



EUROPEAN MEDICINES AGENCY
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Patient Health Protection

Twenty-second 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.

The Director-General of the World Health Organization (WHO) announced on 10 August 2010 that the world has moved from phase 6 of influenza pandemic alert to the post-pandemic period (see WHO statement [here](#)). In advance of this development, the Agency's Committee for Human Medicinal Products (CHMP) recommended that three of the centrally authorised pandemic vaccines used in Europe should be given full marketing authorisations allowing for their use outside a declared influenza pandemic.

Since Europe is now in the post-pandemic period, this 22nd update is the last pandemic pharmacovigilance update published by the Agency. It includes reports of adverse drug reactions received by EudraVigilance up to 8 August 2010. These are reports of *suspected* reactions 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.

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.



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.

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.

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 CHMP re-assessed the benefit-risk profile of Celvapan, Focetria and Pandemrix. Taking into account the comprehensive information available on the clinical safety and efficacy of these vaccines, the CHMP concluded that the benefit-risk profile of these vaccines continues to be positive. Consequently, the CHMP recommended the further use of the vaccines within the EU in the authorised indication even after the pandemic was declared over.

The vast majority of the adverse reactions that had been reported to EudraVigilance as of 8 August 2010 are considered to be non-serious.

As of 8 August 2010, in the EEA, at least 38.6 million people had been vaccinated with 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 Arepanrix, Celvapan, Focetria and Pandemrix and 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 13 August 2010, the European Centre for Disease Prevention and Control (ECDC) concluded that, during the weeks of 26 July to 8 August 2010, epidemiological indicators showed no influenza activity in the 19 reporting EU countries.

By 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 on the influenza A/H1N1 pandemic.

In its [weekly update](#) dated 13 August 2010, the WHO reported that Influenza H1N1 (2009) virus transmission remains locally intense in parts of India and New Zealand.

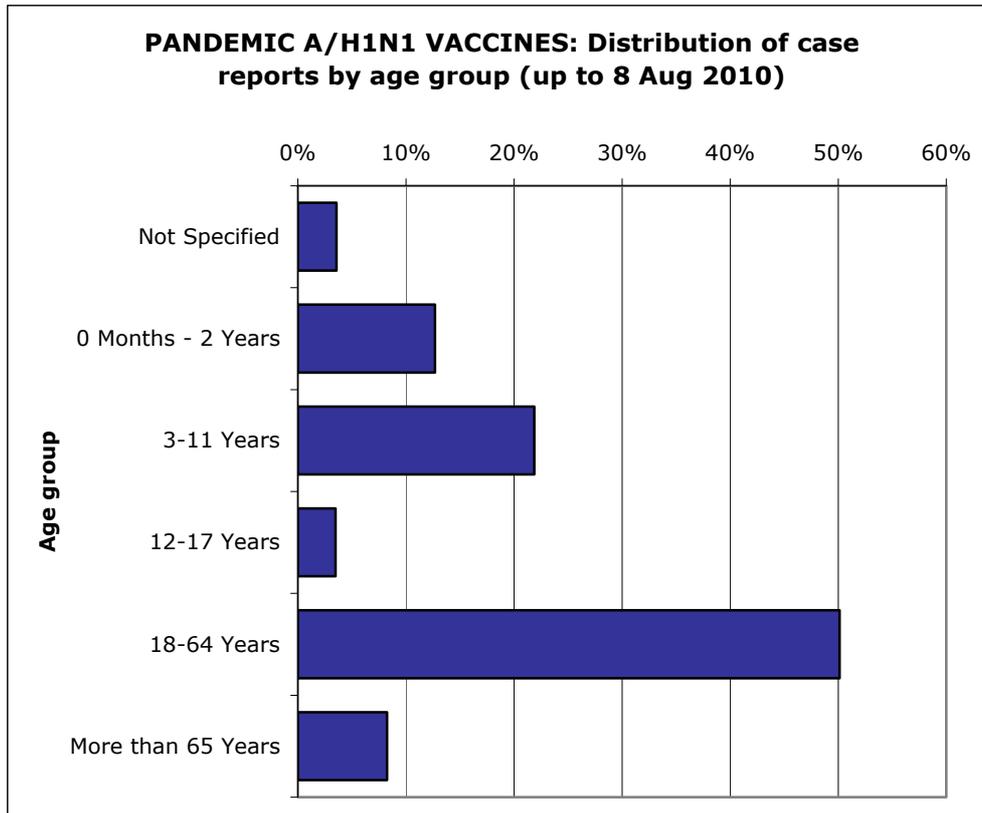
Based on epidemiological data, a preliminary estimate of vaccine field effectiveness (VE) from Germany, which was [published in Eurosurveillance](#), indicates for Pandemrix an excellent VE in people aged 14-59 years (96.8%; 95% confidence interval (CI): 95.2-97.9) and moderately high VE in those

aged 60 years or older (83.3%; 95% CI: 71.0-90.5. [Other published data from Scotland](#) have reported a VE of 95.0% (95% CI 76.0 to 100.0). 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 during the season 2009/10. Its preliminary data from eight countries (France, Hungary, Ireland, Italy, Romania, Portugal, Spain and United-Kingdom) consistently showed good vaccine effectiveness of the pandemic vaccines.

