**Int J Med. Public Health. 2021; 11(1):40-43.**
A Multifaceted Peer Reviewed Journal in the field of Medicine and Public Health
www.ijmedph.org | www.journalonweb.com/ijmedph

*Original Article*

# An Epidemiological Study of Clustering of Adverse Events Following Immunization (AEFI) in a Remote Village of India using Gum Boots Epidemiology

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## ABSTRACT

**Background:** Despite the unquestionable public health benefits of immunization, rare incidents of Adverse Events Following Immunization (AEFI) remain a cause of concern. Following few deaths after vaccination in a village of Jharkhand, India, an epidemiological investigation was carried out by the experts of a medical college to find out the cause of deaths and recommend state health further to prevent such incidences in future. **Materials and Methods:** The epidemiological investigation was conducted as a field study which comprised of observational visit of the AEFI site, key interviews of all stakeholders, verbal autopsy and desk review of all related documents to immunization. All relevant laboratory and autopsy investigations were done to exclude or include all possible causes. **Results:** On investigation, it was noted that there were five children who developed symptoms of severe gastro-enteritis within six hours of vaccination out of the total thirteen vaccines from the single immunization site and four of them died within 24 hr of vaccination suggestive of features of Toxic shock syndrome. All had a common exposure of Measles vaccine and Vitamin A giving hint towards contamination of vaccine during reconstitution or administration of vaccine. In autopsy findings, there was no external injury reported and the laboratory findings of vaccine vial didn't reveal any significant findings. The attack rate of the event was 100% and case fatality rate was 80%. **Conclusion:** From investigation, it was concluded that the events are due to Immunization error related reaction (a type of AEFI) and causality association tool also classified the event to be consistent causal association to immunization. There is dire need of refresher training for service providers on various aspects of AEFI to avoid recurrences of such events.

**Key words:** AEFI, Gum boot epidemiology, Immunization error related reaction, Programmatic error, TSS.

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**History**
- Submission Date: 05-10-2020;
- Revised Date: 09-01-2021;
- Accepted Date: 28-01-2021;

**DOI : 10.5530/ijmedph.2021.1.8**

**Article Available online**
http://www.ijmedph.org/v11/i1



## INTRODUCTION

Immunization is considered as the most effective public health intervention in eradicating deadly diseases like small pox globally and eliminating poliomyelitis from many regions of the world. Currently, it is estimated that 2-3 million deaths are averted every year globally from vaccines against the vaccine preventable diseases such as diphtheria, pertussis, tetanus and measles.[1] In India, every year more than 27 million birth cohorts are added to our population and hundreds of million doses of various vaccines are administered annually.[2] As the more and more newer vaccines are rolling out in the immunization programs, immunization safety has become imperative. The problem with the vaccines is that the benefits of immunization are not conspicuous particularly in the circumstances when the incidence of the disease is low. In contrast to adverse events that follow after immunization are promptly visible as vaccines are administered to apparently healthy people. Fear of vaccine reactions real or perceived have created vaccine hesitancy amongst the beneficiaries and their family which deters general population from undergoing vaccination or delaying it.[3] Unlike medicines, the expectations of the general public from vaccination are much higher and the problems arising due to vaccine/vaccination are less acceptable.

Despite the unquestionable benefits of vaccination, concern about potential vaccine associated risks including Adverse Events Following Immunization (AEFI) still mongers in the minds of general public. Although these events are extremely rare but people must be educated about its uncommon occurrence against the protective benefits of different vaccines.[4,5] Adverse event 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.*[6] The incident may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom, a disease or death. There are five cause-specific definitions namely vaccine product-related reaction,

**Cite this article :** Kumar D, Majhee L, Kumar S, Kujur A, Mishra R, Kashyap V. An Epidemiological Study of Clustering of Adverse Events Following Immunization (AEFI) in a Remote Village of India using Gum Boots Epidemiology. Int J Med Public Health. 2021;11(1):40-3.

vaccine quality defect-related reaction, Immunization error-related reaction (previously programmatic error), Immunization anxiety-related reaction and coincidental event.[7] AEFIs are classified based on severity and frequency which are (1) common and minor (like fever, local pain and swelling), (2) severe (like pain and swelling which spreads beyond the nearest joint or high grade fever) and (3) serious AEFIs (conditions requiring hospitalization or leading to death or disability).[6] Some events are known to occur after vaccination e.g low grade fever after DPT vaccination which needs to be communicated to the parents firmly but serious or severe events after immunization must be dealt promptly and effectively. Failing to do so may effect immunization coverage due to poor confidence in a vaccine amongst the masses and ultimately have increase in disease incidence. This has been noticed with autism and MMR, encephalopathy and pertussis where proof that adverse event is not due to the vaccines took time and the incidences during that time increased for these diseases.[6,8,9] At the same time, we must accept that vaccines are not 100% innocuous and events may result from deviations in protocols of immunization practices.[1] Thus vaccine-associated adverse reactions and error-related immunization events may occur anywhere and affect otherwise healthy individuals.

