

Active surveillance of adverse events following immunization (AEFI): a prospective 3-year vaccine safety study

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Abstract

Background: Vaccines used in national immunization programs are considered safe and effective but immunization safety has become as important as the efficacy of vaccination programs. The objective of the study was to detect adverse events following immunization (AEFIs) to all vaccines administered to a pediatric population in India.

Methods: The prospective active vaccine safety surveillance study enrolled eligible children in the age group 0–5 years receiving vaccination from the immunization center at JSS Hospital, Mysuru. Study participants were monitored at the site for 30 min following vaccination and a telephonic survey was made after 8 days to identify all AEFIs. Causality assessment of the AEFIs were done using a new algorithm developed by the safety and vigilance department of the World Health Organization.

Results: The incidence of reported AEFIs was 13.7%. The most frequently reported AEFI was fever ($n=3095$, 93.2%) with an incidence of 109.7 per 1000 doses of vaccine administered, followed by persistent crying ($n=69$, 2.4 per 1000 doses of vaccine) and diarrhea ($n=57$, 2.0 per 1000 doses of vaccine). The majorly implicated vaccine for AEFIs was Pentavac® followed by BCG. Consistent causal association to immunization was observed in 93.4% of cases.

Conclusions: A high incidence rate of AEFI was observed in our study population when compared with previous published studies. AEFI surveillance studies help to detect changes in the frequency of adverse events, which may be an alert to consider vaccine quality or identify a specific risk among the local population.

Keywords: active surveillance, adverse events following vaccination, AEFI, causality assessment of AEFIs, immunization, prospective study, serious adverse events, tertiary care hospital, vaccine safety, vaccine safety surveillance

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Introduction

Immunization is one of the most cost-effective public health interventions, preventing 2–3 million deaths every year globally.^{1,2} However, an estimated 21.8 million infants worldwide are still missing out on basic vaccines.² Vaccines are usually administered to healthy people, including entire birth cohorts of infants and in vast numbers.³ Vaccines used in an expanded program of immunization (EPI) are considered safe and effective when used correctly.⁴ However, like

medicinal products, vaccines are not free from adverse events.¹ Adverse events following immunization (AEFI) is defined as ‘any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine.’ The adverse event may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom, or a disease.⁵ The settings in which the vaccines are administered vary from sophisticated tertiary care hospitals to primary health care centers in remote

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areas.³ The setting is of great importance as, along with the vaccines themselves, the process of immunization is also a potential source of adverse events.¹ Vaccines harbor a variety of components, including antigens, stabilizers, adjuvants, antibiotics, preservatives and residual byproducts from the production process, all of which have the potential to cause AEFIs.⁶ The cause-specific classification of AEFIs by the Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO) lists vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction, immunization anxiety-related reaction, and coincidental event. An event can be categorized as coincidental if it was caused by something other than vaccine or immunization process but a temporal relationship with the vaccine exists.⁷ Significant numbers of adverse events (AEs) following vaccination are not due to vaccines.

AEFI surveillance in India was started in 1985 along with the Universal Immunization Program (UIP), but AEFI reporting is still suboptimal in the country, with almost no participation from the private sector.⁸ The Pharmacovigilance Program of India (PvPI) follows a spontaneous surveillance method and collects all AEFIs irrespective of the health care setting via Adverse Drug reaction Monitoring Centers (AMCs) across the country, and further transmits this information to a national AEFI committee for investigation and communication as required.^{9,10} But spontaneous reporting system might possibly not collect all AEFIs due to factors such as under-reporting, incomplete reports due to lack of time to fill out forms, health care professionals' tendency to report serious events more frequently than other events, lack of denominator data to calculate incidence rates.^{11,12}

This study aimed to detect AEFI to all vaccines administered to the pediatric population at the immunization center of a tertiary care hospital, Mysuru, and to identify predictors of AEFI.

Methods

Study details and criteria

The study was an active surveillance study, carried out over 3 years. The enrollment period was

from 1 July 2013 to 1 May 2016, and the follow-up period was completed on 30 June 2016. Ethical clearance was obtained from the Institutional Human Ethics Committee of JSS College of Pharmacy, Mysuru before starting the study. The study site was the Immunization center, JSS Hospital, Mysuru, India. The study site functions 7 days a week and receives vaccine supply through the EPI. Vaccines coming under EPI are administered only 2 days a week (Monday and Thursday) whereas vaccines not covered by EPI are administered on all 7 days in the week. The study included all children aged 0–5 years receiving vaccination from the immunization center and who were willing to give informed consent.

