3 June 2010
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Patient Health Protection

Nineteenth 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 23 May 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 positive opinion from the Committee for Medicinal Products for Human Use (CHMP). The formal decision on this vaccine's marketing authorisation from the European Commission is expected shortly. 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 vast majority of the adverse reactions that had been reported as of 23 May 2010 are considered to be non-serious.

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

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 weekly influenza surveillance overview dated 28 May 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that, as of 23 May 2010, influenza activity in Europe had stabilised at low intensity with no geographic spread. While still in pandemic Phase 6 globally, epidemiological and virological indicators are consistent with the 2009/10 influenza season coming to an end in Europe.

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. The World Health Organization (WHO) and ECDC recognise that this figure of 2,900 deaths will only be a proportion of the true number of deaths due to the pandemic in Europe. It will be some time before it will be possible to estimate that proportion. There are important qualitative differences noted in the patterns of mortality seen in seasonal and pandemic influenza. In seasonal influenza, the experience is usually that over three quarters of the deaths are in older persons (those aged 65 years and older) while over three quarters of the confirmed deaths declared during this A/H1N1 pandemic have been in younger persons (under 65 years). Another difference is that deaths from seasonal influenza are unusual among younger healthy persons while for this pandemic 25% to 30% of deaths have been in entirely healthy younger persons.

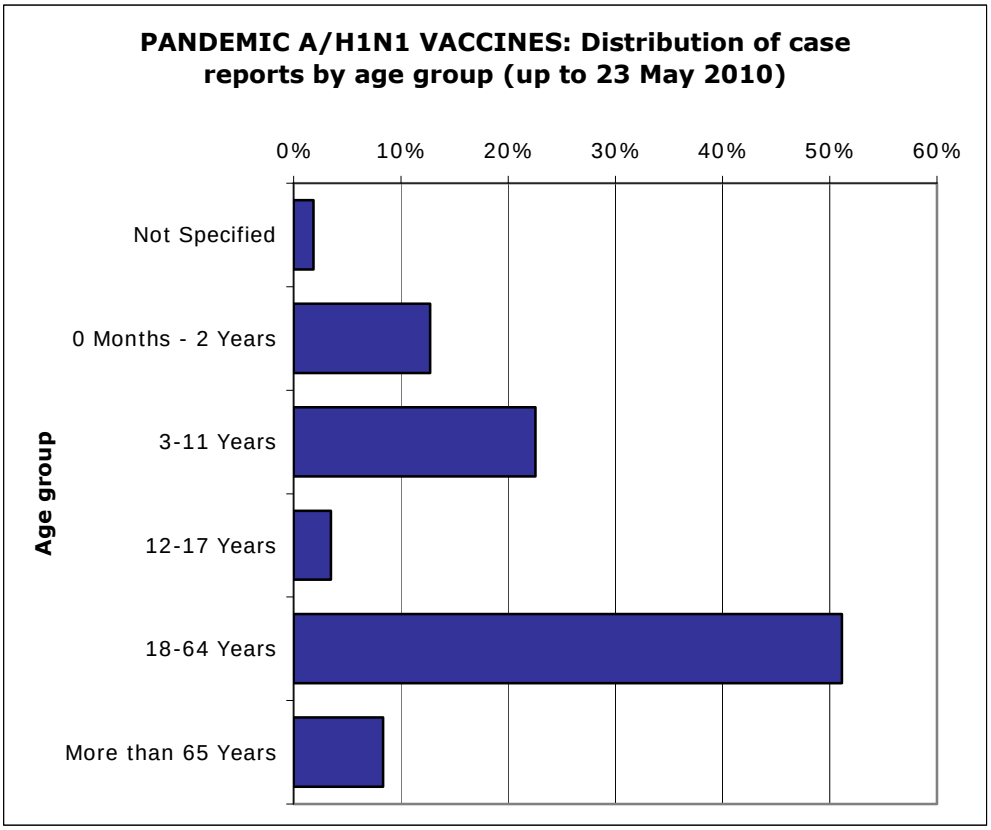
See the ECDC pandemic website and its last weekly executive update dated 4 May 2010 for additional information

In its weekly update dated 28 May 2010, the WHO reported that, as of 23 May 2010, more than 214 countries and overseas territories or communities worldwide have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18,114 deaths.

