Summary of adverse events following immunization reported in Switzerland during 2014

Executive summary

During 2014, Swissmedic received 296 case reports of suspected adverse events following immunization (AEFI) from Switzerland. This is a much higher number of reported cases as compared to 2013 (138 reports), which might reflect an increased incidence of adverse reactions following vaccinations or an increased reporting rate of AEFIs. However, since there are no accurate data available regarding the total number of vaccines/doses administered during 2014, a straightforward conclusion cannot be drawn. Notably, during 2014 a significant number of AEFI cases (106 reports) occurring in previous years have been retrospectively submitted to Swissmedic and have also been considered in this evaluation. No new safety signals have emerged from these older retrospective AEFI-reports. As previously, Swissmedic continues to encourage spontaneous reporting of AEFIs in high quality, which enables early detection of new safety signals. Since 2010, important safety topics concerning vaccines are discussed and evaluated by experts of the Swissmedic Human Medicines Expert Committee (HMEC). An increased AEFI reporting rate followed by a scientific evaluation of relevant cases can lead to risk minimisation measures in order to ensure vaccines safety, if necessary.

Figure 1. Number of AEFI reports per age group and gender, 2014

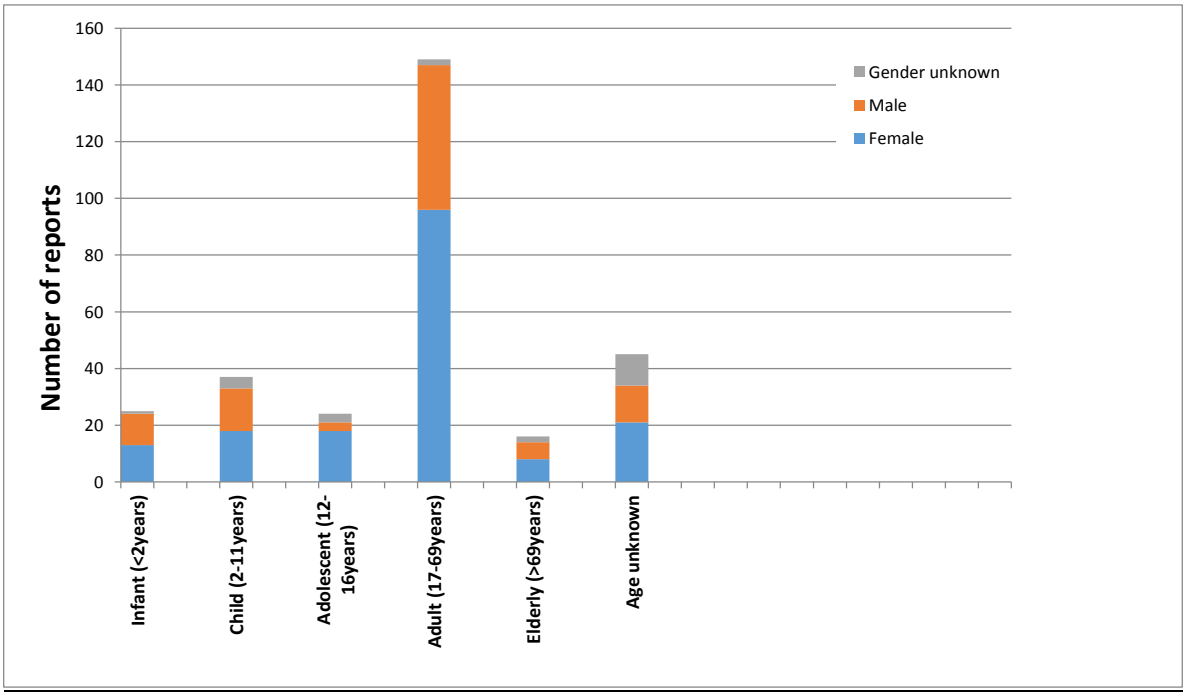

Figure 1 compares the number of reports per age group and gender. The largest number of AEFI reports involved adults (149 reports), followed by children (37 reports) and infants (25 reports). Throughout the year, the number of reports concerning females (174 reports) was higher as the number of reports regarding males (99 reports). In 23 AEFI reports, the gender of the persons remained unknown. A higher difference in gender is apparent in the adults

group (96 reports of females vs. 51 males). In 45 cases (reports), the age of the patients was not recorded.

