EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Descriptive overview of paediatric versus adult ADRs in EudraVigilance

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An agency of the European Union

# Introduction

## Comparison between paediatric and adult suspected adverse drug reactions reported to the European Medicines Agency: implications for pharmacovigilance.

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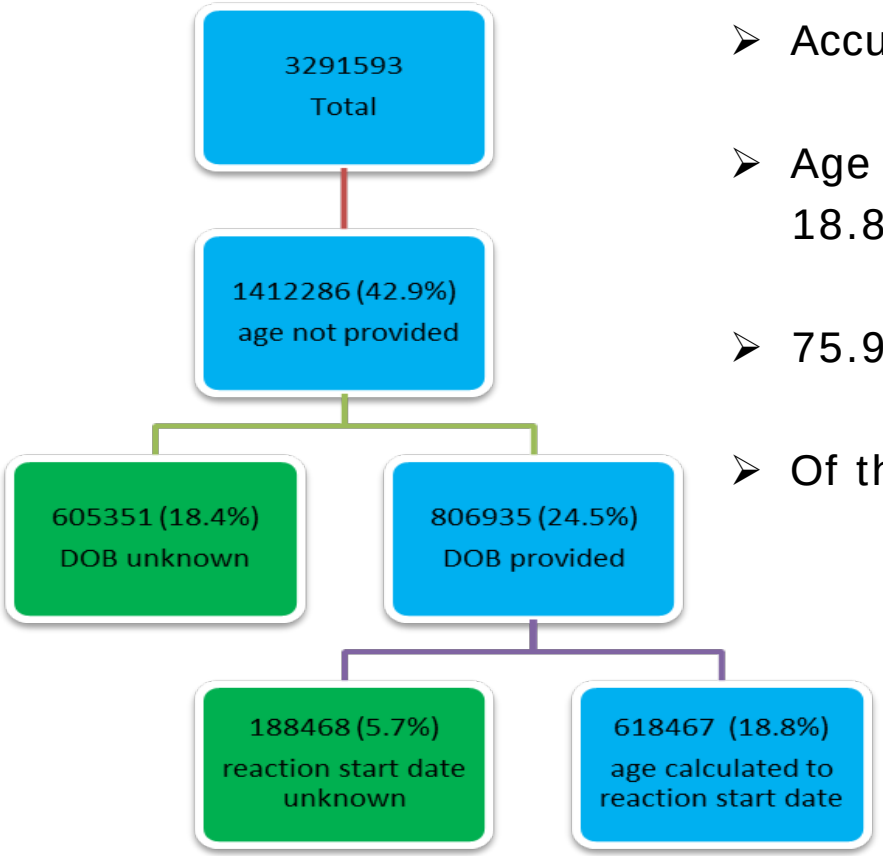
# Spontaneous ADR databases

- Databases systematically collecting reports of ADRs are a cornerstone of pharmacovigilance: on-going large-scale surveillance in the 'real-world' setting.
- Several studies have provided data on ADRs in children reported to national databases e.g. EU MSs, Canada, the US.
- Study in EV to provide a descriptive overview comparing paediatric versus adult ADRs reported across national boundaries to EudraVigilance (EV) as a baseline to explore if lessons can be learned

