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Reactogenicity and safety of second trimester maternal tetanus, diphtheria and acellular pertussis vaccination in the Netherlands

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ABSTRACT

Background: Maternal tetanus-diphtheria-and-acellular-pertussis (Tdap) vaccination is offered to all pregnant women during their second trimester in the Netherlands since December 2019. We assessed second trimester Tdap vaccination reactogenicity and compared with third trimester data from a similar study. For safety assessment, adverse pregnancy outcomes were compared with national data from 2018, before Tdap vaccine-introduction.

Methods: Pregnant women were included between August 2019-December 2021 and received Tdap vaccination between 20 and 24w gestational age (GA). Participants completed a questionnaire on solicited local reactions and systemic adverse events (AEs) within one week after vaccination. Results were compared with historical data on reactogenicity from women vaccinated between 30 and 33w GA (n = 58). Regarding safety-related outcomes, each participant was matched to four unvaccinated pregnant women from the Dutch Perinatal Registry, based on living area, parity and age.

Results: Among 723 participants who completed the questionnaire, 488 (67.5 %) experienced ≥ 1 local reaction with pain at the injection site as most reported reaction (62.3 %), and 460 (63.6 %) experienced ≥ 1 systemic AE with stiffness in muscles/joints (38.9 %), fatigue (28.9 %), headache (14.5 %) and common cold-like symptoms (11.0 %) most frequently reported. 4 women (0.6 %) reported fever (≥38.0C). Symptoms were considered mild and transient within days. No difference in AEs were found between vaccination at 20-24w versus 30-33w GA. 723 participants were matched to 2,424 unvaccinated pregnant women with no increased rates of premature labor, small-for-gestational-age, or other adverse pregnancy outcomes.

Conclusions: Second trimester maternal Tdap vaccination appears safe and well-tolerated. Comparison between second versus third trimester vaccination yielded no reactogenicity concerns.

1. Introduction

Pertussis is a respiratory infectious disease, caused mainly by *Bordetella pertussis*. Especially young unvaccinated infants are at risk of severe disease and sometimes even death [1,2]. In older vaccinated or previously infected children and adults, pertussis often manifests with no or mild symptoms that are frequently unrecognized [3,4]. Nevertheless, *B. pertussis* is readily transmitted by (a) symptomatic persons after infection and passed on to infants without sufficient immunological protection as they are too young to be fully vaccinated [5,6]. In response to the re-emergence of pertussis since the late 1990 s and in particular, following a large epidemic wave of pertussis in 2012, maternal vaccination with tetanus-diphtheria-and-acellular-pertussis (Tdap) is offered in several countries to protect newborns against pertussis in the first months after birth [7]. Maternal pertussis-specific IgG antibodies that rise upon vaccination during pregnancy are actively transferred from mother to fetus, providing passive neonatal immunity until the infant vaccination series offers protection against clinical disease [8–14]. Since December 2019, maternal Tdap vaccination is offered to all Dutch pregnant women from 22 weeks gestational age (GA) onwards.

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The vaccination is shown to be well-tolerated by pregnant women, although the majority of women experience transient mild to moderate local reactions and systemic adverse events (AEs) shortly after vaccination. Current knowledge about vaccine reactogenicity is mostly limited to third trimester Tdap vaccine administration [9,15–17]. However, an increasing number of countries encourage women to get vaccinated during the second trimester of pregnancy in order to provide a sufficient amount of time for antibody transfer in case of preterm labor. We aimed to assess the frequency of local reactions and systemic AEs within one week after maternal Tdap vaccine administration between 20 and 24 weeks GA. Results were compared to reactogenicity data from a historical cohort of pregnant women who received a Tdap vaccination between 30 and 33 weeks GA [18]. As a second objective, we assessed the longer-term safety of second trimester Tdap vaccination with respect to adverse pregnancy outcomes (before and after birth) and compared outcome frequencies with background incidences from 2018, i.e. before maternal Tdap vaccination was implemented under the National Immunization Program in the Netherlands.