Figure 2. Number of reports per vaccine group (ATC code) and seriousness, 2014

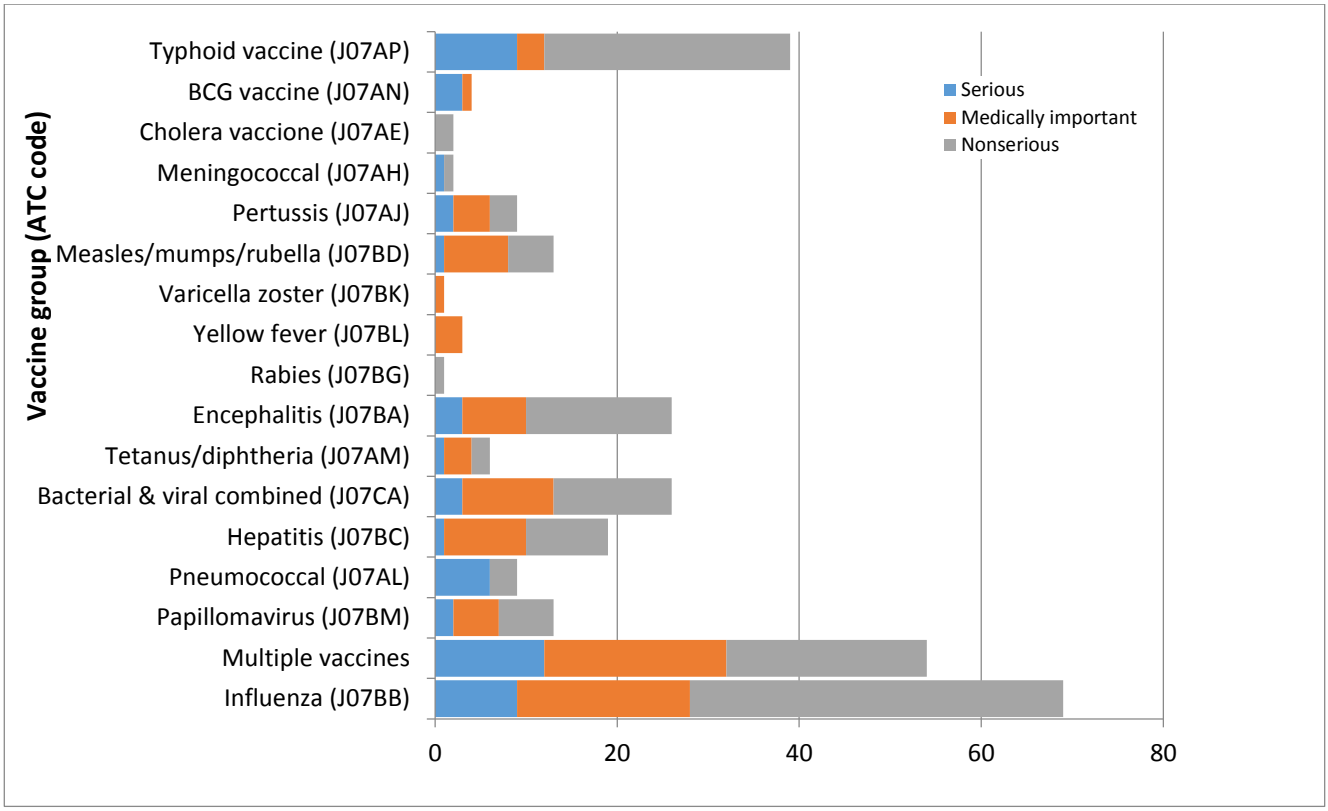

Figure 2 shows the number of spontaneous AEFI reports grouped per vaccine group (ATC code) and seriousness. There are no data available regarding the number of doses administered in each vaccine group and therefore this figure does not show which vaccine group displayed a higher AEFI rate (as number per 100'000 doses). Generally, a safety report is assessed as 'serious' if it involves an adverse event leading to death, to hospitalization or to prolongation of an existing hospitalization, if it was life threatening or resulted in a significant or persistent disability or a congenital anomaly. A report is assessed as 'medically important' if it does not fulfil the criteria for 'seriousness' mentioned but it involves an event considered to be medically significant. All other reports are assessed as 'not serious' (e.g. self-limiting adverse events with good recovering). Of the 296 spontaneous reports received in 2014, 92 (31.1%) were not-serious, 151 (51%) were medically important events and 53 (17.9%) of the AEFIs included events with serious consequences. The relative frequencies (percentages) of serious and medically important reports were close to those recorded during the previous year 2013.