Overview of centrally authorised vaccines

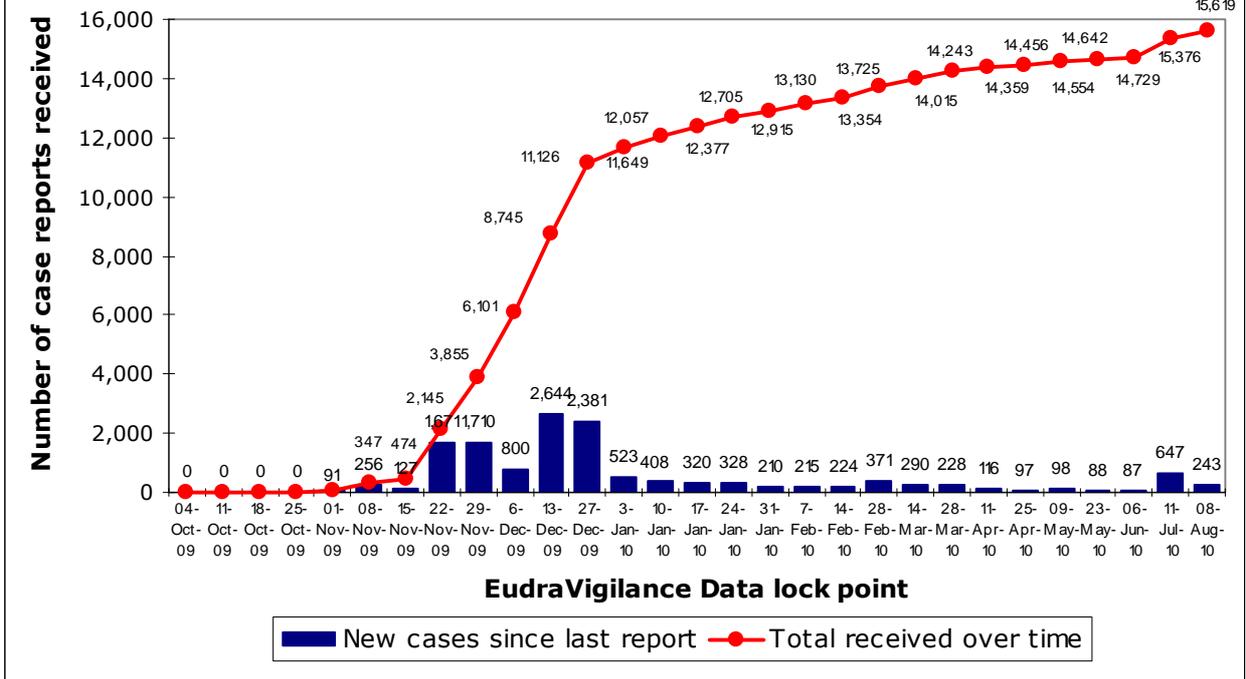
As of 8 August 2010, a total of 15,619 case reports had been received from the EEA by EudraVigilance since the authorisation of the centrally authorised vaccines (Arepanrix, Celvapan, Focetria and Pandemrix) in the EEA. This represents an increase of 243 reports compared with the previous update.

The graph below shows the age distribution of all the reports received by EudraVigilance up to 8 August 2010.



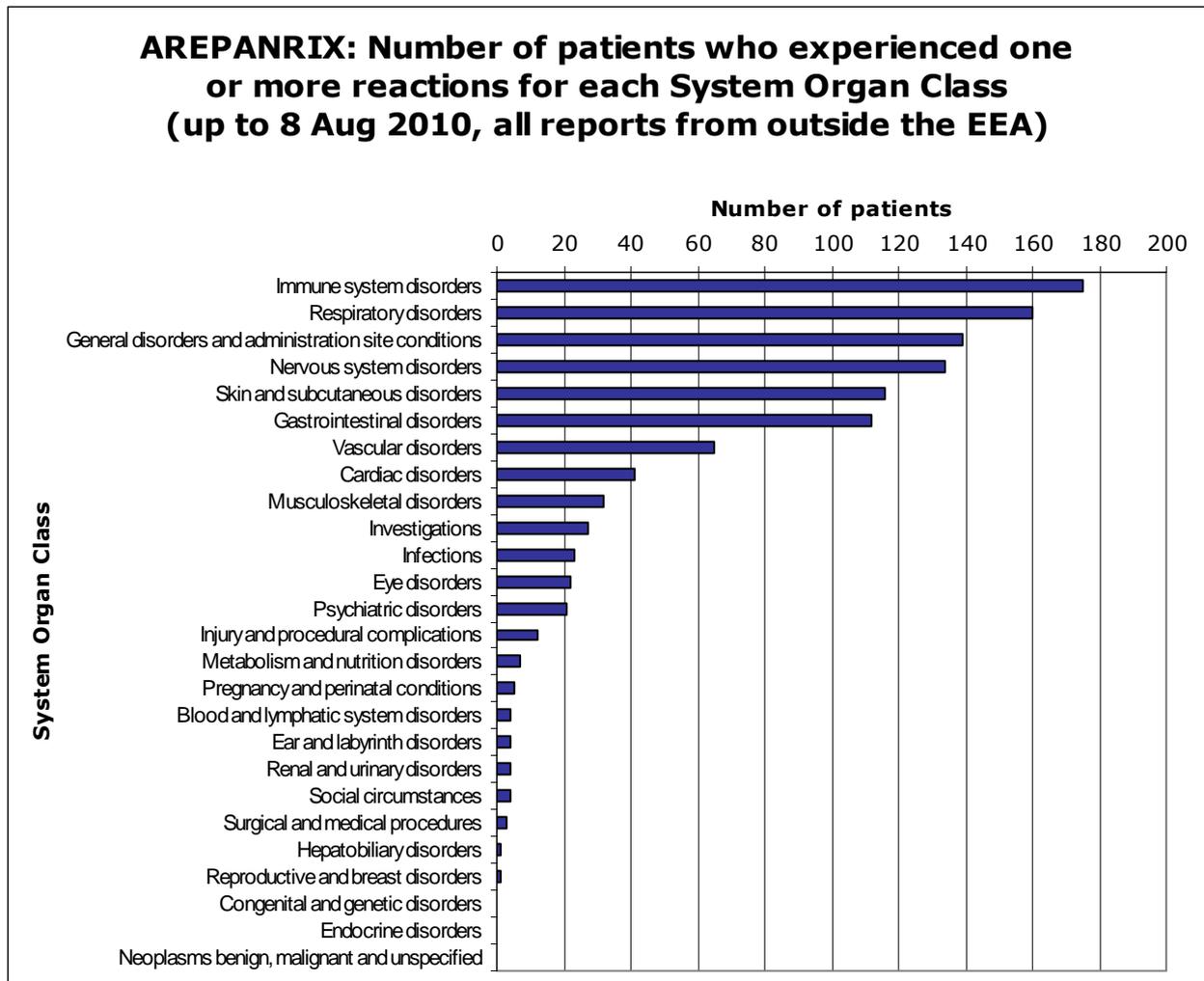
The graph below shows the cumulative numbers of adverse reaction reports received by EudraVigilance for the three centrally authorised vaccines marketed in the EEA (Celvapan, Focetria and Pandemrix), with the number of new adverse reaction reports received between each update.