# Methods

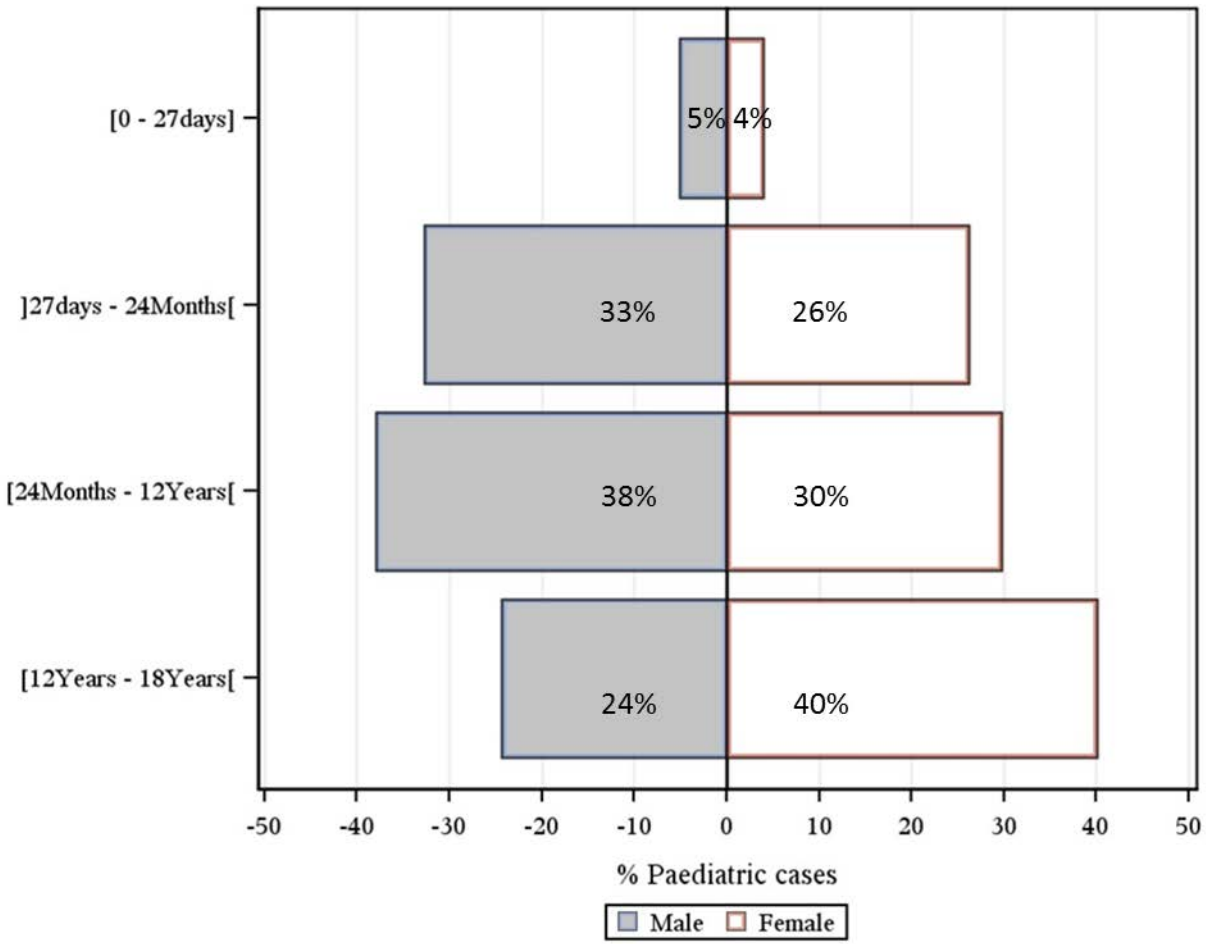
- Reports in EV from inception of EU PV system (January 01 1995) to cut off 13 June 2013 analysed for overall numbers, age, gender, primary source (EEA/non-EEA)
- Age defined as birth to last day of 17$^{th}$ year inclusive
- If age not provided then, where possible, calculated from date of birth to date of reaction

# Reporting of age



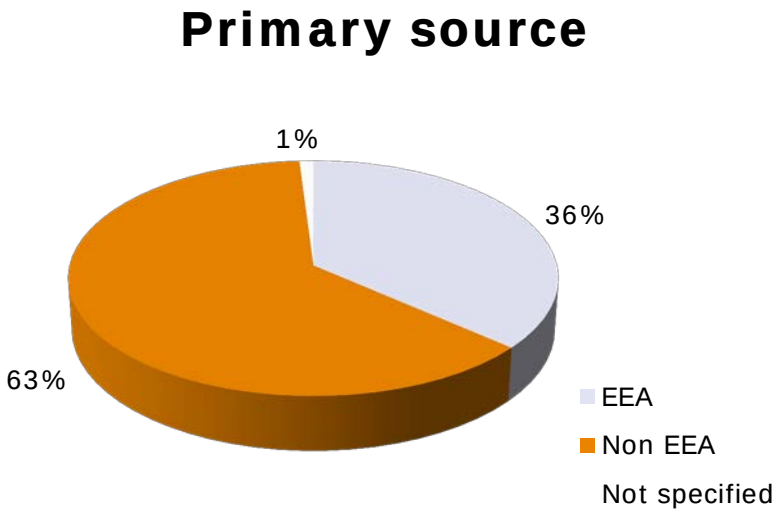

- Accurate age provided: 57.1%
- Age could be calculated in a further 18.8%
- 75.9% could be used in the analysis
- Of these 11.2% (279,359) < 18 years

