Varicella Immunogenicity with 1- and 2-Dose Regimens of Measles-Mumps-Rubella-Varicella Vaccine

Henry R. Shinefield, Steve Black, and Barbara J. Kuter

A quadrivalent vaccine combining measles, mumps, rubella, and varicella antigens (MMRV) was developed to increase the coverage of varicella vaccine and reduce the number of injections children receive. Although the varicella antigen is as immunogenic in the latest formulation of MMRV vaccine as when it is administered alone, up to 14% of vaccine recipients do not achieve protective levels of anti-varicella antibodies after a single dose, which can result in breakthrough varicella. A second dose of varicella vaccine raises response rates to 99% and was recently recommended by the Advisory Committee on Immunization Practices. Giving the second dose 3 months after the first (at ~15 months of age) would provide more protection against varicella but would necessitate a change in the childhood vaccination schedule, which currently calls for a second dose of MMRV vaccine between the ages of 4 and 6 years.

Varicella vaccine (Varivax; Merck) was introduced as a routine childhood vaccine in the United States in 1995. Administration of varicella vaccine at the same time as other childhood immunizations, including the measles-mumps-rubella vaccine (henceforth referred to as “MMR”), was shown to be generally well tolerated and immunogenic [1]; however, the rates of varicella vaccine coverage have not risen as high as those of MMR coverage. In 2004, 93% of children in the United States had received at least 1 dose of MMR by 3 years of age, but only ~88% had been vaccinated against varicella [2].

Inclusion of varicella vaccine with the 3 MMR antigens in a single combination vaccine (MMRV) would bring varicella coverage in line with that of MMR and would reduce the number of injections that children receive. Various vaccine formulations combining these 4 antigens have been developed over the past 20 years [3–5], but the response to the varicella component in early versions was generally lower in the combined vaccines than when varicella vaccine was given separately [1, 5]. For example, a combination vaccine that contained a varicella-zoster virus (VZV) dose of ~4000 pfu, slightly higher than the ~3500 pfu in Varivax, induced geometric mean titers (GMTs) of antibodies to the varicella component that were only approximately half of those induced when varicella vaccine was given as a separate injection at the same time as MMR (GMTs of 6.8 gpELISA units/mL after MMRV vs. 12.4 gpELISA units/mL after MMR plus varicella ~6 weeks after vaccination; P<.001) [6]. In a different formulation of MMRV (Priorix Tetra; GlaxoSmithKline) evaluated by another vaccine manufacturer, reducing the amount of the measles and mumps antigens increased the immune response to varicella, suggesting that there was an interaction between these components and varicella when they were administered at a single injection site [4].

More recently, MMRV was reformulated by Merck, using higher doses of VZV. The results of a dose-
response study [7] indicated that a sufficiently high dose could overcome the interaction with MMR that had resulted in lowered varicella immunogenicity. In a study of 480 children 12–23 months of age, a formulation of MMRV with 4.81 \( \log_{10} \) \( \sim \)64,565) pfu of VZV (ProQuad; Merck) was used to evaluate the safety and immunogenicity of 1 or 2 doses of MMRV in comparison with single doses of MMR and varicella vaccine given concomitantly [8]. Immunogenicity was comparable when the children received a single dose of MMRV plus placebo or MMR plus varicella vaccine (table 1), confirming that the earlier low response to varicella vaccine had been overcome. A separate study of 1915 children 12–15 months of age [9] showed that the immunogenicity of the MMRV components was not significantly affected by the addition of Haemophilus influenzae type b/hepatitis B (Hib/HepB) and diphtheria-tetanus-acellular pertussis (DTaP) vaccinations at the same visit (but at different injection sites), potentially simplifying the immunization schedule further. Specifically, the response rates (89.7% and 90.9%) and GMTs (13.8 and 15.4 gpELISA units/mL) to the varicella component of MMRV were similar whether Hib/HepB and DTaP were given on the same day or 6 weeks later, respectively [9]. The response to the pertussis antigen was significantly lower when all 3 combination vaccines were given concomitantly [8], a level shown to correlate with long-term protection [13]. Furthermore, outbreaks of chickenpox have occurred in vaccinated children [14–16]. Breakthrough disease tends to be less severe than natural disease [17–20], but the virus can be spread to susceptible individuals, and the presence of any varicella rash is associated with a higher subsequent risk of herpes zoster [21–23]. The Advisory Committee on Immunization Practices recently provisionally recommended a second dose of a varicella-containing vaccine [24]. A second dose of varicella vaccine would increase protection against natural varicella, because 99% of those receiving a second dose achieve seroprotective titers \( \geq 5 \) gpELISA units/mL with a substantial boost in GMT (table 1) [8, 10, 11, 25]. In addition, the recommendation for a second dose of varicella vaccine might mean that children who missed the first recommended dose will be more likely to receive at least 1 dose.

MMR is already recommended as a 2-dose regimen, with a first dose routinely given at 12–15 months of age, followed by a booster at school entry (4–6 years of age), to increase the likelihood of measles seroconversion [26–28]. Current practice

### Table 1. Measles, mumps, rubella, and varicella response rates and geometric mean titers (GMTs) \( \sim \)6 weeks after vaccination.

