Tolerability of MenACWY-TT Vaccination in Toddlers in the Netherlands; A Questionnaire Study

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Research article

Keywords: MenACWY-TT vaccine, MenC-TT vaccine, toddlers, tolerability, reactogenicity

DOI: https://doi.org/10.21203/rs.3.rs-366394/v1

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Abstract

**Background:** In May 2018, the monovalent MenC-TT conjugate vaccine given at 14 months of age within the National Immunization Programme in the Netherlands was replaced by a 4-valent MenACWY-TT conjugate vaccine.

**Methods:** Results from a questionnaire about local reactions and systemic events within 4 days after vaccination were compared with data from a comparable tolerability study of a monovalent MenC-TT vaccine.

**Results:** The response rate was 5.5% (1157/20966 questionnaires). Any local reaction was reported for 3.7% of the toddlers, with the highest percentage found for local redness at the injection site (2.9%). Any systemic event was reported for 32.4% of the toddlers, with listlessness (22.4%) most often reported. Fever was the only symptom more frequently reported after MenACWY-TT vaccination compared with MenC-TT vaccination (adj OR 1.61; 95% CI 1.29-2.01).

**Conclusions:** the 4-valent MenACWY-TT vaccine showed to be a little more reactogenic compared with to the monovalent MenC-TT vaccine, with a higher risk of fever within 4 days after vaccination. For the other factors no increased risks were found. Overall, this study shows that MenACWY-TT vaccination is well tolerated in toddlers.

**Background**

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is a life-threatening condition which, if left untreated, can lead to a case fatality ratio of up to 50% (1). After a steep rise of meningococcal C disease around 2000 in the Netherlands, all children between 1 and 19 years of age were vaccinated against meningococcal serogroup C disease (MenC) in a large campaign in 2002. From that point in time, MenC vaccination was included in the National Immunisation Programme (NIP) for children at 14 month of age, concomitantly with the first MMR vaccination. After 2002, a rapid decline of MenC IMD by more than 93% was observed. A decade after the introduction of the MenC vaccination, serogroup C IMD still remained at a very low level (2).

Since 2015, the Netherlands experienced an increase of serogroup W IMD (3). Before that time, MenW IMD was rare, with an average annual incidence 0.02 cases per 100,000. From 2015 the incidence started to increase reaching 0.5 IMD cases per 100,000 in 2017. In September 2017, the Dutch minister of Health decided to implement quadrivalent conjugate meningococcal (MenACYW-TT) vaccination to control the increase in serogroup W IMD. The target groups were toddlers aged 14 months where MenC conjugate vaccine (MenC-TT) was replaced by a MenACYW-TT conjugate vaccine and teenagers aged 13–14 years with a single MenACYW-TT vaccination (3).

The MenACYW-TT vaccine included in the NIP is licensed in the Netherlands in 2012 (4). Several clinical trials showed that this vaccine to be safe and well tolerated in toddlers, adolescents and young adults (5–17). However, after major changes in the NIP, the profile of frequently occurring adverse events (AEs) after vaccinations needs to be assessed as part of the policy in the Netherlands of monitoring safety and tolerability. Therefore, we evaluated the tolerability of the MenACYW-TT vaccination in toddlers in a questionnaire study about the occurrence of AEs, potential medical interventions and absence from childcare or work following vaccination. In addition, the results regarding the occurrence of AEs were compared with data from a previous tolerability study of MenC-TT vaccine which was conducted by the Netherlands Pharmacovigilance Centre Lareb several years ago.

**Methods**

**Study population and setting**

The study population consisted of two groups of healthy children, vaccinated with either monovalent MenC-TT or with quadrivalent MenACYW-TT around the age of 14 months, according to the NIP schedule in the Netherlands at the time of investigation. Data on local reactions and systemic AEs from the MenC-TT vaccinated group were obtained by the Netherlands Pharmacovigilance Center Lareb in 2014–2016 (report available on request). Data from the MenACYW-TT vaccinated group were collected from October 2018 to December 2019 and are described in the present study. The study design of both studies was similar.

Children from the southern part of the Netherlands were randomly selected from the vaccination register (Praeventis) of the RIVM (National Institute for Public Health and the Environment).

