EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Lessons learnt from Influenza A(H1N1) vaccines benefit-risk monitoring

ENCePP Plenary meeting

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1. Safety database at time of authorisation

Pandemrix

- H5N1 vaccine: 6,100 subjects
  - 300 children 3-9 years, 5,071 adults 18-60 years, 729 elderly >60 years
- H1N1 vaccine: 130 adults 18-60 years

Focetria

- H5N1 vaccine: 1,496 subjects
  - 145 children 6-35 months, 96 children 3-8 years, 93 children 9-17 years, 989 adults 18-60 years, 173 elderly >60 years
- H1N1 vaccine: none

Celvapan

- H5N1 vaccine: 836 subjects
  - 556 adults 18-60 years, 280 elderly > 60 years
- H1N1 vaccine: none

Safety profiles observed with H5N1 vaccines expected to be generally applicable to A/H1N1 vaccines. Limited data in children and pregnant women.

European Medicines Agency

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

HMA Heads of Medicines Agencies

European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring

European Strategy published on 5 November 2009

http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/european_strategy.pdf

or: EMEA website → Pandemic influenza website → Latest news

2. Vaccine safety surveillance

Marketing Authorisation Holders

- Monthly simplified Periodic Safety Update Reports (s-PSUR)
  - Summary of important information from spontaneous reports and analysis of safety issues in populations at risk
- PASS of 9,000 subjects for each vaccine stratified by age
  - As soon as vaccination starts
- Pregnancy registries
  - Creation or collaboration with existing pregnancy registries
- Rare disorders (eg. Guillain-Barré syndrome) and populations at risks
  - Active surveillance
- Effectiveness studies
  - Collaboration between ECDC (I-MOVE consortium), EMA and MAHs

Vaccine safety surveillance

EMA and Member States

- Strenghtening of the spontaneous reporting system
  - list of Adverse Events of Special Interest (AESIs)
  - standardised list of data to collect (eg batch number)
  - weekly distribution of EudraVigilance reaction monitoring report
  - observed-to-expected analyses
- Procedures for rapid assessment and decision-making
  - e.g. variation of product information for high fever after 2nd dose
- Collection of EU-wide information
  - vaccination policies
  - exposure data
  - background rates on adverse events of special interest
- Collaboration with research projects relevant for A/H1N1 vaccine B/R monitoring
  - 43 projects, 8 multicountry, 35 national (14 countries)