2. Methods

2.1. Study population and setting

This study is part of a large prospective cohort study among pregnant women regarding acceptance, reactogenicity and immunogenicity of maternal Tdap vaccination between 20 and 24 weeks GA [19]. In brief, antenatal care providers invited women during the first trimester of pregnancy to participate in the study over the period from August 2019 throughout November 2021. Tdap immunization was provided by the antenatal care provider between 20 and 24 weeks GA. One week after Tdap vaccine administration, participants completed a digital questionnaire on solicited local reactions and systemic AEs occurring within the first seven days after vaccination, occurrence of similar systemic symptoms in the week prior to vaccination, and how they perceived the severity of all symptoms (mild, moderate or severe). The study was organized in accordance with the Declaration of Helsinki. Permission to conduct this study was obtained from the Central Commission on Research Involving Human Subjects (registration number NL66966.000.18) and participants gave consent for linking their questionnaire data to the Dutch perinatal registry.

Reactogenicity data were compared with data from a randomized controlled trial that studied immunogenicity of maternal Tdap vaccination in the period from January 2014 to February 2016, and additionally assessed reactogenicity after Tdap vaccination between 30 and 33 weeks GA, making use of the same Tdap vaccine [18].

Details on population-wide adverse pregnancy outcomes were retrieved from the Dutch Perinatal Registry (DPR) database [20]. To date, the DPR covers data on (adverse) pregnancy outcomes of about 98 % of all deliveries in the Netherlands up to and including the year 2020. Data from 2021 were not available yet. Records on adverse pregnancy outcomes of the participants were identified by linking our study population to the DPR database based on date of birth of the mother, living area (4-digit postal code), and date of expected delivery. If data were unavailable from the DPR, they were retrieved from medical records provided by the antenatal care provider (n = 384).

2.2. Tdap vaccine

All participants received a Tdap vaccine (Boostrix®) that contains adsorbed pertussis antigens, i.e. pertussis toxin, filamentous hemagglutinin and pertactin, and inactivated toxoids of diphtheria and tetanus [21]. The Tdap vaccine was administered as a single 0.5 mL intramuscular injection in the upper arm deltoid muscle. In case participants were ill or had fever (≥38.0℃), administration was postponed until recovery.

2.3. Reactogenicity questionnaires

Demographic data including age, country of birth, education level, number of previous pregnancies and number of own children were collected, next to data on local reactions and systemic AEs within one week after vaccination. Participants reported the day of onset since vaccination, severity (self-reported as mild, moderate or severe) (for fever we used categories low-grade 38.0–38.9℃, moderate-grade 39.0–39.9℃, high-grade 40.0–40.9℃ and hyperpyrexia ≥ 41.0℃) and duration of AE in days. Solicited local reactions included pain; erythema; swelling; and induration at the injection site. Systemic AEs included fever (if ≥ 38℃); headache; fatigue; nausea; vomiting; regular uterine contractions; diarrhea; dizziness; decreased appetite; stiffness in muscles or joints; itch; excessive transpiration; rash; swelling in neck, armpits or groins; sore throat; common cold-like symptoms; coughing; fainting; and flu or flu-like symptoms. Women also filled in whether or not they experienced any of these systemic events in the week before vaccination. Data on additional medical consultation pre- or post-vaccination, usage of analgesics or absence from work as a result of any of the abovementioned complaints were documented.

For comparison of reactogenicity between early vaccinated (20–24 weeks GA) vs late vaccinated (30–33 weeks GA) women, we compared post-second-trimester Tdap vaccination data with a small historical comparator cohort of mothers vaccinated between 30 and 33 weeks, who reported in a similar questionnaire on experiencing fever; headache; fatigue; stiffness in muscles or joints and pain, induration, swelling and erythema at the injection site after Tdap vaccination [18]. The use of analgesics and additional medical consultation were also assessed and presented in the category "other AE".

2.4. Safety data on adverse pregnancy outcomes

Participants were each linked to four mothers in the DPR database from the year 2018, matched on date of birth of the mother (allowing a maximum age difference of 3 years), living area (4-digit postal code) and parity. These control mothers were presumed to be unvaccinated since Tdap vaccination was introduced at the end of 2019 in the Netherlands.

The following adverse pregnancy outcomes were assessed: small for gestational age, defined as lower than 10th percentile of Hoftiezer [22]; pregnancy duration shorter than $37^{0/7}$ weeks; and a composite outcome consisting of either one or more of the following outcomes: congenital anomalies, perinatal mortality, low Apgar-score, i.e. < $7^{/10}$ at 5 min, admission to a neonatal intensive care unit ward.

2.5. Statistical analysis

Analyses were performed using R software version 4.0.4. We had a study population of 723 participants available, for which sample size calculations were based on the immunogenicity part of this study, that was described previously [19].