Pandemic A/H1N1 influenza vaccines: Reports of ADRs (EEA; up to 8 August 2010)



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 8 August 2010, a total of 279 reports had been received by EudraVigilance from outside the EEA. This represents an increase of 120 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:
 - Immune disorders: anaphylactic reaction, hypersensitivity;
 - Respiratory disorders: dyspnoea, throat tightness, cough, pharyngeal oedema, wheezing, dysphonia, throat irritation, respiratory disorder, tachypnoea, respiratory paralysis;
 - General disorders and administration-site conditions: chest discomfort, pyrexia, asthenia, fatigue, product quality issue, malaise;

- Nervous-system disorders: dizziness, paraesthesia, Guillain-Barré syndrome, hypoaesthesia, headache, paralysis flaccid, hyporeflexia, depressed level of consciousness, cranial nerve paralysis, tremor;
- Skin and subcutaneous conditions: urticaria, angioedema, erythema, rash, pruritus, hyperhidrosis;
- Gastrointestinal disorders: nausea, paraesthesia oral, dysphagia, vomiting, hypoaesthesia oral;
- Vascular disorders: flushing, pallor;
- Cardiac disorders: cyanosis, tachycardia;
- Musculoskeletal disorders: muscular weakness, pain in extremity, myalgia;
- Investigations: heart rate irregular, blood pressure increased;
- Infections: nasopharyngitis, sepsis, transmission of an infectious agent via a medicinal product;
- Eye disorders: eye pruritus, lacrimation increased, ocular hyperaemia, eyelid oedema;
- Psychiatric disorders: anxiety, agitation, confusional state;
- Injury and procedural complications: fall, drug exposure during pregnancy;
- Metabolism and nutrition disorders: decreased appetite;
- Pregnancy and perinatal conditions: abortion spontaneous, stillbirth;
- Blood and lymphatic system disorders: pancytopenia, thrombocytopenia;
- Ear and labyrinth disorders: hyperacusis;
- Renal and urinary disorders: haematuria;
- Social circumstances: activities of daily living impaired;
- Surgical and medical procedures: endotracheal intubation;
- Hepatobiliary disorders: liver injury;
- Reproductive and breast disorders: menorrhagia.

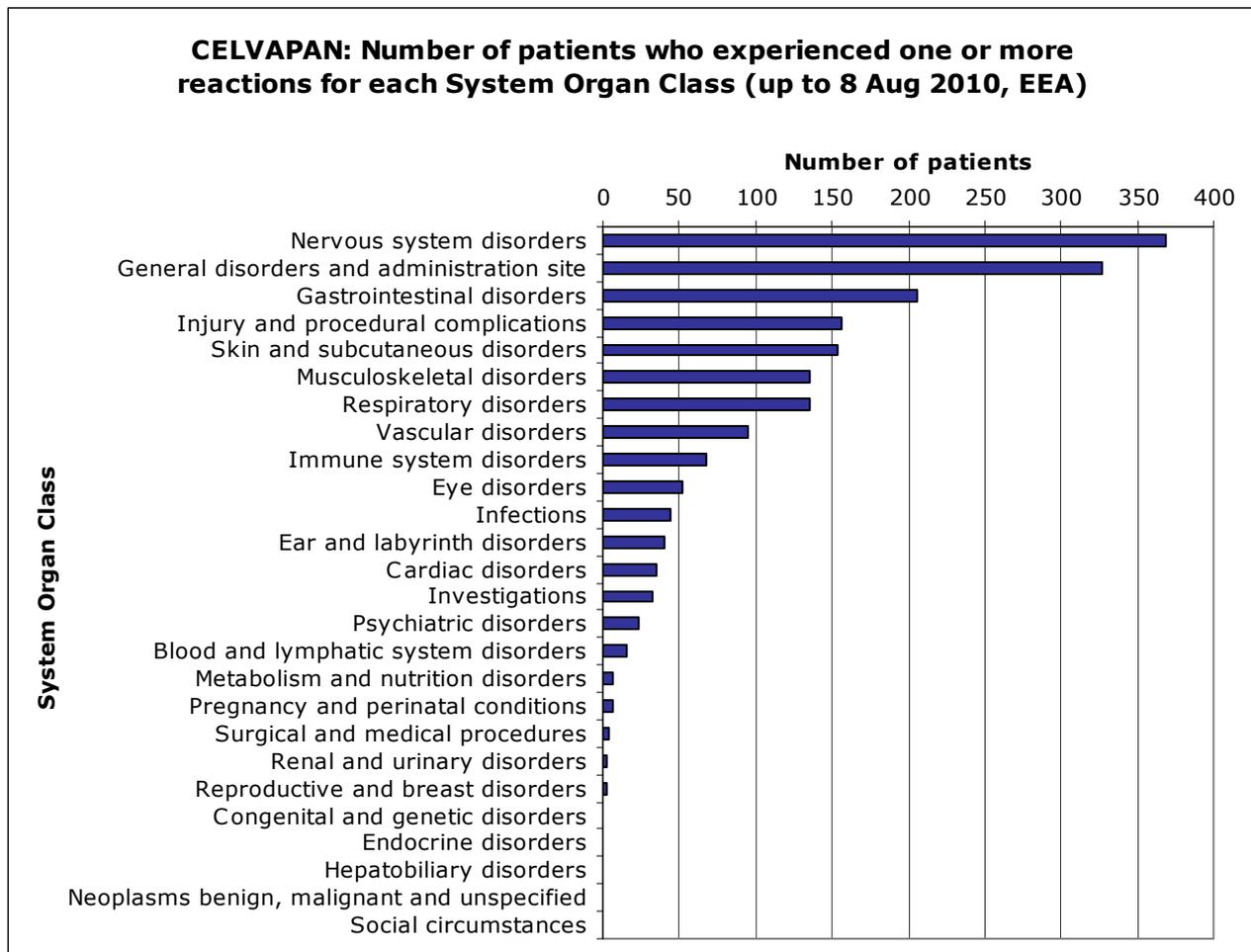
Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included anaphylactic reaction, cough, cyanosis, dyspnoea, angioedema, urticaria, throat tightness, pyrexia, nausea, erythema, rash, pallor, flushing, anaphylactic shock, hypersensitivity, depressed level of consciousness and wheezing.
- Since the last update, no new fatal cases have been reported to EudraVigilance. From authorisation to 8 August 2010, a total of nine fatal cases had been received in EudraVigilance. There is no indication that any of these cases could be associated with Arepanrix.