In a remote village of Patan block, Palamu which is supposed to be a socially unrest district of Jharkhand, India, few deaths have been reported after a vaccination session from a single site. District Rapid Response Team (DRRT) came into action and started the preliminary investigation. Since there were clustering of AEFI, an investigation team comprising of various subject experts from a medical institution was formed with the aim of providing expert opinion in the current incident of AEFI and suggest further course of action with recommendations for avoiding such events in future.

## MATERIALS AND METHODS

The epidemiological investigation along with the causality assessment of deaths occurred after vaccination was done to ascertain the most probable cause of deaths and take corrective actions.[10] The investigation was conducted as a field study which followed the standard principles of Gum boots epidemiology/Field Epidemiology. This included observational visit of the immunization site (Longia Anganwadi centre), village where the incident occurred, surrounding of the deceased's home, Community Health Centre (CHC) Patan, Cold chain room and District Hospital, Palamu where one of the deceased was managed before death. Key interviews (on various aspects related to this event) of doctors (treating doctor of the dead child, service provider Auxiliary Nurse Midwifery (ANM), her helping hand (husband), Accredited Social Health Activist (ASHA/Sahiya), Anganwadi worker (AWW), Cold Chain Handler, local villagers, influencers, parents/relatives of the deceased and other people of health dept. involved directly or indirectly in this event. Verbal autopsy was done for ascertaining the cause of deaths in this event by asking the chronology of events and various information from parents and others who witnessed the events. Desk review of important documents such as due list for the particular immunization session, Immunization (MCTS) register, AEFI case reporting forms, cold chain register and AWW register.

The steps used in this particular AEFI investigation are:

(1) Confirmation of the information in report. (2) Investigate and collect data regarding all vaccinees, events, suspected vaccines with their logistics and other non-vaccinated children/adults. (3) Assessment of immunization services viz. observation of cold chain, immunization procedures, information about open vials, training of the vaccinators and immunization load. (4) Formulation of working hypothesis. (5) Testing of hypothesis and causality assessment using laboratory and autopsy findings. (6) Conclusion of investigation with communication of findings and recommendations. (7) Maintain AEFI surveillance

### Observations and Findings

The incident occurred on April 8, 2018 in two of the three remote hamlets of Loinga village which is known by Loinga-I, Loinga-II and Asnor after the vaccination on April 7, 2018 in Patan block of Palamu district, Jharkhand, India. The village is approximately 14 kms away from the cold chain point (CHC, Patan) and vaccines reached outreach site in vaccine carrier maintaining cold chain by a vaccine delivery volunteer. Two days back i.e on April 5, 2018, immunization was also done in Loinga-I village by the same service provider ANM but there was no such incidence. It is noteworthy fact that she has been involved in immunization activities for more than 25 years but no any complaints have been noted in the past and villagers were satisfied with the care and response during vaccination. Within 24-30 hr, four children out of thirteen children vaccinated in the same session site died with almost similar chronology of events based on the verbal autopsy, desk review of documents available and key interviews by the investigating team. (Table 1). Apart from the four deaths, another AEFI also occurred in a male child born on June 16, 2016 who was given Measles-2, JE-2, DPT-B and Vitamin-A at around 11:30 am, April 7, 2018 at the same session site also developed similar symptoms of gastro-enteritis within six hours but was timely referred to a government tertiary center (Medical College and Hospital) in the capital city of Jharkhand. He was the fifth one to receive common vaccine Measles and Vitamin A. With the timely intervention and appropriate management, he was saved and was under observation in the Pediatrics department until April 19, 2018 when he was discharged with full recovery. From his blood investigations, signs of infection were evident but in blood culture, no microbe was isolated as antibiotics were initiated before sample collection.

It is to be noted that none of the above children had symptoms of any ailment before vaccination and neither they were on any drugs nor they ingested any food item from a common source. There was no any disease outbreak reported from this village during this season and there was negative family history of any relevant disease common to all the deceased.

