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Pattern of Serious Adverse Events Associated with Administration of Different Vaccines: A US Vaccine Adverse Event Reporting System (VAERS) Database Analysis

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ABSTRACT

Background: Different vaccine adverse event surveillance systems have been developed down the years to act as an early warning system to detect signals regarding adverse events following vaccination. Different types of serious adverse events were characterized through the analysis of US VAERS registry. **Methods:** The VAERS data from 2010-2019 was analysed statistically for exploration of different types of serious adverse events and the signs and symptoms associated with administration of these vaccines. Vaccines implicated in serious adverse events through VAERS were further explored for correlates in WHO Vigibase database. **Results:** The maximum number of patients with serious events were administered FLU3 vaccine (n=4024, 12.71%), followed by PNC13 (n=2740, 8.66%), VARZOS (n=2310, 7.30%), PPV (n=1964, 6.20%) and HIBV vaccine (n=1448, 4.57%). Of all symptoms in patients with serious adverse events, pyrexia was the major symptom in patients with life threatening illness (16.06%), hospitalization (18.83%), prolongation of hospitalization (19.64%), disability (12.05%) and mortality outcome (9.95%). Among the top three vaccines implicated in serious adverse events, analysis through WHO Vigiaccess database found general disorders and administration site conditions and skin and subcutaneous tissue disorders to be the MedDRA major system organ classes for both pnemococccal and varicella zoster vaccine. **Conclusion:** FLU3 (Influenza), PNC13 (pneumococcal) and VARZOS (varicella zoster) vaccines were the top three vaccines implicated in serious adverse events through VAERS database analysis though a cause and effect relationship cannot be established through the this data alone.

Keywords: Adverse Event, Database, Vaccine, VAERS.

INTRODUCTION

According to WHO, adverse event following immunization is "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine".[1] If such event is not addressed rapidly and adequately, it can result in a negative impact on the whole vaccination program.

Events thought to be related to the administration of a vaccine need not necessarily be due to the vaccine itself, but can be related to underlying disease, concurrent medications, due to human or programme error or can be purely coincidental.

Different vaccine adverse event surveillance systems like US vaccine adverse event reporting system (VAERS),[2] Canadian Adverse Events Following Immunization Surveillance System (CAEFISS),[3] Database of Adverse Event Notifications (DAEN) (Australia: both drugs and vaccines),[4] VigiBase®, the World Health Organization's global database for ADRs (Uppsala Monitoring Centre, Sweden),[5] have been developed down the years to act as an early warning system to detect signals regarding these adverse events following vaccination.

Our aim in this study was to characterize different types of serious adverse events and understand the correlates associated with administration of various vaccines through the analysis of US VAERS registry.

MATERIALS AND METHODS

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Vaccine Adverse event reporting system (VAERS)
VAERS is US based national vaccine surveillance system to detect safety issues in the US licensed vaccines. It is co-managed by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) and accepts reports of adverse events following immunization. VAERS accepts reports not only from health care providers and vaccine manufacturers but also from vaccinated individuals and other sources.

The VAERS data consists of three csv (comma separated value) data files which hold the information on recipients' socio demographic variables, the vaccines administered, the adverse events experienced and other relevant clinical history. The standardized MedDRA (Medical Dictionary for Regulatory Activities) dictionary is used for coding the signs and symptoms of adverse events.

According to the definition under Code of Federal Regulations, a serious adverse drug experience consists of one or more of the following events: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.[6]

The VAERS data from 2010-2019 (till14.3.2019) was downloaded from the official VAERS website, imported into IBM ® SPSS ® v 20.0.0 and analysed statistically for exploration of different types of adverse events, specially the serious events, and the signs and symptoms associated with administration of these vaccines. Further, vaccines implicated in serious adverse events through VAERS were further explored for correlates in WHO Vigibase database.[5]

RESULTS

[Table 1] describes the frequency distribution of vaccine recipients who suffered serious adverse events following immunization (n=331519). The maximum number of recipients were hospitalized (n=13797, 4,16%), followed by suffering disability (n=4546, 1.37%) and life threatening illness (n=3960, 1.19%). Mortality outcome was observed in 1417 (0.43%) recipients.