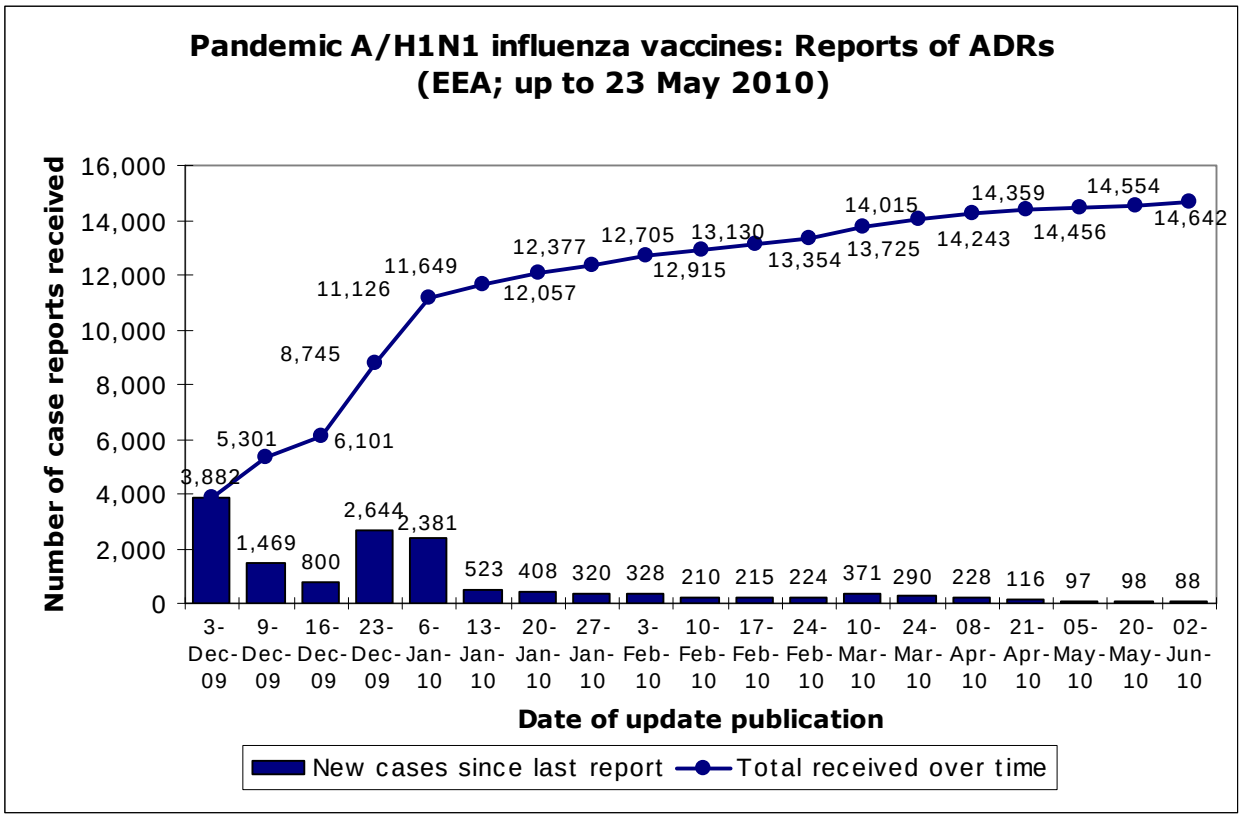
Published estimates of vaccine field effectiveness based on epidemiological data are starting to become available, such as a recent estimate published in an article of Eurosurveillance, which indicates for one of the pandemic vaccines a significant field effectiveness as good as (if not better than) 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 23 May 2010, a total of 14,642 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 88 reports compared with the previous update. The graph below displays the age distribution of all the reports received by EudraVigilance:



