

# Effect of gender on reporting of MMR adverse events in Saudi Arabia

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تأثير الجنس على التبليغ عن الأحداث الضائرة التالية للتطعيم ضد الحصبة والنكاف والحصبة الألمانية في المملكة العربية السعودية

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**الخلاصة:** تم تقييم مأمونية حملات التمنيع باللقاح الثلاثي ضد الحصبة والنكاف والحصبة الألمانية للأطفال السعوديين (من عمر 6 سنوات إلى 13 سنة)، وتقييم تأثير الاختلاف في الجنس على التبليغ عن الأحداث الضائرة التالية للتمنيع. كما تم رصد 160 مدرسة لمدة 14 يوماً و19 مستشفى محلياً لمدة 10 أسابيع بعد التلقيح. وكانت معدلات وقوع الأحداث الضائرة على النحو التالي: 26.5 حالة لكل 10 000 لقاح لجميع الأحداث الضائرة الناجمة عن اللقاح الثلاثي ضد الحصبة والنكاف والحصبة الألمانية (وكانت في الإناث أعلى بنسبة يعتد بها إحصائياً من الذكور)؛ وحالة واحدة للتهاب السحايا العقيم الناجم عن الذرية Urabe لكل 295 000 لقاح؛ و40.2 حالة حمى (للإناث) لكل 10 000 لقاح و0.9 حالة حمى (للذكور) لكل 10 000 لقاح؛ و5.4 حالة التهاب النكفية لكل 10 000 لقاح (في الإناث) و0.9 حالة التهاب النكفية لكل 10 000 لقاح (في الذكور). وقد ثبت أن اللقاح الثلاثي ضد الحصبة والنكاف والحصبة الألمانية المحتوي على ذرية النكاف Urabe كان مأموناً للأطفال من عمر 6 أعوام إلى 13 عاماً. ولوحظت فروق تفاعلية واضحة بين الذكور والإناث، وهو ما ينبغي أن يؤخذ في الحسبان عند تصميم الدراسات المستقبلية.

**ABSTRACT** We evaluated the safety of a measles–mumps–rubella (MMR) immunization campaign for Saudi children (age range: 6–13 years) and gender differences in reporting post-MMR adverse events. After vaccinations were administered, we monitored 160 schools for 14 days and 19 hospitals in the 8 cities under study for 10 weeks. Incidence rates were: all MMR adverse events, 26.5/10 000 MMR vaccines (significantly higher in females than males); Urabe strain aseptic meningitis, 1.0/295 000; fever, 40.2/10 000 (females) and 0.9/10 000 (males); and parotitis, 5.4/10 000 (females) and 0.9/10 000 (males). Combined MMR vaccine containing the Urabe mumps strain was safe for children aged 6–13 years. Gender differences regarding reactogenicity were evident and should be considered when designing future studies.

## Influence de la sexospécificité sur les réactions indésirables notifiées pour le ROR en Arabie saoudite

**RESUME** Nous avons évalué la sécurité d'une campagne de vaccination contre la rougeole, les oreillons et la rubéole (ROR) pour les enfants saoudiens (âge compris entre 6 et 13 ans) et la sexospécificité dans les réactions postvaccinales indésirables notifiées. Après la vaccination, nous avons surveillé 160 écoles pendant 14 jours et 19 hôpitaux dans les 8 villes couvertes par l'étude pendant 10 semaines. Les taux d'incidence étaient les suivants : toutes réactions indésirables associées au ROR, 26,5 pour 10 000 vaccins ROR (significativement plus élevé chez les filles que chez les garçons) ; méningite aseptique due à la souche Urabe, 1,0 pour 295 000 ; fièvre, 40,2 pour 10 000 (filles) et 0,9 pour 10 000 (garçons) ; et parotidite, 5,4 pour 10 000 (filles) et 0,9 pour 10 000 (garçons). Le vaccin ROR associé contenant la souche Urabe pour les oreillons était sûr pour les enfants âgés de 6 à 13 ans. La sexospécificité en ce qui concerne la réactogénicité était évidente et devrait être prise en compte dans la conception des futures études.

