Results from a Randomized Clinical Trial of Coadministration of RotaTeq, a Pentavalent Rotavirus Vaccine, and NeisVac-C, a Meningococcal Serogroup C Conjugate Vaccine

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RotaTeq (Merck & Co. Inc./Sanofi Pasteur MSD) is a three-dose, oral pentavalent rotavirus vaccine for the immunization of infants from 6 weeks of age for the prevention of rotavirus gastroenteritis. The primary objective of the present trial was to demonstrate that RotaTeq can be coadministered with meningococcal serogroup C conjugate vaccine (MenCC; NeisVac-C; Baxter Healthcare) to healthy infants without impairing the protective immune responses to MenCC. This was an open-label, randomized, comparative study conducted in Finland. The study was designed to assess concomitant versus sequential administration of RotaTeq and MenCC on the immune response to both vaccines. Healthy infants (n = 247), aged 6 to 7 weeks, were recruited. Coadministration of MenCC with RotaTeq was noninferior to sequential administration for the seroprotection rate against meningococcal serogroup C (the proportion of infants with a serum bactericidal antibody titer using baby rabbit complement of ≥8 was 100% in both groups). The other responses to MenCC (titer of ≥1:128, ≥4-fold increase in titer, and geometric mean titers [GMTs]) and the responses to RotaTeq (IgA and SNA response to G1 to G4 and P1A[8], GMTs, and ≥3-fold increase in titer) were comparable between groups, including a ≥3-fold IgA increase in >96% of the infants in both groups. Concomitant administration of the first doses of MenCC, diphtheria and tetanus toxoids and acellular pertussis vaccine, inactivated poliovirus vaccine, and Haemophilus influenzae type b conjugate vaccine (DTaP-IPV-Hib), and RotaTeq was associated with a higher rate of vomiting and diarrhea than concomitant administration of MenCC and DTaP-IPV-Hib, but that was not observed after the second concomitant administration. The convenience of concomitant administration of RotaTeq and MenCC may, however, outweigh the additive effect of mostly mild adverse events reported after the individual administration of each vaccine. These results support the coadministration of RotaTeq and MenCC.

Globally, rotavirus is a leading cause of severe diarrhea in infants and young children (16). Throughout the world, most children are infected with rotavirus by 3 to 5 years of age, regardless of socioeconomic status or standards of health and sanitation (8, 15).

The potentially serious nature of rotavirus gastroenteritis (RVGE) in childhood constitutes a substantial public health burden in the European Union. There are 23.6 million children younger than 5 years of age in Europe, and it has been estimated that these children experience 3.6 million episodes of rotavirus disease each year, resulting in almost 700,000 outpatient visits, more than 87,000 hospitalizations, and 231 deaths (18). In addition, data from the REVEAL study (20) show that rotavirus infections are responsible for one-third of consultations in primary care and up to two-thirds of hospitalizations or emergency department consultations for acute gastroenteritis.

Most RVGE episodes occur in children aged between 3 months and 3 years (10, 20). These data support the need for universal immunization against rotavirus in early infancy (24).

RotaTeq (Merck & Co. Inc., Whitehouse Station, NJ/Sanofi Pasteur MSD, Lyon, France) is a three-dose, oral pentavalent rotavirus vaccine. It is a live attenuated human-bovine reassortant rotavirus vaccine consisting of the genes encoding the G1, G2, G3, G4, and P1A[8] outer capsid proteins of human rotaviruses in monoreassortants containing a bovine rotavirus genetic background. RotaTeq has been demonstrated to be efficacious, immunogenic, and well tolerated when it is given alone or concomitantly with routine childhood vaccines (4, 5, 17, 21, 22, 23, 24). On the basis of the current summary of product characteristics (SmPC) for RotaTeq in Europe, the first dose should be given at between 6 weeks and 12 weeks of age and all three doses should be given before 26 weeks of age (13).

