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Dr. Swati Deshpande
Principal Investigator,
Associate professor,
Department of Community
Medicine G.S. Medical College
& KEM Hospital Maharashtra,
India

Dr. Ashwini Sapkal
Junior Resident,
Department of Community
Medicine G.S. Medical College
& KEM Hospital Maharashtra,
India

Comparison of adverse events following immunization before and after introduction of pentavalent vaccine in children in an urban area: A retrospective study

Dr. Swati Deshpande and Dr. Ashwini Sapkal

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Abstract

Context: The Global Alliance for Vaccines and Immunisations (GAVI) and World Health Organization (WHO) recommended the use of pentavalent vaccine in developing countries to replace the DPT vaccine. The underlying reason was to be able to increase the uptake of the hepatitis B and Haemophilus influenza b vaccines in these countries. It is important to study the adverse events associated with the pentavalent vaccine, as it has been part of the national paediatric immunization schedule of India since 2014.

Aim: To study & compare Adverse Events Following Immunization before and after introduction of pentavalent vaccine in children under seven years of age.

Settings and Design: This retrospective cross-sectional study was conducted in District immunization office of a metropolitan city.

Methods and Material: Detailed records of 61 reported cases from District immunization office of a metropolitan city

Statistical analysis used: SPSS version 22.0.

Results: After introduction of pentavalent vaccine most frequent presentations were pain (36.1%), fever (36.1%), febrile seizures (30.5%), seizures other than febrile (22.2%) and local swelling (16.67%). In the groups before and after introduction of pentavalent vaccine respectively, 03 (12.0%) and 06 (16.7%) cases died, out of these 06 deaths, 04 (66.7%) were directly due to pentavalent vaccine.

Conclusions: There was an increase in unexplained deaths after introduction of pentavalent vaccine (Age group – 0 -24 months). Hence, it is recommended that rigorous research should be conducted to increase the investigations and reporting of AEFI cases associated with pentavalent vaccine.

Keywords: AEFI, pentavalent vaccine, immunization

Introduction

According to WHO reports, immunization has led to increase in life expectancy, reduction in mortality and morbidity of infectious diseases^[1]. In India millions of doses of vaccines are administered annually^[2].

The GAVI and WHO recommended the use of pentavalent vaccine in developing countries to replace the DPT vaccine. The underlying reason (as per GAVI website) was to be able to increase the uptake of the hepatitis B and Hib vaccines in these countries.^[3, 4] Following introduction of pentavalent vaccine the countries like Bhutan, Sri Lanka and Pakistan observed unexplained deaths after immunization^[5, 6, 7]. This brings us to study the AEFI related to Pentavalent Vaccine.

Aim and Objectives

The aim of this study was to compare Adverse Events Following Immunization before and after introduction of pentavalent vaccine in children under seven years of age.

Our specific objectives were to study the socio-demographic profile of children who reported with signs and symptoms before and after introducing Pentavalent Vaccine, assess the pattern of occurrence of AEFIs following introduction of pentavalent vaccine and to suggest recommendations based on study findings.

Corresponding Author:
Dr. Ashwini Sapkal
Junior Resident,
Department of Community
Medicine G.S. Medical College
& KEM Hospital Maharashtra,
India

Subjects and Methods**Study Design:** retrospective cross-sectional study.**Total Study Period:** 2 months**Study Area:** District immunization office, EPI (Extended Programme of Immunization) department of a metropolitan city.**Sample Size:** On the basis of records available the sample size is **61**. This includes the AEFI cases from 22th November 2014 to 21st November 2016.**Study Subjects:** All AEFI cases notified in the F South ward office.

For present study two groups were considered:

Group A: 1 year before introduction of Pentavalent vaccine [N=25] i.e. 22th November 2014 to 21st November 2015.**Group B:** 1 year after introduction of Pentavalent vaccine [N=36] i.e. 22th November 2015 to 21st November 2016.**Sampling Method:** Complete Enumeration method.**Inclusion Criteria:** 1. Study subjects having complete data.
2. Study subjects < 7 years of age**Exclusion Criteria:** Adverse events caused by vaccines which were not included in Universal Immunization schedule.**Ethical Consideration:** Approval for the study was taken from Ethical Committee of the institute. (EC/OA-72/2018) Assurance was given that confidentiality will be maintained.**Study Procedure:** Permission to conduct the study was obtained District immunization office. Approval for conduction of the study is taken from ethical committee of the institute. The sample size being 61, the study tools has been analysed as per available records. Data pertaining to reported all the AEFI cases of city were collected from EPI (Extended Programme of Immunization) District immunization office of a metropolitan city for the period of January 2014 to December 2016.**Study Tools:** The case reports from the year 22th November 2014 to 21st November 2016 of all AEFI cases were procured and analysed to identify factors associated with reported AEFI. The (CRF) case reporting form, (PCIF) preliminary case investigation form, (FCIF) final case investigation form and verbal autopsy were analysed. Data from PCIF includes-Section A – Basic Details, Section B - Relevant patient information prior to Immunization, Section C – Details of first examination of reported AEFI case. Data from CRF includes Immunization status, Data from FCIF includes Details of hospitalization and Data from Verbal Autopsy Form included Provisional Diagnosis. All the responses were tabulated & graphically represented wherever required. Descriptive statistic was calculated and discussed for the different variables under study including the pattern of occurrence of AEFI cases after the introduction of Pentavalent vaccine. Chi-square test was applied to find out association between demographic characters and outcome.**Results**

