Original Article

Adverse Reactions Following Immunization with MMR Vaccine in Children at Selected Provinces of Iran

Abdoulreza Esteghamati MD MPH[1], Abbasali Keshtkar MD MPH PhD •[2,3], Ramin Heshmat MD PhD[3], Mohammad Mehdi Gouya MD[4], Masoud Salar Amoli MD[4], Shahnaz Armin MD[5], Frank Mahoney MD[6]

Abstract

Background: Several adverse events following immunization (AEFI) have been attributed to immunization with live attenuated measles, mumps, and rubella (MMR) vaccines. The MMR vaccine was introduced into the routine infant immunization schedule in 2003, followed by a second dose of vaccine at school-entry for children 4 to 6 years of age. The objective of this study was to characterize adverse reactions following MMR vaccination in Iran.

Methods: Children who received the MMR vaccine and resided in five selected provinces of Iran were examined weekly for four weeks to detect well-known AEFIs that included: parotitis, fever and convulsions, convulsions without fever, encephalopathy, and anaphylactic reactions. Incidence of AEFIs were calculated and compared among recipients in both age groups.

Results: During the follow-up period, trained providers reported 792 AEFIs. Parotitis was the most frequent event occurring in 1.8% of recipients. Of 14,109 children vaccinated at 12 months of age the following AEFIs occurred: parotitis (147), fever and convulsions (8), convulsions (7), encephalopathy (1), and anaphylactic reactions (1). Of 29,338 children vaccinated at 4 to 6 years of age, parotitis, fever and convulsions, encephalopathy, and anaphylaxis occurred in 626, 5, 1, and 1 child, respectively; no convulsions without fever were reported in this age group.

Conclusion: Parotitis is the most frequent AEFI among MMR vaccine recipients in Iran. Incidence rates of AEFIs following MMR vaccination in Iran are similar to rates of AEFIs reported in other studies.

Keywords: adverse event, Iran, measles-mumps-rubella vaccine

Introduction

Measles, mumps, and rubella (MMR) are contagious viral diseases associated with high mortality and morbidity that usually cause complications.[1] Immunization with the MMR vaccine that consists of live attenuated viruses provides protection for all three diseases in a single injection.[2] If administered properly, live attenuated measles vaccine can induce life-long immunity in greater than 85% of those vaccinated with one dose and about 90% with two doses.[3] Mass vaccination campaigns and the Expanded Program of Immunization (EPI) have increased vaccine coverage in the world with a substantial impact on reduction of measles morbidity and mortality.[4]

MMR vaccine has been found to be associated with some adverse events that may occur following vaccination. Minor reactions that are occasionally observed include fever, short-lasting respiratory symptoms, febrile convulsions, parotitis, and with a relatively low incidence, neurological complications. In some cases aseptic meningitis occurs up to 42 days after administration of mumps vaccination.[5] These unintended events cause a major concern both for parents and health-care system administrators.[6]

A systematic review of published articles concerning the frequency of unintended events following immunization with MMR compared to no vaccination or placebo showed an association of MMR with a lower incidence of upper respiratory tract infections, higher incidence of irritability, a similar incidence of other adverse effects compared to placebo and a likely association with benign thrombocytopenic purpura (TP), parotitis, joint and limb complaints, and aseptic meningitis (mumps Urabe strain-containing MMR). Exposure to MMR is unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps Jeryl-Lynn strain-containing MMR).[6]

According to the National Immunization Program in Iran, all children should be initially vaccinated at 12 months and, for the second time, at 4 – 6 years of age.[7] It is necessary

Authors' affiliations: [1]Department of Pediatrics, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, [2]Golestan Research Center of Gastroenterology and Hepatology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, [3]Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran,[4]Bureau of Immunization and Vaccine-Preventable Diseases, Center for Disease Control, Ministry of Health and Medical Education, Tehran, [5]Department of Pediatrics, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [6]Division of Communicable Diseases, Eastern Mediterranean Regional Office, World Health Organization, Cairo, Egypt.
Corresponding author and reprints: Abbasali Keshtkar MD MPH PhD, Department of Social Medicine, Faculty of Medicine, Falsafi Educational Complex, Gorgan, Iran, Telefax: +98-171-442-1221,
E-mail: abkeshtkar@yahoo.com
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to consider both safety and immunogenicity of vaccines in evaluation of national immunization programs, therefore we aimed to evaluate the incidence of adverse events following immunization (AEFIs) after routine administration of the MMR vaccine in Iran. The study was conducted in five provinces among children aged 12 months and 4 – 6 years of age.