Study procedure

Eligible children were enrolled into the study after explaining the study procedure to the parents or legally acceptable representative (LAR) and obtaining their written informed consent. All subjects were monitored in the waiting area of the immunization center at the study site for the occurrence of any unsolicited systemic reactions for 30 min following their vaccination. Parents/LAR of children were provided with a validated patient information leaflet in the local language that had information on vaccination, possible AEFIs and the contact details of the study team. In case of any AEs, parents were advised to visit the study site or contact the study team at any time using a toll-free number for 30 days following the vaccination. On day 8 following vaccination, a telephonic follow up was conducted with all the enrolled study population irrespective of whether the parents/LAR contacted the study team or not within the week following vaccination. The study team used a suitably designed case report form to collect the required data from the enrolled study population in case of an AE. The case report form had provision to document demographic details of the child, allergic status, past medical history, and AE details. The AEFI section of the case report form was developed based on WHO's AEFI core variables, and had provision to collect details of the vaccine, description of AEFI, date and time of start of AEFI, date and time of stop of AEFI, duration of the AEFI, severity, seriousness, details of medical attention sought due to AEFI, management of AEFI, outcome of the developed AEFI, details of the

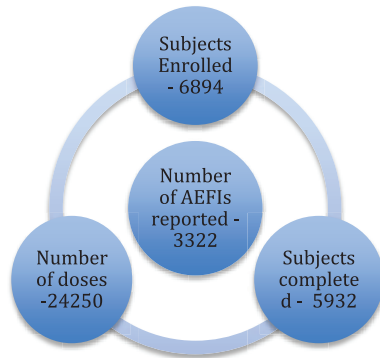


Figure 1. Consort diagram of subjects enrolled.

reporter (parent/LAR), and a free space for any additional information. If any member of the study population visited the hospital for any reason within the active follow-up period of 8 days, the information was collected from the hospital information system using their registration number at the hospital. Any further information required for the causality assessment of the AEFI was ascertained by making another phone call to the study participant wherever necessary.

Assessment of AEFI

The causality assessment was performed by the AEFI causality assessment team of the study site, composed of two senior professors of Pediatrics, a clinical pharmacist and a clinical pharmacologist who have interest and experience in the area of vaccine safety. Brighton collaboration case definitions were used for the valid diagnosis of AEFIs. Causality assessment of AEFIs was performed using WHO's new causality assessment algorithm by checking the eligibility, and using the checklist and algorithm. Finally, the AEFIs were categorized as per the causality assessment classification.⁶ Bivariate analysis was used as the statistical tool (confidence interval of 95%) for the identification of predictors of AEFI.

Results

The total number of children enrolled for the active surveillance of AEFI was 6894 (28,183 doses) and 5932 (24,250 doses) of the study population were followed (3421 boys and 2511 girls), with a response rate of 86.0%. Various reasons for the drop-out rate of 14.0% (CI: 1.80–58.30)

included: unable to contact parents, relocation from city, and consent withdrawn (0.1%). The details are presented in Figure 1. Of the 24,250 doses of vaccines administered to the study population, 3322 AEFIs were reported from 2628 vaccinated subjects. The incidence of reported AEFIs in our study was 13.7%. The incidence of AEFIs for children of <1 year of age was 15.3%, and for children between the ages of 1 and 5 years, AEFI incidence was 6.6%.

Among the study participants with AEFIs, 1380 (52.5%, CI: 50.60–54.40) were boys and 1248 (47.5%, CI: 45.60–49.40) were girls. Infants enrolled (28 days to 1 year of age) in the study had a higher prevalence of AEFIs (29.3%) compared with neonates (0–28 days of age–11.1%). Table 1 provides the characteristics of the study population, and Figure 2 provides the distribution of different vaccines and number of doses administered during the study period

The most frequently reported AEFI was fever [93.2% ($n=3095$)], followed by persistent crying [2.1% ($n=69$)] and diarrhoea [1.7% ($n=57$)]. The vaccines for which AEFIs were most frequently reported were Pentavac® [Diphtheria+ Tetanus+wholecellpertussis(DTwP) + Hepatitis B (Hep B)+ Hemophilus Influenza B (HiB)] followed by Bacillus Calmette Guerin (BCG) vaccine. Fever was the main reaction reported with Pentavac® administration, and accounted for 94.5% of the total AEFIs reported with Pentavac®. The incidence of AEFIs with Pentavac® decreased with age. We observed 84.4% ($n=2220$) of AEFIs with administration of the first dose of Pentavac® containing vaccine at 6 weeks of age followed by second dose (12.5%, $n=330$) at 10 weeks and a third dose (4.5%, $n=119$) at 14 weeks of age. Details of the reported AEFIs are presented in Table 2. All children recovered from the AEs.