Percentages and 95 % confidence intervals (95 % CI) of pregnant women experiencing systemic AEs or local reactions within one week since vaccination were described by type, perceived severity and duration of the AE. Occurrence of AEs after versus before second trimester (early) Tdap vaccination was analyzed using binary

generalized mixed models (GLMM), while adjusting for multiple comparisons and expressing odds ratios (OR) with corresponding 95 % CI.

Risk ratios with 95 % CI were calculated for the assessment of reactogenicity after early (20-24w GA) vs late (30-33w) maternal vaccination.

We calculated risk ratios and 95 % CIs for the abovementioned adverse pregnancy outcomes between our Tdap vaccinated population and the matched section of the DPR population in 2018.

3. Results

3.1. Second trimester Tdap vaccinated participants

974 participants received a maternal Tdap vaccination between 20 and 24 weeks GA of whom 723 (74 %) completed the questionnaire. Mean age of the participants was 32 years, mean GA at Tdap vaccination was 22.0 weeks. Further details on demographics are shown in Table 1.

3.2. Solicited local reactions

Of all 723 participants, 488 participants (67.5 %) experienced at least one local reaction within the week after vaccination. Pain at the injection site was the most reported AE (62.2 %) (Fig. 1) and was reported predominantly as mild (49.6 %) or moderate (38.4 %). Nevertheless, 12.0 % of women experienced pain as severe. Induration, swelling, or erythema at the injection site were reported in 23.9 %, 16.9 % and 11.7 % of cases, respectively (Fig. 2). Participants reported a median onset of pain immediately after vaccination, while erythema, swelling and induration started after a median of one day after vaccination. Solicited local reactions lasted 3–5 days.

3.3. Systemic adverse events

After vaccination, 460 participants (63.6 %) reported at least one systemic AE (Fig. 1). Most reported systemic AEs after vaccination were stiffness in muscles and/or joints (38.9 %, 95 % CI 29.4–49.2), fatigue (28.9 %, 95 % CI 20.5–39.0), headache (14.5 %, 95 % CI 8.5–23.3), and common cold-like symptoms (11.0 %, 95 % CI 5.8–19.1) (Fig. 2). Symptoms were predominantly reported as mild to moderate (range 59.7 %-74.2 %) and lasted 2–7 days. 4 participants (0.6 %) reported fever, of whom 3 with low-grade and 1 with moderate-grade fever, that lasted one to two days. More detailed information about severity, baseline frequency, onset and duration of symptoms are presented in Figs. 1 and 2.

At baseline, 263 participants (36.4 %) reported at least one systemic event in the week before vaccination. Following Tdap vaccination, stiffness in muscles and/or joints (OR = 32.5, 95 % CI 11.0–95.6), rash (OR = 8.0, 95 % CI 1.3–50.3), headache (OR = 4.6, 95 % CI 2.0–10.8), nausea (OR = 3.7, 95 % CI 1.3–10.8), fatigue (OR = 3.7, 95 % CI 1.9–7.0) and itch (OR = 3.0, 95 % CI 1.1–8.5) (Fig. 2) were more frequently reported.

3.4. Additional medical consultation, analgesics use and absence from work

Medical consultation for any symptom after Tdap vaccination was seen in 2.8 % of cases. Consultation usually consisted of an extra healthcare visit at the antenatal care provider for complaints like fatigue, regular uterine contractions, nausea and/or a headache (Fig. 2). The use of analgesics for any symptom after Tdap vaccination was reported in 10.8 % of cases and was used for one or two days, mainly for moderate or severe headache, fatigue, sore throat, or common cold-like symptoms and coughing. Staying home from work after Tdap vaccination was observed in 3.5 % of the participants. The absence lasted one to two days in half of the cases but

Table 1
Demographics of pregnant women vaccinated between 20 and 24 weeks of gestation.

