Australian Government
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Therapeutic Goods Administration

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Increased Reports of Allergic Adverse Events Following 2015 Influenza Immunisation

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Background

- Early in the 2015 influenza season, the Therapeutic Goods Administration (TGA) observed an increase in reports of allergic adverse events following influenza immunisation (AEFII) compared with previous years.
- In the TGA Adverse Drug Reaction System (ADRS) database, allergic adverse events are included in a broader category known as Immune System Disorders (ISDs).
- Initial evaluation of the reported cases suggested an increase in the number of ISD AEFII as a percentage of total AEFII from 13% in 2013 and 12% in 2014, to 21% in 2015.
- This occurred in the context of:
  - two strain changes for the 2015 vaccine (Table 1 on next slide)
  - a month's delay in the commencement of the national influenza vaccination program.

Background

Table 1: Composition of influenza virus vaccines for use in the southern hemisphere influenza season

	Influenza virus vaccines			
	Trivalent vaccines			Quadrivalent Vaccines
Year	Vaccine virus 1	Vaccine virus 2	Vaccine virus 3	+ Vaccine virus 4
2016	A/California/7/2009 (H1N1)pdm09-like virus	A/Hong Kong/4801/2014 (H3N2)-like virus	B/Brisbane/60/2008-like virus	B/Phuket/3073/2013-like virus
2015	A/California/7/2009 (H1N1)pdm09-like virus	A/Switzerland/9715293/2013 (H3N2)-like virus	B/Phuket/3073/2013-like virus	B/Brisbane/60/2008-like virus
2014	A/California/7/2009 (H1N1)pdm09-like virus	A/Texas/50/2012 (H3N2)-like virus	B/Massachusetts/2/2012-like virus	B/Brisbane/60/2008-like virus *
2013	A/California/7/2009 (H1N1)pdm09-like virus	A/Victoria/361/2011 (H3N2)-like virus	B/Wisconsin/1/2010-like virus	B/Brisbane/60/2008-like virus *
2012	A/California/7/2009 (H1N1)pdm09-like virus	A/Perth/16/2009 (H3N2)-like virus	B/Brisbane/60/2008-like virus	
2011	A/California/7/2009 (H1N1)-like virus	A/Perth/16/2009 (H3N2)-like virus	B/Brisbane/60/2008-like virus	

* Quadrivalent influenza vaccines were not marketed in Australia in 2013 and 2014

Objectives

- To investigate:
  - whether the increase persisted throughout the season and
  - whether any increase was related to a specific age group, sex, brand of vaccine, or jurisdiction.

Methods

- ISD AEFII data from cases reported to the TGA from 1 January 2011 to 31 December 2015 were downloaded into Excel from the TGA ADRS database.
- Numbers and proportions were tabulated for five selected allergic AEFII:
  - anaphylaxis
  - angioedema
  - asthma/bronchospasm
  - urticaria
  - hypersensitivity*.
- Total ISD AEFII data were also tabulated.

(All as a proportion of the total AEFII.)

(* includes; hypersensitivity, acute allergic reaction, allergy, allergy not otherwise specified, environmental allergy, systemic allergic reaction, and upper respiratory tract hypersensitivity reaction, site unspecified.)

Methods

- To consider young adults and women of child bearing age separately, ages were analysed in the following groups:
  - 0-4 years
  - 5-14 years
  - 15-44 years
  - 45-64 years
  - 65+ years.
- Each group was also analysed by sex.

- Odds ratios (OR) were calculated for the 2015 proportions compared with the average of the preceding four years.

Results

- The total number of case reports of AEFII for 2015 was 594*

(*includes the small number of reports from quadrivalent vaccines, which were not available through the 2015 National Immunisation Program).

- The percentage of ISD reports as a proportion of total AEFII:
  - at initial review in May 2015 this was 21%
  - at the end of 2015 the percentage had dropped to 18%
  - this remained significantly above the previous four year average of 12% (OR 1.55, 95%CI 1.21 – 1.99; *p* 0.001) (Figure 1 on next slide).

