Effects of the Live Attenuated Measles-Mumps-Rubella Booster Vaccination on Disease Activity in Patients With Juvenile Idiopathic Arthritis

A Randomized Trial

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Importance The immunogenicity and the effects of live attenuated measles-mumps-rubella (MMR) vaccination on disease activity in patients with juvenile idiopathic arthritis (JIA) are matters of concern, especially in patients treated with immunocompromising therapies.

Objectives To assess whether MMR booster vaccination affects disease activity and to describe MMR booster immunogenicity in patients with JIA.

Design, Setting, and Participants Randomized, multicenter, open-label clinical equivalence trial including 137 patients with JIA aged 4 to 9 years who were recruited from 5 academic hospitals in the Netherlands between May 2008 and July 2011.

Intervention Patients were randomly assigned to receive MMR booster vaccination (n=68) or no vaccination (control group; n=69). Among patients taking biologics, these treatments were discontinued at 5 times their half-lives prior to vaccination.

Main Outcomes and Measures Disease activity as measured by the Juvenile Arthritis Disease Activity Score (JADAS-27), ranging from 0 (no activity) to 57 (high activity). Disease activity in the year following randomization was compared between revaccinated patients and controls using a linear mixed model. A difference in JADAS-27 of 2.0 was the equivalence margin. Primary immunogenicity outcomes were seroprotection rates and MMR-specific antibody concentrations at 3 and 12 months.

Results Of 137 randomized patients, 131 were analyzed in the modified intention-to-treat analysis, including 60 using methotrexate and 15 using biologics. Disease activity during complete follow-up did not differ between 63 revaccinated patients (JADAS-27, 2.8; 95% CI, 2.1-3.5) and 68 controls (JADAS-27, 2.4; 95% CI, 1.7-3.1), with a difference of 0.4 (95% CI, −0.5 to 1.2), within the equivalence margin of 2.0. At 12 months, seroprotection rates were higher in revaccinated patients vs controls (measles, 100% vs 92% [95% CI, 84%-99%]; mumps, 97% [95% CI, 95%-100%] vs 81% [95% CI, 72%-93%]; and rubella, 100% vs 94% [95% CI, 86%-100%], respectively), as were antibody concentrations against measles (1.63 vs 0.78 IU/mL; $P=.03$), mumps (168 vs 104 RU/mL; $P=.03$), and rubella (69 vs 45 IU/mL; $P=.01$). Methotrexate and biologics did not affect humoral responses, but low patient numbers precluded definite conclusions.

Conclusion and Relevance Among children with JIA who had undergone primary immunization, MMR booster vaccination compared with no booster did not result in worse JIA disease activity and was immunogenic. Larger studies are needed to assess MMR effects in patients using biologic agents.

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JUVENILE IDIOPATHIC ARTHRITIS (JIA) is the most common childhood rheumatic disease, with a prevalence between 16 and 150 per 100 000.[1] Patients with JIA may be susceptible to infections through the immunosuppressive effect of their disease or its treatment.[2,3] Preventing infections in patients with JIA requires effective and safe vaccinations that induce protective immune responses, have no severe adverse effects, and do not affect JIA disease activity.

The live attenuated measles-mumps-rubella (MMR) vaccine is administered to children worldwide via national immunization programs (NIPs). In immunocompromised patients, concern exists about the safety of live attenuated vaccines given the theoretical risk of enhanced replication of the attenuated pathogens in these patients.[4] The safety of MMR vaccination in particular has been questioned in patients with JIA because the rubella component has been linked to the induction of arthritis in small uncontrolled studies.[5] Although controlled trials have failed to establish this association,[6] the pos-