An increasing number of new vaccines are used in pediatric vaccination schedules in Europe; concomitant vaccination is intended to minimize the inconvenience of adding these new vaccines and to improve vaccination coverage. The concomitant use of RotaTeq with licensed pediatric vaccines, including...
diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), inactivated poliovirus vaccine (IPV), *Haemophilus influenzae* type b conjugate vaccine (Hib), hepatitis B vaccine, hexavalent vaccine (combined vaccine against diphtheria, tetanus, pertussis, poliomyelitis, *H. influenzae* type b, and hepatitis B), pneumococcal conjugate vaccine, and oral poliomyelitis vaccine, has been evaluated in phase III clinical trials (4, 5, 17). Meningococcal serogroup C conjugate vaccine (MenCC) was not used routinely in the countries in which the initial studies with RotaTeq were undertaken; consequently, the concomitant administration of RotaTeq with MenCC has not been investigated (2, 21, 23).

The primary objective of this study was to demonstrate that RotaTeq can be administered concomitantly with MenCC to healthy infants without impairing the rate of antibody seroprotection against meningococcal serogroup C. Additionally, the study was designed to describe the immunogenicity and the safety of RotaTeq and MenCC when they are administered concomitantly.

**MATERIALS AND METHODS**

**Study design.** This was an open-label, randomized, comparative trial conducted in Finland from January to March 2007 at nine regional vaccination clinics under coordination from the University of Tampere Medicine Vaccine Research Center. The study was designed to assess concomitant versus sequential administration of RotaTeq and MenCC.

The meningococcal serogroup C seroprotection rate in the present study was defined as the proportion of infants who achieved a serogroup C serum bactericidal antibody (SBA) titer using the Farrington and Manning method (9) for the comparison of rates. The SBA cutoff of ≥8 at 28 to 42 days after the second dose of MenCC and at 24 to 25 weeks of age. The SBA target strain was C11 (C:16:P1.7-1,1), and the complement source was baby rabbit serum (rSBA; Pel-Freeze Incorporated, Rodgerson, AZ). SBA titers were expressed as the reciprocal of the final serum dilution giving ≥50% killing at 60 min. For computational purposes, SBA titers of ≤4 were assigned a value of 2. The immune response to MenCC was measured 28 to 42 days after the second dose of MenCC at the Vaccine Evaluation Unit, Manchester Royal Infirmary, Manchester, United Kingdom. The response to RotaTeq was measured 42 days (±3 days) after the third dose of RotaTeq for rotavirus-specific IgA by enzyme-linked immunoabsorbent assay (ELISA) and for serotype-specific rotavirus neutralizing antibody (SNA) against human serotypes G1, G2, G3, G4, and P1A[8] (11) at the Cincinnati Children’s Hospital Medical Center (CCHMC; Cincinnati, OH) (Table 1). Seroconversion was defined by an increase in the antibody titer by a factor of 3 or more from baseline.

**Ethical conduct.** Signed, informed consent was obtained from at least one parent or legal representative for each infant in the study.

The Independent Ethics Committee of the Joint Authority of the Hospital District of Pirkanmaa (Tampere, Finland) approved the study protocol. The study was conducted in accordance with national and local requirements and the ethical principles of the World Medical Association Declaration of Helsinki (25). The compositions of the study populations (all infants who received at least one dose of a study vaccine and whose immunogenicity was assessed). The safety population included all vaccinated infants with safety follow-up at the corresponding visit.

**Table 1. Schedule of vaccine administration and immunogenicity parameters**

| Parameter                  | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 |
|----------------------------|---------|---------|---------|---------|---------|---------|
| **Age window**             | 6–7 wk  | 10–11 wk| 15–16 wk| 20–21 wk| 24–25 wk and visit 4 + 28–42 days| visit 5 + 42 ± 3 days |
| **Group 1**                |         |         |         |         |         |         |
| **Group 2**                |         |         |         |         |         |         |
| **Blood samples**          | RotaTeq | RotaTeq | RotaTeq | RotaTeq | RotaTeq | RotaTeq |
| **Meningococcal serogroup C SBA antibody** | / | / | / | / | / | / |
| G1, G2, G3, G4, and P1A[8] SNA | / | / | / | / | / | / |
| Serum anti-rotavirus IgA    | /       | /       | /       | /       | /       | /       |

* a Routine pentavalent DTaP-IPV-Hib was permitted at visits 2 and 4 in both groups.

b / indicates that the particular activity associated with the parameter took place at the indicated time.