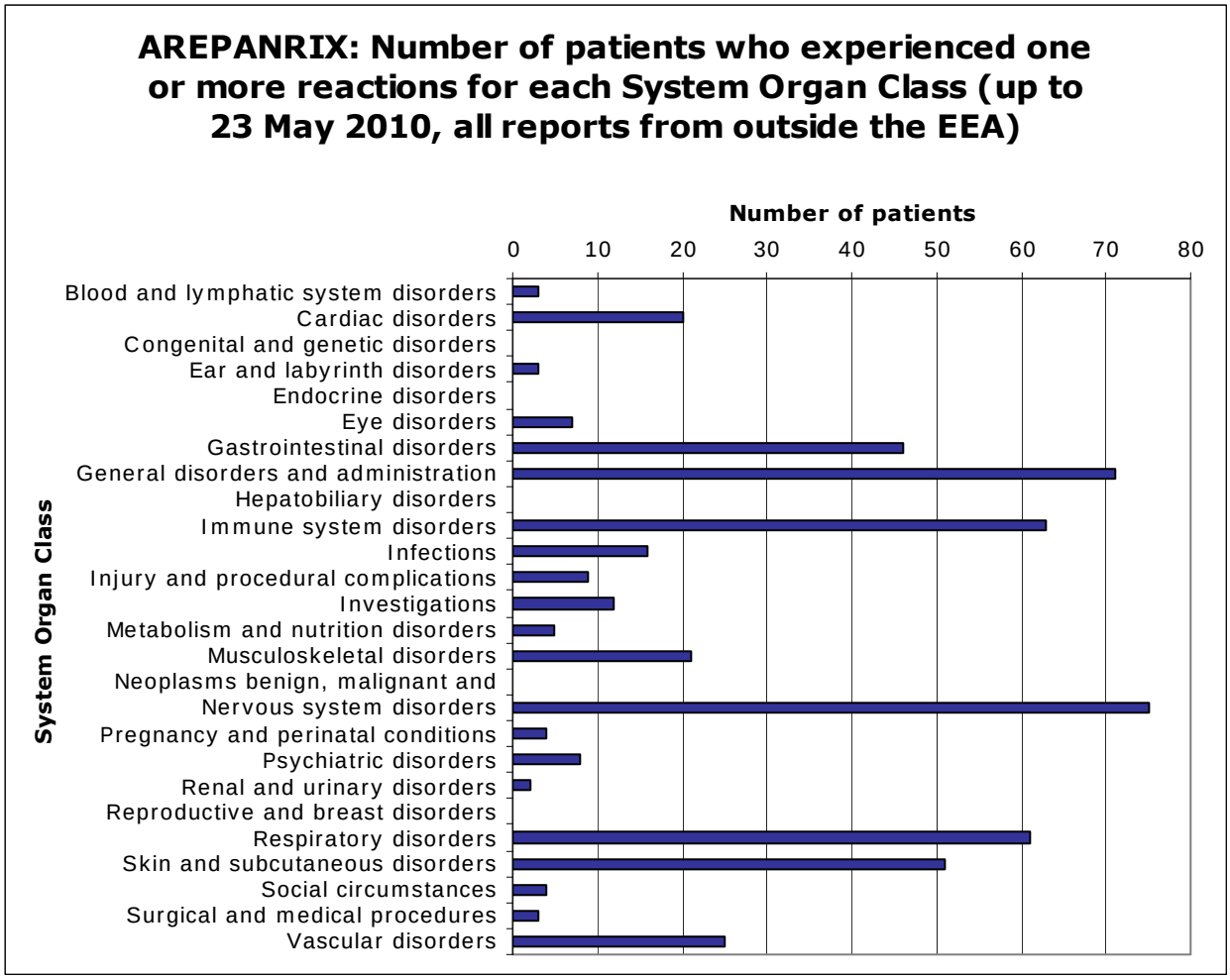
The graphs below display the cumulative numbers of adverse reaction reports received by EudraVigilance for the three centrally authorised vaccines marketed in the EEA (Celvapan, Focetria and Pandemrix), as well as the number of new adverse reaction reports received between each update:



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 23 May 2010, a total of 148 reports had been received by EudraVigilance from outside the EEA. This represents an increase of ten 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, dizziness, hypoaesthesia, hyporeflexia, paralysis flaccid, cranial nerve paralysis, headache;
  - General disorders and administration-site conditions: pyrexia, asthenia, product quality issue, fatigue;
  - Immune disorders: anaphylactic reaction, hypersensitivity;

