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Original Research Paper

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THE INCIDENCE OF ADVERSE REACTIONS DUE TO NEWER VACCINES IN RURAL TERTIARY CARE TEACHING HOSPITAL: A PHARMACOVIGILANCE STUDY

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ABSTRACT Immunization constitutes one of the most operative and modern public health measures for preventing serious diseases. Drugs are given for therapeutic purposes to diseased patients but vaccines are the modern tools for prevention of healthy individuals from diseases. Therefore, it is highly expected that, vaccines are much safer as compared to drugs. Newer vaccine as per some studies claimed to be responsible for though rare but serious adverse reaction and Clinical trials are not enough to suggest less risk of adverse reaction so post- licensure studies are advised in India and other countries. A total of 1116 children participated in the study. Out of these 567 (50.8%) were girls and 549 (49.1%) were boys. Overall total of 2598 doses of vaccines were administered to participants. These vaccines are MMR, Rotavirus, Inactivated Polio Vaccine (IPV), Pneumococcal and Hib vaccines. A total of 221 non-serious suspected adverse reactions are found in our study.

KEYWORDS : Vaccines, Adverse Reactions, WHO, UNICEF.

Introduction

"Immunization has been great public health success story, the lives of millions of children have been saved, millions have the chance for a longer, healthier life, a greater chance to learn, to play, to read, to write, to move around freely without suffering". Nelson Mandela 2002, chair vaccine fund board. [1] Modern immunization developed in India in 19th century, parallel to the Western world. By early 1970s, many childhood diseases had almost disappeared from developed countries. But scenario was not the same for poorer countries like India. in 1974, fewer than 5% of children, worldwide were immunized by one year of age against diphtheria, polio, tuberculosis, pertussis, measles, and tetanus.[2] That's why WHO launched the Expanded Programme on Immunization (EPI) in 1974 to bring vaccination against these six diseases to many underserved areas. India launched its first vaccine more than 50 years back: BCG in 1962 [3] as a part of National Tuberculosis Program. In last 2 decades, there were lots of administrative changes in UIP. It was given status of National Technology Mission in 1986 to give a sense of urgency and commitment in achieving the goals; then it was made part of Child Survival and Safe Motherhood (CSSM) programme in 1992 and Reproductive and Child Health (RCH) programme in 1997.[4] In 2012 Government of India declared 2012 as "Year of Intensification of Routine Immunization". In 2013**,** India along with other South-East Asia Region, declared commitment towards measles elimination and rubella/congenital rubella syndrome (CRS) control by 2020. In 2014, India had a historic achievement and was certified as "polio free country" among South EastAsia Region (SEAR).[5]

Vaccine preventable diseases protected by vaccination under universal immunization programme are: Diphtheria, Pertussis, Tetanus, Tuberculosis, Measles, Hepatitis B, Japanese Encephalitis (commonly known as brain fever), Meningitis and Pneumonia caused by Haemophilus Influenza type B. [5] In 2014, the number of reported cases of diphtheria, Japanese encephalitis, Measles, Pertussis, Polio, Rubella, Neonatal tetanus and total tetanus are 6094, 1657, 24977, 46706, 0, 4870, 492, 5017 respectively.[6] According to the most recent nationwide Coverage Evaluation Survey(CES), covering all States and Union Territories of India, conducted during November 2009 to January 2010 by UNICEF, the national fully immunized (FI) coverage against the six vaccines included in UIP in the age-group of 12-23 month old children are 61% whereas it was 54.1% and 47.3% as reported by District Level Household and Facility Survey (DLHS-3) (2007-08) and National Family Health Survey (NFHS-III) (2005-06), respectively.[5,7]