**Vaccine administration.** RotaTeq was available as a 2-ml solution in a prefilled squeezable tube indicated for oral administration. MenCC (NeisVac-C; Baxter Healthcare Corporation, Deerfield, IL) was available in 0.5-ml prefilled syringes for intramuscular administration.

**Schedule of immunogenicity and safety assessments.** (i) Immunogenicity. Sera were analyzed for meningococcal serogroup C antibody by the SBA assay as previously described (12). The SBA target strain was C11 (C:16:P1.7-1,1), and the complement source was baby rabbit serum (rSBA; Pel-Freeze Incorporated, Rodgerson, AZ). SBA titers were expressed as the reciprocal of the final serum dilution giving ≥50% killing at 60 min. For computational purposes, SBA titers of ≤4 were assigned a value of 2. The immune response to MenCC was measured 28 to 42 days after the second dose of MenCC at the Vaccine Evaluation Unit, Manchester Royal Infirmary, Manchester, United Kingdom. The response to RotaTeq was measured 42 days (±3 days) after the third dose of RotaTeq for rotavirus-specific IgA by enzyme-linked immunoabsorbent assay (ELISA) and for serotype-specific rotavirus neutralizing antibody (SNA) against human serotypes G1, G2, G3, G4, and P1A[8] (11) at the Cincinnati Children’s Hospital Medical Center (CCHMC; Cincinnati, OH) (Table 1). Seroconversion was defined by an increase in the antibody titer by a factor of 3 or more from baseline.

(ii) Safety. Diarrhea, vomiting, and temperature (solicited systemic adverse events) were monitored daily from day 0 to day 6 after administration of MenCC either concomitantly with RotaTeq or alone. Injection-site reactions from day 0 to day 6 after MenCC vaccination and systemic and serious adverse events from day 0 to day 13 after administration of either vaccine were reported spontaneously. Deaths and serious vaccine-related adverse events were monitored throughout the study.

**Statistical analyses.** (i) Study populations. The sizes of the study populations for the analyses of primary and secondary objectives are described in Table 2. The main immunogenicity analysis was carried out on the per protocol population (all infants without protocol deviation that may interfere with MenCC immunogenicity), and the supportive analysis was carried out on the full analysis population (all infants who received at least one dose of a study vaccine and whose immunogenicity was assessed). The safety population included all vaccinated infants with safety follow-up at the corresponding visit.

(ii) Calculation of sample size. The sample size for the study was calculated using the Farrington and Manning method (9) for the comparison of rates.
TABLE 2. Study populations

| Populationa | No. (%b) of individuals |
|-------------|-------------------------|
|             | Group 1 | Group 2 | All          |
| Randomized  | 124 (100)| 123 (100)| 247 (100) |
| Full analysis| 114 (91.9)| 119 (96.7)| 233 (94.3) |
| Per protocol for MenCC | 104 (83.9)| 106 (86.2)| 210 (85.0) |
| Per protocol for RotaTeq | 98 (79.0)| 104 (84.6)| 202 (81.8) |
| Safety      | 116 (93.5)| 122 (99.2)| 238 (96.4) |
| Visit 1     | NAa      | 122 (99.2)| 122 (99.2) |
| Visit 2 (first dose of MenCC) | 116 (93.5)| 122 (99.2)| 238 (96.4) |
| Visit 3     | NAa      | 120 (97.6)| 120 (97.6) |
| Visit 4 (second dose of MenCC) | 115 (92.7)| 120 (97.6)| 235 (95.1) |
| Visit 5 (third dose of RotaTeq) | 109 (87.9)| 118 (95.9)| 227 (91.9) |

