



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 June 2010
EMA/395118/2010
Patient Health Protection

Twentieth 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 Tamiflu¹. 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 6 June 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.



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 6 June 2010 are considered to be non-serious.

As of 14 June 2010, in the EEA, at least 38.5 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 46.1 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.

This twentieth pandemic update is the last update to be published every two weeks. Subsequent pandemic pharmacovigilance updates will be published every month. The twenty-first update will be published by the Agency during the week starting on 19 July 2010.

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 4 June 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that, as of 28 May 2010, sentinel surveillance systems in many European countries have stopped monitoring the rates of influenza-like illness or acute respiratory infection. Reports from countries where data are still available indicate that influenza activity in Europe has stabilised at low intensity with an absence of geographic spread. Although the pandemic remains at 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 [monthly executive update](#) dated 4 May 2010 for additional information

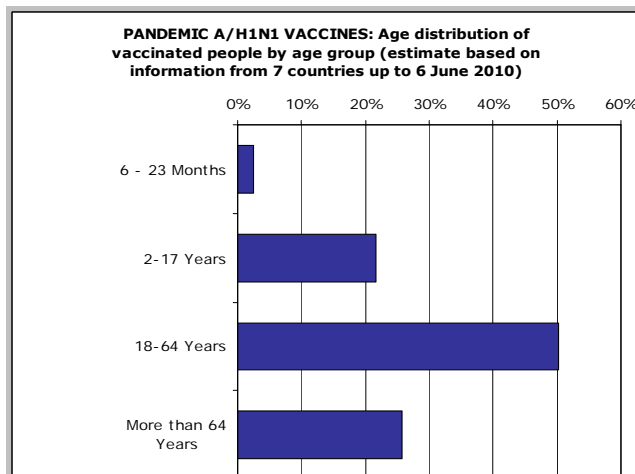
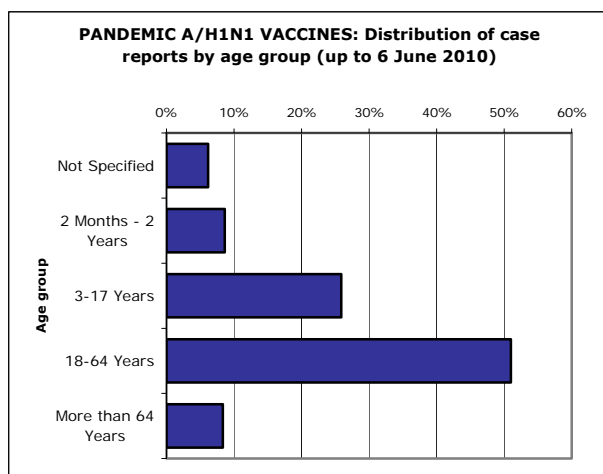
In its [weekly update](#) dated 11 June 2010, the WHO reported that, as of 6 June 2010, more than 214 countries and overseas territories or communities worldwide have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18,156 deaths.

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.

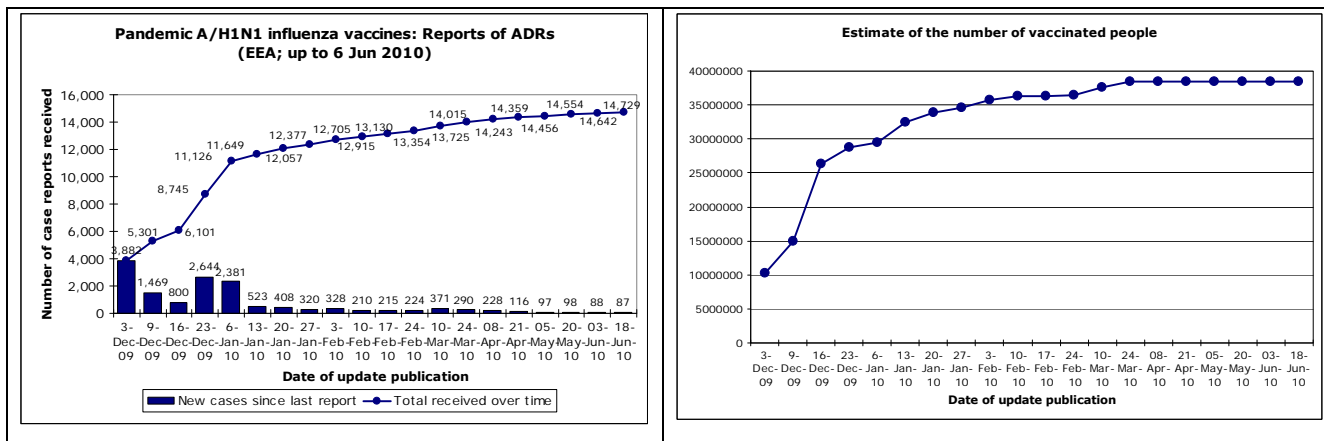
Overview of centrally authorised vaccines

