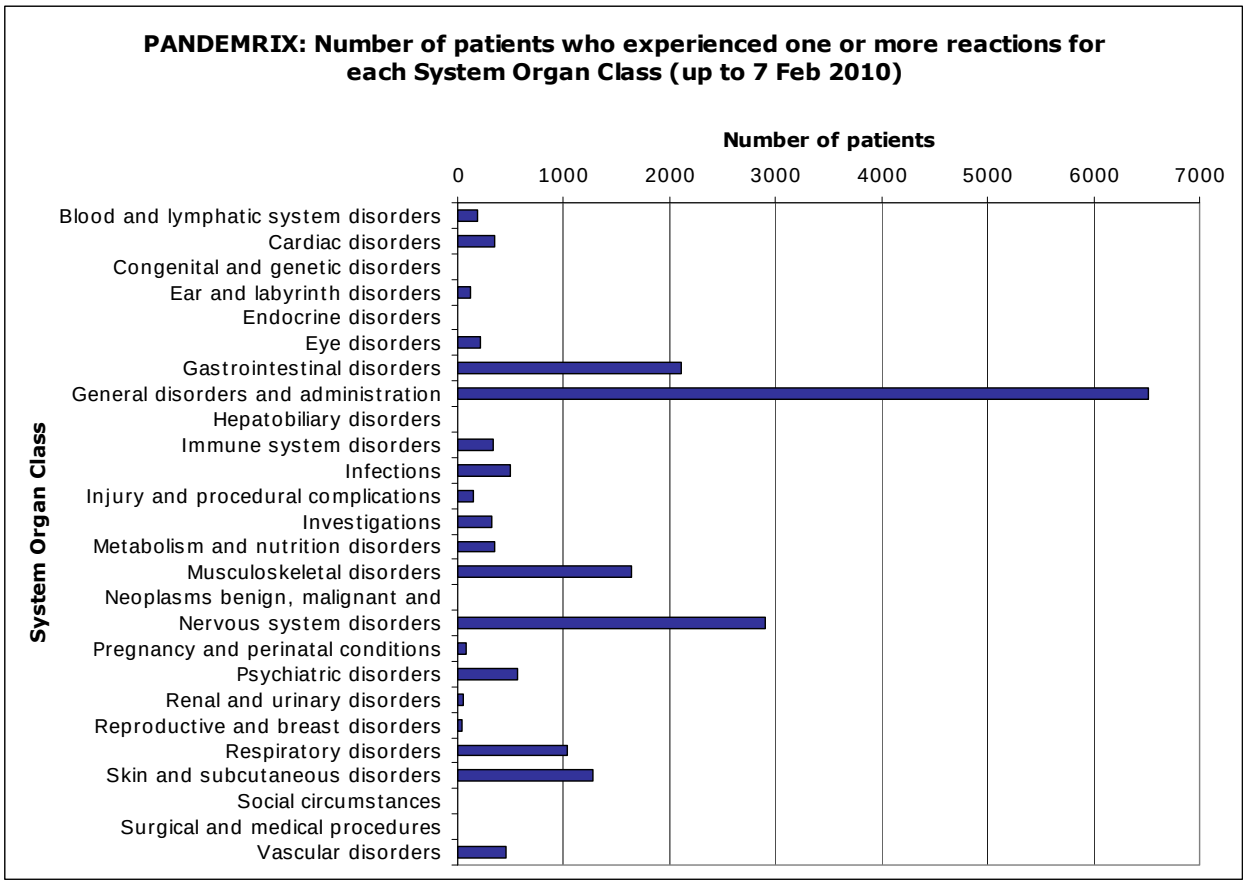
- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, muscle spasms, musculoskeletal pain, back pain, sensation of heaviness, rheumatoid arthritis;
- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, swelling face, rash generalised, eczema;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia, throat irritation;
- 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: listlessness, insomnia, nightmare, restlessness, tearfulness;
- Eye disorders: eyelid oedema, visual impairment, eye irritation, eye swelling, eye pain;
- Vascular disorders: hypotension, flushing, hypertension, pallor, haematoma, peripheral coldness;
- Investigations: body temperature increased, blood pressure increased, heart rate increased;
- Blood and lymphatic disorders: lymphadenopathy;
- Metabolism and nutrition disorders: decreased appetite;
- Immune system disorders: hypersensitivity, anaphylactic reaction.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included pyrexia, headache, hyperpyrexia, vomiting, cough, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, fatigue, influenza-like illness, rash, dyspnoea, malaise, urticaria, convulsion, and pain in extremity.
- Since the last update, two new fatal cases following vaccination with Focetria have been reported to EudraVigilance. One of these cases was from the EEA and the other from outside the EEA. Both were females (51 and 57 years old) and in both cases the cause of death reported was myocardial infarction. Overall, these reports do not suggest that the vaccine could have contributed to the death in any of these cases.