Fever was the most commonly reported reaction, with almost all vaccines associated with an incidence of 109.7 per 1000 doses of vaccine administered. The second most commonly reported AEFI was persistent crying, with an incidence of 2.4 per 1000 doses, followed by diarrhoea, with 2.0 cases per 1000 doses. Injection site reactions like pain and swelling at the injection site accounted for 0.6 and 1.7 per 1000 doses of vaccines administered, respectively.

Table 1. Characteristics of the study population.

Characteristics		Number
Gender		
Male	Total enrolled	3421 (57.7%)
Female	Total enrolled	2511 (42.3%)
Age of children developed AEFIs		
Neonates (0–28 days)		165 (5.0%)
Infants (28 days to 1 year)		2871 (86.4%)
Toddlers (1–4 years)		286 (8.6%)
Term of birth		
Full term		5612 (94.6%)
Pre-term		320 (5.4%)
Body weight		
Normal (2.5 to 4.0 Kg)		4995 (84.2%)
Low (2.5 to 1.5 kg)		706 (11.9%)
Very low (less than 1.5 kg)		231 (3.9%)
Past history of any illness		
No		445 (7.5%)
Yes		5487 (92.5%)
Past history drug intake		
No		101 (1.7%)
Yes		5831 (98.3%)
AEFI, adverse events following immunization.		

Predictors of AEFI

Bivariate analysis identified neonates, toddlers low birth weight and very low birth weight as predictors for development of AEFIs, irrespective of the vaccine administered. The details are collected in Table 3.

Causality assessment of AEFI

The criteria for selecting cases for causality assessment using WHO's causality assessment algorithm are as follows: serious events; occurrence of events above the expected rate or of unusual severity; signals; AEFIs caused by immunization

errors; significant events of unexplained cause occurring within 30 days of immunization; events causing significant parental or community concern.⁶ We tried to assess the causality of all the reported events using the said algorithm irrespective of the above-mentioned criteria; 93.4% of the reported AEFIs had consistent causal association to immunization and 0.9% of the events had indeterminate causal relationship with vaccines. Events were assessed as indeterminate, as the temporal relationship was consistent but there was insufficient definitive evidence for the vaccines causing the event. Only five reported AEFIs were immunization error-related reactions; 5.3% of reactions had inconsistent causal association to vaccination (coincidental events); and 0.4% of the reactions were unclassifiable due to incomplete information available for causality assessment. The majority of AEFIs were mild or moderate in severity, but 13 reactions were serious in nature and the affected babies were hospitalized. There was one death following vaccination, and, during the causality assessment, this was categorized as a coincidental event. There was no need for any medical attention in 97.0% of cases and all children recovered from AEFI within 1–2 days of occurrence. Remaining doses of vaccines were discontinued for the serious AEFIs.

Discussion

Immunization safety has become as important as the efficacy of vaccines in the national vaccine-preventable disease (VPD) programs. Expectations from vaccinations are much higher, and problems arising from the vaccine or vaccination are less acceptable to the general public.^{2,13} All events were reported within 8 days or during telephonic follow up; the full follow-up period was 30 days. The incidence of AEFI in our study was 13.7%, which is in the same range as previously published studies. Two similar studies done in India identified the incidence of AEFI as 20.8% and 11.9%,^{14,15} and studies done by researchers from Iran and Spain identified the incidence as 19.0% and 22.7%, respectively.^{16,17} The majority of the AEFIs observed among our study population were from children aged <1 year, which is similar to previous studies as most vaccines in the EPI schedule are given to this age group.¹⁵ We observed that the incidence of AEFIs were relatively high among girls (1577 AEFIs/10,265 doses