[Figure 1] shows the 6 way venn diagram [7] (non proportionate) depicting the interrelationship between different categories of serious adverse reactions suffered by the vaccine recipients. The overlapping regions indicate the recipients suffering multiple types of serious events.

[Table 2] depicts the types of vaccines administered to patients with serious adverse events. The maximum number of patients with serious events were administered FLU3 vaccine (n=4024, 12.71%), followed by PNC13 (n=2740, 8.66%), VARZOS (n=2310, 7.30%), PPV (n=1964, 6.20%) and HIBV vaccine (n=1448, 4.57%).

[Table 3] shows the pattern of vaccine administration to patients with different types of serious adverse events. The maximum number of patients who suffered mortality outcome had been administered PNC13 (13.05%), FLU3 (7.77%) and RV5 (7.50%) vaccine. Among other serious events, FLU3 vaccine was administered in maximum patients with life threatening illness (15.23%), hospitalization (13.06%), prolongation of existing hospitalization (21.35%) and disability (13.33%). Among the patients who subsequently had birth defect/congenital anomaly, the associated vaccines were FLU4 (14.29%), followed by HEP (10.2%), MMR (10.2%) and TDAP vaccine (10.2%).

[Table 4] shows the MedDRA dictionary coded symptoms in patients having suffered different types of serious adverse events. Of all symptoms, pyrexia was the major symptom in patients with life threatening illness (16.06%), hospitalization (18.83%), prolongation of hospitalization (19.64%), disability (12.05%) and mortality outcome (9.95%). In patients with life threatening illness, Guillain-Barre syndrome was observed in 10.66% patients, 8.41% in hospitalized patients and 17.74% patients with prolongation of existing hospitalization. It is notable that exposure during pregnancy was observed in 28.13% patients with birth defect/congenital anomaly.

Table 1: Descriptive analysis of patients with different types of serious adverse events (n=331519 recipients)

Type of event	Frequency	Percentage
Death	1417	0.43
Life threatening illness	3960	1.19
Hospitalization	13797	4.16
Prolongation of hospitalization	1105	0.33
Disability	4546	1.37
Birth defect/Congenital anomaly	32	0.01

Table 2: Vaccines administered to patients with serious adverse events (n=31653 vaccines).

Name of vaccine	Frequency	Percentage
FLU3	4024	12.71
PNC13	2740	8.66
VARZOS	2310	7.30
PPV	1964	6.20
HIBV	1448	4.57
RV5	1404	4.44
HPV4	1354	4.28
TDAP	1263	3.99
MMR	1220	3.85
FLU4	1200	3.79
VARCEL	1127	3.56
HEP	1031	3.26
DTAPIPVHIB	1027	3.24
HEPA	997	3.15
DTAPHEPBIP	945	2.99
Others	7599	24.01

Table 3: Pattern of vaccine administration to patients with different types of serious adverse events