Parents of selected children received an invitation letter to participate in the study, together with a flyer with information on the study. Parents could register as participant at a website by creating an account until 4 days after the MenACYW-TT vaccination of their child. In the registration process, the scheduled vaccination date of the toddler was asked to be filled in and informed consent from their parents was obtained.
Four days after the scheduled vaccination date, the parents received an email invitation to access the first questionnaire with their account on the website. This questionnaire asked about symptoms observed within four days after immunization (local reactions and systemic events). The invitation to fill in the second and third questionnaire was sent 14 and 28 days after the vaccination date, respectively. These questionnaires collected additional data on AEs not recovered after filling in the first questionnaire, and about systemic events related to the MMR vaccination. Results from these questionnaires will be reported separately.

A reminder was sent 2 days after the first questionnaire and 5 days after the second and third questionnaire.

Vaccines

The MenACWY-TT vaccine (Nimenrix®) was given intramuscularly in the right arm. The 0.5-ml dose contained Neisseria meningitidis-group A polysaccharide 5 µg, Neisseria meningitidis-group C polysaccharide 5 µg, Neisseria meningitidis-group W-135 polysaccharide 5 µg, and Neisseria meningitidis-group Y polysaccharide 5 µg, conjugated to tetanus toxoid carried protein 44 µg.

The MenC-TT vaccine (NeisVac-C®) was given intramuscularly in the right arm. The 0.5-ml dose contained Neisseria meningitidis-group C polysaccharide 10 µg, conjugated to tetanus toxoid carried protein 10–20 µg, absorbed on aluminium hydroxide, 0.5mg Al $^{3+}$ hydrated.

The 0.5-ml dose of MMR vaccine contained $\geq$ 12,500 p.f.u. mumps virus (Jeryl Lynn), $\geq$ 1,000 p.f.u. measles virus, and $\geq$ 1,000 p.f.u. rubella virus (M-M-R-Vaxpro®, MSD), and was administered subcutaneously in the left arm.

Questionnaire

The questionnaire included questions about the onset of local reactions and systemic events within four days after vaccination. Local reactions included swelling, redness, blue, induration, warmth, itch and pain at the injection site. Systemic events addressed sleeping problems, fever, being listless/apathetic, decreased appetite, vomiting, diarrhea, somnolence, rash, and other complaints. The presence was dichotomized (yes/no).

Information about the course of each symptom was also collected: time to onset, outcome, duration and impact (see Table 2 and Table 3 for grading scales). Additionally, the use of analgesics, occurrence of medical intervention, absence from childcare and/or other activities, and parents’ or guardians’ absence from work were asked.

Background information was collected regarding gender, medical history (i.e. positive when child regularly suffers from one or more of the following: coughing/shortness of breath, vomiting and/or diarrhea, infections, rash, hypersensitivity/allergy, other), number of children in household and attending daycare.

Statistical analysis

Assuming a percentage of fever of 8.2% (95% CI 6.7–10.1) in children participating in the MenC-TT study of Lareb, a 95% confidence level and a width of the confidence interval of 5%, the sample size should be 1239 adolescents to be able to detect an absolute elevated risk of 1.5% (18).

Assuming a response rate of 10% and a drop-out rate of 40%, about 20600 parents were needed to be invited for participation.

Differences in baseline characteristics between the two study groups were calculated using the Chi-square test and Mann-Whitney U test. The percentage of infants experiencing AEs within 4 days after immunization and 95% CIs were computed by type and severity of the AE. Binary logistic regression analysis was used to calculate odds ratios (ORs) for the relationship between local reactions and systemic AEs (dependent variables) and type of vaccine (independent variable) adjusted for gender, medical history, number of children in household, attending daycare. Proportions of absence from child-care and/or other activities, parents’ absence from work, and medical intervention within 4 days after vaccination were calculated with their 95% CIs.

Analyses were performed using SPPS statistics 24.

Results

Response rate and population characteristics

In total, 20966 invitations letters were sent to parents from children who were eligible for the MenACWY-TT vaccination. Of these, 1500 agreed to participate (7.2%). The response rate for the questionnaire on symptoms within 4 days after vaccination was 5.5% (n = 1157) and a little lower than the response rate in the comparative MenC-TT study of Lareb (6.4% (n = 2727).

Of all respondents, 50.1% concerned male toddlers (see Table 1). In the MenACWY-TT study 76.9% of the children attended daycare, which is more than in the previous MenC-TT study (60.3%; p < 0.01). In the MenACWY-TT study, a medical history was reported for 39% of the toddlers, with coughing/shortness of breath (17.9%) and rash (16.1%) as most reported. In the MenC-TT study, these comorbidities were less frequent (29.2%),
also with rash (11.4%) and coughing/shortness of breath (11.0%) most frequently reported. Furthermore, the distribution in season of vaccination was significantly different between the two groups (p < 0.01).