From the epidemiological point of view, all the four children died had common exposure of Measles vaccine and Vitamin A and the symptoms preceding death developed in these children within 6-8 hr of vaccination. The attack rate of the event is 100% and the case fatality rate is 80%. From the course of events following immunization in these children, the possibility of contamination of Measles vaccine or Vitamin A solution given to the children leading to Toxic Shock Syndrome (TSS) like features (Table 1) during reconstitution of vaccine/handling of vaccine or Vitamin A solution or administering it without observing aseptic measures cannot be ruled out.[11,12] This is typical in Staphylococcal infection and the symptoms corroborates with the same. But for confirmation of the source of infection, vial along with the contents were sent to central laboratory at Kasauli, Himachal Pradesh, India but no significant findings in relation to bacteriological examination were reported. There were also issues with documentation and verbatim which needs to be looked upon with finer details. Before investigations, the possibility of distortion of the evidences (eg changing of vials or syringes) cannot be ruled out and the laboratory findings might not corroborate with the events. All cases were vaccinated at the same facility and vaccine with the same lot and batch was used at other immunization sites on same day but there were no such incidences reported which clearly indicates about programmatic error. This is a prima-facie case of Immunization error related reaction which is one of the type of AEFI based on the findings of the investigation

until proved otherwise and causality assessment tool also determined the current AEFI consistent association to immunization.

## DISCUSSION

Amongst all AEFI, Immunization error related reaction is the one which is preventable and is caused by deviating from ideal procedures of handling, prescribing or administrating vaccine. It may lead to a cluster of events in a particular area associated with vaccination. This is generally observed with a particular vaccinator or health facility or inappropriate handling and preparation of even a single vial of vaccine.[7] In this investigation, events support the abovementioned facts and can be concluded that Immunization error related reaction may be the most appropriate reason for all the four AEFI deaths and the development of symptoms in lone survivor of the current AEFI.[1,6] In the years when auto-disable (AD) syringes were not available, immunization error was seen in the form of infections arising due to usage of non-sterile injections which has reduced significantly.[10]

The symptoms developing after an im munization error may lead to the most likely cause of the event. In these cluster of events, all of the vaccinees became ill after getting a common vaccine i.e Measles and Vitamin A within few hours of vaccination. The symptoms of vomiting, diarrhea, lethargy and high fever suggest *Staphylococcal aureus* infection in these children and the likely diagnosis to be Toxic shock syndrome which may have resulted due to contamination of vaccine/Vitamin A during reconstitution or administration. This may be confirmed if the vial/ bottle used in the immunization is sent for bacteriological examination. Toxic shock syndrome is a rare disease but potentially fatal due to a toxin or toxins produced by certain strains of *S. aureus.* These preformed toxins are exotoxins also known as superantigen toxin that allows the nonspecific binding of Major Histocompatibility Complex (MHC) II with T cell receptors resulting in polyclonal T-cell activation. These polyclonal T cell activation affects multi-organ dysfunction by producing cytokine storm. The toxin implicated in *S. aureus* infections is TSS toxin-1 or TSST-1 which needs to be confirmed from laboratory for the correct diagnosis of Staphylococcal Toxic Shock Syndrome or the 2011 case definition by Centre for Disease Control (CDC) must be followed.[11-14] There have been cases of TSS due to use of tampons in females during menstruation in late seventies and eighties which accounted for more than 50%-70% of all cases in women of reproductive age.[15]

Early recognition of TSS is important, because of its fulminant clinical course and the prognosis depends on the prompt initiation of therapy. Adequate management of a child with TSS at appropriate time may save the child as was in the case of the fifth child vaccinated with Measles and Vitamin- A who was timely referred to the tertiary center. Management of TSS includes hemodynamic stabilization, aggressive fluid resuscitation and appropriate antibiotics to destroy the bacteria in the body. An adjuvant therapeutic neutralizing antibodies in the form of intravenous immunoglobulin that can block superantigen may be included.[16]

Effective and prompt reporting of adverse events following immunization (AEFI) is the most crucial step in making sure that vaccine products are safe and are being properly administered following standard operating procedures. Yet nearly half the world's population exists in nations without an operational system for monitoring AEFI.[17,18] The Global Vaccine Safety Initiative (GVSI) aims to have monitoring of vaccine safety in place uniformly even in low-resource settings. A common global database is formed by WHO for pooling of AEFI data from different countries so that rare severe reactions due to vaccines are captured and monitored. Most severe AEFI are not true vaccine reactions; rather, they are coincidental health events or the anxiety related immunization events.[19,20] Few severe and serious AEFI resulting due to Immunization error related reaction which are avoidable are also noted. Sometimes they are so serious and of acute nature, that before health department is notified, events turn into deaths. But the important aspect is its surveillance which will provide the data for taking action in controlling preventable AEFI as in the current AEFI clusters. Surveillance of AEFI is an indispensable element of vaccine safety monitoring. In most of the parts of world, passive surveillance systems rely predominantly on health care providers. In India, depending on the type of AEFI, these are first brought to the notice of the health system by patient directly, vaccinator, treating physician, supervising immunization staff, local media or pharmacy dispensing the vaccine in private sector.[10] In this current AEFI, it was brought to the state from the local legislators through influencers of the village. But the priority should be to initiate case management over case reporting and health authorities need to instantly respond to all