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## Introduction

Safety studies and post-marketing surveillance are important steps in the drug licensing process. The safety of vaccines in particular has always been of special concern because of the large-scale nature of vaccination programme delivery to young children. Accordingly, systematic collection of vaccine adverse event reactions (VAER) is an important part of the Expanded Programme of Immunization (EPI) during both routine vaccinations and large-scale campaigns. Many factors that affect the type and the magnitude of adverse reactions have been reported and an important one of these is sex.

Many studies have reported that female sex is a risk factor for the development of adverse drug reactions across various drug types [1–3]. For vaccines in particular, higher mortality of females among infants receiving high titre Edmonston–Zagreb measles vaccines [4,5] and male/female differences in the patterns of immune response and effect have been reported [6]. Apart from these few findings, there are few studies on gender differences in adverse drug reactions among children, especially for vaccines.

Revaccination policies adopted in many countries to control measles have raised various safety issues including those concerning the second vaccine dose. We evaluated the safety of an measles–mumps–rubella (MMR) vaccine delivered to children aged 6–13 years via a primary schools-based mass vaccination campaign and identified sex-related differences in reporting MMR adverse event reactions following the campaign.

## Methods

As part of a measles elimination programme in Saudi Arabia [7–9], an MMR campaign was conducted in two phases. The first phase was conducted in October 1998 and targeted children in intermediate and secondary schools. The second phase was conducted in January–February 2000 for children in primary school and the first-year of intermediate school, i.e. children aged 6–13 years. Of the target population of 2 412 078 children, 96.6% received the vaccine during the campaign. A safety study was conducted during the second phase of the campaign as part of the evaluation process.

### Vaccine

Trimovax® (Pasteur-Merieux, France) MMR vaccine was used for the campaign. It contains the Urabe AM9 mumps strain, Schwarz measles strain and Wistar RA 27/3 rubella strain. The same lot of MMR vaccine was used for the entire study. Vaccines were transferred and administered according to standard operating procedures.

### Sample

A two-stage random sampling technique was used. In the first stage, eight cities were randomly selected to represent the study population (Mecca and Al-Medina in the west; Buraydah and Unayzah in the centre; Al-Qatif and al-Hufuf in the east; and Khamis Mushayt and Belgurashi in the south). In the second stage, all children from 20 primary schools (10 all-male and 10 all-female schools) were selected from each of the eight cities (44 904 children) for schools-based surveillance for MMR

adverse event reactions, excluding aseptic meningitis. In addition, all 19 hospitals in the eight cities were used for hospital-based active surveillance for aseptic meningitis (target population of 295 000 students). For 14 days after MMR vaccination, schools were under active surveillance. Using a special form for VAER, health visitors followed up with children in the schools and reviewed absenteeism records. Children complaining of any medical sign or symptom and children absent from school due to medical causes were referred to school health physicians.

The VAER forms included information for identifying cases and for reporting specific adverse events such as fever, parotitis, seizures, rash and allergic reactions and aseptic meningitis. For aseptic meningitis, the 19 hospitals in the eight cities were put under active surveillance for 10 weeks after the MMR campaign. Any child aged 6–13 years with a diagnosis of aseptic meningitis as per the Centers for Disease Control and Prevention definition [10] was investigated by collecting three specimens of cerebrospinal fluid, saliva and urine. Specimens were sent to the United Kingdom's National Institute of Biological Standards and Control for viral studies under strict supervision according to standard protocols.

### Statistical analysis

Data were analysed using SPSS version 10. The chi-squared test was used to compare qualitative data. Adverse event reactions were expressed as incidence absolute risk (AR) and relative risk (RR) with a 95% confidence interval (CI) to compare gender differences. The denominator used for aseptic meningitis was 295 000, i.e. all targeted vaccinated children in the eight cities, while for other adverse events, the denominator was 44 904, i.e. vaccinated children

in the 20 selected schools from each of the eight cities.