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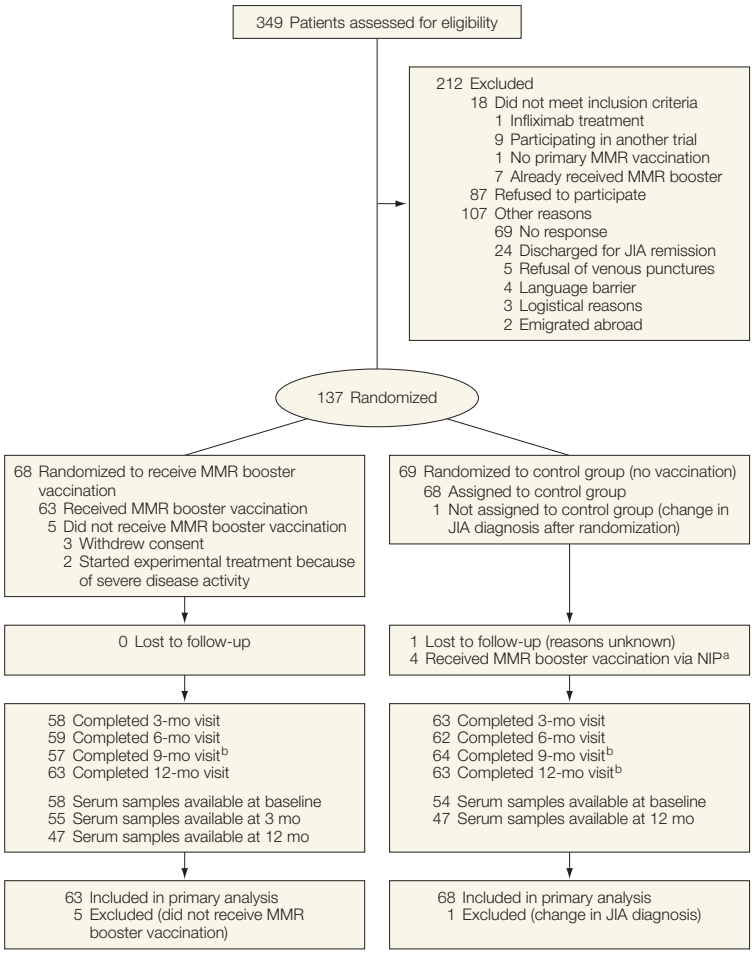
Figure 1. Participant Flow



MMR indicates measles-mumps-rubella; JIA, juvenile idiopathic arthritis.
[a] Four patients in the control group aged 8 to 9 years received the MMR booster vaccination via the National Immunization Program (NIP) at 6-month (n=1), 9-month (n=1), or 12-month (n=2) follow-up. Visits after MMR booster vaccination were excluded from the analysis.
[b] Disease activity as measured by the Juvenile Arthritis Disease Activity Score involving 27 joints could not be calculated for 1 of the patients who completed this visit.

sible relationship between MMR vaccination and arthritis raised concerns about the effect of MMR vaccination on JIA disease activity. Initial investigations have shown no worsening of disease activity after revaccination,[7,8] but these have been small or retrospective studies lacking a nonvaccinated control group, leaving both the effects of MMR vaccination on JIA disease activity and its immunogenicity controversial, particularly in patients prescribed immunosuppressive drugs.

To assess whether MMR booster vaccination affects disease activity in patients with JIA and to describe the humoral immune response induced by MMR booster vaccination, we conducted a randomized clinical equivalence trial. For 12 months, disease activity and seroprotection rates were compared between revaccinated and control patients.

METHODS

Study Design and Participants

A multicenter, open-label randomized trial was performed in the pediatric rheumatology department of 5 Dutch university medical centers (Utrecht, Groningen, Amsterdam, Rotterdam, and Maastricht). Patients aged 4 to 9 years were recruited from May 2008 to July 2011. All patients meeting the International League of Associations for Rheumatology criteria for JIA[9] were eligible for enrollment, including patients taking glucocorticoids, disease-modifying antirheumatic drugs, or the biologics etanercept or anakinra. Exclusion criteria were use of infliximab (because of its tendency to accumulate during treatment), participation in another trial, and primary immunodeficiencies (FIGURE 1).

In the Netherlands, the MMR booster vaccination is routinely administered via the NIP at age 9 to 10 years. To enable a randomized approach and at the same time avoid withholding a routine immunization from patients, patients aged 4 to 9 years who had not yet received their routine MMR booster vaccination were eligible for participation. This way, patients randomized into the control group would eventually receive their routine MMR booster via the NIP after completion of the study. Patients were randomized using a computer-generated sequence operated by an independent research organization (Julius Clinical Research). Randomization at a 1:1 ratio, in randomly varying block sizes, was stratified by center. Treatment allocation was concealed to patients, research staff, and clinical staff until randomization. Patients and clinical staff could not be masked to allocation because no placebo vaccines were used in the control group. Research staff was similarly not masked because they had to allocate patients to the vaccination group and administer the vaccine. Laboratory staff measuring the erythrocyte sedimentation rate and MMR-booster induced serologic responses were masked to treatment allocation.

The study was ethically approved by the Central Committee on Research Involving Human Subjects (The Hague, the Netherlands) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients' parents/guardians.

Vaccination

The MMR vaccines applied in the Dutch NIP were used; ie, MMR-NVI (Netherlands Vaccine Institute) and M-M-RVAXPRO (Sanofi Pasteur). These mutually exclusive vaccines both contain live attenuated measles (Edmonston strain), mumps (Jeryl Lynn strain), and rubella (Wistar RA 27/3 strain) viruses.

