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Patient Health Protection

Twenty-first pandemic pharmacovigilance update

This report summarises the adverse drug reactions reported after the use of the centrally authorised pandemic vaccines Arepanrix, Celvapan, Focetria and Pandemrix, and the antiviral Tamiflu[1]. 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 numbers of people receiving each vaccine, the number of reports for the four 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 managed by the European Medicines Agency for the collection and evaluation of reports of suspected adverse drug reactions to medicinal products. EudraVigilance 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 11 July 2010. Except for Arepanrix, which is not marketed in the European Economic Area (EEA), the graphs represent aggregated data related to the EEA only, and provide an overview of the reporting situation in the EEA. The updated safety information considers worldwide cases from EudraVigilance.

[1] Humenza is a further pandemic vaccine that has received a marketing authorisation from the European Commission. As this vaccine is not marketed and no adverse reaction reports have been received by EudraVigilance, this vaccine is not included in this update.

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

Key messages

The benefit-risk balance of the centrally authorised pandemic vaccines Celvapan, Focetria and Pandemrix and of the antiviral Tamiflu used for the current H1N1 influenza pandemic continues to be positive.

The vast majority of the adverse reactions that had been reported to EudraVigilance as of 11 July 2010 are considered to be non-serious.

As of 19 July 2010, in the EEA, at least 38.6 million people had been vaccinated with one of the three centrally authorised vaccines marketed in the EEA, Celvapan, Focetria or Pandemrix. When the information available for the nationally authorised vaccines is included, the total rises to at least 46.2 million people. Some of these have received two doses of a vaccine, but the percentage varies between countries. These figures are not expected to vary significantly before the next seasonal influenza vaccination period.

For further information on the known adverse reactions included in the authorised product information for the centrally authorised pandemic vaccines Arepanrix, 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 bi-weekly influenza surveillance overview dated 19 July 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that, as of 11 July 2010, all reporting countries experienced low influenza intensity.

In the week ending 2 May 2010, there had been a total of 2,900 deaths due to the pandemic announced by EU/European Free Trade Association (EFTA) Member States. Click here for a breakdown by country.

See the ECDC pandemic website for additional information.

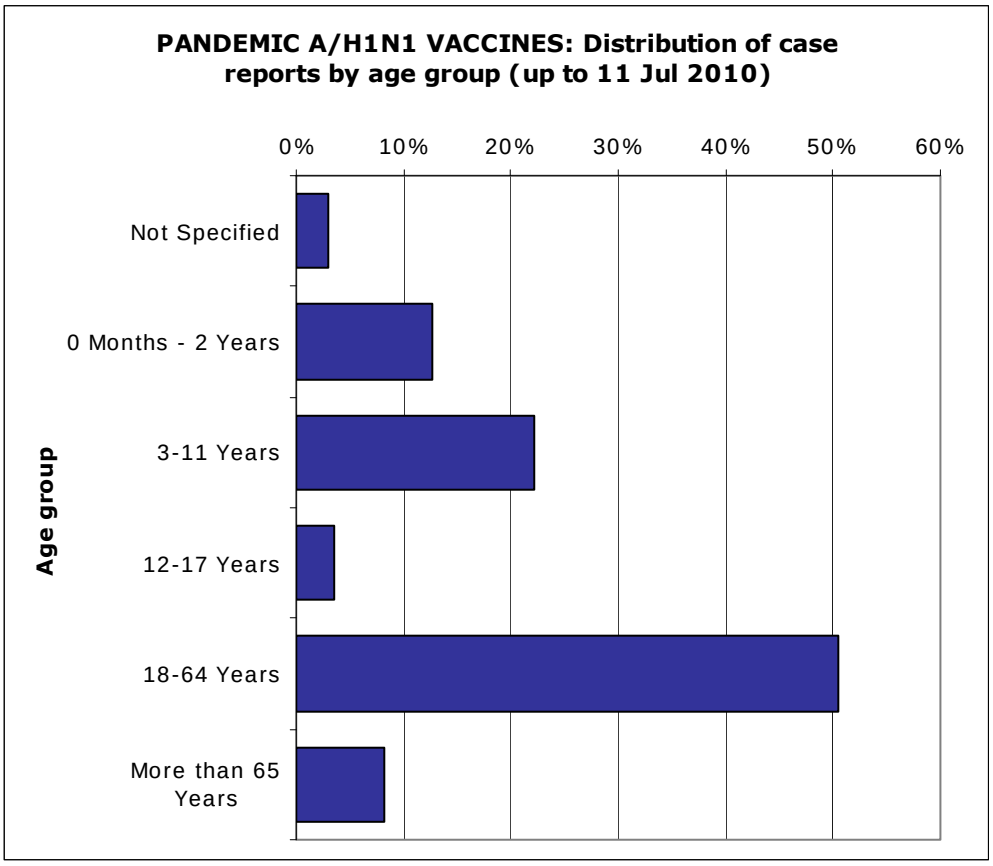
In its weekly update dated 16 July 2010, the WHO reported that, as of 12 July 2010, more than 214 countries and overseas territories or communities worldwide have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18,337 deaths.

Published estimates of vaccine field effectiveness based on epidemiological data are starting to become available, such as a recent estimate published in an article of Eurosurveillance, which indicates for one of the pandemic vaccines a significant field effectiveness as good as (if not better than) that seen with seasonal influenza vaccines. See also the latest ECDC Executive Science Update no 11 (April–June 2010) for an overview of the ECDC funded Influenza Monitoring of Vaccine Effectiveness (I-MOVE) project and of its preliminary findings during the season 2009/10. However, it is not possible to derive vaccine specific field estimates of effectiveness from these studies.