a Randomized population, all infants assigned to a group by randomization; full analysis population, all randomized infants who received at least one dose of the study vaccines and who had any immunogenicity evaluation after vaccination; per protocol population, all infants without protocol deviations that may interfere with MenCC immunogenicity (i.e., for the primary analysis) or RotaTeq immunogenicity; safety population, all infants who received at least one dose of the study vaccines and who had safety follow-up data.

b Percentages are calculated on the basis of the number of randomized infants.

Assuming 98 evaluable infants in each group for the per protocol population, an expected meningococcal serogroup C seroprotection rate of at least 97% (3, 19) in group 2 (sequential vaccine administration), and no difference between groups, the study was expected to have approximately 90% power to reach its primary objective.

(iii) Statistical methods. The noninferiority of the meningococcal serogroup C seroprotection rate (rSBA titers ≥ 8) in group 1 (concomitant vaccine administration) compared with that in group 2 (sequential vaccine administration) was concluded if the lower bound of the two-sided 95% confidence interval (CI) around the difference in seroprotection rate (group 1 minus group 2) was above −10%. The CI around the difference in seroprotection rate was calculated using the method proposed by Miettinen and Nurminen (14). Stratification by center was used for the main statistical model; results without stratification were also calculated.

Immunogenicity and safety data for RotaTeq and MenCC within each group were evaluated using a descriptive analysis. After the initial evaluation of the safety results, a post hoc between-group analysis (calculation of chi-square tests (6)) was used to examine the differences in solicited systemic adverse events at visits 2 and 4.

RESULTS

Characteristics of study population. Of the 249 infants who were screened for the study, 247 (105 [42.5%] female, 142 [57.5%] male; mean age ± standard deviation, 7.1 ± 0.5 weeks) were randomized to group 1 (concomitant administration; n = 124) or group 2 (sequential administration; n = 123). Eleven (8.9%) infants in group 1 (including 8 infants who withdrew before any study vaccination) and 6 (4.9%) infants in group 2 were withdrawn from the study (Fig. 1).

There was a mean age difference between the two groups at the administration of the first RotaTeq dose (group 1, 11.0 ± 0.8 weeks; group 2, 7.2 ± 0.6 weeks) and the second RotaTeq dose (group 1, 21.0 ± 0.8 weeks; group 2, 15.9 ± 0.7 weeks) due to the study design. There were no other relevant differences between the two groups in demographic characteristics at baseline.

Immunogenicity. The primary immunogenicity analysis was carried out on the per protocol population for MenCC. All infants from both groups achieved the meningococcal serogroup C seroprotection level (rSBA titer of ≥8) at 28 to 42 days after the second dose of MenCC. The lower bound (−3.7%) of the 95% CI around the difference in seroprotection rate (group 1 minus group 2) was above −10% (Table 3), so it was concluded that the meningococcal serogroup C seroprotection rate in group 1 was noninferior to that in group 2. The seroprotection rate was also 100% in the full analysis population for both groups. All analyses carried out on the full analysis population and on the per protocol population for MenCC confirmed the noninferiority of concomitant administration.

The two groups were also generally comparable for the other immunogenicity endpoints for the MenCC response: rSBA titer of ≥128, the number of infants with a ≥4-fold increase in titers from pre- to postvaccination, and geometric mean titers (GMTs) (Table 4).

The rotavirus IgA seroresponses rates (≥3-fold increase from pre- to postvaccination) were comparable in both groups, based on descriptive analysis, with 96.9% and 98.1% of infants in the concomitant and sequential administration groups, respectively, displaying at least a 3-fold increase in IgA response (Table 5). The SNA responses to G1 to G4 and P1A[8] and GMTs were also comparable in both groups.