Figure 3. Number of AEFI reports per reporter qualification and seriousness, 2014

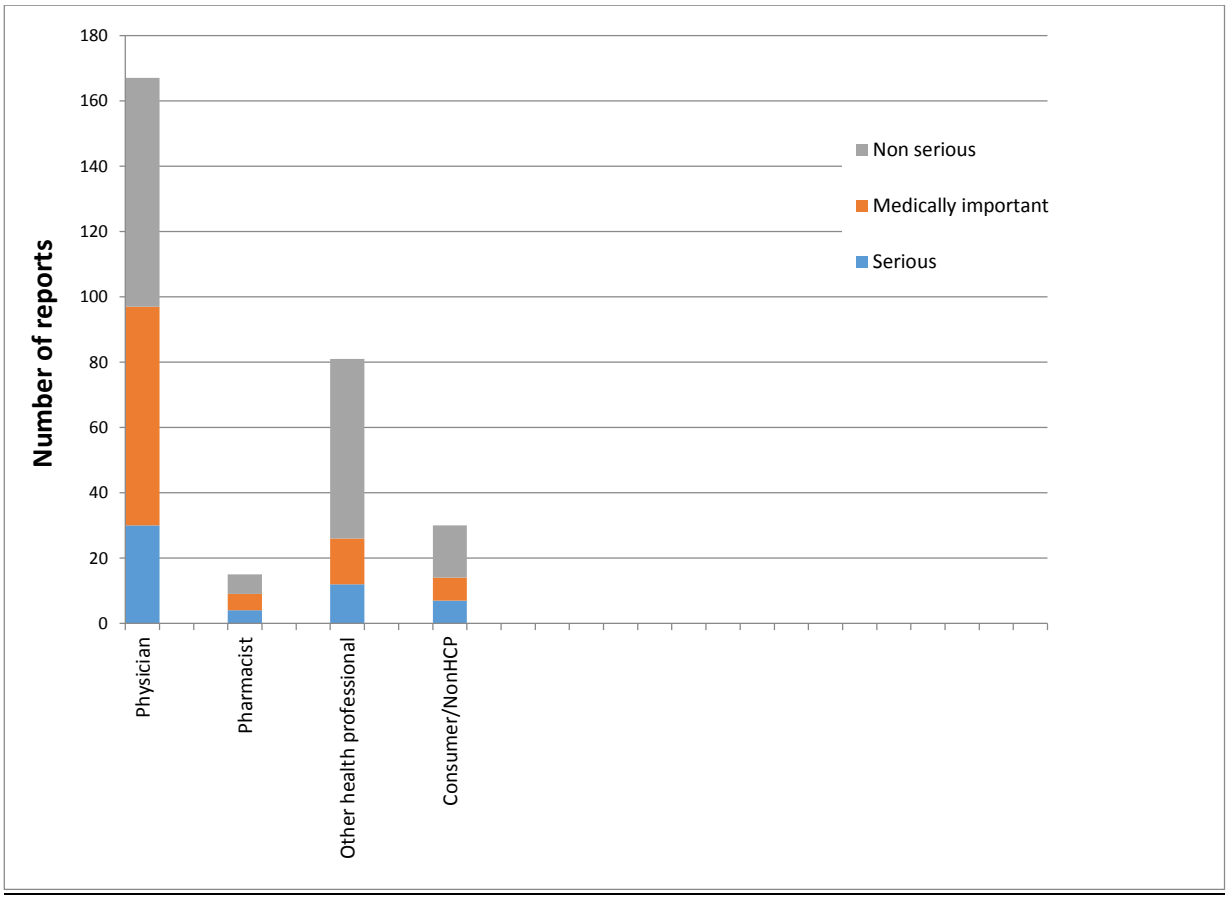

Figure 3 shows the number of Swiss AEFI reports in 2014 grouped by primary reporter and seriousness. The largest group of AEFI cases (167 of 296) were primarily reported by physicians, including also a higher number of reports assessed as serious or medically important (97 of 167 reports). The vast majority of cases was primarily reported by health care professionals mostly providing medically confirmed data and good quality of individual AEFI reports.

