Profile of adverse events following immunization with measles rubella vaccine at a tertiary care hospital in East Delhi, India

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Abstract

Background: As a part of a measles and rubella (MR) campaign, the MR vaccine replaced the two-dose measles vaccine at 9–12 months and 16–24 months of age under the Universal Immunization Program (UIP). Although adverse events following immunization (AEFIs) following the measles and MMR vaccine at 9 months of age have been studied, AEFIs following the MR vaccine at 9 months of age have not been studied. As the MR vaccine a is very recent introduction in the UIP for routine immunization at 9 months of age, we intend to investigate the AEFI profile of MR vaccination at 9 months of age by active surveillance.

Aim: We aimed to study the profile of the AEFIs with MR vaccine at 9–12 months of age in children vaccinated at the immunization clinic at the Pediatrics Department of a tertiary care hospital in East Delhi, India.

Methods: Our study was a prospective observational study (telephonic survey). Children who attended Pediatrics OPD for the first dose of the MR vaccine at 9–12 months of age were enrolled in the study. Demographic details of the children who received the first dose of MR vaccine at 9–12 months of age at the immunization clinic of the hospital were recorded in a case record form. A telephone survey was conducted on day 7 and day 30 post-vaccination for AEFIs.

Result: A total of 278 children were enrolled in the study, but 7 were unavailable for the further telephone survey. A total of 42 (15.5%) AEFIs were reported, of which 39 (94%) were in the initial 7 days and 3 (6%) were in the following 21 days following immunization. Of the AEFIs reported, the most common symptom was fever (38%), followed by upper respiratory tract infection (30.9%), local swelling at injection site (26.1%), and skin rash (4%).

Conclusion: MR vaccine introduced in National Immunization Schedule is found to be safe for use in children except for a few minor reactions.

Keywords: adverse events following immunization (AEFIs), Delhi, measles rubella vaccine

Introduction

India has a high burden of morbidity and mortality from vaccine preventable diseases (VPDs) in children. Measles and rubella are VPDs. In India, more than 2.5 million children acquire measles infection, and close to 49,000 infected children die each year.1 Measles-related deaths are due to its complications, such as severe diarrhea with dehydration, pneumonia, and encephalitis.

Rubella infection during the first trimester of pregnancy causes miscarriages, fetal death, and congenital rubella syndrome (CRS). Rubella infection has caused birth defects in almost 40,000 children nationwide.1 Though there is no specific treatment for measles and rubella, both can be prevented by the highly efficacious and cost-effective measles- and rubella-containing vaccines.
First and second doses of measles vaccines were introduced in the Universal Immunization Program (UIP) in 1985 and 2010, respectively. As per the Health Management Information System (HMIS), the countrywide coverage of measles containing vaccine 1 (MCV1) stands at 90% and as per National Family Health Survey-4 (NFHS-4 survey, 2015–16), the country-wide coverage of Measles Containing Vaccine at age 12–23 months stands at 81.1%. According to WHO and UNICEF 2018 data, MCV1 and MCV2 have an estimated coverage of 90% and 80%, respectively. According to 2014 Joint Reporting Format (JRF) data, the country-wide coverage of MCV1 and MCV2 stood at 83% and 40%, respectively, which was far below the expected 95% for measles elimination. Following the South East Asia regional committee resolution in September 2013, India had set a goal for measles elimination and rubella/CRS control by 2020. To achieve this goal, the National Technical Advisory Group of Immunisation (NTAGI), in June 2014, recommended the introduction of the measles–rubella (MR) vaccine in routine immunization programs following a nationwide MR campaign to increase population immunity against measles and rubella. Before the MR campaign, measles-only vaccine was being given at 9 months of age under the UIP in all the states, while MMR vaccine was being given at 15 months of age in a few states under the UIP. In contrast, the private sector generally vaccinates in accordance with the Indian Academy of Paediatrics (IAP) schedule, which recommend 3 doses of MMR for routine vaccination at 9, 15, and 60 months, respectively. Both doses of measles vaccines provided at 9–12 months and 16–24 months under the UIP have been replaced by the MR vaccine after the MR campaign in a phased manner.

The MR vaccine used in the immunization program is a live-attenuated vaccine containing the Edmonston strain of measles and the RA 27/3 strain of rubella. The same components are part of MMR vaccine used in state immunization programmes in India and in the private sector for immunization at 9 months, 15 months, and 5 years and is by the same manufacturer. The MR vaccine used in India is WHO prequalified.