Celvapan

As of 8 August 2010, a total of 897 reports of serious adverse reactions had been received by EudraVigilance. This represents an increase of three 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 company² 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, paraesthesia, syncope, 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;
 - Injury and procedural complications: medication error, drug exposure during pregnancy, drug administration error, underdose, wrong technique in drug usage process;
 - Skin and subcutaneous conditions: hyperhidrosis, pruritus, rash, urticaria, erythema;

² As stated by the marketing authorisation holder in the periodic safety update report dated 17 June 2010.

- Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness, muscle spasms;
- Respiratory disorders: oropharyngeal pain, cough, dyspnoea, rhinorrhoea, wheezing, asthma;
- Vascular disorders: pallor, flushing, hypotension, peripheral coldness;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Infections: rhinitis, nasopharyngitis;
- Ear and labyrinth disorders: vertigo;
- Cardiac disorders: tachycardia, palpitations;
- Investigations: body temperature increased;
- Psychiatric disorders: sleep disorder;
- Blood and lymphatic system disorders: lymphadenopathy;
- Metabolism and nutrition disorders: decreased appetite;
- Pregnancy and perinatal conditions: premature baby;
- Surgical and medical procedures: caesarean section;
- Renal and urinary disorders: pollakiuria, renal impairment, urinary incontinence;
- Reproductive and breast disorders: epididymitis.

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. From authorisation to 8 August 2010, a total of two fatal cases had been received in temporal association with Celvapan. These two cases are not considered causally associated with the vaccine.
- A review of the clinical safety data provided by the MAH was performed by the CHMP in the context of the recommendation for a full marketing authorisation for Celvapan.

Clinical trials

Results of clinical trials received since authorisation suggested a comparable safety profile to that observed for seasonal flu vaccines and in previous clinical trials with the H5N1 mock-up vaccine. According to these results, headache occurred more frequently in adults than in the elderly. In children, local reactions were observed to occur at a low rate and the most frequent symptom was injection site pain in all age groups. The majority of subjects experienced no systemic reactions within seven days after vaccination and no related serious adverse events occurred during the study period up until 21 days after the second vaccination.

Observational cohort study

The analysis included safety data from 1,000 subjects aged 2 months to over 60 years enrolled in an observational cohort study as of 11 March 2010. Overall, the frequency of systemic and local reactions was comparable between children up to 5 years of age and subjects in older age groups. In adults and children above 5 years of age, the rate of systemic reactions seemed to increase with age and showed the highest rate in adults between 18 and 44 years of age. On the other hand, the frequency of local reactions seemed to be constant across age groups with a tendency for fewer injection site reactions in children.

Spontaneous reports of adverse reactions

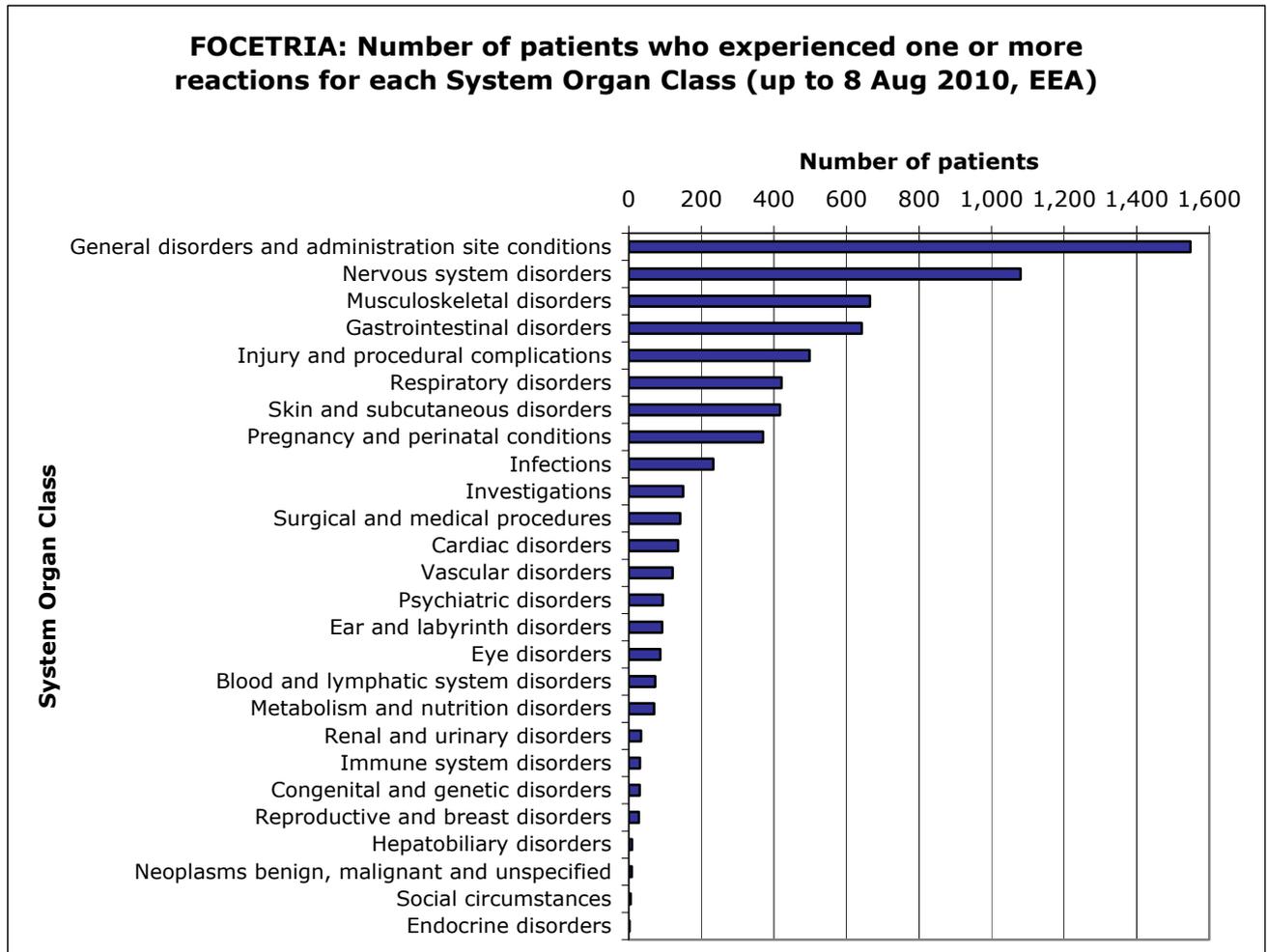
The safety profile of Celvapan was generally similar to that reported in clinical studies and comparable to that seen for seasonal flu vaccines. No fatal outcome with a possible causal relationship as assessed by the CHMP was reported.