Figure 4. Number of AEFI reports per age group and seriousness, 2014

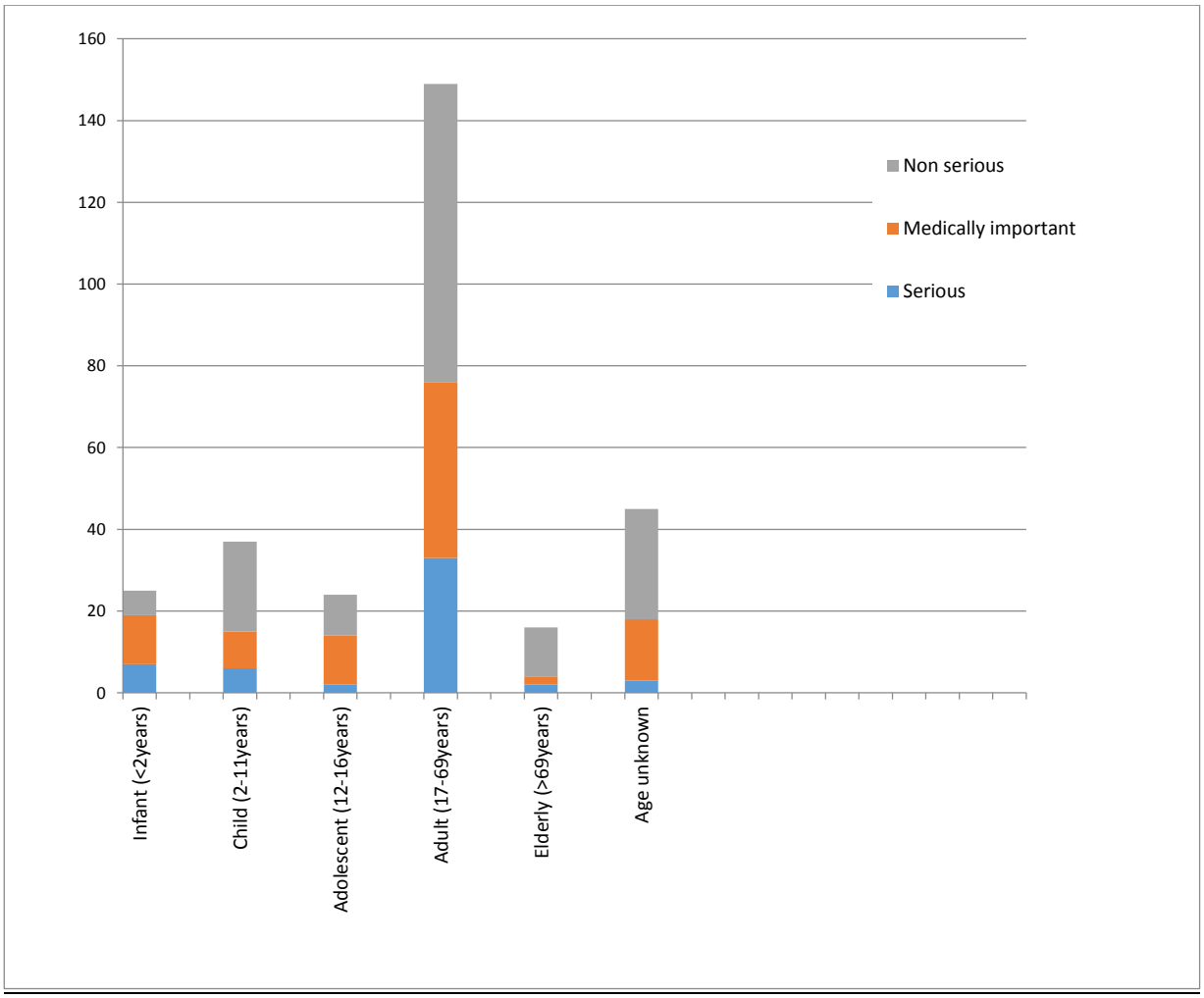

Figure 4 shows the number of spontaneous AEFI reports by age group and seriousness. It becomes apparent that a lower number of serious reports have been recorded in the age groups of adolescents (2 of 24 reports) and elderly (2 of 16 reports), whereas most of the cases were reported in the age group of adults (33 serious cases of 149 reports).