WHO/Council for International Organization of Medical Sciences (CIOMS) has defined an adverse event following immunization (AEFI) as any untoward medical occurrence that follows the immunization and which does not necessarily have a causal relation with the usage of the vaccine. The adverse events may be any unfavorable or unintended sign of an abnormal laboratory result, symptoms, or diseases.

According to AEFI 2015 guidelines of the Government of India, AEFIs are broadly classified into three categories: common minor AEFI, which includes fever, rash, and local reactions; Serious AEFI, which results in hospitalization, death, or significant disability; and severe AEFI, which includes any adverse event of increased severity.

AEFI reporting in India, like many other countries, is a passive reporting process. The MR vaccine is highly safe and well tolerated. Side effects following MR vaccination are mostly mild and transient and are similar in frequency and severity to those following administration of single antigen products. Reported AEFI following the use of combined vaccines (MR and MMR) are similar to those described with single antigens. Use of MR vaccine can result in mild lymphadenopathy, urticaria, rash, malaise, sore throat, fever, headache, arthralgia, and arthritis. The type and rate of serious adverse events does not differ significantly for MMR or MR combinations compared with the individual antigens.

The Vaccine Adverse Event Reporting System (VAERS) is a vaccine safety surveillance program co-sponsored by the CDC and FDA. It collects and analyzes reports of adverse events following vaccination. It is followed in many countries, such as the USA. It is a passive surveillance based on reports given by doctors or paramedical staff.

As vaccines are given to healthy children, any untoward effect after vaccination has deep-rooted ramifications and possible further dropout from participation in any such events. Pharmacovigilance on vaccines in India is still in a nascent stage. In India, only the measles vaccine was being given at 9–12 months under the UIP. MMR is being used for immunization at 9 months of age in private sectors. As the MR vaccine is a very recent introduction in the UIP for routine immunization at 9 months of age, we intend to find out the AEFI profile of MR vaccination at 9–12 months of age in the pediatrics population in our hospital.

The MR campaign was launched nationwide in 2017 in India in a phased manner. The MR
vaccine was introduced at our center in May 2018 as MCV1 and MMR vaccine was continued as MCV2, which was replaced by the MR vaccine a few months later. In Delhi, the campaign was to be started on 16 January 2019 but was deferred by the high court, stating that informed consent had not been sought from parents/wards of children.12 The halt of the campaign was a result of parents’ objection due to unsubstantiated rumors spread about adverse effects of the vaccine. In this context, the present study becomes even more meaningful.

Material and methods
We conducted a prospective observational study in the Department of Pediatrics of a tertiary care teaching Hospital of Delhi for a duration of 3 months (1 January–31 March 2019). A sample size was calculated with the known incidence rates of 0.05 for fever and rash following the measles vaccine. With a confidence interval of 95% and power of 80%, the minimum sample size was calculated to be 198. Considering a dropout rate of 20%, the sample size came to 238. Children who attended Pediatrics OPD for the first dose of MR vaccine at 9–12 months of age were enrolled in the study after explaining the protocol and taking written informed consent from parents/guardians. Approval was obtained from an institutional ethical committee prior to conduction of the study. The MR vaccine was given to all the eligible children in right arm at a dose of 0.5ml subcutaneously in the immunization room. Exclusion criteria for the MR vaccination were: those who were severely immunocompromised, severe allergic reaction to the vaccine constituents, anaphylactic/anaphylactoid reactions to neomycin, a history of anaphylactic reactions, and cow’s milk allergy.6 Children were kept under observation for 30 min post-vaccination to look for any anaphylactic reaction.

A case record form was designed, similar to a VAERS form, which included basic demographic information and vaccine details (batch number, manufacturing date, expiry date, and company) and adverse events noted by parents. A telephone survey was conducted after ensuring that the phone number provided was that of the caregiver who was also accompanying the child for vaccination and the same person was available for telephone conversation. The telephone survey was conducted on day 7 and day 30 post-vaccination. Both the surveys were conducted by the same pediatrician to avoid bias. Caregivers were first asked open-ended questions about any type of reaction that appeared following vaccination. This was followed by closed-ended questions regarding possible adverse events such as pain, fever, and rash. If any positive response was found, the type of management sought for such events were also documented. Data was cross-validated only if the caregiver responding to the phone call was not either of the parents. Confidentiality of the data collected was ensured. Data was entered in a Microsoft Excel sheet and subsequently analyzed in an Excel sheet.

