

A study of adverse vaccine events among pediatric age group in a tertiary medical college hospital

Gramle Amol^{1*}, Asmita Narayan², R. Shubha¹

¹Department of Pharmacology, Spathagiri Institute of Medical Sciences & Research Center, Bengaluru, Karnataka, India, ²2nd Year MBBS student, Spathagiri Institute of Medical Sciences & Research Center, Bengaluru, Karnataka, India

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***Correspondence to:**

Dr. Gramle Amol,
Email: amolgramle@gmail.com

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ABSTRACT

Background: Vaccines are pivotal health products that are used and administered prophylactically to a large number of healthy individuals. A significant proportion of vaccines are administered to the pediatric age group, particularly to the neonates and infants as part of the national immunization programmes. As with any drug, untoward reaction can occur with the administration of vaccines. Most of the clinical trials with the vaccines are conducted and validated in a relatively small sample size. Active monitoring as part of the Pharmacovigilance programme is imperative to identify rare or deferred adverse vaccine events (AVE).

Methods: A prospective, single center, observational, naturalistic study on report forms in pediatric age group, who may develop AVE in Spathagiri Institute of Medical Sciences and Research Center, Bengaluru, was conducted during the study time window, from February 20, 2014, to April 20th, 2014. Children under 5 years of age were included in the study. All children more than 5 years of age were excluded from the study. The causality assessment were attempted to be recorded as per the Naranjo score, which is used to quantitatively evaluate the association between AVE and vaccines.

Results: 19.04% of children aged 1-5 years of age documented with adverse event following immunization (AEFI) (p=0.036). It was found that either a naïve or the fully immunized children suffered from the AEFI most of which was trivial. Fever was the most common AEFI reported followed by an excess cry. The incidence of fever reported was substantially high following the DPT vaccine.

Conclusions: All the AEFI received through the telephonic calls were documented. There was no mortality or a major adverse event reported. Maximum AEFI were documented in the neonates and the children 1-5 years of age which was statistically significant. In addition, the study provides a scope for further research with reference to the inter-age group variability. The immune mechanism behind such a difference also needs to be explored.

Keywords: Vaccines, Adverse vaccine events, Neonates

INTRODUCTION

Vaccines are pivotal health products that are used and administered prophylactically to a large number of healthy individuals. A significant proportion of vaccines are administered to the pediatric age group, particularly to the neonates and infants as part of the national immunization programmes.^{1,2} With growing scientific evidence and frequent changes in the practice guidelines, on an average the pediatric age group receives around 20 vaccines as per the vaccination schedule including multiple combination vaccines. In India, the vaccination schedule is drafted as per the Universal Immunization Programme (UIP). The vaccines are administered across a wide range of government and private hospitals.

Scientific literature and evidence-based medicine have proved that pediatric immunization prevents serious diseases, but the administration of these vaccines to healthy children also involves risks of adverse drug reactions (ADRs), which in some conditions are potentially serious. The current body of evidence on ADRs from immunization therapy at the population level is partly contradictory across countries, time periods and childhood immunization programmes. The objective of our study was to characterize reported adverse events following immunization (AEFIs) among children who are administered vaccines in our hospital.

The Global Advisory Committee on Vaccine Safety, an expert clinical and scientific advisory body was established

by the World Health Organization (WHO) to provide independent and scientifically rigorous advice on vaccine safety issues. The issue of vaccine safety has various implications and having a well-established study for observing and documenting the AEFI is, therefore, highly imperative.

As with any drug, untoward reaction can occur with the administration of vaccines. Adverse vaccine events (AVE) are defined as health effects that occur after immunization that may or may not be related to the vaccine. Continuous monitoring to actively detect the development of AVEs is, therefore, crucial and paramount.^{3,4} Most of the clinical trials with the vaccines are conducted and validated in a relatively small sample size. Active monitoring as part of the Pharmacovigilance programme is imperative to identify rare or deferred AVEs.⁴ Differences in the response of the individual immune system may account for rare cases of adverse events.⁵

