10 February 2010
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Patient Health Protection

Tenth pandemic pharmacovigilance weekly update

This update has been prepared by the European Medicines Agency to provide a summary of the adverse drug reactions reported after the use of centrally authorised pandemic vaccines and antivirals. It also provides information on the evolution of the H1N1 pandemic, an estimate of how many doses of vaccines and antivirals have been distributed or administered in Europe, and other available information on the benefits and risks of the vaccines and antivirals. The centrally authorised pandemic medicines concerned in this update are the vaccines Celvapan, Focetria and Pandemrix and the antiviral Tamiflu.

This update includes reports of *suspected* reactions that were observed after the medicines were administered. This does not mean that these reactions were caused by the medicines. They could be a symptom of another illness or they could be associated with another product taken by the patient. Healthcare professionals are actively encouraged to report events occurring after vaccination.

It should be noted that, due to differences in the numbers of people receiving each vaccine, the number of reports shown for the three different vaccines cannot be used to compare the safety or the benefit-risk balance of the vaccines.

As a single patient may experience several reactions that will be included in a single report, the total number of reactions may not be equal to the total number of patients. In addition, as some patients have received two doses of the vaccines, the total number of doses administered is not necessarily equal to the total number of patients vaccinated.

Reports are collected on a continuous basis in EudraVigilance. EudraVigilance is a database and management system 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 European Medicines Agency, and the early detection and monitoring of possible safety signals in relation to reported adverse reactions. This update includes reports received by EudraVigilance up to 24 January 2010. The graphs represent aggregated data related to the European Economic Area (EEA) only, and provide an overview of the reporting situation in the EEA. The updated safety information also considers worldwide cases from EudraVigilance.

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

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Key messages

As of 5 February 2010, in the EEA, at least 37.3 million people, including at least 312,000 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 43.2 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 31 January 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 of death reported to EudraVigilance in temporal association with Celvapan, Focetria, Pandemrix or vaccines without a brandname, excluding cases of intra-uterine death and stillbirth, has been performed for this update and is further discussed below for each vaccine. The review identified a total of 155 cases, including 3 cases for vaccines without a brandname. An immediate cause of death has been found in 97 reports and sudden or unexplained death has been mentioned in 58 reports. The evaluation of these 58 reports has shown that the death could be explained by an underlying pathology in 41 reports and by the advanced age of the patient in 8 reports. Information is lacking for an assessment in five reports. In the four remaining reports, the patient suddenly died 4, 7, 16 and 21 days after the vaccination. These delays do not suggest a link between the deaths and the vaccination. There is no evidence that the vaccines contributed to the death of the vaccinated patients. Background statistics of mortality in Europe suggest that each day about 1,000 persons would die out of 37,3 million vaccinated, mainly due to complications of chronic diseases and age. This number should be considered when interpreting the number of deaths reported after vaccination.

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 5 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 EU/EEA countries and medium intensity transmission was confined to five countries, all in Eastern or South-eastern Europe. Elsewhere intensity was low. Transmission of the pandemic virus continues at low levels on a local or regional basis in another six countries. There is no indication of any increase in the incidence of non-pandemic influenza viruses since the beginning of the New Year. Overall since October 2009, 99% of all sub-typed specimens were identified as pandemic virus. The number of reported cases of severe acute respiratory infections (SARI) continued to decline.