As of 6 June 2010, a total of 14,729 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 87 reports compared with the previous update.

The graphs below displays the age distribution of all the reports received by EudraVigilance up to 6 June 2010 and the age distribution of the vaccinated population, approximated from a compilation of available data from seven countries (Belgium, Denmark, France, Greece, Norway, Portugal and Sweden).



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), with the number of new adverse reaction reports received between each update, and an estimate of the number of vaccinated people according to information received from Member States. This graph takes into account a review of the exposure data provided by each Member State, which explains some differences with previous updates.



In addition to a summary of the reports received by EudraVigilance up to 6 June 2010, this 20th pharmacovigilance pandemic update presents below for each vaccine an overview of the available clinical safety data from clinical trials and the post-marketing experience reviewed by the CHMP in April 2010 in the context of the re-assessment of the benefit-risk profile.

Since the last update, the European Medicines Agency has been made aware of the publication of preliminary results of a study on the risk of Guillain-Barré syndrome (GBS) following vaccination against A/H1N1 pandemic influenza in the United States, where the vaccines are different from those authorised in the EU.² The study shows a very small excess risk of GBS in people vaccinated compared with those who were not vaccinated, which corresponds to 0.8 additional cases of GBS for every 1 million vaccinations. If confirmed, this small risk would be no more than that found with seasonal influenza vaccines. This is also much smaller than the risk observed during the 1976 swine flu vaccination campaign where around 10 excess cases per 1 million vaccinations were reported. In addition, the causality has not been confirmed as some patients had other illness which could have been the cause of GBS. To date, the other surveillance systems used to monitor the safety of the pandemic vaccines in the USA have not detected any statistically significant association with GBS. These results are in line with the conclusions of group of experts convened by the European Medicines Agency in March 2010 to review the data on reported cases of GBS. The expert group concluded that there was not enough evidence to establish a link but that if an increased risk of GBS does exist, it would probably be of a very small magnitude.³ The Agency is currently awaiting the results of epidemiological studies carried out in several European countries.