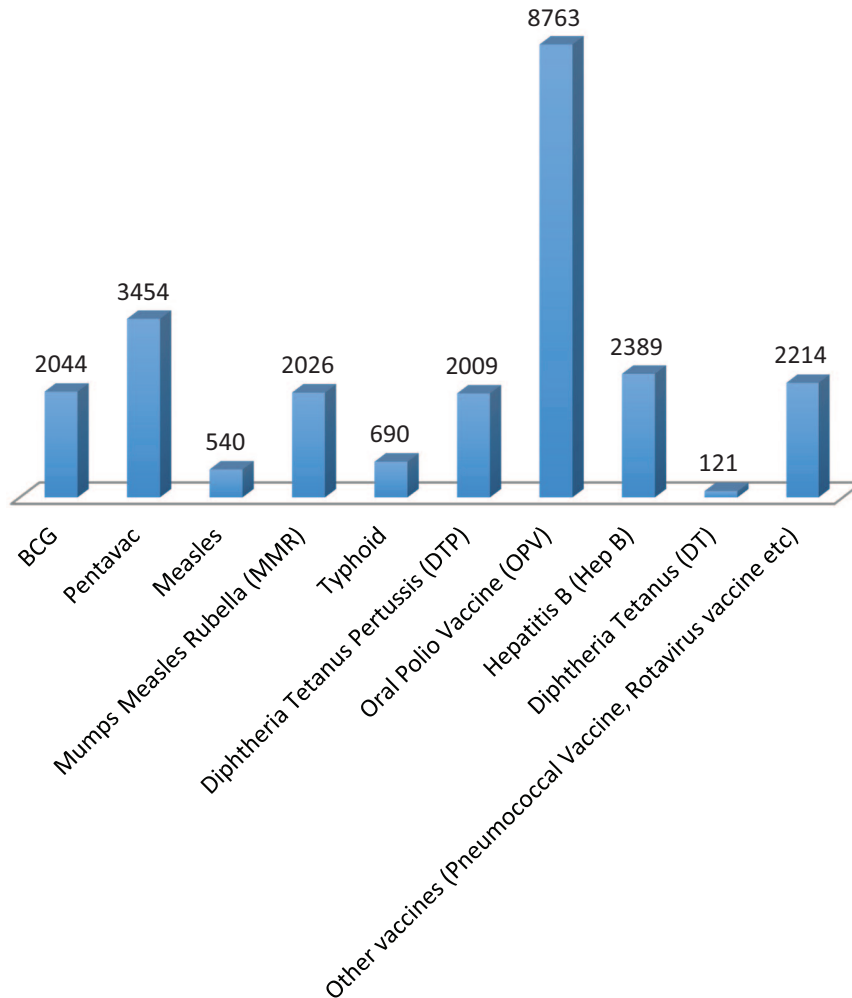


Figure 2. Distribution of vaccines

Other vaccines: Rotavirus vaccine, Pneumococcal vaccine, Hepatitis A vaccine, Typhoid vaccine, Varicella vaccine, etc.

equals 15.4%) compared with boys (1745 AEFIs /13,985 doses equals 12.5%) in the study population, which is contradictory to findings reported by other researchers.^{15–17} The majority of the study population (98.3%) had a past history of drug intake at the time of vaccination for various medical conditions, but this was not a predictor for the development of AEFIs as the *p* value was 0.543.

The most common AEFI reported in this study was fever, followed by injection site reactions, as in previously published studies from India, the United States, and China.^{16,18} Studies from other parts of the world reported swelling at the site of injection as the most commonly observed AEFI.^{15,19}

Most AEFIs were reported with DTP-containing vaccines (Pentavac® and Quadravac®), as seen in previously published studies.^{15,20,21} It was observed that the rate of AEFIs was highest with the first administration of DTP-containing vaccines, and that the rate decreased with subsequent administration, consistent with earlier literature.¹⁵ The incidence of fever is generally high following the first dose of a DTP-containing vaccine, and the incidence decreases with subsequent doses, whereas local reactions increase with the number of doses. Precautions to decrease local reactions, such as allowing the vaccines to reach room temperature before administration, resuspension by rotating the vaccine, performing intramuscular injection

Table 2. Details of reported AEFIs.