Results
A total of 278 children were enrolled in the study but 7 were unavailable in further telephone survey. Out of the 271 children for whom survey could be completed, 141 (52.1%) were males and 130 (47.9%) were females. A total of 42 (15.5%) AEFIs were reported, of which 39 (94%) were in the initial 7 days and 3 (6%) were in the following 21 days. A total of 31 parents reported adverse events in their children while 240 vaccine recipients did not report any AEFIs.

Of the AEFIs reported, the most common was fever (38%), followed by upper respiratory tract infection (30.9%), local swelling at injection site (26.1%), and skin rash (4%) (Table 1). Eleven children had more than one AEFI. The most common combination was fever and swelling at the injection site (n=9) followed by fever with URI (n=2). According to AEFI classification, all the cases were minor events. No serious or severe AEFIs were noted. Four children visited local practitioners for upper respiratory infection and two for skin rashes.

Discussion
The UIP in India is among the largest immunization programs in the world, targeting 27 million infants.13 AEFI surveillance has a very important role to guide vaccine safety, prompt management of adverse events, and to reduce any negative effect on a vaccination program. A study from the Serum Institute of India demonstrated that an
indigenously produced MMR vaccine has a good immunogenicity and safety profile. While comparing the immunogenicity and side-effect profile of a new MMR vaccine (having Hoshino mumps strain) with the existing Serum Institute MMR vaccine, authors found no difference in the side-effect profile of the two groups. Interestingly, in both these studies, the components used for measles and rubella remain the same as in the MR vaccine introduced nationwide in India. Both the studies reported only minor adverse events, with the maximum reported event being fever. The methodology followed in our study was very similar to the study conducted by Joshi et al. and Aherkar et al. However, no study has reported AEFIs with MR vaccine at 9 months of age. All the other studies have reported AEFIs following the measles vaccine alone or the MMR vaccine. Reported incidence of AEFIs in the present study was 15.5%, which is comparable to the study by Joshi et al. where reported AEFIs following measles vaccination was 12.9% and Bhargava et al., where reported AEFIs following MMR vaccine was 19.4%.

In our study, the most common adverse event was fever, which is similar to the finding of the study conducted by Joshi et al. and Aherkar et al. although both studies reported the events following measles vaccine alone.

Probable mechanisms of development of all these events are postulated to be live viral activity, injection related direct needle trauma, immune-mediated reaction, and cytokines production. In our study, we did not find any serious or severe AEFIs.

Our study was unique as it was a prospective study evaluating AEFIs following MR vaccine at 9–12 months of age. However, limitations of the study include: first, the short duration of the study due to which long-term AEFIs could have been missed; second, the telephone survey, where minor ailments may be missed; third, cause-specific categorization of AEFIs was not attempted; fourth, no grading of AEFIs was done; fifth, the study was conducted at a tertiary care set up, thereby limiting the applicability of the results to the population of the primary health center, camp set up, and private organizations where vaccine storage, the skill of the person vaccinating, and socioeconomic background of the parents of the child vaccinated may be different. Lastly, the study was not powered to capture uncommon/rare adverse events.

### Conclusion

The current study was aimed at finding the possible adverse events of the MR vaccine, which has been introduced recently at 9 months of age under the UIP. Active surveillance helped in finding and reporting of minor adverse events that could have been missed in the passive reporting of AEFIs. The MR vaccine introduced in the NIS is found to be safe for use in children except for a few minor reactions. More studies are required to evaluate the delayed and rare AEFIs.

| AEFI reported | Number of AEFIs | Within 7 days post-vaccination, n (%) | 7–30 days post-vaccination, n (%) | Total Per 100 doses n (%) |
|---------------|----------------|--------------------------------------|-----------------------------------|--------------------------|
| Local Swelling | 11 (26.2)       | –                                    | 4.0                               | 11 (26.2)                |
| Other reaction (abscess, induration) | – | – | – | – |
| Systemic Fever | 14 (33.3)       | 2 (4.7)                             | 5.9                               | 16 (38)                  |
| URI | 12 (28.6)       | 1 (2.4)                             | 4.7                               | 13 (31)                  |
| Skin Rash | 2 (4.8)        | –                                    | 0.73                              | 2 (4.8)                  |

AEFI: adverse event following immunization; URI: upper respiratory infection.
Author contribution
All the authors were involved in the conceptualization of study design, data acquisition, data analysis, literature search, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. The manuscript has been read and approved by all the authors. Singh Aaradhana is the guarantor of the study.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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References
1. World Health Organization. India’s measles-rubella vaccination campaign a big step towards reducing childhood mortality, addressing birth defects, https://www.who.int/southeastasia/news/detail/05-02-2017-india-s-measles-rubella-vaccination-campaign-a-big-step-towards-reducing-childhood-mortality-addressing-birth-defects (2016, accessed April 2020).