Vaccine safety surveillance

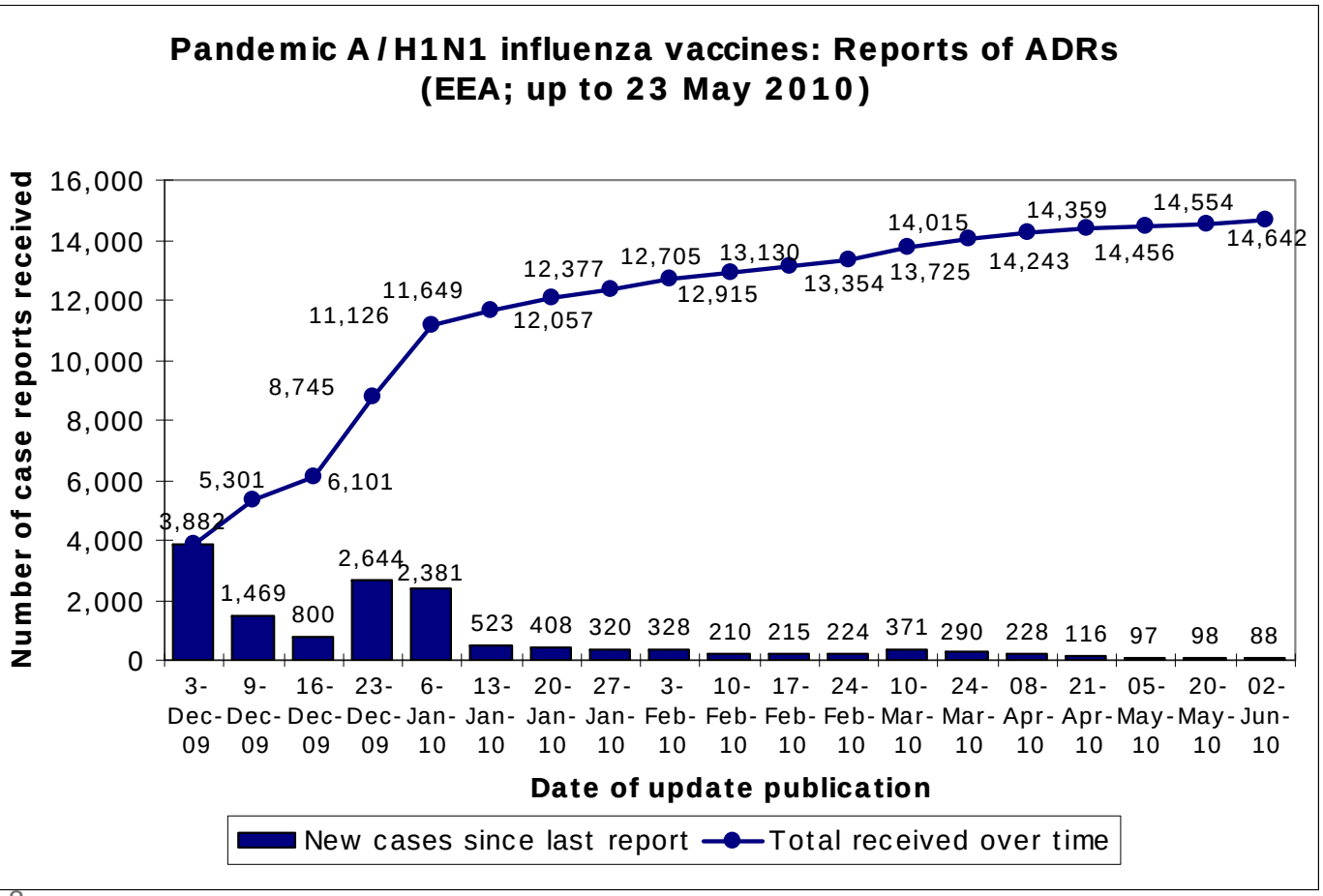
EMA and Member States

- Establishment of Pandemic Pharmacovigilance Rapid Response Expert Group (PREG)
  - Weekly teleconferences, more if needed
  - Analysis of emerging safety issues and recommendations
  - Rapid response to concerns raised by Member States

- Weekly Pandemic Pharmacovigilance Updates published on EMA website
  - Exposure data
  - Overall benefit-risk evaluation
  - List of most frequent reactions per system organ class
  - Review of all fatal cases
  - Safety updates: new safety concerns, PREG conclusions