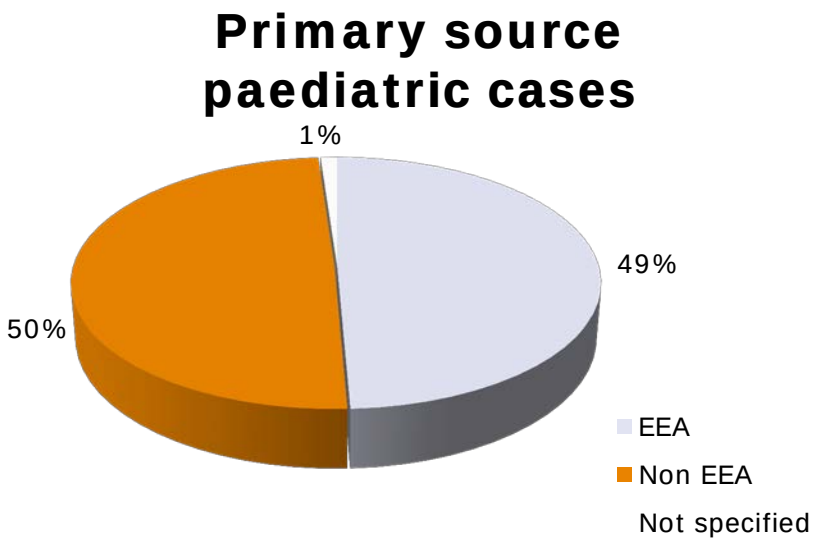
# Gender



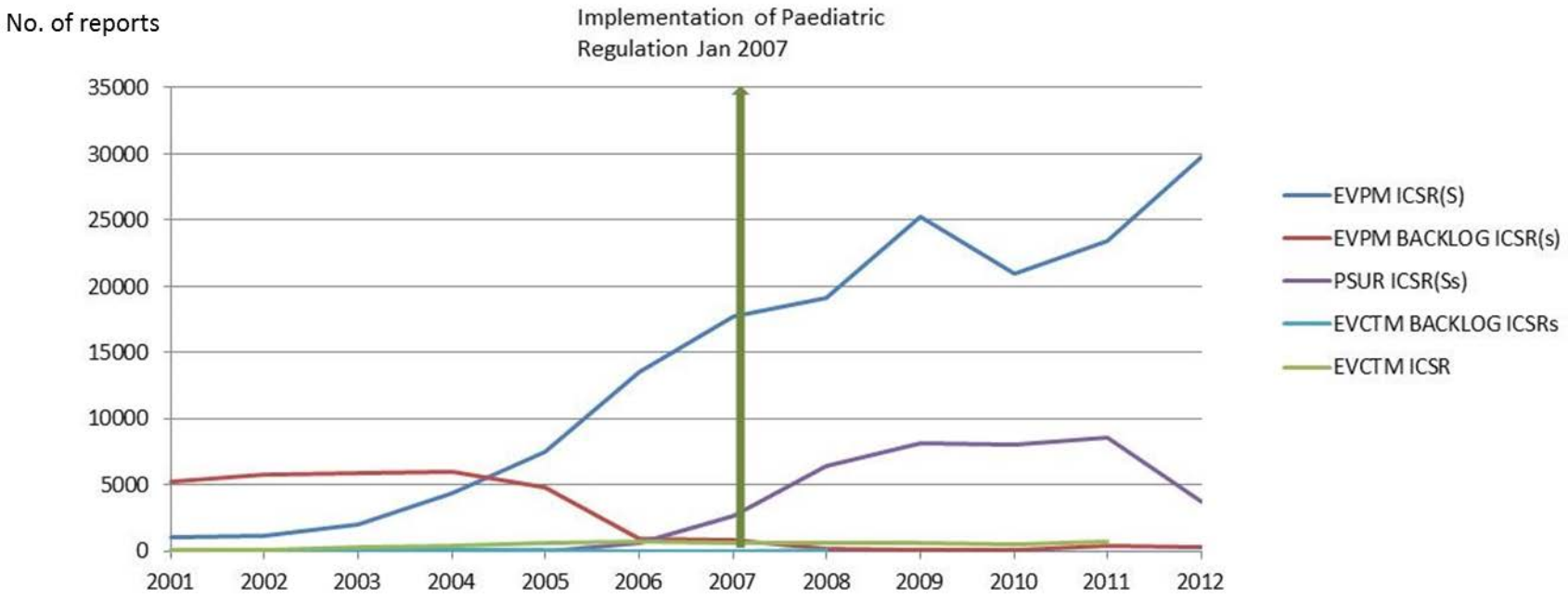

**Similar overall (F 48% and M 47%) but difference in the age distribution**

# Geographic origin



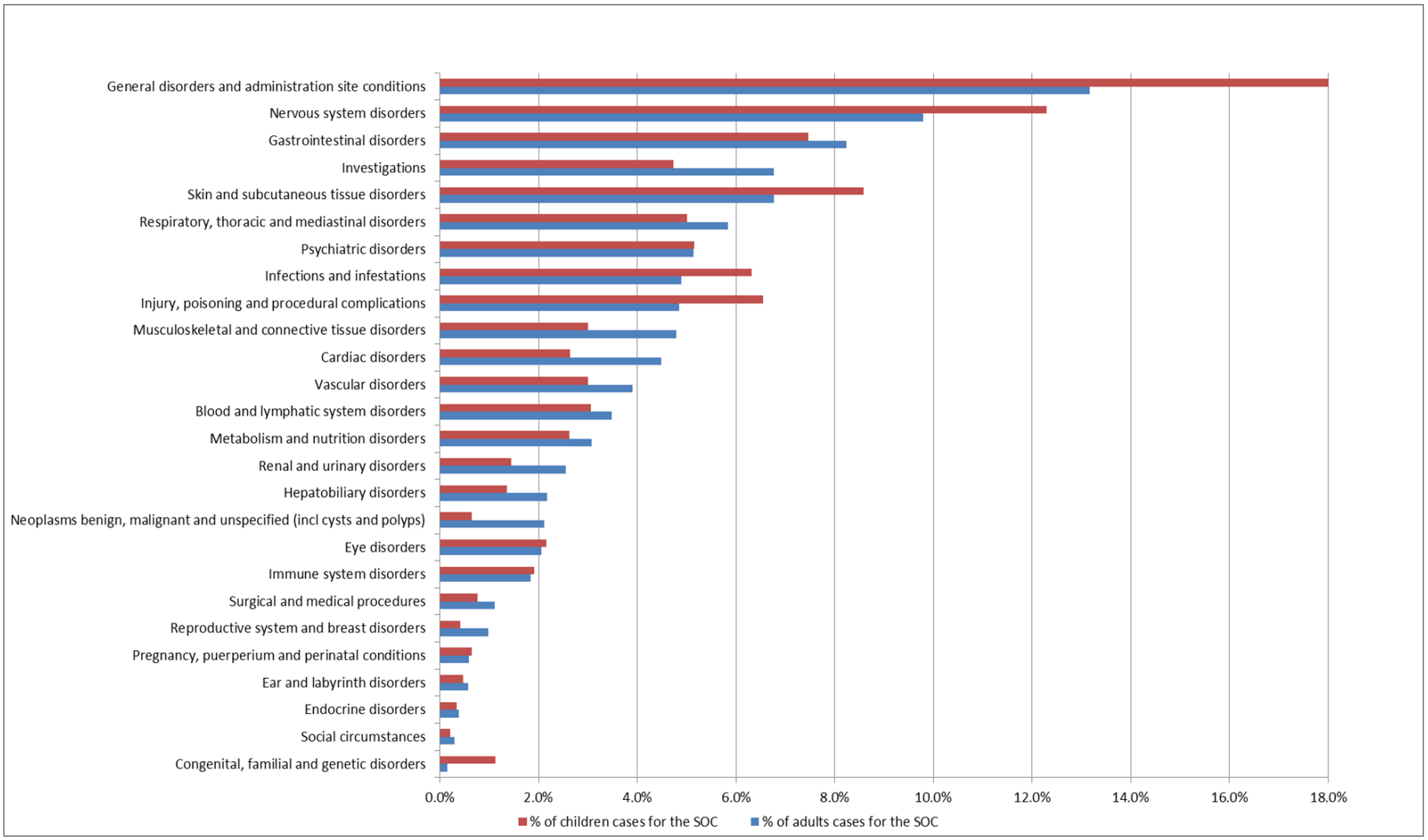



# Reporting over time




*EudraVigilance Post-authorisation Module (EVPM); EudraVigilance Clinical Trials Module (EVCTM); Individual Case Safety Reports (ICSR); Periodic Safety Update Reports (PSUR)