In present study a total of 61 AEFI cases were enrolled. Out of those 25 cases were before pentavalent and 36 cases were from after introducing of pentavalent.

Table 1: Demographic Profile of Cases of before and after introducing Pentavalent Vaccine

Particular	1 year before Pentavalent [N=25]	1 year after Pentavalent [N=36]
Age-Group	0-6 Months	12 (48.0%)
	7-12 Months	01 (4.0%)
	13-24 Months	08 (32.0%)
	25-48 Months	01 (4.0%)
	> 48 Months	03 (12.0%)
	Mean±SD	16.48±19.20 Months
Gender	Male	15 (60.0%)
	Female	10 (40.0%)

- Out of 25 cases before introduction of Pentavalent vaccine 12 cases (48.0%) were from age-group of 0-6 months and 01 case (4.0%) from age-group of 7-12 months and 25-48 months.
- Similar findings were noted in cases after introduction of pentavalent vaccine. Out of 36 cases-19 cases (52.8%) were from age-group of 0-6 months and 01 case (4.0%) from age-group of 25-48 months.
- In both the groups, 15 (60.0%) and 21 (58.3%) cases were males, respectively from the groups before and after introduction of pentavalent vaccine.

Table 2: Determinants associated with AEFI

	1 year before Pentavalent [N=25]	1 year after Pentavalent [N=36]
Past history of similar events	01 (4.0%)	00
Adverse events after previous vaccination (s)	00	00
History of vaccine, drug and food allergy	00	00
Pre-existing illness (past 30 days)	04 (16.0%)	03 (8.3%)
Congenital Disorder	00	01 (2.8%)
History of hospitalization in past 30 days	01 (4.0%)	00
Was the patient on any concomitant at the time of AEFI	00	00
Family history of any disease (relevant to AEFI) or allergy	01 (4.0%)	01 (2.8%)

- Pre-existing illness was reported in 04(16.0%) cases before introduction of and 03 (8.3%) cases after introduction of pentavalent vaccine.
- 1case (4.0%) each reported past history of similar events, required hospitalization in past 30 days and family history of any disease (relevant to AEFI) or allergy in the group before introduction of pentavalent vaccine.
- 01 case (2.8%) was known case of congenital disorder and 01 (2.8%) cases reported family history of any disease (relevant to AEFI) or allergy in the group after introduction of pentavalent vaccine.

Table 3: Sign & Symptoms in Children

	1 year before Pentavalent [N=25]	1 year after Pentavalent [N=36]
Pain	01(4.0%)	13(36.1%)
Swelling	01(4.0%)	06(16.67%)
Redness	01(4.0%)	05(13.9%)
Fever (temp >38 c)	18(72.0%)	13(36.1%)
Irritability	13(52.0%)	08(22.2%)
Malaise	0	6(16.7%)
Febrile seizure	19(76.0%)	11(30.5%)
Muscle Pain	01(4.0%)	00
Headache	03(12.0%)	00
Loss of appetite	00	00
seizure	16(64.0%)	08(22.2%)
Allegoric Reactions	01(4.0%)	00
Other	00	07(19.4%)

- In the group before introduction of pentavalent vaccine 19(76.0%) reported Febrile seizures, 18(72.0%) were having Fever (temp >38 c), 16(64.0%) were having seizures other than febrile.
- In the group after introduction of pentavalent vaccine 13(36.1%) reported Fever (temp >38 c) and pain, 11(30.5%) were having Febrile seizure and 8(22.2%) reported irritability and seizures other than febrile.