Vaccination was postponed in cases of fever or infections within 48 hours or methylprednisolone pulse therapy within 1 month prior to vaccination. Because current consensus-based guidelines recommend withholding live attenuated vaccines in patients using biologics,[10] biologics were stopped prior to vaccination at 5 times their half-life (ie, etanercept was stopped 2 weeks prior until 1 week after and anakinra 2 days prior until 3 days after vaccination).

Study visits occurred at baseline and every 3 months for 12 months in conjunction with regular clinical care. When regular visits were not required, no study visits were scheduled.

Outcome Measures

The primary outcome measure was JIA disease activity as measured by the Juvenile Arthritis Disease Activity Score including 27 joints (JADAS-27).[11] The JADAS-27 is a composite score consisting of 4 of the 6 American College of Rheumatology core criteria for JIA disease activity.[12] The JADAS-27, ranging from 0 (no disease activity) to 57 (maximum activity), is calculated as the sum of its components: the physician's global assessment of disease activity; the parent's global assessment of overall well-being, measured on a 10-cm visual analog scale ranging from 0 ("very well") to 10 ("very poor"); the number of joints with active arthritis; and normalized ESR.

The secondary measure of disease activity was the risk of a flare and the total number of flares in the year after MMR vaccination.[13] A disease flare was defined as worsening of 30% or more in at least 3 of the 6 core criteria, without simultaneous improvement of 30% or more in at least 2 criteria, with at least 2 active and/or limited joints if the joint count was used as a criterion of a flare.[13] Flare occurrence was assessed at every study visit, and the cumulative number of flares was assessed at 12 months.

Throughout follow-up, medication use was documented. In revaccinated patients, infection with the attenuated viruses and adverse events reported in standardized diaries for 12 days after vaccination were documented as measures for vaccine safety.

To assess vaccine efficacy, signs of measles, mumps, or rubella disease were registered using the MMR surveillance worksheet of the Centers for Disease Control and Prevention.[14] Since the incidence of naturally occurring infections is low in the Netherlands,[15] immunogenicity was used as surrogate measure of efficacy.

MMR-specific immunoglobulin G antibody concentrations, expressed as geometric mean concentrations (GMCs), were determined with a bead-based multiplex immunoassay using Luminex technology as described previously[16] in 1 laboratory (National Institute of Public Health and the Environment [RIVM], Bilthoven, the Netherlands). Cutoff values for seroprotection were 0.20 IU/mL for measles and 10 IU/mL for rubella.[17] Since no international reference serum for mumps exists, an in-house reference was used, with a seroprotection level of 45 RIVM units (RU)/mL.[18]

Primary immunogenicity outcome measures were seroprotection rates and MMR-specific GMCs at 12 months. In revaccinated patients, the increase in MMR-specific GMCs 3 months after vaccination was also described.

Statistical Analysis

A difference of 2.0 points in the JADAS-27 was the equivalence margin and therefore considered clinically relevant.[19] A treatment group difference of less than 2.0 points in the JADAS-27 in either direction would lead to the final conclusion of no effect of vaccination on disease activity. Detecting this difference with a power of 85% at a 2-sided significance level of .05 requires a sample size of 59 patients in each group. To compensate for dropouts, 10% more patients were included, leading to a sample size of 130 patients.

Baseline characteristics and medication use during follow-up were compared between the 2 groups with the Pearson χ^2 test, Fisher exact test, Mann-Whitney *U* test, or *t* test, as appropriate.

Statistical analysis was performed on data from the modified intention-to-treat population, defined as all randomized participants who did not withdraw. If patients in the control group were vaccinated via the national immunization program during follow-up, only visits prior to their MMR booster were included in the analysis. Disease activity (JADAS-27) was compared between revaccinated and control patients throughout follow-up using a linear mixed model, which enables a repeated-measurement analysis with irregularly timed measurements, and included randomization group and time as fixed factors, a random intercept, and a random effect of time to account for clustering of observations within individuals. The nonsignificant interaction between randomization group and time was dropped from the model. Preplanned subgroup analyses were performed for JIA subtypes and for patients taking methotrexate and post hoc subgroup analysis was performed in patients taking biologics. When the limit of the 95% confidence interval of the difference in JADAS-27 lay within the zone of indifference (ie, a JADAS-27 difference of 2.0), we concluded that disease activity in the 2 groups was equivalent.

To assess whether revaccination induced flares, the 12-month cumulative number of flares was compared between groups using the *t* test and by calculating the relative risk of a flare at 3 months and throughout 12-month follow-up using the Pearson χ^2 test.