A cumulative review of anaphylactic reactions performed by the MAH showed that the observed overall number of anaphylactic reactions associated with Celvapan was higher than the expected number of 1 to 10 cases of anaphylactic reactions per million doses administered of any vaccine. However, several limitations of the analysis have been noted and other risk factors should be considered. Additional data concerning cases of anaphylaxis have been requested to the company to evaluate this risk.

Based on the available data from spontaneous reporting, no increased risk of Guillain-Barré syndrome related to Celvapan was identified. No particular safety concern has been identified in the paediatric population or in pregnant women. The benefit-risk balance of Celvapan was considered favourable.

Focetria

As of 8 August 2010, a total of 3,479 reports had been received by EudraVigilance (an increase of 149 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 company³ 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, pain, chest pain, asthenia, injection-site pruritus, feeling cold, feeling abnormal, injection-site haematoma, injection-site warmth, oedema peripheral;
 - Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, syncope, tremor, hypoaesthesia, dysgeusia, Guillain-Barré syndrome, presyncope, convulsion, migraine;

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

- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, back pain, muscle spasms, musculoskeletal pain, sensation of heaviness, rheumatoid arthritis;
- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Injury and procedural complications: drug exposure during pregnancy;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia, throat irritation, productive cough, respiratory disorder;
- Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, rash generalised, swelling face, eczema;
- Pregnancy and perinatal conditions: premature baby, premature labour, post-partum haemorrhage, pre-eclampsia, obstructed labour, obstructed labour;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, infection, pharyngitis, herpes zoster;
- Investigations: body temperature increased, blood pressure increased, haemoglobin decreased, ultrasound scan abnormal, C-reactive protein increased, blood pressure diastolic decreased, heart rate increased;
- Surgical and medical procedures: caesarean section, vacuum extractor delivery, artificial rupture of membranes, evacuation of retained products of conception;
- Cardiac disorders: palpitations, tachycardia, arrhythmia, atrial fibrillation;
- Vascular disorders: hypertension, haemorrhage, pallor, hypotension, flushing, haematoma, peripheral coldness;
- Psychiatric disorders: listlessness, insomnia, nightmare, moaning, restlessness, tearfulness;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Eye disorders: visual impairment, eyelid oedema, eye irritation, conjunctivitis, eye swelling, vision blurred, diplopia, eye pain;
- Blood and lymphatic disorders: lymphadenopathy;
- Metabolism and nutrition disorders: decreased appetite, gestational diabetes;
- Renal and urinary disorders: urinary retention, dysuria, proteinuria, renal impairment;
- Immune system disorders: anaphylactic reaction;
- Congenital and genetic disorders: hypospadias;
- Reproductive and breast disorders: vaginal haemorrhage, uterine pain;
- Hepatobiliary disorders: hyperbilirubinemia;
- Neoplasms benign, malignant and unspecified: breast cancer, lung carcinoma cell type unspecified stage IV;
- Social circumstances: infant;
- Endocrine disorders: thyroid disorder.

Updated safety information

- The most frequently reported suspected adverse reactions in children since authorisation included drug exposure during pregnancy, pyrexia, headache, premature baby, hyperpyrexia, vomiting, cough, small for dates baby, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, fatigue, influenza like illness, large for dates baby, dyspnoea, rash, malaise, urticaria, infection and convulsion.
- Since the last update, no new fatal case has been reported to EudraVigilance in relation to Focetria. From authorisation to 8 August 2010, 33 fatal cases temporally associated with Focetria had been received in EudraVigilance. A possible cause of death other than the vaccine has been found in all of these cases.
- A review of the clinical safety data provided by the MAH was performed by the CHMP in the context of the recommendation for a full marketing authorisation for Focetria.

Clinical trials

Results from a clinical trial in children and adolescents between 6 months and 17 years of age suggested a comparable safety profile with that reported for the H5N1 mock-up vaccine. The use of half dose of vaccine was associated with a slight reduction of local reactogenicity in subjects of any age. Reactogenicity after the second dose was generally lower compared with the first dose. The data provided in children from 6 to 35 months confirmed that the vaccine was generally safe and no severe adverse events were reported. Results of clinical studies in adults and the elderly showed that there is no unexpected risk associated with the use of Focetria. These results have been assessed and reflected in the product information.

Observational cohort studies

Two observational cohort studies had been initiated to assess the safety of Focetria in the population. The MAH had submitted preliminary data from a first study relating to 8,274 persons followed up for up to three weeks post-vaccination and from a second study on 1,000 enrolled patients. The patterns of adverse events observed in these studies were comparable and could be considered in line with the post marketing surveillance data. Overall, no particular new safety concern was identified from these interim reports from the two observational studies.

Spontaneous reports of adverse reactions

The data available at the time of analysis did not indicate any change in the expected severity or frequency of such events as compared with the clinical studies. However, a number of unexpected adverse reactions were identified and had been or were to be included in the product information: lymphadenopathy, palpitation, tachycardia, asthenia, muscular weakness, pain in the extremity, cough, diarrhoea and vertigo. The majority of deaths occurred in the elderly and were likely related to severe underlying conditions. In seven cases, the deaths were assessed as unexplained and the MAH was requested to provide additional information. There was no clear evidence suggesting that the vaccine contributed to the subjects' death.

An evaluation by the MAH of all cases of anaphylaxis reported up to 22 February 2010 identified a total of 245 cases but 190 cases of them (78% of the total) were found not to be anaphylaxis according to standard definitions. No particular safety concerns had been identified in the paediatric population.

