HSA Health Sciences Authority

ANALYSIS OF ADVERSE EVENT (AE) REPORTS FOR YEAR 2017

May 2018 • Vol.20 • No.1

Key Points

- The total number of adverse event (AE) reports has stabilised at around 20,000 reports per year in the last five years (2013 to 2017), with a significant increase of reports from general practitioners (GPs) in 2017 compared to previous years
- The most commonly reported vaccine AE in children aged 12 years and below was seizures (febrile and afebrile seizures) with the measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1* and pneumococcal conjugate vaccines
- Hepatic reactions constituted 11.0% of AEs associated with complementary health products (CHPs) in 2017, an increase from 6.2% in 2016

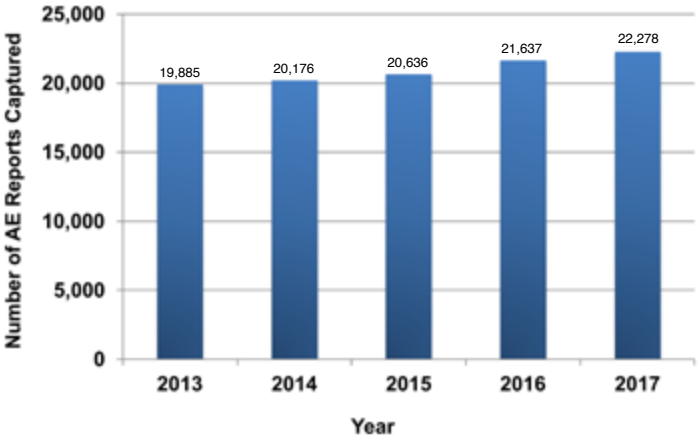
This review provides an analysis of the AE reports received by the HSA in 2017. It covers pharmaceutical drugs (i.e. chemical or biologic drugs and vaccines) and complementary health products, and highlights reporting patterns which may be of interest to healthcare professionals.

REPORT ANALYSIS FOR 2017

(a) Volume of reports

In 2017, HSA received a total of 22,278 valid reports, reflecting a stable trend of around 20,000 AE reports a year over the past five years (Figure 1).

Figure 1. Number of valid reports captured in the AE database from year 2013 to 2017 based on date of receipt



(b) Source and types of reports

The majority of reports received were associated with chemical drugs (96.5%), followed by vaccines (1.5%), biologics (1.1 %) and complementary health products (0.9%), which included Chinese Proprietary Medicines (CPM), health supplements, traditional medicines and cosmetics. Public hospitals and institutions contributed the most reports (55.8%), followed by polyclinics (37.4%). Of note, we have seen a significant increase in the number of reports received from GP clinics this year, from 0.4% in past 3 years to 3.6% this year. The remaining reports were from product registrants (2.5%), private hospitals (0.4%), and private specialist clinics (0.2%). Doctors (83.7%) contributed the most number of reports, followed by pharmacists (11.2%). Reports from dentists, nurses and research coordinators have also been received.