# Proportion of paed v's adult cases by SOC



# Most frequent reported PTs

| Rank | PT | Number (%) of paediatric reports | PT | Number (%) of adult reports |
|---|---|---|---|---|
| 1 | **Pyrexia** | 37548 (13) | **Nausea** | 92985 (4) |
| 2 | **Vomiting** | 15652 (6) | Dyspnoea | 83411 (4) |
| 3 | Convulsion | 12009 (4) | **Pyrexia** | 72736 (3) |
| 4 | **Rash** | 10432 (4) | **Vomiting** | 65325 (3) |
| 5 | **Headache** | 9512 (3) | **Headache** | 64341 (3) |
| 6 | Crying | 8601 (3) | **Dizziness** | 61635 (3) |
| 7 | **Urticaria** | 8567 (3) | **Diarrhoea** | 57071 (3) |
| 8 | **Diarrhoea** | 7467 (3) | **Rash** | 53847 (2) |
| 9 | **Nausea** | 7464 (3) | Death | 53748 (2) |
| 10 | Drug ineffective | 6024 (2) | Fatigue | 52309 (2) |

| Rank in EV | Active Substance | Number (%) of paediatric reports | Active Substance | Number (%) of adult reports |
|---|---|---|---|---|
| 1 | Pneumococcal polysaccharide conjugate vaccine (adsorbed) | 24493 (9) | **Etanercept** | 146600 (7) |
| 2 | Human papillomavirus vaccine | 22487 (8) | Varenicline | 40873 (2) |
| 3 | Measles, mumps and rubella vaccine (live) | 13435 (5) | Infliximab | 40809 (2) |
| 4 | Diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rDNA), poliomyelitis (inactivated.) And haemophilus type b conjugate vaccine (adsorbed) | 12328 (4) | Acetylsalicylic acid | 31371 (1) |
| 5 | Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) | 8954 (3) | Pregabalin | 30830 (1) |
| 6 | Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed) | 8691 (3) | Clozapine | 30486 (1) |
| 7 | A/California/7/2009 (H1N1)v-like virus | 7041 (3) | Calcium chloride, sodium chloride, glucose, sodium lactate, magnesium chloride | 25591 (1) |
| 8 | Mycobacterium bovis, Danish strain 1331 | 5887 (2) | Dabigatran | 24057 (1) |
| 9 | Rotavirus vaccine, live, oral, pentavalent | 5389 (2) | Drospirenone, ethinylestradiol | 21463 (1) |
| 10 | Isotretinoin | 5156 (2) | Quetiapine | 21338 (1) |
| 11 | Methylphenidate | 4370 (2) | Calcium chloride, glucose, anhydrous, sodium chloride, sodium lactate, magnesium chloride | 21330 (1) |
| 12 | **Etanercept** | 4116 (1) | Atorvastatin | 20475 (1) |
| 13 | **Paracetamol** | 3933 (1) | **Paracetamol** | 20155 (1) |
| 14 | Hepatitis B vaccine | 3905 (1) | Methotrexate | 20011 (1) |
| 15 | Haemophilus type b conjugate vaccines | 3850 (1) | Zoledronic acid | 19655 (1) |
| 16 | Varicella virus | 3375 (1) | Diclofenac | 19540 (1) |
| 17 | Ibuprofen | 3217 (1) | Risperidone | 19328 (1) |
| 18 | Carbamazepine | 3078 (1) | Rofecoxib | 19316 (1) |
| 19 | Ciclosporin | 3045 (1) | Levonorgestrel | 19121 (1) |
| 20 | Valproic acid | 3032 (1) | Olanzapine | 18852 (1) |
| **Total** | | **149782 (51)** | | **611201** (28) |

# ‘Top 20’

- For children: 51% of total (28% in adults)
- For children: 13 of the 20 are vaccines (0 for adults)