Pandemrix

As of 7 February 2010, a total of 9,819 reports had been received by EudraVigilance (an increase of 187 reports since the previous update). Data available on 5 February 2009 from Member States and from the company[3] indicate that at least 84.7 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 27.8 million patients have been vaccinated.



Distribution of adverse reactions by system organ class

- In reports received from the EEA, the most frequently reported 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 erythema, injection-site swelling, pain, oedema peripheral, asthenia, injection-site induration, injection-site inflammation, chest pain, feeling hot, local reaction, chest discomfort;
  - Nervous-system disorders: headache, dizziness, paraesthesia, syncope, somnolence, hypoaesthesia, crying, febrile convulsion, convulsion, lethargy, tremor, loss of consciousness, poor quality sleep, presyncope, facial palsy, hypersomnia, Guillain-Barré syndrome, hypotonia;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, lip swelling, dry mouth, swollen tongue, abdominal discomfort, hypoaesthesia oral, dysphagia, lower abdominal pain;

[3] As stated by the marketing authorisation holder in the periodic safety update report dated 15 January 2009.

- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, back pain, limb discomfort, musculoskeletal pain, neck pain, muscle spasms, arthritis;
- Skin and subcutaneous conditions: rash, erythema, urticaria, hyperhidrosis, pruritus, rash generalised, angioedema, cold sweat, swelling face, rash erythematous, dermatitis allergic, rash pruritic, pruritus generalised, facial hypoaesthesia, petechiae, eczema, rash macular, skin reaction, vesicular rash;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, tachypnoea, pharyngeal oedema, throat tightness, bronchospasm, sneezing, dysphonia, respiratory failure, productive cough, pulmonary embolism, respiratory distress, hyperventilation, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, nightmare, hallucination, confusional state;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, herpes zoster, swine influenza, cellulitis, bronchitis, ear infection, lower respiratory tract infection;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, hot flush, peripheral coldness;
- Metabolism and nutrition disorders: decreased appetite, oligodipsia, dehydration;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, cardiac failure, atrial fibrillation, bradycardia, cardiac arrest;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;
- Investigations: body temperature increased, blood pressure decreased, blood pressure increased, heart rate increased, body temperature decreased, heart rate decreased;
- Eye disorders: eye pain, eye swelling, vision blurred, ocular hyperaemia, eyelid oedema, diplopia, conjunctivitis;
- Blood and lymphatic system disorders: lymphadenopathy, thrombocytopenia;
- Injury and procedural disorders: medication error, vaccination failure, contusion;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain.