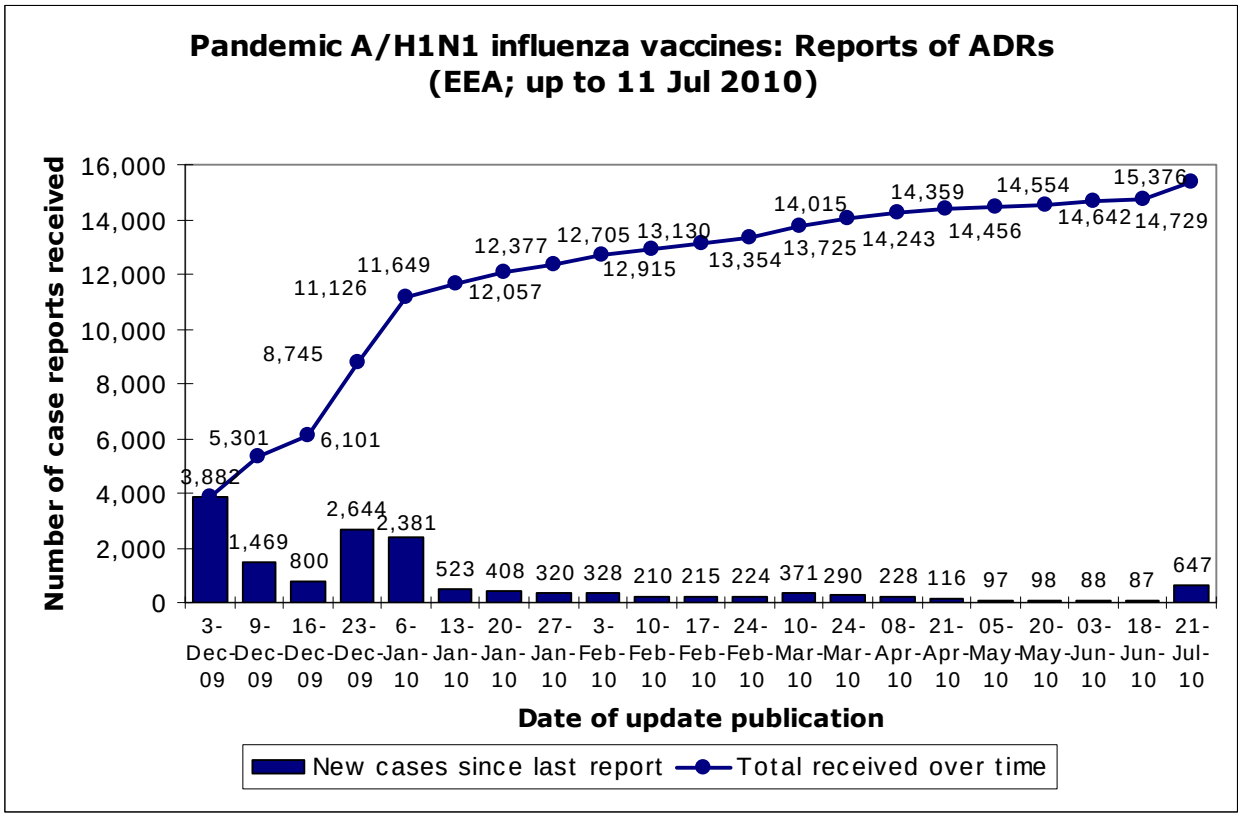
Overview of centrally authorised vaccines

As of 11 July 2010, a total of 15,376 case reports had been received from the EEA by EudraVigilance since the authorisation of the centrally authorised vaccines (Arepanrix, Celvapan, Focetria and Pandemrix) in the EEA. This represents an increase of 647 reports compared with the previous update. The large number of reports received since the last update is explained by the large number of non-serious reports that had not yet been transmitted for Celvapan (see below).

The graph below shows the age distribution of all the reports received by EudraVigilance up to 11 July 2010.