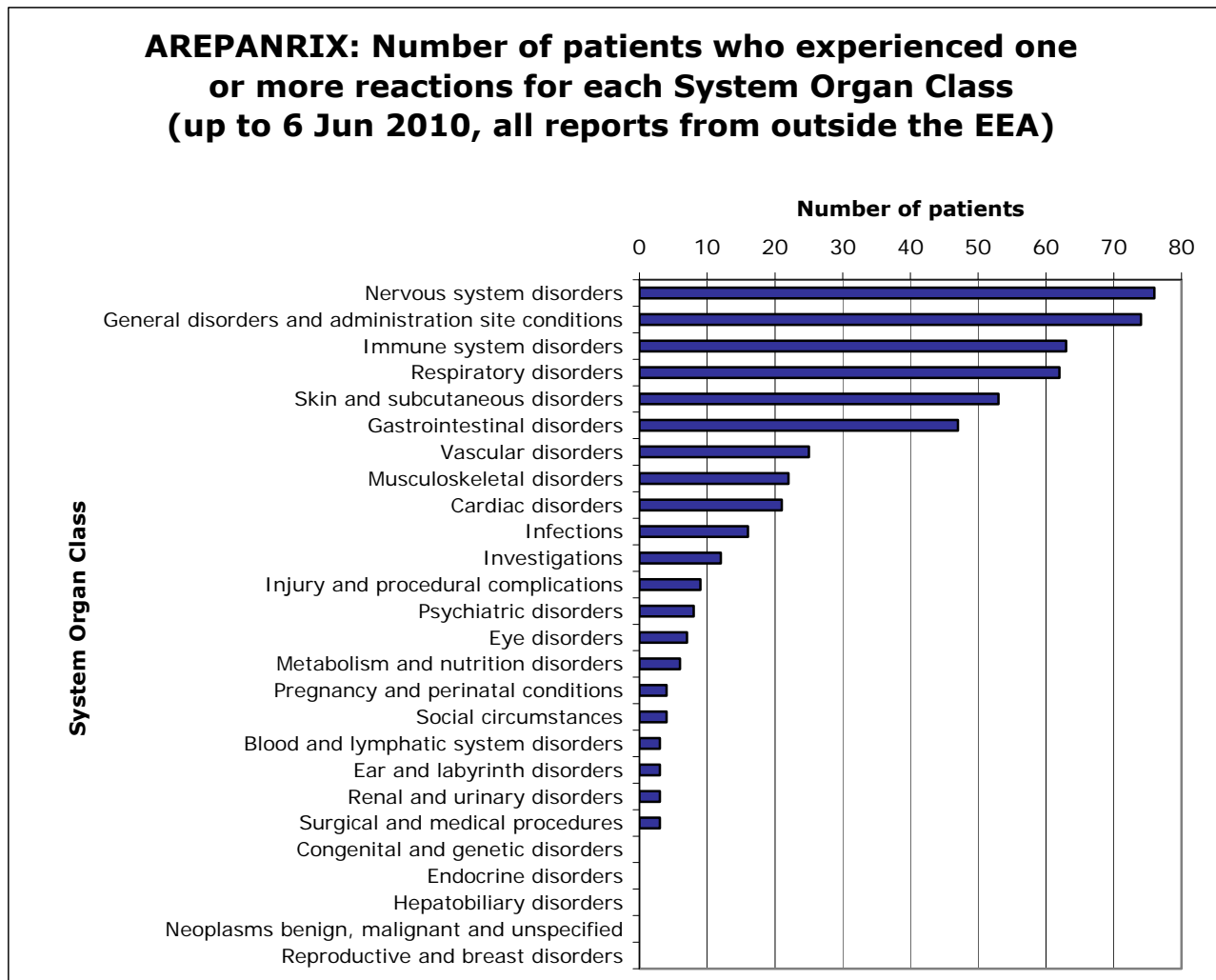
A list of specific topics discussed in previous updates is included in [Appendix 1](#).

² http://www.cdc.gov/mmwr/preview/mmwrhtml/mm59e0602a1.htm?s_cid=mm59e0602

³ Appendix 1 of the Sixteenth pandemic pharmacovigilance update contains a summary of the expert group report. See: <http://www.ema.europa.eu/pdfs/influenza/25590710en.pdf>

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 6 June 2010, a total of 151 reports had been received by EudraVigilance from outside the EEA. This represents an increase of three 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;
 - Respiratory disorders: dyspnoea, throat tightness, cough, pharyngeal oedema, respiratory paralysis, respiratory disorder;

