Protective Immunity in Macaques Vaccinated with Live Attenuated, Recombinant, and Subunit Measles Vaccines in the Presence of Passively Acquired Antibodies

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The presence of maternal antibodies is one of the main causes of measles vaccine failure. To evaluate the interference of passively acquired antibodies with vaccine efficacy, macaques (n = 16) were vaccinated with live attenuated measles vaccine in the presence or absence of passively acquired measles virus–specific monkey serum antibodies. As little as 0.1 IU of virus-neutralizing antibody/mL of serum abrogated the induction of specific serum IgM, IgG, and virus-neutralizing antibodies. This effect was also demonstrated in monkeys vaccinated with live recombinant vaccinia virus expressing the hemagglutinin and fusion proteins of measles virus but not in monkeys vaccinated with the same proteins incorporated into immune-stimulating complexes. All of the monkeys vaccinated in the presence of virus-neutralizing antibodies (n = 9) were still largely protected from intratracheal challenge with wild type virus. This protection is probably mediated by the observed specific T lymphocyte responses.

Infection with measles virus (MV) is generally believed to provide lifelong protective immunity against measles in humans [1, 2]. There is evidence to suggest that this immunity is based on the continued presence of virus-neutralizing (VN) antibodies directed against the hemagglutinin (H) and fusion (F) glycoproteins of MV and on the presence of virus-specific T lymphocytes [2−4]. Infection with vaccine virus also leads to an efficient stimulation of these immune responses, although there are indications that the vaccine-induced levels of VN antibody and specific T cell responses are considerably lower [5−8].

Although measles vaccination has been quite successful in developing countries, the World Health Organization estimates that worldwide, 45 million cases of measles continue to occur annually, of which >1 million are fatal [2, 9, 10]. The most important cause of measles vaccine failure, which is predominantly observed in developing countries, is generally believed to be interference by maternally derived MV-specific antibodies at the time of vaccination [11−13]. The inability of the presently used live attenuated vaccines to induce protection in the presence of maternal antibodies and the continued circulation of MV in partly vaccinated populations [14−18] would strongly favor the use of vaccines that are effective in the presence of MV-neutralizing antibodies [9, 10, 12, 13, 19]. This would allow vaccination at an earlier age, provided that the infant’s immune system is sufficiently mature to mount the required immune response. Several attempts, albeit all with limited success, have been made to achieve this goal, including the use of high-titered vaccines. Although high-titered live measles vaccines have been shown to improve seroconversion in young infants (4−6 months of age) [10, 20], they have also been associated with an increased mortality in children during the first years following vaccination in certain developing countries [21].

Recently, we developed a macaque model for infection with either wild type or live attenuated measles viruses (MV-Bil and MV-Schwarz, respectively), in which the kinetics of viral replication and antibody development were studied [8]. Here we present data obtained with this model investigating the influence of different levels of VN serum antibodies on the outcome of vaccination with MV-Schwarz, with a recombinant vaccinia virus (rVV-FH), and with immune-stimulating complexes (MV iscom). The latter two vaccine candidates were both based on the principle of inducing protective immunity by presenting the F and H glycoproteins in an immunogenic way [22, 23].

Materials and Methods

Cynomolgus monkeys From a colony of MV-seronegative cynomolgus monkeys, housed in groups of 6−10 at the National Institutes of Public Health and Environmental Protection, 2- to 3-year-old healthy male and female animals were used. Four animals were housed in an isolator before and during the vaccination and challenge period with recombinant vaccinia virus (see below).

Vaccine preparations. The following three vaccine preparations were used in immunization experiments: attenuated Schwarz
measles vaccine (Rouix vaccine lot G0334; 10^{10} 50% CCID_{so}/dose; Institut Mérieux, Lyon, France); recombinant vaccinia virus expressing the F and H proteins of MV (rVV-FH), containing 10^{6.0} pfu/mL gradient-purified virus [22] (F. Wild, Lyon, France); immune-stimulating complexes containing the F and H proteins (MV iscom, lot LVM 310394), prepared from purified MV as previously described [23].

**Passive transfer of MV-specific antibodies.** Sera were collected and pooled from 16 cynomolgus monkeys previously infected with MV-BIL [8]. This pool (BMS94) had a specific VN antibody titer of 2560/mL or 40 IU/mL when compared to the titer of the first international standard for anti-MV serum (serum 66/202, 5 IU of anti-MV antibody/mL; provided by NIBSC, Potters Bar, UK). To obtain monkeys with predetermined levels of specific VN antibodies at the time of immunization (range, 0.0–0.16 IU/mL), different volumes of serum BMS94 were transferred intravenously to naive monkeys 48 h before vaccination.