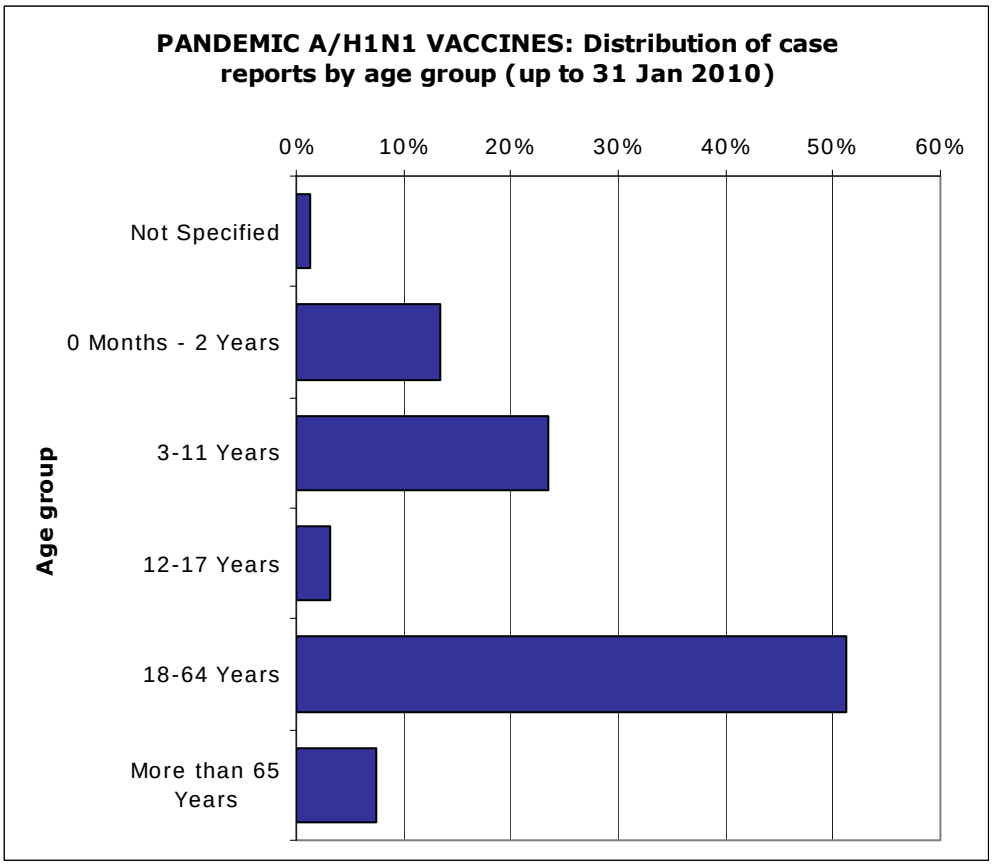
See the ECDC pandemic website, its current risk assessment and its weekly executive update for additional information.

In its weekly update dated 5 February 2010, the World Health Organization stated that, as of 31 January 2010, worldwide more than 209 countries and overseas territories or communities have

reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 15,174 deaths.

Overview of centrally authorised vaccines

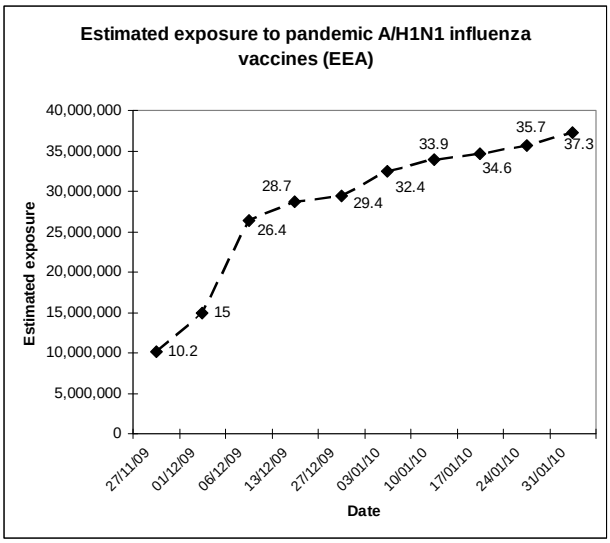
As of 31 January 2010, a total of 12,915 case reports had been received by EudraVigilance since the authorisation of the three centrally authorised vaccines. This represents an increase of 210 reports compared with the previous update, reflecting the increase in the number of people vaccinated. The graph below displays the age distribution of all adverse reaction reports received by EudraVigilance as of 31 January 2010.

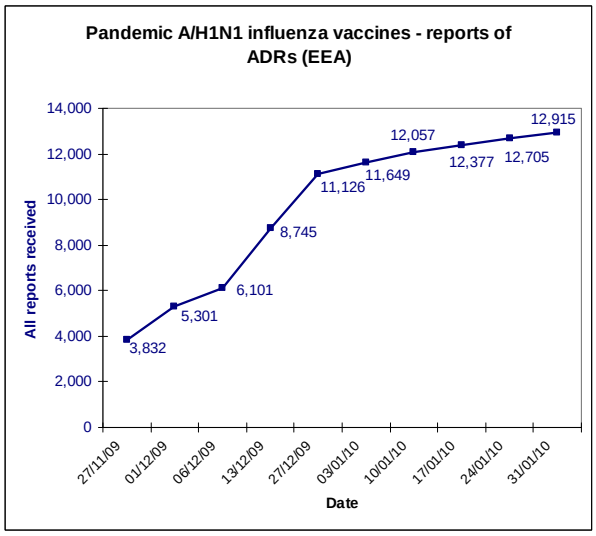


Data available on 5 February 2010 from Member States and from the vaccine marketing authorisation holders indicated that at least 128 million doses had been distributed and at least 37.3 million patients had been vaccinated with one of the three centrally authorised vaccines in the EEA. From the limited information received from seven EEA countries by 5 February 2010, at least 312,000 pregnant women had been vaccinated. When the information available for the nationally authorised vaccines is included, at least 132.3 million doses had been distributed, with at least 43.2 million people (including at least 351,000 pregnant women) vaccinated in Europe.