Figure 5 provides an overview on the AEFI reports received during 2014, as grouped by the primary MedDRA System Organ Classes (SOCs) concerned (i.e. regarding the leading AEFI of each report). The following five organ classes were most frequently involved in reports after immunization: General disorders and administration site conditions (130 reports, 44%); Nervous system disorders (87 reports, 29%); Skin and subcutaneous tissue disorders (58 reports, 28%); Injury, poisoning and procedural complications (57 reports, 19%); Musculoskeletal and connective tissue disorders (53 reports, 18%).

Figure 5. Number of AEFI reports in Switzerland by System Organ Classes, 2014

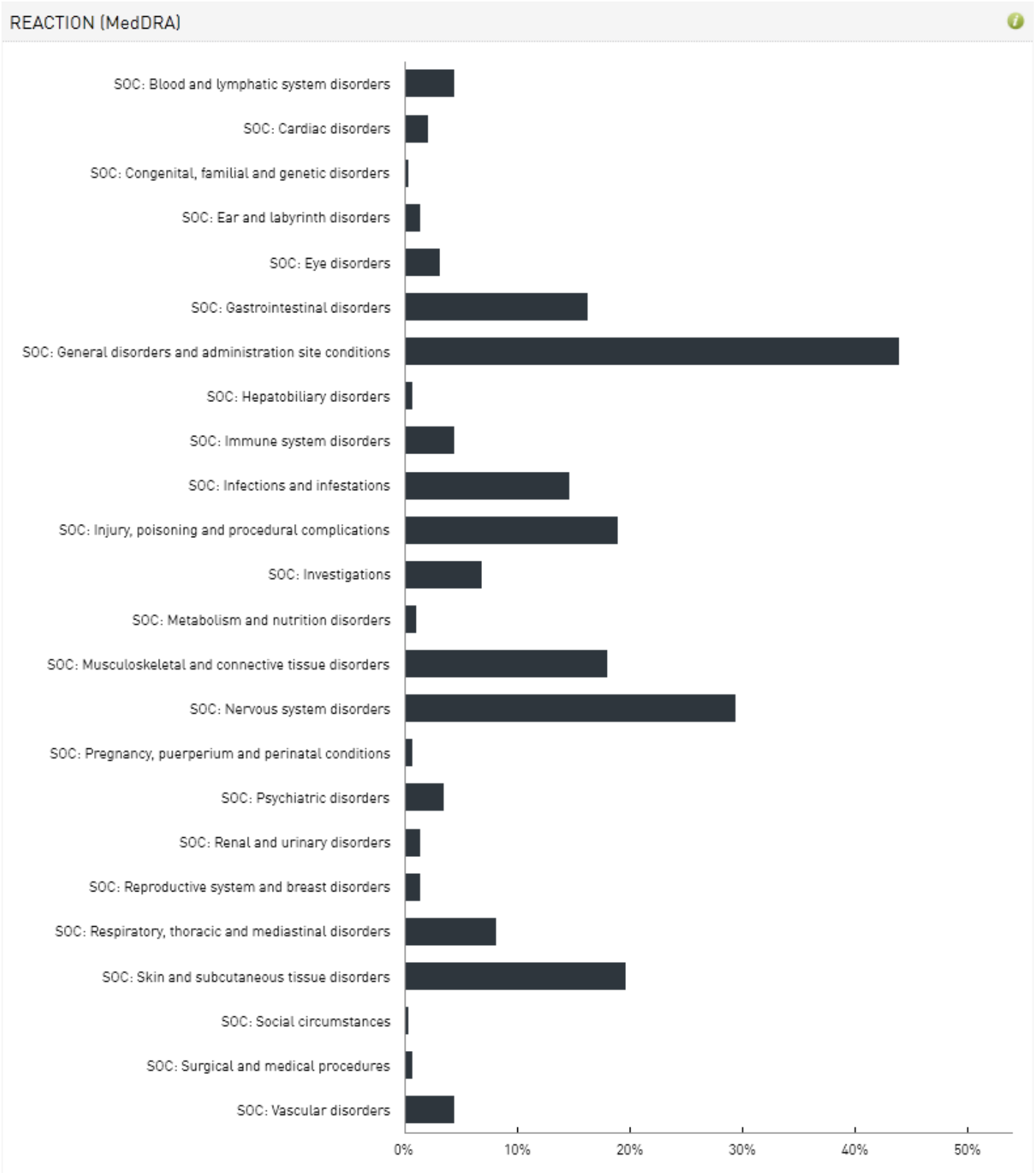

Figure 6. AEFI reports by vaccine group (ATC code) and top 3 involved System Organ Classes, 2014