**Vaccination.** Monkeys were inoculated intramuscularly with one dose of MV-Schwarz (animals 1–8). Two of these monkeys (nos. 7 and 8) were revaccinated with MV-Schwarz 4 weeks after the first vaccination. At days 7, 9, and 11 after vaccination, peripheral blood mononuclear cells (PBMC) were collected from heparinized blood for MV isolation by cocultivation procedures as described [8]. Eight other monkeys were inoculated twice intramuscularly at an interval of 4 weeks with 10^{6.2} pfu/dose rVV-FH (nos. 9–12; scarification) or with 10 pfu/dose MV iscom (nos. 13–16). At weekly intervals, blood samples were collected from all vaccinated monkeys and treated with heparin.

**Challenge with MV-BIL.** Monkeys vaccinated 12 months before with MV-Schwarz (nos. 4–6) or 13 months before with either MV-Schwarz (nos. 7 and 8), rVV-FH (nos. 9–12), or MV iscom (nos. 13–16) were challenged intratracheally with 10^{3.0} pfu/mL gradient-purified virus [22] (F. Wild, Lyon, France) and subsequently challenged with MV-BIL [8]. Two MV-seronegative monkeys (nos. 17 and 18) were included as controls in this challenge study. At days 3, 6, 9, 13, and 17 after infection with MV-BIL, nasopharyngeal wash, heparinized peripheral blood, and lung lavage samples were collected for MV isolation by cocultivation procedures, as previously described [8].

**Serologic assays.** Plasma samples were obtained from heparinized blood and heat-inactivated for 30 min at 56°C. The presence of MV-specific IgM and IgG antibodies in these samples was tested in ELISAs as described [8, 23, 24]. IgM ELISA results were expressed as optical density (OD) values at 450 nm; IgG ELISA titers were expressed as the reciprocals of dilutions of individual sera showing 50% of the maximal OD value at 450 nm. VN assays were conducted by modification of methods previously described [8, 23]. Briefly, serial dilutions of plasma samples (50 μL/well) were incubated with 50 μL of 100 CCID_{so} of Edmonston B virus for 1 h at 37°C in round-bottomed tissue culture plates (Costar, Cambridge, MA). A 50-μL suspension containing 5 × 10^{5.0} cells of the human B lymphoblastoid cell line (B-LCL) JP [25] was added to each well. Plates were incubated for 5 days at 37°C and visually monitored for cytopathic changes. VN antibody titers were expressed as reciprocals of the highest serum dilutions still giving 100% reduction of cytopathic changes.

**Proliferative and cytotoxic T lymphocyte (CTL) assays.** PBMC were isolated from heparinized blood of vaccinated animals by centrifugation on a gradient, containing 4% (wt/vol) dextran-500 (Sigma, St. Louis) and 32% (vol/vol) of a standard metrizoate solution containing 32.8% (wt/vol) natrium-metrizoate (Nycomed, Oslo). These PBMC were stored at –135°C until herpesvirus papiovirus–transformed B-LCL were established from the PBMC of individual animals. Briefly, PBMC (2 × 10^{6.0}/mL) were infected for 1 h at 37°C with 1 mL of supernatant fluid of the herpesvirus papiovirus–producing cell line SS94 (gift of R. Bontrop, TNO, Rijswijk, Netherlands). Cells were washed and cultured in RPMI 1640, supplemented with 10% (vol/vol) fetal bovine serum (HyClone Laboratories, Logan, UT), 2 mM L-glutamine, penicillin (100 U/mL), and streptomycin (100 μg/mL) (referred to as FBS-medium). Phytohemagglutinin-M (Boehringer, Mannheim, Germany) was added once at a concentration of 20 μg/mL. Stable herpesvirus papiovirus–transformed B-LCL were established after 4–6 weeks of culture in FBS-medium. MV-specific proliferative responses were carried out with frozen stocks of PBMC, cultured in round-bottomed microtiter plates (Costar) at a density of 2 × 10^{6.0} cells/well in 150 μL of FBS-medium supplemented with 1% (vol/vol) pooled monkey serum. PBMC were cultured for 72 h in the presence or absence of UV-irradiated MV (0.3 μg/well) and were pulsed with 0.5 μCi of [3H]thymidine over the last 18 h of culture. Results were expressed as the mean counts per minute ± SD of triplicate cultures.