Table 1
Characteristics of the participants

| Characteristics                      | Study population MenACWY-TT (n = 1157) | Study population MenC-TT (n = 2727) | p-value |
|--------------------------------------|----------------------------------------|-------------------------------------|---------|
| Gender (n; %)                        | 580 (50.1)                             | 1401 (51.4)                         | P = 0.48|
| Male                                 | 577 (49.9)                             | 1326 (48.6)                         |         |
| Female                               |                                        |                                     |         |
| Season of vaccination (n; %)         | 240 (20.7)                             | 750 (27.5)                          | P < 0.01|
| Q1                                   | 329 (28.4)                             | 436 (16.0)                          |         |
| Q2                                   | 265 (22.9)                             | 747 (27.4)                          |         |
| Q3                                   | 323 (27.9)                             | 794 (29.1)                          |         |
| Q4                                   |                                        |                                     |         |
| Length in cm (mean; sd)              | 77.9 (3.2)                             | 78.4 (3.3)                          | P < 0.01|
| Weight in kg (mean; sd)              | 10.1 (1.1)                             | 10.2 (1.3)                          | P < 0.01|
| Number of children in household (n; %)| 634 (54.8)                             | 1518 (55.7)                         | P = 0.35|
| 1                                    | 403 (34.8)                             | 932 (34.2)                          |         |
| 2                                    | 99 (8.6)                               | 197 (7.2)                           |         |
| 3                                    | 12 (1.0)                               | 40 (1.5)                            |         |
| 4                                    | 1 (0.1)                                | 13 (0.5)                            |         |
| >=5                                   | 8 (0.7)                                | 26 (1.0)                            |         |
| Unknown                              |                                        |                                     |         |
| Attending daycare (n; %)             | 264 (22.8)                             | 1057 (38.8)                         | P < 0.01|
| No                                   | 890 (76.9)                             | 1644 (60.3)                         |         |
| Yes                                  | 3 (0.3)                                | 26 (1.0)                            |         |
| Unknown                              |                                        |                                     |         |
| Comorbidity (n; %)                   | 703 (60.8)                             | 1930 (70.8)                         | P < 0.01|
| No                                   | 454 (39.2)                             | 797 (29.2)                          |         |
| Yes                                  |                                        |                                     |         |

Local reactions after MenACWY-TT vaccination

Table 2 shows the frequency, severity, onset time and duration of local reactions that occurred within 4 days after vaccination. Within these period, parents reported one or more local reactions in 43 children (3.7 %) with a total of 103 local reactions reported. Injection site redness was the most commonly reported local reaction. Most of the reactions were recovering or had already recovered within 4 days after vaccination (88.3%). The mean time of onset of the different local reactions was within 17 hours after vaccination and ranged from 0–72 hours. The mean duration was 32.3 hours (range 0–72 hours). None of the parents reported that local reactions had high impact.
### Table 2
Reported Frequency of local reactions within 4 days after MenACWY-TT vaccination

| Local reaction        | MenACWY-TT vaccination (n = 1157) |
|-----------------------|-----------------------------------|
|                       |                                   |
| Swelling (n; %)       | 21 (1.8)                          |
| Redness (n; %)        | 34 (2.9)                          |
| Pain (n; %)           | 8 (0.7)                           |
| Blue (n; %)           | 5 (0.4)                           |
| Induration (n; %)     | 18 (1.6)                          |
| Warmth (n; %)         | 15 (1.3)                          |
| Itch (n; %)           | 0                                 |
| Other (n; %)          | 2 (0.2)                           |
| Size of the reaction (cm) |                        |
| 1–2                   | 22 (51.2)                         |
| 3–5                   | 6 (13.9)                          |
| >5                    | 29 (67.4)                         |
| Recovered from local reactions (n; %) | 9 (20.9) |
| Yes                   | 4 (9.3)                           |
| No, but it is recovering | 1 (2.3)                          |
| No, not recovered     | 32 (74.4)                         |
| Unknown               | 11 (25.6)                         |
| Impact of the reaction (n; %) |                     |
| No                    | 16.8 (15.9; 0–72)                 |
| Moderate              | 32.3 (20.3; 0–72)                 |
| High                  |                                   |
| Mean onset time in hr (sd; range) |                   |
| Mean duration in hr (sd; range) |                  |