The graphs below display, for the three centrally-authorised vaccines, the cumulative numbers of adverse reaction reports received by EudraVigilance over time and the estimated number of people vaccinated, as given in the previous weekly updates. The estimated exposure is derived from information obtained from Member States and is considered to be an underestimate of the true number of people vaccinated. Both curves are reaching a plateau, which indicates a decrease in the

number of new adverse reaction reports received by EudraVigilance and the number of new vaccinations with the three centrally-authorised vaccines.



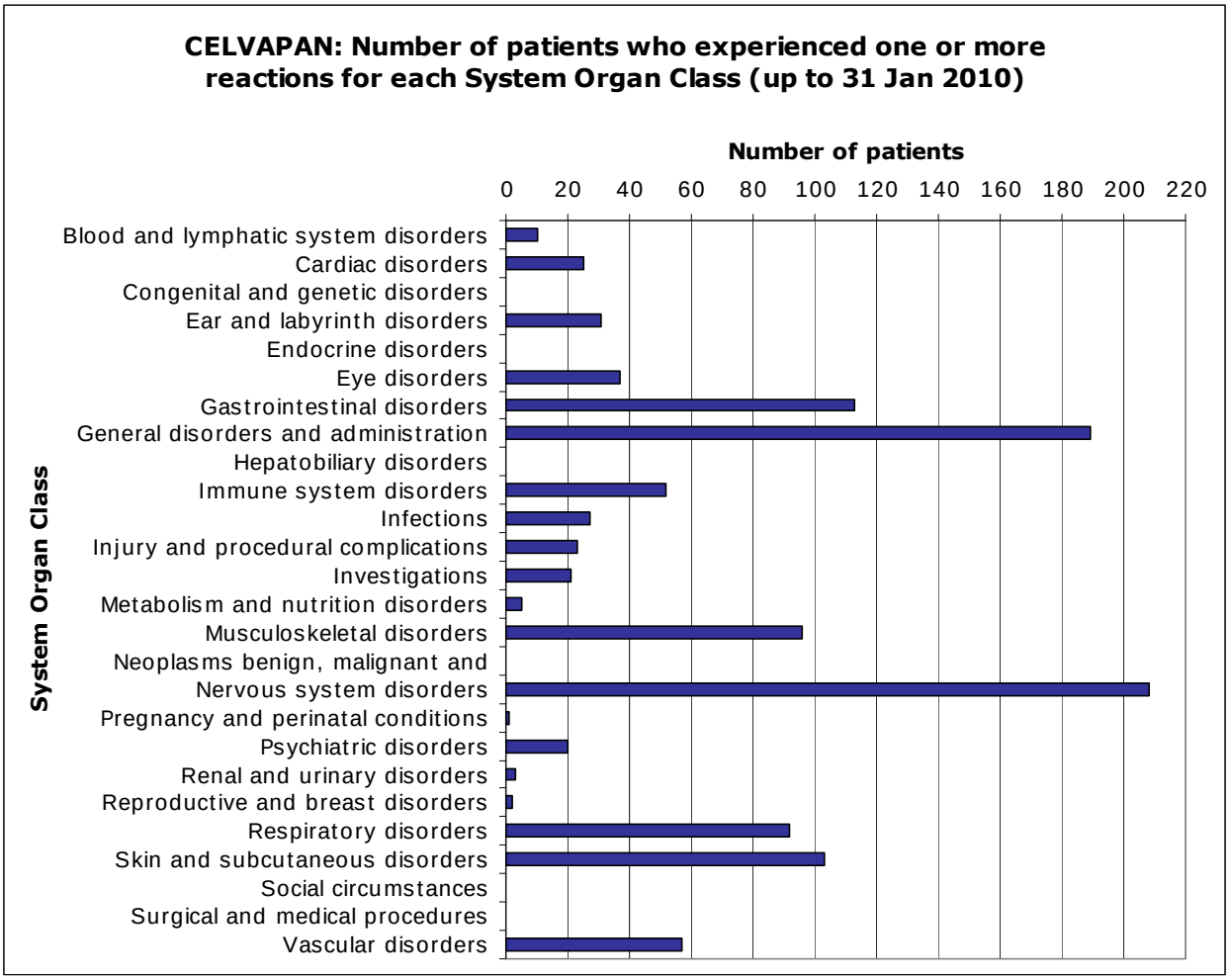


Nine cases of medication error involving Pandemrix and Celvapan were reported in the 7th weekly update. Since this update, 13 additional cases have been reported to EudraVigilance. Three cases lack information for an assessment. In six cases, the patient received Celvapan for the first dose and Pandemrix for the second dose. The four remaining reports concerned Pandemrix only: two children received Pandemrix when their parents had requested that Celvapan be given, a 5-year-old patient received an adult dose of Pandemrix, and an adult patient received only half a dose of Pandemrix. Adverse reactions consistent with the known safety profiles of the two vaccines were reported in two medication error cases and resolved within a few days.