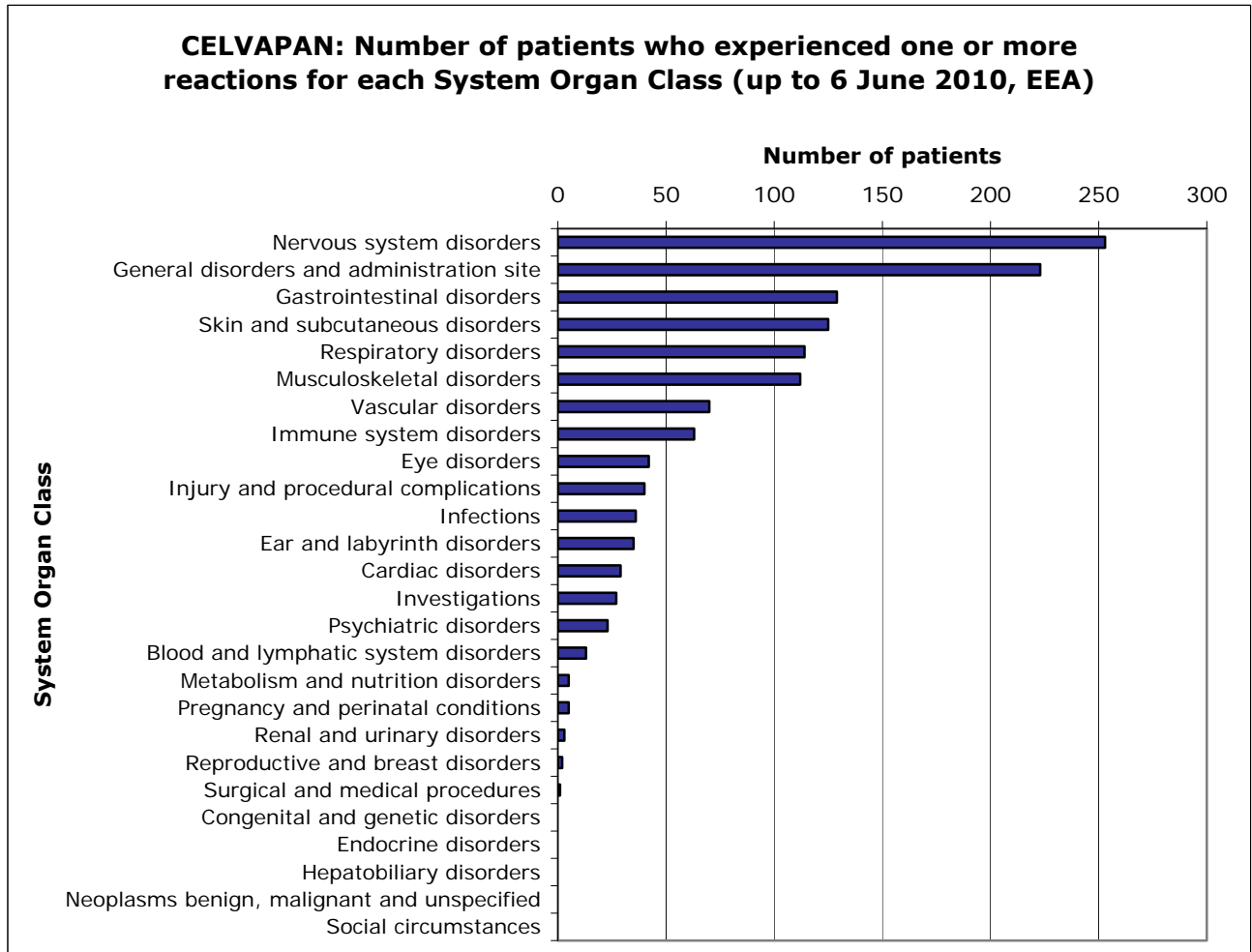
- Immune disorders: anaphylactic reaction, hypersensitivity;
- Skin and subcutaneous conditions: angioedema, urticaria, erythema, rash, pruritus;
- Gastrointestinal disorders: nausea, vomiting;
- Vascular disorders: flushing, pallor;
- Musculoskeletal disorders: muscular weakness, pain in extremity, myalgia;
- Cardiac disorders: tachycardia, cyanosis;
- Infections: 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 dyspnoea, urticaria, pyrexia, cough, 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 Marketing Authorisation, eight fatal cases have been reported from outside the EEA in patients vaccinated with Arepanrix. Four cases (2 male, 1 female and 1 with unknown gender) had underlying diseases and concomitant medications which may explain the fatal outcomes. Two women aged 67 and 87 years had a diagnosis of Guillain Barré syndrome but it is not known whether their deaths were related to this disease. For a baby aged 8 months and a woman aged 34 years, death was unexplained but there was no indication these fatal cases could be related.

Celvapan

As of 6 June 2010, a total of 558 reports of serious adverse reactions had been received by EudraVigilance (an increase of one report 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 company⁴ 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: 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;

⁴ As stated by the marketing authorisation holder in the periodic safety update report dated 19 April 2010.

