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ADVERSE EVENT FOLLOWING PENTAVALENT IMMUNIZATION IN 6, 10 AND 14 WEEK.

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ABSTRACT

Introduction: Despite the limited data on adverse events following immunization (AEFIs), these events are thought to contribute to vaccine hesitancy. This study aims to thoroughly examine the practices surrounding the reporting and management of AEFIs, providing insights into their potential impact on public trust in vaccines.

Method: This prospective mixed-methods study included 457 in-person interviews with caregivers, 8 key informant interviews, and 7 focus group discussions. Caregivers were recruited at or before their child's 6-week clinic visit and were then evaluated for the presence of AEFIs during subsequent appointments at 10 and 14 weeks, as well as through a follow-up call two weeks after the 14-week visit.

Result: Out of 209 children, 91 (43.5%) received scheduled vaccinations, with follow-up rates of 8.6% at 6 weeks, 41.6% at 10 weeks, and 8.1% at 14 weeks, while 41.6% completed all follow-ups. Common symptoms included pain, fever, and redness, affecting 25.4% of children, with 68.4% requiring medication and most recovering within 5 to 10 days. Notably, 98.6% of the reported cases were duplicates, leaving only 1.4% as primary cases.

Conclusion: The study's findings reaffirm the safety and effectiveness of vaccines, demonstrating that while mild to moderate adverse events such as pain, fever, and redness were common, they were generally manageable and led to full recovery within a short period. The low incidence of severe adverse events underscores the importance of ongoing surveillance and transparent communication with caregivers to maintain public trust in vaccination programs. Overall, the benefits of vaccination significantly outweigh the risks, supporting its continued use as a vital public health measure.

Keywords: immunization, vaccine, adverse events.

INTRODUCTION

The biological component of vaccines causes adverse events following immunization. Adverse events of DPTw, hepatitis B, Hib PRP-T were monitored closely because these vaccines were manufactured by Serum institute of India and was introduced in Iran in November 2014. For vaccine safety it is important to observe vaccine related adverse event. 1119 children were used in mixed cohort study. Children of 2,4- and 6-months age group were referred to Hammad hospital for pentavalent vaccine. Those parents were included in study to whom questionnaire was given and data were collected face to face or by phone. Risk ratio and adverse event were reported by 95% confidence interval cumulative incidence. Association between variable was investigated by using chi square and logistic regression analysis. The cumulative incidence rate of adverse event after 48 hours of pentavalent administration 12.6% was mild fever, 15% loss of appitite,15.8% swelling,10.9% redness,5.5%persistent crying. There was no evidence of encephalopathy and convulsions with pentavalent vaccine(1) To assess ten-year efficacy and immunogenicity two doses of measles, mumps, rubella and varicella vaccine and one dose of monovalent varicella vaccine were administered in children from Czech Republic, Poland, Slovakia, Romania and Lithuania. Twelve to twenty-two months old children were taken from 10 countries of Europe and were randomized in 3:3:1 for receiving two doses of MMRV, two doses of measles mumps rubella and one dose of MMR+vericella or two doses of control group of measles mumps rubella. Vaccine efficacy of varicella was calculated by 95% CI with the detection of epidemiological clinical assessment or viral DNA detection by using Cox proportional hazards regression model 42 days apart. Assessment of immunogenicity was assessed as geometric mean concentration and seropositive rates. Serious adverse event and adverse events were recorded. Total number of children who were vaccinated were 3705 out of which 1590 were MMRV group, 529 were MMR group and 1586 were MMR+V group. Confirmed varicella cases were 663. Varicella adverse event were 97.4% and 95.4% in Slovakia and Lithuania respectively measles mumps and rubella group. In measles mumps rubella+ varicella group 74% and 59.3% in Slovakia and Lithuania respectively. Seropositivity rates in MMRV group were 99.5% to 100%, 98% to 100% in MMR+V group and 50% to 100% in MMR control group at ten years. It was concluded that two doses of varicella zoster provided better protection than one dose of varicella zoster (2)The surveillances on adverse event following pentavalent vaccine (Diphtheria, tetanus, pertussis, poliomyelitis, Hemophilus influenza type) was done in China and also determined reporting level of adverse event following DPT Hib and IPV was higher than other vaccine. In Zhejiang adverse event following immunization were reported to National Event Following Immunization Surveillance System from 2015 to 2020.Adverse event following immunization reporting rates were calculated by age, AEFI severity, city, category of adverse event following immunization. Reporting odds ratio was used and value-1.96SE >1 [SE]) was taken as positive signal. 5726 adverse event following immunization reports followed DTP-IPV/Hib, with 20.01/10000 doses reporting rate, 202 reported adverse event following immunization were vaccine related serious reactions. , including five cases of Guillain Barre Syndrome, two cases of anaphylactic shock and two cases of acute disseminated encephalomyelitis.Fevere, induration and redness were highest among reported cases. For allergic rash (ROR-1.96SE: 1.36), Guillain Barre Syndrome (ROR-1.96SE: 1.16), febrile convulsion (ROR-1.96SE: 1.32) positive signals were obtained. The conclusion was that the four-dose schedule of DTP-IPV/Hib administration was well tolerated in Chinese children as no adverse event which was life threatening or needed hospitalization was observed during six-year time period(3). In 1974 live attenuated vaccine was developed by Michiaki Takahashi and it was herpes virus vaccine. The vaccine was used on immunosuppressed patients rigorously because of life threatening varicella risk in immunocompromised patients. Varicella vaccination proved lifesaving vaccine. Varicella vaccine in healthy children was found safe and it became component of mumps, measles and rubella. In USA two doses of this vaccine were given to children which dropped incidence of varicella among children in USA. Varicella vaccine also reduced incidences of zoster in adults and it is also protective in immunocompromised adults. Immunocompromised get protection due to development of herd immunity. Cell mediated and antibody mediated response are produced after varicella zoster virus or after immunization. The presence of antibodies plays an important role to prevent second attack of