2. International Institute for Population Sciences (IIPS) and ICF. National family health survey (NFHS–4), 2015-16. Mumbai, India: IIPS, http://rchiips.org/nfhs/pdf/NFHS4/India.pdf (2017, accessed April 2020).

3. WHO & UNICEF estimates of immunization coverage: 2018 revision, https://www.who.int/vaccine_safety/initiative/tools/MMR_vaccine_rates_information_sheet.pdf (2014, accessed April 2020).

4. Ministry of Health & Family Welfare. Government of India. National Health Mission. Introduction of measles rubella vaccine (campaign and routine immunization). National operational guideline, 2017.

5. Taneja DK and Sharma P. Targeting rubella for elimination. Indian J Public Health 2012; 56: 269–272.

6. Balasubramanian S, Shah A, Pemde HK, et al. Indian Academy of Pediatrics (IAP) advisory committee on vaccines and immunization practices (ACVIP) recommended immunization schedule (2018–19) and update on immunization for children aged 0 through 18 years. Indian Pediatr 2018; 55: 1066–1074.

7. Gavi: The Vaccine Alliance. MR vaccine supply and procurement roadmap UPDATE November 2017, https://www.gavi.org/sites/default/files/document/measles-rubella-vaccine-roadmap—public-summary.pdf (accessed January 2020).

8. Definition and application of terms for vaccine pharmacovigilance: report of CIOMS/WHO working group on pharmacovigilance, http://file:///C:/Users/Aiims%2044/Desktop/vaccine%20pharmacovigilance/CIOMS_report_WG_vaccine.pdf (accessed 26 September 2018).

9. AEFI: surveillance and response. Operational guideline 2015. Ministry of health & family welfare, Government of India, https://nhm.gov.in/New_Updates_2018/NHM_Components/Immunization/Guidelines_for_immunization/AEFI_Surveillance_and_Response_Operational_Guidelines_2015.pdf (accessed January 2020).

10. World Health Organization. Information sheet: observed rate of vaccine reactions; measles mumps and rubella vaccines, https://www.who.int/vaccine_safety/initiative/tools/MMR_vaccine_rates_information_sheet.pdf (accessed January 2020).

11. Center for Disease Control and Prevention. Food and Drug Administration. Vaccine adverse event reporting system. VAERS form, https://vaers.hhs.gov/resources/vaers_form.pdf (accessed January 2020).

12. Dutt A and Banka R. HC orders deferring MR vaccine campaign in Delhi after parents’ objection. Hindustan Times New Delhi [newspaper online], https://www.hindustantimes.com/delhi-news/hc-orders-deferring-mr-vaccine-campaign-in-delhi-after-parents-objection/story-LQ9L6q0vCiEwiimAWviSAP.html (2019, accessed April 2020).

13. National Vaccine Policy, New Delhi, Government of India, Ministry of health and family welfare, http://mohfw.nic.in/WriteReadData/l892s/1084811197NATIONAL%20VACCINE%20POLICY%20BOOK.pdf (2011, accessed January 2020).

14. Bhargava I, Chhaparwal BC, Phadke MA, et al. Immunogenicity and reactogenicity of indigenously produced MMR vaccine. Indian Pediatr 1995; 32: 983–988.

15. Sood A, Mitra M, Joshi H, et al. Immunogenicity and safety of a novel MMR vaccine (live, freeze-dried) containing the Edmonston-Zagreb measles
strain, the Hoshino mumps strain, and the RA 27/3 rubella strain: Results of a randomized, comparative, active controlled phase III clinical trial. *Hum Vaccin Immunother* 2017; 13: 1523–1530.

16. Joshi ND, Prajapati HK, Solanki KC, et al. Pattern of adverse events following immunization in an Indian teaching hospital. *Int J Med Sci Public Health* 2013; 2: 62–68.

17. Aherkar RY, Deshpande and Ghongane BB. Study of the pattern of adverse events following immunization of children in a tertiary care hospital. *PK Int J Basic Clin Pharmacol* 2016; 5: 609–615.

18. Poland GA, Ovsyannikova IG and Jacobson RM. Adversomics: the emerging field of vaccine adverse event immunogenetics. *Pediatr Infect Dis J* 2009; 28: 431–433.