# Gender Differences in the Reactogenicity of Measles-Mumps-Rubella Vaccine

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**Key words:** measles-mumps-rubella vaccine, sex differences, reactogenicity

## Abstract

**Background:** In trials comparing different formulations of measles vaccine, excess non-specific mortality occurred in female children who received high titer vaccine. These findings suggest a gender-specific effect of measles vaccine.

**Objectives:** To determine whether gender differences exist in the rates of adverse reactions and morbidity in the month following immunization with measles-containing vaccine, and to evaluate whether there is a gender-specific association between the humoral immune response to measles vaccination and post-vaccination morbidity.

**Methods:** Parents completed questionnaires on the health status of 755 infants aged 15–20 months, during the month preceding and the month following the measles-mumps-rubella vaccination. Blood samples were tested for measles antibody titers in a subsample of 237 infants.

**Results:** After controlling background morbidity in the infants, the relative risk of fever and rash following vaccination was 2.35 in females and 1.36 in males. The geometric mean antibody titers against measles were similar in both sexes and there was no significant association between antibody titer and post-vaccination morbidity in either sex.

**Conclusions:** Our findings demonstrate higher rates of adverse effects in females following vaccination with MMR vaccine, irrespective of the humoral response. This study emphasizes the need to consider possible gender differences when evaluating new vaccines.

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In the process of evaluating new vaccines, little attention has been paid to possible gender differences in the effects of the vaccine. Three separate follow-up studies that compared high titer with regular titer measles vaccines observed unexpected excess mortality from various diseases among females receiving high titer vaccine but not among males [1–5]. In addition, the case fatality rate due to measles was higher in HIV-1 seropositive girls who were vaccinated with standard titer measles vaccine than in the unvaccinated group [6]. These observations were even more puzzling, since there is evidence that in children, morbidity for many infectious diseases is higher among males [7] .

Adverse effects of measles vaccination are common and may be related in part to elements of the immune response to the vaccine [8–14]. The aims of this study were to evaluate possible gender differences in adverse reactions to measles-containing vaccine (MMR) at age 15 months. In addition, we explored possible gender-specific associations between the strength of the humoral response and post-vaccination morbidity.

## Materials and Methods

MMR vaccine is routinely administered to all children in Israel. At the time of this study the recommended age for vaccination was 15 months. Childhood immunizations are administered in Israel through family health centers operated directly by the Ministry of Health or under its supervision, and as a result MMR vaccine coverage in Israel by the age of 2 years is around 95% [15].

### Study design and subjects

This prospective study was carried out over a period of several months between May 1993 and April 1994. The study population consisted of 755 children who were followed for one month after vaccination for the first time with MMR vaccine. The outcome variables were side effects and morbidity in the month following vaccination. Possible gender differences in the usual morbidity, unrelated to vaccination, were controlled for by recording diseases in the month before vaccination.

### The questionnaire

Children were enrolled in the study at the time of vaccination. The study was explained to the parents and those who agreed to participate comprised the study population. Two questionnaires were completed. The first was used retrospectively to determine the morbidity in the 4

MMR = measles-mumps-rubella

weeks prior to vaccination and to control for the background rates of diseases resulting from intercurrent infections. The second questionnaire was used prospectively to determine morbidity in the follow-up period. Parents were asked to record any illnesses that occurred during the 4 weeks following vaccination, and to complete the questionnaire at home.

The questionnaire included information on the child's birth date and gender; several questions on parental education; smoking habits; and a list of signs, symptoms and illnesses, such as fever (rectal temperature >38.0°C), rash, ear infection, throat infection, runny nose, vomiting, diarrhea, cough, and use of antibiotics. If the child was sick on a certain day, the date of onset of symptoms and the duration of the illness (in days) was noted. A random subset of children was scheduled for blood sampling 5 to 7 weeks following vaccination.