	Between 20 and 24w GA vaccinated study population (n = 723)[a]	Between 30 and 33w GA vaccinated reference population (n = 58)	p-value
Age in years; mean (sd)	32.5 (4.0)	32.5 (3.3)	1.000
Gestational age in weeks at immunization; mean (sd)	22.0 (1.3)	31.3 (0.8)	<0.001*
Country of birth; n (%)			
The Netherlands	667 (92.3)	NA	NA
Other	56 (7.7)	NA	NA
Education level; n (%)[b]			
Low	24 (3.3)	NA	NA
Middle	187 (25.9)	NA	NA
High	512 (70.8)	NA	NA
Previous pregnancy; n (%)			
Yes	473 (65.4)	NA	NA
No	250 (34.6)	NA	NA
Has own children; n (%) [c]			
Yes	397 (54.9)	21 (36.2)	0.018*
No	326 (45.1)	37 (63.8)	
Self-reported chronic disorder; n (%)[d]			
Yes	148 (20.5)	NA	NA
No	573 (79.5)	NA	NA
Self-reported other pregnancy-related disorder; n (%)[c]			
Yes	70 (9.7)	NA	NA
No	651 (90.3)	NA	NA

aDemographic comparison data were not available for all variables from the reference cohort of women vaccinated in the third trimester of pregnancy. They were shown only if available. No comparison data were available for the 2018 unvaccinated population. b Maternal education level categories, i.e. Low = no education, primary school, pre-vocational education (VMBO), lower vocational education (LBO/MBO-1), lower general secondary education (MAVO/VMBO). Middle = intermediate/secondary vocational education (MBO-2–4), higher/senior vocational education (HAVO), pre-university education (VWO/Gymnasium); High = higher professional education (HBO), University BSc., University MSc., Doctorate. c The reference study asked women specifically how many children they are currently living with in their household. The true percentage of women who have own children might be higher. d Two missings in self-reported chronic disorder or pregnancy-related disorder. * significance p < 0.05.

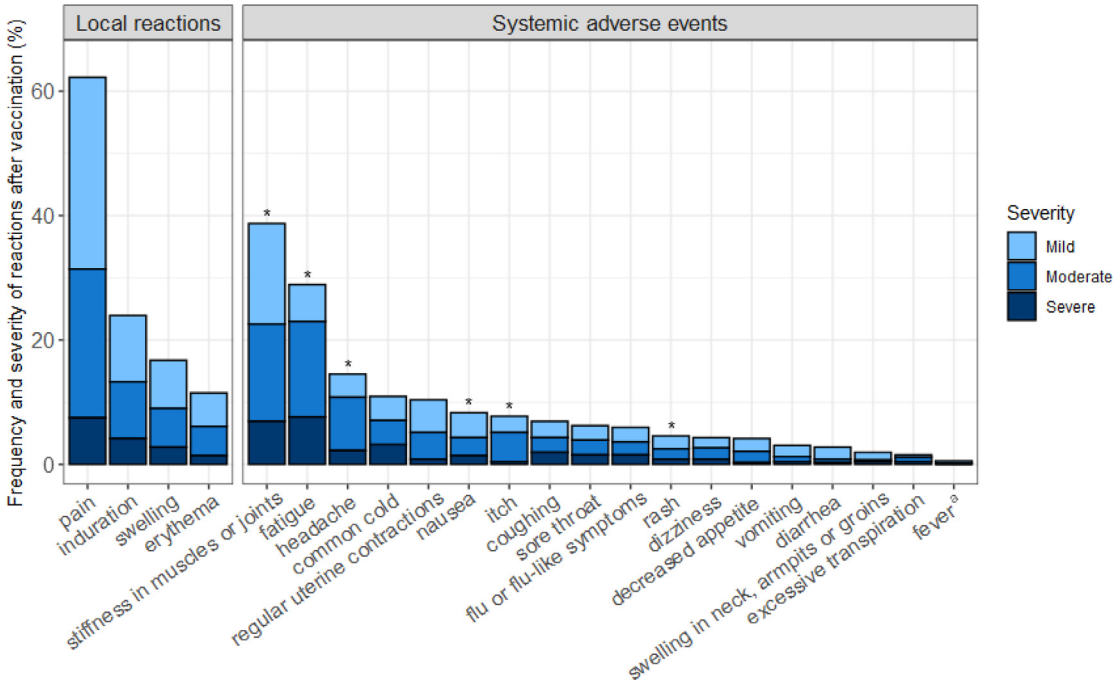

Fig. 1. Frequency and self-reported severity (%) of local reactions at the injection site and systemic AEs within 7 days after maternal Tdap vaccination. [a] For fever, categories were low-grade (mild-blue), moderate-grade (moderate-blue), high-grade (NA), and hyperpyrexia (NA) (see main text for corresponding temperatures) * significant systemic symptoms that were more observed post-Tdap vaccination ($p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