Therefore, DEC separated for children vaccine and non-vaccine

| Rank among top 20 DEC | Active Substance | Reaction PT | Number | % of all reports | Overall Rank in EV |
|---|---|---|---|---|---|
| 1 | Pneumococcal polysaccharide conjugate vaccine (adsorbed) | Pyrexia* | 9580 | 3 | 1 |
| 4 | | Crying* | 3442 | 1 | 4 |
| 19 | | Vomiting* | 1380 | 1 | 20 |
| 20 | | Rash* | 1376 | 1 | 21 |
| 2 | Diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) | Pyrexia* | 4133 | 1 | 2 |
| 17 | | Crying* | 1623 | 1 | 17 |
| 3 | Measles, mumps and rubella vaccine (live) | Pyrexia* | 3878 | 1 | 3 |
| 5 | Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) | Pyrexia* | 3196 | 1 | 5 |
| 14 | | Crying* | 2020 | 1 | 14 |
| 6 | Human papillomavirus vaccine | Headache* | 3175 | 1 | 6 |
| 7 | | Dizziness* | 3085 | 1 | 7 |
| 8 | | Syncope* | 2714 | 1 | 8 |
| 10 | | Nausea* | 2412 | 1 | 10 |
| 13 | | Pyrexia* | 2028 | 1 | 13 |
| 15 | | No adverse event# | 1704 | 1 | 15 |
| 9 | Mycobacterium bovis, Danish strain 1331 | Injection site abscess* | 2434 | 1 | 9 |
| 11 | A/California/7/2009 (H1N1)v-like virus | Pyrexia* | 2120 | 1 | 11 |
| 16 | | Hyperpyrexia | 1644 | 1 | 16 |
| 12 | Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed) | Pyrexia* | 2104 | 1 | 12 |
| 18 | Varicella vaccine (live) | Varicella* | 1622 | 1 | 18 |



* ADR already listed in Product Information

| Rank among top 20 DEC | Active Substance | Reaction PT | Number of cases | % | Overall Rank in EV |
|---|---|---|---|---|---|
| 1 | Paroxetine | Foetal exposure during pregnancy* | 1417 | 1 | 19 |
| 9 | | Atrial septal defect* | 522 | < 1 | 123 |
| 2 | Isotretinoin | Depression* | 1301 | < 1 | 25 |
| 3 | | Inflammatory bowel disease* | 1006 | < 1 | 41 |
| 5 | | Colitis ulcerative± | 752 | < 1 | 69 |
| 6 | | Crohn's disease± | 613 | < 1 | 97 |
| 10 | | Dry skin* | 496 | < 1 | 132 |
| 13 | | Lip dry* | 450 | < 1 | 148 |
| 17 | | Suicidal ideation* | 392 | < 1 | 187 |
| 20 | | Blood triglycerides increased* | 381 | < 1 | 191 |
| 4 | Etanercept | Injection site pain* | 943 | < 1 | 47 |
| 11 | | Injection site erythema* | 473 | < 1 | 141 |
| 7 | Carbamazepine | Pyrexia* | 559 | < 1 | 114 |
| 19 | | Rash* | 383 | < 1 | 190 |
| 8 | Palivizumab | Respiratory syncytial virus infection# | 558 | < 1 | 115 |
| 14 | | Respiratory syncytial virus bronchiolitis# | 445 | < 1 | 151 |
| 12 | Drospirenone, ethinylestradiol | Pain* | 469 | <1 | 145 |
| 15 | Paracetamol | Overdose* | 434 | < 1 | 158 |
| 16 | | Vomiting* | 394 | < 1 | 185 |
| 18 | Octocog alfa | Factor VIII inhibition* | 385 | < 1 | 188 |



* Already listed or included in a warning in Product Information (EMA, or UK for brand leader).

# Key findings

- Descriptive overview of what has been reported cumulatively to EV to date.
- Paediatric ADRs more common under the ‘general and administration site’, ‘nervous system’, ‘skin and subcutaneous disorders’ and ‘infections and infestations’ SOCs.
- Small number of terms e.g. ‘pyrexia’ and ‘crying’ under the general and administrative site SOC and ‘convulsion’ and again ‘crying’ under the nervous system disorder.
- Also differ in terms of substances reported - vaccines
- Confirms paediatric ADRs very different to those from adults ➲ safety profile in adults not necessarily reflective of children

# Implications for paediatric pharmacovigilance

- Relative concentration of paediatric ADRs around limited sets of drugs and reactions could be the focus of specific efforts to prevent ADRs.
- Most frequent reported reactions and substances are known associations: few surprises however did not set out to detect signals
- Supports that paed PhV is not limited to capturing associations ➲ e.g.
  - ✓ continuous signal detection activities,
  - ✓ paediatric query in EV

# Questions and Discussion