varicella vaccine but antibodies don't have enough role in varicella zoster vaccine recovery. Antibodies don't persist throughout in body they appear in blood when individual develop varicella zoster(4). Vaccine related adverse events have been main matter of concern for the public and for the physicians and it is assumed that adverse reaction is due to nature of wild type of live attenuated vaccine. Anaphylaxis after administration of live attenuated vaccine and influenza vaccine, febrile illness after immunization, aseptic meningitis after administration with measles, mumps and rubella after immunization with live virus vaccines, neurological illness associated with pain after administration of human papilloma virus vaccine. Immunization helps in stimulation of innate immunity which in response activate acquired immunity. Acute disseminated encephalomyelitis and idiopathic thrombocytopenic purpura are those adverse events which are associated with autoimmune response. Adverse event following immunization were investigated for systemic reactions, local reactions and anaphylactic reactions. For the development of acquired immunity initiation of initial response is essential(5). Most common cause of severe diarrhea is Rota virus. Two type of Rota vaccine have been licensed Rotate and Rotarix. The main objective was to contribute post vaccine safety evaluation and for this purpose all adverse event following immunization of all Rota vaccine from United States Adverse event reporting system and VigiBase were collected between January to December 2007 to 2017.Reporting odds ratio was performed for analysis. In Vaccine Adverse Event Reporting System 17,750 reports and in VigiBase 6,358 reports were retrieved. 86.2% reports are concerned with RotTaq in Vaccine Adverse Event Reporting System and 67.7% of them in VigiBase related to Rotarix. The most important adverse event following immunization were and vomiting. Diarrhea was 1672 in Vaccine Adverse Event Reporting System and 1961 in VigiBase and vomiting was reported 1746 in Vaccine Adverse Event Reporting System and 1508 in VigiBase. In both database Rota virus vaccine intussusception was ROR was greater than 20. Potential safety signals like livedo reticularis, opisthotonus, bulging fontanelle and hypotonic-hyperresponsive episode(6). For the assessment of four-component meningococcal serogroup B vaccine co-administration and other vaccine interaction causing increased risk of adverse event following immunization compared with separate administration at different visits and also assessment of risk of recurrence of adverse event following immunization. In Europe three randomized control trials were done. 5026 total healthy participants were taken who were falling in two months and fifteen months age group. Interventions of routine vaccines and four-component meningococcal serogroup B vaccine were administered separately one month apart in regular 2,4,6, and 12 months delayed 2 doses of four-component meningococcal serogroup B vaccine more than or equal to 12 months of age and accelerated schedule of 2,3,4 and 12months or concomitantly. Fever was primary outcome which was more than or equal to 38C during first 48 hours after immunization and secondary was diarrhea, change in eating habits, irritability, tenderness and crying at the administration of four-component meningococcal serogroup B vaccine (4CMenB). Incidence of fever was reduced less than or equal to 38C, 75% versus 86% and also other systemic adverse event following immunization. Incidence of injection site tenderness with four-component meningococcal serogroup B vaccine (4CMenB) was increased 66% versus 55% with concomitant administration as compared to separate administration. Moderate to severe fever was long lasting more than 1-day fever. Infants with prior adverse event following immunization have reduced risk of adverse event following immunization with co administration of vaccination. Fever proportion was 79% at 2nd dose with one prior episode, at 3rd dose 44% and 74% with one and two prior episodes respectively, and on 4th dose 29%,45% and 60% with one, two and three prior episodes. The cumulative adverse event following immunization with separate and concomitant administration of four-component meningococcal serogroup B vaccine (4CMenB) and routine vaccines were reduced. The infants who had faced adverse event following immunization after immunization were at the higher risk of same adverse event after subsequent immunization but severity was lesser than before(7).