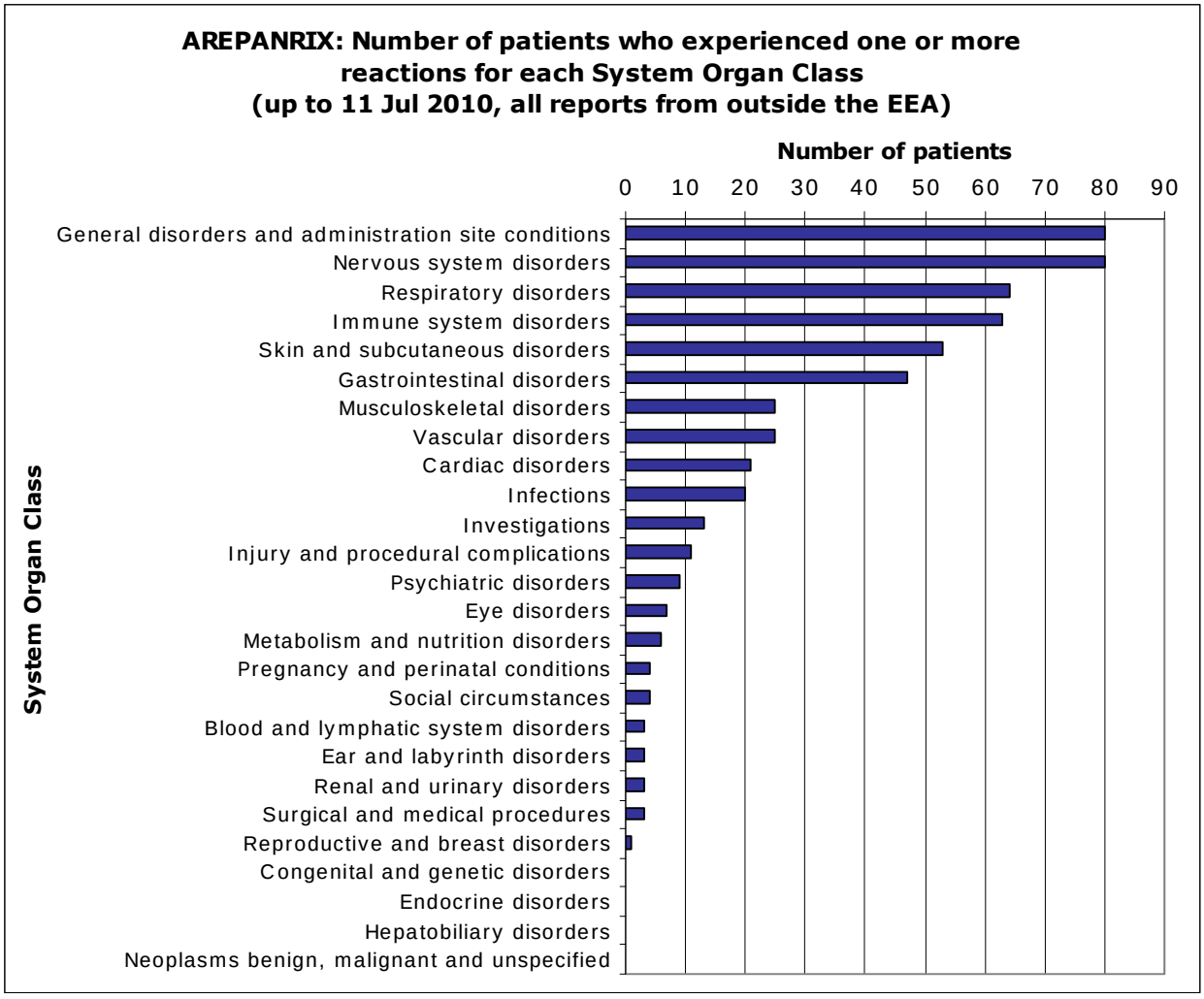
The graph below shows the cumulative numbers of adverse reaction reports received by EudraVigilance for the three centrally authorised vaccines marketed in the EEA (Celvapan, Focetria and Pandemrix), with the number of new adverse reaction reports received between each update.



A list of specific topics discussed in previous updates is included in Appendix 1.

Arepanrix

Although authorised, Arepanrix is not marketed in the EEA. However, it has been available in Canada since October 2009. In accordance with EU legislation, unexpected serious adverse reactions are reported from outside the EEA. As of 11 July 2010, a total of 159 reports had been received by EudraVigilance from outside the EEA. This represents an increase of eight reports compared with the previous update.



Distribution of adverse reactions by system organ class

- The most frequently reported suspected adverse reactions in each system organ class (SOC) experienced by patients since the authorisation of the vaccine are listed below. Because known reactions to the vaccine are not reported from outside the EU, the profile of reports received for Arepanrix is different from that of the products marketed in the EU:
  - Nervous-system disorders: Guillain-Barré syndrome, paraesthesia, hypoaesthesia, dizziness, paralysis flaccid, hyporeflexia, headache, cranial nerve paralysis;
  - General disorders and administration-site conditions: pyrexia, asthenia, product quality issue, fatigue;
  - Respiratory disorders: dyspnoea, throat tightness, cough, pharyngeal oedema, respiratory paralysis, respiratory disorder;