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

Celvapan

As of 31 January 2010, a total of 449 reports had been received by EudraVigilance (an increase of 17 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:
  - Nervous-system disorders: headache, dizziness, syncope, paraesthesia, hypoaesthesia, lethargy;
  - General disorders and administration-site conditions: pyrexia, malaise, chills, fatigue, 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;

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

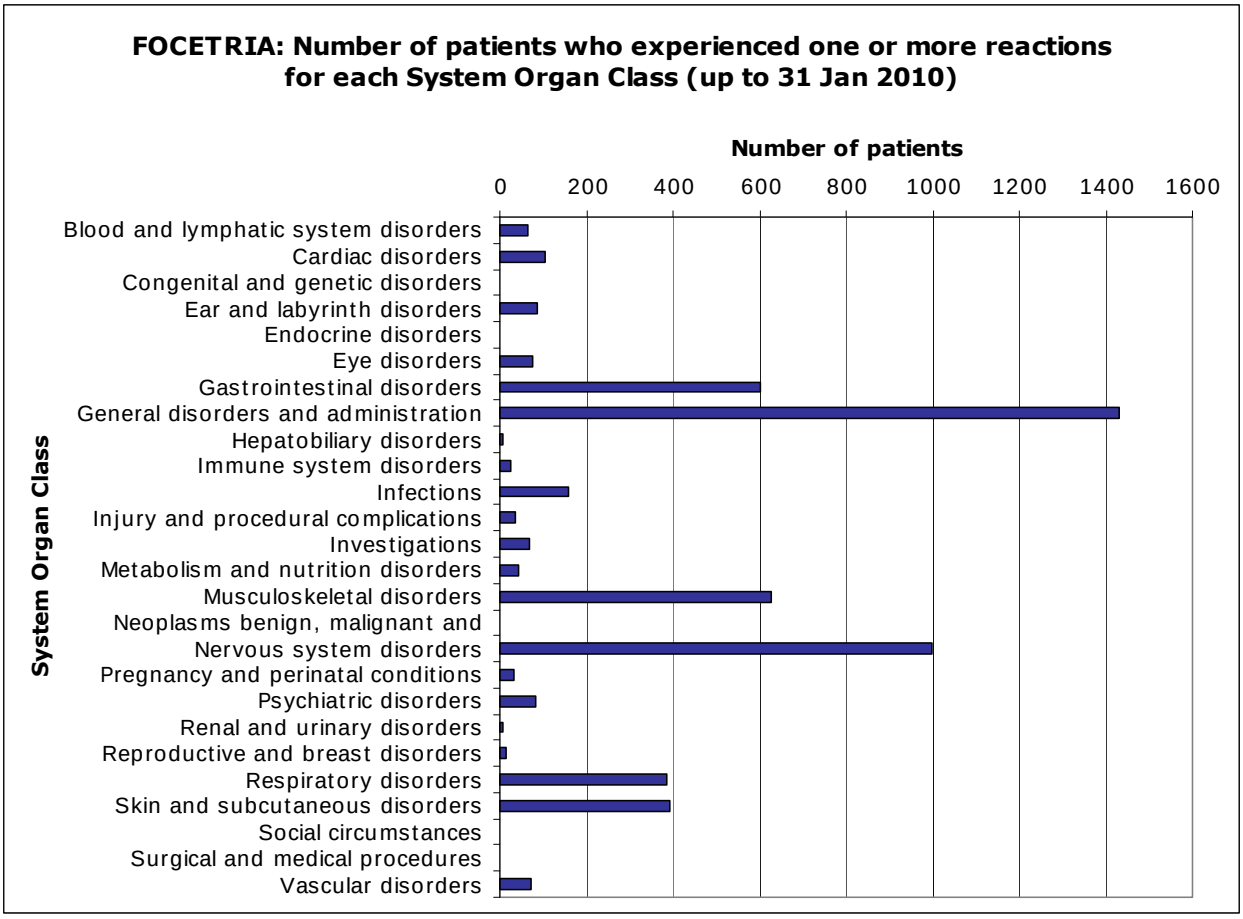
- Skin and subcutaneous conditions: hyperhidrosis, pruritus, urticaria, rash, erythema;
- Respiratory disorders: cough, oropharyngeal pain, dyspnoea;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Ear and labyrinth disorders: vertigo;
- Infections: rhinitis;
- Cardiac disorders: tachycardia;
- 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.
- Since authorisation, two reports of an adverse reaction with a fatal outcome were received. They concerned a 57-year-old male patient with underlying diabetes and cardiac disease who died from an unknown cause ten days after the vaccination, and an 85-year-old male patient who was found dead on the day he was vaccinated. Little information on this case is available.

