

Letter to the Editor

Reduced serologic response to mumps, measles, and rubella vaccination in patients treated with intravenous immunoglobulin for Kawasaki disease

To the Editor:

Standard treatment in Kawasaki disease (KD) consists of the administration of high-dose intravenous immunoglobulin (IVIG). IVIG is a polyclonal immunoglobulin preparation purified from pooled plasma from blood donors. A concern with the use of IVIG is that the passively acquired antibodies may interfere with the serologic response to active immunization.^{1,2} Current guidelines recommend postponing the measles, mumps, and rubella (MMR) vaccination to at least 6 months after IVIG treatment. In The Netherlands, children receive this vaccine at the age of 14 months and 9 years. We evaluated the MMR vaccination response in patients treated with IVIG for KD, in comparison with healthy controls.

We retrospectively included 198 patients with KD (age, 1-9 years) with serum samples obtained between January 2002 and January 2011. At the time of sampling, these patients had received the first MMR vaccine of the national immunization program. Forty-three patients were excluded because of a missing vaccination history ($n = 17$), administration of a booster MMR vaccination ($n = 3$), or blood sampling within 6 months after IVIG infusion ($n = 23$). The latter was to minimize the risk of measuring antibodies from IVIG. Each of the remaining 155 patients was age- and gender-matched to a control subject from the PIENTER-2 study, a cross-sectional seroprevalence study performed in 6386 individuals to evaluate the immunization program.³ Sera of patients and controls (median age, 5.1 years [range, 15 months-8.9 years], 60% males) were tested for specific MMR IgG concentrations by using a fluorescent bead-based multiplex immunoassay. Antibody concentrations were expressed in international units per milliliter (IU/mL, measles and rubella) or RIVM units per milliliter (RU/mL, mumps).⁴ Seroprotection proportions were determined by using cutoff values of 0.2 IU/mL for measles, 10 IU/mL for rubella, and 45 RU/mL for mumps.^{5,6}

For analysis, patients were divided into 3 groups: (1) patients who were vaccinated *before* the IVIG administration ($n = 92$), (2) patients who were vaccinated *after* the IVIG administration ($n = 58$), and (3) patients who did not receive IVIG because of a delayed or missed diagnosis ($n = 5$). Antibody concentrations and seroprotection proportions were compared between patients and controls by using paired t tests and χ^2 tests (or Fisher exact tests, when appropriate). IgG concentrations are reported as geometric mean concentrations (GMC).

When we compared the 92 patients who were vaccinated *before* the IVIG administration with the controls, no differences were found in IgG concentrations or seroprotection proportions (Table I). The same was observed for the 5 untreated patients, although the numbers were too small for further analysis.

In the 58 patients who were vaccinated *after* the IVIG administration, additional analyses were performed. First, we investigated the relationship between the interval from IVIG administration to vaccination and the IgG concentrations. The correlation was strong for measles ($\rho = 0.680$, $P < .001$; Spearman's rank test), moderate for rubella ($\rho = 0.435$, $P < .001$),

TABLE I. Serologic response in patients with KD who were MMR vaccinated before the IVIG infusion in comparison with matched controls

	Patients with KD (n = 92)	Controls (n = 92)	P value	OR (95% CI)*
GMC†				
Measles	1.89 (1.54-2.29)	1.54 (1.26-1.88)	.160	–
Mumps	126 (102-156)	115 (93-143)	.559	–
Rubella	58 (48-70)	51 (41-63)	.272	–
Seroprotection proportion				
Measles	97.8% (90/92)	100% (92/92)	.497	1.0 (1.0-1.1)
Mumps	83.7% (77/92)	80.4% (74/92)	.564	1.3 (0.6-2.7)
Rubella	95.7% (88/92)	92.3% (85/92)	.351	1.8 (0.5-6.4)

OR, Odds ratio.

*The OR indicates the odds of having protective antibody concentrations for patients with KD compared with matched controls.

†GMC data are expressed as mean with 95% CI, given in IU/mL for measles and rubella and in RU/mL for mumps.

and weak for mumps ($\rho = 0.273$, $P = .039$). Subsequently, we evaluated the serologic response on the basis of the interval between IVIG and vaccination. Of the 58 patients, 20 patients (35%) had been vaccinated within 6 months, 11 (19%) within 6 to 9 months, and 27 (47%) after more than 9 months. Fig 1 shows the serologic response. In comparison with the matched controls, patients vaccinated within 6 months had a lower GMC against measles ($P < .001$), mumps ($P = .046$), and rubella ($P = .036$). In the patients vaccinated between 6 and 9 months, a lower GMC ($P = .002$) and proportion of seroprotection ($P = .005$) were also observed against measles, but not for mumps or rubella. When vaccinated after more than 9 months, there were no differences between patients and controls. Finally, we compared the patients who received 1 dose of IVIG ($n = 40$) or 2 doses ($n = 18$) of IVIG, and found no differences (seroprotection proportions against measles: 55% vs 61%, $P = .664$; mumps: 80% vs 72%, $P = .511$; and rubella: 93% vs 78%, $P = .111$, respectively). The numbers of patients were too small for further analysis in subgroups based on the interval from IVIG administration to vaccination.