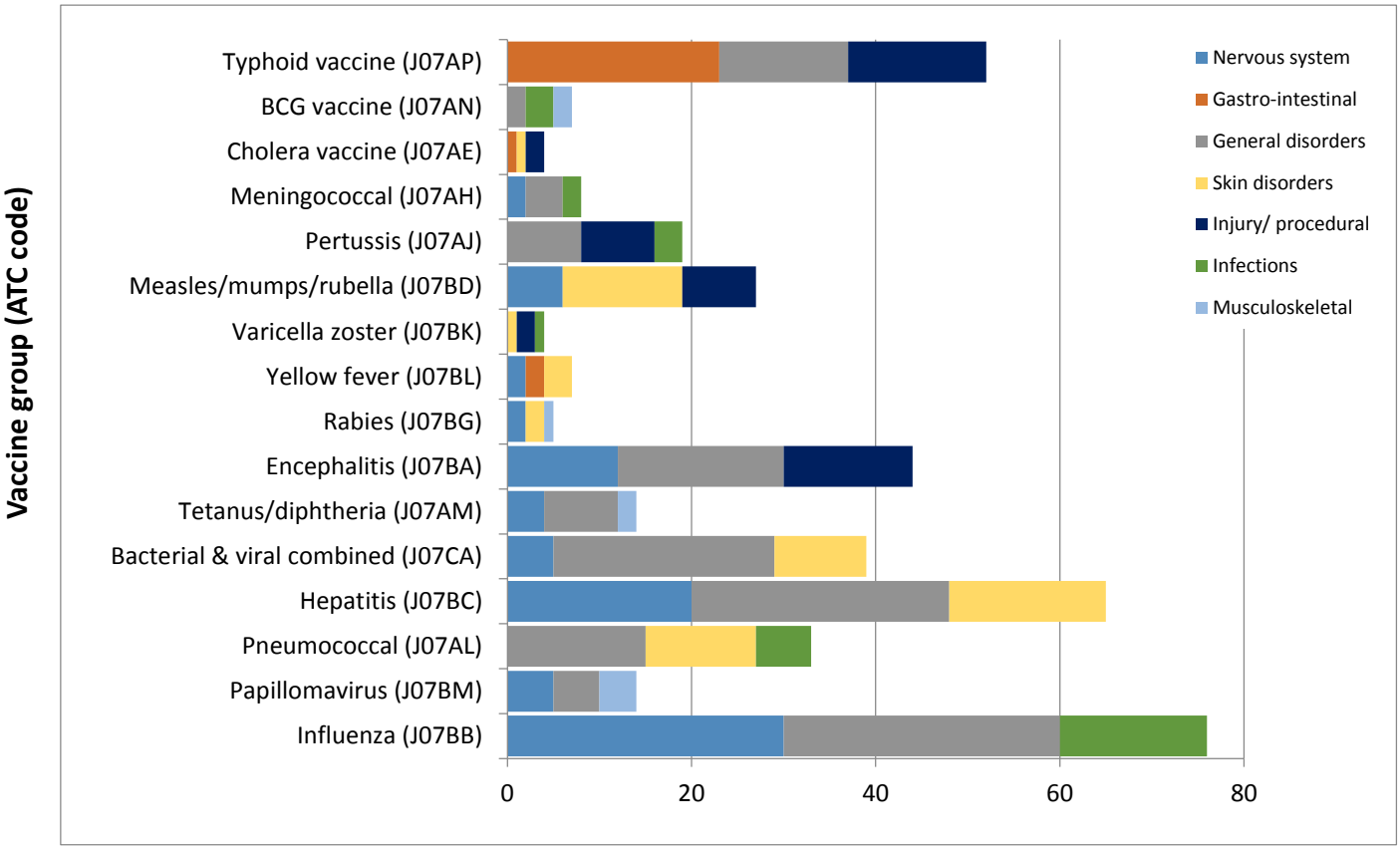

Figure 6 shows the AEFI reports by vaccine group (ATC code) and top 3 MedDRA system organ classes concerned. Notably, most of the vaccines have a significant part of their frequently reported adverse events classified in the SOCs: General disorders and administration site conditions; Injury, poisoning and procedural complications; Skin and subcutaneous tissue disorders.

Table 1. Overview on the most frequent AEFIs of all reports, 2014

Adverse event	System Organ Class	Number of reports
Injection site reactions	General disorders and administration site conditions	96
Fever	General disorders and administration site conditions	53
Erythema/ Rash/ Urticaria	Skin and subcutaneous tissue disorders	42
Headache	Nervous system disorders	38
Nausea/ Vomiting	Gastrointestinal disorders	32
Asthenia/Fatigue	General disorders and administration site conditions	25
Drug administration errors	Injury, poisoning and procedural complications	21
Diarrhoea	Gastrointestinal disorders	18
Myalgia	Musculoskeletal and connective tissue disorders	16
Abdominal pain	Gastrointestinal disorders	14
Malaise	General disorders and administration site conditions	12
Pruritus	Skin and subcutaneous tissue disorders	11

Table 1 displays the most frequent AEFI as reported during 2014 (>10 reports): injection site reactions; fever; exanthema/ rash/ urticaria; headache; nausea/ vomiting; asthenia/ fatigue; vaccine administration errors; diarrhoea; myalgia; abdominal pain; malaise; pruritus.

Table 2. The most frequent AEFIs classified as 'serious' or 'medically important', 2014

Adverse event	System Organ Class	Number of reports
Injection site reactions	General disorders and administration site conditions	25
Fever	General disorders and administration site conditions	25
Headache	Nervous system disorders	22
Erythema/ Rash/ Urticaria	Skin and subcutaneous tissue disorders	22
Nausea/ Vomiting	Gastrointestinal disorders	10
Drug ineffective/ Vaccination failure	Injury, poisoning and procedural complications	9