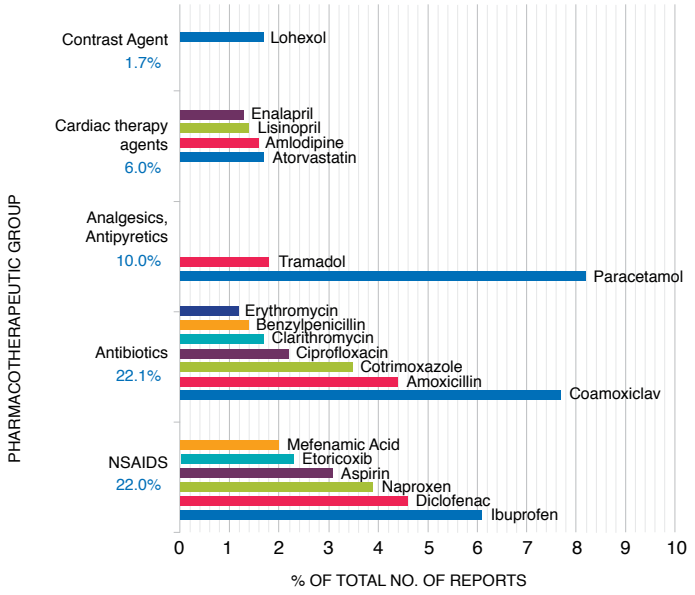
(c) Demographics

The patients' profile reported in our ADR reports closely reflect the local racial distribution, with the Chinese constituting 69.7% of AE reports, followed by Malays (12.9%) and Indians (8.7%). Of those with gender reported, females accounted for 60.7% of the reports. Patients aged 50 to 59 years old (16.8%) comprised the highest number of reports, followed by 60 to 69 years old (16.1%).

(d) Suspected drugs

The top 20 suspected drugs came from the following pharmacotherapeutic groups: nonsteroidal anti-inflammatory agents (NSAIDs) (22.0%), antibiotics (22.1%), analgesics and antipyretics (10.0%), cardiac therapy agents (6.0%), and contrast agents (1.7%) (Figure 2).

Figure 2. Top 20 drugs (by active ingredients) suspected of causing AEs



(e) Adverse events

More than half of the AEs reported were associated with skin reactions (51.6%), followed by those affecting the body as a whole (e.g. oedema, anaphylaxis) (18.5%), and gastrointestinal system disorders (6.0%). Most of these reactions were non-serious reactions (e.g. rash, periorbital oedema, nausea and vomiting). Selected serious AEs and their suspected drugs are summarised in Table 1.

Table 1. Drugs suspected of causing serious AEs

Description	WHO preferred terms	Suspected active ingredient(s) (number in bracket denotes the number of times the drug has been implicated in 2017#)	Top 10 suspected active ingredient(s) (number in bracket denotes the cumulative number of times the drug has been implicated from 2012 to 2016^)
Skin disorders	Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)	Etoricoxib (6), Omeprazole (5), Allopurinol (5), Lamotrigine (4), Cotrimoxazole (4), Diclofenac (4), Piperacillin and tazobactam (3), Coamoxiclav (3), Sulfasalazine (2), Mefenemic acid (2), Ceftriaxone (2), Meropenem (2), Levetiracetam (2)	Allopurinol (27), Cotrimoxazole (25), Omeprazole (25), Coamoxiclav (20), Phenytoin (14), Carbamazepine (14), Lamotrigine (13), Etoricoxib (13), Diclofenac (11), Cirprofloxacin (11)
Body as a whole	Anaphylactic Reaction	Coamoxiclav (14), Naproxen (12), Ibuprofen (10), Ceftriaxone (9), Ciprofloxacin (8), Diclofenac (7), Amoxicillin (6), Iohexol (6), Cefazolin (4), Moxifloxacin (4)	Diclofenac (58), Paracetamol (48), Ibuprofen (47), Coamoxiclav (39), Naproxen (35), Aspirin (34), Ceftriaxone (32), Amoxicillin (23), Ciprofloxacin (21)
Renal disorders	Azotaemia, Creatinine Clearance Decreased, Renal Tubular Disorder/Necrosis, Renal Failure Acute/Chronic, Nephritis Interstitial, Renal Function Abnormal	Enalapril (5), Diclofenac (4), Ciprofloxacin (4), Hydrochlorothiazide (4), Etoricoxib (3), Coamoxiclav (3), Cotrimoxazole (2), Lisinopril (2)	Ciprofloxacin (27), Losartan (23), Enalapril (20), Diclofenac (19), Cotrimoxazole (17), Etoricoxib (13), Lisinopril (12), Hydrochlorothiazide (11), Metformin (9), Omeprazole (9)
Hepatic disorders	Jaundice, Hepatitis, Hepatitis Cholestatic, Hepatic Failure, Hepatocellular Damage, Liver Injury, Coma Hepatic	Coamoxiclav (4), Azathioprine (3), Fenofibrate (2), Atorvastatin (2)	Azathioprine (17), Cotrimoxazole (16), Coamoxiclav (15), Atorvastatin (12), Simvastatin (8), Isoniazid (8), Pyrazinamide (7), Valproic acid (7), Phenytoin (6), Allopurinol (5), Ketoconazole (5)

 # More than one suspected drug may be implicated in a single AE report. Only active ingredients implicated more than once are listed here.
^ Based on onset date of the AE.