### Results

There were six cases of aseptic meningitis reported in the vaccinated group (4 females and 2 males) with four cases reported within 10 days of vaccination and the other two cases reported within 20–60 days after vaccination. Polymerase chain reaction analysis of cerebrospinal fluid samples showed that the causative agent was Urabe mumps strain in only one case, a female aged 11 years who presented eight days after vaccination. All six cases recovered without complications. The confirmed case of aseptic meningitis associated with Urabe strain was defined as 'clinical aseptic meningitis' as per laboratory confirmation by mumps virus-specific RT-PCR revealing a nucleotide sequence of the SH gene generated from the child's cerebrospinal fluid sample.

Our study found that the risk of Urabe-associated aseptic meningitis after MMR vaccination was 1/295 000 vaccinated children. The incidence of other adverse events per 10 000 vaccinated children is given in Table 1. The overall VAER was 26.5/10 000 vaccinees. The overall incidence of VAER was 51.0/10 000 vaccinees for females compared to 2.7/10 000 for males ( $P = 0.0001$ ) with an overall RR of 19.3 (95% CI: 8.51–43.94).

The incidence for all types of adverse events was higher for females than males. (It was significantly higher for females for all VAER except allergic reactions.) Females were at higher risk of fever (RR = 45.7, 95% CI: 11.5–185.5), parotitis (RR = 6.1, 95% CI: 1.4–27.5) and fever with parotitis (RR = 5.1, 95% CI: 1.1–23.4). This pattern was consistent in the eight cities.

Table 1 Measles-mumps-rubella vaccine post-immunization adverse events

VAER	Total		Sex				Age group (years)				P-value <sup>a</sup>
	(n = 44 904)		(n = 22 747)		(n = 22 157)		(n = 22 800)		(n = 22 104)		
	No.	I	No.	I	No.	I	No.	I	No.	I	
Fever	91	20.3	2	0.9	89	40.2	50	22.1	41	19.1	0.0001
Parotitis	14	3.1	2	0.9	12	5.4	0	0.0	14	6.3	0.014
Fever and parotitis	12	2.7	2	0.9	10	4.5	5	2.1	7	3.2	0.038
Allergic reactions	2	0.4	0	0.0	2	0.9	2	0.8	0	0.0	-
Total	119	26.5	6	2.7	113	51.0	57	25.0	62	28.6	0.0001

<sup>a</sup>P-values for chi-squared comparing incidence in females versus males.

I = Incidence, i.e. the number of new cases per 10 000 primary school children vaccinated with the MMR vaccine.

All cases of parotitis without fever occurred in children aged  $\geq 10$  years. Age did not affect the incidence of other adverse events.

## Discussion

A higher rate of adverse events in females following vaccination with MMR vaccine has been reported elsewhere, in which the RR of fever and rash following vaccination was 2.35 in females and 1.36 in males [11]. Nonetheless, not all studies have found these gender differences. One reason for this discrepancy might be the relatively low power of some studies [12].

Higher reactogenicity in females has also been observed in other vaccines [13] with girls found to have experienced more pain and itching than boys ( $P < 0.001$ ) following diphtheria/tetanus vaccination [14]. Females have also been reported to experience significantly more local reactions than males after inactivated influenza vaccine [15].

Gender effects in pharmacokinetics and pharmacodynamics in general may be involved in the higher incidence of adverse

drug reactions in females. Pharmacokinetic studies have shown that the rate of systemic clearance adjusted for body mass may be significantly different in women than in men, which may be partly explained by drug metabolism. Gender differences have also been demonstrated in drug response at the receptor level. Many, but not all, such gender-related differences can be explained by the effect of sex hormones [16,17].