For MV-specific CTL responses, PBMC (2 × 10^{5.0} cells/well) were cultured for 6 days in the presence of autologous MV-infected B-LCL (3 × 10^{5.0} cells/well) in 150 μL of FBS-medium supplemented with 1% (vol/vol) pooled monkey serum. Cultures were expanded for another 6 days in the presence of 50 IU/mL recombinant human interleukin-2 (Eurocetus, Amsterdam) and were subsequently incubated for 4 h at different effector-to-target ratios with [3H]-labeled uninfected and MV-infected B-LCL (experiment 1) as described [25]. Results were expressed as the mean percentages of specific target cell lysis ± SD of triplicate cultures. In some experiments, 12-day cultures of PBMC were restimulated with autologous MV-infected B-LCL and tested for specific CTL activity 12 days after the second stimulation (experiment 2).

**Results**

**Viral replication and serum antibody response on MV-Schwarz vaccination in the presence of MV-specific antibodies.** Five monkeys (nos. 4–8) were vaccinated intramuscularly with one standard dose of MV-Schwarz in the presence of increasing levels of passively transferred serum (BMS94), as shown in table 1. This transfer resulted in specific serum IgG ELISA titers of 5, 18, 69, 85, and 100 and VN titers of <5, <5, 5, 10, and 10, or <0.08, <0.08, 0.08, 0.16, and 0.16 IU/mL, before vaccination. From MV-seronegative monkeys (nos. 1–3), vaccinated in the same way, MV-Schwarz could consistently be isolated at day 7 or day 9 (or both) after vaccination. This was also true for monkeys 4 and 5, with VN antibody titers <0.08 IU/mL at the time of vaccination. In the latter 2 monkeys, the kinetics and maximum levels of MV-specific IgM, IgG, and VN antibody responses were similar to those observed in the MV-seronegative monkeys vaccinated with MV-Schwarz (table 1) [8]. No MV-Schwarz could be isolated...
Table 1. Measles virus (MV) replication and development of specific antibody responses in monkeys vaccinated with MV-Schwarz in the absence (monkeys 1–3) or presence (monkeys 4–8) of increasing amounts of MV-specific antibody.

<table>
<thead>
<tr>
<th>Experiment, monkey no.</th>
<th>IgG at day 0*</th>
<th>VN (IU/mL) at day 0†</th>
<th>MV infection‡</th>
<th>IgM at days 14–18§</th>
<th>IgG at day 28</th>
<th>VN (IU/mL) at day 28∥</th>
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<td>1</td>
<td>&lt;5</td>
<td>&lt;0.08</td>
<td>Day 7</td>
<td>+</td>
<td>5000</td>
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<td>2</td>
<td>&lt;5</td>
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<td>Day 9</td>
<td>+</td>
<td>2000</td>
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<td>3</td>
<td>&lt;5</td>
<td>&lt;0.08</td>
<td>Day 7, 9</td>
<td>+</td>
<td>4500</td>
<td>5.1</td>
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<tr>
<td>4</td>
<td>5</td>
<td>&lt;0.08</td>
<td>Day 7</td>
<td>+</td>
<td>5500</td>
<td>10.2</td>
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<tr>
<td>5</td>
<td>18</td>
<td>&lt;0.08</td>
<td>Day 7, 9</td>
<td>+</td>
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<td>6</td>
<td>69</td>
<td>0.08</td>
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<td>7</td>
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<td>0.16</td>
<td>Negative</td>
<td>—</td>
<td>70</td>
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<tr>
<td>8</td>
<td>100</td>
<td>0.16</td>
<td>Negative</td>
<td>—</td>
<td>160</td>
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* Specific serum IgG antibody titer.
† Virus neutralizing antibody titer.
‡ MV-infected cells in peripheral blood mononuclear cells.
§ Specific serum IgM antibody.
∥ From the PBMC of monkeys 6, 7, and 8, with VN antibody titers ≥0.08 IU/mL at the time of vaccination. In these 3 monkeys, a clear interference with the induction of MV-specific serum antibodies was observed after vaccination, since no MV-specific IgM could be demonstrated on MV-Schwarz vaccination (table 1). Also, the levels of MV-specific IgG or VN antibodies 4 weeks after vaccination were significantly lower than those observed in the other 5 monkeys (table 1). On day 28, monkeys 7 and 8 were vaccinated for the second time with MV-Schwarz, when their VN titers had decreased to ~0.1 IU/mL. Again, specific IgM serum antibodies were not induced (figure 1A1), and MV-Schwarz could not be isolated from their PBMC (data not shown). However, their specific antibody levels measured in the IgG ELISA and VN assay slightly rose, to ~1000 and 2.5 IU/mL, respectively (figure 1A). Within 3 months, however, these titers decreased to the levels found before the second vaccination (figure 1A).