Death (n=2575 vaccines)		Life threatening illness (n=6521 vaccines)		Hospitalization (n=23031 vaccines)	
Vaccine	**Percentage**	**Vaccine**	**Percentage**	**Vaccine**	**Percentage**
PNC13	13.05	FLU3	15.23	FLU3	13.06
FLU3	7.77	PNC13	7.93	PNC13	9.32
RV5	7.5	RV5	4.89	VARZOS	7
HIBV	7.07	VARZOS	4.66	PPV	6.6
DTAPIPVHIB	6.21	HPV4	4.62	RV5	4.89
HEP	5.75	TDAP	4.55	HIBV	4.74
DTAPHEPBIP	5.71	HIBV	4.37	TDAP	3.93
HPV4	4.93	MMR	4.23	FLU4	3.63
VARZOS	4.27	VARCEL	3.97	MMR	3.57
FLUX	4.23	FLU4	3.93	VARCEL	3.53
OTHERS	33.51	OTHERS	41.62	OTHERS	39.73
Prolongation of hospitalization (n=1663 vaccines)		**Disability (n=6437 vaccines)**		**Congenital anomaly/ Birth defect (n=49 vaccines)**	
Vaccine	**Percentage**	**Vaccine**	**Percentage**	**Vaccine**	**Percentage**
FLU3	21.35	FLU3	13.33	FLU4	14.29
PPV	10.52	VARZOS	11.23	HEP	10.2
TDAP	6.01	HPV4	8.12	MMR	10.2
PNC13	5.89	MMR	4.86	TDAP	10.2
HPV4	5.05	TDAP	4.75	PNC13	8.16
HEP	4.27	PPV	4.69	FLUC4	6.12
HIBV	3.49	FLU4	4.61	VARCEL	6.12
FLU(H1N1)	3.25	PNC13	4.47	DTAP	4.08
HEPA	3.19	HEP	3.46	DTAPIPVHIB	4.08
RV5	3.07	HEPA	3.4	FLU3	4.08
OTHERS	33.91	OTHERS	37.05	OTHERS	22.45

Table 4: Pattern of serious adverse event coded terms according to MedDRA dictionary

Death (n=1417)		Life threatening illness (n=3960)		Hospitalization (n=13797)	
Term	**Percentage**	**Term**	**Percentage**	**Term**	**Percentage**
Death	80.66	Pyrexia	16.06	Pyrexia	18.83
Autopsy	12.77	Dyspnoea	13.18	Vomiting	9.68
Pyrexia	9.95	Guillain-Barre syndrome	10.66	Guillain-Barre syndrome	8.41
Resuscitation	7.97	Vomiting	10.43	Headache	7.78
Unresponsive to stimuli	7.55	Asthenia	9.19	Dyspnoea	7.33
Dyspnoea	5.36	Blood test	7.6	Asthenia	6.89
Vomiting	5.22	Headache	7.6	Herpes zoster	6.87
Cardiac arrest	4.66	Intensive care	7.45	Hypoaesthesia	6.74
Influenza	4.66	Pain	7.07	Pain	6.64
Malaise	4.59	Hypoaesthesia	6.82	Muscular weakness	6.15
Prolongation of hospitalization (n=1105)		**Disability (n=4546)**		**Congenital anomaly/ Birth defect (n=32)**	
Term	**Percentage**	**Term**	**Percentage**	**Term**	**Percentage**
Pyrexia	19.64	Pain	15.79	Exposure during pregnancy	28.13
Guillain-Barre syndrome	17.74	Pain in extremity	12.3	Electroencephalogram abnormal	12.5
Hypoaesthesia	11.31	Pyrexia	12.05	Seizure	12.5
Asthenia	10.68	Fatigue	9.99	Abortion spontaneous	9.38
Lumbar puncture	10.5	Headache	9.68	Caesarean section	9.38
Nuclear magnetic resonance imaging	9.59	Nuclear magnetic resonance imaging	9.06	Electroencephalogram	9.38
Muscular weakness	9.05	Hypoaesthesia	8.73	Foetal death	9.38
Dyspnoea	8.6	Injection site pain	8.51	Maternal exposure before pregnancy	9.38
Immunoglobulin therapy	8.51	Muscular weakness	8.42	Nuclear magnetic resonance imaging	9.38
Intensive care	8.51	Asthenia	8.16	Nuclear magnetic resonance imaging brain abnormal	9.38

Table 5: Adverse reactions of three major vaccines implicated in serious adverse events through WHO VigiAccess® (till 13 May 2019) database.