A number of investigators have started to explore reasons for gender differences in reactogenicity to vaccines. A study by Mitchell reported a difference between males and females in the pattern of immune response after re-immunization with rubella vaccine [18]. The study suggested that this difference might partially explain why females are more predisposed to adverse outcomes with rubella immunization. Similar studies in measles vaccination have also shown gender differences in patterns of cellular immune response and in vitamin A levels following measles immunization [19].

The higher incidence of fever among females in our study compared with other studies can to some extent be explained by

the use of school absenteeism records in the present study. Absenteeism due to medical causes is a reflection of individual perceptions of health, in which gender plays an important part. Females may have higher rates of absenteeism because education for girls may have a lower cultural priority than for boys and 'mild fever' may be a reason given to allow young girls to remain at home from school. While these factors might explain higher rates of female absence due to mild fever, they do not explain why females had five times more parotitis without fever than males. Parotitis is an objective sign, easily detected by the school health visitor if the child is attending class or by the physician if the child is absent and referred to the school health physician. This is strongly indicative of a real increase in parotitis among females compared with males.

An important aspect of the present study population is that in Saudi Arabia, female and male schools are separate. Female interviewers were used in surveillance at female schools and male interviewers at male schools. Both male and female interviewers were trained in adverse event surveillance techniques by the same investigators, using the same methodology. Evidence has been found that gender of the interviewer does not affect the subject's response to questions of medical symptoms, especially when, as in the case of the present study, surveillance depended mainly upon objective signs such as fever and swelling of the parotid gland [21].

The overall incidence of VAER in this campaign was higher than that reported in

other studies. In an Australian MMR vaccination programme [22], the VAER incidence was 5.24/100 000 doses. The incidence of post-MMR aseptic meningitis per 10 000 vaccinees has been reported variously to be 16.6, 11.6, 3.2 and 0, depending on different Urabe strains manufactured by different companies [23]. Other studies have reported the MMR vaccine to be non-reactogenic when given at 6 years of age [24].

In the present campaign, approximately 92% of children had been previously vaccinated with MMR vaccine at 12 months of age or at school entry. This might explain the lower incidence, especially for associated aseptic meningitis, as pre-campaign mumps antibody may neutralize the mumps virus in the vaccine. In comparing safety data from different studies, variables such as age and history of previous vaccination need to be considered.

## Conclusion

Our study found that the overall incidence of MMR adverse events was relatively low, suggesting that the MMR vaccine was safe when given to children aged 6–13 years, especially children with a history of MMR vaccination. Our findings support that gender is an important factor during the evaluation of vaccines, and therefore, that it needs to be addressed in future study designs. Further work is required to explain the mechanisms of the observed differences between males and females.

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### **Regional launch of the report *State of the World's Vaccines and Immunization***

Under the patronage of Her Excellency Mrs Suzanne Mubarak, First Lady of the Arab Republic of Egypt, the WHO Regional Office for the Eastern Mediterranean held the regional launch of the latest edition of the *State of the World's Vaccines and Immunization* in Cairo on 20 November 2002. The report charts the many issues surrounding vaccines and immunizations, arguing their power as the most effective public health interventions, highlighting gaps between the industrialized world and the developing countries, and calling on national governments, nongovernmental organizations, donors and partners to make greater investments as an integral part of a well-functioning health system.

Dr Hussein A. Gezairy, WHO Regional Director for the Eastern Mediterranean, addressed the invitees during the launch on behalf of WHO. The ceremony was attended by representatives of governments and eminent personalities from the Region as well as partners who have played a major role in the area of vaccines and immunizations at the regional level and assisted in the successful implementation of the Expanded Programme on Immunization and the Poliomyelitis Eradication Programme. The report is available free online at: [http://www.who.int/vaccines-documents/DocsPDF04/www5OWV\\_E.pdf](http://www.who.int/vaccines-documents/DocsPDF04/www5OWV_E.pdf)