Focetria

As of 31 January 2010, a total of 2,851 reports had been received by EudraVigilance (an increase of 14 reports since the previous update). Data available on 5 February 2010 from Member States and from the company[2] indicated that at least 37.1 million doses of Focetria had been distributed in the EEA, and at least 7.7 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 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, injection-site pruritus, pain, 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;
  - Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, muscle spasms, musculoskeletal pain, back pain, sensation of heaviness, rheumatoid arthritis;

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

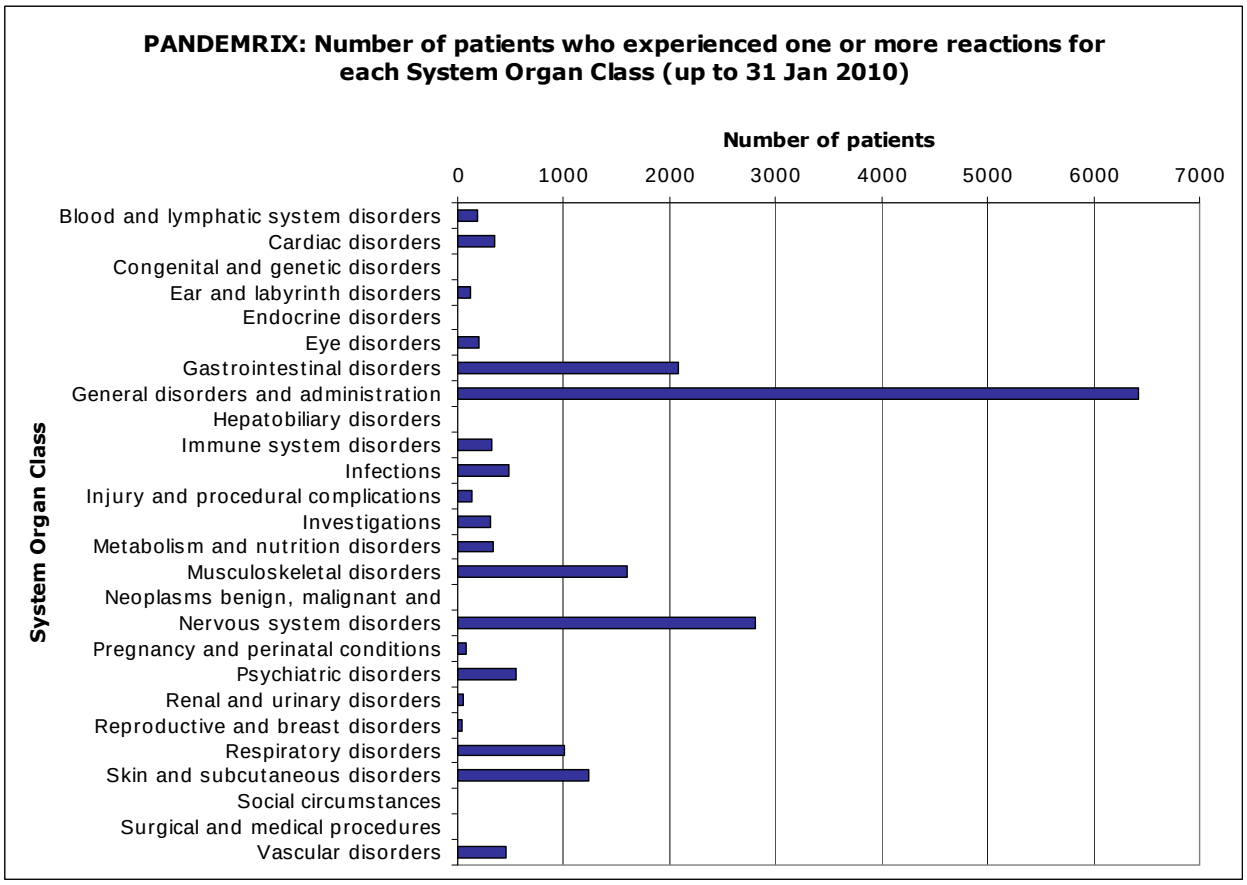
- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, swelling face, rash generalised, eczema;
- 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, convulsion, pain in extremity and urticaria.
- Since the last update, no fatal cases have been reported in people vaccinated with Focetria.
- Since authorisation, twenty reports of deaths or of adverse reactions with a fatal outcome were received in EudraVigilance. They include a two-year-old child for which the available information is not sufficient for an assessment and 19 adults (15 males and 14 females) aged between 26 and 89 years. Twelve patients were 65 years old or more. A clear cause of death was identified in six of these patients, including cerebral haemorrhage, cardiac failure or pneumonia. Unexplained death was reported for five patients who had severe underlying diseases such a renal impairment with dialysis, cardiac disorder, ischemic heart disease or chronic obstructive pulmonary disease. Information was inadequate for one patient. Among the seven adults aged less than 65 years, the cause of death was identified as being myocardial infarction in two cases, cardiac failure in one case (this patient also had a congenital cardiac anomaly), oesophageal and gastric bleeding in one case, acute meningoencephalitis in one case and an unexplained death in two patients who had type II diabetes and hypertension. Overall, these reports do not suggest that the vaccine could have contributed to the death in any of these cases.