Vaccine/Active Ingredient, Total records	Major ADRs	No. of records	Year	ADRs	%age
Prevenar(Pneumococcal), n=172031	General disorders and administration site conditions	122860	2019	6386	4
	Skin and subcutaneous tissue disorders	45594	2018	22916	13
	Nervous system disorders	33840	2017	19459	11

	Infections and infestations	23482	2016	10642	6
	Musculoskeletal and connective tissue disorders	21287	2015	12494	7
	Gastrointestinal disorders	21010	2014	11732	7
	Investigations	19953	2013	9800	6
	Psychiatric disorders	14923	2012	4997	3
	Respiratory, thoracic and mediastinal disorders	13531	2011	9230	5
	Injury, poisoning and procedural complications	12778	2010	46668	27
Fluad/Fluarix(Influenza), n=213357	General disorders and administration site conditions	133096	2019	13005	6
	Nervous system disorders	56605	2018	27264	13
	Skin and subcutaneous tissue disorders	50197	2017	18963	9
	Musculoskeletal and connective tissue disorders	42307	2016	11710	5
	Gastrointestinal disorders	29603	2015	15933	7
	Respiratory, thoracic and mediastinal disorders	27993	2014	14435	7
	Infections and infestations	23677	2013	13136	6
	Injury, poisoning and procedural complications	19797	2012	5033	2
	Investigations	19104	2011	12695	6
	Vascular disorders	9922	2010	46327	22
Varivax(Varicella Zoster), n=129190	General disorders and administration site conditions	80328	2019	9341	7
	Skin and subcutaneous tissue disorders	52167	2018	19037	15
	Infections and infestations	34376	2017	9319	7
	Nervous system disorders	20114	2016	4825	4
	Injury, poisoning and procedural complications	15560	2015	7291	6
	Musculoskeletal and connective tissue disorders	11528	2014	7686	6
	Investigations	10049	2013	7165	6
	Gastrointestinal disorders	9857	2012	2605	2
	Respiratory, thoracic and mediastinal disorders	5931	2011	5095	4
	Psychiatric disorders	4869	2010	42383	33