Safety. After visit 2 and visit 4, when both groups received MenCC, the percentage of infants with systemic adverse events from day 0 to day 13 was generally comparable in both groups (Table 6), although after visit 2 (after the first dose of MenCC) there were more infants in group 1 (75.0%) than in group 2 (62.3%) with systemic adverse events. At visit 2, solicited systemic adverse events (diarrhea, vomiting, and pyrexia, mostly of mild intensity) between day 0 and day 6 were observed more frequently in group 1 (46.6% of infants) than in group 2 (29.5%). A post hoc comparison between groups at visit 2 (after the first dose of MenCC) showed a statistically significant difference for vomiting (19.8% of infants in group 1 versus 9.8% of infants in group 2; P = 0.03) and a trend to a higher incidence for diarrhea (23.3% in group 1 versus 14.8% in group 2; not significant). No statistically significant differences were found at visit 4 (after the second dose of MenCC): in group 1, when RotaTeq and MenCC were administered concomitantly, vomiting and diarrhea were reported in 10.4% and 13.0% of infants, respectively, whereas they were reported in 10.0% and 12.5% of infants, respectively, in group 2 when MCC was administered alone.

At visit 2, the incidence of unsolicited systemic adverse events between day 0 and day 13 was also higher in group 1 (62.1% of infants) than in group 2 (50.0%). This difference was mainly due to irritability (38.8% of infants in group 1 versus 24.6% of infants in group 2). At visit 2, after the first dose of MenCC, at least one injection-site reaction was reported in more infants in group 1 than in infants in group 2 (13.8% versus 8.2%).

After visit 1 in group 2 (when RotaTeq was given alone), the systemic adverse events that were reported in >10% of the infants were diarrhea (13.1%), flatulence (13.1%), and irritability (10.7%). Vomiting was reported in 5.7% of infants.

After visit 3 in group 2 and visit 5 in both groups (when RotaTeq was given alone), no events were reported in >10% of the infants. After visit 3, two events were reported in >5% of the infants: diarrhea (8.3%) and irritability (7.5%). The safety profile after the third dose of RotaTeq at visit 5 was comparable in both groups, with only diarrhea being reported in >5% of infants (6.4% in group 1 and 5.9% in group 2).
Irritability was reported in 4.6% of infants in group 1 and 3.4% in group 2. One infant in each group experienced nonserious, mild hematochezia (bloody mucus in the feces). The group 1 event was considered to be related to RotaTeq, and the group 2 event was considered to be related to MenCC. Another infant from group 2 had a nonserious allergy (hypersensitivity) of moderate intensity 5 days after the third dose of RotaTeq which was not considered to be related to the study vaccine.

Only two serious adverse events occurred, one in each group. One infant in group 1 had an episode of epilepsy of moderate intensity, starting 13 days after visit 4, and one infant in group 2 had a severe viral infection, starting 9 days after visit 4.

TABLE 3. Serogroup C meningococcal rSBA seroprotection rate at 28 to 42 days after the second dose of MenCC

| Group 1 (n = 104) | Group 2 (n = 106) | % difference between groups<sup>b</sup> (95% CI) |
|------------------|------------------|-----------------------------------------------|
| No. (%) of infants seroprotected | 95% CI          | No. (%) of infants seroprotected | 95% CI          | 0 (-3.7, 3.7) |
| 104 (100)        | (96.5, 100)      | 106 (100)        | (96.6, 100)      |                  |

<sup>a</sup> Seroprotection was a titer of ≥8, calculated by noninferiority analysis using stratification by center (per protocol population for MenCC).

<sup>b</sup> Group 1 minus group 2.
administration of vaccines. The frequency of adverse events associated with coadministration together (23.3% diarrhea, 19.8% vomiting) suggests that the doses of the three vaccines RotaTeq, MenCC, and routine pentavalent DTaP-IPV-Hib when they are administered together (14.8% diarrhea, 9.8% vomiting) compared and we feel that, compared with sequential administration of RotaTeq and MenCC may, however, outweigh the slight increase in risk of mild diarrhea and mild vomiting associated with coadministration of these vaccines.