Sl. No.	Age group	Vaccines	Number (%)	Type of reaction with number of children affected
1	Neonates (ages 0–4 weeks)	BCG + OPV + Hep B	165(5.0)	Fever (158), Cough (4), cold(2), Abscess formation (1)
2	Infants (ages 4 weeks–1 year)	Pentavac® +OPV	2560 (77.1) (Dose No.1: 2150 Dose No.2: 330 Dose No 3: 119)	Fever (2417), Diarrhoea (22), Persistent Crying (58), breathlessness (1), Swelling at injection site (28), Rashes (03), Cough (12), Cold (7), Seizure (12) ^a
3		Pentavac® + Rotavirus + OPV	47(1.4) (Dose No 1: 47)	Fever (32), Diarrhea(8), Persistent Crying (7),
4		Pentavac® +Pneumococcal vaccine (PCV)	23(0.7) (Dose No: 23)	Fever (18), Persistent Crying (4), cough and cold (1)
5		Quadravac® (DTP + HiB) +OPV	157(4.7)	Fever (143), Severe Pain at injection site (08), Vomiting (01), Rashes (01), Cough and Cold(4)
6		Measles	83(2.5)	Fever (72), Loose stools (9), Cough (2)
8		Measles+ Japanese Encephalitis (JE)+ DTP	1(0.03)	Seizure (01) ^a
9	Toddlers (ages 1–2years)	DTP	50(1.5)	Fever (44), Severe pain at injection site (3), cold(2), Neuropathy (1)
10		Mumps Measles Rubella (MMR) vaccine	105(3.1)	Fever (94), Loose stools (08), Swelling at injection site (3)
11		Hepatitis A	69(2.1)	Fever (64), Diarrhoea(5)
12		Typhoid vaccine	51(1.5)	Fever (42), Loose Stools (5), cold (4)
13		Varicella vaccine	11(0.03)	Fever (11)

^aCases of serious AEFIs.
AEFI, adverse events following immunization.

immediately without aspiration, positioning the child upright, and child distraction techniques, etc., are carried out at the study site as a routine practice. This is possibly the reason for the low rate of local reactions seen in our study population; however, these precautions have no effect on the incidence of fever.^{22,23}

The major reason for injection site reactions with Pentavac® may be due to the presence as adjuvant of aluminium salts, which are added to

enhance vaccine efficacy.¹⁹ Improper administration technique also contributes to injection site reactions. In a study conducted in Japan diarrhoea was a common minor AEFI after oral polio vaccination (OPV),²⁴ and that reaction was also evident in our patient population who received oral polio along with other vaccinations. In earlier studies, a high incidence of lymphadenitis following BCG vaccination was observed, and this was rarely observed in our study population¹⁷; however, 99.4% of events were coincidental and one

Table 3. Predictor analysis of reported AEFIs.

Characteristics	OR (CI)	p value
Gender		
Male	1 (Reference)	
Female	1.2 (0.7–1.9)	0.292
Age		
Neonates (0–28 days)	0.3 (0.1–1.0)	0.014
Infants (28 days to 1 year)	1 (Reference)	
Toddlers (1–4 years)	0.5 (0.3–2.4)	0.042
Term of birth		
Full term	1 (Reference)	
Pre-term	0.8 (0.3–0.2)	0.519
Birth weight		
Normal (2.5–4.0 kg)	1 (Reference)	
Low (2.5–1.5 kg)	0.1 (0.1–0.3)	<0.001
Very low (<1.5 kg)	0.2 (0.1–0.7)	0.016
Past history of any illness		
No	1 (Reference)	
Yes	1.0 (0.4–2.6)	0.512
Past history drug intake		
No	1 (Reference)	
Yes	0.6 (0.1–5.3)	0.543
AEFI, adverse events following immunization.		

event was a immunization-error-related reaction. Serious AEFIs were rare in our study population, and all cases that were categorized as serious were hospitalized. Seizure following DTP-containing vaccines was the most common serious event, as in other studies.¹⁷ All the seizures occurred with administration of a first dose of a DTP-containing vaccine. As seizures may be due to the presence of the Whole Cell Pertussis portion of the vaccine, subsequent doses were cancelled.

Only 18.6% of cases sought medical attention due to AEFI, and 38% of the AEFIs were

symptomatically treated; the remaining did not receive any treatment. Parents either visited their pediatrician or made a telephonic enquiry about the symptoms. There was no major change in the immunization schedule due to the AEFI occurrence except for serious events. The observation that neonates and toddlers were at higher risk of developing AEFIs points to the need for active AEFI monitoring in this age group.