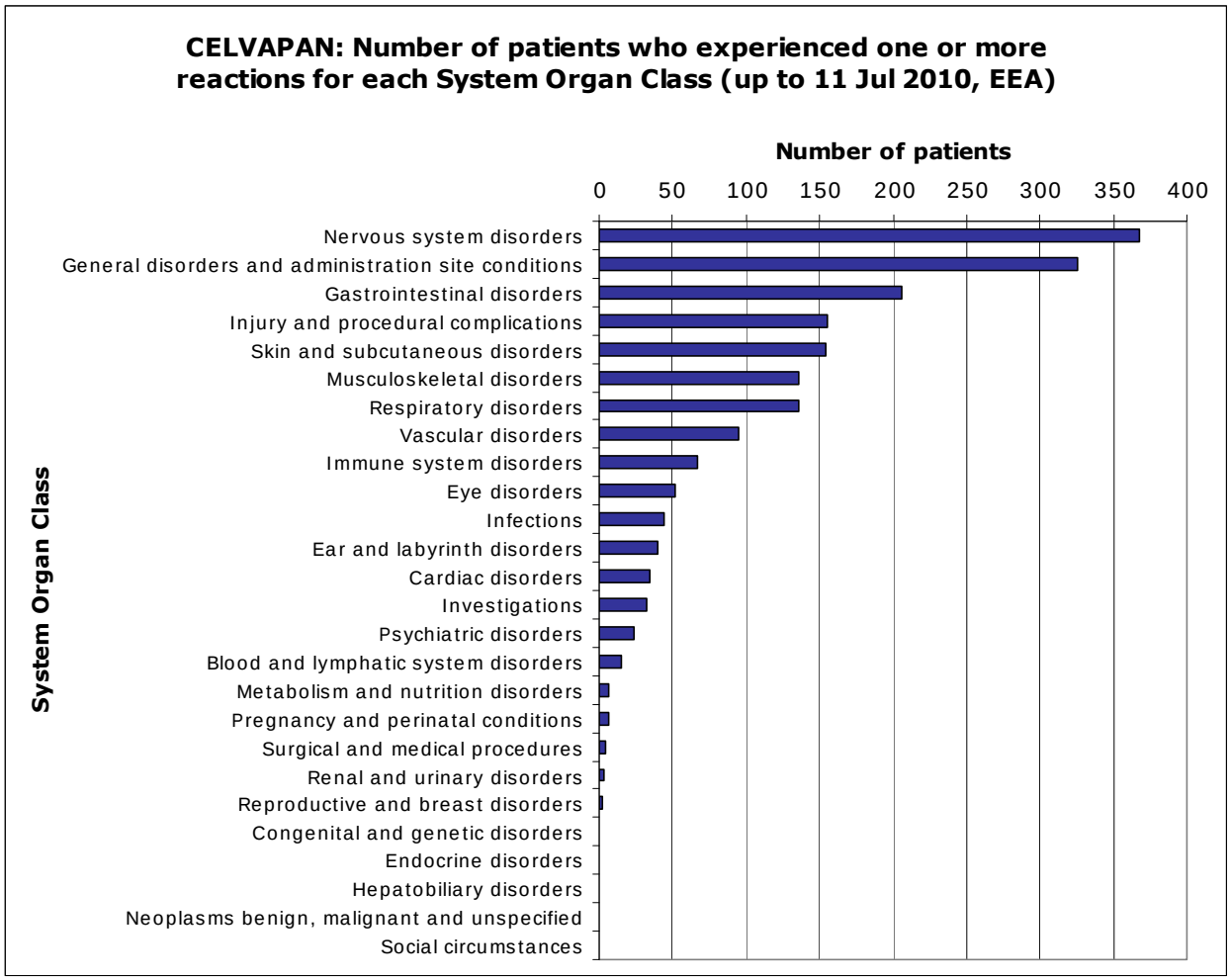
- Immune disorders: anaphylactic reaction, hypersensitivity;
- Skin and subcutaneous conditions: angioedema, urticaria, erythema, rash, pruritus;
- Gastrointestinal disorders: nausea, vomiting;
- Vascular disorders: flushing, pallor;
- Musculoskeletal disorders: muscular weakness, pain in extremity, myalgia;
- Cardiac disorders: tachycardia, cyanosis;
- Infections: sepsis, transmission of an infectious agent via a medicinal product, nasopharyngitis.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included pyrexia, cough, dyspnoea, urticaria, angioedema, anaphylactic reaction, cyanosis, anaphylactic shock, erythema, vomiting, hypersensitivity, febrile convulsion, rash, flushing, nausea, depressed level of consciousness, headache, tremor, throat tightness, pruritus, skin discolouration and pallor.
- Since the last update, a new fatal case occurring in Canada was reported to EudraVigilance. It concerned a 10-month old child who experienced cyanosis and died three hours after the vaccination. From autopsy, no cause of death could be identified.

Celvapan

As of 11 July 2010, a total of 894 reports of serious adverse reactions had been received by EudraVigilance. This represents an increase of 336 reports since the previous update. From these, 326 reports are non-serious reports that had not been previously transmitted to EudraVigilance. No change in the number of people vaccinated with Celvapan has been communicated since the last update. According to the information provided by the company[2] and Member States, at least 11.7 million doses had been distributed to EEA countries up to 17 May 2010. It is estimated that at least 566,000 patients have been vaccinated with Celvapan in the EEA.



Distribution of adverse reactions by system organ class

- In reports received in EudraVigilance 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 are:
  - Nervous-system disorders: dizziness, headache, syncope, paraesthesia, hypoaesthesia, lethargy, somnolence, tremor;
  - General disorders and administration-site conditions: pyrexia, fatigue, malaise, asthenia, chills, injection-site pain, feeling hot, influenza-like illness, chest discomfort, pain;
  - Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, oral paraesthesia;

[2] As stated by the marketing authorisation holder in the periodic safety update report dated 19 April 2010.