3. What worked well

1. Spontaneous reports – only source of data on vaccine safety until 01/10

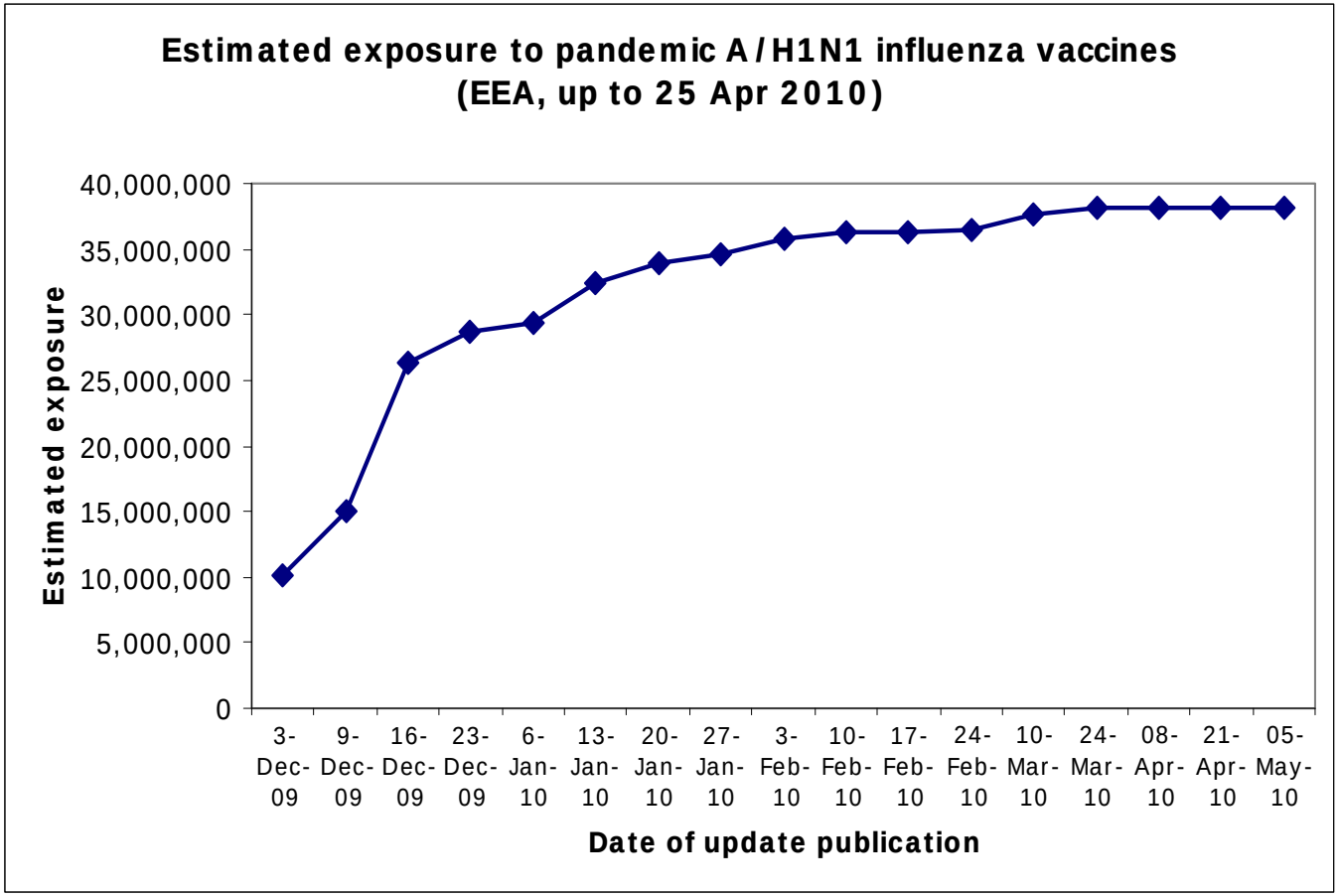


Eudravigilance

Celvapan:	557
Focetria:	3,096
Pandemrix:	10,014

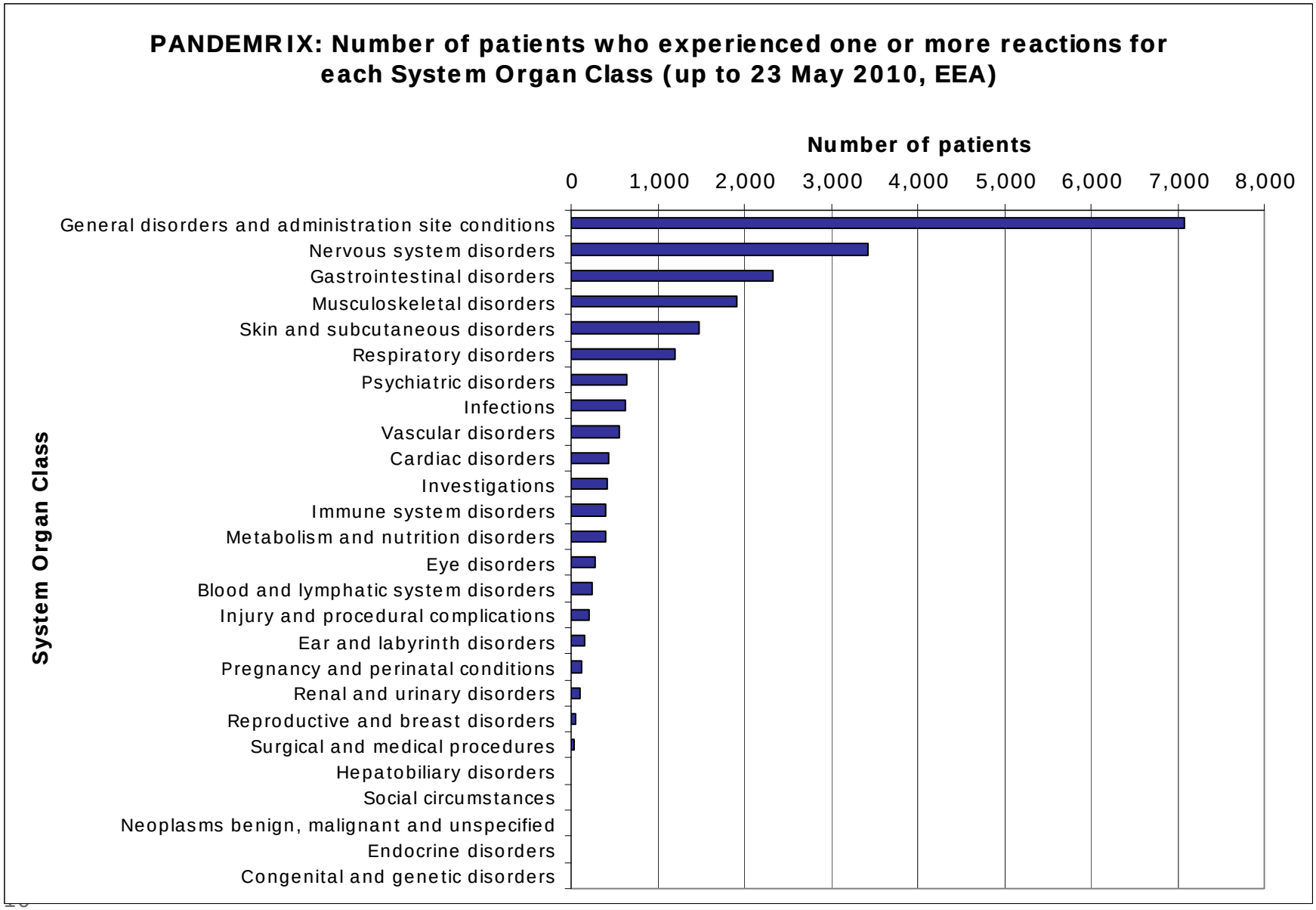
Ad-hoc weekly EMA survey of EEA members.