We hypothesized that MMR booster vaccination would increase

the seroprotection rate and MMR-specific antibody concentrations. At 12 months, seroprotection rates were compared between revaccinated patients and controls using the Fisher exact test, and MMR-specific GMCs were compared using the *t* test. The relative increase in MMR-specific GMCs 3 months after vaccination was tested by the *t* test for paired samples. The relative increase in MMR-specific antibodies and absolute MMR-specific GMCs were compared between patients with and without methotrexate or biologics at the time of vaccination using the Mann-Whitney *U* test and the *t* test, respectively. These comparisons (SPSS Inc) were 2-sided at a statistically significant α level of .05.

Table. Baseline Patient Characteristics

Characteristics	MMR Booster Group (n = 63)	Control Group (n = 68)
Age, mean (95% CI), y	6.3 (5.9-6.7)	6.5 (6.2-6.9)
Disease duration at inclusion, mean (95% CI), y	2.7 (2.3-3.1)	3.0 (2.6-3.5)
Female, No. (%)	46 (73)	41 (60)
Seroprotection rate, No. (%)[a]		
Measles	56 (97)	50 (93)
Mumps	45 (78)	47 (87)
Rubella	52 (90)	54 (100)
IgG concentration, geometric mean (95% CI)		
Measles, IU/mL	1.60 (1.14-2.25)	1.30 (0.90-1.87)
Mumps, RU/mL	101 (74-137)	117 (86-160)
Rubella, IU/mL	29 (15-56)	51 (41-64)
Juvenile idiopathic arthritis subtype, No. (%)		
Oligoarticular, persistent	32 (51)	40 (59)
Oligoarticular, extended	8 (13)	4 (6)
Polyarticular	14 (22)	13 (19)
Rheumatoid factor–positive	1/14	1/13
Systemic onset	6 (10)	9 (13)
Psoriatic arthritis	3 (5)	2 (3)
Disease activity		
JADAS-27, mean (95% CI)	2.8 (1.8-3.7)	2.7 (1.8-3.5)
Joints with active arthritis, median (IQR)	0 (0-1)	0 (0-0)
Parent's/patient's well-being, median (IQR)[b]	0.3 (0-2.0)	0.5 (0-2.0)
CHAQ disability index, median (IQR)[c]	0.3 (0-0.7)	0.3 (0-0.6)
Physician's global assessment of disease activity, median (IQR)[b]	0 (0-1.0)	0.2 (0-1.0)
Erythrocyte sedimentation rate, median (IQR), mm/h	10 (5-14)	9 (4-15)
Medication use		
Methotrexate, No. (%)	29 (46)	31 (46)
Dosage, median (IQR), mg/m^2/wk	10.6 (9.7-11.2)	11.4 (8.9-15.9)
Nonsteroidal anti-inflammatory drugs, No. (%)	38 (60)	36 (53)
Leflunomide, No. (%)	1 (2)	1 (1)
Tumor necrosis factor antagonist, No. (%)[d]	6 (10)	4 (6)
Dosage, median (IQR), mg/wk	15 (11-22)	21 (16-25)
Interleukin 1 receptor antagonist, No. (%)	3 (5)	2 (3)
Dosage, median (IQR), mg/kg	1.6 (1.2-1.8)	1.4 (0.5-2.3)
Oral glucocorticoids, No. (%)[e]	2 (3)	1 (2)

Abbreviations: CHAQ, Childhood Health Assessment Questionnaire; IgG, immunoglobulin G; IQR, interquartile range; JADAS-27, Juvenile Arthritis Disease Activity Score including 27 joints; MMR, measles-mumps-rubella; RU, National Institute of Public Health and the Environment (RIVM) units.
[a] MMR-specific antibody concentrations could be assessed in 112 patients at baseline.
[b] A 10-cm visual analog scale was used in which higher scores indicate poorer well-being or more active disease.
[c] CHAQ scores range from 0 (best) to 3 (worst).
[d] The type of tumor necrosis factor antagonist used was etanercept in all patients except for 1 patient in the MMR group who took adalimumab, 10 mg/wk.
[e] Glucocorticoid dosages in the MMR group were 0.19 and 5.0 mg/kg/d; the patient in the control group took 2.4 mg/kg/d.

RESULTS

Baseline Patient Characteristics

Of 349 patients screened, 137 underwent randomization and 131 were analyzed in the modified intention-to-treat analysis (Figure 1). Disease activity scores could not be calculated in 1 or more visits of 26 patients (20%). Patients with missing JADAS-27 data, primarily those with oligoarticular JIA (n = 20 [78%]) were equally distributed between the MMR booster group (n = 13 [21%]) and the control group (n = 13 [19%]). Patients with and without missing JADAS-27 data received similar treatments. Similarly, patients with and without missing serum samples had comparable demographic and clinical characteristics.