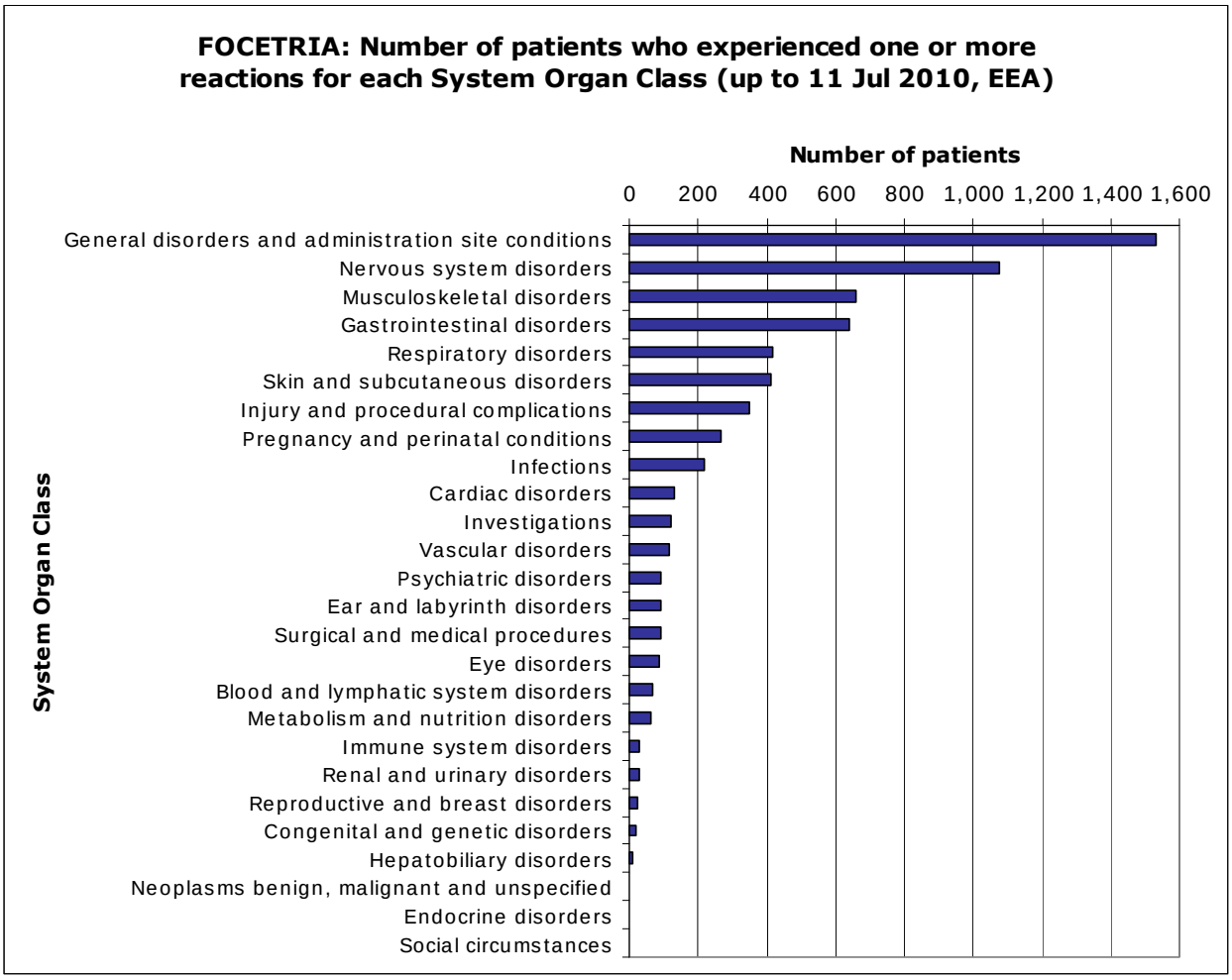
- Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness, muscle spasms;
- Skin and subcutaneous conditions: hyperhidrosis, pruritus, rash, urticaria, erythema;
- Respiratory disorders: oropharyngeal pain, cough, dyspnoea;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Ear and labyrinth disorders: vertigo;
- Infections: rhinitis, nasopharyngitis;
- Cardiac disorders: tachycardia, palpitations;
- Investigations: body temperature increased;
- Psychiatric disorders: sleep disorder;
- Injury and procedural complications: medication error, drug exposure during pregnancy.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included dizziness, medication error, vomiting, nausea, pallor, pyrexia, headache, hypersensitivity, syncope, underdose, injection site pain, rash, fatigue, malaise, diarrhoea, vision blurred, feeling hot and wrong technique in drug usage process.
- Since the last update, no new fatal cases have been reported to EudraVigilance in people vaccinated with Celvapan.

Focetria

As of 6 June 2010, a total of 3,330 reports had been received by EudraVigilance (an increase of 184 reports since the previous update). No change in the number of people vaccinated with Focetria has been communicated since the last update. Data available on 17 April 2010 from Member States and from the company[3] indicated that at least 36 million doses of Focetria had been distributed in the EEA, and at least 6.5 million patients had 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 are:
  - 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, pain, asthenia, injection-site pruritus, feeling cold, injection-site haematoma, injection-site warmth, oedema peripheral, feeling abnormal;
  - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, syncope, tremor, hypoaesthesia, dysgeusia, Guillain-Barré syndrome, presyncope, convulsion, migraine;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, back pain, muscle spasms, musculoskeletal pain, sensation of heaviness, rheumatoid arthritis;

[3] As stated by the marketing authorisation holder in the periodic safety update report dated 31 March 2010.