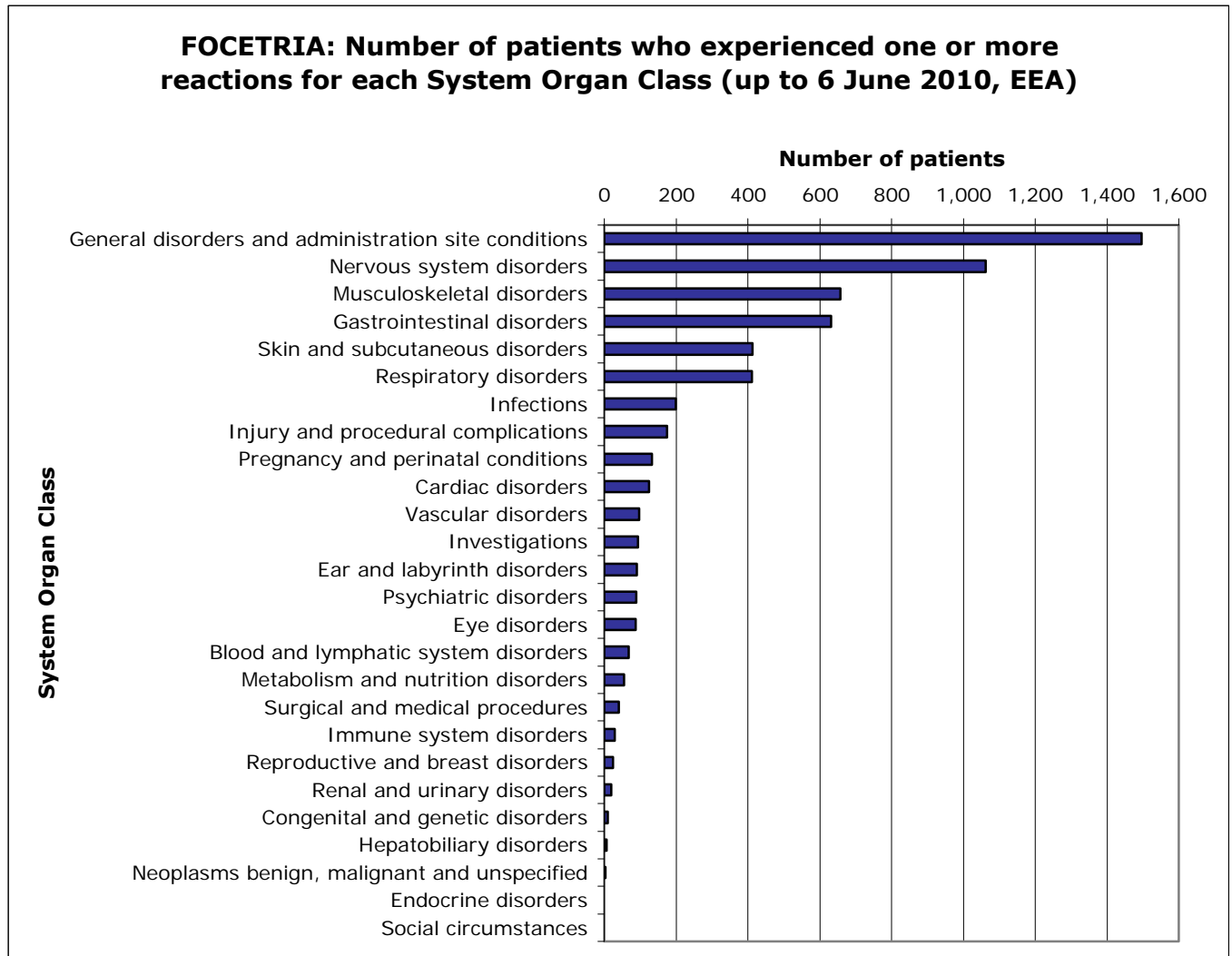
- Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness;
- Skin and subcutaneous conditions: hyperhidrosis, pruritus, urticaria, rash, erythema;
- Respiratory disorders: oropharyngeal pain, cough, dyspnoea;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: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

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 by EudraVigilance in people vaccinated with Celvapan. Since authorisation, a total of two fatal cases have been received in temporal association with Celvapan. However, these two cases are not considered causally associated with the vaccine.

Focetria

As of 6 June 2010, a total of 3,146 reports had been received by EudraVigilance (an increase of 50 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 company⁵ 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;

⁵ According from the last periodic safety update report dated 31 March 2010.