Immunization against vaccine-preventable diseases is one of the safest and the most cost-effective interventions to improve child survival. Health care professionals, immunization providers and the parents/guardians of the immunized are to be sensitized, to report any AEFI. It is also necessary to have an active vaccine vigilance unit in an institution for increasing the standards of care. As of 2013, in response to recommendations for an improved system of governance for vaccine safety monitoring,⁶ a new statutory Advisory Committee on the Safety of Vaccines has been established to evaluate vaccine safety. Under the similar lines, it was thus proposed as part of the project to initiate and implement this program in the institution. Any medical events occurring after vaccination, that are regarded as “serious” and/or “unexpected” should be reported.^{7,8} In addition, an established causal association with vaccination is not a pre-requisite for reporting.⁹

A considerable emphasis has been placed on reporting of such adverse events in the recent past. Pre-licensure clinical trials are not powered to detect rare adverse events for new vaccines that occur with a frequency of <1 in 1,000 or with delayed onset, as they are usually tested in homogeneous, healthy study populations.¹⁰ The risk of AEFI with vaccination is always weighed against the risk of not immunizing a child.

In India, with approximately 26 million infants born each year, hundreds of millions doses of vaccines are administered annually.¹¹ Despite a relatively low rate of AEFI, because of the high absolute number of beneficiaries, there is a risk of a few serious adverse events in the vaccinated children.

National AEFI guidelines in India

There are two sets of national guidelines available in India. The detailed version is called “Operational Guidelines,” and

a shorter version is for “standard operating procedures.”¹² These guidelines, based on the WHO suggested framework,¹³ were developed through a consultative process with various stakeholders, including various Government departments involved in immunization program, state government program managers, academic institutions, independent subject experts, Drug Controller General of India officials, development partners, etc.

The AEFI reactions can broadly be classified as “serious AEFIs” (death, disability, cluster, and hospitalization) which need to be reported immediately and investigated as per the laid down procedures. The other, i.e., “minor AEFIs” are reported through monthly reporting systems in Universal Immunization Programme in Government of India. For the programmatic purpose, the AEFIs are classified in five broad categories of programmatic error, vaccine reaction, injection reactions, coincidental, and unknown.

Importance of AEFI

The vaccines are foreign for human bodies, given to healthy infants and children. In the natural process of developing immunity, a vaccine may cause fever, erythema, local pain, etc. Besides, there is a slight risk of foreign body reaction to the components in the vaccines. These factors are likely to cause some concerns in the caregivers/parents. Whatever the cause, an AEFI may upset people to the extent that they may refuse further vaccination for their children. This may lead to the children much more likely to get a vaccine-preventable disease, become seriously ill, disabled, and risk death. AEFI surveillance, therefore, helps to preserve public confidence in the immunization program. Though, the majorities of AEFIs are mild, settle without treatment, and have no long-term consequences; very rarely, serious adverse reaction can occur. The vaccination programs work in a “paradox” meaning thereby that the focus of attention changes with the implementation of immunization program-when the vaccination coverage increases and disease burden reduces drastically; more cases of the AEFI attract the attention of the people than the disease in the community.⁴

AEFI surveillance strengthening in India

AEFI surveillance in India started with the launch of UIP in 1985. However, the AEFI reporting remained suboptimal for long in the country. In 2005/2006, the Government of India, with technical assistance from the WHO/National Polio Surveillance Project India and other development partners, prepared the National AEFI Surveillance and Response Operational Guidelines. These guidelines were widely disseminated across the country among medical officers in Government sector. Since then many national, state and district level AEFI surveillance workshops for immunization program managers have been conducted. The national guidelines were further revised and updated in 2010. These efforts have contributed in improving AEFI surveillance in

India, and the country reported the highest ever number of serious AEFI in 2010 (395 versus 55 in 2006).

Aims and objectives

Since, no database was available in our college; the primary intent of the study was as follows:

1. To establish an active surveillance of vaccine-related adverse events among pediatric age group over a period of 2-month
2. To procure data pertaining to the vaccine-related adverse events
3. To observe the spectral variation in the vaccine-related adverse events in different strata (neonates, infants, children <5 years of age). The age wise distribution of the children is depicted in Figure 1.

METHODS

A prospective, single center, observational, naturalistic study on report forms in pediatric age group, who may develop AVE in Sathgiri Institute of Medical Sciences and Research Center, Bangalore, was conducted during the study time window, from February 20, 2014 to April 20th, 2014.