With respect to possible limitations of the present study, the nature of the study design (open label) may lead to a potential for bias in reporting safety outcomes. The trial was not designed to assess the differences between groups in solicited systemic adverse events at visits 2 and 4. The safety assessment of RotaTeq in so few infants in the present study is limited in comparison with the safety profile documented from adverse event monitoring in more than 70,000 infants in phase III trials (2, 7, 21, 23).

In conclusion, concomitant administration of RotaTeq and MenCC in healthy infants at between 3 months and 5 months events reported after the individual administration of each vaccine. These events are not considered clinically significant, and we feel that, compared with sequential administration of vaccines, the convenience of concomitant administration of RotaTeq and MenCC may, however, outweigh the slight increase in risk of mild diarrhea and mild vomiting associated with coadministration of these vaccines.

5. The events resolved in 4 and 7 days, respectively, and were not considered to be related to either study vaccine. No deaths occurred in either group. There was one withdrawal from the study due to an adverse event, a dark green loose stool that occurred in either group. There was one withdrawal from the study population due to an adverse event, a dark green loose stool that occurred in either group. There was one withdrawal from the study population due to an adverse event, a dark green loose stool that occurred in either group.

The results of the present study demonstrate that MenCC is immunogenic when it is administered concomitantly with RotaTeq. The vaccines can be coadministered without impairing the antibody seroprotection rate against meningococcal serogroup C (100% seroprotection rate in both groups). The primary objective of this study was achieved. The immunologic findings for RotaTeq observed in the present study are consistent with those described in other clinical trials (2, 21, 23), with >96% of the vaccine recipients achieving at least a 3-fold increase in serum rotavirus IgA antibody titer. SNA responses to G1 to G4 and P1A[8] and GMTs were also as expected from previous trials (2, 17, 21, 23).

### DISCUSSION

The gastrointestinal events reported with RotaTeq are consistent with the current knowledge of this vaccine, including diarrhea and vomiting in infants receiving their first dose of RotaTeq. In a detailed safety analysis of 11,722 vaccine recipients evaluated in three phase III studies with RotaTeq, mild diarrhea and vomiting occurred more frequently among those who received RotaTeq than among those who received placebo (10.4% versus 9.1% and 6.7% versus 5.4%, respectively) (7). The reported incidence of diarrhea and vomiting occurring after the first dose of RotaTeq when it was administered alone (15.1% diarrhea, 5.7% vomiting) and the first doses of MenCC and routine pentavalent DTaP-IPV-Hib when they are administered together (14.8% diarrhea, 9.8% vomiting) compared with the higher incidence of these adverse events after the first doses of the three vaccines RotaTeq, MenCC, and routine pentavalent DTaP-IPV-Hib when they were administered together (23.3% diarrhea, 19.8% vomiting) suggests that the frequency of adverse events associated with coadministration of several vaccines represents the additive effect of the adverse