Pandemrix

As of 31 January 2010, a total of 9,632 reports had been received by EudraVigilance (an increase of 183 reports since the previous update). Data available on 5 February 2009 from Member States and from the company[3] indicate that at least 83.3 million doses of Pandemrix had been distributed in the EEA. It is estimated that at least 27.6 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, crying, hypoaesthesia, febrile convulsion, convulsion, lethargy, tremor, loss of consciousness, poor quality sleep, presyncope, hypersomnia, facial palsy, hypotonia;
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, lip swelling, dry mouth, swollen tongue, hypoaesthesia oral, abdominal discomfort, 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, rash macular, dermatitis allergic, rash pruritic, pruritus generalised, facial hypoaesthesia, petechiae, eczema, skin reaction, vesicular rash;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, tachypnoea, pharyngeal oedema, throat tightness, bronchospasm, sneezing, dysphonia, productive cough, respiratory failure, hyperventilation, pulmonary embolism, respiratory distress, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, nightmare, hallucination, confusional state;
- Infections: rhinitis, pneumonia, nasopharyngitis, influenza, herpes zoster, swine influenza, cellulitis, ear infection, bronchitis, 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, cardiac arrest, bradycardia;
- 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 swelling, vision blurred, eye pain, 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

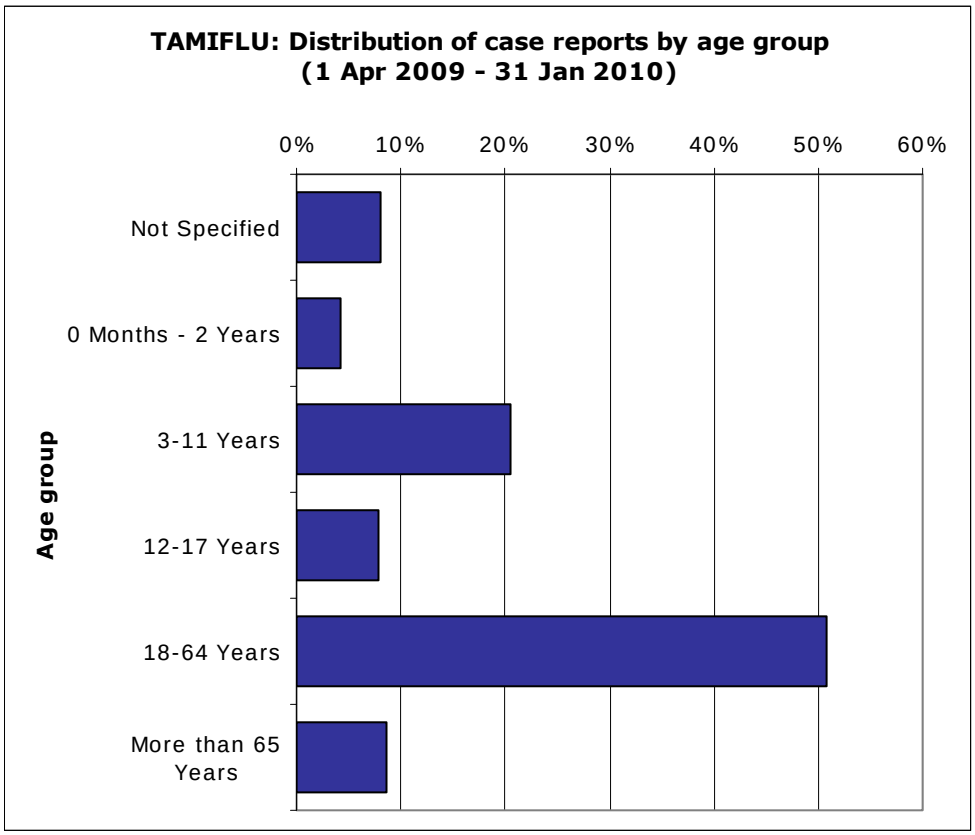
- Since the last update, eight fatal cases from the EEA have been received. In two reports, the cause of death was cardiac (cardiovascular collapse and myocardial infarction). One report concerned a 42-year-old woman who experienced status epilepticus with coma the day after the vaccination. The issue of seizures with a fatal outcome has been discussed in the 4th update and is still being investigated. In five cases, sudden death occurred within 2 days after the vaccination. One of these cases was an 87-year-old woman with cardiac arrhythmia and bronchopulmonary infection. No medical history or no cause of death is mentioned in the reports for the four other patients who were aged 75, 51, 79 and 96 years. There is no evidence that the vaccine was related to any of these cases of sudden death.