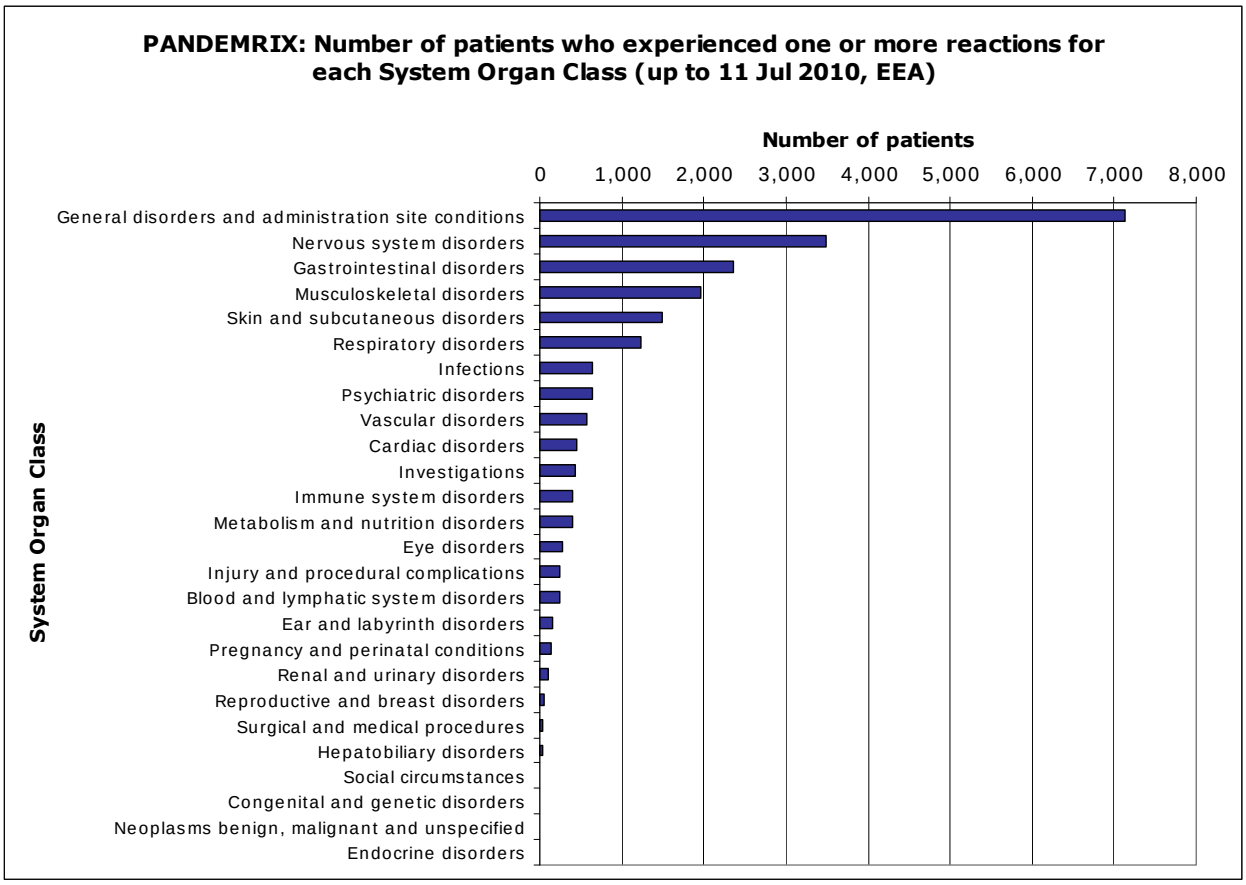
- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, rash generalised, swelling face, eczema;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia, throat irritation, productive cough;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, infection, pharyngitis, herpes zoster;
- Cardiac disorders: palpitations, tachycardia, arrhythmia, atrial fibrillation, cyanosis;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Psychiatric disorders: listlessness, insomnia, nightmare, moaning, restlessness, tearfulness;
- Eye disorders: visual impairment, eyelid oedema, eye irritation, conjunctivitis, eye swelling, vision blurred, diplopia, eye pain;
- Vascular disorders: hypertension, haemorrhage, hypotension, pallor, flushing, haematoma, peripheral coldness;
- Investigations: body temperature increased, blood pressure increased, C-reactive protein 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 drug exposure during pregnancy, pyrexia, headache, hyperpyrexia, premature baby, vomiting, cough, nausea, abdominal pain, diarrhoea, injection-site pain, small for dates baby, myalgia, fatigue, influenza like illness, dyspnoea, rash, large for dates baby, urticaria, malaise and convulsion.
- Since the last update, one new fatal case originating from outside the EEA has been reported to EudraVigilance. It concerns a male child aged 2.5 years who had febrile convulsions during the night following the second dose of Focetria and developed cardio-pulmonary arrest.

Pandemrix

As of 11 July 2010, a total of 11,185 reports had been received by EudraVigilance (an increase of 135 reports since the previous update). Data available on 19 July 2010 from Member States and from the company4 indicate that at least 131.8 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 30.8 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 are:
  - 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, chest pain, injection-site inflammation, feeling hot, gait disturbance, chest discomfort, local reaction;
  - Nervous-system disorders: headache, dizziness, paraesthesia, syncope, somnolence, hypoaesthesia, crying, convulsion, febrile convulsion, tremor, loss of consciousness, lethargy, Guillain-Barré syndrome, presyncope, facial palsy, hypersomnia, poor quality sleep, hypotonia;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, dysphagia, lip swelling, dry mouth, swollen tongue, abdominal discomfort, hypoaesthesia oral, lower abdominal pain;

[4] As stated by the marketing authorisation holder in the periodic safety update report dated 9 April 2010.

- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, muscular weakness, musculoskeletal stiffness, back pain, musculoskeletal pain, limb discomfort, neck pain, muscle spasms, arthritis;
- Skin and subcutaneous conditions: rash, urticaria, erythema, hyperhidrosis, pruritus, rash generalised, angioedema, cold sweat, swelling face, rash erythematous, rash macular, rash pruritic, dermatitis allergic, pruritus generalised, petechiae, facial hypoaesthesia, rash maculo-papular, eczema, night sweats, vesicular rash, skin reaction;
- Respiratory disorders: dyspnoea, cough, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, respiratory failure, throat tightness, pharyngeal oedema, tachypnoea, bronchospasm, respiratory distress, sneezing, dysphonia, pulmonary embolism, hyperventilation, productive cough, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, confusional state, hallucination, anxiety, nightmare;
- Infections: rhinitis, pneumonia, nasopharyngitis, influenza, herpes zoster, H1N1 influenza, cellulitis, lower respiratory tract infection, bronchitis, respiratory tract infection, ear infection, bronchopneumonia, gastroenteritis, infection, sepsis, urinary tract infection;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, peripheral coldness, hot flush;
- Metabolism and nutrition disorders: decreased appetite, oligodipsia, dehydration, hypoglycaemia, polydipsia;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, cardiac failure, atrial fibrillation, bradycardia, cardiac arrest, angina pectoris, myocarditis;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;
- Investigations: body temperature increased, blood pressure decreased, blood pressure increased, heart rate increased, weight decreased, C-reactive protein increased, transaminases increased, heart rate decreased, blood creatine phosphokinase increased, body temperature decreased;
- Eye disorders: vision blurred, eye pain, eye swelling, visual impairment, diplopia, ocular hyperaemia, eyelid oedema, photophobia, conjunctivitis;
- Blood and lymphatic system disorders: lymphadenopathy, thrombocytopenia;
- Injury and procedural disorders: medication error, drug exposure during pregnancy, vaccination failure, fall, contusion;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain.