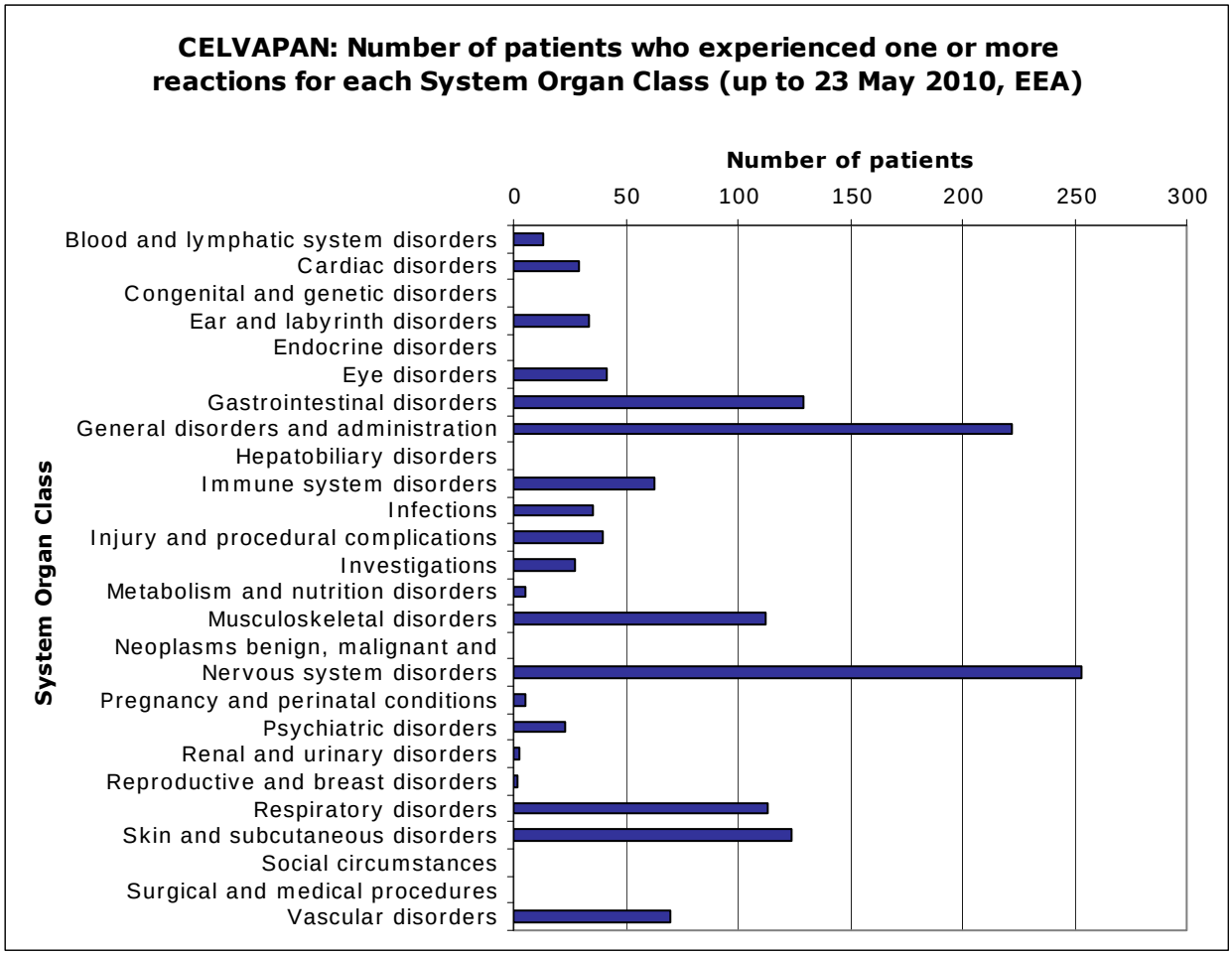
- Respiratory disorders: dyspnoea, throat tightness, cough, pharyngeal oedema, respiratory paralysis, respiratory disorder;
- Skin and subcutaneous conditions: angioedema, urticaria, erythema;
- Gastrointestinal disorders: nausea;
- Vascular disorders: flushing, pallor;
- Musculoskeletal disorders: muscular weakness, pain in extremity, myalgia;
- Cardiac disorders: tachycardia, cyanosis;
- Infections: transmission of an infectious agent via a medicinal product, nasopharyngitis.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation include dyspnoea, urticaria, cough, angioedema, anaphylactic reaction, pyrexia, cyanosis, anaphylactic shock, erythema, hypersensitivity, febrile convulsion, rash, flushing, nausea, depressed level of consciousness, headache, tremor, throat tightness, pruritus, skin discolouration and pallor.
- Since the last update, no fatal cases have been reported from the EEA in people vaccinated with Arepanrix.

Celvapan

As of 23 May 2010, a total of 557 reports had been received by EudraVigilance (an increase of two reports since the previous update). 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 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: 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, pain;
  - Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, oral paraesthesia;
  - Skin and subcutaneous conditions: hyperhidrosis, pruritus, urticaria, rash, erythema;
  - Respiratory disorders: oropharyngeal pain, cough, dyspnoea;