Vaccine adverse event (VAE) reports

There were 313 AE reports suspected to be associated with vaccines, of which 235 reports (75%) involved children aged 12 years and below, which is the age group of vaccinees under the National Childhood Immunisation Schedule. Majority of these reports (n=205) involving the paediatric population were captured by KK Women's and Children's Hospital (KKH) active surveillance sentinel site, which screens all paediatric hospital admissions for possible relationship to recent vaccination.[1]

The most commonly reported AE in children aged 12 years and below was seizures (febrile and afebrile seizures) with the measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1* and pneumococcal conjugate vaccines. Other more commonly reported AEs included lymphadenitis with Bacillus Calmette Guerin (BCG) vaccine, as well as injection-site reactions, rash, Kawasaki disease, meningitis, thrombocytopenia and vaccine failure involving a variety of vaccines.

Based on yearly trend analysis, there were more reports of febrile seizures with the MMR vaccine and afebrile seizures with the 5-in-1 vaccine in 2017 compared to preceding year. All patients recovered without sequelae. Overall, the number of AE reports received remained consistent with the expected frequencies of AE occurrence listed in the package inserts (PI) of the vaccines or in the literature.

The commonly reported vaccines suspected to cause AEs in adults and children above 12 years of age were the human papillomavirus (HPV), pneumococcal, seasonal influenza and tetanus toxoid vaccines. The commonly reported AEs included rash, angioedema and injection-site reactions associated with a variety of vaccines.

Compared to 2016, there were more reports of injection-site reactions with Prevenar 13 (PCV13) vaccine in adults, describing injection-site cellulitis, inflammation, induration or pain. Out of the 16 injection-site reaction reports with PCV13, seven cases were assessed as serious by the reporting doctor. This corresponded with a higher take-up rate of PCV13 vaccine in adults in 2017. This could have contributed to the increase in the AE reports as doctors started to vaccinate more patients and report these AEs. Based on the PI of PCV13 vaccine, vaccination-site erythema and induration/swelling were very common (≥10%) in adults aged ≥18 years old and the elderly. Severe vaccination-site pain/tenderness and severe limitation of arm movement in adults were very common (≥10%) in those aged 18-39 years and common (1 to <10%) in all other age groups.

**5-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio and Haemophilus Influenza Type B vaccine*

Complementary health products (CHP) AE reports

There were 160 AE reports involving CHPs including cosmetics, similar to the preceding year. Sixty-five reports (41.0%) were associated with glucosamine-containing products, describing mostly hypersensitivity reactions (e.g. rash and itch).

There were 17 reports (11.0%) of hepatic reactions (e.g. transaminitis and jaundice), of which ten patients were hospitalised. Two of the patients were exposed to *Radix Polygoni Multiflori* (also known as Heshouwu or 何首乌), amongst the many other ingredients in their complementary health product intake. China Food and Drug Administration had issued an alert on the possible risk of hepatotoxicity associated with the oral intake of *Radix Polygoni Multiflori* in 2014 and this overseas alert was featured in the HSA ADR News Bulletin in 2014.[2] While hepatotoxicity may be idiosyncratic, other risk factors include overdose, prolonged usage, medical history of prior liver injury and the concomitant use of other hepatotoxic drugs.

With the help of astute clinicians, HSA detected 11 adulterated CHPs which resulted in the issuance of four press releases in 2017.[3] The common adulterants detected included corticosteroids (e.g. dexamethasone), antihistamines (e.g. chlorpheniramine) and analgesics (e.g. piroxicam).

References

1. *Vaccine 2014; 32(39): 5000 – 5005*
2. *HSA ADR News Bulletin 2014 Dec; 16: 2*
3. *http://www.hsa.gov.sg/press_releases*