It is recommended to defer live-attenuated vaccines after IVIG administration, but there is no clear consensus about the appropriate time interval. In Japan, an interval of 6 to 7 months is recommended on the basis of a study by Sonobe⁷ that measured the persistence of measles antibodies from IVIG. Of the 28 patients with KD tested after 6 months, 25 had negative titers. After 7 months, all 8 patients tested had negative titers. International guidelines of the Advisory Committee on Immunization Practices and the American Academy of Pediatrics advise measles vaccination after an interval of more than 11 months post-IVIG. This recommendation is based on extrapolation of the results of a study by Siber et al¹ who showed that an intramuscular dose of immunoglobulin (80 mg/kg) inhibited the serologic response to measles up to 5 months, and on the half-life of passively administered immunoglobulins. However, estimates of the half-life of IgG differ among studies, and the duration of interference can therefore not be predicted precisely. In addition, it

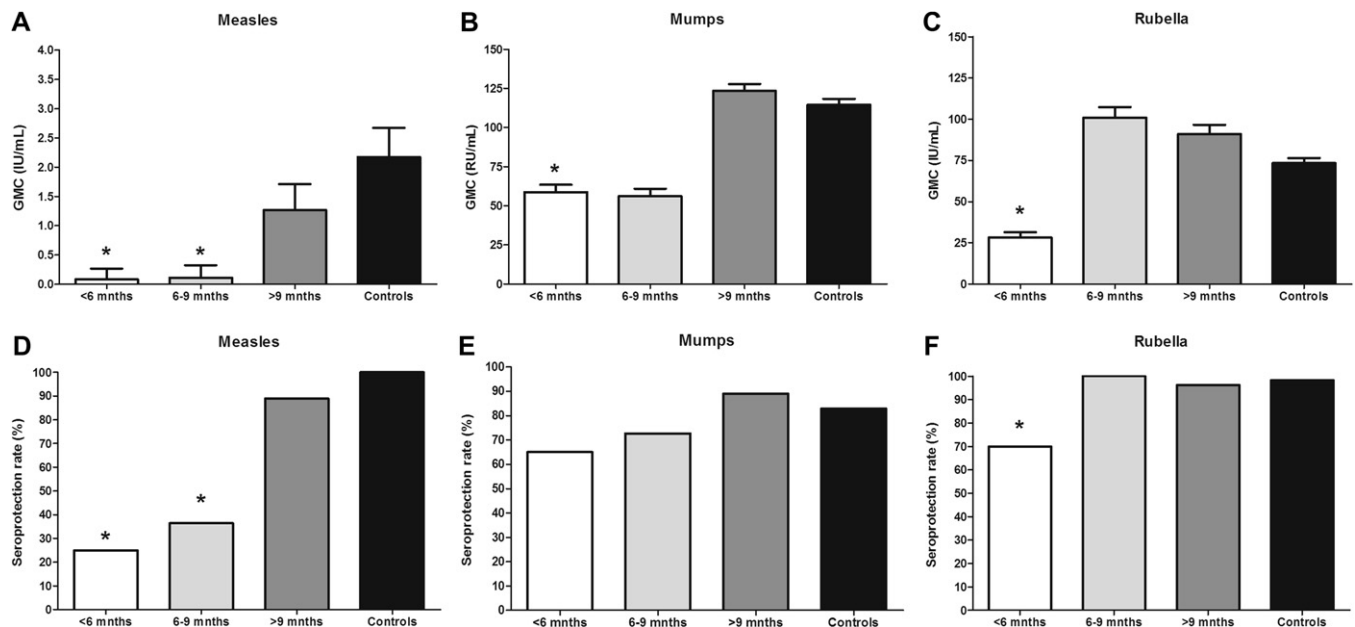


FIG 1. GMC $\pm$ SE (A-C) and seroprotection proportions (D-F) against MMR in subgroups of patients vaccinated after the administration of IVIG based on the interval in months between the administration of IVIG and MMR vaccination (<6 months, $n = 20$; 6-9 months, $n = 11$; and >9 months, $n = 27$). * $P < .05$ compared to matched controls.

has been shown that measles vaccination may fail in young children even though levels of maternal antibodies declined to undetectable levels.⁸

We evaluated the MMR vaccine effectiveness in our large cohort of patients with KD and found a normal response in patients vaccinated *before* the IVIG administration, in contrast to prior findings.⁹ Results of the 58 patients vaccinated *after* the IVIG administration indicated a reduced effectiveness of the mumps and rubella vaccination up to 6 months and 9 months for measles. We therefore recommend an interval of more than 9 months after IVIG administration. The 11-month interval recommendation by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics may be longer than strictly necessary.

Another clinically relevant finding is that 35% of the patients who received the MMR vaccine after the IVIG administration were vaccinated within 6 months, despite the Dutch guideline recommending a 6-month interval. The percentage was even substantially higher (18 of 23 = 78%) when only those patients were evaluated who were older than 8 months at the moment of treatment. These were the patients who did not automatically achieve the 6-month interval when they reached the age for vaccination. Our cohort of patients is referred from all over the country, suggesting that Dutch medical personnel carrying out the immunization program are generally unaware of the guidelines.

The measles component of the vaccine seems to be less immunogenic in the presence of passively acquired antibodies than the mumps and rubella components. There are 2 possible explanations. First, IVIG possibly contains higher levels of measles antibodies, as compared to the levels of mumps and rubella antibodies. Second, attenuated measles virus may be more easily hampered by IVIG than attenuated mumps and rubella virus. Both options (ie, increase in concentrations and avidity of

anti-measles IgG) were tested and could not be substantiated in 5 different IVIG batches (data not shown).

In conclusion, we recommend postponing the MMR vaccination to at least 9 months after IVIG administration and aim at an increased awareness of the guidelines.

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