### Systemic AEs after MenACWY-TT vaccination

Parents reported one or more systemic events for 32.4% (n = 375) of the children. A total of 971 systemic AEs were reported. Of these symptoms, listlessness was most often reported (22.4%), with a mean duration of 2.4 days. After that, sleeping problems (13.9%) and fever (13.4%) were most commonly reported (see Table 3). The mean onset time of systemic AEs ranged from 23.9–60.3 hours and the mean duration ranged from 20.3–41.4 hours. From all children with a systemic AE, 61.8% had recovered, or almost recovered within 4 days. The impact for almost all systemic AE ranged from none to moderate. Exceptions were sleeping problems and vomiting, with a high impact as reported by 9.9% and 8.1% of the parents, respectively. Children with a reported local reaction experienced more often systemic AEs (60.5%) than children without a reported local reaction (31.3%) (p < 0.001). This association was particularly observed in case of sleeping problems (p = 0.04), listlessness (p < 0.001) and other AEs (p = 0.04).

Parents from children with a medical history reported significantly more often vomiting after vaccination than children without a medical history (OR 2.24, 95% CI 1.15–4.38). No other significant associations between adverse events and medical history were found.
Table 3
Reported frequency of systemic events within 5 days after MenACWY-TT vaccination (n = 1157)

|                  | Treated n (%) | Recovered \(^a\) n (%) | Impact \(^a\) n (%) | Mean onset time | Mean recovery time |
|------------------|---------------|-------------------------|---------------------|----------------|------------------|
|                  | Yes | Almost | No | No | Low | Moderate | High |
|                  | hr (sd; range) | hr (sd; range) |
| Sleeping problems| 161 (13.9) | 12 (7.5) | 63 (39.1) | 33 (20.5) | 58 (36.0) | 51 (31.7) | 64 (39.8) | 30 (18.6) | 16 (9.9) | 23.9 (25.0) | 40.7 (22.4) |
| Fever            | 155 (13.4) | 101 (65.2) | 85 (54.8) | 26 (16.8) | 39 (25.2) | 56 (36.1) | 77 (49.7) | 27 (10.4) | 2 (0.2) | 42.0 (34.0) | 33.5 (21.9) |
| Listlessness/apathetic | 259 (22.4) | 13 (5.0) | 111 (42.9) | 58 (22.4) | 86 (33.2) | 92 (35.5) | 137 (52.9) | 6 (5.0) | 3 (1.2) | 30.4 (30.6) | 1–72 |
| Decreased appetite | 121 (10.5) | 2 (1.7) | 38 (31.4) | 39 (32.2) | 42 (34.7) | 70 (57.9) | 41 (33.9) | 6 (8.2) | 4 (3.3) | 36.1 (30.1) | 0–120 |
| Vomiting         | 37 (3.2) | 2 (2.7) | 26 (70.3) | 6 (16.2) | 4 (10.8) | 7 (18.9) | 20 (54.1) | 1 (3.2) | 3 (8.1) | 36.7 (28.7) | 0–96 |
| Diarrhea         | 73 (6.3) | 2 (6.5) | 25 (34.2) | 26 (35.6) | 19 (26.0) | 39 (53.4) | 25 (34.2) | - | 3 (4.1) | 44.2 (33.2) | 0–168 |
| Rash             | 71 (6.3) | 2 (6.5) | 25 (34.2) | 26 (35.6) | 19 (26.0) | 39 (53.4) | 25 (34.2) | - | 3 (4.1) | 44.2 (33.2) | 0–168 |
| Convulsion       | 31 (2.7) | 7 (10.3) | 14 (45.2) | 8 (25.8) | 9 (29.0) | 14 (45.2) | 15 (48.4) | 2 (10.0) | 1 (3.2) | 29.8 (31.8) | 0–120 |
| Other            | 68 (5.9) | 0 | 19 (27.9) | 11 (16.2) | 38 (55.9) | 48 (70.6) | 14 (20.6) | 1 (1.5) | 60.3 (41.7) | 0–168 |
|                  | 1 (0.1) | 2/20 (10.0) | 1 (100) | - | - | 1 (100) | - | 6 | 6 | 41.4 (21.4) | 4–96 |
|                  | 65 (5.6) | 9 (45.0) | 2 (10.0) | 9 (45.0) | 8 (40.0) | 8 (40.0) | 2 (10.0) | 37.1 (29.4) | 0–96 |

\(^a\) The sum of the numbers may not count to the total number because of unknowns

Absence and medical intervention after MenACWY-TT vaccination

Absence from attending childcare within 4 days after vaccination was reported in 10.2% of the children. The median duration was 1–2 days (see Table 4).