| Parameter | Group 1 (n = 104) | Group 2 (n = 106) |
|-----------|------------------|------------------|
| SNA response to G1 | n (%) | 102 (98.1) | 103 (98.1) |
| 95% CI | 93.2, 99.8 | 93.3, 99.8 |
| GMT | 1,457.8 | 1,262.3 |
| 95% CI | 1,251.5, 1,698.2 | 1,074.8, 1,482.5 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| SNA response to G2 | n (%) | 33 (33.7) | 40 (38.5) |
| 95% CI | 24.4, 43.9 | 28.2, 47.5 |
| GMT | 41.9 | 44.3 |
| 95% CI | 33.7, 52.2 | 35.6, 55.1 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| SNA response to G3 | n (%) | 44 (44.9) | 48 (46.2) |
| 95% CI | 34.8, 55.3 | 36.3, 56.2 |
| GMT | 64.7 | 76.4 |
| 95% CI | 51.1, 82.0 | 59.8, 97.5 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| SNA response to P1A[8] | n (%) | 32 (32.7) | 40 (40.4) |
| 95% CI | 23.5, 42.9 | 30.9, 50.5 |
| GMT | 111.2 | 124.3 |
| 95% CI | 88.3, 140.0 | 99.1, 156.0 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| IgA antibody titer (units/ml) | n (%) | 95 (96.9) | 102 (98.1) |
| 95% CI | 91.3, 99.4 | 93.2, 99.8 |
| GMT | 290.6 | 363.1 |
| 95% CI | 215.1, 392.5 | 290.3, 454.2 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| SNA response to G4 | n (%) | 44 (44.9) | 48 (46.2) |
| 95% CI | 34.8, 55.3 | 36.3, 56.2 |
| GMT | 64.7 | 76.4 |
| 95% CI | 51.1, 82.0 | 59.8, 97.5 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| SNA response to G3 | n (%) | 33 (33.7) | 39 (37.5) |
| 95% CI | 24.4, 43.9 | 28.2, 47.5 |
| GMT | 41.9 | 44.3 |
| 95% CI | 33.7, 52.2 | 35.6, 55.1 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| SNA response to G2 | n (%) | 33 (33.7) | 40 (38.5) |
| 95% CI | 24.4, 43.9 | 28.2, 47.5 |
| GMT | 41.9 | 44.3 |
| 95% CI | 33.7, 52.2 | 35.6, 55.1 |

| Parameter | Group 1 (n = 98) | Group 2 (n = 104) |
|-----------|------------------|------------------|
| SNA response to G1 | n (%) | 44 (44.9) | 48 (46.2) |
| 95% CI | 34.8, 55.3 | 36.3, 56.2 |
| GMT | 64.7 | 76.4 |
| 95% CI | 51.1, 82.0 | 59.8, 97.5 |
Solicited systemic adverse event
Serious adverse event
updated to include concomitant administration of RotaTeq
childhood vaccines (4, 5, 17). The SmPC of RotaTeq has been
when it is given alone or concomitantly with other routine
has been demonstrated to be immunogenic and well tolerated
addition of new vaccines to immunization programs. RotaTeq
costs associated with extra health visits and (ii) facilitating the
vines has several potential benefits, including (i) reduction of
tion in early childhood. Concomitant administration of vac-
related to RotaTeq were consistent with those observed in phase III
or of the rotavirus vaccine. The overall immune response rates
of age did not adversely affect the immunogenicity of MenCC
or of the rotavirus vaccine. The overall immune response rates
to RotaTeq were consistent with those observed in phase III
clinical trials in which the clinical efficacy of RotaTeq was
confirmed (2, 17, 21, 22, 23). The concomitant administration of
vaccines resulted in higher rates of local and systemic adverse
events (days 0–13)
Related to RotaTeq
Related to MenCC
Solicited systemic adverse event
(days 0–6)
Diarrhea
Vomiting
Pyrexia
Related to RotaTeq
Related to MenCC
Unsolicited systemic adverse events (days 0–13)
Related to RotaTeq
Related to MenCC
Serious adverse event
(visits 2–3 or visit 4–5)
Withdrawal due to adverse event
(visits 2–3 or visit 4–5)