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

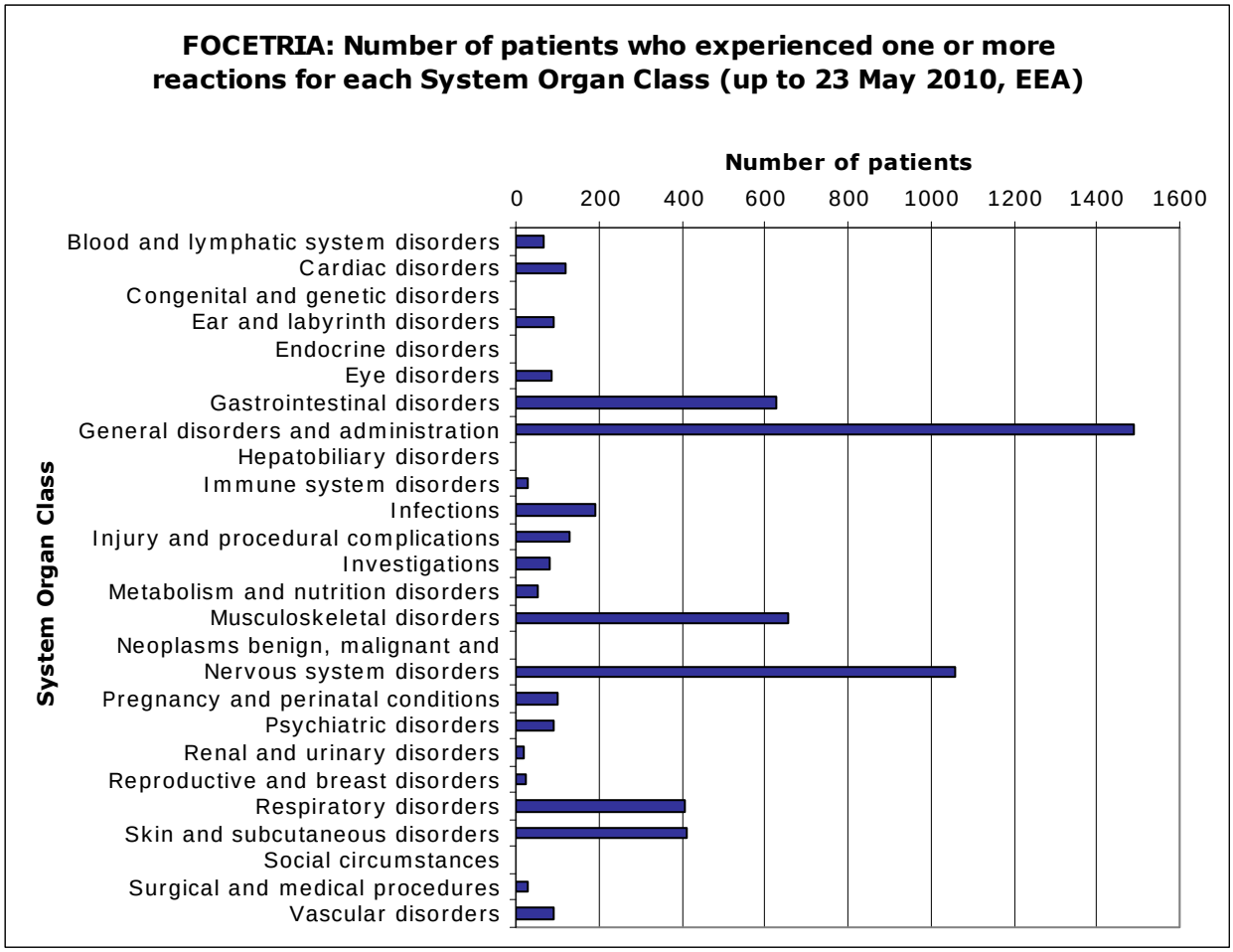
- Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Injury and procedural complications: medication error;
- Infections: rhinitis, nasopharyngitis;
- Ear and labyrinth disorders: vertigo;
- Cardiac disorders: tachycardia, palpitations;
- Investigations: body temperature increased;
- Psychiatric disorders: sleep disorder;

Updated safety information

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

Focetria

As of 23 May 2010, a total of 3,096 reports had been received by EudraVigilance (an increase of 35 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, asthenia, pain, injection-site pruritus, feeling cold, injection-site haematoma, injection-site warmth, oedema peripheral, feeling hot;
  - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, tremor, hypoaesthesia, syncope, dysgeusia, Guillain-Barré syndrome, presyncope, convulsion, migraine;

[3] According from the last periodic safety update report dated 31 March 2010.