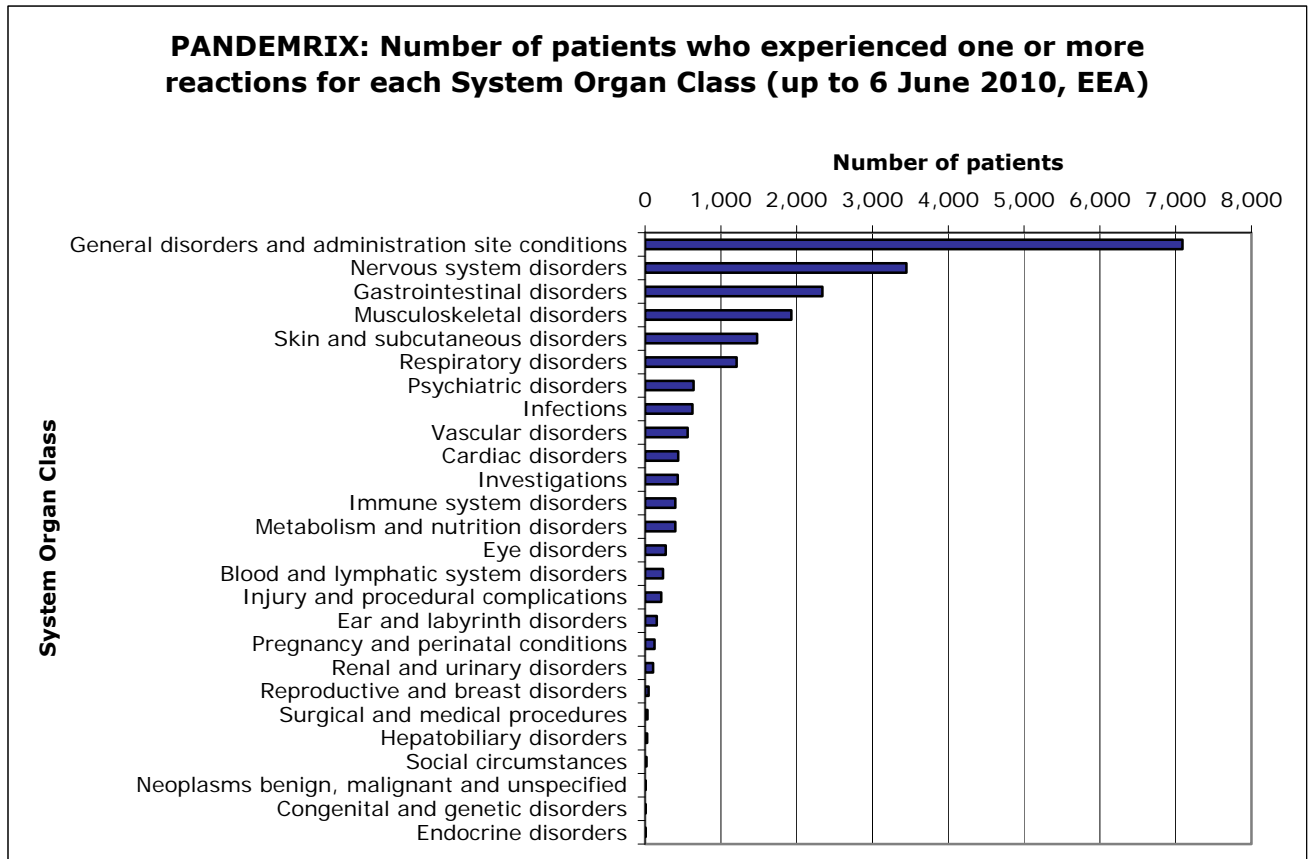
- Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, tremor, hypoaesthesia, syncope, dysgeusia, Guillain-Barré syndrome, presyncope, convulsion, migraine;
- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, 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;
- Cardiac disorders: palpitations, tachycardia, arrhythmia, atrial fibrillation, cyanosis;
- 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;
- Vascular disorders: hypertension, hypotension, flushing, haemorrhage, 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, drug exposure during pregnancy, vomiting, cough, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, premature baby, fatigue, influenza-like illness, dyspnoea, rash, urticaria, malaise and convulsion.
- Since the last update, no fatal cases have been reported in people vaccinated with Focetria. Cumulatively, 32 fatal cases temporally associated with Focetria have been received in EudraVigilance. A possible cause of death other than the vaccine has been found in all of these cases.

Pandemrix

As of 6 June 2010, a total of 11,050 reports had been received by EudraVigilance (an increase of 36 reports since the previous update). Data available on 31 May 2010 from Member States and from the company⁶ 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;

⁶ As stated by the marketing authorisation holder in the periodic safety update report dated 9 April 2010.