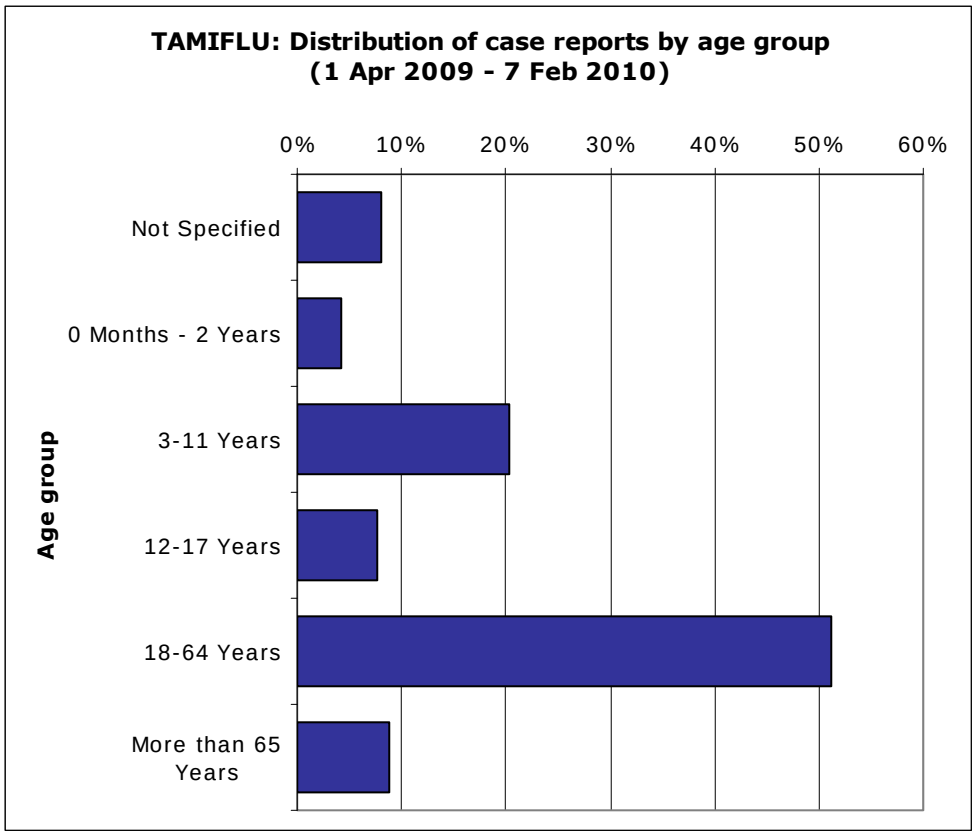
Updated safety information

- Since the last update, one new fatal case from the EEA has been received by EudraVigilance. It concerned a 91-year-old woman who presented acute renal failure and myocardial infarction 13 days after the vaccination. This case is unlikely to be causally associated with the vaccine.
- 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, injection-site erythema, somnolence, listlessness, crying, injection site swelling, pallor, dyspnoea, influenza-like illness, syncope, myalgia, pain in extremity, febrile convulsion and tearfulness.