	Week before vaccination		Week after vaccination			OR[a] (95% CI)
	% (95% CI)	Median duration, days (IQR)	% (95% CI)	Median onset time since vaccination, days (IQR)	Median duration, days (IQR)	
Systemic adverse events						
Stiffness in muscles or joints	4.0 (1.3-10.5)	7 (4-8)	38.9 (29.4-49.2)	1 (0-1)	3 (2-5)	32.5 (11.0-95.6)*
Rash	1.8 (0.3-7.4)	8 (8-8)	4.7 (1.7-11.4)	1 (0-3)	7 (3.75-8)	8.0 (1.3-50.3)*
Headache	7.1 (3.1-14.4)	3 (2-8)	14.5 (8.5-23.3)	1 (0-2.25)	2 (2-4)	4.6 (2.0-10.8)*
Excessive transpiration	0.6 (0.0-5.5)	7.5 (5.75-6.25)	1.5 (0.2-7.0)	2.5 (1-4)	4 (2-8)	4.5 (0.4-47.5)
Swelling in neck, armpits or groins	0.8 (0.0-6.0)	8 (5.75-8)	1.9 (0.3-7.6)	1 (1-1)	4.5 (2.25-8)	3.7 (0.5-25.9)
Nausea	4.6 (1.6-11.3)	8 3.75-8)	8.3 (4.0-16.0)	1 (0-2.5)	4 (2-8)	3.7 (1.3-10.8)*
Fatigue	18.5 (11.7-27.8)	8 (5-8)	28.9 (20.5-39.0)	1 (0-1)	4 (2-8)	3.7 (1.9-7.0)*
Itch	4.8 (1.8-11.6)	8 (8-8)	7.9 (3.7-15.5)	1 (0-2)	7 (2-8)	3.0 (1.1-8.5)*
Coughing	4.3 (1.4-10.9)	8 (8-8)	6.9 (3.0-14.3)	1 (0-3.75)	7 (4-8)	2.6 (0.9-7.2)
Sore throat	3.1 (0.8-9.2)	5 (3.25-7.75)	6.2 (2.6-13.4)	2 (1-3)	4 (3-6)	2.4 (1.0-5.9)
Flu or flu-like symptoms	3.3 (0.9-9.6)	5 (2.5-7)	6.0 (2.4-13.1)	1 (1-3)	4 (2-5)	1.9 (0.9-4.4)
Decreased appetite	3.2 (0.9-9.4)	8 (4-8)	4.1 (1.4-10.7)	0 (0-1.75)	5 (3-8)	1.7 (0.5-5.6)
Diarrhea	1.7 (0.2-7.2)	2.5 (1.75-8)	2.8 (0.7-8.8)	3 (1-5)	2 (1-3.5)	1.7 (0.6-5.4)
Fainting	0.3 (0.0-5.1)	8 (8-8)	0.4 (0.0-5.3)	2 (1.5-3)	2 (1.5-5)	1.5 (0.1-23.6)
Common cold-like symptoms	8.7 (4.3-16.5)	8 (6.5-8)	11.0 (5.8-19.1)	1 (0-3)	7 (4-8)	1.5 (0.8-2.8)
Fever	0.4 (0.0-5.3)	2 (2-2.5)	0.6 (0.0-5.5)	1 (1-1.5)	1.5 (1-2)	1.3 (0.1-13.4)
Regular uterine contractions	9.1 (4.5-17.0)	6 (2-8)	10.4 (5.4-18.5)	1 (0-2)	4 (2-8)	1.3 (0.6-2.9)
Vomiting	3.0 (0.8-9.2)	2 (1-8)	3.0 (0.8-9.2)	1 (0-4.75)	2.5 (1-8)	1.0 (0.3-3.1)
Dizziness	5.3 (2.0-12.2)	8 (3-8)	4.3 (1.5-10.9)	1 (0-2)	5 (2-8)	0.7 (0.2-1.9)
Local reactions at injection site						
Pain	NA	NA	62.2 (51.9-71.6)	0 (0-1)	3 (2-5)	NA
Induration	NA	NA	24.1 (16.3-33.8)	1 (0-1)	4 (3-7)	NA
Swelling	NA	NA	17.0 (10.5-26.1)	1 (0-1)	5 (3-7)	NA
Erythema	NA	NA	11.6 (6.3-20.0)	1 (0-1)	5 (3-7)	NA
Other						
Analgesics use	8.0 (3.8-15.6)	1.5 (1-2)[b]	10.9 (5.8-19.1)	NA	1 (1-2)[b]	1.6 (0.8-3.1)
Absence from work	4.6 (1.7-11.4)	2 (1-2)[b]	3.5 (1.0-9.8)	NA	1.5 (1-2)[b]	0.7 (0.3-1.7)
Additional medical consultation	6.1 (2.5-13.2)	NA	2.8 (0.7-8.8)	NA	NA	0.4 (0.2-1.0)