Updated safety information

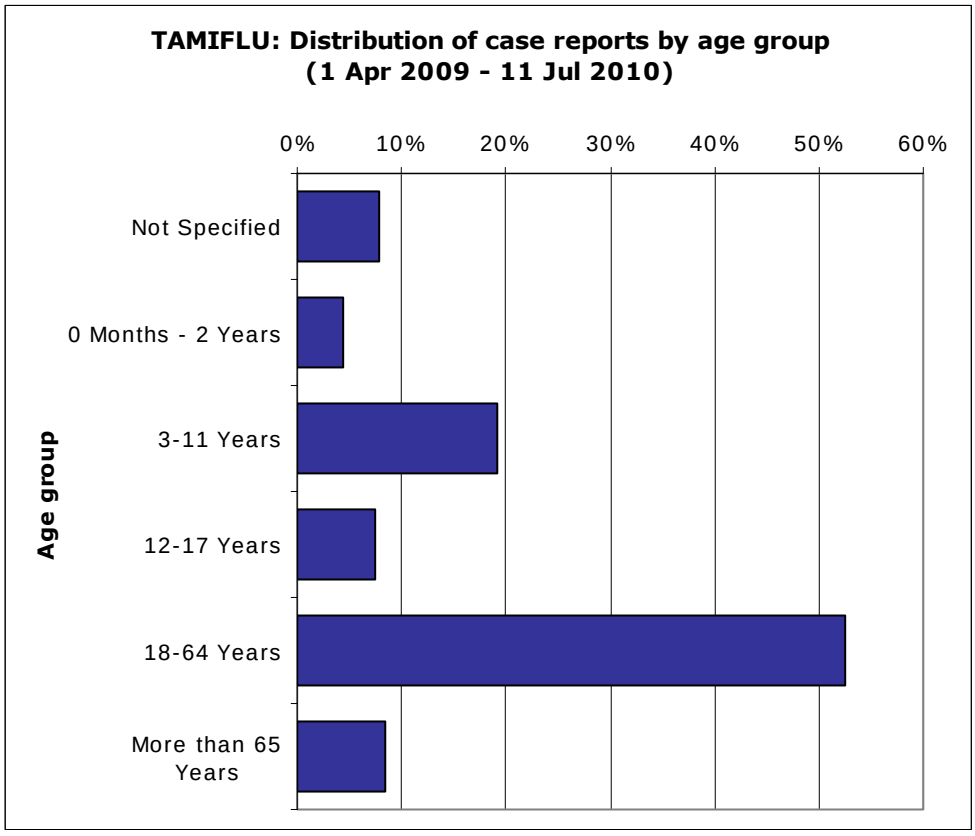
- The most frequently reported suspected adverse reactions in children since authorisation included pyrexia, hyperpyrexia, vomiting, injection-site pain, headache, diarrhoea, cough, fatigue, rash, decreased appetite, nausea, abdominal pain, malaise, injection-site erythema, crying, somnolence, pallor, injection site swelling, listlessness, syncope, dyspnoea, pain in extremity, influenza-like illness, febrile convulsion, myalgia, urticaria, dizziness, tearfulness and erythema.

- Since the last update one new case of death has been received by EudraVigilance in relation to Pandemrix. It concerns a woman aged 65 years who presented with an acute disseminated encephalomyelitis after the second dose of vaccination. She developed respiratory insufficiency and died four months after the vaccination.

Antiviral medicines

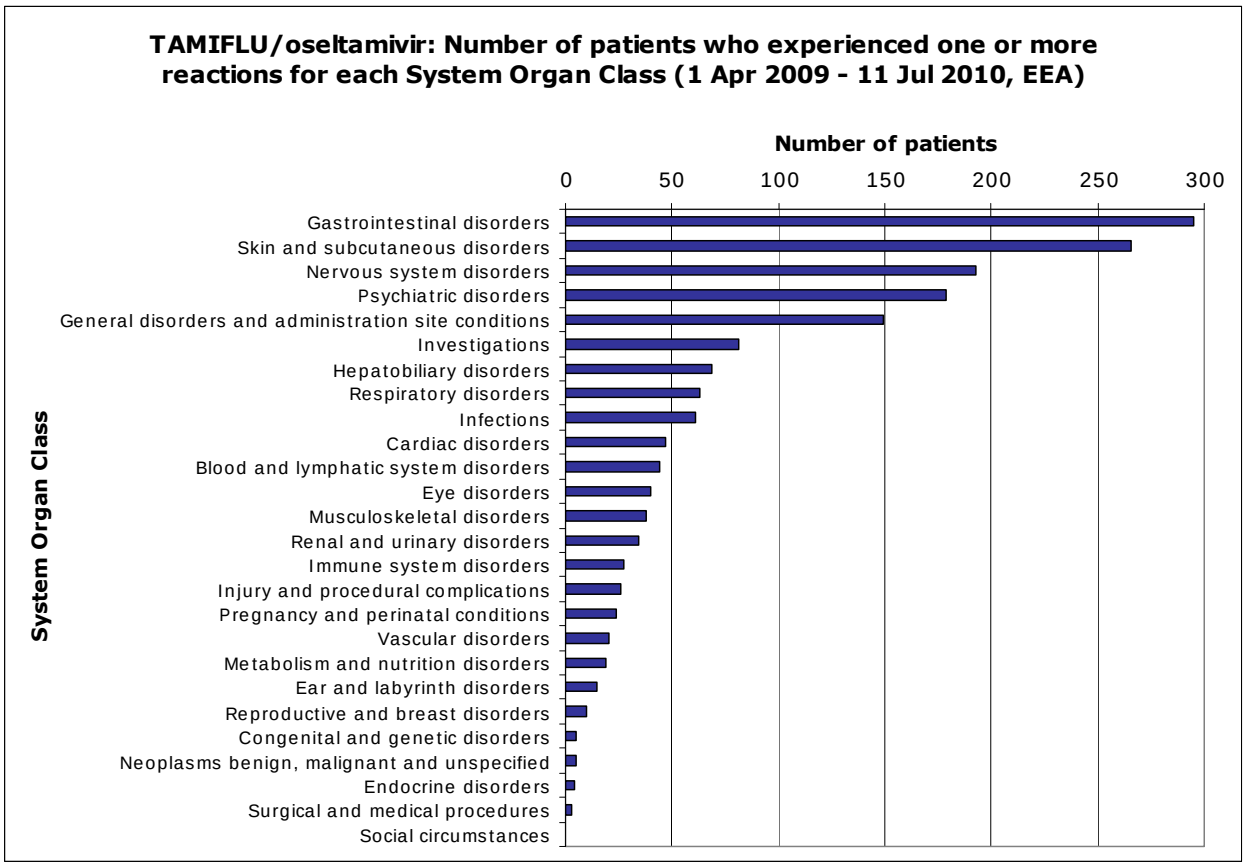
Tamiflu (oseltamivir)