TABLE 6. Safety summary following visits 2 and 4 for the safety population

| Event | Group 1 (RotaTeq + MenCC, n = 116) | Group 2 (MenCC, n = 122) | Group 1 (RotaTeq + MenCC, n = 115) | Group 2 (MenCC, n = 120) |
|-------|-------------------------------------|--------------------------|-------------------------------------|--------------------------|
|       | No. (%) of infants | 95% CI | No. (%) of infants | 95% CI | No. (%) of infants | 95% CI | No. (%) of infants | 95% CI |
| MenCC injection-site reaction (days 0–6) | 16 (13.8) | 8.1, 21.4 | 10 (8.2) | 4.0, 14.6 | 28 (24.3) | 16.8, 33.2 | 26 (21.7) | 14.7, 30.1 |
| Systemic adverse event (days 0–13) | 87 (75.0) | 66.1, 82.6 | 76 (62.3) | 53.1, 70.9 | 61 (53.0) | 43.5, 62.4 | 58 (48.3) | 39.1, 57.6 |
| Related to RotaTeq | 76 (65.5) | 56.1, 74.1 | NA (NA) | NA | 49 (42.6) | 33.4, 52.2 | NA (NA) | NA |
| Related to MenCC | 68 (58.6) | 49.1, 67.7 | 62 (50.8) | 41.6, 60.0 | 45 (39.1) | 30.2, 48.7 | 51 (42.5) | 33.5, 51.9 |
| Solicited systemic adverse event (days 0–6) | 54 (46.6) | 37.2, 56.0 | 36 (29.5) | 21.6, 38.4 | 34 (29.6) | 21.4, 38.8 | 32 (26.7) | 19.0, 35.5 |
| Diarrhea | 27 (23.3) | 15.9, 32.0 | 18 (14.8) | 9.0, 22.3 | 15 (13.0) | 7.5, 20.6 | 15 (12.5) | 7.2, 19.8 |
| Vomiting | 23 (19.8) | 13.0, 28.3 | 12 (9.8) | 5.2, 16.6 | 12 (10.4) | 5.5, 17.5 | 12 (10.0) | 5.3, 16.8 |
| Pyrexia | 10 (8.6) | 4.2, 15.3 | 9 (7.4) | 3.4, 13.5 | 21 (18.3) | 11.7, 26.5 | 12 (10.0) | 5.3, 16.8 |
| Related to RotaTeq | 51 (44.0) | 34.8, 53.5 | NA (NA) | NA | 31 (27.0) | 19.1, 36.0 | NA (NA) | NA |
| Related to MenCC | 33 (28.4) | 20.5, 37.6 | 29 (23.8) | 16.5, 32.3 | 26 (22.6) | 15.3, 31.3 | 29 (24.2) | 16.8, 32.8 |
| Unsolicited systemic adverse events (days 0–13) | 72 (62.1) | 52.6, 70.9 | 61 (50.0) | 40.8, 59.2 | 47 (40.9) | 31.8, 50.4 | 45 (37.5) | 28.8, 46.8 |
| Related to RotaTeq | 53 (45.7) | 36.4, 55.2 | NA (NA) | NA | 28 (24.3) | 16.8, 33.2 | NA (NA) | NA |
| Related to MenCC | 57 (49.1) | 39.7, 58.6 | 46 (37.7) | 29.1, 46.9 | 29 (25.2) | 17.6, 34.2 | 37 (30.8) | 22.7, 39.9 |
| Serious adverse event (visits 2–3 or visit 4–5) | 0 (0) | 0.0, 3.3 | 0 (0) | 0.0, 3.3 | 1 (0.9) | 0.4, 7.1 | 0 (0) | 0.0, 3.3 |
| Withdrawal due to adverse event (visits 2–3 or visit 4–5) | 0 (0) | 0.0, 3.3 | 0 (0) | 0.0, 3.3 | 0 (0) | 0.0, 3.3 | 0 (0) | 0.0, 3.3 |

* Visit 2, infants received a first dose of routine pentavalent DTaP-IPV-Hib concomitantly to study vaccine(s) in 93.7% of infants.
* Visit 4, infants received a second dose of routine pentavalent DTaP-IPV-Hib concomitantly to study vaccine(s) in 95.3% of infants.
* Number (percent) (calculated within the vaccinated infants) of infants presenting at least once the considered event.
* NA, not applicable.
* Post hoc analysis, no statistically significant difference.
* Post hoc analysis, P = 0.03.
* Epilepsy related to neither RotaTeq nor MenCC.
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