Table 4: Hospitalization required and outcome of cases

	1 year before Pentavalent [N=25]	1 year after Pentavalent [N=36]
Hospitalization required	23 (92.0%)	34 (94.4%)
Died	03 (12.0%)	06 (16.7%)

- 23 (92.0%) cases and 34 (94.4%) of cases required hospitalization before and after introduction of pentavalent vaccine respectively.
- In the groups before and after introduction of pentavalent vaccine respectively, 03 (12.0%) and 06 (16.7%) cases died, out of these 06 deaths, 04 (66.7%) were directly due to pentavalent vaccine.

Discussion

In this present study, adverse effects before and after introducing of pentavalent vaccine were common in age of 0-24 months.

The results obtained in the present study showed that the most frequently reported reactogenicity associated with pentavalent vaccine was pain and Fever (temp >38 c), cases were having pain with an incidence rate of 36.1%. This finding is in line with the results obtained by Edna in his meta-analysis, in which some minor reactions such as pain

and redness were more prevalent among the children who received the combined vaccine.^[8] The results of a study conducted in China revealed that the majority of the adverse events following immunization were reported to be non-serious events; fever and injection site reaction were the most common forms of reactogenicity experienced after immunization^[9]. Moreover, in other Iranian studies on the adverse events associated with DTP and pentavalent vaccination, mild fever was found to be the most commonly experienced complication that occurred after vaccination^[10, 11, 12].

In present study, Out of 25 cases in the group before introducing Pentavalent vaccine, 03 (12.0%) died. whereas this no. was 06(16.7%) in the group after introducing of pentavalent vaccine. Out of these 06 deaths, 04(66.7%) indirectly due to pentavalent vaccine.

Similar findings were noted in a retrospective cohort study where Sadoh AE *et al*^[13] have compared the prevalence of adverse events following pentavalent and DTP vaccines in Nigeria. They reported that the rate of pentavalent-related adverse reactions was higher than DTP (22.2% vs. 13.5%). Before being introduced in India the pentavalent vaccine was introduced in Srilanka and Bhutan. In both these countries, use of this vaccine was found to be temporally associated with AEFI including unexplained deaths [14].

A trial on pentavalent vaccine was conducted in Kerala. The probability that a cluster of sudden infant death syndrome (SIDS) following immunization had occurred by chance In the case of the deaths following the pentavalent vaccine, the estimated SIDS rate is five times greater than the all-cause mortality rate of the state. The majority of deaths after the administration of the pentavalent vaccine have followed the first dose. This pattern of the adverse events taking place predominantly after the first dose also suggests that these are non-random events, nor can they be explained by SIDS, which actually peaks in the third month of life^[15].

India introduced pentavalent vaccine from Serum Institute of India (Pentavac) in December 2011. Up to the first quarter of 2013, 83 serious AEFI were reported, some of which were associated with fatality. Government of India, has reported 4.7 additional deaths (95% CI: 3.5-5.9) within 72 hours of immunization, per million vaccinated with Pentavalent vaccine compared to children receiving DPT instead ($P < 0.0001$). Using data from states with good reporting of adverse events, we estimate that there are likely to be 7020–8190 additional deaths each year in the country, because of the shift from DPT to Pentavalent vaccine. This is a huge mortality burden. These findings were correlating with present study finding of deaths after introducing of pentavalent vaccine group^[16].

The majority of deaths after the administration of the pentavalent vaccine have followed the first dose. This pattern of the adverse events taking place predominantly after the first dose also suggests that these are not random events, nor can they be explained by sudden-infant-death-syndrome (SIDS), which actually peaks in the third month of life (when most babies are likely to be getting their second dose of immunisation).

It is said that the deaths associated with pentavalent vaccine are merely coincidental SIDS deaths, associated temporally with immunization and they are unrelated to vaccination and the vaccine used^[14].

Conclusion

- Adverse effects following immunisation of pentavalent vaccine were common in age 0-24 months.
- Most frequent presentations were pain (36.1%), fever (36.1%), febrile seizures (30.5%), seizures other than febrile (22.2%) and local swelling (16.67%).
- From this study it is concluded that there is probable increase in unexplained deaths after introducing of pentavalent vaccine, 04 (66.7%) deaths were due to pentavalent vaccine itself.
- Hence it is recommended that rigorous research should be done on population-based investigations on AEFI of pentavalent vaccine.

Recommendation

1. Stringent and precise instructions should be given for reporting of data for AEFI related to pentavalent vaccine.
2. History of pre-existing illness and past history of AEFI should not be missed by person immunizing the child because these are the main factors contributing to mortality observed in present study.
3. Regular refresher trainings of all the health care personnel should be held to reduce AEFI.
4. More such studies should be conducted in various regions to have generalized recommendations on this issue.

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