Antiviral medicines

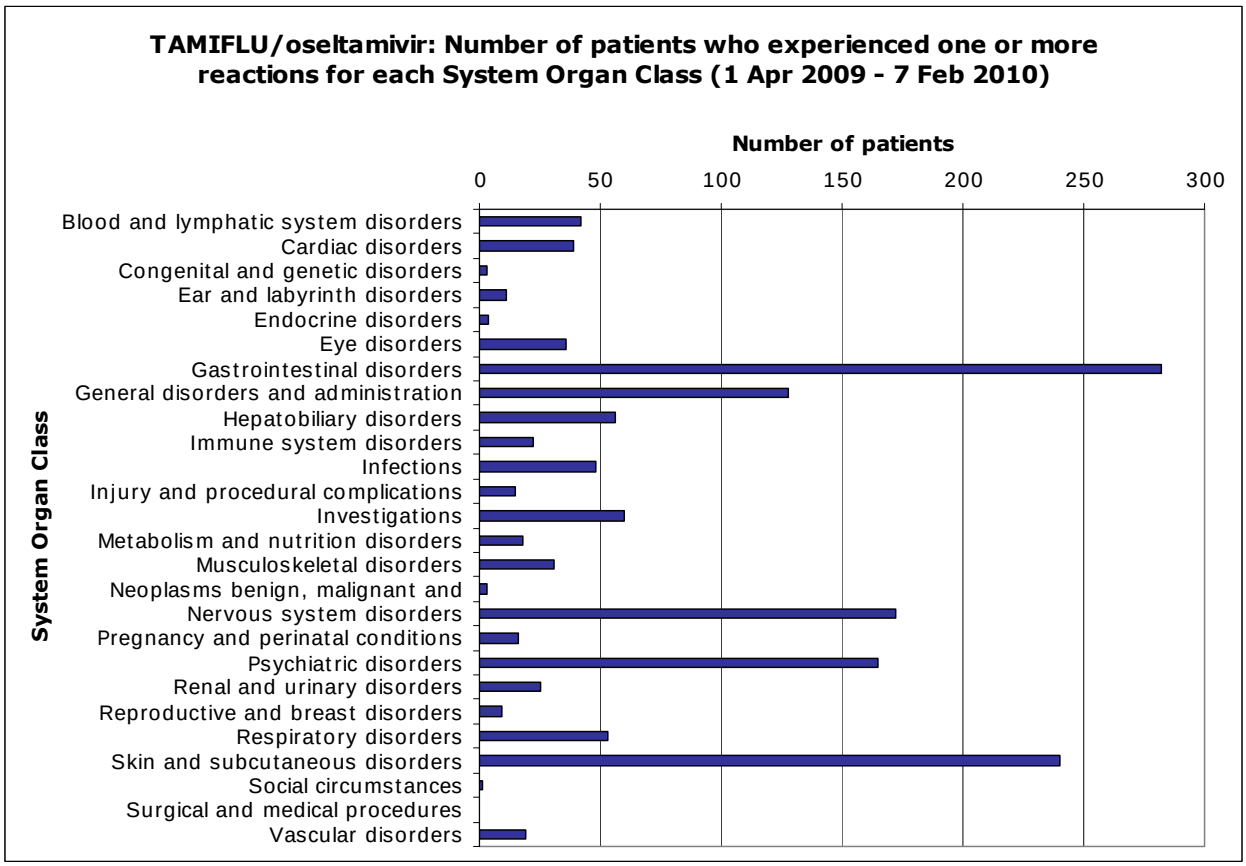
Tamiflu (oseltamivir)

From 1 April to 7 February 2010, a total of 1,002 reports worldwide were received by EudraVigilance (an increase of 11 reports since the previous update). The graph below displays the age distribution of patients experiencing an adverse reaction reported to EudraVigilance.



According to information received from the marketing authorisation holder, exposure to Tamiflu is estimated to be at least 21.1 million patients during the pandemic period of 1 May to 31 December 2009[4].

[4] As stated by the marketing authorisation holder in the pandemic safety report dated 27 January 2010.



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, pancreatitis, swollen tongue, dyspepsia, haematemesis, pancreatitis acute;
  - Skin and subcutaneous conditions: rash, rash generalised, urticaria, swelling face, erythema, pruritus, Stevens-Johnson syndrome, rash erythematous, rash pruritic, blister, rash macular, angioedema;
  - Nervous-system disorders: headache, convulsion, paraesthesia, dizziness, tremor, syncope, cerebrovascular accident, nystagmus, somnolence, epilepsy, burning sensation, dysgeusia;
  - Psychiatric disorders: hallucination, confusional state, nightmare, anxiety, insomnia, delirium, hallucination visual, disorientation, agitation, abnormal behaviour, panic attack, depressed mood, mental disorder, psychotic disorder;
  - General disorders and administration-site conditions: malaise, death, pyrexia, chest pain, influenza-like illness, oedema peripheral, drug interaction, fatigue, condition aggravated, drug ineffective, general physical health deterioration, pain, face oedema, multi-organ failure, gait disturbance;

- Investigations: liver function test abnormal, international normalised ratio increased, hepatic enzyme increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, prothrombin time prolonged;
- Respiratory disorders: epistaxis, dyspnoea, chronic obstructive pulmonary disease;
- Infections: pathogen resistance, influenza, lower respiratory tract infection, pneumonia;
- Hepatobiliary disorders: hepatitis, hepatic failure, acute hepatic failure, hepatotoxicity, cholestasis.