- A cumulative review of cases of death reported in temporal relationship with Pandemrix identified a total of 130 reports. Among these, a clearly identified cause of death unrelated to the vaccine was identified in 80 reports. They included 47 reports of cardiac death caused by events like myocardial infarction, acute heart failure, circulatory collapse or cardiomyopathy, 20 reports of respiratory failure associated with conditions such as bronchopneumonia, pulmonary infection or acute pulmonary oedema and 13 reports mentioning other causes of death including intestinal gangrene, HIV infection with cardiopathy, rupture of the aorta, multi-organ failure (two patients), anaphylactic shock associated with an antibiotic, sepsis, transplant rejection, cerebral haemorrhage, drug intoxication and status epilepticus (three patients). Cases of transplant rejection following administration of Pandemrix have been discussed in the first, second and third update, with the conclusion that they were likely caused other factors, such as lack of compliance to immunosuppressive therapy. Cases of seizures with a fatal outcome have been discussed in the fourth update. This issue is being thoroughly investigated. The 50 remaining reports included cases reported as sudden death or unexplained death. Among these, 34 reports suggest that the patient suffered from an underlying condition that could be responsible for the fatal event, this condition being most frequently severe hypertension, cardiac arrhythmia, previous myocardial infarction, severe renal impairment, chronic obstructive pulmonary disease or pulmonary infection. In 16 reports, there is no information mentioning the cause of death or underlying morbidity. Seven of these patients were older than 75 years and four reports lacked information for an assessment. The four remaining patients suddenly died 4, 7, 16 and 21 days after the vaccination. These long delays suggest that there is no causal relationship with the vaccine. Overall, there is no indication that the vaccine could have contributed to the reported deaths.
- Seven of the 130 reports of death concerned children: one critically ill 21-month-old patient who was scheduled for cardiopulmonary transplantation, four children with a congenital cardiac anomaly, one two-year-old patient with a chronic kidney disease, one two-year-old patient who died from a H1N1 infection and asystoly, and one two-year old patient who died following administration of either Pandemrix or Focetria with an unknown latency. This case lacked information for an assessment. None of these cases suggests a causal relationship between the death and 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, listlessness, somnolence, crying, injection site swelling, pallor, dyspnoea, influenza-like illness, myalgia, pain in extremity, syncope and tearfulness.
- Since authorisation, six cases of pancreatitis or acute pancreatitis were received by EudraVigilance. The delay between the vaccination and the beginning of the symptoms ranged from less than one day to 24 days after the vaccination. The patient recovered in five cases and the outcome was unknown in the remaining one. In one case, the high amount of alcohol consumption may provide a plausible explanation for the pancreatitis. Two cases may be explained by an underlying medical condition (a recent history of pancreatitis and a dyslipidemia), as well as by concomitant medications that are known to be associated with the occurrence of pancreatitis. Two cases lacked information for an assessment and one case experienced pancreatitis four to five days after the vaccination and fully recovered within a few days. This single case without an alternative explanation does not suggest that the vaccine may increase the risk of pancreatitis.