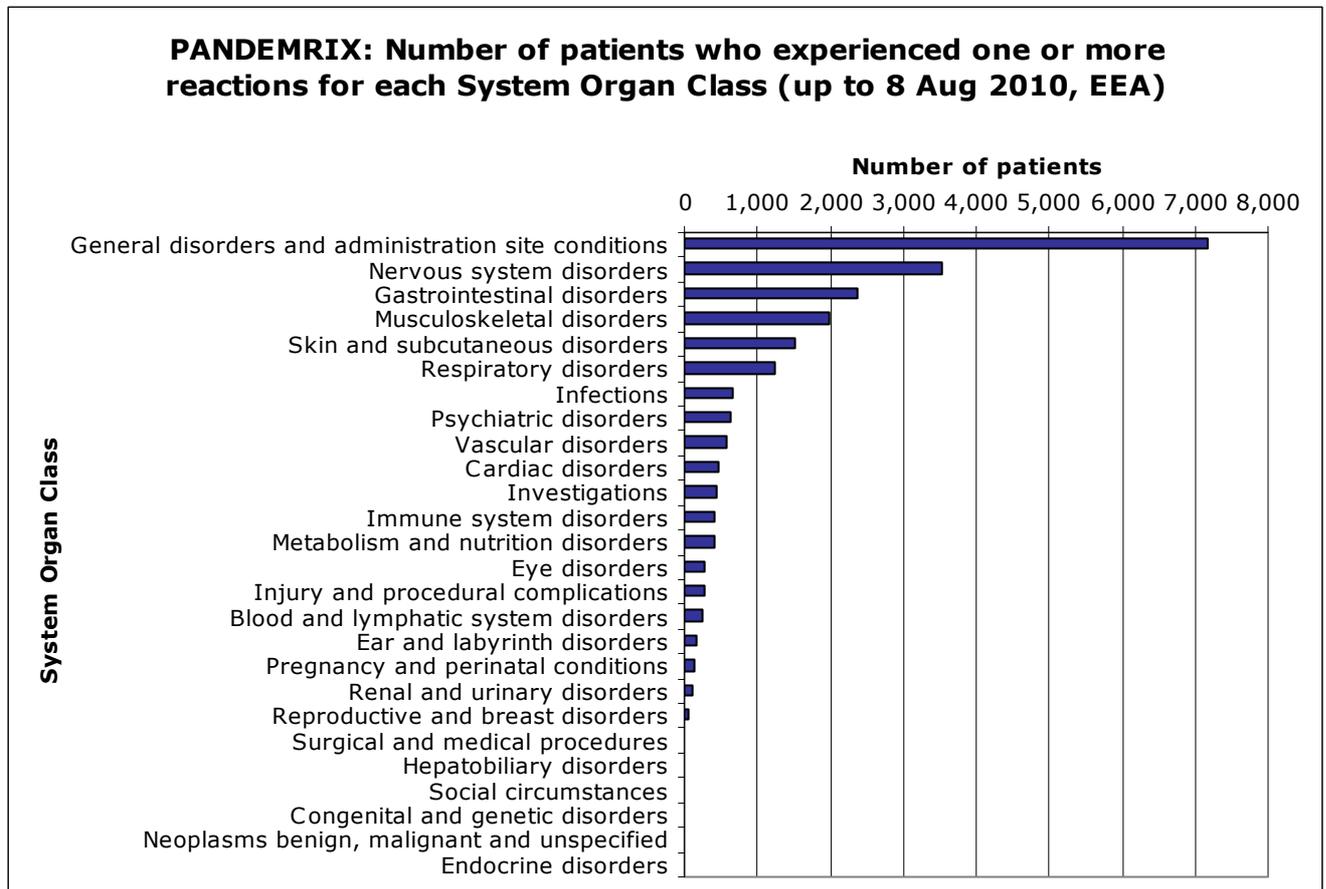
The analysis included 14 cases of intra-uterine deaths (after 20 weeks of pregnancy) reported to the MAH up to 5 February 2010. Considering that the incidence of intra-uterine death has been estimated as 2.6 - 9.1 per 1000 live births, the number of vaccinated pregnant women who would

coincidentally experience an intrauterine foetal death would have been between 192 and 764, which was much higher than the number of reported cases. Ten cases of miscarriage had also been reported to the MAH. Being the incidence of miscarriage in the general population around 10 to 12% according to published data, there was no indication that cases of miscarriage could have been associated with the use of Focetria.

Based on the available data, it was concluded that the safety profile of Focetria could be considered similar to the adjuvanted seasonal influenza vaccine.

Pandemrix

As of 8 August 2010, a total of 11,276 reports had been received by EudraVigilance (an increase of 91 reports since the previous update). Data available on 8 August 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, febrile convulsion, convulsion, tremor, loss of consciousness, lethargy, Guillain-Barré syndrome, facial palsy, presyncope, hypersomnia, poor quality sleep, hypotonia;

⁴ 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, dry mouth, swollen tongue, 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, rash pruritic, dermatitis allergic, pruritus generalised, petechiae, facial hypoaesthesia, rash maculopapular, 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;
- Infections: pneumonia, rhinitis, nasopharyngitis, influenza, herpes zoster, H1N1 influenza, cellulitis, lower respiratory tract infection, bronchitis, bronchopneumonia, respiratory tract infection, gastroenteritis, sepsis, ear infection, urinary tract infection, infection;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, confusional state, hallucination, anxiety, nightmare;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, peripheral coldness, hot flush;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, atrial fibrillation, cardiac failure, bradycardia, angina pectoris, cardiac arrest, myocarditis;
- 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;
- 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, diplopia, ocular hyperaemia, eyelid oedema, photophobia, conjunctivitis, eye rolling;
- Injury and procedural disorders: medication error, drug exposure during pregnancy, vaccination failure, fall, contusion;
- Blood and lymphatic system disorders: lymphadenopathy, thrombocytopenia, idiopathic thrombocytopenic purpura;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Pregnancy and perinatal conditions: abortion spontaneous, intra-uterine death, stillbirth, abortion, abortion late;
- Renal and urinary disorders: renal failure acute, renal failure, renal pain;

- Reproductive and breast disorders: vaginal haemorrhage, breast pain, suppressed lactation;
- Surgical and medical procedures: resuscitation, endotracheal intubation;
- Hepatobiliary disorders: jaundice;
- Social circumstances: disability;
- Congenital and genetic disorders: ankyloglossia congenital;
- Neoplasms benign, malignant and unspecified: neoplasm malignant;
- Endocrine disorders: autoimmune thyroiditis.

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, febrile convulsion, influenza-like illness, myalgia, urticaria, dizziness, erythema, tearfulness and erythema.
- Since the last update, five new fatal cases from the EEA have been received by EudraVigilance in relation to Pandemrix. They concerned two women and three men with ages ranging from 66 to 85 years. Two patients were reported to experience myocardial infarction, two fatal outcomes occurred in the context of pneumonia and sepsis, and one patient with a history of coagulation disorder died from a duodenal ulcer perforation. From authorisation to 8 August 2010, a total of 160 cases had been received in EudraVigilance. There is no indication that any of these cases could be associated with Pandemrix.
- A review of the clinical safety data provided by the MAH was performed by the CHMP in the context of the recommendation for a full marketing authorisation for Pandemrix.