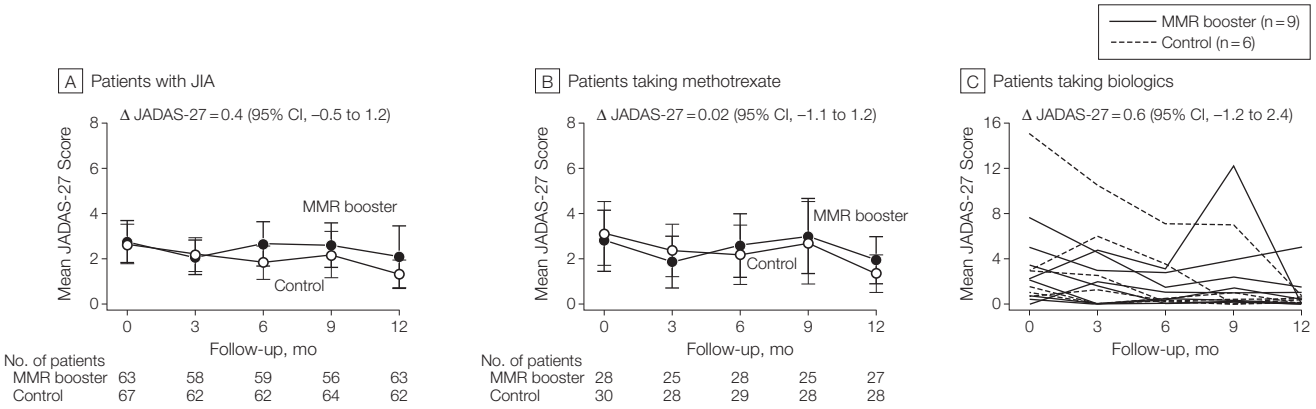
No significant differences in baseline characteristics existed (TABLE) except for lower seroprotection rates against rubella in the MMR booster group (n = 52 [90%]) compared with the control group (n = 54 [100%]; $P = .03$). Nine patients in the MMR booster group were taking biologics; 2 of these took oral glucocorticoids concomitantly.

JIA Disease Activity in Revaccinated Patients and Controls

The mean JADAS-27 during the total follow-up period did not differ significantly between revaccinated patients and control patients, as the JADAS-27 difference was within the equivalence margin of 2.0 points (JADAS-27 difference over time, 0.4; 95% CI, −0.5 to 1.2) (FIGURE 2A). This was also true for patients taking methotrexate (JADAS-27 difference over time, 0.02; 95% CI, −1.1 to 1.2) (Figure 2B) or biologics (JADAS-27 difference over time, 0.6; 95% CI, −1.2 to 2.4) (Figure 2C) and for various JIA subtypes, although small subgroup sample sizes did not allow conclusions.

The mean number of flares per patient did not differ significantly between the MMR booster group (0.44; 95% CI, 0.28-0.61) and the control group (0.34; 95% CI, 0.20-0.49), nor did the percentage of patients with 1 or more flare during follow-up (FIGURE 3).

Figure 2. Mean Disease Activity Levels During 12 Months of Follow-up by Randomization Group



JADAS-27 indicates Juvenile Arthritis Disease Activity Score including 27 joints; JIA, juvenile idiopathic arthritis; MMR, measles-mumps-rubella. Error bars indicate 95% CIs. Δ indicates the difference in JADAS-27 scores over time between randomization groups.

The relative risk of a flare in revaccinated patients compared with controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up (FIGURE 4). Similar results were found in patients using methotrexate or biologics, although small patient numbers precluded definite conclusions.

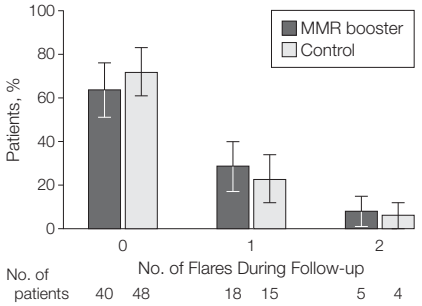
During follow-up, the numbers of patients treated with intra-articular glucocorticoid injections (5 revaccinated patients [8%] vs 7 controls [10%]; $P=.62$) or methotrexate (36 revaccinated patients [57%] vs 32 controls [47%]; $P=.25$) did not differ significantly between revaccinated and control patients. Three patients, all in the control group, started oral glucocorticoids during follow-up. Of those starting biologics, 2 were in the control group and 1 was in the MMR booster group.

No disease due to infections with attenuated viruses occurred in patients treated with immunosuppressive drugs. Transient local injection site reactions occurred in the majority of patients (n=37 [65%]). In 2 of the 3 revaccinated patients reporting increased joint problems, this was caused by stopping biologic treatment prior to vaccination. Serious events were comparable between groups and were judged unrelated to MMR booster vaccination (all adverse events are summarized in eTable 1 and eTable 2; see http://www.jama.com).