For Maharashtra it is reported to be 69.0 % and 78.6% as per District Level Household and Facility Survey (DLHS-3) (2007-08) and Coverage Evaluation Survey (CES) (2009) respectively. Vaccine unacceptance by people may obstruct victory of an immunization programme.[8,9] AEFI is a medical event that takes place after an immunization that causes concern and is believed to be caused by immunization.[10,11] Government of India has given operational guidelines for adverse events following immunization surveillance and response. It includes data on vaccines under UIP. But many newer combination vaccines like pneumococcal vaccine, IPV vaccine which are suggested by IAP and followed by members of IAP; are still less studied. Thus very less data is available on newer and combination vaccines and many studies are needed related to pharmacovigilance of adverse reaction due to these vaccines. It will benefit the society by building up confidence in people about safety of vaccination and maximum coverage of pediatric age group.

Material and method

The study was carried out at Department of Pharmacology, M.G.I.M.S.Sewagram(Wardha). The study was approved by Institutional Ethics Committee and verbal informed consent taken from children' parents. This population comprised of children aged 0 to 14-year attending pediatrics department (OPD) in a Rural Tertiary Care Teaching Hospital, for vaccination. The children were accompanied by parent or guardian who, after giving his/her informed oral consent, agreed to take part in the study.

The numbers of adverse event reports were calculated in five age groups:
0-1 month (neonates),
1–12 months (infants),
1–3 year (toddler),
3–6 year (pre-school)
And 6-14 year (school going).

Each child's detail record book was maintained which contained, name, age, sex, birth weight, contact number, address, name and batch number of vaccine(s) and history of previous vaccination. A two-phase telephone survey of parents or guardians was

conducted, consisting of an initial call at one week and a second call at 30 days after the vaccine administration date. The parents of children were questioned about the appearance of any type of reaction that had followed administration of the vaccine. This list of most frequent expected adverse reactions was drawn up from the classifications used by the Vaccine Adverse Event Reporting System(VAERS).[12] The VAERS form was used to record the adverse reaction.[13] Data was evaluated according to patient demography, nature of the reaction, vaccine suspected for adverse reaction. Causality and seriousness of adverse reaction was assessed using World Health Organization guidelines.

RESULTS AND OBSERVATIONS

A total of 1116 children participated in the study. Out of these 567 (50.8%) were girls and 549 (49.1%) were boys. Overall total of 2598 doses of vaccines were administered to participants. These vaccines are MMR, Rotavirus, Inactivated Polio Vaccine (IPV), Pneumococcal and Hib vaccines. A total of 221 non-serious suspected adverse reactions (out of total 1116 children who participated in study) were detected for 2598 doses of vaccines administered i.e. 44.3 adverse reactions per 1000 doses of vaccines. Of these adverse reactions to vaccines, 47.3% occurred in girls and52.7% in boys which was statistically not significant. All reactions were reported at the time of the first telephone call. Most of the adverse reactions appeared in 1–12 months' group (infants), followed by0-1-month group (neonates). Out 221 AR, 137 (62.1%) AR were noted in 1-12 months of age group of children followed by 72 (32.6%) AR were noted in 0-1 month of age group. But according to rate of adverse reactions per 1000 doses of administered vaccine, most common is Hib vaccine (548), followed by Pneumococcal vaccine (148), MMR vaccine (101.4), Inactivated Polio Vaccine (IPV) (14.6), and Rotavirus (0.8) with least rate of adverse reaction.

Vaccine Administered	Total no. of doses of vaccines Administered	Total no of children received vaccines	No.of Adverse Reactions (AR)	Rate per 1000 doses Administered
MMR	345	216	99	101.4
Rotavirus	1209	483	2	0.8
IPV	888	358	23	14.6
Pneumococcal	94	38	26	148
Hib	62	21	71	548
Total	**2598**	**1116**	**221**	

MMR vaccine and its adverse reactions: -

Total 216 participants received MMR and total doses received were 345.Total 99 adverse reactions out of total 221, were due to MMR. Out of total 99 adverse reactions, most common is pain at injection site (20), followed by redness at injection site (17), and measured temperature indicating fever of 39 - 40.50 degree Celsius (17).