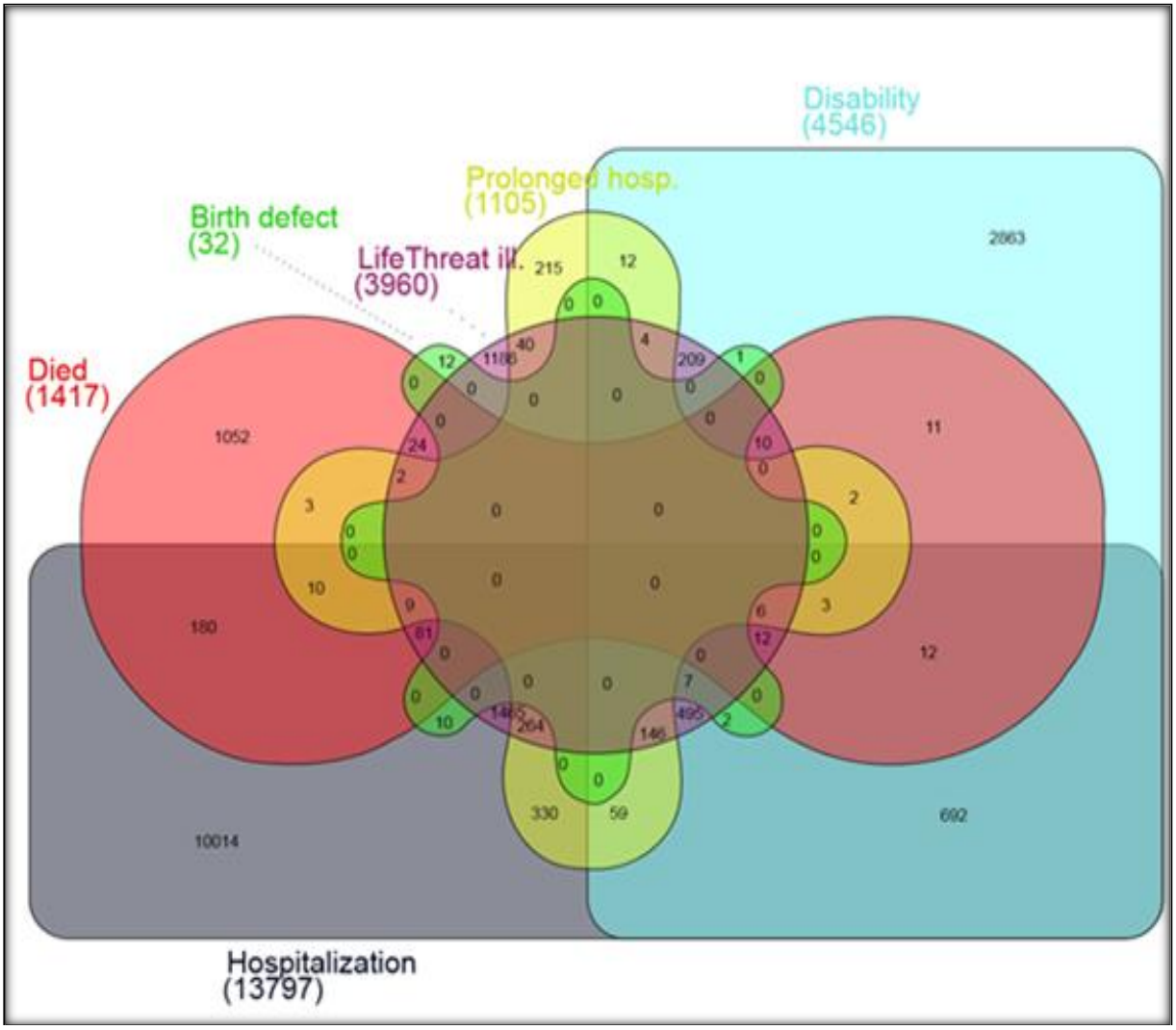

Figure 1: Venn Diagram depicting the interrelationship between different categories of serious reactions