Causality assessment

New classifications of AEFIs are vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction (formerly ‘programme error’), immunization anxiety-related reaction, and coincidental event.⁶ Recent Iranian and Indian studies classified 74.8% and 14.5% of AEFIs as vaccine product-related reactions, respectively,^{16,25} whereas the majority of AEFIs (93.4%) observed in this study were vaccine product-related reactions.

AEFIs categorized under consistent causal association to vaccination were 93.4% in our study, whereas a similar Indian study by Singh and colleagues described 53.0% of AEFIs under this category.²⁵ The difference in numbers may be due to the fact that the Singh study included AEFIs resulted in clusters, hospitalized or requiring hospitalization, death or resulting in disability, which were all reported from national immunization programs. The rate of programmatic error/immunization error-related reactions in previous studies were 12.7% and 14.9%.^{13,20} We observed only five cases of programmatic/immunization error-related reaction in our study. The major reason for fewer immunization error related-reactions in our study may be due to the experience of the immunization center staff, and strict adherence to vaccine handling procedures. The reason for more immunization error related reaction in the study conducted by Singh and colleagues could be due to the possible involvement of health care providers (HCPs) from different centers with varying degrees of training and experience in the immunization process, as the study included AEFIs reported from EPIs. Lack of experience of immunization center staff can be a major contributing factor to these kind of reactions, and can easily be overcome by proper training of the staff involved in the vaccine handling process. There were no reports of vaccine quality defect-related

reactions in our study, similar to another Indian study.²⁵ Immunization anxiety-related reactions are mainly observed in the adolescent/adult population.²⁶ This was evident in our study too. We did not observe any immunization anxiety-related reactions as we enrolled babies of 0–5 years. However, an earlier study reported a higher rate of immunization anxiety-related reaction (22.0%) as the study enrolled adolescents as well as children of younger age.²⁵

There were 0.9% ($n=30$) indeterminate cases of AEFI. The indeterminate AEFIs are worthy of more focus as they may represent new vaccine-linked events or potential signals. A previously published study showed a higher rate (29.0%) of indeterminate cases,²⁵ possibly due to the fact that the reported AEFIs were from EPIs covering the entire Indian population, and even included AEFIs generated from mass immunization campaigns, whereas our study enrolled a population vaccinated only at the study site, and the study team itself reported the AEFIs. AEFIs categorized under inconsistent causal association to immunization were fewer in our study (5.3%), where the reported reactions were caused by exposure to something other than suspected vaccine, whereas a previous study showed 29.3% of reported AEFIs under this category. A higher percentage of unclassifiable events (11.4%), where adequate information for the causality assessment was not available, was observed in the study conducted by Singh and colleagues, and the current study observed only 0.4% of AEFIs as unclassifiable. Large differences in the number of unclassifiable events may be due to differences in methodology, as we followed single centre active surveillance while Singh and colleagues followed a nationally inclusive spontaneous reporting method restricted to severe/serious AEFIs.

Limitation

Because of the high dropout rate of 14.0%, we could not assess AEs in the discontinued population. The most commonly reported AEFI was fever; the number may be an overestimation as data was collected from parents through telephonic follow up.

Conclusion

The vaccines used in the EPI programs are safe, and the AEFIs observed were nonserious. The

training and experience of HCPs involved in immunization programs are important in preventing immunization error-related reactions, as reflected in this study. Similar active multi-centric studies across the country will help to generate more safety data, especially for newly introduced vaccines. Such a national AEFI database will be helpful in understanding vaccine safety issues in the country to provide feedback to HCPs on public concerns of vaccine safety, which will enable them to communicate effectively with the public to maintain their confidence/trust in vaccines.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

1. World Health Organization. Global manual on surveillance of adverse events following immunization. http://www.who.int/vaccine_safety/publications/aeft_surveillance/en/ (2014, accessed 16 February 2017).
2. World Health Organization. Immunization coverage fact sheet, <http://www.who.int/mediacentre/factsheets/fs378/en/> (2014, accessed 22 January 2017).
3. Plotkin SA and Plotkin SA. A short history of vaccination. In: Plotkin SA, Orenstein WA and Offit PA (ed.) *Vaccines*. 6th ed. Philadelphia: Elsevier Saunders, 2013, pp.1–13.
4. Vashishtha VM and Kumar P. 50 years of immunization in India: progress and future. *Indian Pediatr* 2013; 50: 111–118.
5. World health organization. Vaccine safety basics learning manual, http://www.who.int/vaccine_safety/initiative/tech_support/ebasic/en/ (2013, accessed 12 December 2014).
6. World health organization. Causality assessment of adverse events following immunization user guide for revised WHO classification, http://www.who.int/vaccine_safety/publications/aeft_manual.pdf (2013, accessed 13 March 2014).