**Table 1.** Incidence rates of signs, symptoms, and illnesses in infants during the month before and the month following vaccination with MMR

| Illness | Before (B) | After (A) | A–B | 95% CI | *P* |
|---|---|---|---|---|---|
| **Males** (n=395) | | | | | |
| Fever >38°C | 16.20% | 22.02% | 5.82% | 0.35–11.29 | <0.001 |
| Rash | 4.06% | 15.19% | 11.13% | 7.10–15.18 | <0.001 |
| Ear infection | 15.22% | 8.86% | –6.36% | -10.84– -1.81 | 0.008 |
| Use of antibiotics | 28.43% | 18.73% | –9.70% | -15.50– -3.74 | 0.002 |
| **Females** (n=360) | | | | | |
| Fever >38°C | 10.00% | 23.61% | 13.61% | 8.24–18.98 | <0.001 |
| Rash | 2.78% | 21.39% | 18.61% | 14.05–23.17 | <0.001 |
| Ear infection | 8.61% | 5.56% | –3.05% | -6.80–0.69 | 0.150 |
| Use of antibiotics | 25.00% | 16.39% | –8.61% | -14.50– -2.73 | 0.006 |

**Table 2.** Gender differences in the change in morbidity rates (%) from the month before to the month after vaccination with MMR

| Illness | Males | Females | RR | 95%CI | *P* |
|---|---|---|---|---|---|
| Fever >38°C | 5.82% | 13.61% | 2.35 | 1.45–3.76 | <0.001 |
| Rash | 11.13% | 18.61% | 1.36 | 1.15–1.61 | 0.002 |
| Ear infection | 6.36% | –3.05% | 0.63 | 0.38–1.04 | 0.057 |
| Use of antibiotics | 9.70% | –8.61% | 0.94 | 0.71–1.23 | 0.720 |

### Validation of the response to questionnaires

The physicians of 50 randomly selected children whose parents reported having visited the physician during the 2 month period (either before or after vaccination) were contacted and asked to confirm whether the child had visited the clinic, the dates of clinic visits, and the clinical findings.

### Antibody testing

Venous blood, 5 ml, was obtained from each child in the subgroup who came for blood testing. Sera were kept frozen at –20°C prior to testing. Anti-measles antibodies were measured using the hemagglutination inhibition test [16].

### Statistical analysis

Comparisons between the incidence rates of the various illnesses in males and in females were done using the chi-square test with continuity correction. The distributions of the characteristics of the male and female groups were compared using chi-square analysis. The difference in the magnitude of the change in incidence rates for the different symptoms 4 weeks after versus the 4 weeks preceding vaccination was compared between males and females using chi-square analysis. Relative risks were computed together with test-based confidence intervals. The unpaired Student's *t*-test was used to test differences between duration of illness pre- and post-vaccination. Student's *t*-test was used for statistical comparisons between the antibody log geometric mean titers.

The minimum sample size was chosen to detect a 10% difference in change in morbidity between males and females with a type 1 error of 5% and a power of 80%.

## Results

Of 920 parents approached, 755 (82.1% response) completed the questionnaires and returned them after 4 weeks. The results of the verification of the parents' report by the child's physician showed that for 43 of 50 children, the diagnosis and the date of the clinic visit (within a week) reported by the parents were correct. For the remaining seven children, there was no documentation of physician's visit during that period. Blood samples were obtained from a subset of 236 of 320 children who were scheduled for blood sampling (73.7% response). For nine subjects, insufficient blood was available for testing.

### Gender differences in symptoms and signs before and after vaccination

The incidence rates of the different signs, symptoms and illnesses before and after vaccination by gender are shown in Table 1. In both sexes, following vaccination, there were significant increases in the rates of fever and rash. Thus, the incidence rate of fever increased from 16.20% before vaccination to 22.02% after vaccination in males ($P<0.001$), and from to 10.00% to 23.61% in females ($P<0.001$). The risks of developing fever and rash after vaccination were significantly greater in females than in males. The relative risk for fever was 2.35 (95% confidence interval 1.45–3.76, $P<0.001$) and 1.36 for rash (95% CI 1.15–1.61, $P=0.002$) [Table 2]. Analysis of the data by week demonstrated that the increases in the incidence were confined to the first and second week after vaccination.

Some positive changes were observed in both sexes in the third and fourth week following vaccination. There was a

CI = confidence interval

significant decrease in the incidence rates of ear infections in males [Table 1], and non-significant decreases in the incidence rates of cough, runny nose and throat infections in both sexes (data not shown). The decrease in the incidence rates of ear infections in males was greater than in females (RR 0.63, 95% CI 0.38–1.04, $P=0.057$).

### Anti-measles antibody titers

The antibody GMT for males was 142.3±99.5 and for females 142.5±85.3, which were not statistically different ($P=0.38$). Antibody titers were higher than 1:128 in 21.5% of the males and 22.3% of the females ($P=0.88$). In both sexes, there were no significant differences in antibody GMTs between children who developed any signs, symptoms and illnesses and those who did not. The comparison between the antibody GMTs of children who developed fever and rash and those who did not (by sex) is given in Table 3. There was no significant difference in the amount of change from pre- to post-vaccination incidence rates of the various signs, symptoms and illnesses in children whose antibody titer was >1:128 and those whose antibody titer was equal to or less than 1:128.