From all parents or guardians, 5.5% were absent from work to take care of the vaccinated child, with a median of also 1–2 days.
Table 4
Frequencies in absence and medical intervention after MenACWY-TT vaccination

| After vaccination | n (%) |
|-------------------|-------|
| Absence from childcare (n = 433) | 329 (76.0) |
| No | 16 (3.7) |
| Yes, < 1 day | 22 (5.1) |
| Yes, 1–2 days | 6 (1.4) |
| Yes, > 2 days | 60 (13.9) |
| Not applicable | 354 (81.8) |
| Absence from work (n = 433) | 8 (1.8) |
| No | 13 (3.0) |
| Yes, < 1 day | 3 (0.7) |
| Yes, 1–2 days | 55 (12.7) |
| Yes, > 2 days | 948 (81.9) |
| Not applicable | 209 (18.1) |
| Analgesic use | 40 (19.1) |
| No | 61 (29.2) |
| Yes | 47 (22.5) |
| Start analgesic use (n = 209) | 61 (29.2) |
| 0–6 hrs after vaccination | 95 (45.5) |
| 6–24 hrs after vaccination | 79 (37.8) |
| 24–48 hrs after vaccination | 35 (16.7) |
| >48 hrs after vaccination | 410 (96.0) |
| Duration of analgesic use (n = 209) | 7 (1.6) |
| <1 day | 7 (1.6) |
| 1–2 days | 3 (0.7) |
| >2 days | |
| Medical intervention (n = 427) | |
| No | |
| Call to general practitioner/youth doctor | |
| Visit general practitioner/youth doctor | |
| Other | |

Analgesics within 4 days after vaccination were used by 18.1% of the children. Almost all of them used paracetamol to treat fever and the median duration was less than 1 day (see Table 4). For eight children, the general practitioner or youth doctor was called for medical advice, and another twelve children visited the GP or youth doctor for their AEs. Main reasons for contacting the GP were fever (n = 7; including one child with febrile convulsions, local reactions (n = 2), extensive crying (n = 2) and anxiousness of the parents (n = 2).

Comparison AEs after MenACWY-TT vs. MenC-TT vaccination

Fever was the only symptom with a higher risk after MenACWY-TT vaccination compared to MenC-TT vaccination (adj OR 1.61; 95%CI 1.29–2.01) (see Table 5). For local reactions as well as for the other systemic events, no increased risks were found after MenACWY-TT vaccination.

Table 5. Risk of AEFI within 4 days after MenACWY-TT vaccination compared to MenC-TT vaccination
|                      | OR unadj (95% CI)a | OR adj (95% CI)b |
|----------------------|--------------------|-----------------|
| All Local Reactions  | 1.12 (0.77–1.62)   | 1.08 (0.74–1.57)|
| Fever                | 1.71 (1.38–2.13)   | 1.61 (1.29–2.01)|
| Decreased appetite   | 0.92 (0.74–1.15)   | 0.88 (0.70–1.11)|
| Vomiting             | 1.00 (0.68–1.48)   | 0.96 (0.64–1.42)|
| Diarrhea             | 0.98 (0.74–1.29)   | 0.97 (0.73–1.29)|
| Listlessness/Somnolence | 0.91 (0.77–1.07) | 0.88 (0.74–1.04)|
| Rash                 | 1.25 (0.92–1.69)   | 1.20 (0.88–1.63)|
| Convulsion           | 0.59 (0.06–5.27)   | 0.76 (0.08–6.94)|
| All systemic events  | 0.96 (0.83–1.11)   | 0.93 (0.80–1.08)|

a Ref category MenC-TT vaccination
b Adjusted for gender, comorbidity, number of children in household, attending daycare

**Discussion**

In the present study we evaluated the tolerability of the newly introduced MenACWY-TT vaccine in the NIP in toddlers. Our results show that solicited systemic AEs like listlessness, fever and sleeping problems frequently occur, although most of them recovered within 4 days. The frequency of rash was much lower, but the majority of the children had not recovered after 4 days. However, rashes are also a known adverse event of MMR vaccination which usually occurs 5–21 days after vaccination. Therefore, overlapping frequencies of this adverse event from both vaccines may explain the longer duration. A follow-up questionnaire showed that only 2 children experiencing rash within 4 days after vaccination, did not recover within 30 days after vaccination (data not shown). The impact for most of the systemic AEs was mild to moderate, but parents reported on a high impact of sleeping problems and the vomiting, while hardly mentioning problems with local reactions.