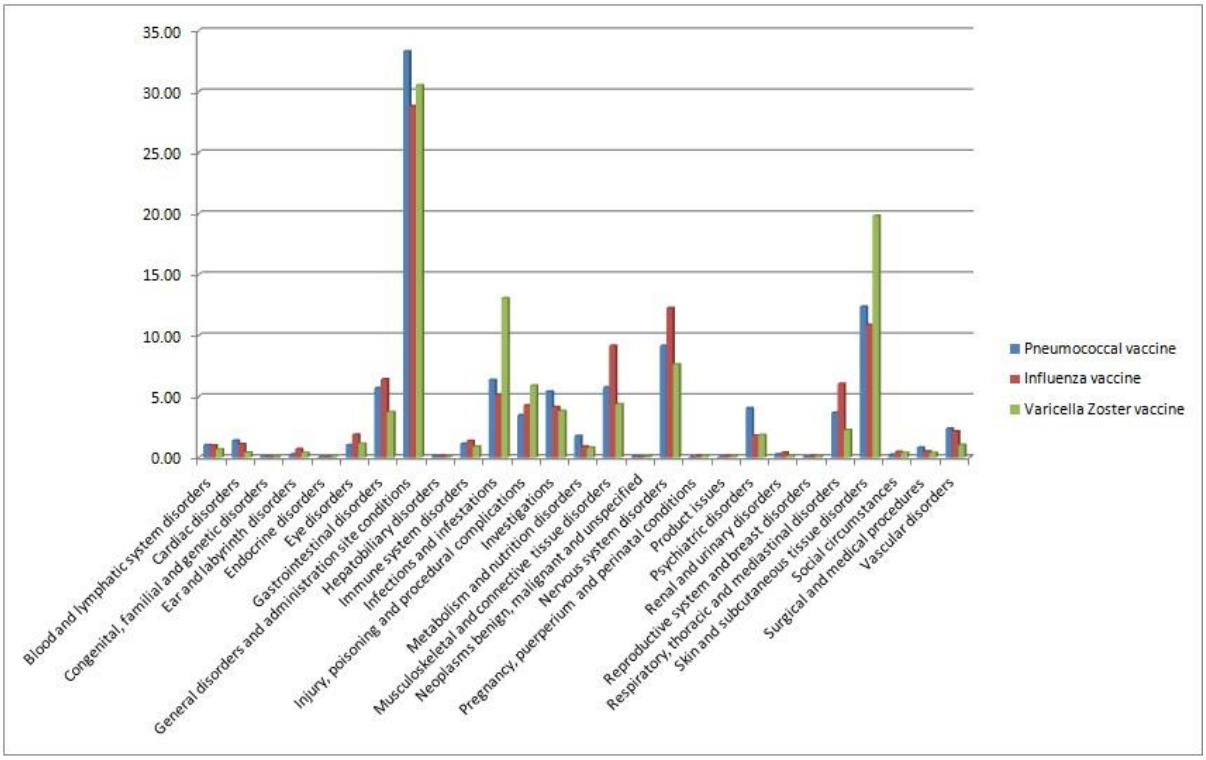

Figure 2: Adverse reactions of three major vaccines implicated in serious adverse events through WHO VigiAccess® (till 13 May 2019) database.

Table 6: Vaccine names by code

Vaccine Code	Vaccine Type
DTAP	DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE
DTAPHEPBIP	DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE + HEPATITIS B + INACTIVATED POLIOVIRUS VACCINE
DTAPIPVHIB	DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE + INACTIVATED POLIOVIRUS VACCINE + HAEMOPHILUS B CONJUGATE VACCINE
FLU3	INFLUENZA VIRUS VACCINE, TRIVALENT
FLU4	INFLUENZA VIRUS VACCINE, QUADRIVALENT
FLUC4	INFLUENZA VIRUS VACCINE, QUADRIVALENT, CELL-CULTURE- DERIVED
FLU(H1N1)	INFLUENZA(H1N1)MONOVALENT
FLUX	INFLUENZA VIRUS VACCINE (NO BRAND NAME)
HEP	HEPATITIS B VIRUS VACCINE
HEPA	HEPATITIS A
HIBV	HAEMOPHILUS B CONJUGATE VACCINE
HPV4	HUMAN PAPILLOMAVIRUS 4-VALENT
MMR	MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE
PNC13	PNEUMOCOCCAL 13-VALENT CONJUGATE VACCINE
PPV	PNEUMOCOCCAL VACCINE, POLYVALENT
RV5	ROTAVIRUS VACCINE, LIVE, ORAL, PENTAVALENT
TDAP	TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID AND ACELLULAR PERTUSSIS VACCINE, ADSORBED
VARCEL	VARIVAX-VARICELLA VIRUS LIVE
VARZOS	VARICELLA-ZOSTER VACCINE

[Table 5] depicts the types of major ADRs for the top three vaccines implicated in serious adverse events through WHO Vigiaccess database.[5] General disorders and administration site conditions and skin and subcutaneous tissue disorders were the MedDRA major system organ classes for both the pnemococccal and varicella zoster vaccine. The major classes of ADRs for influenza vaccine comprised of general disorders and administration site conditions and nervous system disorders [Figure 2].

DISCUSSION

Our study made an attempt to evaluate and analyse the US VAERS registry data in the last 10 years (2010-19) and understand the magnitude of different kinds of serious adverse events and the vaccines associated with these. Previous body of research has mostly focused on either specific adverse events,[8,9] or individual vaccine safety profiles.[10,11] Some studies have analysed the VAERS for birth defects/mortality outcome. Our analysis found that hospitalization (n=13797, 4.16%) and disability (n=4546, 1.37%) were the most common serious adverse events suffered by the vaccine recipients. FLU3, PNC13, VARZOS, and PPV were among the top vaccines associated with serious adverse events. Among the major symptoms associated with these serious events were pyrexia, Guillain-Barre syndrome, dyspnoea, vomiting, fatigue and asthenia.

Moro PL and Arana J, in 2015, in their study on deaths reported to the United States VAERS (1997–2013) found no concerning pattern among the death reports and their analysis on main causes of mortality were consistent with the most common causes of death in the US population.[12]

In 2016, Haber P and Arana J in their study of post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged >=19 years old in the United States, (VAERS: 2012–2015), found injection site erythema (28%), injection site pain (24%) and fever (22%) as the most frequent AEs among persons aged 19–64 years who were given the vaccine.[13]

In 2017, Moro PL and Cragan J studied major birth defects after vaccination reported to the VAERS (1990-2014) and found that major birth defects were reported infrequently, with no disproportional reports of any particular condition.[14]

It is important to understand that VAERS is a passive surveillance system and represents unverified health event reports; therefore it is subject to under/over reporting, reporting bias and inconsistency in quality of reports.