Immunogenicity of MMR Revaccination

All revaccinated patients were seroprotected against measles and rubella after vaccination, including patients taking biologics at the time of revaccination. Two (3%) were seronegative for mumps at 12 months. One patient was taking methotrexate, 9.3 mg/m^2 per week, at the time of vaccination and showed a small increase in mumps-specific antibodies at 3 months (from 26 to 62 RU/mL), but antibodies dropped below seroprotection levels (35 RU/mL) at 12 months. The increase in measles- and rubella-specific antibodies was also marginal (both 1.1-fold). The other patient had active oligoarticular JIA and methotrexate, 8.3 mg/m^2 per week, was started just after vaccination, followed by etanercept at 9 months. This patient was seronegative for measles, mumps, and rubella at baseline and failed to produce a serologic response to mumps, whereas measles-specific antibodies increased 17-fold and rubella-specific antibodies 179-fold. At 12 months of follow-up, 5 controls (8%) were seronegative for measles. One of these controls had seroprotective antibody levels against measles at baseline. Twelve controls (19%) were seronegative for mumps, 4 of whom had seroprotective antibody concentrations at baseline, and 4 controls (6%) had turned seronegative for rubella.

Figure 3. Percentage of Patients With Flares by Randomization Group



MMR indicates measles-mumps-rubella. Error bars indicate 95% CIs.

At 3 months after vaccination, increased antibody concentrations against measles, mumps, and rubella were detected in revaccinated patients (FIGURE 5). At 12 months after vaccination, antibody concentrations were significantly higher compared with controls against measles, mumps, and rubella. The humoral responses induced by revaccination did not differ significantly between patients with and without methotrexate or biologics, but patient numbers were too small for unambiguous conclusions (eFigure).

No measles, mumps, or rubella disease occurred in revaccinated patients. In the control group, 1 patient presented with acute-onset parotitis at 12 months after inclusion, but laboratory testing for mumps was not performed. This patient had protective mumps-specific antibody levels (220 RU/mL) at baseline.

DISCUSSION

In this randomized trial, MMR booster vaccination did not result in a significant difference in JIA disease activity and was immunogenic in patients with JIA. Vaccination generated high seroprotection rates (97%-100%) and a sustained increase in MMR-specific antibodies.

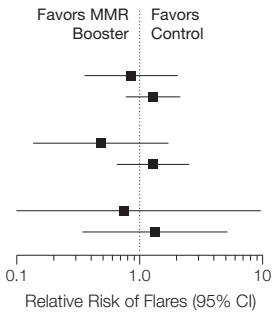
The safety of MMR vaccination has been questioned because disease flares have been described after MMR vaccination.[20] Our trial does not show an effect of vaccination on disease activity. Our results are supported by previous studies (1 nested case-control study including 15 patients and 1 retrospective study including 207 patients) showing that MMR booster vaccination does not affect disease activity.[7,8] Our randomized design enabled us to demonstrate that there is no relationship between MMR booster vaccination and JIA disease activity. Even in patients taking methotrexate, the difference in the JADAS-27 between revaccinated patients and controls (0.02 points; 95% CI, −1.1 to 1.2) was below the equivalence margin of 2.0.[19]

The increasing use of biologics in JIA treatment requires insight into the safety and efficacy of live attenuated vaccines in patients taking biologics. Current recommendations state that live attenuated vaccines should generally be withheld in patients taking biologics because of the lack of safety data, although booster vaccinations can be considered on a case-by-case basis.[10] In our study, the 9 patients taking biologics who received the MMR booster showed no disease caused by attenuated viruses or severe adverse events. This concurs with other studies of live attenuated vaccines in patients taking tumor necrosis factor (TNF) antagonists: no serious adverse events occurred after the MMR booster in 5 patients with JIA or after the yellow fever booster in 21 patients with rheumatoid arthritis .[7,21] Although these data suggest that booster live attenuated vaccines are indeed safe in patients taking TNF antagonists, larger studies are required for definite conclusions. Furthermore, it remains unknown whether stopping biologics prior to vaccination is necessary for safety reasons. Biologics were continued in the 2 previous studies without significant adverse events.[7,21]

High vaccine-induced seroprotection rates are crucial to maintain herd immunity.[22] In this study, MMR revaccination induced high seroprotection rates in patients with JIA, including those taking methotrexate or biolog-