CAP vaccines:

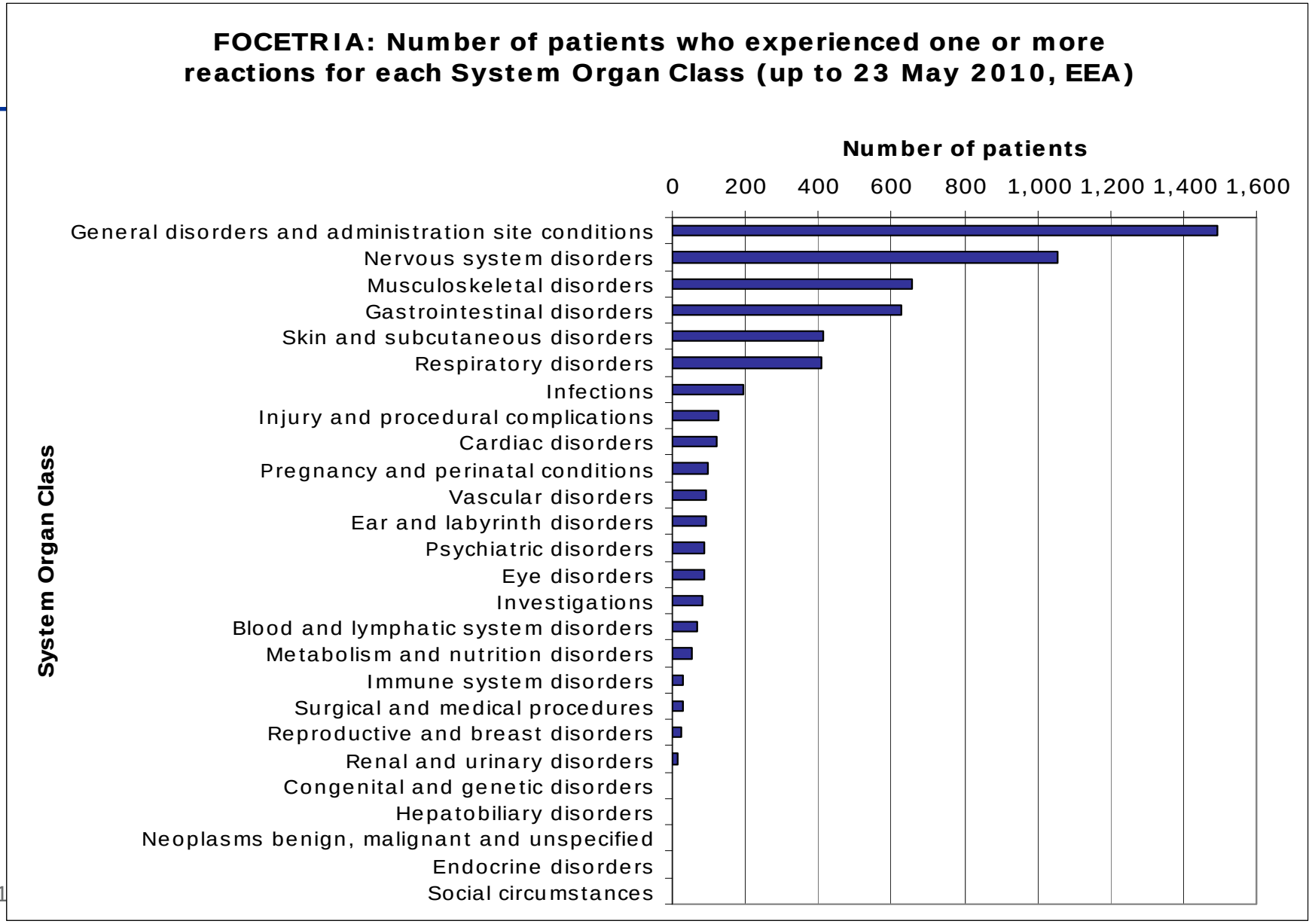


Celvapan:	0.6 m.
Focetria:	6.5 m.
Pandemrix:	30.7 m.