**Table 1: Chronology of events in AEFI occurred at Loinga village of Palamu district, Jharkhand, India.**

| S.no. | Child1 | Child 2 | Child 3 | Child 4 |
|---|---|---|---|---|
| DOB | 21.3.17 | 14.10.2016 | 30.06.16 | 15.11.16 |
| Sex | M | F | M | M |
| Vaccines/ Items given | Measles-1<br>Vitamin A-1 | Measles-2, JE-2,<br>DPT-B, Vit.A-2 | Measles-2, JE-2,<br>DPT-B, Vit A-2 | Measles-2, JE-2,<br>DPT-B, Vit A-2 |
| Time of vaccination | 11:30 am, 7.4.18 | 11:40am, 7.4.18 | 11:45 am, 7.4.18 | 11:50 am, 7.4.18 |
| Sign and Symptoms | Fever, vomiting, excessive crying. Sluggishness, continuous diarrhea, fever and eye rolling. | Vomiting, diarrhea, lethargic with cold and clammy body parts.<br>No fever was reported. | Fever, vomiting, expression of discomfort, excessive crying, 3 episodes of diarrhea., restlessness and lethargy. | Vomiting, raised temperature, uncontrolled loose stools and lethargy. |
| Time of Death | At 2:15 pm,<br>8.4.18 | At 4:00am,<br>8.4.18 | At 4:00 am,<br>8.4.18 | At 3:00 am, 8.4.18 |
| Autopsy and Laboratory findings | No significant findings in Autopsy and laboratory investigations. | | | |

reported AEFI. Also there is fewer AEFI reported, which is a limitation of passive surveillance, so active surveillance of AEFI may be thought of which will detect more AEFI, more of which will be milder ones.

When an AEFI occurs, appropriate action should be taken in the form of proper communication. But generally it is more of *ad-hoc* response rather it needs to be part of broader communication plan with resources and staff trained in place and manner to be responded correctly and timely. Sustained advocacy for political commitment and resources supporting immunization goals is the main component of successful communication which is to be managed in synchrony with health services and ought to be based on sound surveillance system.[21]

## CONCLUSION

From the initial investigation, it seems that the events are due to Immunization error related reaction (a type of AEFI) but further autopsy report and visceral analysis will be able to establish it more precisely by inclusion or by exclusion. Thus vaccine-associated adverse reactions and error-related immunization events should be promptly identified for further response which may occur anywhere and affect otherwise healthy individuals. Re-enforcement of various aspects of immunization particularly AEFI case studies in refresher training of service providers must be done. Principle of Primum-non-nocere must be stressed in training and must be practiced religiously while using any drug/vaccine across all levels of health care services. Although there is AEFI committee at all levels but their response must be proactive in capturing all AEFI and take timely action.

## ACKNOWLEDGEMENT

We are thankful to officials from State Health, Government of Jharkhand, ITSU, GOI, UNICEF and WHO for their support in carrying out the investigation.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**AEFI:** Adverse event Following Immunization; **ANM:** Auxiliary Nurse Midwifery; **ASHA:** Accredited Social Health Activist; **AWW:** Anganwadi worker; **CHC:** Community Health Centre; **CDC:** Centre for Disease Control; **DPT:** Diphtheria Pertussis Tetanus; **DRRT:** District Rapid Response Team; **GVSI:** Global Vaccine Safety Initiative; **JE:** Japanese Encephalitis; **MCTS:** Maternal Children Tracking Register; **MHC:** Major Histocompatibility Complex; **MMR:** Measles Mumps and Rubella; **TSS:** Toxic Shock Syndrome; **WHO:** World Health Organization.

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**Cite this article :** Kumar D, Majhee L, Kumar S, Kujur A, Mishra R, Kashyap V. An Epidemiological Study of Clustering of Adverse Events Following Immunization (AEFI) in a Remote Village of India using Gum Boots Epidemiology. Int J Med Public Health. 2021;11(1):40-3.