From 1 April 2009 to 11 July 2010, a total of 1,135 reports worldwide were received by EudraVigilance (an increase of 18 reports since the previous update). The graph below displays the age distribution of patients who experienced an adverse reaction reported to EudraVigilance.



According to information received from the marketing authorisation holder,[5] exposure to Tamiflu is estimated to be at least 22.9 million patients during the pandemic period of 1 May 2009 to 31 May 2010.

[5] As stated by the marketing authorisation holder in the periodic safety update dated 25 June 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 are:
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, lip swelling, mouth ulceration, haematemesis, pancreatitis, pancreatitis acute, swollen tongue;
  - Skin and subcutaneous conditions: rash, rash generalised, urticaria, erythema, swelling face, pruritus, Stevens-Johnson syndrome, angioedema, rash erythematous, rash pruritic, erythema multiforme, dermatitis bullous, rash macular, blister, rash maculo-papular;
  - Nervous-system disorders: headache, convulsion, paraesthesia, dizziness, epilepsy, tremor, somnolence, syncope, burning sensation, nystagmus, psychomotor hyperactivity, balance disorder, cerebrovascular accident, coordination abnormal, disturbance in attention, dysgeusia;
  - Psychiatric disorders: hallucination, confusional state, insomnia, nightmare, anxiety, delirium, hallucination visual, disorientation, abnormal behaviour, agitation, depression, panic attack, sleep disorder, aggression, depressed mood, hallucination auditory, mental disorder, psychotic disorder;
  - General disorders and administration-site conditions: malaise, death, pyrexia, drug ineffective, chest pain, condition aggravated, drug interaction, influenza-like illness, fatigue, oedema peripheral, general physical health deterioration, pain, multi-organ failure, face oedema, gait disturbance, asthenia;

- Investigations: liver function test abnormal, hepatic enzyme increased, international normalised ratio increased, blood triglycerides increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, blood creatinine increased, aspartate aminotransferase increased;
- Respiratory disorders: epistaxis, dyspnoea, pulmonary embolism, cough, chronic obstructive pulmonary disease;
- Infections: pathogen resistance, influenza, pneumonia, hepatitis A, pneumonia viral, bacterial infection, bronchitis;
- Hepatobiliary disorders: hepatitis, cholestasis, acute hepatic failure, hepatic failure, cytolytic hepatitis, jaundice, hepatotoxicity.

Updated safety information

- 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, convulsion, nightmare, epistaxis, urticaria, diarrhoea, headache, nausea, abdominal pain and delirium.
- Since the last update, three new case reports worldwide have been received by the EudraVigilance system with a fatal outcome following oseltamivir use. None of the cases occurred within the EEA. In two cases the cause of death was not provided. One case occurred in 2006 and was reported in the context of an avian pandemic registry. The cause of death was pneumonia.

Appendix 1

Specific topics discussed for H1N1 vaccines in previous updates

SOC	Topic	Update number		
		Celvapan	Focetria	Pandemrix
Blood and lymphatic system disorders	Haematopoietic cytopenia			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, 20	10, 20	10, 20
	Fever, local reaction and drowsiness following second 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
	Demyelinating disorders	11	11	11
	Encephalitis		3, 5	
	Facial palsy or paresis	8	4, 8	7
	Guillain-Barré syndrome	4, 5, 11, 16, 20	2, 4, 5, 11, 16, 20	1, 3, 4, 5, 6, 11, 16, 20
	Multiple sclerosis	11	5, 11	5, 11
	Neuralgic amyotrophy			9
	Neuritis, polyneuritis, polyradiculoneuritis, peripheral neuropathy, polyneuropathy			6
	Paraesthesia	2		
	Paralysis and paresis	7	8	3
	Seizures		8, 13	13
	Seizures with fatal outcome			4
Pregnancy, puerperium and perinatal conditions	Intra-uterine death		4	
	Pregnancy-related events	11	2, 11	1, 2, 11

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