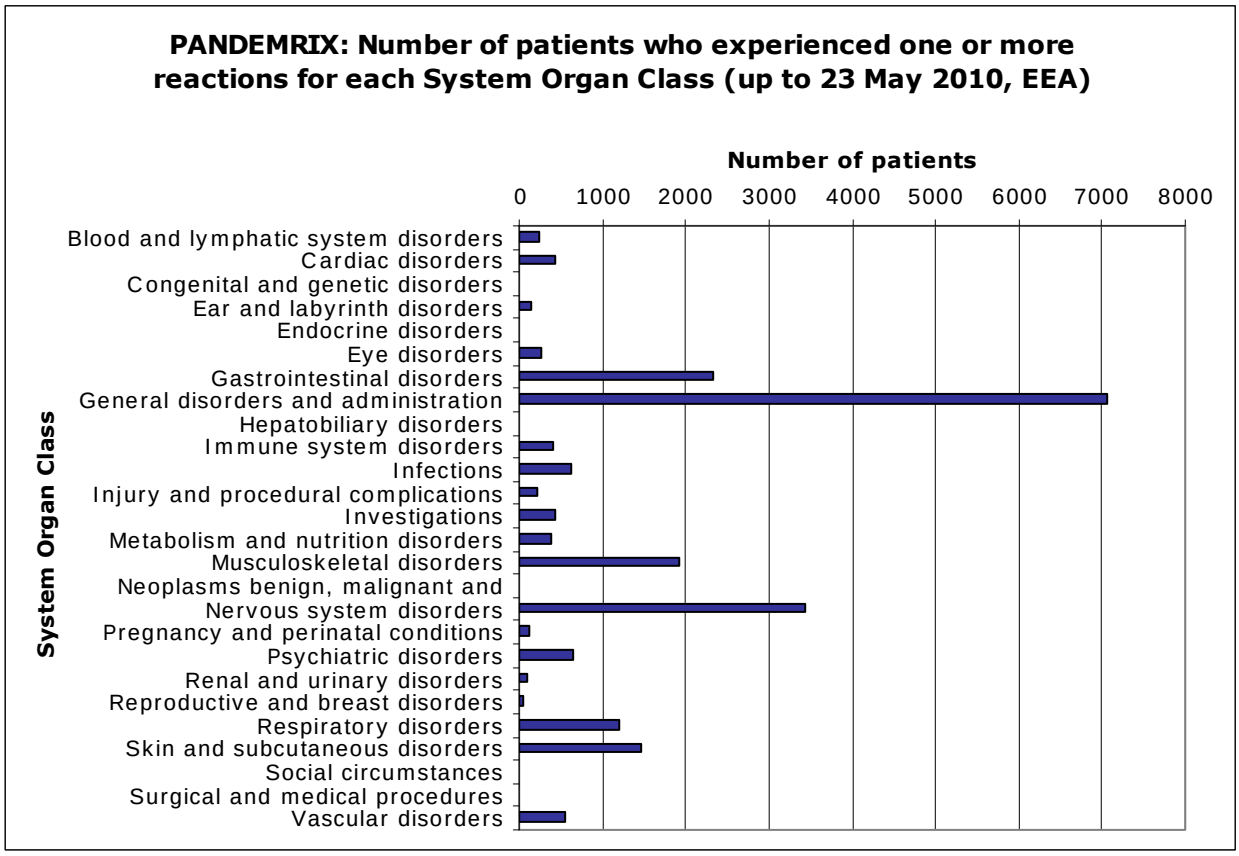
- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, muscle spasms, musculoskeletal pain, back pain, sensation of heaviness, rheumatoid arthritis;
- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, rash generalised, swelling face, eczema;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia, productive cough, throat irritation;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, pharyngitis, herpes zoster;
- Injury and procedural complications: drug exposure during pregnancy, contusion, vaccination failure;
- Cardiac disorders: palpitations, tachycardia, arrhythmia, atrial fibrillation, cyanosis;
- Pregnancy and perinatal conditions: pre-eclampsia, premature baby, intra-uterine death, premature labour;
- Vascular disorders: hypertension, hypotension, flushing, pallor, haematoma, peripheral coldness;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Psychiatric disorders: listlessness, insomnia, nightmare, restlessness, tearfulness;
- Eye disorders: visual impairment, eyelid oedema, eye irritation, conjunctivitis, eye swelling, vision blurred, diplopia, eye pain;
- 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, drug exposure during pregnancy, cough, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, fatigue, influenza-like illness, rash, dyspnoea, urticaria, malaise and convulsion.
- Since the last update, no fatal cases have been reported in people vaccinated with Focetria.

Pandemrix

As of 23 May 2010, a total of 11,014 reports had been received by EudraVigilance (an increase of 51 reports since the previous update). Data available on 31 May 2010 from Member States and from the company[4] indicate that at least 131.7 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 30.7 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, chest discomfort, local reaction;
  - Nervous system disorders: headache, dizziness, paraesthesia, syncope, somnolence, hypoaesthesia, crying, febrile convulsion, convulsion, tremor, lethargy, loss of consciousness, Guillain-Barré syndrome, presyncope, facial palsy, hypersomnia, hypotonia, poor quality sleep;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, dysphagia, lip swelling, swollen tongue, dry mouth, 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, dermatitis allergic, rash pruritic, pruritus generalised, facial hypoaesthesia, petechiae, rash maculo-papular, eczema, night sweats, vesicular rash, skin reaction;
- Respiratory disorders: dyspnoea, cough, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, throat tightness, pharyngeal oedema, tachypnoea, bronchospasm, respiratory failure, respiratory distress, sneezing, dysphonia, pulmonary embolism, hyperventilation, productive cough, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, hallucination, anxiety, confusional state, nightmare;
- Infections: rhinitis, pneumonia, nasopharyngitis, influenza, herpes zoster, H1N1 influenza, cellulitis, bronchitis, lower respiratory tract infection, respiratory tract infection, ear infection, gastroenteritis, bronchopneumonia;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, peripheral coldness, hot flush;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, cardiac failure, atrial fibrillation, cardiac arrest, bradycardia, angina pectoris, myocarditis;
- Investigations: body temperature increased, blood pressure decreased, blood pressure increased, heart rate increased, weight decreased, transaminases increased, C-reactive protein increased, heart rate decreased, body temperature decreased;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;
- Metabolism and nutrition disorders: decreased appetite, oligodipsia, dehydration, hypoglycaemia, polydipsia;
- Eye disorders: vision blurred, eye pain, eye swelling, visual impairment, ocular hyperaemia, diplopia, eyelid oedema, photophobia, conjunctivitis;
- Blood and lymphatic system disorders: lymphadenopathy, thrombocytopenia;
- Injury and procedural disorders: medication error, vaccination failure, fall, contusion;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain.