**Table 3.** Anti-measles HI antibody GMTs by presence of fever or rash, in the month following vaccination in male and female infants

| Illness | | Males (n=133) Antibody GMT | *p* | Females (n=94) Antibody GMT | *p* |
|---|---|---|---|---|---|
| Fever >38°C | yes | 145.55 | 0.72 | 142.61 | 0.87 |
| | no | 139.32 | | 145.33 | |
| Rash | yes | 117.89 | 0.23 | 145.07 | 0.95 |
| | no | 146.28 | | 143.79 | |

GMT = geometric mean titer

## Discussion

The findings in the present study demonstrate that following administration of a measles-containing vaccine, fever and rash are significantly more common in females than in males. Both reactions are commonly observed after measles vaccination [10]. Since the increases in rates of fever and rash among vaccinees were confined to the first 2 weeks after vaccination, it is reasonable to assume that these were adverse reactions to the vaccine. Following rubella vaccine, general complaints (including fever, rash, headache, sore throat and tiredness) have been described as more common in adult women than in young adult males [17,18], but not in children.

Previous studies on the reactogenicity of MMR vaccine in small children did not report the results by gender of the vaccinees [8–13]. Since the children were vaccinated with MMR vaccine, the observed adverse events and morbidity could be the result of the effect of each of the vaccine components. However, it has been shown that vaccination against measles in combination with the other two antigens does not increase the risk for adverse reactions in comparison with vaccination with measles vaccine alone [9]. Thus it is reasonable to assume that the gender differences in adverse events were due to the measles antigen. No gender difference in measles antibody titer was found in the present study, although it has been described in adults receiving a second vaccine dose [19], and in children who had received vitamin A supplementation with measles vaccine [20].

A decrease in the incidence rates of ear infections in the third and fourth week was observed in both sexes, however it was substantially greater in males than in females. It is possible that a larger sample size would yield a statistically significant difference.

No association was found between the antibody titer and the rates of adverse reactions and short-term morbidity following vaccination. While we could not locate other studies on short-term gender differences in adverse effects following MMR vaccination, several reports described gender differences in the immune response in the long-term, which may be relevant to this issue. It is known that following vaccination with live measles vaccine there is a temporary suppression of the immune response to some antigens [21–23]. Immunological studies of children examined 2 years after vaccination with high titer measles vaccine have shown gender differences in the degree of immune suppression, with lower T cell proliferation in response to phytohemagglutinin in females compared with males [24]. Since the appearance of rash following measles vaccination is considered an expression of the cellular immune response [14,25], further studies should address the possibility that the sex differences observed in the adverse effects of the measles vaccine occur at the cellular level.

In the present study the information used to control for "usual" illnesses (during the month prior to vaccination) was provided retrospectively by the parents. While recall bias may have influenced the responses, there is no reason to suspect that such bias was differential between males and females. Thus it should not affect the validity of the comparison between sexes. The questionnaires completed during the period following vaccination may have been influenced by the parents observing the children more closely after vaccination. Validation of the parents' reports against physicians' records did not indicate large discrepancies. Furthermore, there is no reason to suspect that such bias would be present differentially in males and females, and thus the validity of the comparison between sexes should not be affected.

In conclusion, compared with males, females are at higher risk of suffering fever and rash following MMR vaccination. The major implication of the findings in this study is that the

reactogenicity of new vaccines should be studied separately in each sex.

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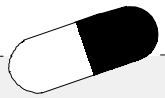
*Don't speak unless you cam improve on the silence.*
*Spanish proverb*

## *Capsule*



### Alcohol consumption and risk of stroke

Berger et al. evaluated the effect of light-to-moderate alcohol intake on the risk of stroke, with separate analyses of ischemic stroke and hemorrhagic stroke. The analyses were based on a prospective cohort study of 22,071 male physicians, aged 40 to 84, who were participating in the Physicians' Health Study. At base line, the participants reported that they had no history of stroke, transient ischemic attack, or myocardial infarction and were free of cancer. Alcohol intake, reported by 21,870 participants at base line, ranged from none or almost none to two or more drinks per day.

The authors concluded that light-to-moderate alcohol consumption reduces the overall risk of stroke and the risk of ischemic stroke in men. The benefit is apparent with as little as one drink per week. Greater consumption, up to one drink per day, does not increase the observed benefit.

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