METHODS

Study design and settings

This prospective mixed-methods study included both qualitative and quantitative research techniques and was carried out at 10 immunizing health facilities in hospital settings in Karachi. The lead investigators and co-authors, who were the study collaborators, oversaw the whole data collection, facility visits, interviews, and focus group discussions under strict adherence to the study protocol, following predetermined criteria and guidelines. The World Health Organization's (WHO) 30 cluster sampling approach was used to determine the sample size for the cluster survey design. All of the places in Karachi were included in a multi-stage cluster sampling technique. Focus group discussions (FGDs) with child care providers and key informant interviews (KIIs) with vaccination program managers, health care professionals (HCWs), and other significant participants were used to gather qualitative data. Face-to-face interviews were used to gather quantitative data from parents of children receiving vaccinations at 6-week intervals with the possibility of follow-up at the subsequent 10- and 14-week intervals.

Data collection

Between August and November 2022, a group of skilled research assistants gathered all of the quantitative data. Four experienced research assistants made up each data gathering team. Face-to-face interviews were done with caregivers who were purposefully chosen to be the first and final caregivers to receive vaccination treatments.

Follow-up methodology

Using a pretested interview delivered questionnaire, demographic information about the child and caregiver, including age, sex, caregiver education level, region of residence, mother occupation, and vaccination administered, was gathered. Research assistants inquired about any adverse reactions the kid may have had after receiving the vaccination, and if so, what they were, as well as what the caregiver did as a result. Additionally, research assistants inquired as to excuses for missing vaccine appointments. Any caregiver whose child missed a scheduled immunization visit at 10 and 14 weeks received a follow-up call one week after the missed appointment in order to find out the reason for defaulting, find out if there were any AEFIs related to the 6, 10, and 14-week vaccinations, and to persuade the caregiver to take the child for the scheduled immunization. A final phone call was made to all caregivers 1-2 weeks following the 14-week immunization to check for any AEFIs related to the given vaccinations. Children were monitored until they had completed the 14-week vaccination visit.

RESULT

Out of the 209 children included in the study, 91 (43.5%) received the scheduled vaccinations, while 118 (56.5%) did not, as detailed in Table 1. Follow-up rates varied across the different vaccination intervals: 18 children (8.6%) were followed up at 6 weeks, 87 children (41.6%) at 10 weeks, and 17 children (8.1%) at 14 weeks. Notably, 87 children (41.6%) completed all scheduled follow-ups, as outlined in Table 2.

Table 1: vaccination of children.

Did your child get vaccination?					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	91	43.5	43.5	43.5
	no	118	56.5	56.5	100.0
	Total	209	100.0	100.0	

Table 2: vaccination duration.

Vaccination duration.					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	6 week	18	8.6	8.6	8.6
	10 week	87	41.6	41.6	50.2
	14 week	17	8.1	8.1	58.4
	all	87	41.6	41.6	100.0
	Total	209	100.0	100.0	

The most frequently reported symptoms during follow-ups included pain, fever, and redness, which were observed in 53 children (25.4%). Inflammation post-vaccination was reported in 22 children (10.5%), and redness alone was observed in 23 children (11.0%). Fever was noted in 12 children (5.7%), and pain was reported in 15 children (7.2%). Pain along with fever was a complaint in 22 children (10.5%), while 62 children (29.7%) experienced all of the aforementioned symptoms, as illustrated in Table 3.

Table 3: symptoms presenting on follow ups.

symptoms					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	pain	15	7.2	7.2	7.2
	fever	12	5.7	5.7	12.9
	inflamation	22	10.5	10.5	23.4
	redness	23	11.0	11.0	34.4
	pain,fever	22	10.5	10.5	45.0
	pain fever redness	53	25.4	25.4	70.3
	all	62	29.7	29.7	100.0
	Total	209	100.0	100.0	

As shown in Table 4, 143 children (68.4%) required medication to manage post-vaccination symptoms, while 66 children (31.6%) did not require any medication. The recovery period varied among the children; a majority of 100 children (47.8%) recovered within 5 days, 59 children (28.2%) within 10 days, and 50 children (23.9%) took more than 10 days to fully recover, as detailed in Table 5.

Table 4: medicine to recover.

Medicine to recover					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	143	68.4	68.4	68.4
	no	66	31.6	31.6	100.0
	Total	209	100.0	100.0	

Table 5: Recovery period.

How many days to recover?					
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	**5 days**	**100**	**47.8**	**47.8**	**47.8**
	10 days	**59**	**28.2**	**28.2**	**76.1**
	more than 10 days	**50**	**23.9**	**23.9**	**100.0**
	Total	**209**	**100.0**	**100.0**	

Table 6 indicates that 206 (98.6%) of the reported cases were duplicates, with only 3 (1.4%) being primary cases.