Updated safety information

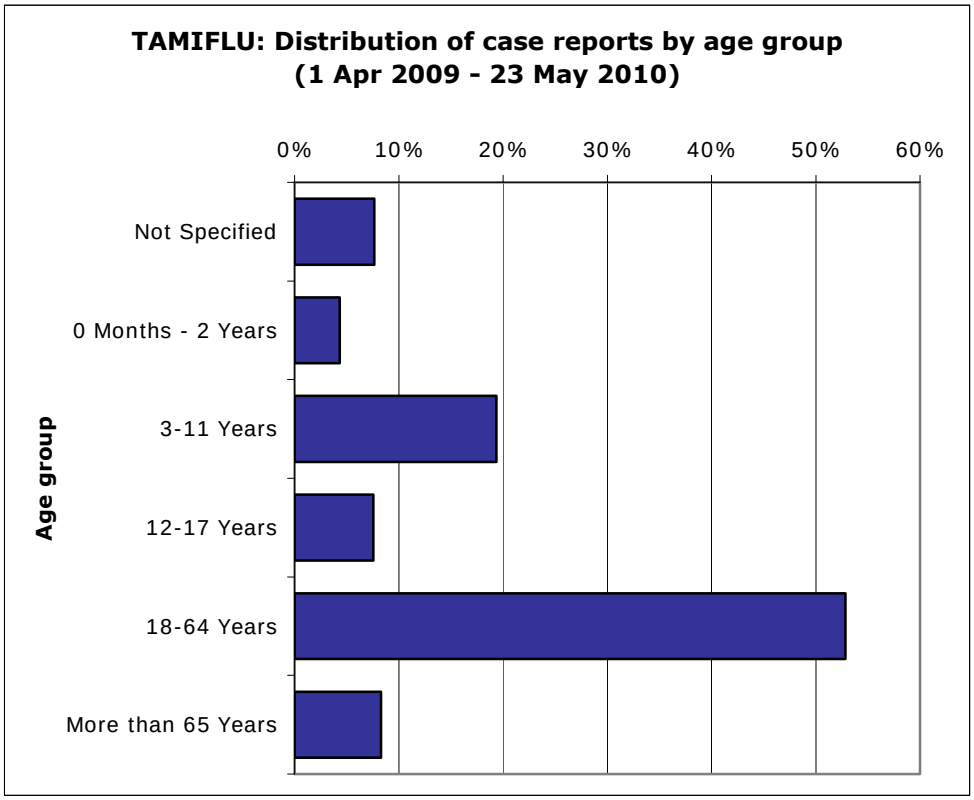
- The most frequently reported suspected adverse reactions in children since authorisation were pyrexia, hyperpyrexia, vomiting, injection-site pain, headache, diarrhoea, cough, fatigue, rash, decreased appetite, nausea, abdominal pain, malaise, injection-site erythema, crying, somnolence, pallor, listlessness, injection site swelling, syncope, dyspnoea, pain in extremity, influenza-like illness, febrile convulsion, myalgia, urticaria, dizziness, tearfulness and erythema.
- Since the last update, one new fatal case following vaccination with Pandemrix has been reported. It concerns a 85 year-old male patient who died of bilateral lung embolism three days after

vaccination. The probable cause of the embolism was an extensive prostate adenocarcinoma with metastases in the lungs.

