Journal of Pharmacovigilance

OPEN ACCESS Freely availableonline

Research Article

Adverse Events following Immunization (AEFI) Surveillance in Qatar: 2014 -2018

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ABSTRACT

Background: Assured quality vaccines and safe immunization practices are pre-requisite to successful immunization programs. All vaccines go through stringent safety checks during pre-licensure stage. Adverse Events Following Immunization (AEFI) Surveillance program is an integral part of any immunization program to monitor the vaccine safety in the post licensure phase. AEFI were being reported to the HP-CDC, Ministry of Public Health, Qatar since long time. In 2014, measures were taken to increase the reporting by increasing awareness about AEFI, importance of reporting and modified AEFI reporting forms were issued to health facilities providing vaccination services. **Objectives:** To determine the characteristics and trends of AEFI and to assess the performance of the Vaccine safety surveillance system. **Methodology:** A record based descriptive study was done using the passively collected AEFI case reports submitted to the EPI section, MOPH from 2014 to 2018. The data was analyzed with respect to the age-gender distribution, characteristics of AEFI, reporting trends over time, timeliness and case completeness and AEFI reporting rates (per 100,000 vaccine doses). **Results:** A total of 148 cases of AEFI have been reported to MOPH from 2014 to 2018. Of these majority were mild reactions and only 10% were severe reactions. The most frequently reported individual AEFI in children, was injection site reaction. Most of the AEFI were reported following MMR (National MMR Campaign) and DTaP vaccine (non-campaign). **Conclusion:** The data confirms the low rate of AEFI being reported in Qatar. Vaccine safety surveillance system is still developing and needs additional methods to complement. However, the current system provides a reference point for the monitoring of the ongoing AEFI reporting trends and characteristics.

Key words: Adverse Event Following Immunization, AEFI Surveillance, Expanded Program on Immunization, Vaccine Adverse Event Registry.

BACKGROUND

Immunization is among the most successful and cost-effective public health interventions [1]. Vaccines have contributed in the global elimination of small pox, elimination of poliomyelitis from several regions of the world and has averted millions of deaths from diphtheria, tetanus, pertussis and measles every year globally. However, as with any biological product, vaccines may be associated with unfavourable or unintended events, abnormal laboratory findings, symptoms or disease.

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Received: August 18, 2020**; Accepted:** August 29, 2020**; Published:** September 2, 2020

Citation: Jesha M M, Samina H, Hamda A J, Hayat K, Soha A B, Hamad A R (2020) Adverse Events following Immunization (AEFI) Surveillance in Qatar: 2014 -2018 J. Pharamacovigil. 8:287. doi-10.35248/2329-6887.20.8.287.

There may be some expected adverse events, with known or plausible theoretical risk such as anaphylaxis, vaccine-strain systemic infection after administration of live vaccines to severely immuno-compromised persons, intussusception after rotavirus vaccine, Guillain-Barre syndrome after inactivated influenza vaccine and vaccine-associated paralytic poliomyelitis from oral poliovirus vaccine. There might be possibilities of identifying some unexpected and unusual effects of the vaccines when these are used at large scale in immunization programs [2,3].

An adverse event following immunization (AEFI) is any untoward medical occurrence which follows vaccination and does not necessarily have a causal relationship with the usage of the vaccine [4]. Adverse events range from mild to severe, and the mild events include fever, pain at injection site and local swelling. Severe reactions can include convulsions, coma and even death. Majority of adverse events following immunization are mild and resolve quickly, but one cannot predict individuals who might have a mild or serious reaction to a vaccine.

In 2011, World Health Organization (WHO) came up with the Global Vaccine Safety Initiative (GVSI) whose primary objective is early AEFI detection and analysis of adverse events to allow appropriate and quick responses to emerging AEFI issues in order to decrease the negative impact on the health of individuals and immunization programme [4]. The WHO mandates the systematic collection, analysis and evaluation of medically important adverse events following immunization (AEFI) for all immunization programmes. WHO classifies AEFIs into five main categories which are vaccine product related reaction, vaccine quality defect related reaction, Immunization programme error related reaction, Immunization anxiety related reactions and coincidental[4]. The Global Advisory Committee on Vaccine Safety (GACVS) proposed a reporting rate of at least 10 severe AEFIs per 100,000 surviving infants and this is the vaccine safety indicator which was adopted by WHO. There is no indicator for minor AEFIs [5].