Clinical trials

Several clinical trials were performed in children from 6 months of age, in adults and in the elderly up to 85 years. Clinical trial data in children aged from 6 months to 35 months showed greater incidence of fever ($\geq 38^{\circ}\text{C}$), local reactions (pain, redness, swelling) and drowsiness, irritability or loss of appetite following the second dose of Pandemrix. General symptoms were most often reported in children aged less than 12 months, but they were of mild intensity. In children aged between 3 to 9 years, the safety profile was considered acceptable. The second adult dose was associated with greater reactogenicity, resulting in higher rates of fever than the first dose, whereas this difference was not observed with the second versus first half adult dose. In adolescents aged between 10 to 17 years, the safety profile of a first adult dose of Pandemrix was generally comparable with that observed after each dose in young adults. Results in adults aged between 18 to 60 years showed that the safety profile of Pandemrix appeared to be generally comparable with that reported with the H5N1 mock-up vaccine and did not raise any new safety issues. In summary, the clinical trial data showed that there was no evidence of any specific safety issues in any age group, other than the issue of high fever after a second dose in children.

Observational cohort study

An analysis of data concerning 8,811 people enrolled in an observational cohort study with a 30-day follow-up had been completed. Overall, 12% of subjects had reported an event. A specific surveillance of reactogenicity revealed relatively high rates of local and general symptoms

compared with the H5N1 and H1N1 clinical studies, although with the same frequency as already stated in the product information. Severe local symptoms and those requiring medical attention occurred at very low rates. This study enrolled 275 women known to be pregnant at the time of vaccination. Although the outcomes of all pregnancies have not yet been reported, it was reassuring that 111 of 119 pregnant women with a known outcome had resulted in a healthy infant, with seven spontaneous abortions and one elective termination (with no apparent congenital defect) accounting for the remainder.

Spontaneous reports of adverse reactions

The majority of spontaneous reports of adverse reactions related to the same post-vaccination signs and symptoms than those reported from clinical studies and listed in the product information. They included headache, nausea, vomiting, diarrhoea, abdominal pain, dizziness, fever, myalgia/arthralgia, fatigue, malaise, asthenia, chills, sweating, allergic ADRs (including dyspnoea and generalised rashes), lymphadenopathy and injection site reactions (including pain, swelling and localised paraesthesia or numbness). The available data did not allow for an assessment of any change in the expected severity or frequency of such events as compared with the clinical studies.

Since many countries prioritised subjects with chronic underlying illnesses for vaccination, there were many spontaneous reports of severe adverse reactions related to cardiac disorders, respiratory disorders, obesity and diabetes-related disorders, or kidney disorders. These disorders likely related to pre-existing conditions and there was no suggestion of any specific safety signals arising from such cases. Several events such as pregnancy outcomes, afebrile seizures, neuropathies or demyelinating disorders remained under close review by the MAH and by regulatory authorities.

Several cases of febrile seizures in young children had been reported across the EU. In light of the evidence that emerged from the paediatric clinical trials regarding fever rates, particularly after the second dose, section 4.8 (Undesirable effects) of Pandemrix's product information was amended to include febrile seizures.

There had been three fatal cases of non-febrile seizures occurring in patients known to have epilepsy, less than 48 hours after vaccination. In one case, the patient had a recent history of poor epilepsy control. This was considered to be a signal requiring thorough evaluation. An epidemiological study has been initiated by the MAH and first results are expected in September 2010.

At the time of analysis, a total of 171 events with a fatal outcome had been reported to the MAH and evaluated in depth. It was concluded that death rates in vaccinees are below the expected rates. The majority of deaths, more than half of which were in elderly patients, appeared to be most likely due to concurrent illnesses. There remained no clear evidence that suggests that the vaccine had contributed to any of these deaths.

The available data on cases of anaphylaxis did not indicate that reporting rates are greater than the generally-expected rate of 1 to 10 cases per million doses observed with other vaccines. Anaphylaxis was included in section 4.8 (Undesirable effects) of the product information during the marketing period.

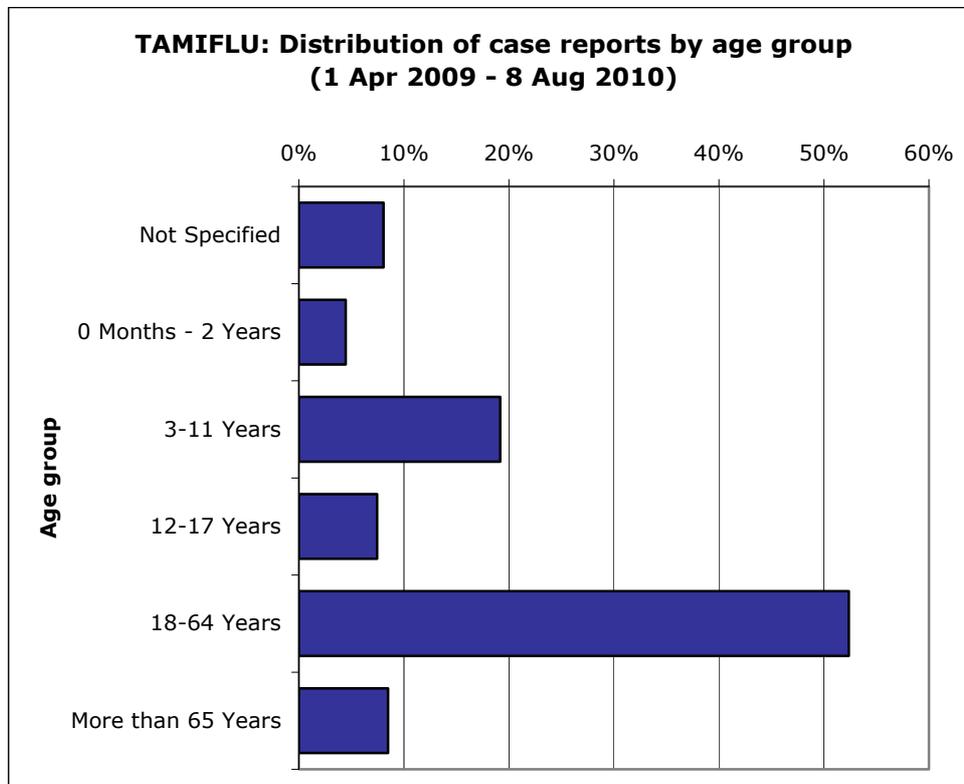
The MAH had also provided a detailed analysis of spontaneous reports of vaccine exposure in pregnancy. The data indicated no excess risk of spontaneous abortion, intra-uterine death or stillbirth in vaccinated pregnant women.