Materials and Methods

Study population

Between August through October 2006, trained providers examined 43,447 MMR vaccine recipients weekly for four weeks to detect any fevers, encephalopathy and anaphylactic reactions. Vaccine recipients were selected for the detection of five well-known AEFIs, including: parotitis, fever and convulsions, convulsions without fever, encephalopathy, and anaphylactic reactions five regions of Iran with varying climates (Iran located in Tehran, Tabriz, Mashhad and Shiraz Medical Universities and residents of Sari, Amol, Babolsar, and Behshahr in Mazandaran Province). The provinces were selected because study subjects were sampled from the four corners of Iran: north (Mazandaran Province), south (Shiraz Medical University), east (Mashhad Medical University) and west (Tabriz Medical University) as well as a significant portion of Tehran's population, located at the center of the country. The population of infants who resided in these districts was almost 200,000 (~17% of Iran's total infant population).

MMR vaccine

The evaluated MMR vaccine was manufactured by Razi Vaccine and Serum Research Institute and distributed within the health-care system by the Iran Center for Disease Control—a subdivision of the Ministry of Health and Medical Education. The vaccine consisted of the following: attenuated AIK measles vaccine, habituated to human diploid cells, attenuated Takahashi anti-rubella virus, initially isolated in Japan from the saliva of an infected patient, which has been attenuated in rabbit and monkey renal cells prior to its habituation to human diploid cells, and the attenuated Hoshino anti-mumps virus received from Kitasato Vaccine Institute in Japan and propagated in chicken diploid cells without contamination. Moreover, the wild strain of the Hoshino virus was attenuated and habituated to human diploid cells at Razi Institute after a multiple of 20 passages through human diploid cells and its preparation for marketing. This vaccine is the only MMR vaccine available in Iran.

Data collection and assessment

We defined five AEFIs to the MMR vaccination based on World Health Organization (WHO) definitions.[8] AEFI case screening was initially performed by a "behvarz" (health worker who provides primary health care in "Health Houses") throughout rural areas and "community health workers" in urban areas. All health workers and staff from health centers and health houses in the study fields were trained to recognize AEFIs, complete data collection forms and refer patients to collaborating physicians. The collaborating

Table 1. Frequency (number of cases) of five adverse reactions following MMR vaccination based on regions and age groups.

Adverse reaction	Parotitis		Febrile seizures		Seizures without fever		Encephalopathy		Anaphylactic reactions		Total	
Region	12 months	4–6 years	12 months	4–6 years	12 months	4–6 years	12 months	4–6 years	12 months	4–6 years	12 months	4–6 years
Tehran	35	148	2	0	1	0	0	0	0	0	38	148
Tabriz	24	58	2	1	0	0	0	0	0	0	26	59
Mazandaran	26	152	3	0	1	0	1	1	1	1	32	154
Shiraz	33	137	1	4	0	0	0	0	0	0	34	141
Mashhad	29	131	0	0	0	0	0	0	0	0	29	131
Total	147	626	8	5	7	0	1	1	1	1	159	633

Table 2. Incidence of parotitis after MMR vaccination based on each region and age groups; effects of age and residency location.

Age group	12 months		4–6 years		Both age groups		Risk ratio 4–6 y to 12 months age group (95% CI)†	Risk ratio of different regions to Tehran (95% CI)
Regions	Total assessed children	Incidence*	Total assessed children	Incidence*	Total assessed children	Incidence*		
Tehran	6952	5.03	12094	12.24	19046	9.61	2.4 (1.7–3.5)	1 (-)
Tabriz	2025	11.85	3913	14.82	5938	13.81	1.3 (0.8–2.0)	1.4 (1.1–1.9)
Mazandaran	1648	15.78	4920	30.89	6568	27.10	1.9 (1.3–2.9)	2.8 (2.3–3.5)
Shiraz	1642	20.10	4239	32.32	5881	28.91	1.6 (1.1–2.3)	3.0 (2.5–3.7)
Mashhad	1842	15.74	4172	31.40	6014	26.60	2.0 (1.3–2.9)	2.7 (2.2–3.4)
Total	14109	10.42	29338	21.34	43447	17.79	2.0 (1.7–2.4)	—

*Incidence in 1000 children or 1000 administered doses of MMR vaccine; †95% CI for risk ratio

Table 3. Incidence of fever and convulsions after MMR vaccination based on region and age groups; effects of age and residency location.