Antiviral medicines

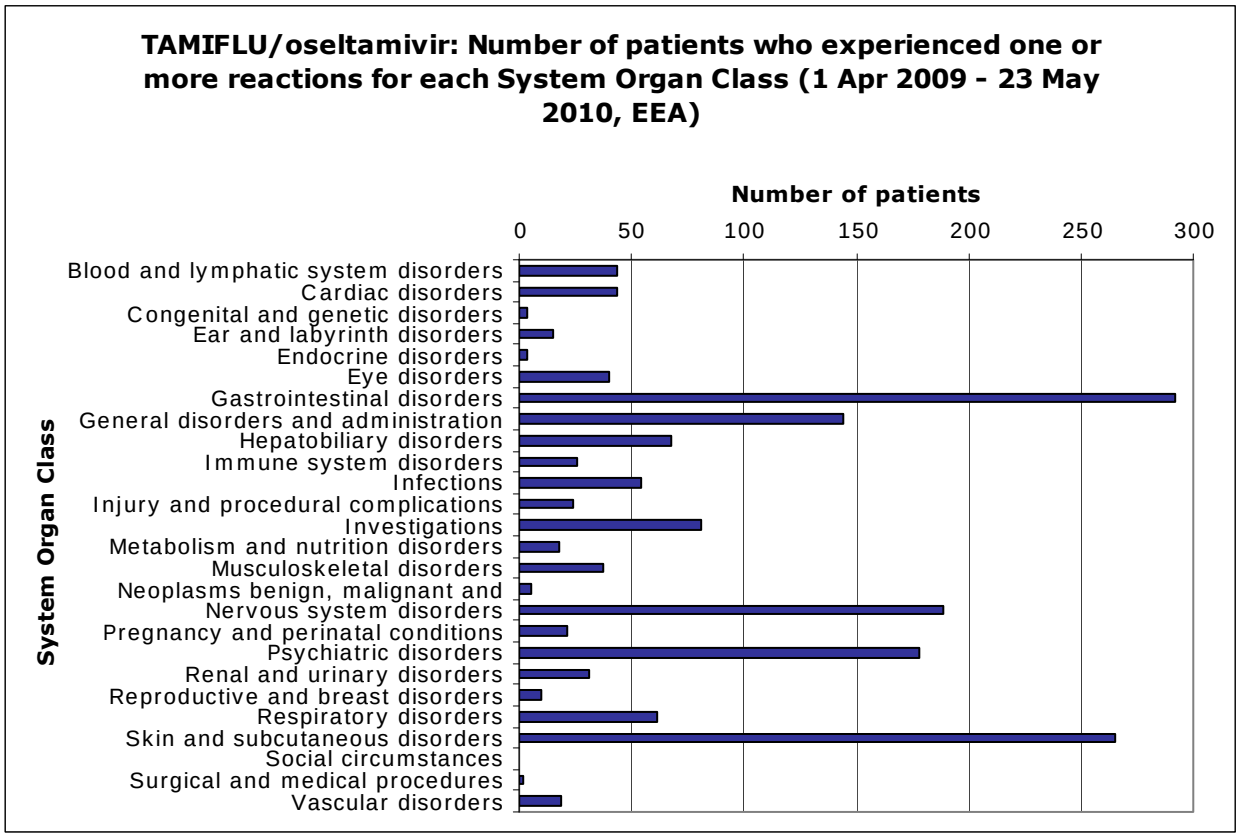
Tamiflu (oseltamivir)

From 1 April 2009 to 23 May 2010, a total of 1,111 reports worldwide were received by EudraVigilance (an increase of ten 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 22.7 million patients during the pandemic period of 1 May 2009 to 31 March 2010.

[5] As stated by the marketing authorisation holder in the periodic safety update dated 23 April 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, dyspepsia, abdominal distension;
  - 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, nightmare, anxiety, insomnia, delirium, hallucination visual, disorientation, abnormal behaviour, agitation, panic attack, sleep disorder, aggression, depression, depressed mood, hallucination auditory, mental disorder, psychotic disorder;
  - General disorders and administration-site conditions: malaise, death, pyrexia, condition aggravated, drug ineffective, drug interaction, influenza-like illness, chest pain, oedema peripheral, fatigue, pain, general physical health deterioration, multi-organ failure, face oedema, gait disturbance;

- 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, hepatic enzyme abnormal, prothrombin time prolonged;
- Respiratory disorders: epistaxis, dyspnoea, pulmonary embolism, chronic obstructive pulmonary disease;
- Hepatobiliary disorders: hepatitis, cholestasis, acute hepatic failure, hepatic failure, jaundice cytolytic hepatitis, hepatotoxicity;
- Infections: pathogen resistance, influenza, pneumonia, hepatitis A, bacterial infection, bronchitis.

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, headache, diarrhoea, nausea, abdominal pain and delirium.
- Since the last update, five new case reports worldwide have been received by the EudraVigilance system with a fatal outcome following oseltamivir use. One of the cases occurred within the EEA. In one case the cause of death was not provided but the patient had recently been diagnosed with acute lymphocytic leukaemia. In another case, the cause of death was related to septic shock and worsening of bacterial pneumonia. The three other cases occurred between 2004 and 2006 and were reported in the context of an avian pandemic registry. The cause of death was not provided.

- 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	10	10
	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	2, 4, 5, 11, 16	1, 3, 4, 5, 6, 11, 16
	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