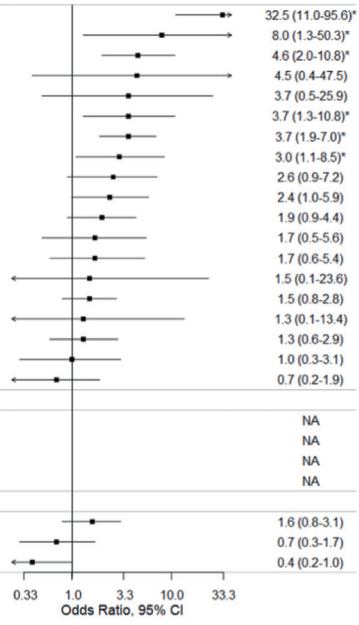

Fig. 2. Occurrence of systemic adverse events and local reactions within 7 days before and/or after maternal Tdap vaccination. CI, confidence interval; IQR, inter-quartile range; OR, odds ratio. [a] Odds ratios for systemic events and other variables were computed by binary generalized mixed models while referring to the week before Tdap vaccination. Severity and duration were not included. [b] duration of analgesics use and absence from work were asked in categories one to two days (1) or three or more days (2). * significance $p < 0.05$.

longer for the other half, in particular when in combination with flu-like illness or common cold-like symptoms.

3.5. Comparison with data from the third trimester

AEs in the 723 participants in our study population were compared with those of 58 participants in the historical control cohort vaccinated between 30 and 33 weeks GA. Among those, 56 of 58 participants (96.6 %) experienced at least one adverse event (local or systemic) in the week after Tdap vaccination, regardless of its severity. The most frequently reported reactions to Tdap vaccination were pain at the injection site (85.7 %) and stiffness in muscles and/or joints (66.7 %). No significant differences in occurrence of AEs were found between women vaccinated between 20 and 24 weeks GA compared to 30–33 weeks GA (Table 2).

3.6. Adverse pregnancy outcomes

In total, the 723 study participants were matched to 2,424 controls from the DPR in 2018. No significantly different risk ratios were observed for any of the adverse pregnancy outcomes; pregnancy duration shorter than $37^{0/7}$ weeks (RR = 1.32, 95 % CI 0.94–1.84), small for gestational age (RR = 0.78, 95 % CI 0.54–1.11) and the composite outcome (RR = 1.16, 95 % CI 0.75–1.82) (Table 3).

4. Discussion

In this study we demonstrated that 67.5 % of participants reported at least one local reaction and 63.6 % one or more systemic AE's within one week after maternal Tdap vaccination in the second trimester of pregnancy (i.e. between 20 and 24 weeks GA). The most reported local reaction was pain at the injection site (62.2 %), that manifested mostly mild and transient within days. Most reported systemic AEs were stiffness in muscles and/or joints (38.9 %), fatigue (28.9 %), headache (14.5 %), and common cold-like symptoms (11.0 %). Fever was reported in 0.6 % of cases. We did not find any significant differences in adverse events between second and third trimester Tdap vaccination based on comparison with a small cohort of women in a study on Tdap vaccination between 30 and 33 weeks GA. Regarding longer-term safety of maternal Tdap vaccination, our findings showed no significantly different rates of adverse pregnancy outcomes after vaccination compared with the Dutch nationwide population in 2018, i.e. before Tdap vaccine-introduction.

In our reactogenicity study, we observed higher local and systemic occurrences of AEs following vaccination, e.g. pain at the injection site, fatigue, headache, compared with many previous studies [15–17,23]. Proportions of AEs tend to differ between studies, very likely due to the different ways how questions are asked, in different populations and countries, and at different times in

Table 2
Risk ratios of second versus third trimester vaccination systemic AEs post-vaccination and local reactions at the injection site.