These data show that the presence of relatively low levels of MV-specific antibodies (VN titers ≥0.08 IU/mL) interfered with the replication of MV-Schwarz and subsequent MV-specific antibody development.

Serum antibody responses on vaccination with rVV-FH in the presence of MV-specific antibodies. Two monkeys were vaccinated twice intradermally with 10^6.2 pfu of rVV-FH (nos. 9 and 10). Within 2 weeks after the first vaccination, specific serum antibody levels measured in the IgG ELISA and VN assay of ~1000 and 1.5 IU/mL, respectively, could be demonstrated. Specific IgM serum antibodies were not detected. The second vaccination did not boost the specific IgG and VN antibody levels significantly (figure 1B). Two other monkeys (nos. 11 and 12) received passively transferred serum (BMS94) before vaccination with rVV-FH, resulting in specific IgG and VN antibody levels of ~150 and 0.12 IU/mL, respectively. Though vaccination of these 2 monkeys with rVV-FH resulted in the development of typical pox-like lesions and vaccinia virus–specific serum antibody responses (data not shown), monkeys 11 and 12 did not develop MV-specific serum IgM, IgG, and VN antibodies on vaccination with rVV-FH (figure 1B). Revaccination with rVV-FH, when VN titers in these monkeys had decreased to ~0.08 IU/mL, resulted in a slight increase of MV-specific serum IgG and VN antibody levels, which were, however, significantly lower than those observed in the animals vaccinated with the rVV-FH in the absence of specific antibodies (figure 1B).

These data show that the presence of the relatively low levels of MV-specific antibodies (VN titers 0.08–0.16 IU/mL) at the time of vaccination seriously interfered with MV-specific antibody responses induced by vaccination with rVV-FH.

Serum antibody responses on vaccination with MV iscom in the presence of MV-specific antibodies. Two MV-seronegative monkeys (nos. 13 and 14) were vaccinated twice intramuscularly with MV iscom containing 10 μg of the F and H proteins per dose. These 2 animals developed transient specific serum IgM antibody responses after both the first and second vaccinations (figure 1C). They also developed a specific IgG serum antibody response after the first vaccination, reaching specific IgG levels of 1700 and 7000 and VN serum antibody levels of 0.16 and 0.64 IU/mL, respectively (figure 1C). Specific IgG and VN serum antibody responses increased significantly within 1 week after the second vaccination to levels of ~3 × 10^3 and 40–80 IU/mL, respectively (figure 1C). Within 4 months, these levels decreased to ~5000–7000 and 5–10 IU/mL, respectively (figure 1C). Two other monkeys (nos. 15 and 16) received passively transferred MV-specific antibodies, resulting in prevaccination specific antibody levels measured in the IgG ELISA and VN assay of 130 and 0.16 IU/mL, respectively. The presence of these antibodies did not interfere significantly with the induction of MV-specific serum IgM,
IgG, and VN antibody responses on vaccination with MV iscom, since both monkeys developed similar levels of specific IgG and VN antibodies as the monkeys vaccinated with these MV iscom in the absence of MV-specific antibodies. Also, the kinetics of antibody development were similar in both groups of monkeys (figure 1C).

These data show that the presence of relatively low levels of passively transferred MV-specific antibodies (VN titers 0.08–0.16 IU/mL) at the time of vaccination did not interfere significantly with MV-specific antibody responses induced by vaccination with MV iscom.