Assured quality vaccines and safe immunization practices are pre-requisite to successful immunization programs. All vaccines go through stringent safety checks during pre-licensure stage. Because most vaccination programmes involve large population compared to the small samples used in their pre-licensor stages, and because some events associated with vaccines are rare or have late onset, or are unexpected or could be population specific, it is important to monitor post licensor. Adverse Events Following Immunization (AEFI) Surveillance program is an integral part of any immunization program to monitor the vaccine safety in the post licensure phase. This helps counter the negative perceptions on vaccination and the resultant vaccine hesitancy by improving transparency in the immunization programmes. Careful and continuous analysis of the post marketing vaccine safety surveillance data provides a means to critically evaluate and communicate up to date information to the public on the benefit-risk profiles of individual vaccines [5,6]. This will in turn help us maintain the public confidence in the Expanded Programme of Immunization (EPI) [7].

Though AEFI surveillance in Qatar started along with the Universal Immunization Programme (UIP) in 1985, the AEFI reporting remained suboptimal for long time. The country has a relatively strong immunization programme as indicated by official estimated vaccine coverage of around 98% for the surviving infants (using the 2018 estimates for DTP coverage as a proxy for the national immunization coverage) and less than 1% drop-out rate between DTP1 and DTP3 coverage [8]. AEFI surveillance and investigation is managed and coordinated by the Expanded Programme of Immunization (EPI) team, a division of the Health Protection -Communicable Disease Control (HP-CDC) section under Ministry of Public Health of Qatar. In 2014, measures were taken to increase the reporting by increasing awareness about AEFI, importance of reporting and modified AEFI reporting forms were issued to health facilities providing vaccination services. The system is now designed to capture any AEFI reports from anywhere in Qatar. Reports of AEFI should contain the following information in a standardized fashion: age and sex of patient, his/her National ID number or Health Card number, address, date of birth, date of immunization, date of onset of AEFI, date of reporting, kind and lot of suspect vaccine(s), description of the AEFI, time interval after immunization, duration of the event, final outcome of AEFI, and any other additional remarks from the reporter. All reported AEFI case reports are then investigated by the EPI physicians. They assess the circumstances around the adverse events and causality assessment is done and recorded in the Vaccine Adverse Event Registry.

OBJECTIVES

To determine the characteristics and trends of the passively reported AEFI case reports from Vaccine Adverse Event Registry in MOPH, Qatar from 2014 to 2018 and to assess the performance of the Vaccine safety surveillance system.

METHODOLOGY

A record based descriptive study was done using the passively collected individual vaccine safety related (AEFI) case reports submitted to the EPI section, MOPH, Qatar from 2014 to 2018. Only AEFI case reports pertaining to children from 0 to 18 years, the target population covered by the Qatar National Immunization Program were included. We excluded those case reports emanating from vaccines not included in the National Immunization Program. In cases of co administration of two or more vaccines in an individual, the reported AEFI was attributed to the vaccine suspected by the EPI investigator.

Descriptive analysis with respect to the age-gender distribution, AEFI presentation patterns, associated vaccines, timeliness, completeness, types and/or classification of the AEFIs and its seriousness and final outcome were done. The overall AEFI reporting rates (per 100,000 vaccine doses) and vaccine specific AEFI reporting rates per 100,000 vaccine doses were calculated. The denominator for calculating the overall AEFI reporting rates, estimated administered doses, was derived by multiplying the population of children who should have been vaccinated by the estimated immunization coverage (2018 estimates for DTP coverage was used as proxy for the national immunization coverage). Assuming the average birth cohort to be 27,178, so over a period of 5 years (2014-2018), 135,890 children should get vaccinated. AEFI rates by vaccine categories were calculated using the administered doses for BCG, HEXA, PENTA, MMR, Hepatitis B, PCV, Varicella, Influenza and Tdap (from the annual Immunization Statistics, EPI section, HP-CDC, MOPH) whereas purchased doses was used for DTaP.

WORKING DEFINITION

An adverse event following immunization (AEFI) is any untoward medical occurrence which follows vaccination and does not necessarily have a causal relationship with the usage of the vaccine [4].