Data included the following information: type of vaccine received, date of vaccination, manufacturer, lot number, and injection site, onset of AVE, current illnesses or medication, history of adverse events following vaccination, concurrent vaccinations (those given during the same visit) and socio-demographic information about the recipient (age, gender) in a minimum sample size of 200 children (<5 years). The graphical distribution of the number of doses of vaccines administered is depicted in Figure 2

Selection criteria

Children under 5 years of age were included in the study. All children more than 5 years of age were excluded from the study.

The causality assessment were attempted to be recorded as per the Naranjo score, which is used to quantitatively evaluate the association between AVEs and vaccines. Furthermore, inter-group comparison with only suspected AVEs definable as certain, probable or possible were attempted to be included in the study though it was not necessary based on the review of certain articles. Statistical analysis of inter-group variability was also conducted. The common adverse event following immunization received in the study in depicted in Figure 3

RESULTS

As prophylactic vaccines are intended to be used in healthy people, their safety must be excellent to have a widespread, continuing acceptance.

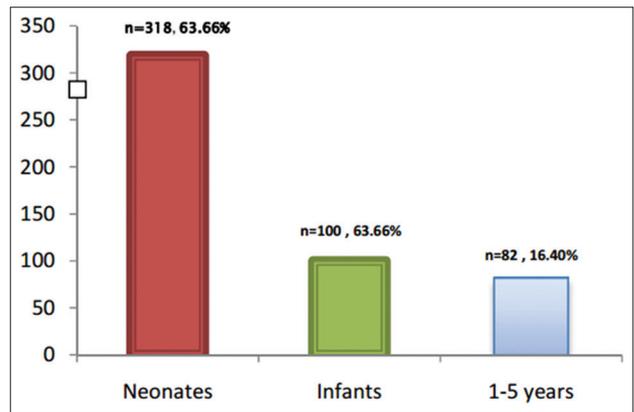


Figure 1: Age wise distribution of the children.

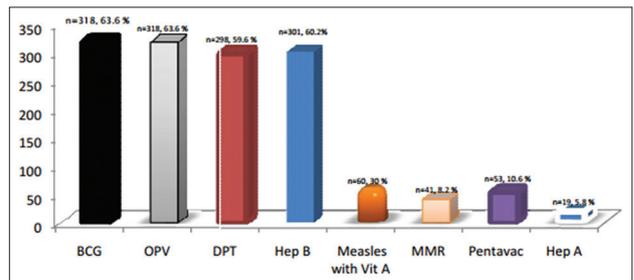


Figure 2: Distribution of number of doses of vaccines administered.

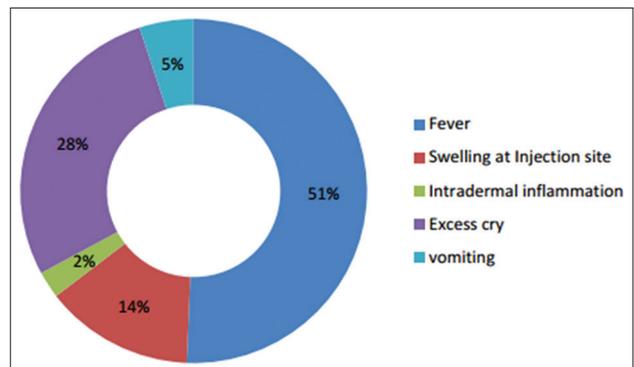


Figure 3: The common adverse event following immunization received in the study.

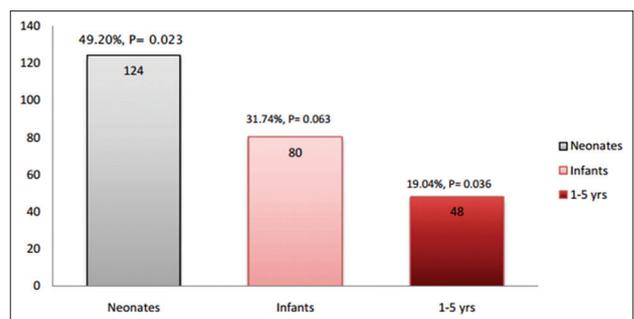


Figure 4: Graphical depiction of the spectral variation of the adverse event following immunization in different age groups with respect to the level of significance.