Cell-mediated immune responses on vaccination in the presence or absence of MV-specific antibodies. To study the induction of MV-specific T cell responses in the vaccinated and infected monkeys, PBMC were collected from all animals before vaccination (day 0) and 28 days after the first vaccination with MV-Schwarz, rVV-FH, and MV iscom. No specific proliferative responses were measured in any of the PBMC collected at day 0. Four weeks after vaccination with MV-Schwarz, significant MV-specific proliferative responses were measured in the PBMC of monkeys 3, 4, 7, and 8 but not in monkeys 5 and 6. This absence of a specific response in the latter 2 animals may have been due to relatively high background values and too low frequencies of proliferating T cells, using these culture conditions (figure 2A). Expanded PBMC cultures of monkeys 4 and 7, which had VN serum antibody levels of <0.08 and 0.16 IU/mL, respectively, at the time of vaccination with MV-Schwarz, were also tested for MV-specific CTL responses toward uninfected and MV-infected autologous B-LCL. In the cultures from both of these monkeys, MV-specific CTL activity was demonstrated (figure 2B, experiment 1). PBMC cultures of monkey 7 stimulated for the second time with MV-infected autologous B-LCL showed an increased MV-specific CTL activity (figure 2B, experiment 2). In monkeys vaccinated with rVV-FH and MV iscom, both in the absence (nos. 9, 10, 13, and 14) and the presence (nos. 11, 12, 15, and 16) of MV-
specific antibodies, specific proliferative responses were found (figure 2B). Furthermore, in expanded PBMC cultures of monkeys 10 and 14, specific CTL activity was found (figure 2B, experiments 1 and 2).

These data show that MV-specific proliferative T cell responses and CTL responses were induced in monkeys vaccinated with MV-Schwarz, rVV-FH, and MV iscom in both the presence and absence of MV-specific antibodies.

Protective immunity on vaccination with MV-Schwarz, rVV-FH, and MV iscom in the presence or absence of MV-specific antibodies. Between 12 and 15 months after vaccination, all of the monkeys vaccinated with MV-Schwarz, rVV-FH, and MV iscom, except monkey 3, were challenged intratracheally with $10^{3.0}$ CCID$_{50}$ of MV-BIL. The patterns of virus isolation and serologic responses observed in 2 naive monkeys (nos. 17 and 18), included as controls, were similar to previously found patterns in MV-BIL-infected naive monkeys [8]. These included MV isolation kinetics from PBMC, lung lavage cells primarily consisting of alveolar macrophages and pharyngeal epithelial cells, the development of VN IgG and IgM antibodies (figure 3), and the kinetics of IgM and IgG antibody development (data not shown). Besides monkeys 1 and 2, which had been vaccinated in the absence of MV-specific antibodies [8], monkey 4, which had received the lowest amount of the serum pool BMS94 before vaccination, proved to be completely protected: No virus was isolated and no rise in VN antibody (figure 3) was observed on MV-BIL challenge. In all of the other monkeys that had received higher amounts of the serum pool before vaccination (nos. 5–8), the observed protection proved to be incomplete (figure 3). This was evidenced by a clear rise in specific IgG and VN antibody levels and by the demonstration of low numbers of MV-infected cells in their lungs (nos. 5–8) and/or PBMC (no. 6) at day 3 and/or day 6 after challenge (figure 3). None of these animals developed specific IgM responses on challenge (data not shown). Partial protection was also demonstrated in monkeys vaccinated with rVV-FH and
Figure 3. Numbers of measles virus (MV)-infected cells/10^6 cells in peripheral blood mononuclear cells (PBMC), lung lavage cells (LLC), and pharyngeal epithelial cells (PEC) of MV-seronegative control monkeys (nos. 17 and 18) and MV-Schwarz–vaccinated monkeys (nos. 1, 2, 4–8) at different times after intratracheal challenge with 10^3.0 CCID50 of MV-BIL. Lines represent MV-neutralizing antibody titers in IU/mL of corresponding animals at different times after challenge.

MV iscom. With the exception of monkey 9, low numbers of MV-infected cells were demonstrated in PBMC or lung lavage cells (or both) of these animals at day 3, 6, and/or 9 after MV-BIL challenge (figure 4). All monkeys vaccinated with rVV-FH and MV iscom developed a significant rise in specific IgG and VN serum antibody levels after challenge (figure 4).

These data show that monkeys vaccinated with MV-Schwarz, rVV-FH, and MV iscom, irrespective of their serologic response on vaccination in the presence or absence of specific antibodies, were largely protected from challenge with MV-BIL.