Age groups / Regions	12 months		4–6 years		Both age groups			
	Total assessed children	Incidence*	Total assessed children	Incidence*	Total assessed children	Incidence*	Risk ratio 4–6 y to the 12 months age group (95% CI) †	Risk ratio of different regions to Tehran (95% CI)
Tehran	6952	28.8	12094	0	19046	10.5	0 (-)	1 (-)
Tabriz	2025	98.8	3913	25.6	5938	50.5	0.3 (0.02–2.9)	4.8 (0.8–28.8)
Mazandaran	1648	182.0	4920	0	6568	45.7	0 (-)	4.4 (0.7–26.0)
Shiraz	1642	60.9	4239	94.4	5881	85.0	1.6 (0.2–13.9)	8.1 (1.6–41.7)
Mashhad	1842	0	4172	0	6014	0	0 (-)	—
Total	14109	56.7	29338	17.0	43447	29.9	0.3 (0.1–0.9)	—

* Incidence in 1000 children or 1000 administered doses of MMR vaccine; †95% CI for risk ratio

Table 4. Incidence of adverse reactions following MMR vaccination based on age group.

Age groups / Adverse reaction	12 months		4–6 years		Both age groups	
	Incidence	(95% CI)*	Incidence	(95% CI)	Incidence	(95% CI)
Parotitis†	10.4	8.8–12.2	21.3	19.7–23.1	17.8	16.6–19.1
Fever and convulsions‡	56.7	24.5–111.7	17.0	5.5–39.8	29.9	15.9–51.1
Convulsions (without fever)‡	49.6	20.0 – 102.2	0	—	16.1	6.5–33.2
Encephalopathy‡	7.1	1.8 – 39.5	3.4	0.9–19.0	4.6	0.6–16.6
Anaphylactic reactions‡	7.1	1.8 – 39.5	3.4	0.9–19.0	4.6	0.6–16.6

*Confidence intervals for incidence were calculated by the binomial exact method; †Incidence in 1000 children or 1000 administered vaccine doses; ‡Incidence in 100000 children or 100000 administered vaccine doses.

physicians (three physicians in each area) examined patients with suspected AEFIs and verified or disproved the adverse event. Data collection forms were sent to the Disease Control Committee in each province for review and confirmation of the event. After confirmation, the AEFI report was classified as a confirmed event and entered in the national database for monitoring AEFIs. Based on the above instructions, the time period determined for patients to be at risk for adverse reactions was considered as two to three weeks (three weeks for parotitis and two weeks for other adverse reactions). The occurrence of these signs after the defined time period was not considered related to the MMR vaccine.

Data analysis

The incidence of AEFIs was calculated by dividing the number of events to the total number of evaluated children in each region. Since the occurrence of AEFIs was rare, we utilized the binomial exact method to calculate an estimated incidence and confidence interval. The frequency of AEFIs between the two age groups using risk ratios and the 95% confidence intervals were compared. Data analyses were performed using SPSS for Windows version 13 and STATA version 8 software. *P* values less than 0.05 were considered statistically significant.

Results

Overall, 14,109 children aged 12 months (32.5%) and 29,338 children aged 4 to 6 years (67.5%) were vaccinated and monitored during the study period. Seven hundred and ninety-two AEFIs were reported (Table 1). Parotitis, the most common AEFI, occurred in 1.8% (18 per 1000) of vaccine recipients. The incidence of parotitis ranged from 9.6 per 1000 vaccine recipients in Tehran to 28.9 in Shiraz and was higher among older vaccine recipients in all study sites. In all of the regions, the occurrence of parotitis among children 4 – 6 years old was twice that of children aged 12 months (risk ratio=2.0, 95% confidence interval: 1.7 – 2.4). The risk of parotitis in Tehran's children was lower than the other regions (Table 2). The incidence of febrile seizures was 30 per 100,000 vaccine recipients and 3.5 times higher among 12 month old vaccine recipients when compared to those aged 4 to 6 years old. There was considerable variability in the incidence of febrile seizures by study site. The risk of febrile seizures in children from both Tabriz and Mazandran was higher than those from Tehran, although the difference was non-significant. However, in Shiraz the occurrence was almost eight times that of Tehran's children ($P<0.05$; Table 3). The incidence rates of seizures without convulsions, en-

Table 5. Incidence of adverse reactions following MMR vaccination in comparison with other studies.