Results

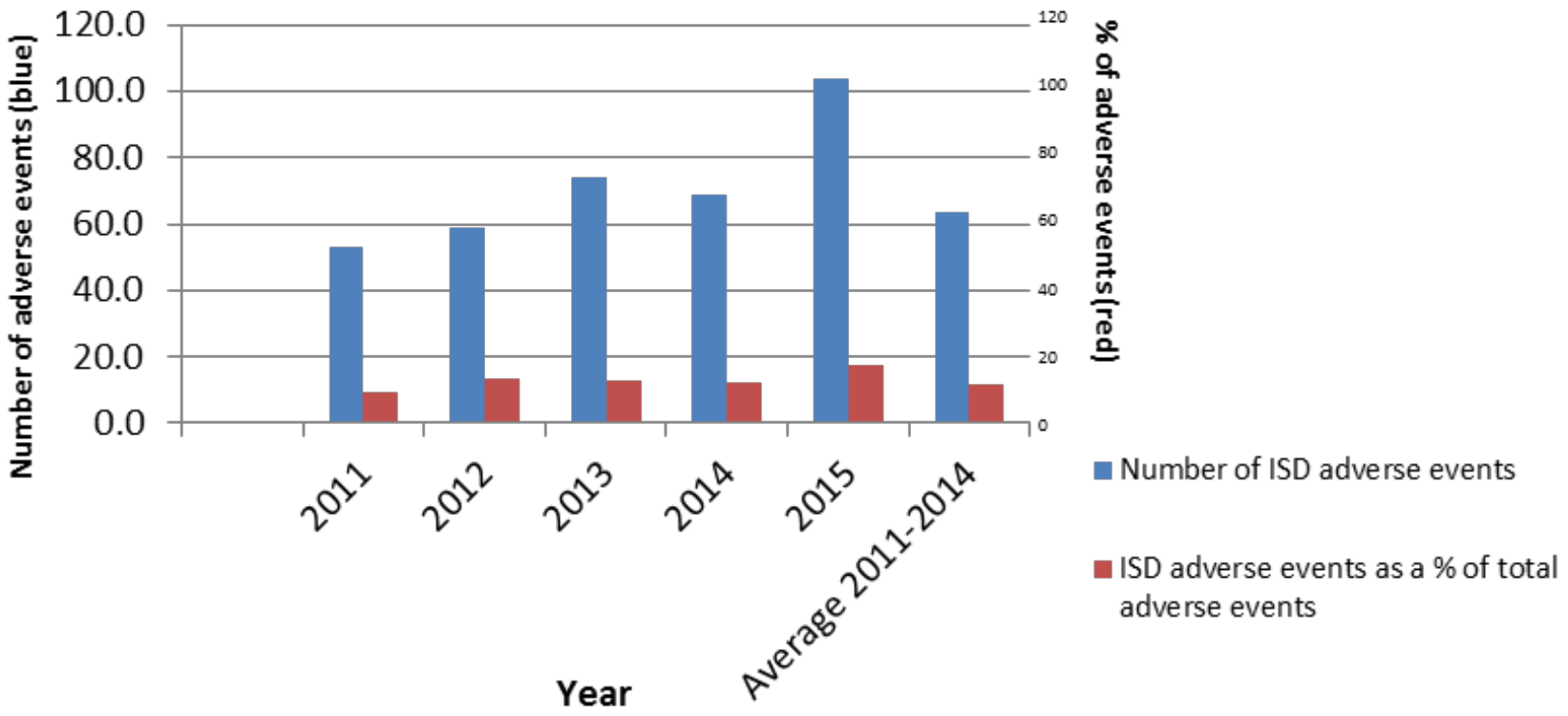

Figure 1: Number of Immune System Disorder adverse events (ISDs) and ISDs as a percentage of total AEFII, by year 2011-2015

Results

- For total ISD cases as a proportion of total AEFII compared to the average of the previous 4 years, a significant increase was seen in:
  - males in the 5-14 year age group (n/N=6/22, OR 3.54, 95%CI 1.11-11.33; *p* 0.033) and in
  - females in the 45-64 year age group (n/N=35/157, OR 1.88, 95%CI 1.19-2.98; *p* 0.007)
  - but not in females in the child bearing age group (15-44 years) (n/N=27/140, OR 1.46, 95%CI 0.90-2.37; *p* 0.127).

- No specific vaccine brand was identified as having disproportionally more adverse events in 2015.

- About a month's delay was noted in the peak reporting of adverse events
  - consistent with the delay in the start of influenza vaccination through the National Immunisation Program.

Results

- Of the selected allergic AEFII analysed, statistically significant increases were seen in the proportions of anaphylaxis (OR 1.99, 95%CI 1.01 – 3.94; *p* 0.047) and hypersensitivity (OR 2.92, 95%CI 1.72 – 4.97; *p* <0.005) compared with the average of the previous four years.

- The overall number of case reports of anaphylaxis and hypersensitivity were low (13 and 25 respectively).

- The rate of anaphylaxis per 100,000 doses of influenza vaccine distributed was 0.2.

- Anaphylaxis cases were reported by; Vic (6), WA (3), ACT (1), NT (1), SA (1) and unknown (1).
  - The relatively higher numbers reported from Victoria and Western Australia may be a result of enhanced ascertainment of cases in these states.

Conclusions

- No cause has been identified for the observed increase in the proportion of ISD AEFII:
  - there was no indication that particular vaccine brands were the cause
  - ISD adverse events were observed across vaccine brands, sex/age groups and jurisdictions
  - there were no abnormalities identified by the TGA batch release program and no clusters to indicate a possible batch problem
  - given the wide variation from year to year, the 2015 ISD AEFII levels may simply be at the high end of a natural variation.

Conclusions

- There has been no change to the risk/benefit of influenza vaccines in use in Australia to warrant regulatory or programmatic action.

- Allergic AEFII have continued to be monitored during 2016
  - to date, the proportion of ISDs to the total AEFII is similar to the 2011-2014 average.

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1. WHO. Influenza: vaccines: WHO recommendations on the composition of influenza virus vaccines. 2016. World Health Organization. [2016; cited 2016 September 05]; Available from: http://www.who.int/influenza/vaccines/virus/recommendations/en/

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