Discussion

Using a previously established macaque model for MV infection [8], we showed in the present study that levels ≥0.08 IU/mL of passively transferred homologous MV-specific antibody interfered with the replication of vaccine virus and with the induction of MV-specific antibodies on vaccination with MV-Schwarz. This level of ~0.1 IU/mL VN antibody corresponds to levels of VN serum antibody that in epidemiologic studies were shown to interfere with the outcome of measles vaccination in infants: In children with low levels of maternal antibodies, no or a suboptimal increase in specific serum antibody titers was found on exposure to wild type MV [5, 14–17]. We also showed that the induction of MV-specific antibody in young monkeys on vaccination with rVV-FH was almost completely abolished by the presence of 0.16 IU/mL MV-neutralizing antibody in the sera of these animals. This proved not to be the case with an MV iscom vaccine, which induced high titers of MV-specific serum antibodies both in the absence and presence of 0.16 IU/mL VN antibody. Similar experiments
in mice immunized with rVV expressing the individual glycoproteins of MV and in cotton rats immunized with rVV expressing the G or F proteins of respiratory syncytial virus also demonstrated the inability of recombinant vaccinia vaccines to induce humoral responses against these viruses in the presence of specific antibodies [26, 27]. This is not true for the induction of anti-vaccinia virus immunity [28]. Although our experimental results do not explain this apparent difference, we speculate that a previously shown mechanism of down-regulation of the “foreign” glycoproteins by specific antibody [29], which does not affect the production of vaccinia virus progeny, is at the basis of this phenomenon. However, this postulated effect of down-regulation may not or may only partially affect the induction of T cell-mediated immunity, since a certain level of expression followed by peptide presentation to T lymphocytes might still occur.

About 1 year later, all of the monkeys vaccinated with each of the respective vaccines, either in the absence or in the presence of the MV-specific antibody, proved to be completely or partially protected from intratracheal challenge with MV-BIL. Since monkeys with undetectable or very low titers of VN antibody at the time of challenge also proved to be protected, like the monkeys vaccinated ~1 year earlier with MV-Schwarz or rVV-FH in the presence of >0.08 IU of VN serum antibodies, this protection could not or could only partly be attributed to the presence of vaccine-induced VN serum antibody. Therefore, we postulate that the MV-specific T cell memory that was shown to be induced by the respective vaccines in the presence or absence of MV-specific antibodies was responsible for the observed protection. Although the present experiments do not allow conclusions about the nature or phenotype of the induced T cells, the observations strengthen the hypothesis that humans may be protected from measles on the basis of the presence of a cell-mediated immune response in the relative absence of specific antibody [30, 31]. Consequently, it may be speculated that infants vaccinated in the presence of low levels of maternal antibody may also develop partial protection from subsequent wild type MV infection. However, as many children
immunized in the presence of maternal antibody do not appear to develop any detectable protection against measles, the level of this protection may be related to the level and duration of maternal antibody present in young children.

It should be stressed that besides the monkeys vaccinated with MV-Schwarz in the absence of MV-specific antibodies, virtually all of the other monkeys vaccinated in the absence or presence of MV-specific antibody showed low numbers of MV-infected cells in their lungs or blood (or both) on challenge. The MV-infected cells in the lungs, which were observed within days after challenge, probably resulted directly from local viral replication at the site of challenge. In some animals, this apparently not only resulted in a short-lived and low-level cell-associated viremia but also in significant rises of specific IgG and VN serum antibody responses. As none of these animals developed specific IgM antibody responses on challenge, the results may be interpreted as a booster phenomenon. It may be speculated that longer after vaccination, the observed levels of protection would have declined in these monkeys due to a waning immunity, reminiscent of the secondary vaccination failures observed in adolescents vaccinated in childhood with live attenuated measles vaccine [5, 18, 19]. The protection induced by vaccination with rVV-FH in the presence of MV-specific antibody was clearly less complete than that induced in the absence of antibody. In contrast, the protection induced by MV iscom was, like the specific antibody response induced by this candidate vaccine, not affected by the presence of the specific antibodies at the time of vaccination.

It is tempting to translate the data generated in this study as being supportive for initiating the evaluation of certain candidate measles vaccines in humans. However, the present study was limited by the use of low levels of passively transferred antibody and by a challenge infection carried out \( \sim 1 \) year after vaccination only. Furthermore, only the issue of interference by preexisting antibodies and not that of an immature immune system could be addressed in this study, since for practical reasons no infant monkeys could be used. Further evaluation of the potential of the respective vaccine candidates in the monkey model should therefore include studies with higher levels of transferred antibodies and with longer vaccination challenge intervals, as well as studies in baby monkeys from mothers with different levels of MV-specific maternal antibodies. The potential of MV iscom to induce both VN antibody and protection in the absence of preexisting VN antibodies would especially favor the selection of this vaccine for human trials.

Acknowledgments

The helpful advice by the WHO Task Force on Measles Vaccination, in selecting vaccine candidates and experimental designs, is gratefully acknowledged. Furthermore, we thank Nico Schmidt for technical assistance in the vaccination experiments, Jolande Boes for preparing the MV iscom preparation, and Rik de Swart and Conny Kruyssen for help in preparing the manuscript.

References