RESULTS

A total of 232 case reports of AEFI have been reported to MOPH from 2014 to 2018. Only AEFI case reports pertaining to children from 0 to 18 years (the target population covered by the Qatar National Immunization Program) and those pertaining to vaccines in the National Immunization Program were considered. Hence we analyzed 148 case reports.

Socio demographic characteristics- Out of the total 148 cases, 51.3% were females and 16.2% (24) were Qataris. Nearly half (49.3%) were aged between 1 to 5 years (Table 1).

Table 1: Nine gave family history of allergy.

Age Group (years)	*Frequency*	*Per cent*
<1	*23*	*15.5%*
1-5	*73*	*49.3%*
6-10	*25*	*16.9%*
11-18	*27*	*18.3%*
Total	*148*	*100%*

Reporting Trends: The overall AEFI reporting rate for 2014- 2018 was 1.11 per 100000 vaccine doses. Figure 1 shows the year wise distribution of the cases. There was a gradual increase in the reporting over the years, the spike in 2016 can be explained by the National MMR campaign which accounts for more than half (57.1%) the AEFI reported that year.

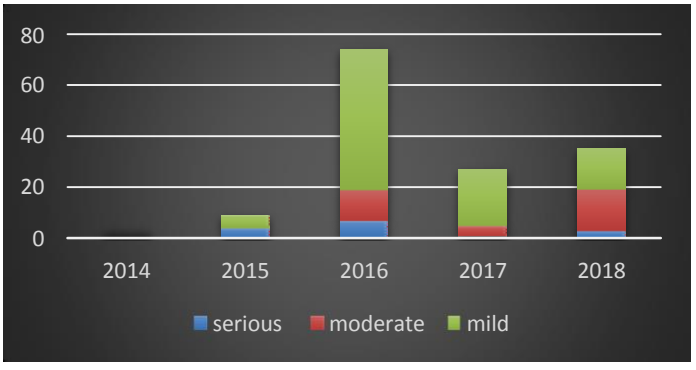

Figure 1: Distribution of the AEFI cases across the 5 year period [2014-2018]

Seriousness and outcome assessment: More than half (54.1%) were generalized AEFI. Majority were mild reactions (65.3%), 24.2% were moderate reactions and 10.5% were severe reactions. Less than 10 serious AEFI cases were reported to MOPH each year, **which is less than the recommended vaccine safety indicator by WHO.** Figure 2 depicts the classification of the reported AEFI cases. The peaking in anxiety related mild AEFI can be explained by the National MMR Campaign in 2016. There were no deaths among the reported cases.

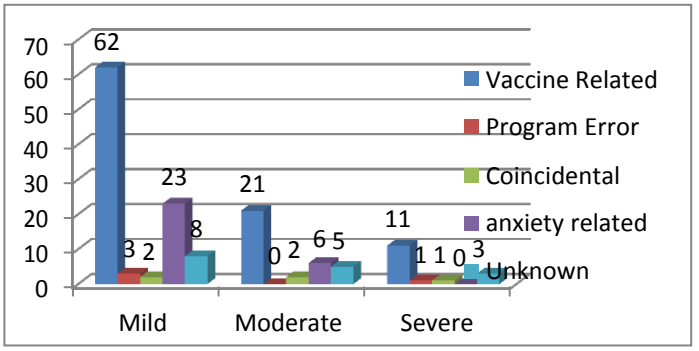

Figure 2: Classification of the reported AEFI cases

Associated Vaccine: Table 2 shows the distribution of AEFI based on the vaccine involved and their respective AEFI rates. Most of the AEFI were reported following MMR (51 cases) and majority of these are accounted by the National MMR Campaign in 2016 (44 cases). AEFI rate for all MMR doses was found to be 31.84/100,000 administered doses, whereas when the doses administered during MMR campaign was exclude the rate was found to be 5.06/ 100,000 administered doses. The most commonly involved individual vaccine apart from campaign was DTaP vaccine (38 cases) followed by combination of Hexa / Penta with PCV-13 Vaccine (30cases). There were only two cases reported post BCG vaccination. Two cases each were seen with Rotavirus and Men B Vaccine but these were administered in combination with other vaccines.