7. World health organization. Global manual on surveillance of adverse events following immunization, www.who.int (2014, accessed 8 January 2018).
8. Chitkara AJ, Thaker N, Vashishta VM, *et al.* Adverse Event Following Immunization (AEFI) surveillance in India: position paper of Indian Academy of Pediatrics 2013. *Indian Pediatr* 2013; 50: 739–741.
9. Budhiraja S. Pharmacovigilance in vaccine. *Indian J Pharmacol* 2010; 42: 116–119.
10. Karande S, Gogtay NJ and Kshirsagar NA. Efficacy and safety of vaccines in Indian children: a review. *Pediatric Perinat Drug Ther* 2003; 5: 124–134.
11. Palleria C, Leporini S, Chimirri S, *et al.* Limitations and obstacles of the spontaneous adverse drug reactions reporting: two ‘challenging’ case reports. *J Pharmacol Pharmacother* 2013; 4: S66–S72.
12. Matsuda S, Aoki K, Kawamata T, *et al.* Bias in spontaneous reporting of adverse drug reactions in Japan. *PLoS One* 2015; 10: e0126413.
13. World Health Organization. State of the world’s vaccines and immunization, third edition. http://whqlibdoc.who.int/publications/2009/9789241563864_eng.pdf (accessed 6 February 2017).
14. Joshi ND, Prajapati KH, Solanki KC, *et al.* Pattern of adverse events following immunization in an Indian teaching hospital. *IJMSPH* 2013; 2: 62–68.
15. Adherkar RY, Deshpande PK and Ghongane BB. Study of the pattern of adverse events following immunization of the children in a tertiary care hospital. *IJBCP* 2016; 5: 609–615.
16. Khazaei S, Rezaeian S, Razani M, *et al.* Adverse Events Following Immunization(AEFI) in children under 7 years of age during 2014 in Hamedan Province, Iran. *Int J Pediatr* 2016; 4: 1697–1703.
17. Carrasco-Garrido P, Gallardo-Pino C, Jimenez Garcia R, *et al.* Incidence of adverse reactions to vaccines in a pediatric population. *Clin Drug Invest* 2004; 24: 457–463.
18. Zhou W, Pool V, Iskander JK, *et al.* Surveillance of safety after immunization: Vaccine Adverse Effect Reporting System (VAERS): United States, 1991–2001. *MMWR Surveill Summ* 2003; 52: 1–24.
19. Yu Hu, Qian Li, Luoya Lin, *et al.* Surveillance for adverse events following immunization from 2008 to 2011 in Zhejiang Province, China. *Clin Vaccin Immunol* 2013; 20: 211–217.
20. Mansoor O and Pillans PI. Vaccine adverse events reported in New Zealand 1990–5. *N Z Med J* 1997; 110: 270–272.
21. Mahajan D, Roomiani I, Gold MS, *et al.* Annual report: surveillance of adverse events following immunization in Australia, 2009. *Commun Dis Intell* 2010; 34: 259–276.
22. Taddio A, Appleton M, Bortolussi R, *et al.* Reducing pain of childhood vaccination: an evidence based clinical practice guideline (summary). *CMAJ* 2010; 182: 1989–1994.
23. Agac E and Gunes UY. Effect of pain of changing the needle prior to administering medicine intramuscularly: a randomised controlled study. *J Adv Nurs* 2011; 67: 563–568.
24. Sugawara T, Ohkusa Y, Taya K, *et al.* Diarrhoea as a minor adverse effect due to oral polio vaccine. *Jpn J Infect Dis* 2009; 62: 51–53.
25. Singh AK, Wagner AL, Joshi J, *et al.* Application of the revised WHO causality assessment protocol for adverse events following immunization in India. *Vaccine* 2017; 35: 4197–4202.
26. World Health Organization. Clusters of anxiety related reactions following immunization. Weekly epidemiological report, http://www.who.int/vaccine_safety/committee/topics/global_AEFI_monitoring/wer9103.pdf?ua=1 (2016 accessed 22 January).

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