Hypoaesthesia	Nervous system disorders	7
Exposure during pregnancy	Injury, poisoning and procedural complications	7
Abdominal pain	Gastrointestinal disorders	6
Pain in extremity	Musculoskeletal and connective tissue disorders	6

Table 2 summarizes the most frequent AEFIs assessed as 'serious' or 'medically important' (>5 reports). The two tables (Table 1 and Table 2) are displaying similar distributions of reported AEFIs. Additionally, 7 case reports with 'hypoaesthesia' as well as 7 reports with 'vaccine exposure during pregnancy' – an event assessed as medically important by the primary reporters in these cases - are listed in the table with serious AEFIs.

Among other serious or medically important cases during 2014, 9 AEFIs of 'drug ineffectiveness' or 'vaccination failure' have been reported with regard to: pneumococcal vaccine (2 cases); pertussis vaccine (2 cases); typhoid vaccine (1 case); MMR vaccine (1 case); varicella zoster vaccine (1 case); influenza vaccine (1 case); diphtheria vaccine (1 case).

Neurological AEFIs reported as serious were:

- One case of 'hypotonic-hyporesponsive episode' in a 4-month-old male infant following the administration of several different vaccines: tetanus vaccine/diphtheria vaccine/ hepatitis b vaccine/ pertussis vaccine/ polio vaccine/ haemophilus influenza type B vaccine and pneumococcal vaccine, outcome 'recovered'.
- Three case-reports of 'multiple sclerosis': 1 case after hepatitis A vaccine (outcome reported as 'unknown'); 1 case after hepatitis B vaccine (outcome reported as 'recovered/resolved with sequelae'); 1 case following immunization with both hepatitis A and hepatitis B vaccines (outcome reported as 'not recovered').
- Two cases of 'narcolepsy' following A/H1N1 Influenza pandemic vaccine: one case in a 23-year old women (outcome 'unknown' at the time of reporting); and one case

received as literature report (Reference 1) concerning a 15-year old female adolescent (with outcome reported also as 'unknown').