- 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;
- 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, lower respiratory tract infection, bronchitis, respiratory tract infection, ear infection, gastroenteritis, bronchopneumonia;
- 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, cardiac arrest, angina pectoris, bradycardia, 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, 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,

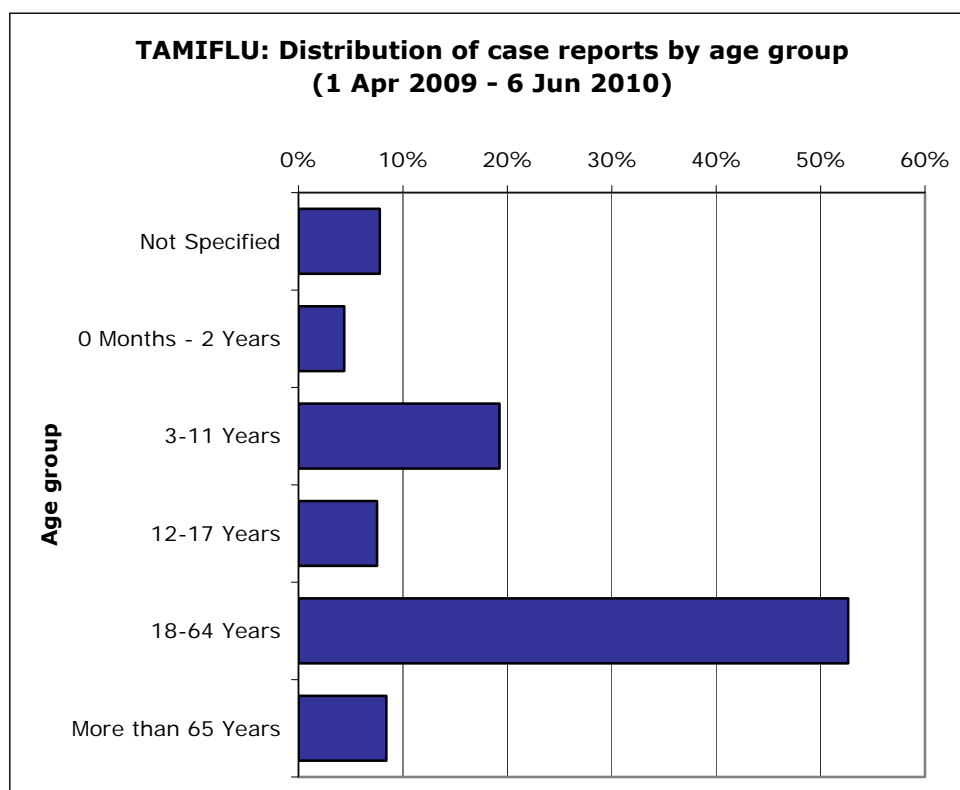
pallor, listlessness, injection site swelling, syncope, dyspnoea, pain in extremity, influenza-like illness, febrile convulsion, myalgia, urticaria, dizziness, tearfulness and erythema.

- Since the last update no new cases of death associated with Pandemrix has been received. Cumulatively 154 cases have been received. However, there is no indication that any of these cases could be associated with Pandemrix.

Antiviral medicines

Tamiflu (oseltamivir)

From 1 April 2009 to 6 June 2010, a total of 1,117 reports worldwide were received by EudraVigilance (an increase of six 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,⁷ 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.

⁷ As stated by the marketing authorisation holder in the periodic safety update dated 23 April 2010.

TAMIFLU/oseltamivir: Number of patients who experienced one or more reactions for each System Organ Class (1 Apr 2009 - 6 Jun 2010, EEA)



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, chest pain, condition aggravated, drug ineffective, drug interaction, influenza-like illness, 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;
- Infections: pathogen resistance, influenza, pneumonia, hepatitis A, bacterial infection, bronchitis;
- Hepatobiliary disorders: hepatitis, cholestasis, acute hepatic failure, hepatic failure, jaundice cytolytic hepatitis, 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, headache, diarrhoea, nausea, abdominal pain and delirium.
- Since the last update, no new case report with a fatal outcome following oseltamivir use has been received by the EudraVigilance system.

- 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		<u>9</u>	<u>8</u>
	Erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)			<u>3, 6</u>
	Leukocytoclastic vasculitis		<u>5</u>	
	Photosensitivity reaction			<u>2</u>
	Systemic lupus erythematosus rash			<u>8</u>
Vascular disorders	Circulatory collapse	<u>3</u>		
	Vasculitis			<u>6</u>