Adverse reaction	Current study	WHO report[8]	Barlow et al. [11]	Patja et al.[12]	Weibel et al. [13]	Davis et al. [14]	Griffin et al. [15]	D›Souza et al.[16]
Parotitis †	17.8 (16.6–9.1)	10–20	Not reported	Not reported	—	—	—	0.0024
Fever and convulsions ‡	29.9 (15.9–1.2)	33.3	15.3 (9.5–23.4)	0.9 (0.6–1.3)	—	25–34	—	0.06
convulsions (without fever) ‡	4.6 (0.6–16.6)	Not reported	1.5 (0.2–5.3)	0.1 (0.02–0.3)	—	—	21.8 (5.9–55.8)	0.24
Encephalopathy ‡	4.6 (0.6–16.6)	0.1	Not reported	Not reported	0.06 (0.05–0.09)	—	—	0.06
Anaphylactic reactions ‡	4.6 (0.6–16.6)	0.1–5	Not reported	1.4 (1.0 –1.9)	—	—	—	0.06

Numbers in parentheses are 95% CI for incidence; † Incidence in 1000 children or 1000 administered vaccine doses; ‡ Incidence in 100000 children or 100000 administered vaccine doses

cephalopathy and anaphylaxis were considerably lower than those of parotitis and febrile seizures (Table 4).

Discussion

In 2003, the EPI program in Iran implemented a plan to eliminate measles and rubella through the use of a mass vaccination campaign and introduction of a two dose schedule using the MR vaccine. In 2005, the National Vaccine Advisory Committee recommended the inclusion of mumps into the National Infant Immunization Program. Mumps is asymptomatic in one third of the patients, however, parotitis is observed in 60 – 70% of those infected with mumps. In countries that do not have the mumps vaccine, outbreaks of mumps infections occurs every two to five years with children between the ages of 5 to 9 years being the most affected.[9] Before the mumps immunization, the annual incidence of this disease was reported based on passive surveillance systems as 100 – 700/100,000.[9]

The incidence of parotitis and febrile seizures observed in this study was generally similar to the incidence reported by WHO and observed in other studies (Table 5). We observed slightly higher rates of convulsions without fever, encephalopathy, and anaphylaxis.

Scant published data has existed on the incidence of mumps infection in the eastern Mediterranean and other developing countries prior to the launch of immunization against this disease. Based on unpublished data from Oman, the annual incidence of mumps infection varied between 269 to 783 per 100,000 children.[9] In Israel, the reported annual incidence of mumps infection was 80 – 162 per 100,000 based on passive surveillance system data.[10]

The incidence of parotitis, fever and convulsions, and anaphylactic reactions in children in this study was in the range declared by WHO, however, the incidence of encephalopathy in our study was higher than the WHO range. There is considerable diversity in published reports on the incidence of AEFIs following MMR vaccinations. The cause of this diversity may be attributable to the following:

• Variations among studies and methods of data collection. Numerous studies related to adverse reactions from the MMR vaccine worldwide have been performed. In a group of studies, data has been collected from a surveillance system that monitors adverse reactions following immunization in different countries. These systems usually lack required validity and necessary qualifications; thus they underestimate the incidence of common adverse reactions. In another group, the data has been related to disease registry systems performed at hospitals of each region, but these studies also have limitations (although less than the previous studies). Instead, in the other group, the data has been obtained from population-based cohort studies that can be considered as studies with high levels of quality in this group.

• Difference in case definition or time period between vaccination date and appearance of adverse reactions.

• Difference in type and nature of vaccine and the strains.

• Difference in ethnical properties or other causes related to the nature of the participants.

The main limitation of our study was the lack of a control group with which to compare the incidence of adverse reactions in vaccinated and unvaccinated groups. Immunization of all children throughout the country who had the criteria for vaccination made it unethical to have a control group, who would not be vaccinated. Designing a population based case-control study requires assessing adverse reactions at the community level. This approach will meet many limitations and is costly. Performing a hospital-based case-control study can result in assessing the critical outcomes leading to hospital admissions. Besides, the lack of an integrated system for the registration of hospital-admitted patients in our country made this approach unfeasible.

The limitation of all of AEFI studies is causality. The causality proof needs serum or a CSF assay, which is not feasible in large field studies.

Although initial screening by community health workers and referral to collaborating physicians is a good method

with which to increase specificity and rule out false positive rates, it does not guarantee validity (criterion-based validity) and reliability (test, re-test, and concurrent reliability) of data collection.

Our study has some advantages compared to the passive AEFI surveillance system, which generally under-reports incidences whereas the prospective manner of our study allows for the establishment of the Temporality Principle of Hill's Criteria. The acceptable sample size of this study, prospective design and weekly follow-up of all children vaccinated with this vaccine can be considered as positive features of this study. The aim of our study was not just to evaluate the association between MMR vaccine and adverse reactions. The MMR vaccine is produced in our country, therefore having exact information about adverse reactions following the MMR vaccination as well as knowledge about the vaccine's safety is very important.

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