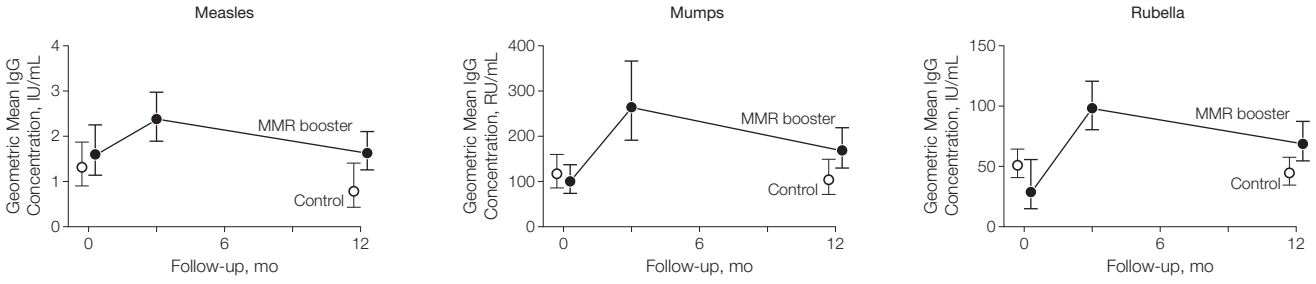
Figure 4. Relative Risk of a Flare at 3 Months and of at Least 1 Flare During 12 Months of Follow-up in Total Cohort and Subgroups Taking Methotrexate or Biologics

Participants	Patients, Total No.		Patients With Flares, No.		Relative Risk (95% CI)
	MMR Booster	Control	MMR Booster	Control	
Total cohort					
Flares at 3 mo	59	63	8	10	0.9 (0.4-2.0)
Flares at 12 mo	63	67	23	19	1.3 (0.8-2.1)
Methotrexate					
Flares at 3 mo	26	29	3	7	0.5 (0.1-1.7)
Flares at 12 mo	28	30	12	10	1.3 (0.7-2.5)
Biologics					
Flares at 3 mo	8	6	1	1	0.8 (0.1-9.8)
Flares at 12 mo	9	6	4	2	1.3 (0.3.-5.1)



MMR indicates measles-mumps-rubella.

Figure 5. Serum Antibody Concentrations Against Measles, Mumps, and Rubella in Revaccinated Patients and Controls



Geometric mean antibody concentrations against measles, mumps, and rubella are shown at baseline (n=58 revaccinated patients and n=54 controls), at 3 months (n=55 revaccinated patients), and at 12 months (n=47 revaccinated patients and n=47 controls). A significant increase in MMR-specific antibody concentrations at 3 months compared with baseline was found in revaccinated patients for mumps ($P<.001$) and rubella ($P=.01$). Significant differences between revaccinated and control patients were found at 12 months for measles ($P=.03$), mumps ($P=.03$), and rubella ($P=.01$). IgG indicates immunoglobulin G; MMR, measles-mumps-rubella; RU, National Institute of Public Health and the Environment (RIVM) units. Error bars indicate 95% CIs.

ics, comparable with seroprotection rates reported in healthy children after MMR revaccination.[23] These data are supported by increasing evidence that live attenuated vaccines are immunogenic in patients with JIA, including patients taking methotrexate and TNF antagonists.[10]

This study had several important limitations. Our data are not applicable to primary MMR vaccinations because these theoretically have a higher risk of disease caused by the live attenuated viruses. One primary live attenuated vaccination that has been studied in pediatric patients with rheumatic diseases is the varicella zoster vaccine. No severe adverse events, generalized varicella infection, herpes zoster, or worsening of disease activity occurred in 25 patients.[24] However, dissemination of rubella virus has been shown after primary rubella vaccination in healthy individuals.[25] It remains unknown whether this potential dissemination after primary MMR vaccination threatens patients with JIA, as the safety of primary MMR vaccination has not been studied in patients with JIA. Nevertheless, the main issue for patients with JIA is the safety of MMR booster vaccination because primary MMR vaccinations are generally administered before JIA onset.

Primarily patients with low disease activity were included because of physicians' and/or parents' hesitancy to vaccinate patients with active disease. Therefore, our conclusions may not pertain to patients with high disease activity. Nevertheless, the infection prevention induced by MMR booster vaccination may outweigh small individual risks.

Assessors of JIA disease activity were not blinded to treatment allocation. This is unlikely to have led to observer bias because the JADAS-27 is a composite score including an objective measure, the normalized ESR, measured by study staff blinded to treatment allocation. Normalized ESR values did not differ significantly between revaccinated and control patients at 3 months (ESR, 0.2 [95% CI, 0.0-0.3] mm/h vs 0.1 [95% CI, 0.0-0.2] mm/h; $P = .97$) and at 12 months (ESR, 0.2 [95% CI, 0.0-0.3] mm/h vs 0.1 [95% CI, 0.0-0.3] mm/h; $P = .25$).

To minimize the burden of participation, study visits occurred in conjunction with regular visits and serum samples were drawn only when required for daily clinical care. The bias introduced by the subsequent missing visits and/or serum samples is most likely minimal, as patient characteristics did not differ between patients with and without missing data.