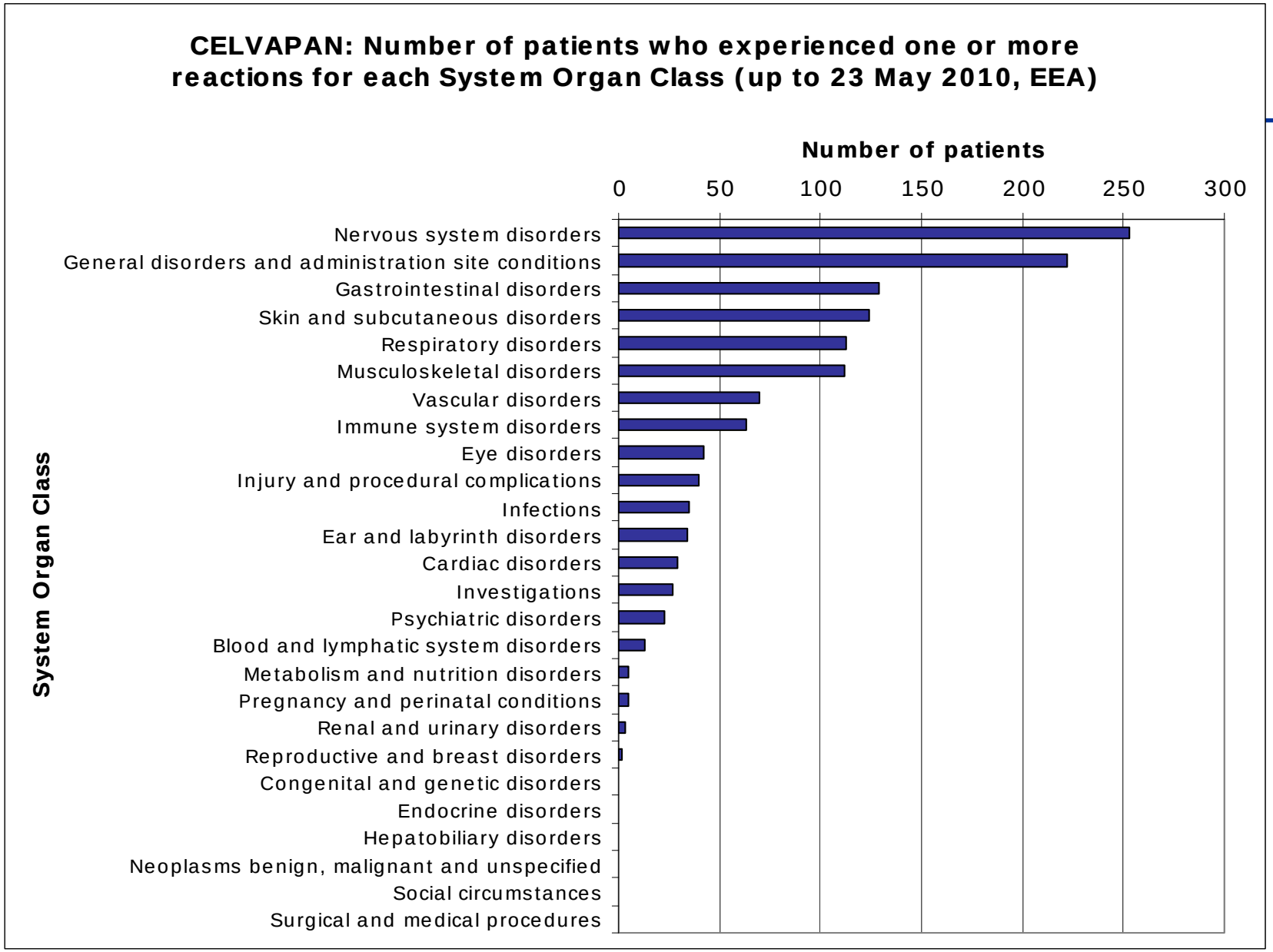
Reported vaccine reactions by SOC: Pandemrix



Reported vaccine reactions by SOC: Focetria



Reported vaccine reactions by SOC: Celvapan



Adverse events of special interest

(EEA+non-EEA) 30/05/2010

Pandemrix

Validation on-going

	Total	Total paediatric
Anaphylactic reaction (narrow SMQ)	329	54
- anaphylactic shock	45	10
- anaphylactoid shock	1	0
Angioedema (narrow SMQ)	550	185
Convulsions (narrow SMQ)	312	199
Demyelination (narrow SMQ, excl GBS)	76	3
- multiple sclerosis	14	1
- multiple sclerosis relapse	19	0
GBS/MS (incl. PT Nerve root lesion); partly validated	75	6
Noninfectious encephalitis (narrow SMQ, excl ADEM)	21	2
Vasculitis (narrow SMQ)	34	8
Facial palsy (PT)	5	6
Neuritis (PT)	25	0

Adverse events of special interest

(EEA+non-EEA) 30/05/2010

Focetria

Validation on-going

	Total	Total paediatric
Anaphylactic reaction (narrow SMQ)	23	4
- anaphylactic shock	5	1
- anaphylactoid shock	0	0
Angioedema (narrow SMQ)	151	24
Convulsions (narrow SMQ)	55	29
Demyelination (narrow SMQ, excl GBS)	16	0
- multiple sclerosis	1	0
- multiple sclerosis relapse	3	0
GBS/MS (incl. PT Nerve root lesion); partly validated	32	0
Noninfectious encephalitis (narrow SMQ, excl ADEM)	8	1
Vasculitis (narrow SMQ)	15	1
Facial palsy (PT)	20	2
Neuritis (PT)	4	0