<table>
<thead>
<tr>
<th>Group, parameter</th>
<th>Varicella(^a)</th>
<th>Measles(^b)</th>
<th>Mumps(^b)</th>
<th>Rubella(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRV + placebo dose 1 ((N = 323))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.(^c)</td>
<td>250</td>
<td>302</td>
<td>295</td>
<td>304</td>
</tr>
<tr>
<td>Response rate (95% CI), %</td>
<td>91.2 (87.0–94.4)</td>
<td>96.0 (93.2–97.9)</td>
<td>99 (97.1–99.8)</td>
<td>95.1 (92.0–97.2)</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>13.0 (11.8–14.4)</td>
<td>284.7 (255.0–317.8)</td>
<td>94.5 (83.1–107.4)</td>
<td>106.2 (95.9–117.7)</td>
</tr>
<tr>
<td>MMR + V ((N = 157))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.(^c)</td>
<td>128</td>
<td>145</td>
<td>150</td>
<td>153</td>
</tr>
<tr>
<td>Response rate (95% CI), %</td>
<td>92.2 (86.1–96.2)</td>
<td>100 (97.5–100)</td>
<td>98.7 (95.3–99.8)</td>
<td>92.8 (87.5–96.4)</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>13.3 (11.7–15.1)</td>
<td>201.0 (177.2–228.1)</td>
<td>68.1 (57.0–81.4)</td>
<td>101.9 (86.6–120.0)</td>
</tr>
<tr>
<td>MMRV + placebo dose 2 ((N = 310))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.(^c)</td>
<td>239</td>
<td>288</td>
<td>283</td>
<td>290</td>
</tr>
<tr>
<td>Response rate (95% CI), %</td>
<td>99.2 (97.0–99.9)</td>
<td>98.6 (96.5–99.6)</td>
<td>100 (98.7–100)</td>
<td>94.8 (91.6–97.1)</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>588.1 (494.1–699.9)</td>
<td>371.6 (334.5–412.8)</td>
<td>227.9 (202.8–256.1)</td>
<td>137.9 (122.9–154.8)</td>
</tr>
</tbody>
</table>

\(^a\) Measured by glycoprotein ELISA (gpELISA). Response rate is based on initially seronegative subjects \( \leq 0.6 \) gpELISA units/mL with postvaccination varicella-zoster virus antibody titers of \( \geq 5 \) gpELISA units/mL.

\(^b\) Measured by ELISA. Response rate for measles, mumps, and rubella is the percentage of initially seronegative subjects who became seropositive after vaccination.

\(^c\) No. of initially seronegative subjects in each treatment group with evaluable serological test results.

Adapted from [8], with permission from Lippincott Williams & Wilkins. CI, confidence interval; MMR, measles-mumps-rubella vaccine; MMRV, measles-mumps-rubella-varicella vaccine; V, varicella vaccine.
is to administer varicella vaccine at the same time as the first dose of MMR. The use of MMRV for both doses according to the current schedule for MMR would enable a second dose of varicella vaccine to be added without increasing the number of injections. A booster dose of varicella vaccine alone 4–6 years after initial vaccination stimulated an anamnestic response in the first week after the second dose, and GMTs remained high at 6 weeks (218.8 gpELISA units/mL) and 3 months (119.0 gpELISA units/mL) [29]. A booster dose of MMRV provided a similarly strong response 6 weeks after vaccination in children 4–6 years of age who had received separate MMR and varicella vaccinations for the primary immunization (317.0 gpELISA units/mL for MMRV vs. 212.4 gpELISA units/mL for a second dose of MMRV plus varicella) [25]. Similar robust immune responses and increased response rates are seen when the booster dose of varicella vaccine is given 3 months after the primary vaccination rather than 4–6 years later [11, 30]. Although an earlier booster dose would provide the added protection sooner, it would not fit with the current schedule for MMR and so would have to be administered as a separate injection of varicella vaccine. Other alternatives would be to change the schedule for MMR, so that a second dose of MMRV could be administered as early as 15–18 months of age [24, 31], or to allow flexibility in the routine vaccination schedule so that all 4 antigens could be administered anywhere between 15 months and 4–6 years of age.

Protective levels of antibodies to a single dose of varicella vaccine have been shown to persist for many years [17, 32, 33]. Although very long-term assessments are not yet possible with MMRV, varicella antibody levels of ≥5 gpELISA units/mL were present 1 year after vaccination with MMRV in 97.5% of those who had experienced seroconversion by 6 weeks [34]; measles, mumps, and rubella antibodies were present in 98.9%, 96.7%, and 99.6%, respectively. This rate is consistent with previous findings at 1 year for varicella vaccine alone [10].

Optimizing the response to the varicella component of MMRV has been a long process that has finally been successful. A quadrivalent vaccine is now available that elicits a strong immune response to varicella in most children. The addition of a second dose of MMRV would provide better protection against varicella without adding an additional injection to the childhood immunization schedule.

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References

20. Johnson CE, Shurin PA, Fattal D, Rome LP, Kumar ML. Live atten-