CONCLUSION

FLU3 (Trivalent Influenza virus vaccine), PNC13 (pneumococcal 13-valent conjugate vaccine) and VARZOS (varicella zoster) vaccines were the top three vaccines implicated in serious adverse events through VAERS database analysis, which were further explored for ADR correlates in Vigiaccess database. It is worth noting that it is not possible to establish a cause and effect relationship between vaccine administration and adverse effect through this analysis alone.

REFERENCES

1. WHO | Adverse events following immunization (AEFI) [Internet]. Who.int. 2019 [cited 10 May 2019]. Available from: https://www.who.int/vaccine_safety/initiative/detection/AEFI/en/
2. Vaccine Adverse Event Reporting System (VAERS) [Internet]. Vaers.hhs.gov. 2019 [cited 10 May 2019]. Available from: https://vaers.hhs.gov/
3. Canada P. Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) - Canada.ca [Internet]. Canada.ca. 2019 [cited 10 May 2019]. Available from: https://www.canada.ca/en/public-health/services/immunization/canadian-adverse-events-following-immunization-surveillance-system-caefiss.html
4. Database of Adverse Event Notifications (DAEN) [Internet]. Therapeutic Goods Administration (TGA). 2019 [cited 10 May 2019]. Available from: https://www.tga.gov.au/database-adverse-event-notifications-daen
5. UMC | VigiBase [Internet]. Who-umc.org. 2019 [cited 10 May 2019]. Available from: https://www.who-umc.org/vigibase/vigibase/
6. Food and Drug Administration. 21 CFR Part 314.80. Postmarketing reporting of adverse drug experiences. Vol 65: Federal Register, 2018.
7. Heberle H, Meirelles GV, Da Silva FR, Telles GP, Minghim R. InteractiVenn: a web-based tool for the analysis of sets through Venn diagrams. BMC Bioinformatics. 2015;16-169.
8. Su J, Moro P, Ng C, Lewis P, Said M, Cano M. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. J Allergy Clin Immunol. 2019;143(4):1465-1473.
9. Mei R, Raschi E, Forcesi E, Diemberger I, De Ponti F, Poluzzi E. Myocarditis and pericarditis after immunization: Gaining insights through the Vaccine Adverse Event Reporting System. Int J Cardiol. 2018;273:183-186.
10. Haber P, Moro P, Ng C, Dores G, Lewis P, Cano M. Post-licensure surveillance of trivalent adjuvanted influenza vaccine (aIIV3; Fluad), Vaccine Adverse Event Reporting System (VAERS), United States, July 2016–June 2018. Vaccine. 2019;37(11):1516-1520.
11. Miller E, Lewis P, Shimabukuro T, Su J, Moro P, Woo E et al. Post-licensure safety surveillance of zoster vaccine live (Zostavax®) in the United States, Vaccine Adverse Event Reporting System (VAERS), 2006–2015. Hum Vaccin Immunother. 2018;14(8):1963-1969.
12. Moro P, Arana J, Cano M, Lewis P, Shimabukuro T. Deaths Reported to the Vaccine Adverse Event Reporting System, United States, 1997–2013. Clin Infect Dis. 2015;61(6):980-987.
13. Haber P, Arana J, Pilishvili T, Lewis P, Moro P, Cano M. Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged ⩾19years old in the

United States, Vaccine Adverse Event Reporting System (VAERS), June 1, 2012–December 31, 2015. Vaccine. 2016;34(50):6330-6334.
14. Moro P, Cragan J, Lewis P, Sukumaran L. Major Birth Defects after Vaccination Reported to the Vaccine Adverse Event Reporting System (VAERS), 1990 to 2014. Birth Defects Res. 2017;109(13):1057-1062.

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