Adverse events of special interest

(EEA+non-EEA) 30/05/2010

Celvapan

Validation on-going

	Total	Total paediatric
Anaphylactic reaction (narrow SMQ)	23	4
- anaphylactic shock	1	1
- anaphylactoid shock	0	0
Angioedema (narrow SMQ)	56	17
Convulsions (narrow SMQ)	12	4
Demyelination (narrow SMQ, excl GBS)	2	0
- multiple sclerosis	1	0
- multiple sclerosis relapse	0	0
GBS/MS (incl. PT Nerve root lesion); partly validated	2	0
Noninfectious encephalitis (narrow SMQ, excl ADEM)	1	0
Vasculitis (narrow SMQ)	4	1
Facial palsy (PT)	1	0
Neuritis (PT)	1	0

Reaction reports in Pregnancy SOC

(EEA+non-EEA) 30/05/10

	Celvapan	Focetria	Pandemrix
Abortion not specified/spontaneous	1	5	74
Amniotic fluid and cavity disorders		1	1
Failed labour		2	
Foetal (growth) complication		2	4
Foetal presentation abnormalities			1
Premature/small for date baby	3	4	4
Haemorrhagic complications		2	3
Pre-eclampia, pregnancy-induced HT		2	
Premature/threatened labour	1	5	6
Maternal complications/ectopic pregnancy		3	6
Placenta abnormalities		4	1
Intra-uterine death, stillbirth		27	34
Umbilical cord complications		3	1
Unintended pregnancies			3

Reports of fatal cases (EEA+non-EEA) 23/05/10

All reports of fatal cases have been reviewed.

- Celvapan : 2 reports: underlying disease and old age
- Focetria: 32 reports – Pandemrix: 157 reports

	F	P
– Respiratory cause (incl. pneumonia, embolism, failure):	3	27
– Cardio-or cerebro-vascular cause (incl MI, arrest, stroke..)	13	53
– Other identified cause	3	16
– Sudden/unexplained death		
– with underlying medical conditions	3	40
– without underlying medical condition or no information	9	21

No single fatal case attributable to vaccine

3. What worked well

2. The Pandemic Pharmacovigilance Rapid Response Expert Group (PREG)

Signals raised by Member States or EMA and discussed by PREG on a weekly basis

Pandemrix:
- allergic reactions
- foetal deaths
- transplant rejection
- exacerbation of pre-existing seizure disorders
- autoimmune thrombocytopenia
- intrauterine death with trace of A/H1N1 genome
- high fever following second dose
- eye disorders
- anaphylaxis in children

Focetria:
- fatal case of encephalitis

Celvapan:
- anaphylactic shock

All vaccines:

- multiple sclerosis/relapse of multiple sclerosis
- polyneuropathies
- demyelinating disorders
- Guillain-Barré syndrome

Ad-hoc Expert group on Guillain-Barré syndrome – 29 March 2010

- Review of O/E analyses based on spontaneous reports from UK, SE, DE, IT, FR and from data from US and Canada is reassuring.
- No evidence of a signal of a similar magnitude as in 1976.
- Association cannot be totally ruled out given uncertainties in observed to expected analyses but any association would translate in very small increase of risk.
- Factors limiting interpretation of data were identified.
- Clustering of many cases between 4 and 29 days needs further investigation.
- On-going epidemiological studies will provide valid data but may not be able to detect small risks given low vaccination coverage.
- Need for pooling data or combining results from studies.

3. What worked well

3. Unprecedented level of communication on safety issues

- Web sites of medicines/vaccine agencies in many Member States
- Weekly EMA pandemic pharmacovigilane updates

4. Areas for improvement of vaccine vigilance system

1. Roles and responsibilities

Respective roles and responsabilities of EMA, ECDC, regulatory agencies and public health authorities in benefit-risk monitoring.

2. Processes and methodologies

- Observed-to-expected analyses
- Background incidence rates of adverse events
- Measures of disproportionality
- Timeliness of data on vaccine effectiveness vs. safety signals

Areas for improvement of vaccine vigilance system

3. Capacity building

- Infrastructure (networking of research centres, common protocols, data sources) for post-authorisation safety and B/R studies for vaccines in the EU
  - e.g. I-MOVE for effectiveness studies - VAESCO
- Pregnancy outcomes: network of centres for sharing information, pooling of data or combining results
- Vaccination coverage data at EU level (+ common age categories)
- System for collecting background rates of medical events at EU level, using a common methodology.
- Independent funding of studies on benefit-risk of vaccines at EU level

5. On-going work

- Assessment of the performance of spontaneous reporting
- Validation and further analysis of AESIs in EudraVigilance data
- Comparison with seasonal vaccines in EudraVigilance data
- Observational studies funded by national authorities in several countries, e.g. Sweden, United-Kingdom, France, Germany, Spain,…
- Studies on pregnancy outcome: ENTIS, EUROCAT, national studies
- VAESCO consortium multinational study on GBS
- Final analyses of effectiveness studies performed by I-MOVE consortium

Forthcoming:

EMA restricted invitation to tender

A/H1N1 pandemic vaccines and pregnancy outcomes

for centres with valid application to Call for Expressions of Interest in Lot 4 (observational research into the safety of vaccines using appropriate study designs)

Thank you !