Updated safety information

- Since the last update, five new worldwide reports of adverse events with a fatal outcome following oseltamivir use have been received by EudraVigilance, two of which were follow-ups of previous cases. All cases occurred within the EEA. Of the three new cases, the death was related to pneumonia in one case, to fulminant hepatitis which was pre-existing before oseltamivir therapy in another case, and to heart failure in one patient concomitantly treated with infliximab for rheumatoid arthritis. In the two follow-up cases, death was related to encephalopathy and to acute renal failure and hyperglycaemia, respectively.
- The most frequently reported suspected adverse reactions reported in children since the beginning of the pandemic in April 2009 were vomiting, rash, hallucination, confusional state, nightmare, convulsion, epistaxis, headache, urticaria, diarrhoea, nausea and abdominal pain.

Appendix

Specific topics discussed for H1N1 vaccines in previous updates

SOC	Topic	Update number		
		Celvapan	Focetria	Pandemrix
Blood and lymphatic system disorders	Haematopoietic cytopenias			8
	Idiopathic thrombocytopenic purpura (ITP)			4, 6
	Leucocytosis, lymphocytosis			8
	Thrombocytopenia		6	6
Cardiac disorders	Cardiovascular accidents		5	
Ear and labyrinth disorders	Sudden hearing loss			4
Eye disorders	Eye disorders	4, 7	7	7
	Photophobia			7
Gastrointestinal disorders	Necrotising oesophagitis and necrotising stomatitis			6
	Pancreatitis	7		10
General disorders and administration site conditions	Death, sudden death	10	10	10
	Fever, local reaction and drowsiness following 2nd dose in children 6-35 months old			1
	Injection site necrosis			3
Immune system disorders	Anaphylactic reactions in children			1
	Anaphylactic shock		2, 3	2
	Anaphylaxis, angioedema, hypersensitivity	2		
	Delayed hypersensitivity reaction type IV			4
	Serum sickness			6
	Transplant rejection			1, 2, 3

SOC	Topic	Update number		
		Celvapan	Focetria	Pandemrix
Infections and infestations	Herpes zoster	9	9	9
Injury, poisoning and procedural complications	Medication error	7, 10		7, 10
Nervous system disorders	Acute disseminated encephalomyelitis (ADEM)		2, 3	
	Cerebral haemorrhage or infarction		1	3
	Encephalitis		3, 5	
	Facial palsy or paresis	8	4, 8	7
	Guillain-Barré syndrome	4, 5	2, 4, 5	1, 3, 4, 5, 6
	Multiple sclerosis		5	5
	Neuralgic amyotrophy			9
	Neuritis, polyneuritis, polyradiculoneuritis, peripheral neuropathy, polyneuropathy			6
	Paraesthesia	2		
	Paralysis and paresis	7	8	3
	Seizures		8	
	Seizures with fatal outcome			4
Pregnancy, puerperium and perinatal conditions	Intra-uterine death		4	
	Pregnancy-related events		2	1, 2

SOC	Topic	Update number		
		Celvapan	Focetria	Pandemrix
Skin and subcutaneous tissue disorders	Bullous dermatitis		9	8
	Erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)			3, 6
	Leukocytoclastic vasculitis		5	
	Photosensitivity reaction			2
	Systemic lupus erythematosus rash			8
Vascular disorders	Circulatory collapse	3		
	Vasculitis			6