Rotavirus Vaccine and its adverse reactions: -

Total 483 participants received Rotavirus vaccine and total doses received was 1209. Only 2 adverse reactions out of total 221, was due to rotavirus vaccine. There are only two adverse reactions due to Rotavirus Vaccine and that is Episodes of screaming/ Persistent crying (02).

Inactivated Polio Vaccine (IPV) and its adverse reactions: -

Total 358 participants received Inactivated Polio Vaccine (IPV) and total doses received were 888. Total 23 adverse reactions out of total 221, was due to Inactivated Polio Vaccine (IPV). Out of total 23 adverse reactions, most common is Pain at injection site (11), followed by swelling at injection site (04) and abscess at injection site (04).

Pneumococcal Vaccine and its adverse reactions: -

Total 38 participants received Pneumococcal vaccine and total doses received were 94. Total 26 adverse reactions out of total 221, were due to Pneumococcal vaccine. Out of total 26 adverse reactions, most common is pain at injection site (09), followed by swelling at injection site (06) redness at injection site (04) and abscess at injection site (04).

Hib Vaccine and its adverse reactions: -

Total 21 participants received Hib vaccine and total doses received were 62. Total 71 adverse reactions out of total 221, were due to Hib vaccine. Out of total 71 adverse reactions, most common was redness at injection site (13), followed by pain at injection site (10), nodule at injection site (10) and swelling at injection site (08).

DISCUSSION

Immunization in India has been at crossways as newer vaccines are being regularly licensed in the country. All vaccines do have inherent risk of AR, but the benefits are undoubtedly immense, and clearly outweigh the risks. Although there is some research done on the AR due to newer vaccines in west, similar studies in Indian scenario is still in its early period. The comprehensive studies on adverse reaction profiles of various newer vaccines are very rare.

Hib Vaccine

In our study among the adverse reaction due to Hib vaccine, most common is redness at injection site, followed by pain at injection site, nodule at injection site and swelling at injection site. In the study of Adverse events following Haemophilus influenzae type b vaccines in the Vaccine Adverse Event Reporting System by Moro PL, Jankosky C, et al reported 29,747 reports after Hib (Haemophilus influenzae type b) vaccines; 5179 (17%) were serious, including 896 reports of deaths. But in our study all adverse reactions are non-serious in nature and there are no deaths reported.[14] As per centers for disease control and prevention, most common adverse reactions following Hib (Haemophilus influenzae type b) vaccine are redness, warmth, or swelling from the shot and fever [15].

Pneumococcal vaccine

PCV13 vaccine (Prevnar 13) is used for vaccination in our study. This is a new 13-valent conjugate vaccine (PCV13) which was launched in India in mid-2010.[16] In our study most common adverse reactions are local reactions viz. pain at injection site, followed by swelling at injection site, redness at injection site and abscess at injection site. All are of non-serious nature. As per centers for disease control and prevention, the most common adverse reactions with PCV13 include local reactions, such as erythema, swelling, pain at the injection site, and limitation of movement of the arm in which the injection was given.[17,18,19] This is comparable with our study. Centers for disease control and prevention official site states that the safety of PCV13 was assessed in 13 studies in which over 4,700 healthy infants and toddlers were administered at least 1 dose of PCV13.The most commonly reported (more than 20% of subjects) adverse reactions were injection-site reactions.[20] This is also comparable with our study.