Back-up slides

Reported vaccine reactions by SOC: Celvapan

- most frequent reactions per SOC

- Nervous-system disorders: headache, dizziness, syncope, paraesthesia, hypoaesthesia, lethargy;
- General disorders and administration-site conditions: pyrexia, malaise, fatigue, chills, asthenia, influenza-like illness, feeling hot, injection-site pain, chest discomfort, pain;
- Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, oral paraesthesia;
- Skin and subcutaneous conditions: hyperhidrosis, pruritus, urticaria, rash, erythema;
- Respiratory disorders: oropharyngeal pain, cough, dyspnoea;
- Musculoskeletal disorders: myalgia, arthralgia, pain in extremity, muscular weakness;
- Vascular disorders: pallor, flushing, hypotension;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactoid reaction;
- Eye disorders: vision blurred;
- Injury and procedural complications: medication error;
- Infections: rhinitis, nasopharyngitis;
- Ear and labyrinth disorders: vertigo;
- Cardiac disorders: tachycardia, palpitations;
- Investigations: body temperature increased;
- Psychiatric disorders: sleep disorder.

Reported vaccine reactions by SOC: Focetria

- most frequent reactions per SOC

- General disorders and administration-site conditions: pyrexia, fatigue, injection-site pain, influenza-like illness, malaise, chills, injection-site erythema, hyperpyrexia, injection-site swelling, injection-site induration, chest pain, asthenia, pain, injection-site pruritus, feeling cold, injection-site haematoma, injection-site warmth, oedema peripheral, feeling hot;
- Nervous-system disorders: headache, dizziness, paraesthesia, somnolence, tremor, hypoaesthesia, syncope, dysgeusia, Guillain-Barré syndrome, presyncope, convulsion, migraine;
- Musculoskeletal disorders: myalgia, pain in extremity, arthralgia, musculoskeletal stiffness, muscular weakness, neck pain, muscle spasms, musculoskeletal pain, back pain, sensation of heaviness, rheumatoid arthritis;
- Gastrointestinal disorders: nausea, diarrhoea, vomiting, abdominal pain, abdominal discomfort, upper abdominal pain, dyspepsia;
- Skin and subcutaneous conditions: rash, pruritus, urticaria, erythema, hyperhidrosis, rash pruritic, dermatitis allergic, angioedema, rash generalised, swelling face, eczema;
- Respiratory disorders: cough, dyspnoea, oropharyngeal pain, asthma, bronchospasm, dysphonia, productive cough, throat irritation;
- Infections: rhinitis, nasopharyngitis, pneumonia, influenza, pharyngitis, herpes zoster;
- Injury and procedural complications: drug exposure during pregnancy, contusion, vaccination failure;

Reported vaccine reactions by SOC: Focetria

- most frequent reactions per SOC (2)

- Cardiac disorders: palpitations, tachycardia, arrhythmia, atrial fibrillation, cyanosis;
- Pregnancy and perinatal conditions: pre-eclampsia, premature baby, intra-uterine death, premature labour;
- Vascular disorders: hypertension, hypotension, flushing, pallor, haematoma, peripheral coldness;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain;
- Psychiatric disorders: listlessness, insomnia, nightmare, restlessness, tearfulness;
- Eye disorders: visual impairment, eyelid oedema, eye irritation, conjunctivitis, eye swelling, vision blurred, diplopia, eye pain;
- Investigations: body temperature increased, blood pressure increased, heart rate increased;
- Blood and lymphatic disorders: lymphadenopathy;
- Metabolism and nutrition disorders: decreased appetite;
- Immune system disorders: hypersensitivity, anaphylactic reaction.

Reported vaccine reactions by SOC: Pandemrix

- most frequent reactions per SOC

- General disorders and administration-site conditions: pyrexia, hyperpyrexia, injection-site pain, fatigue, influenza-like illness, malaise, chills, injection site erythema, injection-site swelling, pain, oedema peripheral, asthenia, injection-site induration, chest pain, injection-site inflammation, feeling hot, chest discomfort, local reaction;
- Nervous system disorders: headache, dizziness, paraesthesia, syncope, somnolence, hypoaesthesia, crying, febrile convulsion, convulsion, tremor, lethargy, loss of consciousness, Guillain-Barré syndrome, presyncope, facial palsy, hypersomnia, hypotonia, poor quality sleep;
- Gastrointestinal disorders: vomiting, nausea, diarrhoea, abdominal pain, upper abdominal pain, paraesthesia oral, dysphagia, lip swelling, swollen tongue, dry mouth, abdominal discomfort, hypoaesthesia oral, lower abdominal pain;
- 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;

Reported vaccine reactions by SOC: Pandemrix

- most frequent reactions per SOC (2)