Among children with JIA who had undergone primary immunization, the use of an MMR booster compared with no booster did not result in worse JIA disease activity and was immunogenic. Larger studies are needed to assess MMR effects in patients using biologic agents.

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REFERENCES

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369(9563):767-778.
2. Beukelman T, Xie F, Chen L, et al; SABER Collaboration. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. *Arthritis Rheum*. 2012;64(8):2773-2780.
3. Salvana EM, Salata RA. Infectious complications associated with monoclonal antibodies and related small molecules. *Clin Microbiol Rev*. 2009;22(2):274-290.
4. British Society for Rheumatology. *Vaccinations in the Immunocompromised Person: Guidelines for the Patient Taking Immunosuppressants, Steroids and the New Biologic Therapies*. London, England: British Society for Rheumatology; 2002.
5. Chantler JK, Tingle AJ, Petty RE. Persistent rubella virus infection associated with chronic arthritis in children. *N Engl J Med*. 1985;313(18):1117-1123.
6. Ray P, Black S, Shinefield H, et al; Vaccine Safety Datalink Team. Risk of chronic arthropathy among women after rubella vaccination. *JAMA*. 1997; 278(7):551-556.
7. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. *Rheumatology (Oxford)*. 2009;48(2):144-148.
8. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. *Ann Rheum Dis*. 2007;66(10):1384-1387.
9. Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004; 31(2):390-392.
10. Heijstek MW, Ott de Bruin LM, Bijl M, et al; EULAR. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis*. 2011;70(10):1704-1712.
11. Consolaro A, Ruperto N, Bazso A, et al; Paediatric Rheumatology International Trials Organisation. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;61(5):658-666.
12. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum*. 1997; 40(7):1202-1209.
13. Lovell DJ, Ruperto N, Goodman S, et al; Pediat-

ric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med*. 2008;359(8):810-820.
14. Centers for Disease Control and Prevention. *Manual for the Surveillance of Vaccine-Preventable Diseases.* In: Roush SW, McIntyre L, Baldy LM, eds. 4th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2008.
15. Rümke HC, Visser HK. Vaccinaties op de kinderleeftijd anno 2004, I: effectiviteit en acceptatie van het Rijksvaccinatieprogramma. *Ned Tijdschr Geneeskd*. 2004;148(8):356-363.
16. Smits GP, van Gageldonk PG, Schouls LM, van der Klis FR, Berbers GA. Development of a bead-based multiplex immunoassay for simultaneous quantitative detection of IgG serum antibodies against measles, mumps, rubella, and varicella-zoster virus. *Clin Vaccine Immunol*. 2012;19(3):396-400.
17. Thakur A, Pedersen LE, Jungersen G. Immune markers and correlates of protection for vaccine induced immune responses. *Vaccine*. 2012;30(33):4907-4920.
18. Andrews N, Pebody RG, Berbers G, et al. The European Sero-Epidemiology Network: standardizing the enzyme immunoassay results for measles, mumps and rubella. *Epidemiol Infect*. 2000;125(1):127-141.
19. Consolaro A, Bracciolini G, Ruperto N, et al; Paediatric Rheumatology International Trials Organization. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the Juvenile Arthritis Disease Activity Score. *Arthritis Rheum*. 2012;64(7):2366-2374.
20. Korematsu S, Miyahara H, Kawano T, et al. A relapse of systemic type juvenile idiopathic arthritis after a rubella vaccination in a patient during a long-term remission period. *Vaccine*. 2009;27(37):5041-5042.
21. Scheinberg M, Guedes-Barbosa LS, Mangueira C, et al. Yellow fever revaccination during infliximab therapy. *Arthritis Care Res (Hoboken)*. 2010;62(6):896-898.
22. Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol*. 2010;17(7):1055-1065.
23. Pebody RG, Gay NJ, Hesketh LM, et al. Immunogenicity of second dose measles-mumps-rubella (MMR) vaccine and implications for serosurveillance. *Vaccine*. 2002;20(7-8):1134-1140.
24. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. *Arthritis Care Res (Hoboken)*. 2010;62(7):1034-1039.
25. Frenkel LM, Nielsen K, Garakian A, Jin R, Wolinsky JS, Cherry JD. A search for persistent rubella virus infection in persons with chronic symptoms after rubella and rubella immunization and in patients with juvenile rheumatoid arthritis. *Clin Infect Dis*. 1996;22(2):287-294.

A man, to be greatly good, must imagine intensely and comprehensively; he must put himself in the place of another and of many others; the pains and pleasures of his species must become his own.

—Percy Bysshe Shelley (1792-1822)