MMR vaccine

Formulations from different manufacturers have different strains of the vaccine virus. Mumps vaccine virus strains include Leningrad-Zagreb, Leningrad-3, Jeryl Lynn, RIT 4385 or Urabe AM9 strains and are grown in chick embryo/human diploid cell cultures. In our study, among adverse reactions due to MMR vaccine, most common is Pain at injection site, followed by redness at injection site, measured temperature indicating fever of 39 - 40.50 degree Celsius. This is comparable to the statements in official site of Center for Disease Control and Prevention (CDCP), which states that common side effects due MMR vaccine are Sore arm from the shot and Fever. We got most common adverse reaction as pain at injection site.[21] CDCP also states that MMR vaccine has been linked with a very small risk of febrile seizures (seizures or jerking caused by fever). Other rare adverse reactions may be swelling in the cheeks or neck, temporary low platelet count, serious allergic reaction due to MMR vaccine. But in our study, there is no febrile seizures, swelling in the cheeks or neck, temporary low platelet count, serious allergic reaction due to

MMR vaccine reported.[21] In the study conducted by Esteghamati A, Keshtkar A, et al on adverse reactions following immunization with MMR vaccine in children at selected provinces of Iran, trained providers reported 792 AEFIs. Parotitis was the most frequent event in their study. But in our study, there is no adverse reaction as parotitis. That may be because parotitis / swelling in the cheeks are rare adverse reaction due to MMR.[21]

Inactivated Polio Vaccine (IPV)

In our rural setup, POLPROTEC [Inactivated Poliomyelitis Vaccine (IPV)] is used. POLPROTEC [Inactivated Poliomyelitis Vaccine (IPV)] is a trivalent vaccine containing an aqueous suspension of Poliovirus Types 1, 2 and 3 (Salk strains) grown in Vero Cell Culture.As per stated in official website of MIMS, the trial had been conducted to compare the immunogenicity and safety of Polprotec with a WHO prequalified vaccine. In this study 575 subjects received at least 1 dose of thevaccine, and post vaccination adverse events were recorded. Among the reported adverse reactions due to Polprotec (IPV), most common were pain at the injection site, erythema and swelling. [22] This is in agreement with our study where the common reported adverse reactions due to Polprotec (IPV) are pain at injection site, swelling at injection site and redness at injection site. Ruuskanen O, Salmi TT, et al had conducted study on adverse reactions and antibody responses of Inactivated polio vaccine in 380 children. They reported fever and irritability as most common adverse reactions. [23] But in our study, fever and irritability due to IPV are not reported adverse reactions. This may be because these are rare adverse reactions due to Polprotec as stated in official MIMS web site. [22]

Rotavirus Vaccine

Currently three live oral vaccines are licensed and marketed worldwide, human monovalent live vaccine and human bovine pentavalent live vaccine and Indian neonatal rotavirus live vaccine, 116 E. In our rural setup, Indian neonatal rotavirus live vaccine, 116 E (ROTAVAC®) is given, which is developed by Bharat Biotech of India. It is launched on 09/03/2015. (24) The randomized, double-blind, placebo-controlled phase III efficacy clinical trial that began in March 2011, enrolled 6,799 infants of six to seven weeks' age at three sites in India. The results of this trial demonstrated good efficacy and a good safety profile; the trial was also approved by the Data Safety Monitoring Board (DSMB). [25] During this Phase 3 clinical trials of the vaccine, infants receiving ROTAVAC® did not experience a significantly higher level of adverse events compared to infants receiving placebo. [26] At its meeting in June 2014, the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety profile of ROTAVAC® using this clinical trial data. Because no cases of intussusception occurred in proximity to the time of vaccination, GACVS noted that the available evidence "argues strongly against" a causative relationship between ROTAVAC® and intussusception and concluded that it supports further use of the vaccine.[27] This is in agreement with our study in which we don't get any intussusception cases as adverse reaction due to ROTAVAC®.

Summary and Conclusion

As vaccine-preventable infectious diseases keep on declining, community have become more and more concerned about the risks related with vaccines. Technological advances and continuously increased knowledge about vaccines have led to the need of focused investigations on the safety of existing vaccines which have sometimes shaped an atmosphere of apprehension. In addition, there are some newer vaccines which came into force recently, creating the matter of public concern, as less studies available on adverse reactions due to these vaccines.

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