- Respiratory disorders: dyspnoea, cough, oropharyngeal pain, asthma, rhinorrhoea, wheezing, epistaxis, throat tightness, pharyngeal oedema, tachypnoea, bronchospasm, respiratory failure, respiratory distress, sneezing, dysphonia, pulmonary embolism, hyperventilation, productive cough, stridor;
- Psychiatric disorders: listlessness, insomnia, tearfulness, sleep disorder, restlessness, hallucination, anxiety, confusional state, nightmare;
- Infections: rhinitis, pneumonia, nasopharyngitis, influenza, herpes zoster, H1N1 influenza, cellulitis, bronchitis, lower respiratory tract infection, respiratory tract infection, ear infection, gastroenteritis, bronchopneumonia;
- Vascular disorders: pallor, circulatory collapse, hypotension, flushing, hypertension, peripheral coldness, hot flush;
- Cardiac disorders: tachycardia, palpitations, cyanosis, myocardial infarction, cardiac failure, atrial fibrillation, cardiac arrest, bradycardia, angina pectoris, myocarditis;
- Investigations: body temperature increased, blood pressure decreased, blood pressure increased, heart rate increased, weight decreased, transaminases increased, C-reactive protein increased, heart rate decreased, body temperature decreased;
- Immune disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction;

Reported vaccine reactions by SOC: Pandemrix

- most frequent reactions per SOC (3)

- Metabolism and nutrition disorders: decreased appetite, oligodipsia, dehydration, hypoglycaemia, polydipsia;
- Eye disorders: vision blurred, eye pain, eye swelling, visual impairment, ocular hyperaemia, diplopia, eyelid oedema, photophobia, conjunctivitis;
- Blood and lymphatic system disorders: lymphadenopathy, thrombocytopenia;
- Injury and procedural disorders: medication error, vaccination failure, fall, contusion;
- Ear and labyrinth disorders: vertigo, tinnitus, ear pain.

5. Stratification by age groups: reactions reported in <18 years (decreasing order of frequency)

Celvapan:

vomiting, hypersensitivity, medication error, syncope, pyrexia, dizziness, nausea, rash, pallor, headache, vision blurred, malaise, fatigue, urticaria, chills, cough, pruritus, somnolence, dyspnoea, hyperhidrosis.

Focetria:

pyrexia, headache, hyperpyrexia, vomiting, drug exposure during pregnancy, cough, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, fatigue, influenza-like illness, rash, dyspnoea, urticaria, malaise, convulsion.

Pandemrix:

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, erythema.

8. Amendments to SPC

- Pandemrix:
  - **Safety data from results of clinical trials with A/H1N1 vaccine**, including children >6 months (reactogenicity)
  - **Post-marketing surveillance**:
    - Immune system disorders: Anaphylaxis, allergic reactions
    - Nervous system disorders: Febrile convulsions
    - Skin and subcutaneous tissue disorders: Angioedema, generalised skin reactions, urticaria

Amendments to SPC

- Focetria:

- Safety data from results of clinical trials with A/H1N1 vaccine, including children >6 months (reactogenicity)

- Post-marketing surveillance:

– Blood and lymphatic system disorders: Lymphadenopathy.

– Cardiac disorders: Palpitation, tachycardia.

– General disorders and administration site conditions: Asthenia.

– Muscoskeletal, connective tissue and bone disorders: Muscular weakness, pain in extremities.

– Respiratory disorders: Cough.

– Skin and subcutaneous tissue disorders: Generalised skin reactions including pruritus, urticaria or non-specific rash; angioedema.

– Gastrointestinal disorders: Gastrointestinal disorders such as nausea, vomiting, abdominal pain and diarrhoea.

– Nervous system disorders: Headache, dizziness, somnolence, syncope. Neurological disorders, such as neuralgia, paraesthesia, convulsions and neuritis.

– Immune system disorders: Allergic reactions, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to shock.

Amendments to SPC

- Celvapan:
  - **Safety data from results of clinical trials** with A/H1N1 vaccine, including children >6 months (reactogenicity)
  - **Preliminary results of pandemic observational study:**
    - –in children above 5 years of age, adolescents and adults: injection site reactions, fatigue, headache, muscle pain, gastrointestinal symptoms
    - –very common reactions reported in children aged 6 months to 5 years: injection site reactions, drowsiness, irritability, loss of appetite

- Post-marketing surveillance:

- Immune system disorder: Anaphylactic reaction*, Hypersensitivity*

  *Such reactions have been manifested by respiratory distress, hypotension, tachycardia, tachypnea, cyanosis, pyrexia, flushing, angioedema, and urticaria

- Nervous system disorders: Febrile convulsion
- Skin and subcutaneous tissue disorders: Angioedema
- Musculoskeletal and connective tissue disorders: Pain in extremity (in the majority of cases reported as pain in the injection site arm)
- General disorders and administration site conditions: Influenza-like illness