Table 2: Vaccine wise distribution of AEFI

Vaccine involved	Frequency	AEFI per 100000 doses
BCG	2	1.53
HEXA+/-PCV	7	3.28
PENTA+/-PCV	23	
PENTA alone	3	12.63
TETRA	2	
DTaP	39	96.3
Tdap	11	8.84
PCV	3	0.49
MMR	51	31.84
Varicella	3	2.14
Influenza	4	0.83
Hepatitis B	1	0.77

Presentation of AEFI: The most frequently reported individual AEFI was swelling with or without redness at the injection site (25) followed by fever (19). Many of these symptoms were seen in combinations.

Table 3: Pattern of presentation of AEFI

Adverse reaction	Number	Percent
Swelling ± redness at injection site	25	16.9
Fever	19	12.8
Cellulitis	15	10.1
Dizziness	14	9.5
Rash	12	8.1
Nausea/ vomiting	8	5.4
Urticaria	6	4.05
Limping	5	3.4
Faint	4	2.7
Crying	4	2.7
Headache	3	2.02
Pruritis	3	2.02
Seizures	3	2.02
Cough	3	2.02

Seizures	3	2.02
Anaphylaxis	3	2.02
Syncope	3	2.02
Wheeze	3	2.02
Hypotension	2	1.3
BCG lymphadenitis	2	1.3
Pain	2	1.3
Injection site abscess	2	1.3
Febrile convulsions	2	1.3
Abdominal pain	2	1.3
Heaviness of chest, breathlessness	2	1.3

Quality of reporting: Timeliness could not be analyzed fully as 41 reports did not have date of AEFI occurrence or date of vaccination. 91 cases were reported timely and 22 were reported after a delay. As per the National guidelines all moderate and severe AEFI are to be reported within 24 hours. In ten cases, the adverse event developed after 24 hours of vaccination but within 7 days post vaccination.

DISCUSSION

There was a gradual increase in the reporting over the years, the spike in 2016 can be explained by the National MMR campaign which accounts for more than half (57.1%) the AEFI reported that year. The overall AEFI reporting rate was found to be very low in our study (1.11/100,000 doses) but gradually increasing. Table 4 shows the comparison of the findings of our study with that of other countries. Similar to our finding, Switzerland (2.7/100,000 distributed doses); Albania (3.9/100,000 administered doses) and China (9.2/100,000 administered doses) had <10/100,000 vaccine doses [9,10,11]. Study from Spain shows 12.4 AEFI per 10,000 doses and Australia 14.6 per 100,000 doses whereas Zimbabwe had very low rates (0.58 per 100,000 doses) [12,13,14]. The variation in rates of AEFI may be due to the different reporting requirements, difference in awareness as well as compliance of reporters. The higher reporting rates may be seen in places with complementary active surveillance like Canada (AEFI reporting rate of 17/100,000 doses) [15].

Our study observed that 10.8% of the passively reported AEFI were serious. Less than 10 serious AEFI cases were reported to MOPH each year, compared to WHO recommendation of ten serious case detection per 100000 surviving infants. Our findings are consistent with findings from Zimbabwe (11%), Australia (11%), US (14.2%) and Germany (19%); whereas China (1%) and Croatia (3%) had markedly lower detection rates [14,13,16,17,11]. One third of the AEFI were classified as serious in a study done in Denmark [18]. These differences probably reflect the variability in reporting regulations and also the bias towards reporting serious AEFI. During passive surveillance the reporting of mild reactions may be neglected, thus leading to underreporting and what we see may just be the tip of the iceberg. In a study on sensitivity of surveillance system in the US, sensitivity varied widely ranging from 72% for Vaccine associated poliomyelitis to less than 1% for acute thrombocytopenic purpure following MMR vaccine and Hypotonic hyporesponsive episodes following DTP containing vaccines. This reflects the under reporting of known outcomes in passive surveillance system [19].

There were few major changes in the National Immunization Schedule during this study period (2014-2018) in 2016 and 2018, which may have an impact on our findings. There was a global shift from trivalent OPV to bivalent OPV; 2 Penta+ 1 Hexa was replaced by 2 Hexa + 1 Penta and because of vaccine shortage, Pentaxim was used instead of Tetra and Tdap was used instead of DTaP. Japanese strain of BCG was used instead of Danish strain during this period.

Due to Tetra vaccine shortage during this period, Pentaxim was used instead. This may be the reason for the very low number of AEFI reported and difficulty in retrieving the denominator (purchased

doses) to calculate AEFI rates for the 2 reported cases of AEFI following TETRA.