During our study period, active vigilance in the study window period was conducted in the medical college hospital with validated reporting forms.

A total of 500 reports were collected from the Pediatric Department during the study period though the minimum sample size that was expected was 200. On an average 20 reports were collected every week (on Thursdays, which was the vaccination day in our institution) and the parents were enquired through a single telephonic conversation next day after vaccination and also instructed to call back if any untoward reactions occurred.

Significance was also found in children aged 1-5 years of age with 19.04% of the children documented with AEFI ($p=0.036$). It was found that either a naïve or the fully immunized children suffered from the AEFI most of which was trivial.

DISCUSSION

The results obtained were the first of its kind to document the inter-age group comparisons among the children. It was found as per the study that a large number of the AEFI that are often missed can be documented by enquiring through a telephonic conversation. Fever was the most common AEFI reported followed by an excess cry. The incidence of fever reported was substantially high following the DPT vaccine.

In a study conducted by Klar et al., *Vaccine safety implications of Ontario, Canada's switch from DTaP-IPV to Tdap-IPV for the pre-school booster*, in the journal *Vaccine*, September, 2014, the incidence of AEFI (fever) reported was 33.1% while it was found to be 51% in our study.

In a study conducted by Thoon et al., *Active surveillance of adverse events following childhood immunization in Singapore*, *Vaccine*, September, 2014, the median interval from vaccination to symptom was 6 days. But in our study, it was in an interval of 1 day with maximum cases reported through the telephonic call. It was more so over with respect to fever the next day and excess cry on the same day of the vaccination. All the cases of AEFI recovered in our study compared to 98.8% in the study by Thoon et al.

The reporting of the AEFI through telephonic conversations was attempted in other studies. In a study conducted by Parrella et al., *Consumer reporting of adverse events following immunization (AEFI): identifying predictors of reporting an AEFI*. *Hum Vaccin Immunother*, 2014, Mar; 10(3):747-54. Epub 2014 Jan 9, the reporting of the AEFI was not associated with the awareness of active surveillance. However, it was found in our study that the parents/guardians were compliant in continuing the further doses of the vaccines that were given at scheduled intervals.

The BCG vaccination was safer in our study with no cases of regional lymphadenitis reported. Only insignificant

intra-dermal inflammation was reported (2%). However, in a study conducted by Soh et al., *Investigations into an outbreak of suppurative lymphadenitis with BCG vaccine SSI[®] in Singapore*, October 7, 2014, *Vaccine*, 32(44): 5809-15; it was found that there was a three-fold spike in the incidence of such adverse events.

It was thus found that there was a mild deviant trend in the reports obtained compared to the studies that were conducted in the current year (2014).

CONCLUSION

An active vaccine vigilance unit was established in the study period. Though the initial intended sample size was 200 for a period of 2-month was to be carried out, a total of 500 vaccinated children over a period of 2-month were included in the study. The number of AEFI that were documented was 252, which included fever, excess cry, injection site reactions, vomiting and intra-dermal inflammation. The common adverse event following immunization received in the study is depicted in Figure 3

It was found that fever was common with the DPT vaccines as was documented with the earlier and the contemporary studies. The Department of Pharmacology and the Department of Pediatrics coordinated in the initiation and continuation of the study. Statistical analysis was conducted only for the inter-age group variability and was found to be significant only in case of the neonates and the children aged 1-5 years. A plausible explanation for such a result could be because of either a naïve or an immature immune system. Thus, the spectral variation was highlighted in the study.

The overall purpose and objective of the study was to establish active vaccine vigilance and document the AEFIs received. Establishment of active vaccine vigilance and the post-licensure surveillance of AEFI is a fundamental and a pivotal activity to improve safety and maintain public, parental and the guardian confidence in vaccines.

Children <5 years of age were included in the study. All the AEFI received through the telephonic calls were documented. There was no mortality or a major adverse event reported. Maximum AEFI was documented in the neonates and the children 1-5 years of age which was statistically significant.

The study provides a scope for further research with reference to the inter-age group variability. The immune mechanism behind such a difference needs to be explored.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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