Table 6: primary and duplicate cases.

Indicator of each last matching case as Primary					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Duplicate Case	206	98.6	98.6	98.6
	Primary Case	3	1.4	1.4	100.0
	Total	209	100.0	100.0	

DISCUSSION

Vaccination is a critical tool for protecting against numerous contagious and life-threatening diseases. However, like all pharmaceutical products, vaccines can cause adverse effects, ranging from mild to severe. While vaccines are highly effective in preventing vaccine-preventable diseases, it is important to acknowledge that, like other medications, they may have associated adverse effects. Despite this, immunization is considered safer than most medicines for two key reasons: 1) vaccines are administered to healthy individuals, thus the risks associated with immunization are generally lower, and 2) adverse events following immunization (AEFIs) are more readily visible within the population, leading to enhanced disease prevention through robust immunization programs. (8).

Since 1990, the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) have employed the Vaccine Adverse Event Reporting System (VAERS) for the surveillance of AEFIs. Investigating AEFIs is crucial to determine any potential associations between vaccines and adverse events. To conduct thorough investigations, it is essential to gather comprehensive epidemiological, clinical, and laboratory data. Continuous monitoring and surveillance of AEFIs are vital for ensuring vaccine safety and efficacy. (9).

AEFI surveillance can be conducted through either active or passive approaches. Passive surveillance relies on spontaneous and unprompted reports from vaccine recipients, healthcare providers, or both, and aims to cover the entire population. However, passive surveillance may be limited by underreporting and lack of detailed information. Active surveillance, on the other hand, reduces underreporting and provides more accurate data but requires more resources than passive surveillance. Structured and detailed scoping reviews, such as those guided by PRISMA Scoping Reviews, are useful for analyzing AEFI data. Bibliographic databases like Embase and OVID-Medline are valuable resources for collecting data on vaccine reactogenicity and self-reported symptoms, making them primary methods for assessing AEFIs. (10)

Vasculitides, a group of diseases characterized by inflammation of blood vessels leading to end-organ injury, have shown temporal associations with vaccine administration. Although some studies have identified associations between vasculitis and vaccines such as BCG, hepatitis, and influenza vaccines, other high-quality studies have found no such associations. A systematic review identified 6,656 articles, of which 157 were assessed for eligibility, and 75 were included in the final analysis. (10).

The World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) have defined anxiety-related AEFIs, which are immunization-related adverse events driven by stress and anxiety. The Global Advisory Committee for Vaccine Safety (GACVS), in collaboration with other health experts, worked in 2015 to redefine, manage, and prevent anxiety-related AEFIs. Anxiety-related AEFIs can lead to the cessation of immunization programs and erode public confidence in vaccines. (11).

Vaccine hesitancy is a significant public health challenge, with AEFIs and vaccine safety playing pivotal roles. Cognitive biases also play an important, though understudied, role in vaccine hesitancy. A quantitative analysis of AEFIs reported to VAERS between 2011 and 2018 found that non-severe AEFIs contributed to greater vaccine acceptance. The literature on vaccine hesitancy and cognitive biases was reviewed and potential cognitive biases affecting vaccination decisions were categorized using the Precaution Adoption Process Model. Among the reported AEFIs, injection site swelling

occurred in 3.21% of cases, fever in 3.66%, and erythema at the injection site in 4.29%. Non-serious AEFIs accounted for 94.5% of reports. Fifteen potential cognitive biases that could impact vaccine decision-making and contribute to vaccine hesitancy were identified. (12).

CONCLUSION

The findings underscore the critical importance of vigilant monitoring and comprehensive surveillance of adverse events following immunization (AEFIs). While vaccines are indispensable in preventing life-threatening and contagious diseases, this study reaffirms that like all medical interventions, they are not without risks. The data demonstrated that although a significant proportion of vaccinated children experienced mild to moderate symptoms such as pain, fever, and redness, these adverse events were generally manageable and did not lead to serious health complications. The majority of children recovered swiftly, typically within five to ten days, with minimal medical intervention required.

These results highlight the efficacy of vaccination programs, especially when coupled with robust AEFI surveillance systems that can promptly identify and address potential safety concerns. Moreover, the study's findings emphasize the importance of transparent communication with caregivers about the potential for mild adverse effects, which can play a crucial role in maintaining public trust in vaccination programs.

Overall, the evidence supports the continued use of vaccines as a safe and effective measure to protect public health. The low incidence of serious AEFIs, combined with the high rates of recovery, reinforces the conclusion that the benefits of vaccination far outweigh the risks. Continuous monitoring and research are essential to further enhance vaccine safety and address any emerging concerns, ensuring that vaccination remains a cornerstone of public health.

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