Antiviral medicines

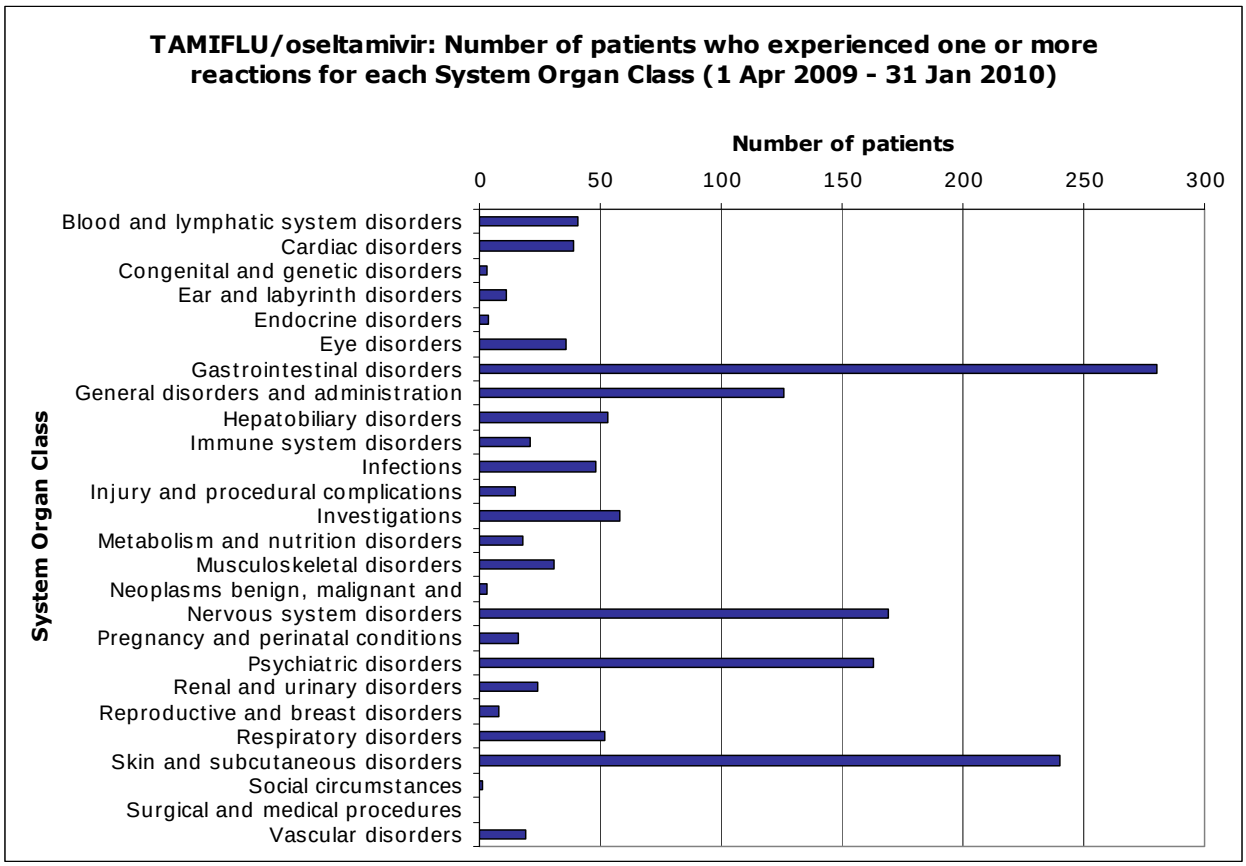
Tamiflu (oseltamivir)

From 1 April to 31 January 2010, a total of 991 reports worldwide were received by EudraVigilance (an increase of 22 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 dated 23 December 2009, exposure to Tamiflu is estimated to be at least 16.3 million patients during the pandemic period of 1 May to 30 November 2009[4].

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



Distribution of adverse reactions by system organ class

- The adverse reaction reports received from the EEA are consistent with the safety profile described in the product information. The most frequently reported suspected adverse reactions experienced by patients in each SOC were as follows:
  - Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, mouth ulceration, lip swelling, swollen tongue, pancreatitis, 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, epilepsy, burning sensation, dysgeusia, somnolence;
  - 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, oedema peripheral, drug interaction, fatigue, influenza-like illness, condition aggravated, drug ineffective, general physical health deterioration, face oedema, multi-organ failure, pain, 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.

Updated safety information

- Since the last update, seven new worldwide reports of adverse events with a fatal outcome following oseltamivir use have been received by EudraVigilance. One case occurred within the EEA. The six other cases occurred outside the EEA. Six of the seven deaths were related to pneumonia or influenza. The remaining report describes a patient who had pre-existing myocarditis. During treatment with oseltamivir, the patient had cardiac ventricular thrombosis and died five days later.
- 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	Acute pancreatitis	7		
	Necrotising oesophagitis and necrotising stomatitis			6
General disorders and administration site conditions	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		7
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

Return to top of document.