Penta with PCV-13 Vaccine. This was in concordance with most studies globally. (Table 4)

Our study stated that swelling at injection site was the most common presentation followed by fever. Several studies reported fever as the most common AEFI presentation followed by injection site reactions [10, 11,20]. Fever and injection site reactions may be explained by the characteristic side effects of DTP containing vaccines. Two cases of BCG lymphadenitis were reported during the study period in our study, similar to the Brazilian study were BCG lymphadenopathy, local abscess and ulcer were reported post BCG [21]. Differently, in Albania no reports post-BCG were seen [10].

The most commonly involved individual vaccine apart from campaign was DTaP vaccine followed by combination of Hexa /

Table 4: AEFI reporting in different countries

Country	Year	Type of surveillance	Target population (age in years)	AEFI rates/ 100,000 administered doses	Vaccine responsible for highest number of reports	Most commonly reported reaction	Serious events
Our Study	2014-2018	passive	0-18	1.11	DTaP (excluding MMR campaign)	Injection site swelling and redness, followed by fever	10.8%
Albania [10]	2003-2015	passive	0-18	3.9	DTP	Fever (58%)	21%
Australia [13]	2011	Passive	All ages	12.5	DTaP-IPV	Injection site reaction	7%
Brazil [21]	1992-2001	passive	All ages	44.2	BCG, DTP	Lymphadenopathy , pain at injection site, fever	
Canada [15]	1994-2004	Passive and active		17		Local reactions and fever	6%
China [11]	2008-2011	Passive		9.2	DTP	Fever followed by injection site reactions	
Czech Republic[22]	2011-2013	passive	0-10	209	DTaP	Fever, Injection site reaction	13%
Denmark [18]	1998-2007	passive	0-17	70.6	MMR	Fever, febrile convulsions, injection site reactions, rash	
Oman [25]	1996-2005	passive	<6	10.8	BCG	BCG adenitis	
Iran[23]	2014	passive	<7	11.8	DTP	Lymphadentis	
India [20]	2011	passive	0-14	99.2	DTP, BCG, Hepatitis B	Fever and Injection site reaction	0.70%

Italy [24]	2006-2011	passive	0-17	46	Hexa	fever	10%
Singapore [26]	2010-2012	Passive + active				BCG adenitis, Fever, febrile convulsions,	
Switzerland [9]	1991-2001	Passive		2.7			21.8%
Spain[12]	2002	passive	0-14	14.6	DTaP-Hib	Injection site oedema and pain	
USA[16]	1991-2001	Passive +active	All ages	11.4	Rotavirus vaccine	fever	14.2%

LIMITATIONS

There was significant variability in quality of AEFI reports. Passive AEFI Surveillance has inherent limitations like under reporting, inadequate awareness regarding AEFI surveillance among health care workers, variability in accuracy and completeness of AEFI reports. Secondly, the unavailability of accurate denominator (number of administered doses) makes AEFI rates less accurate. The overall AEFI reporting rates was calculated using birth cohort as an estimate of the number of children to be vaccinated. The vaccine specific AEFI rates was calculated using purchased doses or administered doses as per availability. Thirdly, the observed temporal relationship between immunization and AEFI cases do not necessarily mean that they are causal. Lastly, limited follow up data reduced our ability fully assess the outcome.

CONCLUSION

The data confirms the low rate of AEFI being reported in Qatar. The passive reporting cannot be taken as the actual incidence rates. Vaccine safety surveillance system is still developing and needs additional methods to complete safety profile. However, the current system provides a reference point for the monitoring of the ongoing AEFI reporting trends and characteristics. Completeness and timeliness of reporting needs to be improved. Regular analysis of reporting and feedbacks will help in improving the existing system.

RECOMMENDATIONS

Strategies have to be employed to strengthen the AEFI Surveillance system. Cross checking the passively reported AEFI with the corresponding section in the Monthly Surveillance data will help to identify any missed cases. Improving health care professional's awareness of vaccine safety reporting and providing appropriate and timely feedback to reporters may help increase the quality (completeness and timeliness) and the number of AEFI being reported. In addition, complimentary active surveillance will increase the detection rates. Linkage of AEFI data with immunization registry, will improve the assessment of surveillance data.

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