	Between 20 and 24w GA vaccinated study population (n = 723)	Between 30 and 33w GA vaccinated reference population (n = 58)	Risk ratio (95 % CI)
Systemic adverse events			
Stiffness in muscles and/or joints	281/722[a] (38.9 %)	37/56[b] (66.1 %)	0.70 (0.48–1.03)
Headache	105/723 (14.5 %)	8/56[b] (14.3 %)	1.01 (0.40–2.58)
Fatigue	209/723 (28.9 %)	25/56[b] (44.6 %)	0.73 (0.44–1.19)
Fever (≥38.0C)	4/723 (0.6 %)	1/57[b] (1.8 %)	0.32 (0.02–4.38)
Local reactions			
Pain	450/723 (62.2 %)	48/56[b] (85.7 %)	0.83 (0.61–1.14)
Induration	174/723 (24.1 %)	8/54[b] (14.8 %)	1.50 (0.60–3.75)
Swelling	123/723 (17.0 %)	7/54[b] (13.0 %)	1.27 (0.47–3.40)
Erythema	84/723 (11.6 %)	13/54[b] (24.1 %)	0.54 (0.26–1.13)
Other			
Analgesics use	79/723 (10.9 %)	1/55[b] (1.8 %)	5.52 (0.56–53.97)
Additional medical consultation	20/723 (2.7 %)	1/55[b] (1.8 %)	1.51 (0.14–15.68)

AE, adverse event; CI, confidence interval; GA, gestational age [a] 1 missing record for stiffness in muscles and/or joints in study population group. [b] 1–4 missing records for all studied variables in reference population group.

Table 3
Risk ratios of adverse outcomes within the study population versus matched DPR population in 2018.

	Prevalence study population (n = 723)	Prevalence matched DPR population 2018 (n = 2,424)	Risk ratio (95 % CI)
Pregnancy duration < $37^{0/7}$ weeks	65/690 (9.4 %)[c]	168/2,406 (7.0 %)[d]	1.32 (0.94–1.84)
Small for gestational age[a]	51/685 (7.4 %)[c]	232/2,369 (9.8 %)[d]	0.78 (0.54–1.11)
Composite outcome[b]	36/681 (5.2 %)[c]	109/2,418 (4.5 %)[d]	1.16 (0.75–1.82)

CI, confidence interval; DPR, Dutch Perinatal Registry [a] Small for gestational age was defined as birthweight lower than the 10th percentile of Hoftiezer [22]. [b] The composite outcome consisted of either one or more of the following outcomes: severe congenital anomalies, perinatal mortality, low Apgar-score, i.e. < $7^{/10}$ at 5 min, admission to a neonatal intensive care unit ward. [c] Numbers were smaller than the number of study participants due to unavailable records within the Dutch Perinatal Registry or local medical record system. [d] Numbers were smaller than the matched 2,424 pregnancies due to unavailable records within the DPR.

pregnancy, predominantly in the third trimester. For example, Fortner and colleagues asked pregnant women to only report events following Tdap immunization if it concerned moderate or severe manifestation [15]. When stratifying our results for perceived severity and comparing only moderate and severe AEs between studies, results of our study navigate closer to the results from Fortner and colleagues (31.4 % moderate-severe pain at the injection site in our study vs 17.9 % by Fortner and colleagues, and 10.8 % moderate-severe headache in our study vs 7.2 % by Fortner and colleagues), though the frequency remains higher. Wanlapakorn and colleagues reported on rates of pain at the injection site after maternal Tdap vaccination (in mild, moderate or severe manifestation) that were more alike our results (76.2 vs 62.2 % in our study), though the authors reported lower rates of swelling (4.1 vs 17.0 % in our study) and erythema (1.4 vs 11.6 % in our study) [23].

For direct comparison of reactogenicity data following Tdap vaccination between second versus third trimester vaccination, we had a small comparator group available, from a similar Dutch population who participated recently in a randomized controlled immunogenicity trial in which women were Tdap vaccinated at 30–33 weeks GA. Here, 96.6 % reported at least one (local and/or systemic) symptom that is somewhat higher than in our data (82.9 %) [18]. Though the limited size of the third trimester comparator groups prevails in-depth analysis, we found no significant differences in AE prevalence, implicating that there are no signs for reactogenicity concerns for Tdap vaccination in the second trimester of pregnancy.

Women in our population were expected to have - in theory - a higher risk for pregnancy complications than those from the randomized controlled study. However, we still have not observed increased occurrence of adverse events following second trimester vaccination, which emphasizes the safety of second trimester Tdap vaccination.