- Three cases of Guillain-Barré syndrome: one case in a 48-year old woman after hepatitis A vaccine and yellow fever vaccine (outcome 'unknown'); one case in a woman of unknown age, following influenza vaccine (outcome 'unknown'); one in a 67-year old woman after influenza vaccination (outcome reported also as 'unknown').

- Two cases of encephalitis: one in a 21-year old subject with unreported gender following influenza vaccine, with outcome 'unknown' at the time of reporting; one case in a 33-year old male after tick-borne encephalitis vaccination, with outcome 'recovered'.

Fatal cases of AEFIs as reported during 2014:

- A case reported in a literature article (Reference 2) describing the occurrence of a varicella-zoster virus meningoencephalitis in a male subject who was 55 years old at the time of the event and had been vaccinated with unspecified diphtheria, tetanus, pertussis, meningococcal, pneumococcal, Haemophilus influenzae b, hepatitis A and B and inactivated poliovirus vaccines for prophylaxis. The subject had a medical history of chicken pox (varicella) during childhood with no identified exposure to the virus prior to the event. He had not been vaccinated for measles or herpes zoster virus. He also had a previous history of acute myelogenous leukaemia that had been treated with allogeneic haematopoietic transplantation. On an unknown date, 244 days after receiving the vaccines mentioned, the patient experienced varicella-zoster virus meningoencephalitis and a cerebrospinal leukemoid reaction. The outcome of the events was fatal despite the treatment consisting of antiviral agents and supportive care. Cerebrospinal fluid and blood polymerase chain reaction revealed varicella-zoster virus infection. The authors of the publication commented, "Disseminated varicella-zoster virus is the most frequent late infection of allogeneic haematopoietic transplantation". Therefore, in the clinical context of this particular patient a causal relationship between the vaccines received by the subject and the reported fatal events appears to be unlikely.

- Another fatal case concerns a 23-month-old male patient who received, when he was 12 months old, the third dose of pneumococcal 13-valent conjugated vaccine. It was stated that the second dose was administered with a delay (not exactly as per recommended scheme). The patient was a premature baby (born in 33 2/7 week of pregnancy, weight at birth 1930 grams), and had no immunodeficiency. No concomitant medications were reported. On unspecified date, the patient developed pneumococcal meningitis, pneumococcal sepsis and otitis media with perforation of tympanic membrane. Pneumococcal serotype 3 was identified by laboratory tests. The patient was hospitalized but died six hours after admission despite intensive therapy. It was not reported if an autopsy was performed. In this case, 'Therapeutic product ineffective' has also been reported as AEFI considering that the vaccine should have prevented the severe pneumococcal infection with serotype 3.

- The third fatal case concerned a 4-month old male child who was immunised with several different vaccines: rotavirus vaccine, pneumococcal vaccine, as well as tetanus/diphtheria/hepatitis B/pertussis/ polio/haemophilus influenza type B vaccine. The child developed Kawasaki's disease and was hospitalised with asystolia and severe cardiac ischaemia due to giant coronary artery aneurisms and obstruction of a large coronary artery. A severe and persistent cardiac failure had to be treated with a left ventricular assist device and by extracorporeal membrane oxygenation. Nevertheless, the subsequent evolution was poor with hepato-renal failure and a large brain infarction leading to the fatal outcome of the patient. Based on the temporal association, the relationship with the vaccines administered was assessed as possible in this particular case. However, a direct causal link between Kawasaki's disease and any of these vaccines has not been proven so far.

References

1. Hidalgo H. et al. Intravenous immunoglobulin treatment in post H1N1 vaccination narcolepsy-cataplexy. J. Neurol. (2012) 259 (Suppl 1): S95; P425.

2. Bhagat R.K. et al. Cerebrospinal leukemoid reaction secondary to VZV meninigoencephalitis in an AML patient post allogeneic bone marrow transplantation. BLOOD. 2013;122:2:300-301