Since the marketing of the vaccine, the MAH had also been requested to provide detailed assessment of cases of eye disorders, herpes zoster infection, facial palsy, pregnancy-related outcomes, paediatric safety review, cyanosis, paralysis/paresis, hypoaesthesia, respiratory obstruction, administration errors, autoimmune haemolytic anaemia, hearing disorders and arthropathies. These analyses revealed no specific safety signals or cause for concern.

Antiviral medicines

Tamiflu (oseltamivir)

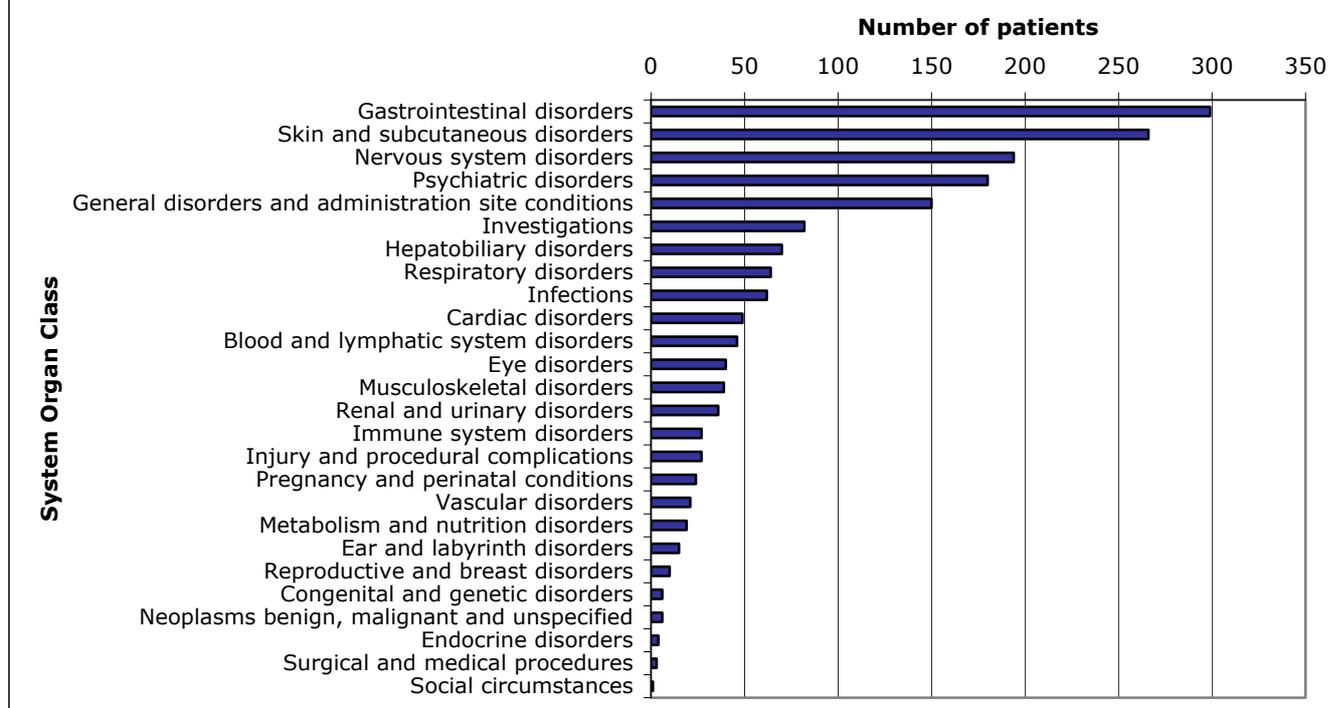
From 1 April 2009 to 8 August 2010, a total of 1,142 reports worldwide were received by EudraVigilance (an increase of seven reports since the previous update). The graph below displays the age distribution of patients who experienced an adverse reaction reported to EudraVigilance.



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.

TAMIFLU/oseltamivir: Number of patients who experienced one or more reactions for each System Organ Class (1 Apr 2009 - 8 Aug 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;
 - 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, lethargy, sensory disturbance;
 - 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, multi-organ failure, pain, 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, hepatic enzyme abnormal, prothrombin time prolonged, white blood cell count increased;
- Hepatobiliary disorders: hepatitis, cholestasis, acute hepatic failure, hepatic failure, cytolytic hepatitis, jaundice, hepatotoxicity;
- Respiratory disorders: epistaxis, dyspnoea, pulmonary embolism, cough;
- Infections: pathogen resistance, pneumonia, influenza, hepatitis A, pneumonia viral;
- Cardiac disorders: palpitations, tachycardia, bradycardia;
- Blood and lymphatic system disorders: thrombocytopenia, pancytopenia;
- Eye disorders: visual impairment, photophobia, conjunctivitis, ocular hyperaemia;
- Musculoskeletal disorders: arthralgia, myalgia;
- Renal and urinary disorders: renal failure acute, renal failure;
- Immune system disorders: hypersensitivity, anaphylactic reaction;
- Injury and procedural complications: drug exposure during pregnancy;
- Pregnancy and perinatal complications: abortion spontaneous;
- Vascular disorders: hypotension, pallor;
- Metabolism and nutrition disorders: decreased appetite;
- Ear and labyrinth disorders: tinnitus, vertigo;
- Reproductive and breast disorders: genital rash, metrorrhagia, penile oedema, vulval ulceration;
- Congenital and genetic disorders: anencephaly;
- Neoplasms, benign, malignant and unspecified: tumour flare;
- Endocrine disorders: hypothyroidism;
- Surgical and medical procedures: abortion induced;
- Social circumstances: sick building syndrome.

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, nausea, headache, abdominal pain and delirium.

- Since the last update, three new case reports with a fatal outcome worldwide have been received by the EudraVigilance system following oseltamivir use. One of the cases occurred within the EEA. In two cases the cause of death was reported as swine flu and in one case the death was related to pneumonitis and occurred in a patient with history of non-Hodgkin's lymphoma and autologous stem cell transplantation.

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		<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>