We found no significantly different ratios for adverse pregnancy-related outcomes after second trimester Tdap vaccination compared with presumably unvaccinated women from before maternal Tdap vaccination introduction. It fits well with other studies, where the maternal Tdap vaccination seems to have a well-established good safety profile [5,6,9–13,24]. In accordance with our findings, a systematic review by McMillan and colleagues concluded that adverse pregnancy outcomes including the risk of preterm delivery were unaffected after maternal Tdap vaccination, though with point estimates (95 % CI) ranging from 0.47 to 1.50 [13]. In addition, the authors reported no increased risk for small for gestational age birth after maternal Tdap vaccination (95 % CI 0.65–1.00), which is in line with our findings.

Although congenital malformations do not seem plausible to have a causal relation with second or third trimester maternal vaccination, the public may interpret (severe) adverse events following maternal vaccination differently, especially when it comes to the opposition to vaccines, in particular when it is administered during pregnancy. These should therefore not be excluded from the combined outcome. Severe congenital anomalies accounted for < 1 % of adverse effects in both the study population as in the 2018 reference population (and the matched cohort) and for this reason, excluding congenital malformations from the composite outcome would probably not affect our results.

Some limitations and biases may have been introduced in our study. To begin with, participants were non-randomized, resulting into that the study may be exposed to selection bias. Women who experienced AEs in the week after the vaccination were probably more likely to respond to the questionnaires than women who did not experience AEs. This could have led to an overestimation of our reactogenicity results. Our study may have also been exposed to reporting bias since study participants were not blinded, knowing they were injected with what they may perceive as a 'novel' vaccine with potential side effects. We therefore expect that overestimations of reactogenicity reporting cannot be excluded. Nevertheless, reported AEs were predominantly described as mild and transient within days, while other studies mostly reported moderate-severe AEs. Another bias we cannot neglect is recall bias, as this study contained a one-time questionnaire on reactogenicity that was completed a week after vaccination. This forced participants to recall the symptoms they experienced in the week before vaccination, including their severity. Furthermore, we used a very small historical comparator cohort to distinguish AEs after second vs third trimester maternal Tdap vaccination. The reason for this choice was that the population and study set-up was more representative for our study compared with other studies in literature. While results showed no differences at first hand, it must be mentioned that the comparator study used different measures for severity of AEs, and that a parallel design would have fitted better to compare reactogenicity at different stages in pregnancy. Nevertheless, our study is reassuring in that with respect to safety, longer-term adverse pregnancy outcomes following maternal immunization in the second trimester are not expected to increase in frequency compared with vaccination in the third trimester. Even though a second trimester Tdap vaccination strategy has already been enrolled in some countries, future research should continue exploring the safety of maternal Tdap vaccination in relation to timing throughout gestation. Lastly, comparing our data to a group of unvaccinated women who gave birth only in 2018 may introduce truncation bias due to exclusion of short pregnancies that ended before 2018 or exclusion of long pregnancies shortly after 2018. However, based on available data, it was not feasible to compare with data of expected delivery and only possible to select records based on the date of delivery in a specific year. We expect that short pregnancies which did not end up in our 2018 reference cohort might be balanced by the short pregnancies following delivery at the end of 2018 and the same holds for long pregnancies leading to delivery after early after 2018 or 2019. In addition, pregnancy duration in the overall Dutch population remained constant over 2018 and 2019 [25]. Taken together, we would anticipate no major truncation bias should be introduced in our reference population. In conclusion, second trimester maternal Tdap vaccination is considered a well-tolerated and safe intervention in pregnant women. Despite the fact that two thirds of women experience local reactions or systemic AEs, complaints were considered mostly mild and all were transient within days. This could be discussed with the antenatal care provider before vaccination, along with its effectiveness and the established safety profile. Comparison between second trimester versus third trimester Tdap vaccination yielded no reactogenicity concerns. No increased adverse pregnancy outcomes were observed following vaccination.

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Contributions

MI, MB, HdM and ES and NvdM designed the study. MI prepared, executed and coordinated the study in the antenatal care facilities and hospitals under supervision of NvdM, MB and ES. MI also linked the questionnaire data to the DPR database under supervision of LB. JK provided (statistical) MI advice, who processed the data, performed statistical analyses and interpretated

the results. MI wrote the manuscript. All other authors critically revised subsequent versions. All authors approved the final version of the manuscript. MI had full access to all study materials and takes responsibility for the integrity of the data and the accuracy of statistical analyses.

Data availability

The data that has been used is confidential.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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