The tolerability of MenACWY-TT observed in our study was in line with that observed in Lareb’s MenC-TT study conducted a few years earlier in a similar group of young children in the Netherlands. Only for fever a higher risk after MenACWY-TT vaccination was found within 4 days after vaccination.

The frequencies of local reactions we found in our study are remarkable lower compared with the results from post-licensure trials. In our study, redness was the most reported local reaction (2.9%), whereas in other studies percentages up to 45% were found for local reactions (10, 12, 19–21). In the clinical trials, irritability was one of the most mentioned solicited general symptoms with frequencies between 15 and 45% (10, 12, 19, 20), whereas in our study, listlessness was the most reported systemic AE (22.4%). Unfortunately, we did not include irritability in our questionnaire, whereas the trials did not describe listlessness. Drowsiness was another frequently mentioned systemic AE in the trials (15–35%), whereas in our study somnolence was hardly reported (2.7%). On the other hand, the results for loss of appetite (10.5% in our study vs. 10–25% in the trials) and fever (13.4% vs. 5–30%) were more consistent. Differences in study design (cross-section vs RCTs, data collection, age distribution) may contribute to the differences in our results and the results from clinical trials. This is underlined by the fact that our results are very similar to the results of Lareb’s MenC-TT study, which had the same study design. Only for fever a significant difference was found between these studies (13.4% for MenACWY vaccination and 8.2% for MenC-TT vaccination), although our result is in line with what is reported in the SMPC of this vaccine (≥ 1:10) (4).

There were a few number of limitations to this study. Compared to Lareb’s MenC-TT study, significant differences were identified in baseline characteristics for comorbidity, attending daycare and seasonality. Although this may influence the frequency of for example fever, no different risk estimations were found between the adjusted and unadjusted analyses. Confounding by any of the covariates is therefore unlikely.

Data from the MenACWY-TT and Lareb’s MenC-TT study were collected in different years. As the circulation of infectious agents differs between years, this may have influenced the frequency of some systemic events, like fever, diarrhea and vomiting. Since many of these events in our study recovered within 4 days, we assume that this effect is limited. However, the actual effect is unknown.

The non-response in both studies was high. A low response rate can give rise to sampling bias if the nonresponse is unequal among the participants regarding exposure and/or outcome. It is not clear to what extent this has occurred in this study. But since they have the same study design, it may be assumed that the reasons for non-response is similar for the MenACWY-TT and MenC-TT study. Therefore it is unlikely that the comparison of these studies is biased.
Conclusions

This questionnaire-based study shows, in line with pre-licensure data, that MenACWY-TT vaccination has a good tolerability. Local reactions hardly occur. Most reported systemic AEs are listlessness, fever and sleeping problems. Most of the events were mild to moderate and transient but the impact of sleeping problems and vomiting was relatively high. The MenACWY-TT vaccine showed to be a little more reactogenic compared to the MenC-TT vaccine, expressed by a higher risk of fever within 4 days after vaccination. For the other factors no increased risks were found. Overall, our study shows that MenACWY-TT vaccination is well tolerated in toddlers.

Abbreviations

AEs Adverse events
IMD Invasive meningococcal disease
MenACWY-TT Meningococcal ACWY vaccine
MenC Meningococcal serogroup C disease
MenC-TT Meningococcal C vaccine
MenW Meningococcal serogroup W disease
NIP National Immunization Programme
RIVM National Institute for Public Health and the Environment

Declarations

Ethics approval and consent to participate

According to Dutch law (i.e., the Medical Research Involving Human Subjects Act (WMO)), internet-based surveys among healthy volunteers do not require formal medical ethical approval (www.ccmo.nl). However, all procedures performed in this study were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained from all adolescents included in the study and their parents.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

The present study was funded by the Ministry of Health, Welfare and Sport. They had no role in the design, collection, analysis, and interpretation of data. Neither did it have any role in the manuscript preparation at any stage and in the decision to submit it for publication.

Authors’ Contribution

JK: Conception and design of the study, analyses, drafted the manuscript. LvB: Conception and design of the study, data collection, critical revision of the manuscript. AK: Conception and design of the study, critical revision of the manuscript. HdM: Critical revision of the manuscript and supervised the whole study process.

All authors have read and approved the manuscript.

Acknowledgements
The authors would like to thank Roger Venema (department DVP of the National Institute for Public Health and the Environment, RIVM) for providing the individual data from the national immunization register Præventis.

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